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M1. Inflammation-induced Transcriptome and Anhedonia

Francis Lotrich*, Beverly French, Charles Ma, Marianne Seney, Etienne Sibille, George Tseng

Western Psychiatric Institute & Clinic, Pittsburgh, Pennsylvania

Background: Inflammatory cytokines, including interferon-alpha (IFN-α), are known to precipitate depression symptoms in humans. Many depression symptoms typically take several weeks to develop. However, only some individuals are vulnerable to this effect (~25%), with most being resilient. We examined whether there would be similar variability in the behavioral effects of IFN-α in mice, and then explored associations between behavior and changes in gene transcription.
Methods: Male BALB/c mice (n = 32) were given daily injections of either vehicle or IFN-α, and then assessed for behavioral alterations from day 14-21 using the following tests: elevated plus-maze, open-field, novelty suppressed feeding, self-grooming following a spray test, cookie test, a two-bottle sucrose choice test, and a forced swimming test. Behavioral results were collated using principal component analyses. After three weeks of daily injections, RNA from punch biopsies of brain tissue (frontal cortex/amygdala) and blood samples were then obtained and examined using Illumina microarrays. Differential expression was determined using LIMMA. With Ingenuity Canonical Pathway analyses, we explored associations of transcripts with behavior.
Results: Four behavioral factors were obtained, only one of which differed between vehicle and IFN-α. There was only a trend for increased anhedonic-like behaviors with IFN-α. Of the 95 transcripts increased by IFN-α in the frontal cortex (FC), 70 were also increased in the blood. Of the 57 increased in both FC and amygdala (AMY), 55 were also increased in the blood. The transcripts increased in both FC and AMY are known to be influenced by IFN-α receptor signaling (p = 4.4 x 10-24) and normally inhibited by TRIM24 (p = 2.6 x10-16). Transcripts changes that most correlated with anhedonic-like behaviors were those regulated by HRas (p = 7x10-7), which is a small GTPase that can activate Raf kinase, and subsequently the MAPK/ERK pathway.
Conclusions: Importantly for human studies, many of the IFN-induced transcripts in the brain are also influenced in the peripheral blood. Many of brain transcripts likely reflect microglial activation. IFN-α only has subtle behavioral effects in mice. Interestingly, anhedonia was most associated with transcripts regulated by HRas. This includes members such as MAPKKK3 and protein kinase C-delta, whose activation can trigger MAPK phosphatase degradation and thus increase activation of the MAPK/ERK pathway. Comparing these results with transcriptional changes in humans may help elucidate why most people don't develop depression in the setting of inflammation and why some do.
Keywords: Depression, cytokine, micro-array, mouse.
Disclosure: Nothing to Disclose.

M2. Dopamine-associated Cached Values Are Not the Primary Determinant of Action Selection

Paul Phillips*, Nick Hollon, Monica Arnold, Vicente Martinez, Mark Walton

University of Washington, Seattle, Washington

Background: Contemporary theories of reward-based decision making posit that dopamine signaling updates cached values associated with stimuli or actions; and that these values are used to compare available options in making choices. Across diagnostic categories of psychiatric disease, pathological changes in decision making have been attributed to changes in this dopamine-associated mechanism. Here we critically evaluated the relationship between dopamine-associated cached values and action selection.
Methods: Dopamine release was monitored in the nucleus accumbens of rats performing decision making tasks. We presented stimuli associated with different actions to the rats unexpectedly to generate dopamine-mediated prediction-error signals that would provide a read out of the cached value. We measures the cached values during devaluation of rewards, during choices requiring the tradeoff between costs and benefits and under conditions that promoted behavioral inflexibility.
Results: Under each of the behavioral tasks we were observed conditions where animals would consistently choose an option that was not associated with the largest cached value. Following reward devaluation, rats' choices reflected the devalued reward immediately but the cached values did not initially and updated following experiential pairing of the cue with the reward at its new value. In tradeoffs between reward size and response requirement, the cached value robustly incorporated the benefit, but not the cost of the option and thus, did not account for all of the economic parameters used in the choice. Indeed, by manipulating the balance between the response cost and the reward size, we could establish conditions where the cached value was reliably highest for the non-preferred option. This finding was replicated even under conditions of behavioral inflexibility (c.f., habit) where model-free valuation systems are thought to predominate. Moreover, systemic dopamine antagonists increased the number of omitted trials, but did not change the allocation of choices between options.
Conclusions: These data indicate that dopamine-associated cached values are not used to decide which of the available options to select, but rather they to energize an action once it has been selected.
Keywords: dopamine, decision making, reward.

Disclosure: Paul Phillips' spouse is an employee of Amgen, Inc and owns stock in that company.

M3. Using a Combination Therapy of N-Acetylcysteine and Varenicline to Inhibit Cue-induced Nicotine Seeking and Relapse-induced Synaptic Plasticity

Cassandra Gipson-Reichardt*, Nicholas Allen, Neringa Stankeviciute, Sade Spencer, Michael Scofield, Yonatan Kupchik, Peter Kalivas

Medical University of South Carolina, Charleston, South Carolina

Background: Tobacco smoking is the leading preventable cause of mortality, and relapse rates remain high. Drug addiction is defined as a chronically relapsing disorder, with a reduction in the adaptive behavioral repertoire to inhibit excessive drug taking. In addition, it has been hypothesized that excessive drug use causes neuroadaptations rendering the organism vulnerable to relapse. Understanding the mechanisms underlying these neuroadaptations is critical in advancing prevention or reversal of nicotine relapse vulnerability. Given the cue dependency of nicotine use, we found cue-dependent rapid nucleus accumbens core (NAcore) synaptic potentiation and glutamatergic signaling in nicotine relapse (Gipson et al. 2013, PNAS). While targeting glutamatergic signaling has shown somewhat effective in preventing cocaine relapse, there is limited utilization of compounds targeting the dysregulation of glutamatergic signaling in promoting smoking cessation. As well, existing smoking cessation treatments are insufficient as smoking relapse rates remain high. Using both N-Acetylcysteine (NAC) and varenicline has shown some clinical promise (McClure, Baker, Gipson et al. 2014).
Methods: Using a rat model of nicotine self-administration (0.02 mg/kg/infusion) and cue-induced reinstatement of nicotine seeking, we examined the efficacy of a combination therapy of NAC (10 and 30 mg/kg, i.p.) and varenicline (1 and 3 mg/kg, s.c.) to inhibit nicotine self-administration and cue-induced nicotine reinstatement. We also quantified relapse-associated NAcore synaptic plasticity via morphological changes in dendritic spine head diameter and electrophysiological estimates of excitatory synaptic transmission (AMPA:NMDA ratio) and the ability of NAC to inhibit relapse-associated alterations in synaptic plasticity. Finally, we quantified NAcore sodium dependent (via glial glutamate transporter GLT1) and independent (via the cysteine-glutamate exchanger, xCT) glial glutamate uptake and examined the ability of NAC to restore down regulated glutamate uptake following withdrawal from nicotine self-administration.
Results: The glutamatergic agent (NAC) and the nicotine replacement agent (varenicline) additively reduced both nicotine self-administration and reinstatement of cue-induced nicotine seeking in a preclinical model nicotine relapse. Varenicline alone was more effective in reducing self-administration rates than NAC alone, however, NAC alone was more effective in reducing cue-induced nicotine seeking. In addition, administration of NAC inhibited rapid, transient spine head diameter and AMPA:NMDA ratio in the NAcore. Withdrawal from nicotine was associated with decreased sodium-dependent glial glutamate uptake (via the glial glutamate transporter, GLT1).
Conclusions: The combination therapy NAC + varenicline further inhibits cue-induced nicotine relapse compared to either treatment alone. As well, varenicline may work better to promote abstinence from nicotine self-administration whereas NAC may work as a relapse prevention aid when administered during periods of abstinence. Cue-induced nicotine relapse is associated with rapid synaptic potentiation, and NAC works to inhibit both nicotine relapse and relapse-associated NAcore plasticity. Further work will be needed to fully evaluate the clinical efficacy of using this combination therapy to improve smoking cessation outcomes.
Keywords: Nicotine, Synaptic Plasticity, N-Acetylcysteine, Varenicline.
Disclosure: Nothing to Disclose.

M4. Local and Global Dynamics of NREM Sleep Slow Waves in Mice: Effects of Preceding State and Time of Day

Vladyslav Vyazovskiy*, Nanyi Cui, Laura McKillop, Simon Fisher

University of Oxford, Oxford, United Kingdom

Background: Spatio-temporal complexity of cortical activity during sleep is manifested in the occurrence of local and global EEG slow waves, alternation of non-rapid eye movement (NREM) and REM sleep episodes and slow homeostatic changes of EEG slow-wave activity (0.5-4 Hz). The mechanisms and physiological relevance of these dynamics remain poorly understood. The aim of this study was to characterize the dynamics of cortical activity in mice, during the first minutes of individual episodes of spontaneous NREM sleep.
Methods: Cortical EEG was recorded in adult male C57BL/6 mice ($n = 6$) from the primary motor (frontal, F) and primary visual (occipital, O) areas, using epidural stainless steel screw electrodes implanted in these regions. An additional screw was implanted above the cerebellum as a reference. The recordings were performed during an undisturbed 24 h period (LD 12:12). Waking, NREM and REM sleep were scored manually in 4-s epochs. NREM sleep onset was defined by the first occurrence of slow waves in the EEG, and disappearance of phasic EMG activity recorded from the nuchal muscle. Individual EEG slow waves were detected as negative deflections below zero on both F and O signals filtered between 0.5-4 Hz. Those events > median slow wave amplitude in artifact-free NREM sleep over the 24-h were included in the analyses.
Results: As expected, EEG slow-wave activity declined progressively during the light period in both derivations, and was enhanced after prolonged spontaneous waking episodes during the dark period. Within individual NREM sleep episodes (average number contributed to the analyses: 42.7 ± 2.6/mouse, average duration: 8.1 ± 0.4 min), the incidence of individual slow waves increased progressively by approximately 20% from the episode onset and reached a plateau within the first 2 min [$p < 0.001$, repeated measures

ANOVA for both F and O]. The amplitude and slopes of individual slow waves similarly increased, albeit at a slower rate (10-13%), while average slow wave duration changed marginally (on average by only 1-2%). At the beginning of NREM sleep episodes, slow waves in the frontal and occipital derivation often occurred in isolation, as quantified by initially longer latencies between consecutive slow waves in the two regions (60% above the values later in the episode). At the beginning of the light period and during the dark phase, when physiological sleep pressure was high, slow waves in both F and O regions were 10-20% less frequent at the onset of the NREM episode, but exhibited a higher amplitude and steeper slopes, compared to the second half of the light period. Notably, slow waves at the beginning of NREM sleep episodes following REM sleep were approximately 50% less frequent, lower in amplitude and had more shallow slopes, compared to slow waves during NREM sleep occurring after waking. Moreover, upon the transition from REM to NREM sleep episodes, the latencies between consecutive frontal and occipital slow waves were approximately 50% longer compared to NREM episodes following consolidated wakefulness.

Conclusions: For the first time this study has characterized the spatio-temporal dynamics of the occurrence of individual EEG slow waves during the first minutes of NREM sleep episodes in mice. Our results highlight a complex picture, where the time of day, as well as immediate preceding state history plays a role. A novel finding was that following REM sleep episodes, NREM sleep initiates in a more "local" fashion, compared to NREM sleep episodes following waking. We speculate that REM sleep leads to a breakdown of large-scale cortical integration, resulting in an emergence of small localized networks. While the mechanisms and functional significance of such a re-setting of brain state after individual REM sleep episodes remains to be investigated, we suggest that it may be an essential feature of physiological sleep regulation.

Keywords: sleep, slow waves, mice, EEG.

Disclosure: Nothing to Disclose.

M5. Lesions of the Pedunculopontine Tegmentum in the Rat Phenocopies Specific Features of Parkinsonism

Stewart Clark*, Duncan MacLaren, Joseph Santini, Ashley Russell, Tamara Markovic

State University of New York at Buffalo, Buffalo, New York

Background: Anatomically and functionally located between basal ganglia and brainstem circuitry, the pedunculopontine tegmental nucleus (PPTg) is in a pivotal position to contribute to integrating sensory input and cortico-basal ganglia output. The PPTg is comprised of three main sub-populations of neurons (glutamatergic, GABAnergic, and cholinergic) and has reciprocal projections to numerous brain areas. Studies in primates have reported akinesia and postural instability following destruction of the PPTg. In humans, the PPTg partially degenerates in Parkinson's Disease (PD) and stimulation of this region is under investigation as a possible therapeutic. In addition, it is well established in rats that non-selective damage to the PPTg disrupts prepulse inhibition (PPI), another symptom seen in PD patients. However, dopaminergic depletion models of PD do not produce PPI deficits. PPI of the acoustic startle reflex (ASR) is the standard measure of sensorimotor gating. A brainstem-midbrain circuitry is widely viewed as mediating both PPI and ASR with the PPTg being a key component. The goal of our study was to determine whether and which aspects of PD symptomology would be mimicked in rats by lesions of the PPTg, and to what extent the cholinergic neurons contribute to lesion-mediated deficits.

Methods: Rats underwent stereotaxic surgery in order to bilaterally microinfuse vehicle, ibotenic acid (non-selective lesion), or Dtx-UII (cholinergic selective lesion) into the PPTg. At various timepoints post-surgery motor tests generally used in rodent models of PD (e.g. open field, rotarod, assessment of fine motor control and behavioral sequencing through pasta handling analysis) and PPI of ASR were performed.

Results: While dopamine depletion models typically have blunted locomotion, neither PPTg lesion group had altered baseline locomotion. However, in the rotarod test both lesion types produced a persistent impairment on the accelerating, but not on fixed speed conditions. Only the group with non-selective lesions of the PPTg showed a deficit in the pasta handling task, and the nature of the deficit is different than that seen in traditional PD rodent models. Non-selective (ibotenic acid) PPTg lesions impaired PPI while having no effect on acoustic startle or prepulse facilitation. Selective depletion of cholinergic PPTg neurons (Dtx-UII lesions) dramatically impaired the ability to generate rapid sequences of startle responses. However, under conditions where stable startle responses were achieved, there were no deficits in PPI.

Conclusions: Collectively our findings point to a role of the PPTg in the symptomology of Parkinsonism. While in PD much of the focus is on the degeneration of the dopaminergic (DA) system, the PPTg of PD patients also undergoes degeneration (up to 40%). In contrast, in Progressive Supranuclear Palsy (PSP; the most common atypical form of Parkinsonism) the PPTg degeneration is more selective to cholinergic neurons. Both idiopathic PD and PSP produce highly visible motor dysfunction. However, PD patients commonly have impaired PPI and normal ASR magnitude, while PSP suffers have reduced ASR. Therefore, we believe that PPTg lesions in rats models specific aspects of PD and PSP. Selective ablation of cholinergic PPTg neurons produces a PSP-like condition: impaired motor function and deficits in ASR. Similarly, the collection of deficits found after non-selective manipulations of the PPTg overlap that of PD. Therefore, PPTg lesions could be useful as an adjunct to or as standalone preclinical models of Parkinsonism and may aid in identifying non-dopaminergic pharmacotherapeutics.

Keywords: pedunculopontine tegmentum, Parkinsonism, motor behavior, prepulse inhibition.

Disclosure: Nothing to Disclose.

M6. Ketamine Reverses Stress-induced Depression-like Behavior in Adolescent C57bl/6 Male Mice

Sergio Iniguez*, Lace Riggs, Jason Alipio, Mirella Hernandez, Bryan Cruz

California State University, San Bernardino, San Bernardino, California

Background: Approximately 10% of children and adolescents are diagnosed with major depressive disorder (MDD). Unfortunately, close to 50% of depressed youth are unresponsive to traditional pharmaceutical treatments, such as fluoxetine (Prozac), which reflects the need to identify alternative compounds for the management of juvenile MDD. In adult populations, ketamine, an N-methyl-D-aspartate receptor antagonist, has recently shown the capacity for rapid-acting antidepressant efficacy in both preclinical and clinical studies. Thus, to examine ketamine's potential as a rapid and effective antidepressant therapeutic agent for juvenile MDD, ketamine was administered to adolescent male c57BL/6 mice while undergoing social defeat stress for 10 consecutive days (postnatal days 35-44) – a stress regimen that results in depression-like behaviors in mice.
Methods: Separate groups of stressed (defeated) and non-stressed (control) male c57bl/6 mice were administered with ketamine (0 or 20 mg/kg) either immediately after each daily episode of defeat (chronic; 10 exposures), or following the last day of stress (acute; single exposure). Twenty-four hr later (postnatal day 45), all mice were tested for depression-like behavior, as inferred from the social interaction/avoidance test.
Results: Defeated adolescent mice administered with saline (chronic or acute) exhibited a depressive-like response (i.e., increased social avoidance) 24 hr after the last episode of stress. Conversely, exposure to ketamine (chronic or acute) prevented the development of the stress-induced avoidance phenotype.
Conclusions: The results from this study indicate that ketamine may be a potential novel therapeutic agent for the treatment of juvenile MDD.
Keywords: ketamine, adolescent, depression, animal model.
Disclosure: Nothing to Disclose.

M7. Sex Differences in the Transcriptome Profile of the Nucleus Accumbens Mediate Susceptibility versus Resilience to Sub-chronic Variable Stress

Georgia Hodes*, Madeline Pfau, Francisca Ahn, Sam Golden, Hossein Aleyasin, Daniel Christoffel, Jian Feng, Li Shen, Eric Nestler, Scott Russo

Icahn School of Medicine at Mount Sinai, New York, New York

Background: Women have a higher occurrence of stress related disorders such as depression and anxiety (Kessler et al., 1994). Basic research has lagged behind clinical studies in including female subjects (Beery and Zucker, 2010) when exploring novel mechanisms to treat these disorders. There is growing concern that off-target effects and insufficient treatment efficacy are due in part to sex differences. The studies presented here examine the biological basis of sex differences in susceptibility and resilience to stress. These data suggest that males and females have different transcriptional profiles in response to stress and these sex differences are regulated by epigenetic mechanisms.
Methods: The sub-chronic variable stress (SCVS) model reveals sex differences in vulnerability to stress. Male and female mice were exposed to 6 days of variable stress and then given a behavioral test battery to examine stress sensitivity. A separate cohort was stressed and used for RNA sequencing from the nucleus accumbens (NAc), a key integrative structure in the circuitry of the reward system. We used viral over-expression or knockout strategies to manipulate DNA methyltransferase (DNMT) 3a levels in NAc and then exposed animals to SCVS. Transcriptional profiles and depression and anxiety-like behavior was measured in males and females.
Results: Males displayed behavioral resilience to 6 days of SCVS whereas females demonstrated stress susceptibility. RNA sequencing revealed that SCVS regulated more genes in males than females. Only 3 % of genes were similarly regulated by stress in males and females suggesting that there is sex specific transcriptional activation in response to stress. Over-expression of DNMT3a shifted males and females to a pro-susceptible state when exposed to a 3 day SCVS. Removing DNMT 3a from the NAc promoted behavioral resilience in females exposed to SCVS shifting their behavioral and transcriptional responses to a male-like pattern.
Conclusions: Together these data indicate that males and females undergo different patterns of transcriptional regulation in response to stress that contribute to sex differences in vulnerability. Thus, sex differences in the occurrence of stress related disorders have a biological basis and development of sex specific treatments may result in greater efficacy and fewer side effects.
Keywords: Stress, Depression, Nucleus Accumbens, Sex differences.
Disclosure: Nothing to Disclose.

M8. Akt Signaling within the Nucleus Accumbens Regulates Functional Reactivity to Chronic Social Defeat Stress in Male Mice

Carlos Bolanos-Guzman*, Eric Parise, Lyonna Alcantara, Omar Sial, Eric Nestler

Florida State University, Tallahassee, Florida

Background: Exposure to stress is one of the highest risk factors associated with the development of neuropsychiatric disorders. Unfortunately, the mechanisms that mediate the differential responses to stress are not well understood. Chronic social defeat stress (CSDS) is an ethologically relevant stress model capable of inducing many of the core symptoms of depression that are measurable in rodents. The mesolimbic dopamine system, which includes the ventral tegmental area (VTA) and its projection regions, namely the nucleus accumbens (NAc), has received considerable attention for its involvement in modulating responses to stress, as the VTA-NAc circuit plays a crucial

role in integrating reward- and emotion-related behaviors. We have previously reported that Akt (thymoma viral proto-oncogene) signaling within the VTA regulates responses to stress; however, its role within the NAc is unknown.
Methods: Adult male mice were subjected to 10 days of CSDS followed by a social interaction test (SIT) 24 hr after the last defeat. Mice were sacrificed either 24 hr (short-term) or 1 month (long-term) after the SIT, and their brains were then processed for mRNA and protein changes in the NAc. To better understand the involvement of Akt in mediating stress-induced behavioral responding, we delivered herpes simplex virus (HSV) vectors overexpressing a constitutively active form of Akt (HSV-Aktca), a dominant negative inhibitor of Akt (HSV-Aktdn), or a wild type form of Akt (HSV-Aktwt) into the NAc and assessed functional reactivity to stress.
Results: Socially defeated mice show significant increases in Akt mRNA in both the short- and long-term conditions when compared to their non-stressed counterparts. We observed increased phosphorylation of Akt protein after CSDS, but only in the long-term group, findings consistent with the enduring behavioral deficits observed in the SIT. Mice receiving microinjections of HSV-Aktca into the NAc and then subjected to a sub-threshold defeat displayed significantly increased social avoidance. Conversely, inhibition of Akt, with HSV-Aktdn, in the NAc was sufficient to reverse the avoidant phenotype induced by 10 days of CSDS.
Conclusions: These results suggest that Akt signaling within the NAc plays a crucial role in gating sensitivity to stress and may, in conjunction with changes in the VTA, mediate the depressive-phenotype induced by CSDS.
Keywords: Social defeat stress, Akt, Depression, Anxiety.
Disclosure: Nothing to Disclose.

M9. The Multimodal Antidepressant Vortioxetine Restores Cognitive Function in Preclinical Models across Several Cognitive Domains

Connie Sanchez*, Alan L Pehrson, Yan Li, Nasser Haddjeri, Maria Gulinello, Francesc Artigas

Lundbeck Research, Paramus, New Jersey

Background: The antidepressant vortioxetine is a serotonin (5-HT)3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the 5-HT transporter (SERT). Its modulation of serotonergic pre- and postsynaptic receptors results in disinhibition of several negative feedback mechanisms. Thus, in rodent studies vortioxetine's combined activity leads to increased 5-HT neurotransmission beyond that of a selective serotonin reuptake inhibitor (SSRI), increased norepinephrine, dopamine, acetylcholine, histamine and glutamate neurotransmission and attenuation of inhibitory GABA interneurons in brain areas of importance for mood and cognitive function, e.g., hippocampus and prefrontal cortex1,2. Furthermore, quantitative electroencephalographic studies in rats suggest that vortioxetine activates cortical circuitries involved in cognitive processing3. Here we review the preclinical evidence for vortioxetine's potential to reverse cognitive deficits in rodent models applying a variety of cognitive disruptors. The results are discussed relative to effects of SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) which were included as comparators and to the literature4.
Methods: Acute effects of vortioxetine on time-induced recognition, fear and social memory deficits were studied in male Sprague Dawley (SD) rats using the object recognition (OR), contextual fear conditioning and social recognition (SR) tests, respectively. Recognition and spatial memory deficits caused by low levels of brain 5-HT were studied in female Long Evans (LE) rats pretreated with the tryptophan hydroxylase inhibitor para-chloro-phenylalanine, which blocks the rate-limiting enzyme involved in 5-HT synthesis. Memory deficits in the 5-HT depleted rats were assessed in the OR and spontaneous alternation tests. Vortioxetine, escitalopram and duloxetine were studied after acute dosing and vortioxetine also after 2 weeks' dosing in food. Vortioxetine's and fluoxetine's effects on age-related visual spatial memory deficits were studied in female C57Bl mice, using the object placement (OP) test after 4 weeks' dosing in food and water, respectively. Using a similar regimen, effects of vortioxetine and fluoxetine on ovariectomy-induced visual spatial memory deficits were studied in female LE rats using the OP test. Vortioxetine's effect on cognitive dysfunction due to disrupted glutamate neurotransmission was studied in male SD rats dosed acutely or subchronically (5 daily doses and 5 days washout) with the NMDA receptor antagonists MK-801 and phencyclidine (PCP), respectively. In MK-801-treated rats acute effect of vortioxetine was studied in the SR test. Vortioxetine's acute effects on PCP-induced deficits of recognition memory and cognitive flexibility were studied in the OR and attentional set shifting tests (AST), respectively. Furthermore, effects of concomitant PCP and vortioxetine (in food) were studied in the latter model. The effect of acute vortioxetine on cognitive dysfuntion due to disrupted cholinergic neurotransmission was studied in male SD rats in the OR and SR tests. Vortioxetine doses targeting clinically relevant levels of brain SERT occupancy ($\approx$50 - 90%).
Results: In normal rats, vortioxetine prevented time-induced deficits in recognition and fear memory, but not in social memory. Vortioxetine but not escitalopram or duloxetine reversed low [5-HT]-induced recognition and spatial memory deficits. Chronic dosing of vortioxetine but not fluoxetine reversed age- and ovariectomy-induced deficits of spatial memory. Furthermore, vortioxetine restored social memory disrupted by MK-801 and PCP-disrupted recognition memory and cognitive flexibility measured as restored performance of the extra-dimensional shift in the AST. Vortioxetine also reversed deficient social and recognition memory induced by scopolamine.
Conclusions: Compared to data on SSRIs and SNRIs in the present study and the literature, vortioxetine shows a more robust improvement of cognitive function across a range of rodent models.Vortioxetine restored cognitive function in preclinical models of several cognitive domains through modulation of multiple neurotransmitter systems, including the monoaminergic, cholinergic and glutamatergic.
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Pharmacol 2014, doi: 10.1111/bph.12782 4. Pehrson et al., Eur J Pharmaco 2014. doi.org/10.1016/j.ejphar.2014.07.044.
Keywords: Cognition, Serotonin Receptors, Feedback Inhibition, Rodents.
Disclosure: Supported by H Lundbeck A/S and Takeda Pharmaceutical Company, Ltd.

M10. Ethanol Withdrawal in Adolescent and Adult Rat

Cynthia Kuhn*, Weston Fleming, Quincy Jones, Reynold Francis

Duke University Medical Center, Durham, North Carolina

Background: Adolescents and young adults consume more alcohol than adults, and early initiation of alcohol use is associated with increased risk of alcohol dependence in adulthood. However, the factors that contribute to this increased intake/risk of dependence are not well understood. The immediate and protracted effects of alcohol withdrawal are thought to contribute significantly to consumption of alcohol by alcohol dependent adults. However, there is remarkably little data about either immediate or protracted alcohol withdrawal in adolescents. We evaluated the behavioral and endocrine effects of mild alcohol dependence in adolescent and adult rats.
Methods: Adolescent (PN 28) or adult (PN 70 or older) male and female rats from Charles River Laboratories were used in all experiments. Animals received 5 days of ethanol treatment (1.5 g/kg, 3 injections at 3 hour intervals). Acute withdrawal was assessed 18 hours after the last dose by quantitating tail rigidity, vocalizations, ventromedial limb flexion, abnormal posture/gait and tremors from 0-2 () = no sign, 1 – moderate, 2 = severe). Post withdrawal anxiety was determined 4 days after the final dose via light/dark box testing to assess protracted withdrawal. Anxiety-related measures (latency to emerge into light, percent time in light, rearing) and locomotor measures (total distance traveled, distance in the dark) were measured. Animals were decapitated at the end of the light/dark test for measurement of serum corticosterone to assess stress-induced hormone release. A separate cohort of animals was injected with ethanol and 1 hour after the 1st, 2nd or 3rd injection to measure blood alcohol content (BAC) in an Analox BAC analyzer. Statistics on all results were analyzed by 3 way ANOVA (age x sex x treatment) using NCSS. All experiments were approved by the Duke University IACUC.
Results: Acute withdrawal signs were comparable in adolescents and adults and did not differ by sex. Ethanol withdrawn adults exhibited significant decrease in time spent in light, enhanced latency to enter light and decreased rearing although responses were somewhat milder in females than males. Alcohol-withdrawn adolescent exhibited less rearing, but other behavioral signs (latency to enter light, time in light) did not show significant changes. Overall, the data show that adolescents and adults exhibited comparable acute withdrawal 24 hours after the end of treatment, but that adults experienced more anxiety assessed 4 days later.
Conclusions: These results suggest that acute withdrawal from ethanol, which largely reflects CNS hyperexcitability mediated by changes in GABA and glutamate function, is comparable in adolescents and adults after a brief (5 days) ethanol exposure. This finding suggests that the neurochemical adaptation mediating these behaviors may be comparable in adolescents and adults. In contrast, the protracted effects were milder in adolescents and adults. The latter, which are mediated largely by CRF, may reflect lesser adaptation of this neural circuitry in adolescents than adults. Future study of these neurochemical mechanisms in alcohol dependent adolescents may provide insight into age-selective pharmacotherapies for alcohol dependence in adolescents.
Keywords: ethanol, withdrawal, adolescence.
Disclosure: Nothing to Disclose.

M11. Inflammatory Pain Impacts Motivation for Heroin Self-administration in Dependent Rats: A Possible Role for Kappa Opioid Receptors

Lucia Hipolito, Sandra Comer, Michael Bruchas, Jose Moron Concepcion*

Columbia University Medical Center, New York, New York

Background: Pain management in opioid abusers raises many ethical and practical difficulties for clinicians, resulting in a general under-treatment of pain in this population. While chronic opioid administration may alter pain states, the presence of pain itself clearly may alter the propensity to self-administer opioids. Data presented here provide new insights that show that inflammatory pain alters heroin seeking through changes in the opioid reward pathway. In addition, given the role of kappa opioid receptors in motivational states, we also examined the role for these receptors in this pain-induced alteration in motivated behavior. The studies shown here will therefore fill a gap in the existing literature by examining the neurochemical mechanisms underlying opioid abuse under conditions of chronic inflammatory pain.
Methods: In the present study, we investigated the effect of chronic inflammatory pain on i.v. heroin self-administration under progressive ratio (PR) schedule of reinforcement. We selected the complete Freund's adjuvant (CFA) rat model of inflammation to assess the effect of chronic inflammatory pain on heroin seeking. In addition, we investigated the neurochemical changes induced by chronic inflammatory pain on DA transmission within the mesolimbic pathway by conducting the in vivo microdialysis studies. Biochemical and immunohistochemical analyses were conducted to examine a role for kappa opioid receptors. All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee at Columbia University.
Results: First we analyzed the effect of inflammatory pain on motivation for heroin and sucrose intake measured in a progressive ratio (PR) schedule of reinforcement. Rats were trained to self-administer 50 μg/kg/infusion heroin or sucrose pellets under FR1, FR2 and FR5 schedules of responding for at least 11 sessions. Afterwards, animals underwent a heroin (50 or 200 /kg/infusion) or

sucrose progressive ratio (PR) baseline session to measure initial ordinal value of the final ratio to which the animal responded (PR step number). Then, a second PR session was performed 48 hours after CFA or saline injection in the hind paw. Inflammatory pain reduced PR step number from baseline to 72% with sucrose as the reward. In animals trained with 50 μg/kg/infusion (dependent rats) the presence of inflammatory pain reduced the PR step number from baseline to 63% with 50 μg/kg/infusion heroin as the reward. Interestingly, this effect of inflammatory pain on motivated behavior for heroin was completely reversed when the heroin dose was increased up to 200 μg/kg/infusion. Overall, our data show that there is a robust decrease in the overall motivational state during inflammatory pain and that this effect is completely reversed when the dose of heroin is increased. We next investigated the effect of inflammatory pain on heroin-evoked dopamine (DA) release in the nucleus accumbens (NAc) given the fact that DA levels influence the motivation for drug intake measured in a PR schedule of reinforcement. Interestingly, we observed that whereas the administration of i.v. heroin (75 μg/kg) triggered an increase in extracellular DA levels, this same dose of heroin only elicited a much smaller increase in DA levels compared to baseline in CFA-treated animals. Therefore, we next examined the effects of a higher dose of heroin (150 μg/kg, i.v.) on accumbal DA release in the NAc in control and in CFA-treated rats. The highest dose of heroin induced a significant increase of DA release in control animals and in CFA-treated animals. Previous data have shown that pain relief, by blocking pain afferents with lidocaine, increases of DA extracellular levels in the NAc. Paw withdrawal thresholds after either 75 or 150 μg/kg heroin i.v. administration were similar in control and pain animals These data strongly suggest that the presence of inflammatory pain selectively impacts the sensitivity to the rewarding properties of heroin. Finally, given the role of kappa opioid receptors in motivational states, we analyzed expression of these receptors in the mesolimbic dopaminergic system and found that kappa receptor expression was significantly increased in the NAc but was not altered in the VTA. We are currently conducting studies to examine whether activation of kappa receptors in the reward pathway is responsible for this pain-induced alteration in motivation for heroin and natural reinforcers.

Conclusions: Exposure to opioids in pain patients with a prior history of drug use has been shown to put them at risk for opioid abuse, dose escalation and/or relapse. However, the effect of pain on opioid intake patterns in animal models of opioid abuse has not been investigated. The results presented here reveal that the presence of inflammatory pain impacts the reinforcing effects of heroin in dependent rats probably via activation of kappa opioid receptors. Taken together, our data also suggest that the presence of pain impacts the effects of opioids (and natural reinforcers) on the reward pathway such that higher doses of the opioid are necessary to produce neurochemical and positively reinforcing behavioral effects.

Keywords: chronic pain, dopamine, nucleus accumbens, heroin self-administration.

Disclosure: Nothing to Disclose.

M12. Binge-eating Behaviour in Rats Induces Changes in Dopamine and Opioid Receptor Binding in the Brain

David Heal*, Sharon Cheetham, Peter Hutson

RenaSci Consultancy Ltd., Nottingham, United Kingdom

Background: Binge-eating disorder (BED) is a common psychiatric condition, affecting ~2% of the adult population and presents as the frequent, compulsive, excessive consumption of highly palatable foods. We have recently developed and pharmacologically characterized a rat model of BED in which rats that are freely-fed on standard chow are given irregular, limited access to chocolate along with normal chow. Over a period of 4 weeks, the rats developed robust, binge-eating of the chocolate with concomitant reductions in their consumption of normal chow. Body weights remained at the same level as control rats maintained on normal chow. We have, therefore, proposed that this paradigm models BED without obesity (Vickers et al, 2013). To increase our understanding of the neurochemical changes underpinning this behavior, a study was conducted to determine whether the development of binge eating was associated with changes in dopaminergic or μ-opioid receptors (both of which are thought to be implicated in BED, Davis et al, 2009) in various brain regions of binge eating rats.

Methods: Two cohorts of lean, female, Wistar rats (Study 1 = 10 and Study 2 = 30) maintained on a reverse dark-light cycle were given free access to normal chow and water, and in addition, were allowed brief (2hr), irregular access to powdered milk chocolate over a period of 4 weeks. Groups of controls (Study 1 = 10 and Study 2 = 25) were treated identically except that an empty glass jar was placed in their cages during the binge sessions. The rats that were given intermittent access to chocolate developed robust patterns of binge eating which consisted of compulsive chocolate consumption in the binge periods with reductions of normal chow intake in these sessions and on the days immediately following them. The bodyweights of the binge eating rats were not significantly different from their respective control groups. On Day 28 of the irregular access protocol, the rats were killed and their brains taken 1 hr after the final bingeing session on chocolate or after presentation of the empty pots to the control groups of rats according to a timed schedule. Brains region were dissected as detailed: Study 1 = striatum and Study 2 = striatum and frontal cortex. In Study 1, the number and affinity of striatal D1 receptors were determined by saturation binding analysis using [3H]SCH 23390 (8 concentrations from 0.1-8nM) with specific binding defined by (+)butaclamol (1uM) and D2 receptors using [3H]raclopride (8 concentrations from 0.125-12nM) defined with (-)sulpiride (1uM). Striatal dopamine reuptake transporter (DAT) sites were labelled with [3H]GBR 12935 (10 concentrations from 0.125-20nM) defined by mazindol (1uM). In Study 2, the number and affinity of μ opioid receptors in the striatum and frontal cortex were quantified using [3H]DAMGO (striatum: 8 concentrations from 0.0625 – 12nM and cortex: 10 concentrations from 0.0625-12nM) defined by naloxone (50uM). Results are presented as mean ± SEM; n = 6-10 rats/group. NS = not significantly different.

Results: The development of binge eating was associated with a reduced number of striatal D1 receptors compared with the non-binge control group (Bmax [fmol/mg protein]: 176 ± 26 versus 287 ± 25; $p < 0.01$) with no change in their affinity. The number D2 receptors (Bmax [fmol/mg protein]: 303 ± 8 versus 289 ± 21; NS] and DAT sites (Bmax [pmol/mg protein]: 2.35 ± 0.26 versus 2.84 ± 0.24; NS) in the striatum were unchanged. The D2 receptor and DAT affinities were unaltered. Compared with its control group, the number of μ opioid receptors was increased in the striatum of the binge-eating rats (Bmax [fmol/mg protein]: 209 ± 13 versus 162 ± 13; $p < 0.02$), but not in the frontal cortex (Bmax [fmol/mg protein]: 296 ± 19 versus 258 ± 13; NS). The affinity of the μ-opioid receptors in both regions was unchanged.
Conclusions: The results show that binge-eating behavior in lean, female rats is associated with a reduction of striatal D1 receptors together with a concomitant increase in the number of μ-opioid receptors. There were no changes in striatal D2 receptor and DAT binding or cortical μ-opioid receptor binding. It has been postulated that there are changes in dopaminergic and opioid systems in subjects with BED (Davis et al, 2009). The findings in our rat model of BED suggest that dysregulation of the dopamine and opioid reward systems in the striatum also have a role the development of binge-eating in rats. References Vickers SP, Heal DJ, Hackett, D, Hutson PH (2013). Effect of lisdexamfetamine in a rat model of binge-eating disorder. SfN abstract: 236.03 Davis CA, Levitan RD, Reid C, Carter JC, Kaplan AS, Patte KA, King N, Curtis C, Kennedy JL (2009). Dopamine for "wanting" and opioids for "liking": a comparison of obese adults with and without binge eating. Obesity 17: 1220-5.
Keywords: Binge-eating disorder, receptors, dopamine, opioid.
Disclosure: David Heal and Sharon Cheetham are full-time employees of RenaSci Ltd. Peter Hutson is a full-time employee of Shire Development Inc. This programme of research was funded by Shire Development Inc.

M13. Reciprocal Thalamo-prefrontal and Prefronto-thalamic Projections Support Spatial Working Memory in Mice

Scott Bolkan, Sebastien Parnaudeau, Abigail Clark, Josh Gordon, Christoph Kellendonk*

Columbia University/New York State Psychiatric Institute, New York, New York

Background: Impairment in working memory is a core, cognitive symptom of schizophrenia. Functional imaging studies in patients and healthy subjects, neuro-physiological studies in non-human primates, and lesion studies in rodents have implicated activity in the mediodorsal thalamus (MD) and medial prefrontal cortex (mPFC) as supporting working memory. However, given the dense, reciprocal connectivity between the MD and mPFC, it is unclear (1) whether direct thalamo-cortical input to the mPFC, (2) whether reciprocal cortico-thalamic input to the MD or (3) whether activity in both projections are required for working memory. To investigate the role of MD-mPFC circuitry in working memory we inhibited MD-mPFC and mPFC-MD projections in a temporally precise and reversible manner. Since the orbito-frontal cortex (OFC) is generally not implicated in working memory we further tested the hypothesis that inhibiting MD-OFC projections will not affect working memory.
Methods: Experiment 1: We stereotactically targeted Adeno-Associated-Virus 5 expressing the light-driven proton pump eArch3.0-EYFP or EYFP to the MD and bilaterally delivered 532 nm light (10mW) to MD afferents in the mPFC or OFC, thereby inhibiting MD-terminal fields in mPFC or OFC. We then tested the behavioral effects of terminal field inhibition in a delayed non-match to sample (DNMS) T-maze task, which assesses working memory in rodents. Mice were first trained to a criterion level of performance under a No Light condition. On subsequent task sessions, within-animal performance was assessed at two delay times (10s or 60s) and three interleaved, pseudo-randomized light conditions (Light OFF, ON mPFC, ON OFC). Experiment 2: We now targeted the reciprocal projection by expressing eArch3.0-EYFP or EYFP in the mPFC and delivering light to the cortico-thalamic terminals in the MD. Within-animal performance was assessed at two delay times (10s or 60s) and two interleaved, pseudo-randomized light conditions (Light OFF, ON MD). In both experiments Arch3.0 was activated during the entire trial including the encoding (sample), the delay and the retrieval (choice) phases of each trial.
Results: Experiment 1: eArch3.0 and EYFP mice showed no significant difference in performance at any light condition under the 10s condition. In contrast, at 60s delays eArch3.0 mice showed a significant drop in performance compared to EYFP controls during ON mPFC – but not OFF mPFC and ON OFC – trials. Experiment 2: eArch3.0 and EYFP mice showed no significant difference in performance at any light condition under the 10s condition. At 60s delays eArch3.0 mice showed a significant drop in performance compared to EYFP controls during ON MD trials but not OFF MD trials.
Conclusions: These findings suggest a critical role for reciprocal activity in MD-mPFC circuitry in the delay-dependent performance of the DNMS working memory task. In contrast, our results do not support a role of MD-OFC projections in working memory. In an effort to uncover the cognitive processes that are supported by MD-mPFC circuitry ongoing studies are investigating the role of inhibiting MD-mPFC and mPFC-MD projections during distinct time points of the task: the sample phase, the delay phase and the choice phase. The results of this temporal dissection will also be presented.
Keywords: working memory, medio-dorsal thalamus, prefrontal cortex, optogenetics.
Disclosure: I have a research contract with Forest Inc. for an unrelated project.

M14. Dissecting the Role of Mesolimbic Dopamine Circuitry in Maladaptive Decision Making after Adolescent Alcohol Use

Abigail Schindler, Kimberly Tsutsui, Jeremy Clark*

University of Washington School of Medicine, Seattle, Washington

Background: Adolescent alcohol use is a major public health concern and is strongly correlated with the develop-

ment of alcohol abuse problems in adulthood. That such experience can be antecedent to problem drinking has been recognized for some time; that such experience may also have durable effects on decision making is a relatively recent consideration. We have previously demonstrated that chronic alcohol use in adolescence promotes a persistent, maladaptive preference for risk in adulthood. In addition, we have shown that phasic dopamine (DA) signaling in response to risky, but not safe, options is increased in alcohol-exposed rats in parallel with altered choice behavior, but the underlying mechanisms remain unknown. Gamma-aminobutyric acid (GABAA) receptors located on DA neurons in the ventral tegmental area (VTA) are a potential candidate for mediating these effects, as these receptors are a main target of ethanol and modulator of DA neuron activity. Therefore, in the present work we tested the hypothesis that chronic alcohol use in adolescence confers risk preference and disinhibition of DA signaling through GABAA modulation of specific mesolimbic circuitry.

Methods: Male rats were given voluntary access to an alcohol or control gelatin for twenty days throughout the adolescent period (post natal days 30-50). After twenty days of withdrawal all animals were prepared for electrochemical detection of DA by fast-scan cyclic voltammetry in the ventral striatum. To examine the hypothesis that alcohol exposure promotes disinhibition of DA signaling, DA measurements were made either in vivo in a standard operant chamber or in an anesthetized preparation after electrical stimulation of the pendunculopontine nucleus (PPT) and the medial forebrain bundle (MFB). Emerging evidence indicates that there are multiple excitatory inputs to the VTA including the PPT and that these circuits may differ in the information that is conveyed and the behaviors that are supported. Specifically, in addition to excitatory glutamatergic and cholinergic neurotransmission, PPT stimulation also elicits GABAA receptor dependent current in VTA DA neurons; raising the possibility that adolescent alcohol intake may promote increased phasic DA release through downregulation of GABAA receptors specifically on DA neurons. Thus, we used a pharmacological approach coupled to the stimulation experiments to explore this potential candidate for mediating alcohol-evoked changes in DA transmission. In the VTA, both DA and GABA neurons express GABAA receptors however, specific pharmacological manipulation is made possible by that fact that the subunit composition differs between the two with $\alpha 2$, $\alpha 3$, and $\alpha 5$ subunits expressed primarily on DA neurons and $\alpha 1$ subunits on GABA neurons. Therefore, we used a receptor $\alpha 2$, $\alpha 3$, and $\alpha 5$ subunit allosteric agonist (L-838,417) to assess the differential consequences of applying this "brake" on DA signaling in animals with and without a history of adolescent alcohol use.

Results: Here we demonstrate that adult rats previously exposed to alcohol during adolescence show increased phasic DA release, as compared to controls, both in vivo after exposure to a novel environment and in an anesthetized preparation after electrical stimulation of the PPT. Striatal DA release via electrical stimulation of the MFB did not differ between alcohol and control rats, suggesting that increased DA release following adolescent alcohol intake occurs via changes within the VTA. Finally, administration of L-838,417 caused a dose-dependent decrease in phasic DA release elicited by PPT stimulation in control rats, and this decrease was enhanced in rats exposed to alcohol during adolescence.

Conclusions: Adolescence is a critical period of maturation where brain development, including the mesolimbic dopamine DA system, may be disrupted by chronic alcohol use. Indeed, this impairment may represent a unique vulnerability of the developing brain as adult rats with identical alcohol exposure do not show comparable deficits in decision making. Maladaptive choice behavior after adolescent alcohol use is accompanied by a persistent disinhibition of dopamine release recorded in vivo and after stimulation of the PPT. The PPT in particular has been linked to the assignment of incentive value and the inactivation of this structure has recently been shown to alter choice behavior under risk. In addition to excitatory glutamatergic and cholinergic neurotransmission, PPT stimulation also elicits GABAA receptor dependent current in VTA DA neurons and alcohol-evoked changes in dopamine release after stimulation of the PPT is normalized by a selective GABAA agonist. Thus, altered GABAA receptor expression located specifically on DA neurons in the VTA is a potential candidate for mediating this circuit-specific disinhibition in DA signaling after adolescent alcohol use.

Keywords: Alcohol, Adolescence, Dopamine, Risk.
Disclosure: Nothing to Disclose.

M15. Autistic-like Behavioral Deficits in Mouse Models of Tuberous Sclerosis Complex Are Severer in TSC2 Mutation than in TSC1 Mutation

Atsushi Sato*, Yukio Takamatsu, Miho Tanaka, Shinya Kasai, Toshiyuki Kobayashi, Okio Hino, Kazutaka Ikeda, Masashi Mizuguchi

Tokyo Metropolitan Institute of Medical Science, Katsushika, Japan

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impairs social behavior. One example underlying ASD is mTORC1 activation in tuberous sclerosis complex (TSC), caused by heterozygous mutations in the TSC1 or TSC2 genes. Neurological and psychiatric manifestation includes cortical tuber, subependymal giant cell astrocytoma (SEGA), ASD, intellectual disability and epilepsy. SEGA and epilepsy responds well to mTOR inhibitors (Krueger, 2010; Krueger, 2013). mTOR inhibitors may relieve ASD in TSC patients (de Vries & Howe, 2007). We reported therapeutic effectiveness of an mTOR inhibitor rapamycin for impaired reciprocal social interaction in adult Tsc1 + /- and Tsc2 + /- mice (Sato, 2012). Intriguingly, TSC2 mutations are associated with severer neurological and psychiatric complications than TSC1 mutations, in human patients (Numis, 2011) and in astrocyte-specific knockout mice (Zeng, 2011). However, whether this is also true for ASD is not known. To examine whether Tsc2 haploinsufficiency indeed results in the severer autistic-like abnormal behaviors, we compared Tsc1 + /- and Tsc2 + /- mice for abnormal behaviors relevant to ASD.

Methods: A Tsc1 + /- and a Tsc2 + /- mouse (Kobayashi, 1999: Kobayashi, 2001) was crossed to obtain WT, Tsc1 + /-,

Tsc2 + /-, and Tsc1/Tsc2 double-heterozygous mice (TscD) on the same genetic background. At 3 months of age or older the mice were analyzed for the following behaviors: Social interaction test: The mouse was left alone in a homecage for 15 min. Then a novel mouse (C57BL/6J) of the same sex was introduced. Behavior was video recorded for 10 min and analyzed for active interaction (e.g., anogenital sniffing, allo-grooming, close following), rearing (standing up with hindpaws) and self-grooming behavior. 3-chambered social approach test: The mouse was left in the chamber divided into 3 compartments (50cm*17cm) in equal size for 10 min. A novel mouse (C57BL/6J) of the same sex (S1) and a metal block (O) was put into a wire cage and presented for 10 min. Then the block was replaced with another novel mouse (S2) and presented for 10 min. In a separate set of experiments, the test mouse was presented with S1 and a cagemate (C) for 10 min. Approach avoidance score was calculated by (time exploring S1) – (time exploring C) (Brodkin, 2004: Page, 2009). Exploration to each cage was measured automatically. Self-grooming test: The mouse was left alone in a cage without bedding material for 10 min. Then behavior was video recorded for 10 min for self-grooming and rearing behavior. Rapamycin (5 mg/kg) or vehicle (10% DMSO) was given intraperitoneally for 2 days, followed by social interaction test and 3-chamber social approach test 24 h after the second injection.

Results: Tsc1 + /-, Tsc2 + /-, and TscD mice showed reduction in time spent exploring a novel mouse in the social interaction test. In the 3-chamber social approach test, the mutant mice approach S1 more than O, an inanimate object. When O was replaced with another novel mouse (S2), however, the mice equally approached S1 and S2. A concern was that this abnormality could be explained by the deficient working memory (Ehninger, 2008). Abnormal stereotypies were also found in the mutant mice. They showed a more intense self-grooming in the social interaction test and the self-grooming test. An increase in rearing was noted in the social interaction test but not in the self-grooming test. Then we tried to exclude the influence of working memory and test whether TSC mutant mice had deficiency in recognizing social novelty. When a cagemate (C) was presented instead of an inanimate object in the 3-chamber social approach test, WT and Tsc1 + /- mice approached S1 for a longer time while Tsc2 + /- and TscD mice equally explored S1 and C. Moreover, the selective approach to the novel mouse, figured out as ''approach avoidance score'', was reduced in half in Tsc1 + /- mice when compared with WT mice. Injection of rapamycin reversed the abnormalities in the social interaction test and the 3-chamber social approach test in adult Tsc1 + /-, Tsc2 + /- and TscD mice.

Conclusions: Haploinsufficient mouse models of TSC showed social deficit and stereotypy, compatible with the two core domains of human ASD. Most of behavioral features relevant to ASD were similar among Tsc1 + /-, Tsc2 + /-, and TscD mice. The mice with Tsc2 heterozygous deletion showed a deficit in discriminating novel mice from familiar ones while Tsc1 + /- mice preferred novel mice like WT animals. In glia-specific knockout mice, Tsc2 mutation aggravated neurological phenotype compared with Tsc1 mutation while no difference was found in mTOR activation and feedback inhibition of Akt (Mietzsch, 2013). This and our finding would suggest the distinct role of Tsc1 and Tsc2 in the brain. Further research should focus on molecular events that give rise to ASD when Tsc1 or Tsc2 is functionally deficient.

Keywords: autism spectrum disorder, tuberous sclerosis complex, rapamycin, mouse.
Disclosure: Nothing to Disclose.

M16. Role for Brain Melanocortin-4 Receptors (MC4Rs) in Excessive Alcohol Drinking and Hyperalgesia in Alcohol-dependent Rats

Nicholas Gilpin*, Emily Roltsch, Brandon Baiamonte, Brittni Baynes

Louisiana State University Health Sciences Center, New Orleans, Louisiana

Background: Up to 50% of U.S. adults with chronic pain use alcohol, and humans with Alcohol Use Disorder (AUD) are more sensitive to painful stimuli during withdrawal (WD). These data suggest that some humans drink alcohol to relieve pain, and that chronic alcohol drinking worsens pain outcomes. Similarly, rats made dependent on alcohol through forced exposure exhibit increases in nociceptive sensitivity (i.e., allodynia, hyperalgesia) during alcohol WD. Brain melanocortin-4 receptors (MC4Rs) have been implicated in alcohol drinking and nociception in rodent models, in general showing that MC4R agonists reduce low-to-moderate alcohol drinking by non-dependent animals, and that brain MC4R antagonism potentiates the analgesic effects of morphine. In these studies, we aimed to explore: [1] the effects of acute alcohol, chronic alcohol, and alcohol WD on thermal nociception in rats, [2] the effects of chronic alcohol on expression of MC4R and its endogenous ligands in brain regions important for alcohol drinking and pain, and [3] the effects of AgRP, an endogenous MC4R inverse agonist, on thermal nociception and alcohol self-administration (SA) in alcohol-dependent rats.

Methods: In Experiment 1, male Wistar rats were trained to self-administer alcohol in a 2-lever operant situation and were tested for thermal nociception using the Hargreaves method. Upon stabilization of both behaviors, animals were exposed to either chronic intermittent alcohol vapor (alcohol-dependent rats) or ambient air (non-dependent drinkers and alcohol-naïve controls). Over weeks of dependence induction, rats were tested for thermal nociception during withdrawal from alcohol vapor with and without prior access to orally self-administered alcohol, and also during alcohol vapor intoxication. After dependence induction, a cannula was implanted in the lateral ventricle (ICV) and animals were infused with 0.0, 0.05, 0.1, or 0.2 ug AgRP in a within-subjects Latin square design 15 min prior to tests for thermal nociception and alcohol SA. In Experiment 2, male Wistar rats were exposed to chronic intermittent (14 hrs/day) alcohol vapor or ambient air for eight weeks, sacrificed 6-8 hours into WD, and brains were processed for immunoreactivity for MC4Rs, alpha-melanocyte-stimulating hormone (a-MSH; melanocortin receptor agonist), and agouti-related peptide (AgRP; MC3/4R inverse agonist).

Results: Non-dependent alcohol drinkers exhibited thermal hyperalgesia relative to alcohol-naïve controls, and this effect was exaggerated by withdrawal from alcohol vapor and was rescued (i.e., analgesia) by alcohol vapor intoxication. Alcohol withdrawal-induced thermal hyperalgesia was abolished by 30 minutes of voluntary oral alcohol self-administration immediately prior to Hargreaves tests. ICV AgRP infusion partially rescued thermal hyperalgesia in alcohol-dependent rats, but did not affect this behavior in non-dependent drinkers or alcohol-naïve controls. Alcohol-dependent rats exhibited escalation of alcohol SA during alcohol withdrawal. ICV AgRP infusion partially reversed this escalated alcohol SA in alcohol-dependent rats, and produced trends toward increasing alcohol SA in non-dependent drinkers. Alcohol-dependent rats exhibited changes in immunoreactive densities for MC4Rs, a-MSH, and AgRP in the central amygdala (CeA) and periacqueductal grey (PAG), but not in the paraventricular hypothalamus (PVN) or bed nucleus of the stria terminalis (BNST).
Conclusions: Our results implicate brain MC4R systems in excessive alcohol drinking and hyperalgesia in alcohol-dependent rats. AgRP reduced alcohol responding in dependent rats, but produced a trend toward an increase in responding by non-dependent rats, which agrees with past data showing that AgRP increases alcohol drinking in non-dependent rats & mice, and suggests MC4R system neuroadaptations in alcohol-dependent rats. AgRP reduced thermal hyperalgesia in alcohol-withdrawn rats, which agrees with past results showing that MC4R antagonism abolishes hyperalgesia during morphine WD, and also prevents development of tolerance to the analgesic effects of chronic morphine. Site-specific MC4R antagonists in amygdala or PAG each reduce nociception in rodents, which is interesting since we observed changes in immunoreactive densities for MC4Rs and its ligands in the CeA and PAG of dependent rats. The sites and directions of our immunoreactivity data agree with data from other rodent models of alcohol use and neuropathic pain. Our data suggest that MC4Rs in CeA and/or PAG may mediate hyperalgesia and/or escalated "alcohol drinking for pain" in alcohol-dependent individuals.
Keywords: melanocortin, amygdala, alcohol, pain.
Disclosure: Nothing to Disclose.

M17. Intraaccumbal Administration of Zeta Inhibitory Peptide (ZIP) Erases Drug Memory and Prevents Cocaine Reinstatement Independent of Pkmzeta

Lisa Briand*, Jordan Karsch, Chris Pierce

Temple University, Philadelphia, Pennsylvania

Background: During abstinence, memories associated with drug-taking persist and the inability to eliminate these drug memories is thought to underlie addiction. Eliminating these drug-paired memories could provide an opportunity for therapeutic intervention. Converging evidence suggest that zeta inhibitory peptide (ZIP) eliminates memories for experience-dependent behaviors, included conditioned drug associations. However, it is not known whether the elimination of these memories alters drug relapse. ZIP is a synthetic compound designed bind the constitutively active form of atypical PKC, PKMζ, a protein implicated in learning and memory. However, recent evidence from PKMζ knockout mice suggests that ZIP may function through alternative mechanisms.
Methods: The current study examined the effect of ZIP administration in the nucleus accumbens on cocaine-primed reinstatement of cocaine seeking, a rodent model of relapse.
Results: We demonstrate that intraaccumbal ZIP blocks cocaine-primed reinstatement when administered 24-hours or 1 week prior to testing. Interestingly, ZIP infusion has no effect on the reinstatement of food seeking. Contrary to what was predicted, PKMζ knockout mice demonstrate an increase in food and cocaine taking and cocaine seeking. Experiments are underway to determine whether this reflects a generalized increase in locomotor response to novelty or altered reward behavior.
Conclusions: These findings suggest that ZIP may be acting independent of PKMzeta. Current studies are underway to determine whether intraaccumbal ZIP inhibits reinstatement behavior in PKMζ knockout mice.
Keywords: Cocaine, Reinstatement, PKMzeta, nucleus accumbens.
Disclosure: Nothing to Disclose.

M18. Determining a Role for Rictor in Susceptibility to Stress and Morphine Reward and Consumption

Sophia Kaska, Sarah Cooper, Megan Kechner, Michelle Mazei-Robison*

Michigan State University, East Lansing, Michigan

Background: Co-morbidity of drug addiction and mood disorders is a significant problem. Both disorders may involve dysregulation of the mesolimbic dopamine (DA) pathway with specific neuroadaptations underlying co-morbidity. Chronic social defeat stress (CSDS) has strong face validity for depression and a dependence on altered ventral tegmental area (VTA) DA neuron activity. Both susceptibility to CSDS and opiate exposure decrease AKT activity in the VTA. Given that AKT is phosphorylated by mammailian target of rapamycin complex 2 (TORC2), we hypothesize that alteration of VTA TORC2 activity will affect susceptibility to CSDS and stress-induced changes in morphine reward. While stress exposure is known to influence drug craving and relapse in humans, study of the effects of stress on opiate intake in preclinical models is limited as most models utilize some form of physical trauma. To overcome this, we use an emotional stress model, where mice witness, but are not physically exposed to, CSDS. Thus, our goal is to determine whether physical and/or emotional stress alter morphine reward and consumption and to determine the role of VTA TORC2 activity in these behaviors.
Methods: For physical CSDS, C57Bl6 mice were subjected to a 5-10 min social defeat episode with a novel CD1 mouse daily for 10 days. Following each defeat episode, the mice were co-housed, but the C57 mouse was physically separated from the CD1 mouse by a barrier that allows sensory interaction. After the tenth defeat, the mice were singly housed and social interaction (SI) testing was performed 24 hours later. For emotional stress, a second male C57 mouse was placed on the opposite side of the perforated partition during the physical stress, such that the mouse experiences the psychological stress of witnessing an

aggressive encounter without physical contact, as described by Warren et al. (2013). The "witness" mouse was then housed across from a novel CD1 mouse for the remaining 24 hours. To assess morphine consumption, we used a two-bottle choice paradigm. Mice were singly housed with two bottles initially containing just water, allowing acclimation to the bottles. The bottles were then filled with 0.2% sucrose and 0.3 mg/ml morphine sulfate or 0.06 mg/ml quinine sulfate, which were measured daily. To determine whether alteration of TORC2 activity affected morphine preference and susceptibility to stress, we utilized c57Bl6 mice that received intra-VTA infusion of either HSV-GFP or HSV-GFP-Rictor to increase TORC2 activity, as well as progeny from floxed-Rictor/TH-Cre crosses, which specifically lack TORC2 activity in DA neurons.
Results: Using a two-bottle choice assay, we found that mice susceptible to physical CSDS exhibited increased morphine preference. Mice exposed to emotional stress also exhibited an increase in morphine preference, despite having only a modest reduction in SI score at this time-point. Importantly, we found that there was a significant negative correlation between SI ratio and morphine preference, where decreasing SI ratio correlates with an increase in morphine reward. These data support the hypothesis that susceptibility to physical or emotional stress increases morphine reward. Similarly, we found that mice susceptible to physical stress exhibit significantly increased morphine conditioned place preference (CPP) compared to control and resilient mice. Interestingly, when morphine consumption was evaluated 14 days after the last defeat, there was not a significant difference in the morphine preference score, but morphine intake was significantly increased in defeated mice and there was a significant negative correlation between morphine intake and SI score, suggesting that the stress effect on morphine reward persists. We next wanted to evaluate the role of TORC2 activity in these changes. We have previously found that increasing and decreasing TORC2 activity in the VTA is sufficient to increase and decrease morphine CPP, respectively. In order to verify that this regulation similarly affected voluntary morphine consumption, we performed the two-bottle choice assay in mice that received either intra-VTA infusion of HSV-GFP or HSV-GFP-Rictor (to increase TORC2 activity) and in Rictor KO mice (to decrease TORC2 activity). As expected, we found that morphine preference was decreased in Rictor KO mice compared to wild-type littermates, an effect that was also observed in heterozygous mice. However, we found that increasing TORC2 activity in the VTA did not increase morphine preference. We are now exploring whether alteration of TORC2 activity increases susceptibility to stress and if TORC2 also mediates stress-induced changes in opiate reward.
Conclusions: Together these data suggest that physical and emotional stress increase morphine reward and that this effect is persistent. Decreasing TORC2 in DA neurons is sufficient to decrease voluntary morphine preference, and we are now determining whether VTA TORC2 activity mediates stress-induced changes in reward, supporting a role for TORC2 as a contributor to co-morbidity. Given the difficulty in treating this co-morbid population, identification of neurobiological mediators is critical in developing improved therapeutics.

Keywords: morphine, VTA, dopamine, stress.
Disclosure: Nothing to Disclose.

M19. Witnessing Maternal Abuse during Post-natal Day 21-27 Induces Depression-like Behavior in Adult Rats

Samina Salim*, Hesong Lui, Gaurav Patki, Ankita Salvi, Naimesh Solanki

University of Houston, Houston, Texas

Background: According to American Psychological Association, approximately 15.5 million children in the United States witness physical or emotional abuse of a parent most commonly that of their mother. While negative effects of physically experiencing domestic or social abuse on children are commonly reported, the effects of witnessing parental abuse on children of abused parents needs further investigation. Studies have found that children who witnessed domestic violence often matched the signs and symptoms of Post-Traumatic Stress Disorder (PTSD). PTSD can develop not only from directly experiencing but also from witnessing traumatic events.
Methods: Recently, our lab group developed a rat trauma witness model (TWM) and reported that rats witnessing traumatic events (social defeat of a cage-mate) exhibited severe behavioral deficits resembling PTSD-like behaviors including anxiety-like and depression-like behaviors as well as cognitive impairment. In the present study we have modified the TWM paradigm to mimic witness of maternal abuse and developed the maternal abuse witness model (MAW). Briefly, a female Sprague-Dawley rat (mother) was introduced into the cage of a Long Evans (LE) rat. The female rat undergoes aggressive attacks from the LE rat and quickly assumes social defeat posture. Natural litters of the female rat placed in separate chambers surrounding the cage witness these attacks. Pups were exposed to daily witness of repeated social defeat of their mother by the male LE rat for 7 consecutive days. One month later, when the pups become 60 day old (considered adults), behavioral outcomes of witnessing maternal abuse during early life (post-natal day 21-27) were examined.
Results: Rats that witnessed maternal abuse (MAW) from post-natal days 21-27, exhibited significant depression-like behavior (examined via forced-swim test) when compared to age and gender matched controls. Interestingly, male rats displayed greater depression-like behavior than female rats. No changes were noted in anxiety-like behavior (examined via open-field and elevated plus maze tests) or learning and memory function (Radial arm water maze test) in both male and female MAW rats. Interestingly, male MAW rats gained more weight than female MAW rats or controls. Food intake was greater in male MAW rats as compared to female MAW rats and controls. Water intake remained unchanged. Elevated levels of corticosteroids and indices of oxidative stress, correlate with depressive phenotype of MAW rats. Studies to investigate the underlying neurobiology of MAW phenotype are currently ongoing.
Conclusions: This model is of immense translational value considering the prevalence of domestic abuse in the United States and worldwide. While, some studies investigating association of maternal stress with increased risk of

negative psychological outcomes on off-springs have been reported, studies examining early life witness of maternal abuse on later life behavioral and biochemical outcomes do not exist. Therefore, understanding the behavioral and biochemical consequences of early life exposure to witnessing maternal abuse using our MAW model is critical. This is the first study to investigate the adult outcomes following repeated witness of maternal abuse during early life.
Keywords: Maternal abuse, PTSD, Depression, Stress.
Disclosure: Nothing to Disclose.

M20. Genetic Dissection of Cerebellar Circuitry in Cognitive, Social, and Affective Behavior

Erik Carlson*, Marta Soden, Julia Licholai, Karn Dhillon, Larry Zweifel

University of Washington School of Medicine, Seattle, Washington

Background: The cerebellum is well known for its role in coordinating temporal and sensorimotor processes. A lesser appreciated, but no less important function of the cerebellum is its role in cognition, social function, and affective state. Humans with discrete cerebellar lesions manifest neuropsychiatric symptoms, including: flattened affect, depression, reduced language and social interactions, disturbances of working memory, spatial cognition, attention, and even psychosis in the absence of motor deficits. In persons with schizophrenia, neuroanatomical and clinical markers of cerebellar dysfunction correlate with the severity of negative symptoms. Aberrant morphology and activity of the cerebellum has also been documented in several psychiatric disorders including autism, bipolar disorder, major depressive disorder, anxiety disorders, and attention-deficit/hyperactivity disorder. The cerebellum is reciprocally connected with limbic system structures including the prefrontal cortex, striatum, ventral tegmental area, amygdala, and hippocampus. The neurotransmitter dopamine is a key modulator of the limbic system and is broadly implicated in mental illness. In addition to direct and indirect connections with the midbrain dopamine system, proteins essential for dopamine production and dopamine signaling have been identified in specific cell types and regions in the cerebellum. To begin to ascertain the function of dopaminoceptive neurons in the cerebellum for cognitive and affective behaviors, we utilized mice with targeted insertion of the Cre recombinase into the dopamine 1 receptor (D1R) locus (Drd1aCre). This mouse line allowed us to selectively isolate and manipulate the D1R containing neurons in the dentate nucleus of the cerebellum. While electrophysiological properties of cells in the dentate nucleus of the cerebellum have begun to be elucidated, virtually nothing is known about how specific neuronal populations within this structure influence behavior.
Methods: To characterize D1R neurons of the DNC and to determine their function in behavior, we virally delivered the Designer Receptor Exclusively Activated by a Designer Drug (DREADD) receptor, HM4Di fused to YFP, to reversibly inhibit this population of neurons. Electrophysiological properties of visually identified D1R-expressing neurons in the lateral/dentate cerebellar nuclei were measured using whole-cell patch clamp in acute cerebellar slices. We also identified synaptic targets of these cells, by injecting a Cre-dependent AAV virus encoding a GFP-labeled synaptophysin, which allows labelling of axon terminals. Finally, we probed the performance of mice expressing HM4Di-YFP (Drd1aCre/+;DNC-HM4Di; $N = 8$) bilaterally versus GFP controls (Drd1aCre/+;DNC-GFP; $N = 13$) in a three-chambered social task, Barnes Maze, Elevated Plus Maze, Rotarod, prepulse inhibition of the acoustic startle reflex, and instrumental conditioning for a food reward on a fixed-ratio schedule.
Results: D1R-expressing neurons of the DNC were categorized into one of two groups based on their size and action potential properties. The first group was composed of small, spontaneously active neurons with a relatively wide action potential width and slow afterhyperpolarization. The second group consisted of larger neurons, most of which did not fire spontaneously. When these cells were induced to fire by current injection, the action potential waveform was narrow and the afterhyperpolarization peak was fast. We also found that clozapine-N-oxide, activation of the DREADD Receptor causes inhibition of neuronal activity in D1R positive cells in the DNC. Cre-dependent expression of a virally-delivered GFP-labeled synaptophysin revealed cerebellonucleo-cerebellocortical projections from D1R-positive cells in the lateral/dentate nucleus. Drd1aCre/+;DNC-HM4Di mice showed alterations in performance in specific behaviors. Drd1aCre/+;DNC-HM4Di mice had significantly poorer performance on Barnes Maze probe trial than controls ($P < 0.05$), without differences in acquisition of the task, or velocity of movement. Drd1aCre/+;DNC-HM4Di mice had significantly less time in the open arms on elevated plus maze than Drd1aCre/+;DNC-GFP mice ($P < 0.05$), lower prepulse inhibition of the acoustic startle reflex than Drd1aCre/+;DNC-GFP mice ($P < 0.05$), and could not discriminate between novel and familiar mice on a three-chambered social task, while Drd1aCre/+;DNC-GFP mice were able to ($P < 0.05$). No changes were seen between groups on a simple instrumental conditioning task for food reward or on Rotarod performance.
Conclusions: Our results indicate that there are two neuronal populations expressing the Dopamine-1 Receptor within the DNC which are required for specific cognitive, social, sensory, and affective behaviors. The properties of these two groups of D1R-expressing neurons are remarkably similar to the properties of small and large glycinergic neurons previously identified in the lateral/dentate cerebellar nuclei (Uusisaari and Knopfel 2010).
Keywords: Cerebellum, DREADD Receptor, Spatial Navigation, Social Cognition.
Disclosure: Nothing to Disclose.

M21. Glucocorticoid-Mediated Dopaminergic Changes and Epigenetic modifications: A Critical Period of Vulnerability to Stress During Adolescence

Minae Niwa*, Richard Lee, Shin-ichi Kano, Makiko Morita, Akinori Nishi, Takatoshi Hikida, Akira Sawa

Johns Hopkins University School of Medicine, Baltimore, Maryland

Background: Developmental alternations induced by stress exposure during adolescence are associated with physical

and behavioral changes. The molecular basis of vulnerability to stress during the adolescent period is largely unknown. We recently reported that psychosocial stress imposed during adolescence in the presence of a genetic risk led to glucocorticoid-mediated neurochemical changes and behavioral deficits in adulthood (Niwa et al, 2013). Due to the similarities between pharmacological response and behavioral deficits, such animal models may be of great use for studying the underlying biology of stress-associated dopaminergic changes and psychotic depression. In the present study, we validate our animal model in the pathophysiology of drug addiction, another dopamine-associated condition. We also examined whether the tyrosine hydroxylase (Th) gene is the exclusive target of epigenetic modifications by glucocorticoids and identified the precise period during which the glucocorticoid receptor (GR) antagonist can ameliorate the pathological changes.
Methods: DISC1 mutant and littermate control mice were exposed to a mild isolation stress during adolescence (five to eight weeks). Epigenetic changes were examined by pyrosequencing. RNA expression changes of genes associated with altered DNA methylation were examined by real-time PCR. The extracellular level of dopamine was measured by in vivo microdialysis. For behavioral tests, the first cohort was performed for conditioned place preference test, and the second cohort was used for prepulse inhibition test followed by forced swim test. Mice were treated with the GR antagonist RU38486 from five to eight, from five to seven, and from eight to ten weeks of age.
Results: Three-week (five to eight weeks of age) adolescent stress in combination with Disc1 genetic risk (GXE) affected alterations in DNA methylation and expression levels of a specific set of genes, Th, Bdnf, and Fkbp5, and resulted in behavioral deficits in conditioned place preference, prepulse inhibition, and the forced swim tests. The epigenetic changes in the mesocortical dopaminergic neurons are prevented by treatment with RU38486, which implicates the role for glucocorticoid signaling in these pathological events. We defined the critical period of GR intervention as the first one-week period during the stress regimen, suggesting that this particular week in adolescence may be a specific period of maturation and function of mesocortical dopaminergic neurons and their sensitivity to glucocorticoids. Enzyme activity of phosphodiesterase 4 (PDE4) was increased in the GXE model. Cocaine-induced place preference in the GXE model was inhibited by treatment with rolipram before place conditioning.
Conclusions: Our model may be useful for studying influence of adolescent stressors on both psychosis/depression and substance use. Beneficial influence achieved by the blockade of aberrant GR signaling from five to six weeks of age during the first week of isolation stress implies that this particular week may reflect a specific period of maturation and function of mesocortical dopaminergic neurons and their sensitivity to glucocorticoids. Early detection of adverse experiences (e.g., social isolation in combination with a genetic risk in this case) and early intervention, particularly at the critical period, may be important in translational applications.
Keywords: adolescent stress, dopamine, epigenetics, glucocorticoid.
Disclosure: Nothing to Disclose.

M22. Cortical Inflammation and Increased Striatal Dopamine in a Nonhuman Primate Model of Maternal Immune Activation

Cameron Carter*, David Amaral, Ryan Phillips, Douglas Rowland, Kimberly McAllister, Simon Cherry, Ana-Maria Iosef, Melissa Bauman

University of California, Davis, Sacramento, California

Background: Recent advances in developmental neurobiology have established a key role for immune molecules such as cytokines and MHC in normal brain development and the maintenance of adult synaptic function. Exposure to a variety of infections during pregnancy is associated with an increased risk of neurodevelopmental disorders in offspring, such as schizophrenia (SZ) and evidence from rodent models suggests that maternal immune activation can lead to altered neurodevelopment and psychosis like phenotypes in adolescent offspring, leading to the hypothesis that alterations in neuroimmune signaling mechanisms may contribute to the altered neurodevelopment, brain connectivity and cognition and behavior that underlie psychosis risk. To bridge the gap between rodent models and human patient populations, we have developed a novel, nonhuman primate model of MIA using a modified form of the viral mimic, polyIC (polyICLC).
Methods: Pregnant rhesus monkeys (Macaca mulatta) received polyICLC injections at the end of the first or second trimesters to produce a transient innate inflammatory response. A separate control group of pregnant rhesus monkeys received saline injections at these time points. Following an initial period of normal development, the MIA-treated offspring develop motor stereotypies and self-directed/self-injurious behaviors, deviate from species-typical social development and demonstrate abnormal gaze patterns when viewing faces. Behavioral pathologies become more pronounced at the animals matured. When the offspring reached puberty we initiated two PET imaging studies to evaluate underlying neuropathology. When the offspring reached puberty we initiated two PET imaging studies to evaluate underlying neuropathology. When the offspring reached puberty we initiated two PET imaging studies to evaluate underlying neuropathology. First we utilized the PET ligand [11C]PK11195 that binds to the mitochondrial 18 kDa translocator protein and is a marker of microglial activation. Whole brain gray matter measures of [11C]PK11195 binding potentials were computed using a modified reference tissue model with white matter as the reference. In order to obtain further validation of the clinical significance of nonhuman primate MIA model we then examined pre-synaptic dopamine levels in the basal ganglia using 6-[18F]fluoro-L-m-tyrosine ([18F]FMT). Binding potentials were computed for the striatum (caudate plus putamen) using a simplified reference model with the cerebellum as the reference.
Results: PET data from MIA-treated offspring show significantly higher cortical binding of 11CPK11195, consistent with increased microglial activation in the MIA NHP's. They also show significantly greater striatal [18F]FMT binding potential than controls, confirming the presence of increased striatal presynaptic dopamine, a molecular biomarker for SZ.

Conclusions: Collectively, the behavior and PET imaging data provide a validation of the clinical relevance of the nonhuman primate MIA model for understanding the neurodevelopmental origins of SZ. In doing so they also provide additional support for a potential role for altered neuroimmune signaling in contributing to the altered development of brain connectivity, cognition and behavior in individuals at risk for the illness.
Keywords: microglial activation, psychosis, dopamine, non-human primate.
Disclosure: Nothing to Disclose.

M23. Impaired Behavioral Flexibility in Neurexin1 KO Rats

Thomas Steckler*, Gaurav Kumar, Talpos John

Janssen Research and Development, Beerse, Belgium

Background: Neurexin 1 (NRXN1) is a presynaptic cell adhesion protein that interacts transsynaptically with neuroligins in a Ca2 + dependent manner and is required for efficient neurotransmission and synapse formation in glutamatergic and GABAergic axons in various brain areas, including in cortical areas and hippocampus. A role for NRXN1 has been suggested for different neuropsychitric disorders, including Autism Spectrum Disorder (ASD).
Methods: In the present study we investigated the effects of NRXN1 knockout (KO) in rats in two hippocampus-dependent spatial touch-screen tasks, a two-choice spatial reversal task (SRT) and a multiple choice spatial search task (AST). In SRT, rats first learned to discriminate between two spatial locations. Response contingencies were repeatedly reversed once rats reached a criterion of 9/10 correct responses, i.e., each rat experienced several reversals per session. In the conceptually related, but spatially more demanding AST, rats had to search for a hidden location on a computer screen. The correct location remained in the same position for blocks of 10 trials (a trial ended when the animal found the correct location) and then switched to a new position, unknown to the animals. Further, AST response requirements were modified to increase need for response shifting (using blocks of only 5 trials) or likelihood for habit formation (using massed trial blocks of two-times 50 trials on one location).
Results: In SRT, NRXN1 KO rats completed less reversals within a session compared to wildtype (WT) rats, suggesting impaired behavioral flexibility. In AST, NRXN1 KO rats showed slower task acquisition and an impaired search strategy, evident during the first trial of each block of 10 trials. Increasing search demands in AST by switching location already after 5 trials led to a more profound deficit in NRXN1 KO rats. A strong perseverative phenotype emerged in KO rats when they were overtrained on a single location, while KO and WT did not differ in search errors under this condition.
Conclusions: These data suggest that NRXN1 KO rats may have a preference for habitual, rather than flexible, goal oriented behaviors, which resembles some of the deficits seen in ASD. The study was supported by the EU-AIMS project that is funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU).

Keywords: autism, ASD, neurexin, behavioral.
Disclosure: All authors are employees of Janssen R&D.

M24. Klf9 Transcriptionally Promotes Resilience to Chronic Stress

Antoine Besnard, Tomer Langberg, Sally Levinson, Kimberly Scobie, David Leonardo, Rene Hen, Amar Sahay*

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Background: There is growing appreciation that psychiatric disorders such as depression and post-traumatic stress disorder arise from inefficient adaptation to risk factors such as stress. Understanding how transcriptional programs respond to stress to confer vulnerability or resilience through their actions on neural circuits will inform strategies to promote adaptive responses in neural circuits to stress. We recently identified Kruppel-like factor 9 (Klf9) as a transcriptional repressor of dendritic spines. Klf9 expression is upregulated by acute restraint stress and glucocorticoids, but is downregulated in response to chronic restraint stress. Based on these observations, we hypothesized that acute silencing of Klf9 promotes resilience to stress induced changes in hippocampal synaptic connectivity, conflict and fear processing, and depression-like behaviors.
Methods: To test our hypothesis, we developed novel transgenic tools to robustly and reversibly silence Klf9 in excitatory forebrain neurons of adult mice at baseline and prior to exposure to chronic restraint stress or chronic administration of glucocorticoids. Using triple transgenic mice to link changes in hippocampal circuitry with behavior, we genetically visualized dendritic spines in hippocampal subpopulations of neurons following acute forebrain silencing of Klf9 and these different stressors.
Results: Inducible silencing of Klf9 in excitatory forebrain neurons in adulthood did not affect contextual encoding or depression-like behaviors at baseline, but produced antidepressant-like behavioral responses in the sucrose preference and forced-swim tests and prevented stress-induced enhancement of fear memory following chronic restraint stress. Furthermore, Klf-9 downregulation blunted the corticosterone response to an acute stressor challenge. These protective effects of inducible Klf9 silencing were mirrored by reversal of chronic restraint stress induced changes in dendritic spines in ventral CA1. Consistent with the moderating effects of inducible Klf9 silencing to chronic restraint stress, inducible silencing Klf9 in excitatory forebrain neurons in adulthood prevented corticosterone-induced overgeneralization of fear and increase in innate anxiety.
Conclusions: Our studies begin to uncover a novel transcriptional mechanism that regulates adaptive responsiveness of neural circuits to multiple forms of stress to confer behavioral resilience. Because Klf9 expression is upregulated in the hippocampus of patients with major depressive disorder and by glucocorticoids, our results suggest that targeting Klf9 or Klf9 dependent circuit

changes may confer resilience to stress related psychopathologies.
Keywords: resilience, stress, hippocampus, fear.
Disclosure: Nothing to Disclose.

M25. Parsing the Role of the Paraventricular Nucleus of the Thalamus in Mediating Individual Variation in Incentive Salience Attribution

Joshua Haight*, Kurt Fraser, Huda Akil, Susan Ferguson, Shelly Flagel

University of Michigan, Ann Arbor, Michigan

Background: The paraventricular nucleus of the thalamus (PVT) sits at the interface between limbic and motor circuits. Thus, its emerging role in mood, motivation and addiction-related behaviors should not come as a surprise. The PVT is well-positioned to translate information about environmental stimuli into motivated behavior and has been implicated in the processing of reward-related cues. However, delineating the specific role of the PVT in these processes has been limited by the inability to parse the incentive motivational from the predictive properties of reward cues. Incentive motivational processes have been shown to play a role in the transition to addiction, and we now have an animal model that provides a way to study the underlying neurobiological mechanisms. When rats are exposed to a Pavlovian conditioning paradigm, wherein a discrete cue predicts food reward, some rats, "goal-trackers" (GTs) only attribute predictive value to the cue and go to the location of food delivery upon cue presentation. Others, termed "sign-trackers" (STs), attribute incentive salience to the cue, as evidenced by their approach toward the cue. We have previously shown that STs are more susceptible to addiction-related behaviors and that distinct neural circuits regulate the sign- vs. goal-tracking response. The PVT appears to be a common node within these circuits, and here we begin to test the hypothesis that the PVT differentially regulates sign- and goal-tracking behaviors.
Methods: We investigated the role of the PVT in the acquisition and expression of sign- and goal-tracking behavior. Ibotenic acid was used to lesion the anterior and posterior PVT. To assess the effects of PVT lesions on the acquisition of sign-and goal-tracking conditioned responses (CRs), we used selectively bred rats lines for which it is known a priori whether these rats are STs or GTs. PVT lesions were performed prior to Pavlovian training, and following recovery rats underwent 12 sessions of Pavlovian conditioning. Each session consisted of 25 trials of cue-reward pairings, wherein the cue was presentation of a lever and the reward was a food pellet. In a separate study, outbred Sprague-Dawley rats were first trained in this Pavlovian conditioning task, and then, after the CRs were acquired, the PVT was lesioned. Following recovery, rats resumed Pavlovian training, and expression of their respective CRs was measured. Rats were also exposed to a conditioned reinforcement test to assess their motivation to work for the cue in the absence of the reward.
Results: Excitotoxic lesions of the PVT differentially affected sign- and goal-tracking behavior. Lesions prior to Pavlovian training did not affect acquisition per se, but seemed to affect "peak performance" after the conditioned responses had been acquired. PVT lesions enhanced sign-tracking behavior in rats with a predisposition to sign-track, and attenuated goal-tracking behavior in rats with a predisposition to goal-track. Interestingly, lesions of the PVT after the CRs had been learned selectively affected GTs and had no effect on the behavior of STs. When compared to sham-operated controls, PVT lesions attenuated the expression of a goal-tracking response, and increased the sign-tracking response in rats previously classified as GTs. In agreement, PVT lesions increased the conditioned reinforcing properties of the cue for GTs, but not STs.
Conclusions: Together, these data suggest that the PVT is involved in mediating both sign- and goal-tracking behaviors, and that this structure plays a critical role in the attribution of incentive motivational properties to reward cues. We believe that "top-down" communication from the prelimbic cortex to the PVT plays an important role in mediating goal-tracking behavior; whereas subcortical processes, including those from the ventral tegmental area to the PVT, are important for sign-tracking behavior. We are currently using double-labeling techniques to identify which cells are actively communicating with the PVT in response to the reward-associated cue. In conjunction, we are also using DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technology to parse the role of specific afferent projections to the PVT in the expression of sign- and goal-tracking behaviors. Given that cue-motivated behavior underlies a number of psychopathologies, including overeating, pathological gambling, and addiction, this work, in identifying critical components of the circuitry subserving incentive salience attribution, could lead to novel therapeutic targets.
Keywords: incentive salience, animal model, paraventricular nucleus of the thalamus, sign-tracking.
Disclosure: Nothing to Disclose.

M26. Region-specific, Differential Dysregulation of Neurotrophic Signaling and Neuroinflammation in Rodent Models of Pathological Neurodevelopment

Thomas Lanz*, Simon Xi, Veronica Reinhart, William Howe, Rouba Kozak, Patricio O'Donnell

Pfizer, Cambridge, Massachusetts

Background: Schizophrenia is a neurodevelopmental disorder in which both genetic and environmental risk factors likely play significant roles. A number of animal models have been developed in which a genetic manipulation or an environmental insult is introduced to alter the normal trajectory of the developing brain. Two such models are the Df1/+ mouse, which models a human 22q11 microdeletion that confers 20-30 fold increased risk of developing schizophrenia, and the gestational methylazoxymethanol (MAM) rat, in which rat embryos are exposed to a teratogen during a critical developmental period. The present study sought to examine and compare the transcriptional alterations in adult brain tissues from these neurodevelopmental animal models, with an emphasis on genes and pathways previously shown to be dysregulated in human post-mortem schizophrenia brains.
Methods: Brains were harvested from adult E17 MAM rats and Df1/+ mice. Frontal cortex, striatum and hippocampus were micro-dissected, flash frozen, and RNA was extracted.

RNA from PFC, STR and HIP was prepared for paired end RNA sequencing. Gene-level results for pathways of interest were followed up by RT-PCR. Data were compared with previously collected gene expression data from post-mortem human schizophrenia brain.

Results: While the global transcriptional profiles of MAM rats and Df1/+ were enriched for only a minority of the genes and pathways differentially expressed in schizophrenia, certain key pathways suggested to be dysfunctional in schizophrenia were similarly impacted in both rodent models. At the level of frontal cortex, a number of transcripts involved in inflammation were upregulated in the MAM rat, including ADAMTS1, ITGAV, and PARP14. Also upregulated in MAM rat frontal cortex were truncated forms of the TrkB receptor and p75NTR. Several GABAergic transcripts showed a trend toward reduction in MAM frontal cortex, but only CALB1 was significantly reduced. In hippocampus, Df1/+ mice showed elevations in many inflammatory transcripts, including those elevated in MAM rat frontal cortex and multiple genes in the JAK-Stat signaling pathway. Both MAM rats and Df1/+ mice showed increased p75NTR and altered TrkB transcripts in hippocampus. The MAM rat showed also a reduction in CCK in hippocampus. The Df1/+ mouse showed a reduction in CCK in striatum, along with reduced NPY and PVALB. Both models showed reductions in BDNF transcripts in striatum.

Conclusions: No animal model fully recapitulates the range of behavioral and neural phenotypes exhibited in schizophrenia, yet different genetic, environmental or pharmacologic manipulations can produce deficits in specific functional domains affected in the human disease state. The present data sought to explore the consequences of a genetic lesion or a prenatal teratogen upon the adult brain transcriptome, with a focus on genes and pathways shown to be dysregulated at the transcriptional level in post-mortem schizophrenia brains. The MAM rat and Df1/+ mouse both show reductions in GABAergic markers and the BDNF-TrkB pathway, though neither model captured the magnitude of changes observed in schizophrenia. Both models also exhibited regionally restricted increases in transcripts associated with inflammation. As schizophrenia is not a purely genetic or purely environmental disorder, these data suggest that models based on such a singular event can replicate some of the molecular changes observed in schizophrenia, but a combination of multiple factors may be necessary to replicate the broad range of behavioral, cognitive, and neural alterations that comprise the disorder.

Keywords: inflammation, neurodevelopment, schizophrenia, BDNF.

Disclosure: All authors are employees of Pfizer, Inc.

M27. Switching From Paroxetine to Vilazodone Significantly Reduces Sexual Side Effects in Male Rats

Ronald Oosting*, Johnny S. W. Chan, Berend Olivier, Pradeep Banerjee

Utrecht University, Utrecht, Netherlands

Background: Sexual dysfunction is a major side effect of antidepressants acting on the brain serotonin system and often leads to noncompliance or discontinuation of treatment. Vilazodone (VLZ) is a combined selective serotonin reuptake inhibitor (SSRI) and 5-HT1A receptor partial agonist approved for the treatment of major depressive disorder in adults. Clinical trial data suggest that the incidence of sexual dysfunction among patients taking VLZ is comparable to patients receiving placebo. Recently we reported that in contrast to the conventional SSRIs citalopram (10 mg/kg) or paroxetine (PAR, 10 mg/kg), vilazodone treatment (3 and 10 mg/kg) in male rats for 1 or 2 weeks exhibited significantly lower sexual side effects (unpublished data). We also observed that VLZ treatment led to ~50% reduction in the levels of both SERT (5-HT transporter) and 5-HT1A receptors in forebrain regions. By contrast, both citalopram and paroxetine treatment led to a much greater decrease in SERT (~90%), and a moderate increase (~20%) in 5-HT1A receptor density. In the present study we further investigated whether the observed differential changes in SERT and 5-HT1A receptor density could be linked to vilazodone's favorable sexual side effect profile due to its partial agonist activity at the 5-HT1A receptor.

Methods: Male rats received once-daily (p.o.) treatment of VLZ, PAR, or vehicle (VEH) for 2 weeks. An additional treatment arm of PAR + buspirone (BUS, a 5-HT1A partial agonist) was included to determine the role of 5-HT1A receptor activation on sexual function. After 2 weeks, treatments were switched for another 7 days as shown in the table below. Doses used of VLZ, PAR, and BUS were 10 mg/kg, 10 mg/kg, and 3 mg/kg, respectively. Male sexual behavior (in particular, ejaculation frequency and latency, total number of mounts and total number of intromissions) was evaluated on day 1 (1 hr after the first dosing), and on days 8, 15, and 23 of drug treatment.

Results: Unlike PAR, VLZ treatment for 2 weeks did not lead to significant decrease in sexual behavior in male rats. For example, ejaculation frequency during a 30 min sexual function test was 3.17 with vehicle, 3.08 - 3.5 with VLZ and 1.00 -1.92 with PAR ($p < 0.05$ vs vehicle). When PAR treatment was switched to either VEH or VLZ for 1 week, sexual behavior in male rats normalized to control levels. This beneficial effect of VLZ treatment was lost when switching treatments from VLZ to PAR, which resulted in a strong reduction in sexual function. The beneficial effect of 5-HT1A receptor activation on male sexual function was also apparent when PAR treatment was switched to PAR + BUS, which improved sexual functioning compared to PAR alone.

Conclusions: This study showed that unlike paroxetine (an SSRI with no activity at 5-HT1A receptors), vilazodone did not exhibit significant sexual side effects in male rats at therapeutically relevant doses. This beneficial effect of VLZ on male sexual function was further confirmed in switch studies. Additionally, the data from PAR vs PAR + BUS arms strongly suggest that activation of 5-HT1A receptors may play an important role in mitigating the sexual side effects caused by conventional SSRIs in this animal model.

Keywords: vilazodone, sexual dysfunction, animal models.

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to disclose. Pradeep Banerjee is an employee of Forest Research Institute, a subsidiary of Actavis plc.

M28. Subchronic Treatment with the Partial Dopamine Agonist Cariprazine Protects Against Ketamine-induced Cognitive Deficits in a Nonhuman Primate Model Relevant to Schizophrenia

Stacy A. Castner, Amanda L. Abbott, Nika Adham, Ashok Rakhit, Stephen Zukin, István Gyertyán, Béla Kiss, Graham V. Williams*

Yale University School of Medicine, New Haven, Connecticut

Background: Antipsychotics have strong efficacy in treating the positive symptoms of schizophrenia but limited efficacy in treating negative symptoms and cognitive impairment. Dopamine D2 antagonists and partial agonists are recognized for their potential to treat schizophrenia and related disorders but the abilities of these mechanisms to improve cognitive function in patients has not been established. Cariprazine is an antipsychotic candidate and a dopamine D3/ D2 receptor partial agonist. It differs from the currently approved D2 receptor partial agonist aripiprazole in that it has a relatively higher dopamine D3 receptor affinity and selectivity, and demonstrates significant occupancy of D3 receptors. As the D3 receptor is expressed primarily in limbic and cortical association areas of the brain there is interest as to whether partial agonists targeted preferentially to this receptor may have improved benefits for cognition which may be evident in schizophrenia (Gross and Drescher, Handb. Exp. Pharmacol. 213:167-210, 2012). We utilized a nonhuman primate model to assess the ability of cariprazine to block cognitive deficits induced by acute ketamine.
Methods: One group of animals was treated with vehicle and then with four different doses of cariprazine, each given for a period of two weeks over a 10 week period. Another group of animals were tested on vehicle alone. Acute ketamine (0.7 – 1.7 mg/kg, IM, sufficient to induce a substantial cognitive deficit in each animal) was administered on the last day of each two week block. Results of cognitive testing performed under the non-ketamine condition on day 13 were compared with results performed following ketamine administration on day 14. Blood samples were collected to examine plasma exposure at each dose. Working memory was assessed on the spatial delayed response task (Roberts BM, et al., Psychopharmacology (Berl.) 210:407-418, 2010). Briefly, animals were tested inside a sound-attenuated apparatus, where they were shown a board with 2 – 7 wells, one of which was baited with a preferred treat and then all of which were covered with identical plaques. An opaque screen was then lowered for a delay of 0 - 4(N) seconds where N varied between 1 and 10. The animals performed 20 trials with pseudorandomized delays and spatial locations. The number of wells and N value were gradually incremented until animals were trained to stability (65– 75% correct ± 2.5 SEM, over at least 10 sessions) prior to study, after which they were kept constant throughout.
Results: At the end of the initial two weeks of vehicle, ketamine induced substantial impairments in spatial working memory in both the cariprazine and the vehicle arms (mean values: 40.8 and 37.5%, respectively) compared to the previous day's performance (70.3 and 69.4%, respectively). Following the first bout at 0.01 mg/kg cariprazine, a substantial protection of working memory from the effects of ketamine was observed (58.4%; post hoc Scheffe, $p = 0.007$) and performance on the previous day was nominally improved (73.0%). We next administered a dose of 0.03 mg/kg and observed not only little or no protection against ketamine (40.8%) but also a deterioration of performance on the previous day (59.5%). We then examined a dose of 0.005 mg/kg to further elucidate the dose-response relationship and found a smaller protection against ketamine than at the dose of 0.01 mg/kg (41.9%) but a more normal level of performance on the previous day (65.8%). Finally, we tested a dose of 0.02 mg/kg and again observed no improvement in cognition (41.7% under ketamine and 68.6% the previous day). In one-way ANOVA tests, there was a statistically significant difference among dose groups within the cariprazine arm ($F[4,28] = 4.405$; $p = 0.007$), but not the vehicle arm ($F[5,30] = 0.748$; $p = 0.594$) for protection against ketamine-induced impairments in working memory performance.
Conclusions: Taken together, these results show possible evidence of an inverted U dose-response relationship for protection against ketamine-induced cognitive deficits by cariprazine. These findings suggest that cariprazine may hold promise for treatment of working memory deficits in schizophrenia.
Keywords: cariprazine, dopamine, schizophrenia, cognition.
Disclosure: Supported by funding from Forest Laboratories, Inc., a subsidiary of Actavis plc, and Gedeon Richter Plc. Stacy A. Castner, Amanda L. Abbott, and Graham V. Williams have no conflicts of interest to disclose. Nika Adham and Ashok Rakhit are employees of Forest Research Institute, a subsidiary of Actavis plc. S. Zukin was an employee of Forest Research Institute, a subsidiary of Actavis plc, at the time of the study. István Gyertyán and Béla Kiss are employees of Gedeon Richter Plc.

M29. Functional Uncoupling of a Single NMDA Subunit in the Prefrontal Cortex Protects against Behavioral Dysfunction after Early Life Stress

Heather Brenhouse*, Prabarna Ganguly

Northeastern University, Boston, Massachusetts

Background: Exposure to early life stress (ELS) increases vulnerability to psychiatric disorders, including depression, drug abuse and anxiety. Because these disorders often first emerge in adolescence or young adulthood, intervening variables found in clinical studies make the role that ELS plays in these diseases difficult to interpret. Here we used maternal separation as an animal model to help clarify the causality of ELS. Growing evidence implicates aberrant development of the prefrontal cortex in ELS effects. Indeed, the prefrontal cortex is a relatively late-maturing region and subserves all higher-order cognitive and emotional functions. We recently reported that maternal separation ELS causes overexpression of the NMDA subunit NR2A in the prefrontal cortex of male adolescents. Elevated NR2A is also

found in developmental models of schizophrenia and is correlated with deficits in working memory, reversal-learning, and sensory gating. Therefore, it is likely that PFC NR2A overexpression is a mechanism underlying the behavioral deficits observed in ELS-exposed adolescents. Here, we aimed to determine whether a discrete manipulation of prefrontal cortex NMDA receptors can prevent ELS-induced anxiety in adolescence. We used the NR2A-specific blocking peptide TAT2A in order to disable NR2A in the early adolescent prefrontal cortex. TAT2A is a highly specific cell-permeable peptide that uncouples the NR2A subunit from the postsynaptic density complex within the dendritic spine, without antagonizing the NMDA receptor. We hypothesized that disabling NR2A during early adolescence would rescue dysfunctional NMDA receptor activity and prevent behavioral deficits after ELS.

Methods: Sprague-Dawley male rats were separated from their mother and littermates for 4hr per day between postnatal days 2-20. Control subjects were left undisturbed except for cage cleaning. On postnatal day 28, subjects ($n = 8$) were implanted with guide cannulae aimed at the medial prefrontal cortex and allowed three days for recovery from surgery. Microinjections of TAT2A (100 μM or 500 μM) or a truncated control peptide were performed through the guide cannulae in awake animals every second day between postnatal days 31-40, for a total of five microinjections. Twenty-four hours following the last microinjection, subjects were tested in the elevated plus maze, with time spent in open and closed arms as well as number of arm crosses recorded over five minutes. The following day, subjects were tested for open field activity in a novel environment, then 3 hours later reintroduced to the same open field. Locomotion during the first three minutes of each exposure was recorded to assess novelty-induced activity and general activity. A separate cohort of subjects ($n = 3$) were microinjected with TAT2A or control peptide using the same schedule as described above and were sacrificed on postnatal day 40 to assess immunoprecipitation of NR2A with the postsynaptic density, in order to confirm uncoupling of NR2A.

Results: Maternal separation ELS resulted in significantly more anxiety-like behavior in the elevated plus maze, evidenced by less time spent in the open arms (main effect of Group: $F[1,35] = 19.73$, $p < 0.0001$). An interaction of Group x Treatment ($F[2,35] = 4.76$; $p = 0.015$) revealed that subjects administered 500 μM TAT2A during early adolescence were protected from ELS-induced anxiety-like behavior. While TAT2A had a dose-dependent effect on elevated plus maze behavior, TAT2A did not protect subjects from increased novelty-induced activity after ELS (Main effect of Group: $F[1,39] = 4.71$, $p = 0.036$; No Group x Treatment interaction). Immunoprecipitation revealed that TAT2A successfully uncoupled NR2A from the postsynaptic density within the prefrontal cortex.

Conclusions: These data suggest that elevated NR2A and the subsequent NMDA dysfunction in the prefrontal cortex is a biological substrate of ELS-attributable anxiety, but not ELS-attributable changes in response to novelty. Results also illustrate that NMDA dysfunction during early adolescence can be targeted to prevent behavioral dysfunction in vulnerable individuals.

Keywords: NMDA, prefrontal cortex, maternal separation, adolescence.

Disclosure: Nothing to Disclose.

M30. Addiction Related Alterations in Hippocampal Neurogenesis and CA1 Structural Plasticity following Extended Access Methamphetamine Self-administration

Melissa Galinato, Jeffery Sobieraj, Alison Caldwell, McKenzie Fannon, Sharon Chaing, Alvaro Navarro, Leyda Villagrasa, Chitra Mandyam*

The Scripps Research Institute, La Jolla, California

Background: The methamphetamine-addicted phenotype can be modeled in rats based on individual differences in preferred levels of methamphetamine intake and a propensity for relapse in withdrawal. The hippocampus is involved in the relapse stage of addiction and the levels of proliferation and neurogenesis of neural stem cells in the hippocampus (a form of neuronal plasticity) can be predicted by methamphetamine-taking and -seeking behaviors. Thus we determined whether addiction-related differences in methamphetamine self-administration would result in differential regulation of proliferation and survival of hippocampal neural stem cells and cell death in the dentate gyrus of the hippocampus and structural plasticity of CA1 pyramidal neurons in the hippocampus.

Methods: Using a population of forty five outbred albino Wistar rats trained to self-administer 0.05 mg/kg methamphetamine for 17 days in 6 hour sessions, we found that rats with higher preferred levels of methamphetamine intake (high responders) exhibited escalation of methamphetamine intake during extended access sessions compared with rats with lower preferred intake (low responders) that maintained low responding for methamphetamine with out escalation in drug intake. After 3 weeks of withdrawal from methamphetamine self-administration high responders had enhanced methamphetamine seeking during extinction sessions and demonstrated greater latency to extinguish drug-seeking behavior. Furthermore, high responders demonstrated greater drug-context-induced and cue-induced reinstatement compared with low responders indicating greater propensity for drug relapse. All animals were injected with the mitotic marker bromodeoxyuridine (BrdU) during withdrawal and were killed 3 weeks later and hippocampal sections were processed for Ki-67 (cell proliferation), BrdU (cell survival) and AC3 (cell death) immunohistochemistry and Golgi-Cox staining.

Results: Stereological assessment of cell numbers demonstrates higher levels of Ki-67 and BrdU, and lower levels of AC3 in high responders compared with low responders. Golgi-Cox analysis demonstrates reduced dendritic arborization of CA1 pyramidal neurons within the apical and basal dendrites in high responders compared with low responders.

Conclusions: These findings suggest that methamphetamine addiction is related specifically to differential alterations in hippocampal neuronal plasticity and these alterations may have the ability to modulate methamphetamine-seeking behavior.

Keywords: Psychostimulant, BrdU, Ki-67, Golgi-Cox.

Disclosure: Nothing to Disclose.

M31. Genetic Disruption of 2-Arachidonoylglycerol Synthesis Reveals a Key Role for Endocannabinoid Signaling in Anxiety Modulation

Sachin Patel*, Brian Shonesy, Rebecca Bluett, Roger Colbran, Danny Winder

Vanderbilt University, Nashville, Tennessee

Background: Endocannabinoid (eCB) signaling has been heavily implicated in the modulation of anxiety and depressive behaviors and emotional learning. Moreover, patients with depression and PTSD have reduced peripheral eCB levels. Despite these intriguing data, the role of the most abundant eCB 2-arachidonoylglycerol (2-AG) in the physiological regulation of affective behaviors is not well understood.
Methods: To determine whether a causal relationship exists between deficient 2-AG signaling and anxiety and depressive behavioral states, we generated mice lacking the primary 2-AG synthetic enzyme diacylglycerol lipase alpha (DAGLa). Targeted lipidomics, behavioral phenotyping, and electrophysiological studies were conduced to evaluate the effects of DAGLa deletion in affective behaviors and amygdala physiology.
Results: Here we show that genetic deletion of the 2-AG synthetic enzyme DAGLα reduces central, but not peripheral, 2-AG levels. DAGLα deletion causes an anxiety-like and a gender-specific anhedonic phenotype associated with impaired activity-dependent eCB retrograde signaling at amygdala glutamatergic synapses. Importantly, augmenting 2-AG levels had the opposite effect, reversing basal and stress-indcued anxiety states.
Conclusions: These data provide the first causal evidence that endogenous 2-AG signaling is critical for the physiological regulation of anxiety-like behaviors and suggest 2-AG deficiency could contribute to the pathogenesis of affective disorders.
Keywords: cannabinoid, CB1, anxiety, PTSD.
Disclosure: Nothing to Disclose.

M32. The Motivation and Synaptic Plasticity Induced by Cue-induced Cocaine Seeking is Reversed by Using Cocaine

Sade Spencer*, Peter Kalivas

Medical University of South Carolina, Charleston, South Carolina

Background: Cues that remind a cocaine addict of drug use are powerful motivators to seek and use cocaine. The cue-induced motivation to seek cocaine is modeled by using cocaine-conditioned cues to reinstate lever pressing in rats withdrawn for weeks from daily cocaine self-administration. We recently found that cue-induced reinstatement of cocaine seeking is mediated by transient synaptic potentiation (t-LTP) in the core subcompartment of the nucleus accumbens that is quantified by increases in dendritic spine diameter and AMPA glutamate currents. The amount of t-LTP is correlated with the intensity of cocaine seeking (number of lever presses) and disappears in parallel with lever pressing over the first 45 min after initiating cued reinstatement. While reinstatement and t-LTP are also induced by giving a noncontingent injection of cocaine, the time course of both behavior and t-LTP differs from cued reinstatement in that the response is absent at 15 min after a cocaine injection and maximal at 45 min. The lack of t-LTP after 15 min of cocaine-induced reinstatement caused us to hypothesize that cocaine is suppressing t-LTP and the motivation to seek drug because the goal (i.e. cocaine) was already achieved, and that the motivation to seek cocaine along with the t-LTP appears at 45 min as the levels of cocaine diminish from the acute noncontingent administration. This possibility fits nicely with the human experience where a cocaine cue motivates drug seeking and presumably t-LTP, but the motivation is suppressed once cocaine is taken until the levels of cocaine in the brain diminish at which time the addict is motivated to seek more drugs. We describe a new animal model to evaluate the role of t-LTP in regulating the motivation to seek cocaine that incorporates three anthropomorphic characteristics of cocaine seeking: 1) cue-induced lever pressing, 2) access to self-administered cocaine 10 min later, and 3) loss of access to cocaine after 45 min of use.
Methods: Adult male Sprague-Dawley rats ($\sim$300 g at start) were trained to self-administer cocaine on an FR1 schedule (2 hrs per day) where responses on an active lever resulted in a drug infusion (0.2 mg) paired with discrete light and tone cues until reaching a criteria of 10 days $\geq$10 infusions. Self-administration was followed by 10-14 days of extinction where lever pressing no longer had any programmed consequences. Reinstatement was modified to include 10 minutes of cue-only responding followed by 45 minutes where cocaine (or saline, controls) was available through the indwelling IV catheter and ending with 65 minutes of within session extinction. Animals were sacrificed at discrete time points along this reinstatement time course to examine changes in t-LTP as measured by quantification of the diameter and density of diolistically labeled dendritic spines on NAc MSNs. All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee at MUSC and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.
Results: Ten minutes of access to cocaine after initiation of ten minutes of cue-induced reinstatement ($t = 20$ min) reduces spine head diameter ($T(74) = 4.442$, $p < 0.0001$) and spine density ($T(74) = 2.011$, $p = 0.0479$) compared to a control group given access to saline. In both groups, spine head diameter at $t = 20$ min correlates with the amount of cue-induced lever pressing ($r2 = 0.3777$, $p = 0.0335$). Conversely, no such relationship between spine density and drug seeking behavior was found. Removal of cocaine access after 55 min of use repotentiated spine head diameter ($F(4,129) = 17.39$, $p < 0.0001$).
Conclusions: Using this novel model of cue-induced reinstatement and access to cocaine, we show that access to cocaine reverses the t-LTP induced by cocaine-conditioned cues commensurate with a reduction in motivation to seek drug. Moreover, when cocaine was subsequently removed, the motivation to lever press for cocaine markedly increased along with a renewal of t-LTP. These results suggest that the increase in spine head diameter tracked the

level of motivation the animal manifested to seek cocaine (i.e. the number of lever presses made) since spine head diameter consistently showed a positive correlation with drug seeking. Because access to cocaine decreased both the motivation to seek drug (lever presses) and t-LTP, we are now investigating the cellular mechanisms by which cocaine access is reducing t-LTP. Initial studies will focus on cocaine-induced dopamine release in the NAcore or prelimbic cortex as the first step in the sequence of cellular events that is reversing cue-induced t-LTP.

Keywords: cocaine, reinstatement, dendritic spine, nucleus accumbens.

Disclosure: Nothing to Disclose.

M33. Deep Brain Stimulation for Autistic Self-injurious Behavior

Andrew Chang, Gene Fridman, Jay Baraban, Irving Reti*

Johns Hopkins University, Baltimore, Maryland

Background: Between a third and half of autistic individuals display repetitive SIB ranging from head banging to self-directed biting and punching. In some patients these behaviors are extreme and unresponsive to traditional pharmacological and behavioral therapies with devastating consequences for the patients and their families. We have found ECT can produce life-changing results with a greater than 90% reduction in frequency of autistic SIB in patients with the most severe forms of self-injury. However, these patients typically require maintenance ECT (mECT) to sustain the improvement gained during the acute ECT course. Such mECT regimes can be as frequent as one treatment every 5 days. However, ECT is associated with cognitive side-effects and the long-term consequences of mECT started as early as childhood in some cases are unknown. Accordingly, there is a need to develop alternative therapies that mimic the beneficial effects of ECT without seizure induction or stimulation of brain regions uninvolved in regulating SIB. Neuromodulation by DBS has the potential to achieve anatomical specificity with minimal off-target effects such as cognitive side-effects associated with ECT. Furthermore, DBS therapy is sustained by implanted electrodes, and repeated procedures under anesthesia are not required like for ECT.

Methods: To evaluate the utility of DBS for autistic SIB, we have used a mouse model developed by Zoghbi and colleagues in which the methyl-CpG binding (mecp2) gene is conditionally deleted in GABAergic neurons (Viaat-mecp2-/y). These mice display excessive stereotyped self-grooming with development of skin lesions, social deficits, and GABAergic dysfunction including reduced mIPSCs and diminished GABA and GAD immunoreactivity. In preliminary studies, we found that a single ECS significantly suppresses their excessive self-grooming, similar to the positive effect of ECT observed in the clinic. In order to test whether DBS could also suppress excessive self-grooming in these mice, we targeted the subthalamic nucleus (STN) due to its central role in response inhibition, regulating output nuclei from the basal ganglia. Moreover, STN-DBS is effective in suppressing repetitive stereotyped behaviors in both monkeys and humans suffering with severe obsessive compulsive disorder. We delivered bilateral monopolar stimulation for 3 hours daily over 3 days. Mice were either conditional knockouts or floxed controls, and received either active or sham stimulation.

Results: Grooming duration was measured over the course of a week following three days of three hour DBS sessions. A two-way repeated measures ANOVA across days 3, 4 and 6 shows a significant main effect of genotype but not of treatment. Importantly, there is a genotype-treatment interaction ($F(1,13) = 20.24$, $p = 0.001$) and post-hoc analysis using Fisher's LSD test shows that self-grooming duration in Viaat-mecp2-/y mice treated with DBS is significantly lower than in Viaat-mecp2-/y mice treated with sham stimulation ($p = 0.001$). Two-way ANOVAs on days 3, 4 and 6 show a significant genotype-treatment interaction on each day. Post-hoc analyses using Fisher's LSD test show that self-grooming duration in Viaat-mecp2-/y mice treated with DBS was significantly lower than in mice treated with sham stimulation on days 4 ($p = 0.01$) and 6 ($p = 0.001$), and marginally significant on day 3 ($p = 0.055$). In sum, we observed suppression of excessive self-grooming for 3 days following DBS before the behavior returned to baseline. Importantly, the suppression of self-grooming was not due to decreased locomotor activity which was unaffected by either treatment or genotype.

Conclusions: Ongoing studies are aimed at determining whether DBS suppresses excessive self-grooming when different brain regions are targeted. Since there are multiple genetic abnormalities which contribute to autism, we are also assessing the effect of DBS in another mouse model of autistic SIB, the Shank3B-/-. Stimulation sites that work in both mouse species would be the strongest candidates for DBS in patients. We are also determining the minimum stimulation time needed for DBS to be effective in order to minimize side-effects, and whether DBS maintains its effectiveness with repeated use. These studies should yield valuable insights into optimized targeting and stimulation for suppressing autistic SIB in patients using DBS. They should also provide clues about brain circuitry which might be harnessed by non-invasive neurmodulatory techniques. Finally, they could also yield insights about targets for reducing SIB associated with other conditions including Lesch-Nyhan, Fragile X and Tourette's Syndromes.

Keywords: autism, self-injurious behavior, deep brain stimulation, electroconvulsive.

Disclosure: This work was funded by a grant from the Simons Foundation Autism Research Initiative.

M34. Developmental Status Shapes Physiological and Behavioral Responses to Traumatic Stress Exposures in Male Rats

Nicole Moore*, Daniel E Altman, Chau V Vuong, Jason C Sousa, Sean R Marcsisin, Victor E Zottig, Raymond F Genovese

Walter Reed Army Institute of Research, Silver Spring, Maryland

Background: Previous studies have shown that early life traumatic stress in rats can produce acute and lasting effects

upon behavior and neuroendocrine status. Response to repeated traumatic stress may also vary as a factor of developmental status. A repeated exposure to the same perceived life-threatening traumatic stressor may intensify the adverse stress response or possibly promote habituation/resilience as multiple exposures provide opportunity to learn, and the direction of this outcome may differ across development.
Methods: To characterize the acute effects of repeated traumatic stress in differing phases of development, the present study used a repeated exposure to underwater trauma (UWT), a brief but intense traumatic event that represents a direct and uncontrollable threat to life. Adolescent and adult rats were exposed to no water, free swim, or UWT once daily for eight days, beginning at P37 (adolescents) or P85 (adults). Behavioral assessments using elevated plus maze (EPM) and acoustic startle response (ASR) were conducted, along with corticosterone analysis at baseline, 1 day, and 7 days after the last UWT exposure.
Results: Preliminary results show a decrease in adolescent EPM exploratory behavior after 8 UWT exposures, but not in adults after UWT or free swim. Free swim treated adolescents showed a smaller decrease in exploratory behavior. Circulating corticosterone was significantly decreased in adolescent UWT exposed rats at 1 and 7 days post-exposure. In free swim adolescents, circulating corticosterone was decreased at 7 days post-exposure.
Conclusions: Preliminary analyses suggest that developmental status may be a robust factor in determining neuroendocrine and behavioral responses to repeated traumatic stress exposures in rats. Additionally, these results begin to build a case for further characterization of response timelines for multiple neuroendocrine markers following a traumatic stress exposure.
Keywords: Adolescence, Traumatic stress, Neuroendocrine, Behavior.
Disclosure: Nothing to Disclose.

M35. Effects of Chronic Social Defeat Stress on Sleep, Body Temperature, and Motor Activity in Mice

Audrey Wells*, Harry Pantazopoulos, Rachel Donahue, Chelsea Webber, Bruce Cohen, William Carlezon Jr

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: Stress is a critical component in the etiology of many chronic psychiatric illnesses, including Major Depressive Disorder (MDD) and Post-Traumatic Stress Disorder (PTSD). Research into the mechanisms by which stress produces core symptoms of mood disorders will facilitate the development of new pharmacotherapies for these illnesses. In MDD and PTSD, dysregulation of sleep and circadian rhythms (i.e., processes that follows an entrainable, 24 h oscillation) are two such symptoms. In rodents, a single bout of restraint stress or conflict with an aggressive conspecific (i.e., social defeat) increases subsequent non-rapid eye movement (NREM) sleep duration and intensity. Moreover, repeated exposure to social conflict blunts the circadian rhythms of activity and body temperature, the latter of which is more profoundly affected in susceptible mice. It is currently unknown whether sleep architecture is altered over the course of repeated, daily (i.e., chronic) exposure to stress. It is also uncertain whether changes in sleep occur concomitantly with, or independently of, alterations in temperature and activity rhythms.
Methods: We examined the effects of chronic social defeat stress (CSDS), a behavioral paradigm that engenders a long-lasting depressive-like phenotype in mice, on sleep and the circadian rhythms of activity and body temperature. Adult male C57BL6/J mice were surgically implanted with telemetry transmitters that enable continuous wireless recording of cortical EEG, neck EMG, body temperature, and activity. Following recovery from surgery, continuous recordings were obtained for 5 baseline days, 10 days of the CSDS (or control) regimen, and for 5 days post-defeat. On each day of social defeat, 1 h into the light cycle (zeitgeber time 1), defeated mice were exposed to a novel, aggressive CD-1 mouse for 10 min, followed by continuous, protected sensory exposure. Control mice were similarly housed opposite a conspecific with continuous, protected sensory exposure, but were never exposed to defeat stress.
Results: Analysis of sleep duration per 24-h cycle (percentage of pre-defeat baseline) across the experimental phases revealed that there were no significant differences in either NREM or REM sleep duration between defeated and control mice. However, analysis of sleep bouts (discrete episodes) indicated an increase in NREM, but not REM, bouts in defeated mice during social defeat, relative to controls. These increases returned to baseline levels during the post-defeat period. Analysis of circadian amplitude (the difference between the maximum and the mean of the wave) and period (duration of a complete oscillation) for activity revealed a decrease in amplitude, but not period, in defeated animals, relative to controls during the second half of the defeat regimen (days 6-10). Furthermore, both body temperature amplitude and period were attenuated in defeated mice, relative to controls, at this same time point. Consistent with previous literature, defeated mice could be subclassified into a susceptible and unsusceptible group based on change in temperature amplitude. Examination of sleep metrics in these subpopulations revealed that NREM bouts were preferentially increased in susceptible, but not unsusceptible mice, relative to controls.
Conclusions: In the present study, CSDS increased number of NREM episodes without producing a corresponding increase in NREM time. This likely reflects impaired sleep continuity. CSDS also decreased circadian amplitude of activity and both amplitude and period of body temperature. Remarkably, the increase in NREM bouts was greater in mice that were susceptible to the effects of CSDS on body temperature rhythm than in those who were unsusceptible. These findings provide a foundation for studies to explore the neural mechanisms by which CSDS alters NREM sleep in susceptible mice.
Keywords: social defeat, sleep, stress, circadian rhythm.
Disclosure: Dr. Carlezon has a US patent covering the use of kappa-opioid receptor antagonists in the treatment of

depressive disorders (Assignee: McLean Hospital). In the last 3 years, Dr. Carlezon has received compensation for professional services from The American College of Neuropsychopharmacology.

M36. Compulsive Eating Reduces Inhibitory Control of Pyramidal Neurons of the Lateral OFC

Jennifer Thompson, Michael Drysdale, Kimberley Pitman, Corey Baimel, Stephanie Borgland*

Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

Background: Compulsive eating occurs when individuals will eat regardless of knowledge of adverse consequences. The orbitofrontal cortex (OFC) is implicated in associative learning and cognitive flexibility. Frontotemporal dementia patients with damage to the lateral OFC compulsively ate even when they reported satiety (PMID: 17909155). Data from OFC lesion studies demonstrate increased perseverative behavior (PMID: 23856628). While these studies have highlighted the role of the OFC in compulsivity, they provide little information on the underlying cellular mechanisms as lesions destroy both the pyramidal neurons and the GABAergic interneurons that tightly control the firing and output of the pyramidal projection neurons. Therefore, we sought to determine if there were cellular adaptations in the lateral OFC associated with compulsive or binge eating.
Methods: To test for cellular neuroadaptations in the lateral OFC associated with compulsive, binging or chow-fed rats, we exposed rats to chow ad libitum (chow-fed) or a cafeteria diet for 6-7 weeks for 23 h/day (extended access), 1 h/day (restricted access) and then used a conditioned suppression model (PMID: 20348917) to assay for compulsivity. After, we prepared OFC brain slices for whole cell patch clamp electrophysiology to record cellular excitability as well as excitatory or inhibitory synaptic transmission onto pyramidal neurons.
Results: After 6-7 weeks of extended access to a cafeteria diet, obese rats did not exhibit conditioned suppression, in contrast to rats restricted to one hour a day of the cafeteria diet or chow-fed rats. OFC pyramidal neurons from extended access rats had greater excitability. This was accompanied by a reduction of inhibitory input to these neurons. Although restricted access rats binge eat their caloric intake during the 1 h exposure to the cafeteria diet, there were no significant changes of OFC pyramidal neurons from these rats compared to chow fed rats.
Conclusions: Taken together, these data suggest that cellular adaptations in the lateral OFC are associated with compulsive, but not binge feeding. Furthermore, these data suggest that after extended access to a cafeteria diet there is an increase in excitability of lateral OFC neurons, likely due to a decrease in inhibitory input.
Keywords: Orbitofrontal cortex, compulsivity, feeding, inhibitory synaptic transmission.
Disclosure: Nothing to Disclose.

M37. Specific Regions Display Altered Grey Matter Volume in μ-Opioid Receptor Knockout Mice: MRI Voxel-based Morphometry

Ichiro Sora*, Kazumasu Sasaki, Akira Sumiyoshi, Hiroi Nonaka, Yoshiyuki Kasahara, Kazutaka Ikeda, F Scott Hall, George R Uhl, Masahiko Watanabe, Ryuta Kawashima

Kobe University Graduate School of Medicine, Kobe, Japan

Background: μ opioid receptor knockout (MOR-KO) mice display several behavioural alterations from wild-type (WT) mice including differential responses to nociceptive stimuli. Brain structural changes have been tied to behavioural alterations noted in transgenic mice with targeting of different genes. Hence, we assess the brain structure of MOR-KO mice.
Methods: Magnetic resonance imaging (MRI) voxel-based morphometry (VBM) and histological methods (Hematoxylin and Eosin (HE) staining/Kluver Barrrela (KB) staining) were used to identify structural differences between extensively backcrossed MOR-KO mice and WT mice. In this study, we have examined the brains of MOR-KO mice to determine the volume abnormalities associated with μ-opioid (MOR) receptor deletion. We scanned whole brain of 42 MOR-KO and 42 WT mice at 12 weeks of age using high resolution, three-dimensional magnetic resonance T2 imaging MRI for automated voxel-based morphometry (VBM) analysis. Histological analysis was performed in the largest volume abnormality region detected in VBM analysis and 7 mice were used for each genotype.
Results: MOR-KO mice displayed robust increases in regional grey matter volume in olfactory bulb, several hypothalamic nuclei, periaqueductal grey (PAG) and several cerebellar areas, most confirmed by VBM analysis. The largest increases in grey matter volume were detected in the glomerular layer of the olfactory bulb, arcuate nucleus of hypothalamus, ventrolateral PAG (VLPAG) and cerebellar regions including paramedian and cerebellar lobules. Histological analyses confirm several of these results, with increased VLPAG cell numbers and increased thickness of the olfactory bulb granule cell layer and cerebellar molecular and granular cell layers.
Conclusions: MOR receptor deletion causes previously undescribed structural changes in specific brain regions, but not in all regions with high MOR receptor densities (e.g. thalamus, nucleus accumbens) or that exhibit adult neurogenesis (e.g. hippocampus). These findings suggest that factors other than elimination of MOR receptor alone may account for some of the behavioral alterations observed in these mice. Volume abnormalities in hypothalamus and PAG may reflect behavioural alterations including hyperalgesia. Although the precise relationship between volume abnormalities and MOR receptor deletion could not be determined based on this study alone, our findings suggest that morphological alterations detected in MOR-KO mice by MRI-VBM methods may relate to some of the behavioral alterations observed in MOR-KO mice and that levels of MOR receptor expression may influence a broader range of neural structure and function in humans than previously supposed.

Keywords: voxel-based morphometry (VBM), periaqueductal grey (PAG), hypothalamus, hyperalgesia.
Disclosure: Nothing to Disclose.

M38. Neuro-cognitive Phenotype of the MAM Model of Schizophrenia

Patrick Tierney, William M. Howe, Damong Young, Lauren O'Malley, Crystal Mavros, Rita Balice-Gordon*, Rouba Kozak

Pfizer, Inc., Cambridge, Massachusetts

Background: Disruptions of the neural circuits that control goal-directed behaviors are hypothesized to underlie the symptoms of a number of neurodegenerative and neuropsychiatric disorders, including schizophrenia. The gestational methylazoxymethanol (MAM) rodent model has been shown to reproduce structural, neurochemical, executive function and behavioral aberrations observed in schizophrenic patients (Grace & Moor, 1998, O'Donnell & Grace 1995). However the ability of MAM-treated animals to make basic stimulus-reward associations, which represent a fundamental part of all goal-directed behaviors including those traditionally described as reflecting "executive" function, remains to be determined. Dopamine neurotransmission in the nucleus accumbens is a necessary component of such stimulus-reward learning (e.g. Flagel et al., 2011), and alteration in the activity of dopamine cell bodies in the ventral tegmental area has been reported in MAM animals. To explore the possibility that aberrant dopaminergic signaling may lead to alterations in fundamental learning processes in the MAM-model, we assessed both stimulus-reward learning, as well as the regulation of mesolimbic dopamine neurotransmission, in the same MAM-treated animals.
Methods: MAM (n = 34) and Sham-treated control animals (N = 26) were trained for 10 days in a Pavlovian conditioned approach task where in the presentation of a conditioned stimulus (CS+; 8 s-long extension of a response lever into an operant chamber) predicted the subsequent availability of a reward (grape-flavored sucrose pellet). Animals' behavior was quantified in terms of the magnitude, direction of, and probability that the CS+ evoked approach behavior. After the completion of behavioral training, animals were anesthetized and implanted with a carbon-fiber electrode for Fast-Scan Cyclic Voltammetry (FSCV; e.g. Clark et al., 2010). We then compared levels of electrically evoked tonic and phasic DA release (10 sec at 5Hz and 400msec at 20 Hz, respectively), and in response to an amphetamine challenge.
Results: MAM animals showed a diminished capacity to form basic stimulus-outcome relationships. There was no difference in the magnitude of the behavior evoked by the presentation of the reward-paired cue between MAM and control animals. MAM and control animals did, however, differ in the probability that the presentation of a reward paired cue evoked any approach behavior at all. Where the magnitude of behavior evoked by the presentation of a reward-paired cue is modulated by motivational processing, the ability of the cue to evoke any change in behavior, regardless of the strength, reflects the learned association regarding the contingency between stimulus and outcome. Thus, the reduction in the probability that the presentation of the reward paired cue evokes an approach behavior is indicative of a fundamental cue-reward learning deficit, as opposed to aberrant motivation. This interpretation is in line with other data we have collected showing MAM animals take longer to acquire proficiency in a visuo-spatial working memory task, but once criterion is reached, show no deficits in working memory. The changes in the peak concentration of DA evoked by tonic electrical stimulation showed no difference between MAM and Sham animals over time. In contrast a difference was observed between MAM and Sham animals with phasic electrical stimulation. In both MAM and Sham animals DA release peaked at 45 min post amphetamine injection. However, only in MAM animals did DA levels remain significantly elevated for more than hour. At 60 min MAM animals had 100% greater DA release to a single phasic electrical stimulation train than did Sham animals. This dissociation in the regulation of tonic vs phasic DA release is consistent with the behavioral results showing normal motivation (i.e. tonic dopamine) but impaired stimulus-reward learning (phasic dopamine).
Conclusions: Together, the available evidence suggests that while the MAM model may be able to inform preclinical studies aimed at developing pharmacotherapies for the treatment of certain domains of neuropsychiatric disorders such as schizophrenia, particularly those designed to re-regulate of mesolimbic dopamine transmission, or compensate for a loss of inhibitory interneuron control of cortical circuitry as has been described elsewhere.
Keywords: Schizophrenia, dopamine, MAM, cognitive deficit.
Disclosure: The authors are employees of Pfizer, Inc.

M39. Consolidation of an Animal Model of Bipolar Disorder Induced by Intracerebroventricular Ouabain

Joao de Quevedo*, Samira Valvassori, Wilson Rodrigues Resende, Camila Oeland Arent, Roger Bitencourt Varela, Edemilson Mariot da Silva, Gustavo Colombo Dal Ponte, Rafaela Tiscoski Amboni, Guilherme Bianchini

University of Texas Health Science Center at Houston, Houston, Texas

Background: Bipolar disorder (BD) presents a complex alternating clinical course with recurrent mood changes including manic and depressive episodes making the development of an adequate animal model challenging. Ouabain, a potent Na + K + ATPase inhibitor, intracerebroventricular (i.c.v) administration in preclinical models has been suggested as a model of mania. However, to date, there are no models that mimic mood episodes, mania and depression, in the same animal. The aim of our study was to evaluate manic- and depressive-like behaviors and cognitive, physiological and neurochemical alterations after a single ouabain i.c.v administration in Wistar rats. Moreover, evaluate the effects of the mood stabilizers, lithium (Li) and valproate (VPA), and the antidepressant imipramine (IMI) on behavioral, physiological and neurochemical alterations induced by ouabain.
Methods: All experimental procedures were performed in accordance with international recommendations for the care and use of laboratory animals and approved by the

Research Ethics Committee for Animal Use of UNESC under protocol 66/2010. Stereotaxic surgery was performed in 192 male Wistar rats, approximately 60 days for implantation of a cannula into the lateral ventricle. After 72 hours of recovery 5 ul ouabain or aCSF were infused intracerebroventricularly (ICV). Immediately after ICV injection, the animals were treated with lithium (Li), Valproic acid (VPA) or saline (Sal) intraperitoneally (IP) during the next 14 days. On the 13rd day, was included Imipramine (IMI) in the IP treatment. The groups are listed follows: aCSF + Sal; aCSF + Li; aCSF + VPA; aCSF + IMI; aCSF + Li + IMI; aCSF + VPA + IMI; Ouabain + Sal; Ouabain + Li; Ouabain + VPA; Ouabain + IM; Ouabain + Li + IMI; Ouabain + VPA + IMI. The locomotor activity was evaluated on the 7th treatment day by the open field test. The anhedonia was evaluated by consumption of sucrose test fulfill from 8th to 14th treatment days. Depressive-like Behavior was assessed using the forced swimming test on 13rd and 14th treatment days. After testing on day 14 the mice were sacrificed and blood removed for analysis of ACTH and adrenal gland for weighing.

Results: Spontaneous locomotor activity behavior in rats was significantly increased 7 days after ouabain injection compared to control, while Li and VPA reversed this ouabain-induced manic-like behavior. Locomotor activity returned to its basal levels 14 days after ouabain injection. However, 14 days after ouabain injection, was observed depressive-like behavior in the animals, such as increase in the immobility time in the forced-swimming test and decrease in the sucrose consumption. The IMI treatment and the adjunctive treatment of Li or VPA with IMI reversed the depressive-like behavior induced by ouabain. However,Li or VPA, per se, partially reversed these behavioral alterations induced by ouabain. The adrenal gland weight was increased after ouabain administration, which was accompanied by an ACTH serum level increased in the depressive-like animals. Li, VPA or the adjunctive treatment of Li or VPA with IMI were able to reverse the adrenal weigh increased induced by ouabain. The mood stabilizers and the adjunctive treatment of mood stabilizer, Li or VPA plus IMI reversed the ACTH levels increased induced by ouabain.

Conclusions: We propose that the ouabain i.c.v administration in preclinical models may be not only a model for manic episodes but also for depressive ones because our results strongly support that ouabain administration leads also to a depressive-like phenotype.

Keywords: bipolar disorder, mania, depression, ouabain.

Disclosure: Nothing to Disclose.

M40. VU0410120, an Inhibitor of the Glycine Transporter 1 (GlyT1), Improves Sociability and Cognition in the BALB/c Mouse Model of ASD, while Eliciting Stereotypic Behaviors in the Swiss Webster Strain

Jessica Burket, Andrew Benson, Jerri Rook, Craig Lindsley, P. Jeffrey Conn, Stephen Deutsch*

Eastern Virginia Medical School, Norfolk, Virginia

Background: The Balb/c mouse strain models features of autism spectrum disorders (ASD), displaying impaired sociability. Relative to the C57Bl/6J and Swiss Webster comparator strains, Balb/c mice have decreased locomotor activity in the presence of a salient social stimulus mouse and diminished time that they spend exploring and in the vicinity of an enclosed social stimulus mouse, among other reliably rated behaviors in a standard social procedure. D-Cycloserine, a partial glycineB agonist, improves the sociability of the Balb/c mouse, consistent with data suggesting that NMDA receptor activation regulates sociability, and the endogenous tone of NMDA receptor-mediated neurotransmission is altered in Balb/c mice. Glycine and D-serine are the endogenous obligatory co-agonists of this glutamate-gated ion channel receptor. Therapeutically targeting the NMDA receptor is challenging because these receptors have both synaptic and extrasynaptic locations, the latter are defined by their distance from the postsynaptic density. Further, synaptic and extrasynaptic receptors differ in subunit composition (i.e., synaptic receptors contain the GluN2A subunit, whereas extrasynaptic receptors contain the GluN2B subunit), and in their preferences for D-serine (i.e., synaptic) or glycine (i.e., extrasynaptic) as obligatory co-agonists. There are some data suggesting that stimulation of synaptic NMDA receptors can be "neuroprotective," whereas (excessive) stimulation of extrasynaptic receptors may be associated with "neurotoxicity." The glycine transporter 1 (GlyT1) is a member of the family of Na + /Cl–dependent glycoprotein transporters with 12-transmembranous domains, which includes the transporters for proline, monoamines and GABA; GlyT1 is widely expressed in astroglial cells throughout the hippocampus, cerebral cortex and cerebellum. Inhibition of GlyT1 is an emerging strategy for activation of the NMDA receptor.

Methods: Test mice were experimentally-naïve, 4-week old male, outbred Swiss Webster and genetically-inbred Balb/c mice (Harlan Laboratories, Frederick, MD). Stimulus mice were 4-week old male ICR mice (Charles River Laboratories, Wilmington, MA). Test mice were individually weighed prior to drug administration and up to 21 mice were tested in each condition. VU0410120 (10, 18 and 30 mg/kg) dissolved in 20% HP-β-cyclodextrin or 20% HP-β-cyclodextrin as vehicle was injected intraperitoneally in a volume of 0.01 ml/g of body weight and behavioral testing was begun 20 minutes later. Sociability was tested in an established mouse behavioral procedure using a 3-compartment apparatus. Spatial working memory was assessed with the standard Y-maze spontaneous alternation test. The novel stereotypic behaviors of "burrowing" with front paws and "jumping" off of hind legs while standing erect with front paws on the walls of the sociability apparatus were rated for 10 minutes during assessment of sociability. Paired t-tests were used to determine effects of VU0410120 on the salience of the enclosed social stimulus mouse for Balb/c and Swiss Webster mice. Within-strain comparisons were made with respect to time spent in the compartment containing the enclosed social stimulus mouse and time spent exploring (i.e., sniffing) the enclosed social stimulus mouse versus time spent in the "nonsocial" compartment and exploring the empty inverted cup. A two-way ANOVA was used to examine effects of strain (Balb/c vs. Swiss Webster),

treatment condition (i.e., VU0410120 vs. vehicle), and their interaction on latency to approach the inverted cup, and exploratory behavior and percentage of spontaneous alternations in the Y-maze. When ANOVA was significant, Tukey-Kramer Multiple Comparison tests were applied in post-hoc comparisons, where appropriate. When a two-way ANOVA could not be performed because of an absence of variance in one of the groups, exploratory multiple comparisons of mean values between groups were performed with Independent Samples t-tests.
Results: The vehicle-treated comparator Swiss Webster strain had a significantly shorter initial latency to approaching the inverted cup containing the stimulus mouse than the vehicle-treated Balb/c mouse (49.87 sec ± 27.7[SEM] vs 264.13 sec ± 44.9[SEM], $p < 0.01$). However, treatment with VU0410120 (10 and 18 mg/kg) significantly decreased the latency of the Balb/c strain compared to its vehicle-treated condition (76.00 sec ± 30.5[SEM], $p < 0.05$ and 44.27 sec ± 19.4[SEM], $p < 0.01$, respectively). Moreover, Balb/c mice treated with VU0410120 (18mg/kg) spent significantly more time in the compartment containing the stimulus mouse (300.43 sec ± 26.9[SEM]) than the compartment containing the empty inverted cup (176.61 sec ± 18.5[SEM], $p < 0.01$). Also, Balb/c mice treated with VU0410120 (10 and 18mg/kg) spent significantly more time exploring/sniffing the inverted cup containing the stimulus mouse (172.98 sec ± 26.6[SEM] and 193.78 sec ± 20.0[SEM], respectively) than the empty cup (74.86 sec ± 16.5[SEM], $p < 0.05$ and 74.12 sec ± 9.2[SEM], $p < 0.001$, respectively). The Swiss Webster strain showed greater locomotor activity in the sociability apparatus and greater exploratory behavior, as reflected in arm entries in the Y-maze, compared to the Balb/c strain. However, even though the Balb/c strain made fewer arm entries than the Swiss Webster strain, the Balb/c strain had a significantly higher percentage of spontaneous alternations in the Y-maze at a dose of 30 mg/kg of VU0410120 compared to its vehicle-treated condition (74.76 ± 4.1[SEM] vs 61.19 ± 2.6[SEM], $p < 0.05$). Importantly, the 30 mg/kg dose of VU0410120 significantly decreased the percentage of spontaneous alternations of the Swiss Webster strain compared to its vehicle-treated condition (30.71 ± 6.0[SEM] vs 63.86 ± 1.4[SEM], $p < 0.0001$). Swiss Webster mice treated with VU0410120 (30 mg/kg) spent significantly more time engaged in repetitive burrowing behavior for each discrete episode of burrowing (199.36 sec ± 54.0[SEM]) than similarly treated Balb/c mice (31.76 sec ± 11.1[SEM], $p < 0.01$). Moreover, the Swiss Webster mice treated with VU0410120 (30 mg/kg) spent significantly more time engaged in "jumping" behavior (29.14 sec ± 12.0[SEM]) and made a significantly greater number of total jumps (43.90 ± 17.7[SEM]) than similarly-treated Balb/c mice (3.38 sec ± 3.4[SEM], $p < 0.05$ and 2.00 ± 2.0[SEM], $p < 0.05$, respectively).
Conclusions: The data show that doses of VU0410120 (i.e., 18 and 30 mg/kg) that improved measures of sociability and spatial working memory in the Balb/c mouse strain elicited intense stereotypic behaviors in the Swiss Webster comparator strain (i.e., "burrowing" and "jumping"). These data support exploration of GlyT1 inhibition as a therapeutic strategy for activation of the NMDA receptor in order to address the symptom domains of impaired sociability and cognition in persons with ASD. However, the data also suggest that genetic factors may influence sensitivity to emergence or worsening of stereotypies as undesired medication side effects of this approach. The existence of selective NMDA receptor ligands, such as agonists and antagonists with precise subunit specificities and allosteric modulators that can positively and negatively influence the ability of L-glutamate to promote channel opening, will facilitate the development of medications for a wide variety of neuropsychiatric indications.
Keywords: Balb/c mouse, glycine transporter 1, autism, Y-maze.
Disclosure: PJ Conn and CW Lindsley receive research support from Bristol Myers Squibb and Astrazeneca and are inventors on multiple patents protecting GlyT1 inhibitors. JA Burket, AD Benson, JM Rook, and SI Deutsch have nothing to disclose.

M41. Paternal Nicotine Self-administration is Associated with Increased Acquisition and Maintenance of Nicotine Taking in Offspring

Heath Schmidt*, Adrian Arreola, Blake Kimmey, Duncan Van Nest, John Mauer

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Recent evidence indicates that paternal smoking is associated with nicotine dependence and increased incidence of childhood cancer in offspring. These findings indicate that tobacco smoke is capable of influencing behavioral phenotypes in future generations. However, the underlying mechanisms by which paternal nicotine exposure influences smoking behavior in subsequent generations are not clear. The goal of this study was to establish a preclinical rodent model of inter-generational susceptibility to nicotine dependence.
Methods: Male rats were allowed to self-administer nicotine (0.03 mg/kg/infusion) on a fixed-ratio 1 schedule of reinforcement for 60 consecutive days, the duration of spermatogenesis in rats. Nicotine-experienced rats and yoked saline controls were then allowed to mate with drug-naïve dams. When the offspring reached 60 days of age, male and female progeny were implanted with jugular catheters and the acquisition of nicotine self-administration was assessed.
Results: Male and female offspring of nicotine-experienced sires self-administered more nicotine when compared to the offspring of yoked saline controls.
Conclusions: These data are consistent with human epidemiological studies and indicate that paternal nicotine exposure increases susceptibility to nicotine taking in offspring. Identifying novel epigenetic mechanisms underlying the transmission of enhanced vulnerability to nicotine dependence will aid in the development of novel smoking cessation medication in generations at high risk for chronic smoking behavior.
Keywords: nicotine, self-administration, transgenerational, epigenetics.
Disclosure: Nothing to Disclose.

M42. Altered Basolateral Amygdala Reactivity in the SERT Ala56 Genetic Mouse Model of Autism Spectrum Disorder

Hideki Iwamoto*, Jeremy Veenstra-VanderWeele, Randy Blakely

Vanderbilt University, Nashville, Tennessee

Background: The autism spectrum disorder (ASD)-associated, serotonin (5-HT) transporter (SERT) coding variant Ala56 exhibits constitutively enhanced transport activity, hyperphosphorylation and an insensitivity to PKG/p38MAPK regulation in vitro (Sutcliffe et al., 2005, Prasad et al., 2005, Prasad et al, 2009). To validate and extend these observations in vivo, we generated SERT Ala56 knock-in mice, reproducing the ASD biomarker hyperserotonemia, and demonstrating basal SERT hyperphosphorylation, enhanced hippocampal 5-HT clearance, and hypersensitivity of multiple 5-HT receptors (Veenstra-VanderWeele et al., 2012). Moreover, SERT Ala56 animals display perturbations in multiple behaviors observed in several other ASD mouse models, including reduced pup vocalizations, altered social function, and repetitive behavior. As structural and functional alterations of the amygdala have been reported in ASD, and might contribute to one or more phenotypes of the SERT Ala56 model, we examined amygdala neuron excitability and serotonin-induced synaptic modulation in these animals.
Methods: We employed field-potential recordings of the basolateral amygdala (BLA) in brain slice preparations, an area of dense serotonergic innervation, from 6-8 wk old mice (homozygous SERT Ala56 or WT littermates), to determine neuronal excitability and synaptic plasticity. The external capsule was electrically stimulated and field potentials were measured from BLA in the presence of GABA receptor antagonist picrotoxin. Whole-cell voltage/current clamp, combined with optogenetics, was utilized to dissect 5HT transmission on principal neurons. Slices from Ai32-ROSA-ChR-EYFP crossed to ePet1-Cre animals were used to optogenetically activate serotonergic projections in amygdala. TTL-triggered LED pulses were used to stimulate the channelrhodopsin-expressing serotonergic fibers through a 40X water-immersion objective.
Results: Fluorescent images of amygdala slices from ChR-EYFP-ePet1-Cre mice revealed as expected substantial serotonergic projections to the BLA. Field potential input-output curves obtained from the BLA of SERT Ala56 mice versus littermate controls demonstrated elevated responses to stimulation, consistent with increased synaptic strength. Tetanic electrical stimulation (5 repeats of 100Hz for 1s separated by 30s) induced long-term potentiation (LTP) that did not differ by genotype. Consistent with our prior in vivo demonstrations of 5-HT receptor hypersensitivity, however, we observed enhanced synaptic depression induced by bath-perfused 5-HT2A/2C receptor agonist (α-methyl 5-hydroxytryptamine). In agreement with the latter findings, optogenetically-induced 5-HT hyperpolarized the principal neurons under current clamp.
Conclusions: Although amygdala dysregulation has been implicated in ASD, the underlying mechanisms have not been understood at a cellular level. Our data demonstrate alterations in serotonergic transmission induced by expression of the hyperfunctional SERT Ala56 variant, possibly arising from a developmental impact on glutamatergic synaptic transmission, as well as heightened sensitivity to 5-HT in the BLA. Our findings suggest that expression of SERT Ala56 can drive higher 5-HT-dependent amygdala reactivity to afferent stimuli, due to a reduction in normal inhibitory inputs that can be revealed as enhanced inhibition when exogenous 5-HT receptor agonists are applied. Ongoing studies seek to determine whether these predictions are consistent with endogenous serotonergic regulation of amygdala activity using in vitro optogenetic methods, and ultimately in relation to behavior using optical stimulation of raphe inputs in vivo. Taken together, our findings argue that disrupted control of synaptic 5-HT homeostasis can drive abnormal amygdala reactivity that may serve as a substrate for behavioral alterations present in the SERT Ala56 model, and possibly in idiopathic ASD.
Keywords: Serotonin transporter, Autism, amygdala, genetic mouse model.
Disclosure: Nothing to Disclose.

M43. Effects of Chronic Aripiprazole Administration on Dopamine Receptors: Comparison with Cariprazine

Frank Tarazi*, Yong Kee Choi, Nika Adham, Béla Kiss, Gyertyán Gyertyán

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: Cariprazine is a novel atypical antipsychotic currently in development for the treatment of acute schizophrenia, bipolar mania, bipolar depression and as adjunctive treatment to antidepressant drugs for major depressive disorders. Cariprazine shares common pharmacological actions with the atypical antipsychotic aripiprazole as partial agonists at dopamine (DA) D3 and D2 receptors. We have recently reported that chronic administration of cariprazine within its antipsychotic-like effective doses altered DA D2, D3 and D4 receptor levels in different rat forebrain regions[1]. In this study we compared the chronic effects of aripiprazole vs. cariprazine on DA receptor subtypes.
Methods: Rats were administered either vehicle or aripiprazole at doses that have shown antipsychotic-like activity in various models (2, 5, or 15 mg/kg) for 28 days. In our recent study[1], three doses of cariprazine (0.06, 0.2, or 0.6 mg/kg) were also administered for 28 days. DA receptor levels were quantified using autoradiographic assays on brain tissue sections from the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), caudate putamen (CPu), hippocampus (HIPP), olfactory tubercle (OT), and islands of Calleja (IC).
Results: Similar to cariprazine[1], chronic treatment with aripiprazole did not alter D1 receptor levels in any brain region tested. Aripiprazole increased D2 receptor levels in mPFC (29%-48%). However, only the high dose of aripiprazole (15 mg/kg) increased D2 receptors in NAc (40%), medial (35%) and lateral (50%) CPu, and HIPP (57%). Similarly, cariprazine increased D2 receptor levels in

mPFC (27%-43%), NAc (40%-45%), medial (41%-53%) and lateral (52%-63%) CPu, and HIPP (38%)[1]. Chronic aripiprazole treatment (5 and 15 mg/kg) significantly increased D3 receptors in OT (15%-37%) and IC (18%-41%). In contrast, cariprazine treatment had more profound effects on D3 receptors as the three doses of cariprazine (0.06, 0.2, or 0.6 mg/kg) dose-dependently upregulated D3 receptor levels in IC (32%-57%), OT (27%-67%), and NAc shell (31%-48%)[1]. Repeated aripiprazole treatment (5 and 15 mg/kg) increased D4 receptors in medial (17%-48%) and lateral (16%-51%) CPu. In addition the high dose of aripiprazole increased D4 receptors in NAc (37%) and HIPP (72%). In contrast, cariprazine treatment dose-dependently increased D4 receptor in NAc (53%-82%), medial (54%-98%) and lateral (58%-74%) CPu, and HIPP (38%-98%)[1].

Conclusions: Chronic aripiprazole treatment (5-15 mg/kg) upregulated D2 and D4 receptor levels in various brain regions. Higher doses of aripiprazole also increased D3 receptor levels in selective brain regions. In contrast, lower doses of cariprazine (0.06-0.6 mg/kg) induced significant increases in D2 and D4 receptors and produced more profound D3 receptor changes in more forebrain regions. These findings suggest that cariprazine is more potent than aripiprazole at DA receptor subtypes, and that D3 receptors play a more prominent role in mediating the actions of cariprazine compared to aripiprazole, which may confer additional clinical benefits on cognitive impairment and mood symptoms associated with schizophrenia and bipolar disorder. [1]Choi YK, Adham N, Kiss B, Gyertyán I, Tarazi FI. Long-term effects of cariprazine exposure on dopamine receptor subtypes. CNS Spectr. 2014 Jun;19(3):268-77.

Keywords: cariprazine, dopamine, antipsychotic.

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M44. Optogenetic Modulation of the Prefrontocortical-Dorsal Raphe Microcircuit Bidirectionally Biases Socioaffective Decisions after Social Defeat

Collin Challis*, Caroline Min, Sheryl G. Beck, Olivier Berton

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Modulating levels of serotonin (5-HT) influences affective perception and response to social threats. However, the circuit mechanisms that control social interaction are not well understood. Understanding these underlying mechanisms could provide the groundwork to develop therapeutic interventions to more precisely treat socioaffective disorders. We examined the organization and plasticity of the microcircuit formed by 5-HT neurons in the dorsal raphe nucleus (DRN) and the ventromedial prefrontal cortex (vmPFC) and its role in social approach-avoidance decisions.

Methods: We use viral-mediated fluorescent tracers, whole cell patch clamp electrophysiology and optogenetic techniques in population-specific Cre-driver mice to explore the function of the vmPFC-DRN microcircuit in the chronic social defeat stress (CSDS) model of depression. All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: We found excitatory vmPFC projections localized to GABAergic areas of the DRN. Using optogenetics with both cFos mapping and electrophysiology, we provide the first direct evidence that vmPFC axons drive synaptic activity and immediate early gene expression in identified DRN GABA neurons through an AMPA-dependent mechanism. We also show that CSDS drove GABAergic sensitization that strengthened local inhibition of 5-HT neurons in mice susceptible, but not resilient, to CSDS. Finally we demonstrate using optogenetics that increasing vmPFC input to the DRN during sensory exposure to an aggressor's cues enhanced avoidance bias. In contrast, optogenetically decreasing vmPFC drive of the DRN or GABAergic neuronal activity within the DRN prevented the acquisition of an avoidance phenotype after CSDS.

Conclusions: These results clarify the functional organization of vmPFC-DRN pathways and identify GABAergic neurons as a key cellular element filtering top-down vmPFC influences on affect-regulating 5-HT output. They also provide a strong foundation for the development of novel circuit-based therapeutic treatments to treat major depression such as deep brain stimulation.

Keywords: depression, serotonin, dorsal raphe, prefrontal cortex.

Disclosure: Nothing to Disclose.

M45. The Role of miRNA Modulation in Inflammation-related Depression

Janet Clark*, Brian Platt, Cassandre Cavanaugh, Baktisha Alla

National Institute of Mental Health/National Institutes of Health, Bethesda, Maryland

Background: There is growing clinical evidence that inflammation can play an important role in the development of depression. Moreover, it is estimated that only 30% of patients with clinical depression ever achieve remission of their symptoms, pointing to a clear unmet medical need for new and better treatments. Treatment of CD-1 mice with a single dose of Bacille Calmette Guérin (BCG) vaccine produces an acute sickness response, chronic elevation in circulating pro-inflammatory cytokines and a chronic inflammation-related depressive phenotype as assessed using various behavioral assays. In addition, our previous studies have shown that 10 to 30% of mice administered BCG show the sickness response and chronic elevation of pro-inflammatory cytokines but are resilient to developing a depressive phenotype. In an effort to understand the neurobiological processes that are altered by chronic inflammation and lead to either a depressive

phenotype or resilience, we have studied changes in miRNA expression in hippocampal tissue from saline control, BCG-'resilient' (BCG-R) and BCG-'susceptible' (BCG-S) mice.
Methods: To study an inflammation-related depressive phenotype, CD-1 mice were dosed with BCG and subsequent measurements of body weight, locomotor activity, and immobility in the tail suspension test (TST) were taken. Spleen weights were determined and plasma cytokine assessments were made at experiment termination. (These data are published in Platt et. al. 2012). Total RNA was isolated from hippocampal tissue using the miRVana isolation kit and cDNA synthesized from this total RNA was analyzed for modulation of miRNA by performing miRNA profiling experiments with samples from saline control, BCG-R and BCG-S mice. Changes in miRNA were assessed using Real-Time RT-PCR and the ABI Rodent miRNA arrays on an ABI 7900HT Fast System. The TargetScan miRNA target prediction data base and relevant literature were used to identify target genes of interest. To determine if mmu-miR-412 and mmu-miR-203 interact with the 3' untranslated region (UTR) for the circadian locomotor output cycles kaput (Clock) gene, Luciferase reporter assays were performed by transfecting HEK-293 cells with plasmids containing miR-412 and miR-203 and the Clock gene 3' UTR sequence. CLOCK protein determinations were made by performing western blot analyses using hippocampal homogenates from BCG-S and saline control mice. Western blots were imaged using the LI-COR Odyssey Infrared Imaging System and changes in protein were determined by performing densitometry on the CLOCK protein bands using the Odyssey software.
Results: miRNA profiling of hippocampal tissue has revealed differential expression of several miRNAs in BCG-R and BCG-S samples as compared with saline controls suggesting that miRNA modulation is involved in resilience to and the development of the inflammation-related depressive phenotype. Of particular interest are miR-412, which is significantly up-regulated (10.34 fold; $p = 0.0149$) in the BCG-S mice and miR-203, which is significantly down-regulated (1.76 fold; $p = 0.0349$) in the BCG-R mice. Bioinformatic algorithms indicate that both of these miRNAs are predicted to have binding sites in the 3' UTR of the Clock gene. Using a luciferase assay system we have now confirmed that these miRNAs can interact with the 3'UTR for the Clock gene. CLOCK protein in hippocampal homogenates from BCG-S mice was significantly reduced relative to saline controls (50% reduction, $p < 0.05$) as determined by Western blot analyses.
Conclusions: We demonstrate for the first time differential modulation of miRNAs in BCG-R and BCG-S mice as compared with saline controls in this mouse model of chronic inflammation-related depressive behavior. In addition, we have confirmed that miR-412 and miR-203 can interact with the 3' UTR for the Clock gene and therefore may regulate expression of the CLOCK protein or translation of Clock gene mRNA. Finally, CLOCK protein in hippocampal samples from BCG-S mice is significantly reduced. Therefore, the BCG model provides a novel means by which to study the cellular mechanisms responsible for the development of inflammation-related depression and may also serve as a means to assess novel pharmacological treatment approaches to this condition. These data suggest that miR-412 and miR-203 may regulate Clock gene expression and that BCG treatment may alter CLOCK protein expression in BCG-S mice through changes in miRNA expression further suggesting that circadian rhythms may be disrupted in this model of inflammation-related depressive behavior.
Keywords: Inflammation, Depression, miRNA, CLOCK.
Disclosure: Nothing to Disclose.

M46. Evaluation of Anti-depression-like Effects of Scopolamine and Ketamine in Monoamine Depletion - and Uncontrollable Stress-induced Rodent Models of Depression

William Eckert*, James Shoblock, Barbara Vaughan, Wayne Drevets, Guang Chen

Janssen Research and Development, San Diego, California

Background: Monoamine depletion is known to induce depression symptoms in remitted patients with a history of major depressive disorder (MDD) as well as in subjects with a family history of MDD and/or genetic polymorphisms implicated in the risk of developing mood disorders. As potential translational models for these effects, preclinical studies showed pretreatment with either alpha-methyl-para-tyrosine (AMPT; an enzyme inhibitor of the synthesis of catecholamines including dopamine and norepinephrine) or para-chloro-phenylalanine (PCPA; an inhibitor of the synthesis of serotonin) block effects of selective serotonin -reuptake inhibitors and selective norepinephrine -reuptake inhibitors in immobility tests, although the pretreatment alone does not alter the immobility. In the current studies, we examined whether depletion of brain monoamines (using AMPT or PCPA) in a stress-sensitive rat strain would result in anhedonia or despair-like behaviors. We also evaluated whether ketamine and scopolamine can produce antidepressant-like effects following monoamine depletion and compared their effects following inescapable foot shock since uncontrollable stress is also effective in the induction of depression-like behavior in preclinical models.
Methods: The stress-sensitive rat strain, Wistar Kyoto, was used in these studies. AMTP (3 injections of 100 mg/kg, i.p. ~12 hours apart) and PCPA (3 daily injections of 300 mg/kg, i.p.) were used to induce depletions of catecholamines and serotonin, respectively. We monitored anhedonia-like deficits using either the female urine sniffing test (FUST; male rats are exposed for 3 min to 2 cotton swabs dipped in either female rat urine or water and total time spent sniffing each swab is recorded) or sucrose preference test (SPT; overnight rats are provided 2 bottles to drink from, one containing 1% sucrose and the other water, and the weight change and preference for consuming sucrose-containing water is recorded). The active avoidance test (AAT; involving presentation of escapable mild foot shocks) was employed to monitor behavioral despair. Subsets of animals also received treatment with ketamine (10 or 20 mg/kg, i.p.)

or scopolamine (0.5 or 1.5 mg/kg, i.p) to evaluate potential rapid antidepressant-like activity in the AAT in these models. Blood and brain samples were collected for neurochemical analyses for levels of monoamines. For comparison, we also show effects of scopolamine and ketamine in AAT following learned helplessness induction using 120 presentations of inescapable foot shocks (1.0 mA).
Results: As expected, AMTP induced significant reductions in brain levels of dopamine ($p<0.001$) and norepinephrine ($p<0.01$) and PCPA induced a significant reduction in brain serotonin levels ($p<0.001$). Surprisingly, AMPT induced a significant increase in brain levels of epinephrine ($p<0.001$). Both monoamine depletion paradigms induced significant anhedonia-like behavior in FUST ($p<0.001$) and AMPT treatment also induced significant anhedonia as measured by SPT ($p<0.001$; PCPA not tested). Likewise, AMPT ($p<0.01$) and PCPA ($p<0.001$) both caused significant increases in latency to escape in the AAT. Scopolamine (1.5 mg/kg) produced a robust, rapid and significant antidepressant like effect (decrease in latency, $p<0.001$ and decrease in failures $p<0.001$) in AAT with both AMPT- and PCPA- pretreatment. Scopolamine at the lower dose (0.5 mg/kg) also produced significant reduction in AAT latencies following AMPT ($p<0.001$; PCPA not tested). By contrast, ketamine (20 mg/kg) produced a significant reduction in AAT latencies ($p<0.001$) and failures ($p<0.001$) with PCPA-pretreatment but at 10 mg/kg had no effect following AMPT-treatment (20 mg/kg not yet tested following AMPT). Consistent with monoamine depletion, 20 mg/kg ketamine failed to alter AAT latencies or failures following inescapable foot shock, while 0.5 and 1.5 mg/kg, i.p. scopolamine significantly reduced AAT latencies and failures.
Conclusions: Monoamine depletion in a stress-sensitive rat strain, similar to the depression-related effects in humans with a history of MDD, caused multiple behavioral deficits related to depression, including one or two measures of anhedonia and one of behavioral despair. Ketamine and scopolamine produce rapid antidepressant effects clinically. In these preclinical models, scopolamine dramatically improved despair-like behavior following both catecholamine depletion and serotonin depletion, as well as following inescapable foot shock; however, ketamine improved this behavior only following serotonin depletion. Interestingly, it has been previously reported that inescapable foot shock can itself deplete brain levels of catecholamines. Evaluations of scopolamine and ketamine in FUST, SPT and other measures of anhedonia are in progress. Together, these data suggest that monoamine depletion in a stress-sensitive strain of rat is a suitable reverse translational paradigm for exploring the underlying neurobiology of depression and for evaluating potential anti-depressant agents working through novel mechanisms which do not depend on monoamine systems for their primary actions. In addition, they support the hypothesis that the anti-depressant effects of ketamine may depend upon sufficient levels of brain catecholamines.
Keywords: Depression, Monoamine Depletion, Anti-depressant, Ketamine.
Disclosure: Primary Employer is Janssen Research & Development, L.L.C.

M47. Chronic Stress Exposure During Early Withdrawal from Extended Access Cocaine Self-administration Facilitates Incubation of Cue-induced Cocaine Craving

Jessica Loweth*, Ryan M. Glynn, J. Amiel Rosenkranz, Marina E. Wolf

Rosalind Franklin University of Medicine and Science, North Chicago, Illinois

Background: A major challenge for treating cocaine addiction is the propensity for abstinent users to relapse. Two important triggers for relapse are cues associated with prior drug use and stressful life events. Human studies indicate that exposure to chronic adverse life events is associated with increased relapse vulnerability, indicating a need for animal models that explore interactions between chronic stress and drug withdrawal. However, the majority of studies investigating stress-induced relapse vulnerability have examined the effects of acute stressors on the reinstatement of previously extinguished drug seeking behavior, a model which may not accurately depict the situation of addicts, who typically do not undergo extinction training and who may relapse after a long drug-free period. To study the effect of chronic stress on withdrawal-dependent changes in relapse vulnerability, we will use the incubation model of craving and relapse in which cue-induced drug seeking progressively intensifies (''incubates'') during withdrawal from extended-access cocaine self-administration.
Methods: Food restriction was used as a mild chronic stressor. Rats self-administered cocaine under extended-access conditions (6 h/d for 10 d) that have been shown to produce incubation of craving. On the day after the last cocaine self-administration session [withdrawal day (WD) 1], rats received a 30-min test for cue-induced cocaine seeking, during which nose-pokes resulted in presentation of the light cue but not cocaine. Rats were then divided into two equivalent groups destined for either control or food restricted conditions. On WD2, the food restricted group began a two week period of mild, chronic food restriction stress in which rats were fed daily so as to maintain their body weight at 90% of their baseline weight for 14 days, with water available at all times. Control rats had ad libitum access to food and water, but were handled in an identical manner to food restricted rats. On WD15 (when food restriction was still in place), rats underwent a second cue-induced seeking test (30 min).
Results: As expected, we found that controls showed greater cue-induced cocaine seeking on WD15 compared to WD1 (i.e., incubation of cocaine craving). Interestingly, food restricted rats showed a more robust increase in seeking on WD15, indicating acceleration or facilitation of incubation. Results in a different set of rats showed that the enhanced cocaine seeking observed in the food restricted rats was due to chronic and not acute stress, as 24 h food deprivation did not alter cocaine seeking behavior. These results are consistent with recent work from the Shalev laboratory showing that 2 weeks but not 3 days of food restriction enhanced cue-induced heroin seeking (D'Cunha et al., 2013; Sedki et al., 2013).
Conclusions: Together, these data indicate that chronic food restriction stress during early withdrawal facilitates incuba-

tion of cue-induced cocaine craving, which is thought to contribute to enhanced relapse vulnerability. Studies are currently underway to determine if this effect of chronic food restriction generalizes to repeated restraint stress and to determine the duration of the effect. In this way, we can compare the effects of a chronic stressful "state" (food deprivation) to repeated episodes of acute stress (restraint stress). Furthermore, by conducting time-course studies, we can determine whether it is the actual deprived, stressed "state" or the history of stress that leads to enhanced cocaine seeking. These studies will lay the groundwork for future studies which will assess the synergistic effects of cocaine and chronic stress exposure during withdrawal on cellular and behavioral measures and, using a stress resilience model, indentify neuroadaptations that can reverse such effects. Together, these studies will ultimately bring us closer to developing effective pharmacotherapies to reduce craving and prevent relapse in abstinent cocaine addicts.
Keywords: self-administration, cocaine seeking, incubation, chronic food restriction stress.
Disclosure: Nothing to Disclose.

M48. High Trait Impulsivity Predicts Food Addiction-like Behavior in the Rat

Clara Velazquez-Sanchez, Antonio Ferragud, Catherine F. Moore, Barry J. Everitt, Valentina Sabino, Pietro Cottone*

Boston University School of Medicine, Cambridge, Massachusetts

Background: Impulsivity is a behavioral trait frequently seen not only in drug-addicted individuals but also in individuals who pathologically overeat. However, whether impulsivity predates the development of uncontrollable feeding is unknown. In this study, we hypothesized that a high impulsivity trait precedes and confers vulnerability for food addiction-like behavior.
Methods: For this purpose, we trained ad libitum-fed male Wistar rats in a differential reinforcement of low rates of responding (DRL) task to select Low- and High-impulsive rats. Then, we allowed Low- and High-impulsive rats to self-administer a highly palatable diet (Palatable group) or a regular chow diet (Chow group) in 1-h daily sessions, under fixed ratio (FR) 1, FR3, FR5, and under a progressive ratio (PR) schedules of reinforcement. In addition, we tested the compulsiveness for food in Low- and High-impulsive rats by measuring the food eaten in the aversive, open compartment of a light/dark conflict test. Finally, we measured the expression of the transcription factor ΔFosB in the shell and the core of the nucleus accumbens, which is a marker for neuroadaptive changes following addictive drug exposure.
Results: The data we obtained demonstrate that impulsivity is a trait that predicts the development of food addiction-like behaviors, including: (i) excessive intake, (ii) heightened motivation for food, and (iii) compulsive-like eating, when rats are given access to highly palatable food. In addition, we show that the food addiction phenotype in high impulsive subjects is characterized by an increased expression of the transcription factor ΔFosB in the nucleus accumbens shell.
Conclusions: These results reveal that impulsivity confers an increased propensity to develop uncontrollable overeating of palatable food.
Keywords: Binge eating, Compulsivity, Eating disorders, Addiction.
Disclosure: Nothing to Disclose.

M49. Effects of Maternal Immune Activation upon Intracranial Self-stimulation and Amphetamine Self-administration

Neil Richtand*, Boris I. Chobrutskiy, D. Clay Archer, Rebecca Ahlbrand, Gerhard Schulteis

San Diego VA Healthcare System, San Diego, California

Background: Maternal immune activation (MIA) represents an animal model providing opportunities to identify altered neurodevelopment in offspring following maternal exposure to viral or bacterial infection. Previous studies have demonstrated behavioral and cognitive abnormalities of relevance to both drug dependence and schizophrenia in adult MIA offspring. For example, amphetamine-induced reinstatement of conditioned place preference for drug-paired chamber was enhanced in adult MIA offspring, suggesting long-standing effects of MIA upon drug-associated learning and memory. More direct measures of drug effects upon brain reward function are provided by determination of intracranial self-stimulation (ICSS) thresholds, and by drug self-administration studies. We hypothesized ICSS thresholds and amphetamine (AMPH) self-administration would be altered in adult MIA offspring. In order to test these hypotheses, we measured AMPH self-administration in adult MIA and control offspring. We also determined ICSS thresholds under baseline conditions and following acute and repetitive experimenter-administered AMPH injections.
Methods: Pregnant Sprague Dawley rats were injected with polyinosinic:polycytidylic acid (poly I:C), lipopolysaccharide (LPS) or vehicle on gestational day 14. Litters were culled to 8 offspring on postnatal day 1, weaned on postnatal day 21, and housed 2 - 3 rats per cage. For self-administration studies, adult male control and MIA offspring were surgically implanted with an indwelling catheter into the right jugular vein and trained to self-administer AMPH beginning 7 days after surgery. Rats were trained to self-administer AMPH in 2-hr sessions using a fixed ratio-1 (FR1) schedule with a 20 sec time out period after the AMPH injection was completed. After stable self-administration was demonstrated, extinction of active lever pressing was achieved through sessions on the FR1 reinforcement schedule with a 20-sec signaled time out schedule, with rats receiving saline infusions in response to active lever presses. Extinction training was continued until rats exhibited 3 consecutive sessions with active lever presses reduced below 10% of presses on the first day of extinction training. Drug-induced reinstatement was then tested by comparison of performance on two consecutive 2-hr FR1 reinforcement sessions, with saline infusion upon active lever pressing. Rats received saline injection (1ml/kg

s.c.) immediately preceding the first session, and AMPH injection (0.3 mg/kg) immediately preceding the second session. Reinstatement was defined as the difference in active lever presses between the first (saline) and second (AMPH) sessions. Following a second round of extinction training, drug-induced reinstatement was again examined following a (1 mg/ kg, s.c.) AMPH injection. For ICSS studies, male offspring were implanted with stainless steel bipolar electrodes (Plastics One® Inc) into the lateral hypothalamus at 9 weeks of age. ICSS was performed according to a modified procedure of the Kornetsky and Esposito discrete-trial current-threshold procedure (Kornetsky and Esposito 1979). Offspring from dams exposed to vehicle, poly I:C, or LPS were tested for reward thresholds for 4 days using intracranial self-stimulation under baseline conditions, and for 4 days following both acute and repetitive experimenter-administered AMPH injections.

Results: Amphetamine-induced reinstatement of drug self-administration was enhanced in MIA compared to control offspring. Active lever pressing in response to saline injection was elevated more than two-fold in MIA compared to control offspring at both AMPH reinstatement doses tested (0.3 and 1.0 mg/kg). ICSS reward thresholds were also measured in MIA and control offspring beginning on postnatal day 70, one week after recovery from ICSS surgery. Thresholds were determined at baseline, and following both acute (0.125, 0.25, 0.50 mg/kg) and repetitive (4 mg/kg) subcutaneous AMPH injections. Preliminary findings suggest that the AMPH dose-effect curve for facilitation of brain reward thresholds may also be shifted in MIA compared to control offspring. Additional data collection will be required to confirm this preliminary observation.

Conclusions: Measurement of ICSS thresholds and drug self-administration provide sensitive methods to identify alterations in reward function following maternal immune activation. Elucidating mechanisms underlying MIA-induced alterations in reward function may identify new avenues for prevention, treatment, and understanding of prognosis in human drug dependence.

Keywords: Amphetamine, Maternal immune activation, Poly IC, Schizophrenia.

Disclosure: Neil M Richtand declares the following potential conflicts of interest: a.) Speakers bureaus: Otsuka Pharmaceutica; Sunovion consultant: Otsuka Pharmaceutica b.) Financial relationships with value greater than $10,000 per year: Speakers bureaus: Otsuka Pharmaceutica; Sunovion c.) Financial relationships constituting more than 5% of personal income: Speakers bureaus: Otsuka Pharmaceutica d.) Grants from pharmaceuticals/biotechnology companies: none.

M50. Dephosphorylated HDAC5 Reduces the Motivation to Take and Seek Cocaine

Maria Carreira, Makoto Taniguchi, Daniel Guzman, Erin Larson, David Self, Christopher Cowan*

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: The transition to cocaine abuse and the development of an addictive pattern of behavior is mediated by changes in nervous system structure and function, which likely include chromatin remodeling and epigenetic mechanisms. Recently, we reported that non-contingent cocaine administration induces transient dephosphorylation and nuclear accumulation of the class IIa histone deacetylase, HDAC5, and virus-mediated expression of the dephosphorylated mutant of HDAC5 in the nucleus accumbens (NAc) reduced cocaine reward behavior in the conditioned place preference assay (Taniguchi et al., 2012, Neuron). As such, we sought to explore the role of the dephosphorylated, nuclear HDAC5 in addiction-related behaviors measured in the rat cocaine intravenous self-administration (IVSA) model.

Methods: Using AAV2 viruses, we expressed wild-type or dephosphorylated mutant (3SA) HDAC5 or GFP alone (vector control) in the medial NAc of adult rats and assessed various cocaine taking and seeking behaviors in the IVSA assay.

Results: Expression of HDAC5 3SA mutant (nuclear localized), but not wild-type HDAC5 or GFP control, attenuated significantly the motivation to self-administer cocaine (progressive ratio). HDAC5 3SA also reduced both the context- and prime-induced reinstatement of cocaine seeking, without affecting cue- or shock-mediated reinstatement. Interestingly, neither HDAC5 3SA nor HDAC5 wild-type overexpression altered stable drug intake (FR1 or FR5) or sensitivity to cocaine (dose-response) in dependent rats.

Conclusions: Taken together, our findings indicate that, unlike wild-type HDAC5, the nuclear-accumulated HDAC5 3SA mutant reduces several cocaine-related behaviors, including conditioned place preference (reward learning & memory), progressive ratio (motivation), and reinstatement of drug seeking after withdrawal. It is interesting to note that HDAC5 3SA did not affect stable cocaine intake, suggesting that it does not play a role in the development of drug self-administration, nor did it alter the dose-response curve, suggesting that HDAC5 3SA does not reduce cocaine behaviors by reducing pharmacological sensitivity to cocaine. However, our findings indicate that HDAC5 3SA reduces the animal's motivation to work for cocaine and to seek cocaine after withdrawal, possibly as a result of a reduced motivational state.

Keywords: epigenetics, HDAC, cocaine, self-administration.

Disclosure: Nothing to Disclose.

M51. Adolescent Alcohol Exposure Alters Adult Frontal Cortical Responses to Ethanol and Stress

Fulton Crews*, Thomas J. Walter, Ryan Vetreno, Wen Liu

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Background: Developing brain is uniquely sensitive to alcohol pathology and binge drinking is common in adolescence increasing risks of disrupting frontal cortical maturation. Stress response neurocircuitry and habituation to stressors involve frontal cortex. To investigate the impact of adolescent binge drinking on adult frontal cortex, neuronal activation was assessed using immediate early gene markers (cFos, Egr1) in multiple brain regions of adult rats challenged with ethanol or restraint stress. Since brain regional cFos is independent of alterations in cortisol, correlations of responses across brain

regions provide insight into adaptations in frontal cortical neurocircuits. Microglia was also assessed since adolescent alcohol exposure has been found to increase neuroimmune signaling.

Methods: Male Wistar rats were treated with an adolescent intermittent ethanol (AIE) model (5 g/kg, i.g., 2 days on-2 off, PND25-55, 16 doses-30 days). Following a 25 day abstinence period and maturation to young adulthood (P80-100), ethanol (2 and 4 gm/kg, i.g.) or restraint stress challenge (wire restraint and submersion in water) were performed, and animals sacrificed after 2 hrs for brain sectioning and immunohistochemistry (IHC) for cFos and Egr1, markers of neuronal activation. Markers of microglia and neuronal subtype markers were also assessed in multiple brain regions.

Results: Ethanol challenge (2 or 4 g/kg) in young adults increased cFos expression in multiple brain regions. Orbital frontal cortex cFos responses correlated with blood ethanol concentrations (74 and 135 mg/dl for 2 and 4 g/kg, i.g. doses respectively). Adult prefrontal cortical subregion responses to ethanol correlated with brain regions having known connections during the moderate ethanol dose challenge (i.e.., 2 g/kg), whereas only VTA and NAc had correlated cFos responses with the binge drinking challenge (i.e., 4 g/kg). Following AIE treatment, adult PFC cFos responses were markedly reduced in all regions. In medial PFC (PrL), cFos responses in Tbr1 + pyramidal projection neurons was lost as was the Egr1 response to ethanol consistent with AIE disconnecting PFC from ethanol responses. Interestingly, NAc cFos responses were enhanced by AIE. Microglia did not express cFos, but in neuronal NAc cFos responses correlated with microglial association. Restraint stress increased cFos in multiple brain regions that correlated with brain regions having known connections. Interestingly, CD11b, complement receptor 3, a MHC microglial marker, was increased in multiple brain regions that correlated with brain regions having known neuronal connections. AIE did not markedly alter PFC or other brain region responses to stress, with the exception of the PVN and BNST, AIE also altered microglia CD11b responses to restraint stress.

Conclusions: These studies are consistent with AIE altering both neurons and microglia in adult brain. Loss of PFC responses to ethanol in adult rat brain may represent habituation to repeated ethanol exposure in adolescence that persists to adulthood. Repeated stress leads to habituation to the stressor that is specific. We found AIE blunted of PFC responses to ethanol, but not restraint stress. Microglia also respond to both ethanol and restraint stress consistent with microglia contributing to stress response neurocircuitry.

Keywords: Adolescent, frontal cortical, stress, alcohol exposure.

Disclosure: Nothing to Disclose.

M52. HIV-1 Transgenic Rats: Self-administration of Sucrose and Cocaine Reveals Selective Dopamine-dependent Motivational Deficits

Rose Marie Booze*

University of South Carolina, Columbia, South Carolina

Background: HIV-associated neurocognitive disorders (HAND) is associated with addiction to illicit drugs, and cocaine is one of the most used illicit drug in the HIV population. To date, there are no studies investigating chronic HIV-1 exposure on cocaine self-administration. The present study used the HIV-1 transgenic (Tg) rat. The HIV-1 Tg rat expresses seven of the nine HIV-1 genes, and produces low, chronic exposure to HIV-1 viral proteins, including neurotoxic Tat and gp120. The HIV-1 transgenic rat is a model for chronic exposure to low levels of HIV-1 proteins in the brain, which also occurs in humans with combination antiretroviral therapy. In previous research from our laboratory we report that the HIV-1 Tg animals exhibit behavioral abnormalities that are consistent with DA dysfunction (Moran et al., 2013) and HAND (Moran et al., 2014). Here, we investigated goal-directed behavior, using operant conditioning methods with IV cocaine or sucrose as reinforcement. We tested the hypotheses that the effect of the transgene is to attenuate motivation, i.e., cocaine- and sucrose-maintained responding. We also explored the potential dopaminergic mechanisms by assessing [3H] dopamine uptake in the prefrontal cortex and striatum of HIV-1 rats.

Methods: Adult female, ovariectomized, HIV-1 Tg ($n = 14$) and control (F344; $n = 15$) rats were trained to respond on one of two active levers for sucrose (5% w/v; inactive lever responses were also recorded). First, rats were assessed for alterations in sucrose taste preference. Then, rats were trained using a fixed-ratio (FR1) schedule of reinforcement using a 5% (w/v) sucrose solution while water restricted. The animals were trained to respond for sucrose to both of two active levers with programmed control for position bias (+ /- 5 consecutive responses on either lever); a back wall lever had no programmed consequences. Following response stabilization daily water restriction was ended; a FR1 schedule of reinforcement was used to determine response rates for different concentrations of sucrose solutions (1%, 3%, 5%, 10%, and 30%) and water. In order to more directly quantify the difference in motivated behavior, a progressive-ratio (PR) schedule of reinforcement was employed using EC50 sucrose concentrations. Two active levers were again available for sucrose, potential position bias was monitored but not controlled. Next, for the cocaine SA experiments, HIV-1 Tg and F344 rats were given access to cocaine in three phases across 31 consecutive days. Rats responded for 0.33 mg/kg/inj, according to a FR 1 schedule for 5 days; 1.0 mg/kg/inj, on a PR schedule for 14 days; and in phase 3, responding for five doses of cocaine (0.01, 0.03, 0.1, 0.33, 1.0 mg/kg/inj) was assessed using the PR schedule for 12 days, with FR 1 (0.33 mg/kg/inj) maintenance days interspersed between PR test sessions. Infusions, break point and active (inactive lever responses) were the dependent measures. Rats were then simultaneously presented with sucrose and cocaine rewards and the choice preference was determined. Finally, synaptosomal [3H]dopamine uptake in rat prefrontal cortex (PFC) and striatum was examined 24 hours after the final self-administration experiment.

Results: Sucrose: There was a significant main effect of genotype; HIV-1 Tg rats responded less than controls in all conditions ($p < .001$). The HIV-1 Tg rat displayed a downward shift ($p < .001$) in the dose-response curve of earned reinforcers in the FR1 task. Similarly, with the PR dose-response curve for active lever presses the HIV-1Tg rats

displayed a downward shift ($p < .001$) compared to control F344 rats. However, there was no significant change in the EC50 as a function of genotype in either the FR1 or PR task. Cocaine: The HIV-1 Tg rats self-administered fewer cocaine infusions relative to F344 rats in each phase of the experiment. Phase 1: F344 rats earned more infusions than HIV-1 Tg rats on the FR1 schedule ($F1,13 = 4.8, p < .05$). Phase 2, the F344 rats received more cocaine infusions than HIV-1 rats across all 14 days on PR ($F1, 13 = 42.3, p < .001$), and earned infusions increased over 14 days ($F1,13 = 5.6 p < .05$; cubic). Phase 3, the PR DRC tests, animals earned more infusions as the dose increased ($F1, 13 = 4.5, p = .05$), and F344 rats earned more infusions than HIV-1 Tg rats, regardless of dose, on each assessment ($F1, 13 = 6.4, p < .05$). Choice: Self-administration trained rats, with a history of both sucrose and cocaine rewards, initially abstained from a return to drug use in favor of sucrose reward. With continued opportunity, a shift occurred to cocaine taking and away from the non-drug sucrose option. Dopamine: The Vmax of [3H]DA uptake was increased in striatum of HIV-1 Tg rats, as compared to F344. Total DAT was not different between HIV-1 Tg and F344 rats but the cell surface DAT expression was increased in striatum of HIV-1 Tg rats. HIV-1 Tg rats showed increased Bmax of [3H]WIN 35,428 binding along with the increased Vmax, which revealed an increase in DA uptake turnover rate (Vmax/Bmax). Results from sucrose self-administration showed that an increase (41%) in Vmax values was observed in striatum but not in PFC of HIV-1Tg rats relative to F344 rats. In contrast, Vmax values were not altered in striatum but decreased by 70% in the PFC of cocaine self-administering HIV-1 Tg rats.

Conclusions: Chronic exposure to HIV-1 viral proteins is associated with a profound motivational deficit in goal-directed behavior for cocaine. The results with sucrose, a natural reward, were far less compelling. HIV-1Tg rats exhibited neuroadaptive changes in striatal DAT function under basal condition by increased DA uptake turnover rate and cell surface DAT expression, which may help to compensate for their damaged DAT function by HIV-1 viral proteins, but failed to compensate when challenged with cocaine. These results may be analogous to individuals with HAND and comorbid disruptions in the mood-motivation facet of depression. Modeling the deficits in motivated behavior in HAND, as previously established for the primary neurocognitive impairments in HAND (Moran et al.,2012a, 2012b, 2013), provides a strong foundation to develop efficacious pharmacotherapeutic interventions.

Keywords: cocaine, dopamine uptake, HIV-1, HAND.

Disclosure: Nothing to Disclose.

M53. Role of 5-HT and KYN Autoantibodies after Social Isolation and LPS Treatment in Female C57BL/6J Mice

Cristina Sánchez*, Cynthia M. Kuhn, Florian D. Zepf

RWTH Aachen University, Aachen, Germany

Background: Autoantibodies against specific neurotransmitters have been suggested to play a crucial role in the underlying pathophysiology of some psychiatric disorders. Depression-related symptoms in rodents can be caused through several mechanisms and there are many studies showing imbalances in the metabolism of serotonin (5-HT), such as a lowered availability of the precursor amino acid tryptophan in animal models. Autoimmune activity against neurotransmitters might interfere with neurotransmission, and a decrease in 5-HT caused by autoimmune reactions against it could contribute to developing depression-related symptoms. We have previously demonstrated that female C57BL/6J mice respond to prolonged social isolation and lipopolysaccharide (LPS) treatment with depression-like behaviors after a forced swim test (FST). Furthermore, it has been suggested that autoimmune function plays a significant role in the development of depressive symptoms. The purpose of the present study was to analyze the additive effects of LPS and social isolation on the detection of 5-HT and kynurenine (KYN) autoantibodies in female mice.

Methods: A single intra-peritoneal injection of bacterial endotoxin (LPS, 0.83 mg/kg dose) or a vehicle (saline) was administrated to adult female C57BL/6 mice from Jackson Laboratories. The animals were immediately housed individually (single housing) or in groups of 5 mice/cage (grouped housing) for 45 days. After this period, depression-like behaviors were assessed with FST and three categories of behavioral activity were scored (latency, swimming and immobility). In order to evaluate the generation of autoantibodies against 5-HT and KYN, blood samples were collected by cardiac puncture and subsequently an ELISA test for autoantibody detection was performed. The effects of treatment and housing were analyzed by a repeated-measures ANOVA followed by F-Fisher post-hoc test.

Results: The present results showed a main effect of housing in terms of isolation in female mice. A single injection of LPS did not show any significant changes on autoantibody detection when compared with saline-treated mice. In contrast, social isolation was associated with an increase as regards the detection of 5-HT-related autoantibodies. When the data of both, LPS and saline-treated mice, were added together, social environment had a significant effect on 5-HT autoantibody detection, but no comparable effects were found after isolation or LPS challenge as regards KYN autoantibodies.

Conclusions: Changes in social environment and an inflammatory challenge as indexed by LPS administration were associated with changes in 5-HT and KYN autoantibody detection in female mice. If the findings of the present study could be replicated, detection of these particular autoantibodies could possibly become a further valuable tool to study the underlying pathophysiology of mood disorders, suggesting that further investigation of manipulations such as social isolation and LPS challenge could be useful strategies for such translational research.

Keywords: serotonin, kynurenine, autoimmunity, mouse.

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M54. Activation of Prefrontal Cortical Parvalbumin Interneurons During the Presentation of Reward-predictive Cues Facilitates Extinction

Dennis Sparta*, Dennis Sparta, Nanna Hovelsø, Alex Mason, Pranish Kantak, Randall Ung, Heather Decot, Garret Stuber

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Background: Forming and breaking associations between emotionally salient environmental stimuli and rewarding or aversive outcomes is an essential component of learned adaptive behavior. Importantly, when cue-reward contingencies degrade animals must exhibit behavioral flexibility to extinguish prior learned associations. Understanding the specific neural circuit mechanisms that operate during the formation and extinction of conditioned behaviors is critical as the dysregulation of these neural processes may lead to maladaptive or pathological behavior, implicated in various neuropsychiatric disorders in humans. The medial prefrontal cortex (mPFC) participates in the behavioral adaptations seen in both appetitive and aversive cue-mediated responding, but the precise cell types and circuit mechanisms sufficient for driving these complex behavioral states remain largely unspecified. Here we applied optogenetic manipulations in combination with electrophysiology and freely moving behavioral tasks to investigate the effect of PV + FSI mediated inhibition within the mPFC on the processing of emotionally salient cues that motivate responding for natural rewards. Specifically, we targeted FSIs in the prelimbic mPFC with ChR2 using genetic and viral strategies to enable selective optical control of these neurons. We explored how selective inhibition of mPFC network activity mediated by optogenetic stimulation of PV + FSIs timelocked to salient reward-predictive cue presentation altered cue-mediated behavioral responding and extinction.

Methods: To examine mPFC postsynaptic currents, Parv-ires-cre mice were injected with AAV5-DIO-ChR2-eYFP to target mPFC parvalbumin interneurons and brain slices were taken for patch-clamp electrophysiology. Photostimulation (5 ms pulses of 1-2 mW, 473 nm light delivery via LED through a 40x microscope objective) was used to stimulate PV + FSI cell bodies and terminals within the mPFC. In a separate cohort of mice, Parv-ires-cre mice were injected with either a cre-inducble ChR2-eYFP or eYFP and began training on a modified Pavlovian conditioning paradigm, in which a cue light and tone conditioned stimulus (CS) presentation (5 s) preceded and terminated with the delivery of 20 μL of a 15% sucrose solution. All training sessions comprised 60 CS presentations that were delivered in a randomized 60-120 s inter-trial interval. All mice were trained for 20-30 sessions to criterion (high anticipatory and reward licking that remained stable (< 10% variation) across three sessions) before extinction testing began. Once stable responding was achieved, all mice underwent an extinction session. The extinction session comprised 200 CS presentations separated by an inter-trial interval of 60-120 s. Throughout the extinction experiment, optical stimulations to selectively activate mPFC PV + FSIs were delivered timelocked to the 5 s CS and sucrose delivery was omitted following all CS presentations. In a separate cohort of animals, ParvmPFC::ChR2 and ParvmPFC::eYFP mice underwent the same Pavlovian conditioning sessions (approx. 20-35 sessions) as described above. Once animals reached stable cued reward licking behavior (> 10% variation for 3 consecutive days), all mice underwent an extinction session where they received 200 CS presentations without sucrose delivery. Additionally, mice received 5 s photostimulation of the mPFC timelocked to the CS presentations. On the subsequent day, all mice were run in the same extinction protocol (200 CS presentations without sucrose delivery). However, they did not receive any photostimulation of the ParvmPFC pathway.

Results: Whole cell recordings from mPFC pyramidal neurons revealed that photostimulation of ChR2-containing cell bodies and fibers originating from Parv-expressing mPFC neurons produced inhibitory postsynaptic currents and formed functional synapses on pyramidal neurons within the mPFC. We found that 73.3% (11/15) of pyramidal neurons in the Prl were light responsive compared to only 41.8% (5/12) of pyramidal neurons within the IL. Therefore these data suggest that PV FSIs preferentially target pyramidal neurons with the PrL of the mPFC. To test whether transient enhancement of mPFC PV + FSI activity could modulate the extinction of cue-reward behavior, we photostimulated ParvmPFC neurons timelocked to cue presentations in an extinction session and quantified licking behavior. We found that ParvmPFC::ChR2 mice extinguished reward-seeking behavior (licking) faster than the ParvmPFC::eYFP mice. When compared across the entire extinction session (200 CS presentations and concurrent optical stimulation without sucrose delivery) ParvmPFC::ChR2 mice displayed significantly less licking behavior than ParvmPFC::eYFP mice during the cue period. A subset of ParvmPFC::ChR2 and ParvmPFC::eYFP mice were run in a subsequent extinction session (200 CS presentations without sucrose delivery) to see if photostimulation of mPFC PV + FSIs on extinction day 1 could alter long term extinction. In this session, both groups did not receive photostimulation. When compared across the entire session (200 CS presentations without sucrose delivery), no difference was observed in licking behavior during the cue period between the ParvmPFC::ChR2 and ParvmPFC::eYFP groups. Taken together, these data suggest that circuit mediated inhibition of the mPFC through selective activation of PV + FSIs during cue processing can acutely facilitate the extinction of highly salient learned cue-reward associations.

Conclusions: Responding to environmental changes and inhibiting maladaptive actions are fundamental components of behavioral flexibility. The mPFC has been identified as a critical circuit node involved in modulating the expression and extinction of cue-mediated behaviors (Kalivas et al., 2006; Peters et al., 2009; Quirk and Mueller, 2008; Sotres-Bayon and Quirk, 2010; Van den Oever et al., 2010). Here, we utilized ChR2-assisted circuit mapping in

order to identify, record, and manipulate PV FSIs within the mPFC. Here we show that PV + FSIs preferentially target pyramidal neurons of the PrL. Additionally, we show that selective activation of PV + FSIs produces a transient global inhibition of mPFC network activity that can accelerate the extinction of a well-learned cue-reward association. Thus, activity of PV + FSIs, may act to facilitate the transition from a cue-driven to flexible behavioral state.
Keywords: optogenetics, electrophysiology, prefrontal cortex, extinction.
Disclosure: Nothing to Disclose.

M55. In Vivo MR Imaging Evidence for Variable CNS Responses to Repeated Binge Ethanol Treatment

Natalie Zahr*, Edith Sullivan, Adolf Pfefferbaum

Stanford University, Stanford, California

Background: Adaptive changes occur in the body in response to repeated exposure to drugs: tolerance is defined as a state of progressively decreased responsiveness, whereas sensitization is defined as increased responsiveness to repeated administration of the same dose of a drug. Although ethanol (EtOH) is known to induce pharmacokinetic tolerance, the effects of EtOH on in vivo, magnetic resonance (MR)-detectable brain measures across repeated exposures have not previously been reported. It was hypothesized that repeated exposure to EtOH would be associated with accumulated brain pathology as detected by MR imaging (MRI) tools.
Methods: The Institutional Animal Care and Use Committees at SRI International approved all procedures. Of 28 rats weighing 340.66 ± 21.93g at baseline, 15 were assigned to the EtOH group and 13 to the control (Ctrl) group. EtOH animals were exposed to 5 cycles of EtOH treatment via a 4-day intragastric binge protocol followed by 7 days of recovery; Ctrl animals received 5% dextrose in volumes equivalent to those given to EtOH animals. Rats in both groups had structural MRI scans and whole brain MR spectroscopy (MRS) at baseline, immediately following each binge period, and after each weeklong recovery period (total = 11 scan sessions).
Results: Average blood alcohol levels (BALs) across each of the five, 4-day binge periods were 286, 295, 288, 305, 316 mg/dL. Blood drawn at the end of the experiment did not show group differences for thiamine ($p = .52$) or its phosphate derivatives (monophosphate $p = .72$, diphosphate $p = .73$). Postmortem liver histopathology provided no evidence for hepatic steatosis, alcoholic hepatitis, or alcoholic cirrhosis. Cerebral spinal fluid (CSF) volumes and MRS metabolites were expressed as the percentage change at a binge scan from the previous recovery level. The resulting response pattern of structural MR imaging to alternating sessions of EtOH and no EtOH showed that volume of the lateral ventricles (19, 13, 17, 17, 11%) and posterior cisterns (38, 31, 30, 14, 23%) enlarged at each binge session followed by recovery during the week without EtOH. The expansion response diminished with repeated EtOH exposure indicating tolerance. By contrast, for MRS metabolites, N-acetyle aspartate (NAA)(-1, -5, -.1, -2, -.4%) and total creatine (tCr)(-5, -11, -3, -5, -4%), lowest levels were observed at the 2nd binge, but these metabolites also showed relatively reduced responses with repeated exposures. The MRS signal response from choline-containing compounds (Cho) appeared to persist in response to repeated EtOH exposure (10, 2, 12, 8, 8%), while that from glutamate (Glu) accumulated (5, 9, 13, 11, 13%). In EtOH rats only, the percentage change in Cho, but none of the other MRS markers (tCr, NAA, Glu), correlated with average BALs over the first 3 binge periods (binge 1: $r = .64$, $p = .0105$; binge 2: $r = .68$, $p = .0056$; binge 3: $r = .70$, $p = .0040$; binge 4: $r = .24$, $p = .3832$; binge 5: $r = .43$, $p = .1244$).
Conclusions: Although the changes in response to EtOH were in expected directions based on previous, single-binge exposure experiments, the current results do not provide support for accruing pathology with repeated binge EtOH exposure. Responses of the lateral ventricles and cistern (larger) and NAA and tCr (lower) appeared to diminish over time, indicating tolerance; the Cho response appeared to persist, and that of glutamate to accumulate, potentially indicating sensitization. Whether accumulation of glutamate with repeated EtOH exposure contributes to the pathology observed in chronic alcoholism requires further exploration.
Keywords: alcoholism, MR imaging, recovery, MR spectroscopy.
Disclosure: Nothing to Disclose.

M56. Transiently Increased Glutamate Cycling is Related to the Rapid Onset of Antidepressant-like Effects

Golam Chowdhury*, Monique Thomas, Mounira Banasr, Ronald Duman, Eric Schaeffer, Douglas Rothman, Kevin Behar, Gerard Sanacora

Yale University School of Medicine, New Haven, Connecticut

Background: Several drugs were recently shown to induce rapid antidepressant effects in clinical trials and rodent models. Although the cellular mechanisms underlying the response remain unclear, reports suggest that increased glutamate transmission mediates these effects. Using 1H-[13C]-nuclear magnetic resonance spectroscopy, we demonstrate that the antidepressant efficacy of three unique drugs with rapid antidepressant properties (ketamine, Ro-25, 6981, and scopolamine), is coupled with a rapid transient rise in synaptic glutamate release and cycling.
Methods: Male Sprague-Dawley rats (6-8 per group) were prepared with tail vein catheters. After 30mins recovery, animals were infused with varying doses of ketamine 1, 3, 10, 30, 80 mg/kg IP diluted in saline/vehicle; Ro25-6981, an NR2B selective agent, dissolved in vehicle (vehicle) at doses of 1, 3, and 10mg/kg IP. Effects were compared to unique control groups receiving IP infusions of saline or vehicle. To further examine the generalizability of the effects to other, non-NMDAR antagonist drugs with rapid acting antidepressant-like actions, we also examined the effects of Scopolamine 25μg/kg. All drugs were administered IP in volumes of 2 mL/kg with exception of the highest ketamine dose (80 mg/kg), which was 3 mL/kg. As determined by the Cmax and onset of observable behavioral changes for each compound, a solution of [1,6-13C2] glucose dissolved in

water (0.75 mol/L per 200 g body weight) was infused for 8 minutes through the catheter, ten minutes after injection of ketamine, seven minutes after injection of scopolamine, and thirty minutes after injection of Ro25-6981. The time course of ketamine's effects on cycling was examined by injecting rats with 30mg/kg ketamine at 0, 10, 30 and 60 mins prior to starting the 8min [1,6-13C2] glucose infusion. To examine the longer-term effect of ketamine administration on cycling, and to match the dosing previously shown to have significant effects on dendritic spine density at 24 hrs (Science 20;329:959-64, 2010. Biol Psychiatry.15;69(8):754-61, 2011), we chose to use the 10mg/kg dose of ketamine for these studies. Rats were quickly sedated and euthanized by focused-beam microwave irradiation. The medial prefrontal cortex (mPFC) was carefully dissected and frozen in liquid nitrogen, along with heart blood drawn immediately after death. The brain tissue was extracted in methanol/HCL and ethanol, centrifuged, and the supernatants lyophilized. Samples were dissolved in phosphate buffered deuterium oxide. The concentration and 13C enrichments of glutamate, GABA and glutamine were determined using 1H-[13C] NMR spectroscopy at 11.74 Tesla. Percentage 13C enrichments of brain amino acids were normalized by their respective blood 13C glucose enrichment (Biol Psychiatry 71(11):1022-5, 2012).

Results: Both NMDAR antagonist drugs increased labeling from 13C-glucose in rat medial prefrontal cortex (mPFC). Dose-response curves of magnitude change of glutamate-C4, GABA-C2, and glutamine-C4 13C enrichments over control follows an inverted U shape for i.p. ketamine at doses of 1, 3, 10, 30 and 80 mg/kg. Ro25-6981 led to a significant increase in magnitude change of glutamate-C4, GABA-C2, and glutamine-C4 13C enrichments over control in mPFC for 10 mg/kg but not for the lower (1 or 3 mg/kg) administered doses [$*p < 0.05$] when compared to vehicle-injected animal groups. Similarly, a single 25μg/kg i.p. dose of scopolamine, increased glutamate, GABA and glutamine 13C enrichments over control from 13C-glucose [$*p < 0.05$] when compared to the vehicle-injected animal group. Ketamine effects on cycling were present within the first 15mins but appeared to normalize over the first hour.

Conclusions: The present study provides the first experimental evidence that a transient glutamate surge is associated with the administration of 3 different drugs, from two distinct classes, that have demonstrated rapid antidepressant-like effects. The effect appears to be transient, as enrichment returned to normal over a period of one hour and was no different from controls at 24hrs after ketamine administration, the time when the behavioral effects are most commonly reported. The fact that the ketamine and Ro25-6981 response curves mirror previous reports of antidepressant-like efficacy suggests the rapid, transient increase in glutamate release could be a common (shared) mechanism initiating the rapid antidepressant response. 13C-Magnetic Resonance Spectroscopy can be relatively easily translated to human studies not only to further characterize the relationship between changes in amino acid neurotransmitter cycling and rapid acting antidepressant-like efficacy but may also help estimate optimal dosing for treatment response in clinical populations.

Keywords: NMDA receptor, glutamate/glutamine cycle, ketamine, magnetic resonance spectroscopy.

Disclosure: Golam Chowdhury: None. Monique Thomas: None. Mounira Banasr: None. Ronald Duman: None. Douglas Rothman: None. Eric Schaeffer: Bristol-Myers Squibb. Kevin Behar: None. Gerard Sanacora: Dr.Sanacora has received consulting fees form AstraZeneca, Avanier Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly & Co., Hoffman La-Roche, Merck, Naurex, Noven Pharmaceuticals*, and Takeda over the last 24 months. He has also received additional research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., Johnson & Johnson, Hoffman La-Roche, Merck & Co., Naurex and Servier over the last 24 months. Free medication was provided to Dr. Sanacora for an NIH sponsored study by Sanofi-Aventis. In addition he holds shares in BioHaven Pharmaceuticals Holding Company and is a co-inventor on a US patent (#8,778,979) held by Yale University. * Greater than $10,000.00 in income.

M57. CRF R1 and R2 Modulation of Accumbal Hyperdopaminergia Reduces Escalated Alcohol and Cocaine Self-administration as a Result of Episodic Social Stress

Klaus Miczek*, Elizabeth Holly, Lara Hwa, Xiao Han, Lucas Albrechet-Souza, Joseph DeBold

Tufts University, Medford, Massachusetts

Background: It has been challenging to capture the clinically documented link between stress and alcohol and drug abuse in reliable animal models in order to delineate the overlapping neurocircuitry of ostensibly aversive stress and intense pleasure. Previously we demonstrated how exposure to repeated intermittent episodes of social defeat stress induced persistent behavioral and neural cross-sensitization to cocaine and amphetamine, and escalated cocaine "binges." We now report a successful rodent model of intermittent social defeat stress that causes a very large, persistent increase in voluntary, preferential and motivated intake of 20% alcohol. We have begun to study the CRF receptor subtypes and binding protein in the VTA-NAcc-PFC and CeA-BNST pathways in order to define targets for reducing escalated cocaine and alcohol self-administration as a result of episodic social defeat stress in mice and rats.

Methods: We performed pharmacology studies for assessing behavioral sensitization, either oral or intravenous self-administration under various schedule and access conditions, intra-VTA and –CeA microinjections for CRF antagonist protection experiments, and in vivo microdialysis of dopamine in mice and rats that were exposed to four or ten episodes of intermittent social defeat stress as intruders in confrontations with an aggressive resident animal. Non-stressed animals served as contemporary controls.

Results: (1) We confirmed that intermittent social defeat stress in mice and in rats increased plasma corticosterone in response to the first and last confrontation, i.e. no habituation. (2) Socially defeated mice and rats showed evidence for persistent behavioral sensitization in response to an amphetamine (1.0 mg/kg) or cocaine (10 mg/kg)

challenge. However, the degree of the sensitized locomotor behavior was not predictive of subsequent oral alcohol or intravenous cocaine self-administration. (3) Socially defeated mice and rats showed an escalated dopamine rise in the NAcc that was systematically related to the severity of the earlier stress experiences. (4) We extended the earlier finding of escalated cocaine self-administration during a 24-h "binge" from rats to mice. (5) We identified the parameters of intermittent social defeat stress that resulted in subsequent escalated consumption of 20% w/v alcohol, with the maximal effect in outbred Swiss and inbred C57BL/6J mice after a moderate number of 30 attack bites per day in less than 5 min resulting in 15-30 g/kg/day intake, preferentially over concurrently available water. (6) Pretreatment with intra-VTA microinjections of the CRFR1 antagonist CP376395, CRFR2 antagonist astressin 2A or with the binding protein inhibitor CRF6-33 prior to each episode of social defeat stress prevented the escalated cocaine or alcohol self-administration.
Conclusions: Exposure to intermittent episodes of social defeat stress causes escalated alcohol and cocaine self-administration in mice and in rats. These effects depend on the species-typical parameters of the social defeat stress and persist for months. Social stress-induced sensitization of locomotor behavior can be dissociated from the escalation of alcohol and cocaine self-administration. Antagonism of extra-hypothalamic CRF R1 and R2 and binding protein, particularly in the VTA, implicate CRF as a crucial neuropeptide that is necessary for social defeat stress to escalate alcohol and cocaine self-administration. The precise mechanisms for CRF-DA interactions, possibly involving GABA interneurons, remain to be characterized.
Keywords: social stress, cocaine, alcohol, CRF.
Disclosure: Nothing to Disclose.

M58. Adolescent Ethanol Exposure Promotes Resilience and Susceptibility to Acute and Chronic Stress-induced Anhedonia, Respectively, in Adult Wistar Rats

Svetlana Semenova*, Nathalie Boutros, Andre Der-Avakian, Soon Lee, Athina Markou

University of California at San Diego, La Jolla, California

Background: Stress reactivity in adulthood may be altered by binge alcohol drinking during adolescence. While studies have shown that binge-like exposure to alcohol during adolescence alters the brain response to physiological stressors in adulthood, the behavioral and neural responses to psychosocial stressors in adulthood after adolescent ethanol exposure are unknown. This study investigated the effects of adolescent intermittent ethanol (AIE) exposure on social stress-induced reward deficits (anhedonia) in adulthood in male Wistar rats.
Methods: Adolescent (PND 28-53) rats received 5 g/kg of 25% (v/v) ethanol three times a day in a 2 days on/ 2 days off exposure pattern. Upon reaching adulthood (PND 60-80), rats were prepared with bipolar stimulating electrodes in the posterior lateral hypothalamus and trained to respond for electrical stimulation. A rate-independent current-intensity discrete-trial threshold procedure was used to assess brain reward function after exposure to social defeat stress. In this procedure, reward threshold elevations are interpreted as reward deficits. Acute social defeat consisted of a single brief confrontation between the experimental rat and an aggressive resident rat. Chronic social defeat involved continuous exposure of the experimental rat to a resident for 10 days. During this time, the experimental rat lived in a protective cage within the resident's home cage and was exposed to brief daily confrontations with the resident rat. Blood corticosterone levels were assessed after acute and chronic social stress.
Results: Chronic, but not acute, exposure to social defeat elevated reward thresholds in both water- and AIE-exposed rats compared to non-stressed control groups. Rats categorized as resilient or susceptible to stress-induced anhedonia had threshold elevations within or greater than 2 standard deviations above the 5-day average baseline threshold, respectively. After acute stress, fewer AIE-exposed rats exhibited threshold elevations compared to water-exposed stressed rats, indicating that AIE-exposed rats were resilient to a single social defeat. In contrast, after exposure to chronic social stress, more AIE-exposed rats exhibited threshold elevations compared to water-exposed rats, indicating that AIE-exposed rats became susceptible to stress-induced anhedonia. Corticosterone levels were increased after exposure to acute and chronic social defeat with no differences between AIE- and water-exposed rats. Across groups, blood corticosterone levels were positively correlated with reward thresholds.
Conclusions: Our results indicate that the magnitude of social stress-induced anhedonia was similar in AIE- and water-exposed rats. Interestingly however, resilience and susceptibility to acute and chronic social stress were differentially affected by AIE exposure. This pattern of results suggests that individuals exposed to ethanol binges during adolescence may have a blunted response to acute, short-term stressors. In contrast, the anhedonic response to chronic stress may be exaggerated in individuals exposed to ethanol binges during adolescence. Susceptibility to chronic stress may lead to the development of depression and alcohol use disorder in adulthood.
Keywords: reward deficit, intracranial self-stimulation, social defeat stress, corticosterone.
Disclosure: AM has received contract research support from Bristol-Myers Squibb, Forest Laboratories, and AstraZeneca and honoraria/consulting fees from AbbVie during the past 3 years. The remaining authors report no financial conflicts of interest.

M59. Viral-mediated Overexpression of miR-495 in the Nucleus Accumbens Shell Reduces Motivation for Cocaine

Ryan Bastle*, Nathan Pentkowski, Robert Oliver, Amy Gardiner, Colton Smith, Jennifer Taylor, Nicholas Galles, Nora Perrone-Bizzozero, Janet Neisewander

Arizona State University, Tempe, Arizona

Background: MicroRNAs (miRNAs) are considered "master regulators" of gene expression due to their ability to post-transcriptionally regulate several genes simultaneously. Dysregulation of miRNAs may be involved in the etiology

of neuropsychiatric disorders, such as drug addiction. We previously found through in silico analysis that miR-495 targets several addiction-related genes (ARGs; see the Knowledgebase of Addiction-Related Genes: http://karg.cbi.pku.edu.cn/) and is preferentially expressed in the striatum. Furthermore, acute cocaine administration (15 mg/kg, IP) downregulates miR-495 expression selectively in the nucleus accumbens (NAc). Using a lentiviral vector (LV-miR-495) to overexpress (OE) miR-495 in the NAc shell (NAcsh) of rats, we found that increasing miR-495 levels decreases the expression of several ARG targets (e.g., Bdnf-L, Camk2a, Arc) compared to LV-GFP controls, suggesting that these genes are regulated by miR-495 in vivo.
Methods: We tested the effects of miR-495 OE on cocaine self-administration (SA). Rats were initially trained to lever press for cocaine (0.75 mg/kg/0.1 mL, IV) on a fixed ratio (FR) 5 schedule of reinforcement. Once stable cocaine SA was achieved, we infused either LV-miR-495 or LV-GFP into the NAcsh. Testing began one week later, including cocaine SA dose-response tests (0, 0.03, 0.1, 0.3, 1.0 mg/kg; FR5) and tests on a progressive ratio (PR) schedule of reinforcement (0.375 & 0.75 mg/kg). Additional controls were tested for the effects of miR-495 OE on an FR and PR schedule of food reinforcement.
Results: While miR-495 OE failed to alter cocaine intake on the FR dose-response function, it did decrease intake on the PR schedule at the high cocaine dose and the slope of the dose-response curves differed across groups. In contrast, we found no group differences in food intake on an FR or PR schedule.
Conclusions: The present findings suggest that miR-495 OE specifically regulates genes in the NAcsh that underlie motivation for cocaine, but not food, reinforcement. Understanding the role of microRNAs in regulating addiction-related changes in gene expression may offer a novel approach to simultaneously normalize a number of genes that are dysregulated in cocaine addicts.
Keywords: Addiction, MicroRNA, Cocaine, Self-Administration.
Disclosure: Nothing to Disclose.

M60. Immune Mechanisms of Prenatal Stress and their Involvement in GABAergic Cell Development

Hanna Stevens*, Rebecca Fine, Samuel Murray

Yale University School of Medicine, New Haven, Connecticut

Background: Prenatal stress (PS) is a risk factor for neuropsychiatric illness, including those in children and adolescence. In animal models, prenatal stress results in persistent changes in behavior and neural functioning. The mechanisms by which stress during embryonic development can induce long-term effects may shed light on the pathophysiology of disorders for which prenatal stress is a risk factor including autism, ADHD, anxiety and schizophrenia. In particular, our lab has investigated mechanisms by which repeated restraint stress in pregnant mice influences the development of GABAergic cells in offspring. The maternal factors influencing the embryonic brain during stress are unclear. Some similarities have been shown between prenatal stress models and models of maternal immune activation. Here, we investigated immune mechanisms involved in prenatal stress.
Methods: We examined the developing brain of GAD67GFP + mice exposed to prenatal corticosterone, IL-6, IL-1beta, or PS with and without cytokine antibodies. We assessed the distribution of GAD67GFP + cells, expression levels of transcription factors involved in inhibitory neuron development, and the morphology of cells expressing Iba1, a marker for microglia, known to respond to cytokines.
Results: The distribution of GAD67GFP + inhibitory neuron progenitors was initially restricted by PS, corticosterone and cytokine exposure; however, this effect persisted only in PS and IL-6-exposed offspring, suggesting that migrational delays of these cells during PS involved IL-6 exposure. Corticosterone-exposed embryos showed a reduction in the number of actively dividing GABAergic progenitors in the ganglionic eminence at earlier time points than found in PS-exposed animals demonstrating potentially different developmental trajectories with corticosterone and PS. Additionally, expression levels of transcription factors and their targets which play a role in inhibitory neuron migration (dlx2, nkx2.1, and erbB4) were differentially affected by PS, cytokine and prenatal corticosterone exposure – some of those decreased in PS embryos were either unaffected or increased in cytokine and corticosterone-exposed animals. Measurements of Iba1 + cells in the embryonic brain following PS revealed a distinct mechanism by which the effects of prenatal stress may impact neuronal development. Compared to controls, PS exposure resulted in, first, a higher density of Iba1 + cells that appeared to be actively phagocytosing apoptotic cells. This was also found in IL-6 exposed embryonic brain. Prenatal stress then went on to increase total numbers and the proportion of ramified Iba1 + cells in the embryonic cortical plate. Blockade of IL-6 signaling by anti-IL6 antibody injection during prenatal stress and its effects on GABAergic and migroglial cell development is currently being investigated.
Conclusions: In sum, exposure to glucocorticoids did not replicate the effect of prenatal stress on GABAergic cells, but cytokine exposure showed very similar developmental trajectories in the development of these inhibitory neuron precursors and of microglia. Prenatal stress may exert developmental effects through inflammatory mediators including IL-6. This work demonstrates that inflammatory systems, including microglia and cytokines, which have an increasingly recognized role in the pathophysiology of neuropsychiatric disorders, may be involved in the mechanisms by which prenatal stress contributes to these illnesses.
Keywords: prenatal stress, microglia, mouse, GABAergic cells.
Disclosure: Research Fellowship from APIRE/Wyeth Pharmaceuticals.

M61. Impact of Excessive Non-normative Sensory Stimulation in Early Life on Vulnerability to the Effects of Cocaine

Shilpa Ravinder, Dimitri Christakis, Jan Marino Ramirez, Susan Ferguson*

University of Washington/Seattle Children's Research Institute, Seattle, Washington

Background: Psychiatric diseases, such as drug addiction and ADHD, are costly public health problems that have

profound consequences to the individual as well as society. Early life experiences, both positive and negative, exert long-lasting effects on neural function and behavior, and can therefore influence susceptibility to developing these diseases. In order to further characterize how negative early life experiences impact subsequent development, we have developed a rodent model of excessive non-normative sensory stimulation (ENS), which mimics excessive media use in infants and toddlers by exposing mice to passive audio and visual stimulation for six hours per day during their critical developmental window (i.e. P10-P52). We have found that this exposure impairs short-term memory and learning, as well as increases risk-taking and decreases anxiety relative to mice reared under standard laboratory conditions.
Methods: In the present study, we sought to better understand the relationship between negative early life experiences and vulnerability to behaviors associated with addiction by examining the effects of ENS on one form of drug-induced behavioral plasticity, locomotor sensitization.
Results: Interestingly, there did not appear to be differences between ENS mice and controls in the development of cocaine-induced locomotor sensitization, yet the saline-treated ENS-exposed mice were hyperactive relative to controls. When normalizing to this hyperactive baseline, ENS-exposed mice unexpectedly displayed blunted locomotor sensitization to cocaine. We are currently performing electrophysiology experiments to determine if these results can be attributed to ENS-induced alterations in nucleus accumbens medium spiny projection neurons. Nonetheless, because the differences in locomotor baselines hinder decisive conclusions, we are also conducting conditioned place preference experiments to assess whether ENS produces alterations in the rewarding effects of cocaine.
Conclusions: Our findings are interesting in the context of ADHD, as Ritalin treatment blunts hyperactive responses in patients but has the opposite effect in controls. In addition, this work has the potential to advance our understanding and raise awareness of the impact of increased access and usage of audio-visual media in infants and young children.
Keywords: cocaine, addiction, mouse models, ADHD.
Disclosure: Nothing to Disclose.

M62. Behavioral, Neural and Endocrine Mechanisms of the Mother-to-Infant Social Transmission of Fear

Jacek Debiec*, Regina Sullivan

University of Michigan, Ann Arbor, Michigan

Background: Parental fear and trauma may be transmitted to their offspring. Despite existing evidence of this transmission the neuroendocrine mechanisms underlying the social transfer of fear remain unknown. We have recently proposed a rat model of the mother-to-infant social transmission of fear (Debiec and Sullivan, PNAS 2014). In our model, infant rats exposed to their mother expressing fear in response to the previously conditioned olfactory conditioned stimulus, CS, acquire lasting aversive responses to this CS. We observed that an exposure to the maternal alarm odor alone paired with the neutral odor was sufficient to produce in pups fear responses to this odor. We found that this mother-to-infant transmission of fear is associated with increased activity of the infant's amygdala. Here, we explored the role of the amygdala and corticosterone (CORT) in the intergenerational transmission of fear.
Methods: Experiment 1: Pups with bilateral intra-lateral and basal amygdala (LBA) cannulae were infused either with a GABA A receptor agonist muscimol ($n = 5$) or saline ($n = 5$) prior to exposure to mother expressing fear in response to the CS odor. On the following day, pups were tested to the maternal CS using a Y-maze test in which a pup has to choose between the CS and a neutral odor. Experiment 2: Pups were exposed either to the odor of the frightened mother ($n = 12$) or the odor of the unfrightened mother ($n = 8$). Subsequently, pups' serum CORT levels were assessed using radioimmunoassay. Experiment 3: Pups received systemic injections of the CORT synthesis blocker metyrapone ($n = 9$) or saline ($n = 7$) prior to exposure the mother expressing fear in response to the CS odor.
Results: Experiment 1: The t-test revealed a significant effect of treatment, $t\ (8) = 4.714$, $p < 0.02$, with the 'Muscimol' group, compared to the 'Control' group, failing to demonstrate the decreased number of the CS-odor choices indicative of learning deficit. Experiment 2: Pups exposed to the odor of the 'Frightened' vs. 'Unfrightened' mother displayed significantly higher levels of CORT $t(16.18) = 2.133$; $p < 0.05$. Experiment 3: Pups from the 'Metyrapone' group failed to show the learned odor aversion ($t\ (14) = 5.465$, $p < 0.002$).
Conclusions: We have demonstrated here that the LBA is critical for the social intergenerational transmission of fear. We have shown that this transmission of maternal fear is associated in infants with increased CORT levels and that CORT blockade prevents mother-to-infant transfer of fear. If confirmed in humans, our findings may help to develop novel preventive and therapeutic approaches aimed at disruption of this early intergenerational transmission of trauma.
Keywords: fear, amygdala, social learning, anxiety.
Disclosure: Nothing to Disclose.

M63. Choice as a Screen for Compulsive Alcohol Drinking in Rats

Eric Augier*, Russell Dulman, Markus Heilig

National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

Background: Alcoholism can be defined as a compulsive alcohol use that is excessive and difficult to control despite negative consequences. A critical problem in current addiction research is to understand the transition between controlled and compulsive alcohol use. While only a minority of human drug users makes the transition to addiction, nearly all rats successfully acquire self-administration, a traditional rodent model of drug abuse. Recently, we developed a mutually exclusive discrete choice procedure where rats were proposed to choose between cocaine and a non-drug alternative (i.e. water sweetened with saccharin) and found that most of them prefer the alternative reward over cocaine.
Methods: Here, we thought to generalize this procedure to alcohol. We first trained non-food-deprived rats to lever

press for 20% EtOH on a fixed-ratio-2 reinforcement schedule for several weeks. After stabilization, rats where proposed to choose between 20% ethanol (EtOH) and saccharin (0.04% and 0.2%), a non-caloric sweetener. Motivation to consume alcohol was assessed using a progressive ratio measurement.
Results: We observed that, when facing a choice between alcohol and saccharin, most alcohol self-administering rats abstain from alcohol in favor of the non-drug pursuit. Moreover, the preference for the alternative reward is dose-sensitive. Interestingly, only a minority (around 15 %) of animals, a subset that aligns with human addiction rates, continues to take the drug despite the opportunity of making a different choice. Naltrexone, a FDA-approved medication for alcohol dependence successfully decreased alcohol choice in a subpopulation of drug preferring rats. Finally, alcohol-preferring rats showed an increased motivation to consume alcohol and were more resistant to quinine-adulteration.
Conclusions: The results indicate that this minority of alcohol-preferring rats could represent a better animal model of alcoholism and that the choice model could be useful to better screen for compulsive animals, testing the abilities of potential new pharmacotherapies to reduce alcohol drinking and may help us elucidate the neural substrates that underlie alcoholism.
Keywords: alcohol, choice, compulsivity, reinforcement.
Disclosure: Nothing to Disclose.

M64. KCNH2-3.1 Transgenic Mice Are a Model of Genetic Risk for Cognitive Impairment

Gregory Carr*, Jingshan Chen, Francesco Papaleo, Daniel Weinberger

Lieber Institute for Brain Development, Baltimore, Maryland

Background: Previously, our group identified single nucleotide polymorphisms (SNPs) in the KCNH2 gene associated with impaired cognitive function and increased risk for schizophrenia. The KCNH2 gene encodes a potassium channel (hERG channel) involved in the regulation of neuronal excitability and the cardiac action potential. The truncated, primate-specific KCNH2-3.1 isoform is enriched in the brains of carriers of the risk SNPs. Risk-associated alleles predict lower IQ, slower processing speed, and altered cognitive processing in carriers. In order to model the effects of increased KCNH2-3.1 expression, we created an inducible transgenic mouse expressing the isoform. The current experiments were designed to identify potential cognitive deficits present in KCNH2-3.1 transgenic mice. We utilized object location (spatial reference memory) and delayed non-match to sample T-maze (working memory) tasks in order to probe the baseline cognitive function of the KCNH2-3.1 transgenic mice.
Methods: The object location test was modified from a previously published protocol (Barker et al., 2007). On day 1 of testing, mice were allowed to freely explore the empty arena for 60 minutes. On day 2, mice were placed back into the open field for a 10 min period where they were allowed to explore two identical copies of an object. One hour later, mice were returned to the arena for the test phase and allowed to explore one copy of the object in the same location as during the sample phase and one copy of the object in a novel location. The two sessions were videotaped and the total exploration time was recorded. The discrimination ratio in the test phase was calculated as the amount of time spent exploring the object in the familiar location subtracted from the time exploring the object in the displaced location divided by the total exploration time. The videotapes were scored by a trained observer blind to genotype and treatment. The procedure for the T-maze task was similar to one previously used in our laboratory (Papaleo et al., 2008). The T-maze apparatus was made of clear acrylic (dimensions of arms: 40 X 10.2 X 17.5 cm). A recessed food cup was located at the end of each arm. Training consisted of 10 paired trials each day. A paired trial consisted of a pseudo-randomly chosen forced run where one arm was blocked and the other arm was baited with a single reward pellet. Following consumption, the mouse was returned to the home cage for a 4-second intratrial delay. After the intratrial delay, the mouse was returned to the maze with access to both arms. The arm blocked on the forced run was now baited with 2 reward pellets. If the mouse traveled down the unbaited arm, this was recorded as an error and the mouse was removed from the maze. Mice were trained using these parameters for 20 days or until they reached 80% accuracy for three consecutive days. Mice were then tested using variable intratrial intervals (4, 30, 60, and 240 seconds).
Results: KCNH2-3.1 transgenic mice displayed significant deficits in object location memory. These deficits were not due to any differences in object exploration in either the sample phase or the test phase. Additionally, these object location deficits were highly selective as the transgenic mice showed no difference in performance in the novel object or temporal order versions of the task. Interestingly, the object location deficit was an emergent cognitive feature in the transgenic mice. When a separate cohort of transgenic mice was tested on PD21, they showed intact object location memory and performance was indistinguishable from their littermate controls. Additionally, the deficit present in adult mice was reversed by turning off expression of the transgenic with doxycycline administration in adulthood. In the T-maze working memory task, KCNH2-3.1 transgenic mice learned the non-match to sample rule at the same rate as their littermate controls. However, when the difficulty of the task was increased by decreasing the intertrial interval, KCNH2-3.1 transgenic mice were significantly impaired during trials with a 4-second interval.
Conclusions: These experiments demonstrate that KCNH2-3.1 transgenic mice have significant cognitive impairment in two domains, spatial memory and working, severely affected in schizophrenia and related disorders. The presence of baseline deficits in learning and memory indicate that these transgenic mice may serve as a model of genetic risk for cognitive impairment. The emergence of the spatial reference memory deficit in adulthood increases the validity of the model for schizophrenia-associated

deficits. Additionally, the efficacy of acute modulation of transgene expression on performance in the object location task shows that at least some of the cognitive dysfunction can be reversed and prevention may not be the only viable intervention strategy. Taken together, these results support the use of KCNH2-3.1 transgenic mice for the study of the neurobiology of cognitive dysfunction and the targeting of hERG channel function for drug discovery efforts.

Keywords: schizophenia, cognition, learning, memory.

Disclosure: Dr. Weinberger is an inventor on an NIH-held patent "Schizophrenia related isoform of KCNH2 and development of antipsychotic drugs" (US patent No. 8101380).

M65. Differential mTOR Signaling Distinguishes Antidepressant-resistant Versus Responsive Animals

Susannah Tye*, Adam Walker, Katheryn O'Connor, Jacalyn Russ, Shari Sutor, Mark Frye

Mayo Clinic College of Medicine, Rochester, Minnesota

Background: Stress, via activation of the hypothalamic-pituitary-adrenal (HPA) axis, elicits release of glucocorticoids into the blood stream. At the level of the cell, glucocorticoid receptor mediated adaptations regulate intracellular pathways responsible for energy homeostasis. One such pathway involves mTOR signaling which mediates cellular responses, including cell growth and plasticity, in response to nutrient availability. mTOR activation has been demonstrated to be a critical therapeutic mechanism of both ketamine and lithium. A brain region of high energy demand in depression is Area 25 (A25) of the subgenual cingulate gyrus. Increased metabolic activity in this region consistently correlates with subjective sadness and clinical depressive states. Conversely, antidepressant efficacy, regardless of treatment modality, is associated with a reduction in this regional activity. The capacity of cells in this region to meet metabolic demands may have important implications for treatment response in depression. To explore this, we have developed a model of antidepressant-resistant depression through a combination of chronic stress exposure and HPA-axis stimulation. Our previous work has indicated that distinct metabolic pathways are engaged in the rodent homologue of A25, the infralimbic cortex (IL), in treatment resistant versus responsive animals when coping with the forced swim test stress. This distinction may contribute to differential antidepressant responses in these animals. The current project has quantified cellular metabolic pathways activated during forced swim test stress and investigated the relationship between pharmaceutical facilitation of mTOR signaling and antidepressant response.

Methods: Male Wistar rats were chronically exposed to social isolation stress and daily stimulation of the HPA-axis during the circadian nadir via IP adrenocorticotropic hormone (ACTH-(1-24); 100μg) at 10am each day over 14 days. On day 14 and 15 antidepressant-resistant and control animals were administered either imipramine (10 mg/kg), imipramine + lithium (10 mg/kg; 100 mg/kg), ketamine (10 mg/kg), or control vehicle saline (0.9%). Antidepressant effects were assessed with an open field and forced swim test. Animals were euthanized 30 minutes after exposure to the forced swim test and brain and blood were collected and frozen on dry ice. Plasma and white blood cells were isolated from blood samples. All tissue was stored at -80°C until utilized in tests. At this time, the IL was dissected and mTOR pathway protein levels (mTOR, AKT, GSK3 and TrkB) were determined in IL and white blood cell tissues with western blot and quantified using a ChemiDoc.

Results: Animals exposed to isolation and daily injection stress demonstrated a depression like phenotype (increased immobility) relative to naïve, pair housed control animals ($p < 0.05$; $n = 8$). In addition to demonstrating this depressed phenotype, animals that were treated with ACTH were non-responsive to imipramine ($n = 8$), while animals receiving daily saline injections demonstrated an antidepressant response to this tricylcic antidepressant through reduced immobility and increased active coping during the forced swim test. Antidepressant efficacy was observed for ACTH pre-treated animals through a combination of either imipramine with lithium ($n = 6$), or ketamine ($n = 6$). A sub-group of ketamine-treated animals were, however, non-responsive to ketamine ($n = 6$). Reductions in immobility behavior directly correlated with levels of phosphorylated mTOR pathway proteins, including mTOR, AKT and GSK3 in the IL ($p < 0.05$). This pattern of phosphorylation was not observed in tricyclic antidepressant-responsive depressed animals. In these animals, phosphorylation status of mTOR pathway proteins following imipramine or ketamine treatment was not correlated with the antidepressant behavioral response. Instead, a direct positive correlation was observed between increased active coping and activation of TrkB ($p << 0.05$). Phosphorylation of TrkB was likewise associated with antidepressant behavioral responses to ketamine and lithium augmentation in treatment resistance animals, but the relationship was not as strong as that observed in antidepressant responsive animals and remained a non-significant trend. Based on these correlative findings, a blood based biomarker was developed to enable direct correlation between peripheral measures, IL target engagement and antidepressant behavior in the forced swim test.

Conclusions: Using preclinical models of tricyclic resistant and responsive depression, we have found that cellular pathways mediating energy metabolism are differentially activated in the IL of resistant relative to responsive animals following exposure to the forced swim test. These responses suggest that cellular energy metabolism is altered by prior stress exposure and that this has important implications for antidepressant response. In rats non-responsive to the tricyclic antidepressant imipramine, stimulation of mTOR signaling in the IL in response to ketamine or impramine in combination with lithium, significantly correlated with antidepressant efficacy as measured by enhanced active behavioral coping during forced swim stress. These findings suggest that regulation of energy homeostasis via activation of the mTOR pathway is necessary for the behavioral expression of active coping under duress. Correlative results identified in the blood provide a peripheral proxy biomarker of IL target engagement and antidepressant

efficacy, which will be useful for mood disorder treatment stratification.

Keywords: depression, treatment resistance, ketamine, mTOR.

Disclosure: Nothing to Disclose.

M66. Effects of Medial Prefrontal Cortex NMDA NR1-Subunit Deletion in Adult Mice on Performance of a Spatial Reference and Working Memory Radial Maze Task

Janet Finlay*, Michael Mana, Thuyanh Nguyen, Melissa Gorham, Robert Greene

Western Washington University, Bellingham, Washington

Background: Dysfunction of glutamate N-methyl-D-aspartate (NMDA) receptors may contribute to cognitive deficits associated with a number of psychiatric illnesses, including schizophrenia and depression. This hypothesis is supported by the observation that NMDA receptor antagonists induce cognitive deficits reminiscent of those observed in psychiatric illness. NMDA receptors exhibit widespread distribution in the brain and a number of NMDA receptor-positive brain regions are thought to contribute to cognitive function, including the hippocampus and cortex. Of relevance to the present study is the role of prefrontal cortex (PFC) NMDA receptors in working memory. The PFC has long been thought to play an important role in working memory based on the observation that lesions or transient inactivation of this region impairs working memory and neurons this area are activated during the delay period of a working-memory task. Characterizing the specific role of PFC NMDA receptors in working memory has been facilitated by the development of mouse models in which the obligatory NR1 subunit of the NMDA receptor can be deleted in a regionally specific manner. Using this approach, results of a recent study indicate that early postnatal NR1 deletion, mostly confined to excitatory neurons in prefrontal and sensory cortices, fails to affect spatial working memory (SWM) as assessed using a spontaneous alternation Y-maze task (Rompala et al., PLOS ONE, 8:e61278, 2013). The goal of the present study was to examine the effects of NR1 subunit deletion restricted to the mouse medial PFC (mPFC) on performance of a, more cognitively demanding, spatial reference memory (SRM) and SWM 6-arm radial maze task. Previously, this task has been used to reveal a distinct role for hippocampal dentate gyrus NMDA receptors in SWM, but not SRM (Niewoehner et al., Eur J Neurosci, 25:837-46, 2007).

Methods: In the present study, NMDA receptor dysfunction was induced on postnatal day 70-90 by bilateral infusions of adeno-associated virus Cre-recombinase into the mPFC of targeted knock-in mice with loxP sites flanking exon 11-22 of the NR1 gene (fNR1 mice). Control fNR1 mice were given sham infusions. Control and deleted mice ($n = 8$/group) were trained and tested in a SRM task. In the SRM task, food was placed in 3 arms of a 6-arm automated radial maze at the start of each trial; the baited arms remained consistent for each mouse across all trials, but randomly varied between mice. At the start of a trial, each mouse was placed in the central chamber of the maze and allowed to enter any of the 6 arms; once an arm was visited and a mouse returned to the central chamber, the entrance to each of the 6 arms was blocked for 10 s. At the end of the 10 s timeout, only the arms that had not been visited during that trial were made accessible and a mouse could choose to enter one of the remaining unvisited arms. This sequence was continued until the mouse had entered all 3 baited arms or the trial was terminated (5 min 50 s). Thus, this phase of the task only assessed SRM errors; that is, entries to arms that were never baited. Throughout behavioral training and testing, mice were given 4 trials/day and tested 6 days/week. Following acquisition of the SRM task, a spatial working memory (SWM) component was added to the task. During this phase, all parameters remained the same with the exception that mice were no longer prevented from re-entering a previously chosen arm. When a mouse re-entered an arm that had already been visited on that trial, this was recorded as a SWM error. SRM and SWM performance were also assessed under conditions of a 5 s and 30 s timeout as well as rotation of the maze.

Results: Control and deleted mice exhibited similar acquisition of the SRM task. Within approximately 12 days of training, control and deleted mice were performing the task to a criterion of 3 correct arm entries and < 1 SRM error (days to criterion $= 11.5 \pm 1.4$ and 12.5 ± 1.2, respectively). Performance of control and deleted mice also did not differ following introduction of the SWM component of the task. On day 1 of SWM testing, control and deleted mice exhibited 1.9 ± 0.5 and 2.1 ± 0.6 SWM errors. By day 15 of testing, SWM errors had declined significantly in both groups to 0.5 ± 0.1 errors in the control group and 0.5 ± 0.2 errors in the deleted group. Whereas reducing the timeout from 10 s to 5 s did not significantly alter SRM or SWM performance of either group, performance of both control and deleted mice was significantly impaired when the delay was extended from 10 s to 30 s or the maze was rotated to dissociate baited arms from the spatial cues. The most robust performance deficits were observed in response to the maze rotation and in this case, there was a tendency for deleted mice to exhibit a greater number of SWM errors than controls (4.0 ± 1.1 and 2.8 ± 0.8, respectively). Further analyses are being performed to assess the degree to which this difference is due to enhanced perseverative responding in the deleted mice.

Conclusions: Results of the present study indicate that regionally restricted dysfunction of PFC NMDA receptors sustained in adulthood, is not sufficient to impair baseline SRM or SWM performance. These data are consistent with a recent study in which early postnatal NMDA receptor dysfunction that is relatively selective for excitatory neurons in prefrontal and sensory cortices, failed to affect SWM as assessed using a spontaneous alternation Y-maze task (Rompala et al., PLOS ONE, 8:e61278, 2013). Our preliminary observation that PFC NR1 deletion exacerbated SWM errors when the spatial map was disrupted by rotating the maze, suggests that performance deficits associated with PFC NMDA receptor dysfunction may only be revealed under conditions of further increases in cognitive demand.

Keywords: depression, schizophrenia, cognition.

Disclosure: Nothing to Disclose.

M67. Upregulation of Dopamine D2 Receptors in the Nucleus Accumbens Indirect Pathway Enhances Motivation and Alters Medium Spiny Neuron Physiology

Eduardo Gallo*, Bo Feng, Jonathan Javitch, Christoph Kellendonk

Columbia University, New York, New York

Background: Dopamine signaling in the nucleus accumbens (NAc) plays a central role in the processing of reward-related information and in goal-directed behavior. The output cells of the NAc, medium spiny neurons (MSNs), typically belong to the direct or indirect pathways, which differ in their respective enrichment of D1 and D2 dopamine receptors (D1Rs and D2Rs). Alterations in striatal D2R availability have been reported in several disorders that are characterized by motivational abnormalities, including schizophrenia, ADHD, and drug addiction. However, whether D2R levels are causally linked to alterations in motivation is not well understood. Recent evidence from our group demonstrated that viral-mediated D2R overexpression in the adult mouse NAc enhances motivation, but it remains unclear which neuronal population mediated this effect. Moreover, whether D2R upregulation leads to alterations in the functional connectivity between the direct and indirect pathway is unknown.
Methods: We selectively overexpressed D2Rs in the NAc indirect pathway (D2-MSNs) by injecting a conditional adeno-associated virus encoding D2R into the NAc of adult D2-Cre transgenic mice. Four weeks later, we tested the effect on motivation using a progressive ratio (PRx2) schedule of reinforcement, where the lever-pressing requirement doubled with each reward. In addition, we used whole cell patch clamp electrophysiology in acute slices to measure intrinsic membrane properties, as well as spontaneous and miniature excitatory postsynaptic currents (s/mEPSCs) of MSNs. We also evoked inhibitory postsynaptic currents (IPSCs) in putative D1-MSNs by optogenetic activation of D2-MSNs overexpressing either D2Rs (D2R-OENAcInd) or EGFP (EGFPNAcInd). We then examined the effect of the D2 agonist quinpirole (1μM) on the evoked IPSCs.
Results: In the PRx2 schedule, D2R-OENAcInd mice pressed significantly more times, earned more rewards and continued to respond later than EGFPNAcInd controls. Similarly, in a concurrent choice random ratio schedule, D2R-OENAcInd mice showed significantly higher lever-pressing for a preferred food over freely-available, less preferred food than controls. These results indicate that D2R upregulation in the indirect pathway of the adult NAc is sufficient to increase motivation. Our slice recordings showed that D2-MSNs, but not D1-MSNs, of D2R-OENAcInd mice are hyper-excitable, an effect associated with reduced inward-rectifying potassium (Kir) channel currents. D2R-overexpressing D2-MSNs showed reduced sEPSC/mEPSC frequency, but not amplitude, suggestive of decreased glutamatergic synaptic input. We then tested whether synaptic output of D2-MSNs onto neighboring D1-MSNs is altered by D2R overexpression in D2-MSNs. Following optogenetic activation of D2-MSNs, IPSC peak amplitude in D1-MSNs was significantly reduced in D2R-OENAcInd mice compared to controls. Quinpirole attenuated baseline IPSC amplitude by $79.1 \pm 9.0\%$ in the D2R-OENAcInd mice and $32.8 \pm 7.0\%$ in the EGFPNAcInd mice ($p < 0.001$; $n = 11$-14 cells/group).
Conclusions: These data suggest that D2R upregulation in D2-MSNs not only leads to significant alterations in intrinsic MSN excitability and excitatory synaptic inputs, but also regulates lateral inhibition of D1-MSNs. This raises the possibility that the increased motivation in the D2R-OENAcInd mice may be associated with disinhibition of the direct pathway. Overall, the present findings suggest that boosting D2R levels in the indirect pathway could be useful in developing effective treatments for motivational dysregulation.
Keywords: D2 receptor, motivation, nucleus accumbens, dopamine.
Disclosure: Nothing to Disclose.

M68. Trace Amine-associated Receptor 1-Mediated Signaling and Dopamine Transport Underlie Methamphetamine's Stimulant Effect in Mice

David Grandy*

Oregon Health & Science University School of Medicine, Portland, Oregon

Background: Worldwide the number of methamphetamine abusers continues to grow burdening communities with increasing demands on healthcare, child welfare and criminal justice services as the drug takes its toll on the physical, emotional and psychological wellbeing of users and their loved ones. Past efforts identified the dopamine transporter as the primary molecular target of methamphetamine and some clinical evidence suggests the dopamine transporter-blocker bupropion can prolong abstinence from methamphetamine use. However, in 2001 methamphetamine was reported to be a full agonist of the Gαs-coupled trace amine-associated receptor 1 (TAAR1) implying a two-hit mechanism of action. Here we show evidence in support of this hypothesis.
Methods: EPPTB was synthesized in-house, dissolved in DMSO and diluted to working concentrations with physiologic saline. All other drugs used were purchased from Sigma-Aldrich St. Louis, MO. Xenopus oocytes were prepared, injected with cRNAs, and then chloride currents recorded under two-electrode voltage clamping conditions according to published procedures. Adult male wild type C57Bl/6J mice and their taar1-deficient littermates were used in all behavioral experiments where locomotor activity was digitally recorded (CleverSys Inc., Reston, VA). The behavioral data were graphed and analyzed by an individual blind to the experimental conditions using Prism 3 (GraphPad Software, San Diego CA). Oocyte recordings were graphed and analyzed using SigmaPlot (Systat Software Inc., San Jose CA). Significant differences ($P < 0.05$) were identified using Student's t-test.
Results: The TAAR1-selective antagonist EPPTB blocked methamphetamine- and bupropion-stimulated chloride conductance in Xenopous oocytes co-expressing mouse TAAR1 and the human cystic fibrosis transmembrane conductance regulator in a concentration-dependent manner

with IC50's of 2.3 ± 0.3nM and 4.3 ± 0.7nM, respectively. Cocaine did not stimulate the receptor. EPPTB displayed no affinity for mouse biogenic amine transporters nor did it produce a significant phenotype in wildtype or taar1-/- mice. In contrast, at the highest dose tested (100 mg/kg, i.p.) EPPTB inhibited approximately 70% of methamphetamine–stimulated (3 mg/kg, i.p.) activity in wildtype mice while having no effect on similarly treated knockout mice. Intraperitoneal co-administration of methamphetamine (3 mg/kg) and bupropion (50 mg/kg) to wildtype mice produced greater activity than either drug alone, an effect absent from knockout mice. Cocaine-stimulated (15 mg/kg, i.p.) activity was the same in wildtype and knockout mice. Significantly, wildtytpe mice administered methamphetamine after receiving bupropion plus EPPTB displayed the same activity profile as wildtype mice treated with bupropion plus EPPTB but not methamphetamine.

Conclusions: The existence of a methamphetamine-activated G protein-coupled receptor that is also activated by bupropion suggests a novel direction for medication development and a molecular explanation for the profoundly distinct interoceptive effects produced by methamphetamine, bupropion and cocaine.

Keywords: bupropion, dopamine, cocaine, locomotion.

Disclosure: Nothing to Disclose.

M69. Overexpression of Corticotropin Releasing Hormone in the Central Nucleus of the Amygdala Alters Anxiety and Anxiety-related Metabolism and Functional Connectivity in Non-human Primates

Andrew Fox*, Jonathan Oler, Do Tromp, Dan McFarlin, Ben Grabow, Miles Olsen, Ethan Brodsky, Rothem Kovner, Marissa Riedel, Eva Fekete, Rasmus Birn, Pat Roseboom, Andrew Alexander, Marina Emborg, Walter Block, Ned Kalin

University of Wisconsin Madison, Madison, Wisconsin

Background: Children with an extremely anxious temperament (AT) are at risk to develop anxiety and depressive disorders later in life. Our group has developed and extensively validated a non-human primate model of this early-life risk. We previously identified the neural substrates of AT to include portions orbitofrontal cortex, hippocampus, portions of the brainstem, and the central nucleus of the amygdala (Ce). The Ce is of particular interest because it has the capacity to induce fear and anxiety responses, via projections to downstream brainstem targets. Moreover, neurotoxic lesions of the Ce that attenuate AT provide causal evidence for Ce involvement in early-life anxiety. Recent work from our lab has demonstrated that early-life variation in AT-related Ce metabolism is primarily the product of non-inherited environmental influences. The Ce contains a rich mixture of peptides that have the potential to modulate anxiety responses. Of particular interest is, corticotropin releasing hormone (CRH), a peptide that mediates the expression of stress reactivity within the HPA axis, as a hormone, and functions as a neurotransmitter within ATs neural substrates, including the Ce. Importantly, because of its role in acute and chronic stress, CRH is ideally suited to mediate environmental influences on Ce function. To understand the consequences of increased Ce-CRH in primate anxiety, we utilized viral vector technology to overexpress CRH in the Ce of young rhesus monkeys to alter AT. We combined this approach with multimodal neuroimaging to examine Ce-CRH induced alterations in brain metabolism along with functional and structural connectivity throughout the AT network.

Methods: We studied 10 young monkeys, 5 of which received bilateral Ce injections (24μl/side) of an adeno-associated virus with a CRH construct (AAV2-CRH). The other 5 animals served as non-operated controls. The AAV2-CRH was mixed with the contrast agent gadolinium (Gd, 0.66 mM), and was administered using convection enhanced delivery. This method was first performed in one pilot animal that at post-mortem demonstrated selective and high levels of CRH expression. To ensure precise localization of the target, the infusion was performed in the MRI allowing for real-time monitoring of the infusion. To estimate the diffusion of AAV2-CRH, we examined the overlap of MR-visible Gd in standard space. AT and brain metabolism were assessed before surgery and again approximately 2 months later for Ce-CRH animals and at similar intervals for the controls during the no-eye-contact (NEC) condition of the human intruder paradigm. During NEC the monkey is placed in a cage and a human enters the room and stands 2.5m from the animal without making eye contact. Freezing, coo vocalizations and plasma cortisol levels in response to NEC were measured, and AT was calculated as the mean of these 3 z-scored variables. Animals received an FDG injection immediately prior to NEC exposure which lasted 30-minutes. After NEC exposure, PET imaging was used to assess integrated brain metabolism that occurred during exposure to the NEC condition. Additionally, MRI measures of structural connectivity with diffusion tensor imaging (DTI) and functional intrinsic connectivity with 'resting' fMRI, were acquired both before and again approximately 2 months after surgery in 5 Ce-CRH injected monkeys, and at corresponding times in 5 unoperated controls. We examined injection-induced changes in AT, regional brain metabolism, regional white-matter integrity (i.e. fractional anisotropy, FA), as well as the synchrony of BOLD fluctuations with fMRI, using the bilateral Ce-CRH injection region as a seed for connectivity analyses.

Results: The precision of the MRI-infusion method was confirmed as all 5 subjects had detectable Gd within an overlapping Ce-region. Animals with CRH overexpression in the Ce demonstrated a significant increase in AT ($p < .05$, one-tailed). Moreover, results demonstrated significant injection-induced increases Ce metabolism in the Ce-CRH group, when compared to control animals ($p < .01$, uncorrected). Furthermore, whole-brain analyses revealed increased metabolism within other AT-related regions, including: OFC, hippocampus, and brainstem ($p < .01$, uncorrected). Results demonstrated functional connectivity with Ce decreased in insular cortex and increased in a region encompassing portions of substantia innominata and internal globus pallidus ($p < .01$, uncorrected). Moreover, voxelwise structural connectivity analyses demonstrated Ce-CRH overexpression resulted in reduced FA in portions of the thalamus ($p < .005$, uncorrected). Importantly, tracto-

graphy analyses suggest these thalamic regions are connected to Ce.
Conclusions: This study underscores the potential for gene delivery in primate models to elucidate the mechanisms of regional gene-expression on distributed brain function, as well as to explore novel treatment strategies for refractory psychiatric illness. Taken together these results indicate that chronically increased Ce-CRH expression influences AT, metabolic activity within ATs neural substrates, as well as long-range functional connectivity and white-matter microstructure. This work, aimed at understanding the effects of increased CRH in the Ce, will help motivate the development of novel interventions designed to prevent the development of anxiety disorders.
Keywords: corticotropin releasing hormone, central nucleus of the amygdala, gene expression, neuroimaging.
Disclosure: Ned Kalin received Honorariums from CME Outfitters and Elsevier; served on the scientific advisory board for Corcept Therapeutics; is a stockholder with equity options in Corcept Therapeutics; and holds patents on: 1) Promoter sequences for corticotropin-releasing factor CRF2alpha and method of identifying agents that alter the activity of the promoter sequences: U.S. Patent issued on 07-04-06; patent #7071323, U.S. Patent issued on 05-12-09; patent #7,531,356, 2) Promoter sequences for urocortin II and the use thereof: U.S. Patent issued on 08-08-06; patent #7087385, and 3) Promoter sequences for corticotropin-releasing factor binding protein and use thereof: U.S. Patent issued on 10-17-06; patent #7122650.

M70. Ethanol is Self-administered Directly into the Central Nucleus of the Amygdala in Wistar Rats

Zachary Rodd*, Christopher Knight, Jamie Toalston, Robert Waeiss, Gerald Deehan, Amy Bracken, William McBride , Sheketha Hauser

Indiana University School of Medicine, Indianapolis, Indiana

Background: Previous research from our laboratory has indicated that ethanol (EtOH) is directly self-administered into subregions of the mesolimbic dopamine system (posterior ventral tegmental area and nucleus accumbens shell). The central nucleus of the amygdala (CeA) mediates numerous EtOH-related behaviors/effects. In particular, the CeA is thought to mediate the anxiolytic actions of EtOH and may produce reinforcement through this manner. The current experiment determined whether EtOH would be directly self-administered into the CeA.
Methods: The intracranial self-administration technique was employed to evaluate the effects of EtOH in the CeA on operant behavior of adult male Wistar rats. One week after surgery to implant a guide cannula aimed at the CeA, subjects were placed in standard operant chambers equipped with two levers (active and inactive). Rats were randomly assigned to one of seven groups (n = 7-12/group) that self-administered (FR1 schedule) artificial CSF (aCSF), 75, 100, 150, 200, 250 or 350 mg% EtOH for the first 4 sessions. During sessions 5 and 6, all groups self-administer aCSF (extinction). During session 7, subjects were allowed to self-administer the original assigned infusate.
Results: Examining the average number of infusions for the first 4 sessions indicated that Wistar rats readily self-administered 200 (32 + 3 infusions/session) and 250 mg% (41 + 3 infusions/session) EtOH directly into the CeA. The highest and lower concentrations of EtOH (350 mg%; 11 + 3 infusions/session) did not differ from aCSF self-infusion levels (10 + 2 infusions/session). Rats self-administering 200 or 250 mg% EtOH directly into the CeA discriminated between the active and inactive levers, extinguished responding during aCSF substitution, and reinstated responding when EtOH was returned to the infusate. The data indicate that EtOH is reinforcing within the CeA, but at higher concentrations than required for either the posterior ventral tegmental area or nucleus accumbens shell.
Conclusions: The results indicate that the CeA supports the rewarding as well as the anxiolytic actions properties of EtOH within the CeA may be based upon the anxiolytic actions of EtOH within this structure. (Supported in part by AA007462 and AA012262).
Keywords: Ethanol, Amygdala, Reward, Self-Administration.
Disclosure: Nothing to Disclose.

M71. Proinflammatory Signaling Regulates Voluntary Alcohol Intake and Escalation of Consumption after Exposure to Social Defeat Stress in Mice

Camilla Karlsson*, Jesse Schank, Faazal Rehman, Estelle Barbier, Jenica Tapocik, Annika Thorsell, Markus Heilig

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

Background: Proinflammatory activity has been postulated to play a role in addictive processes and stress responses, but the underlying mechanisms remain largely unknown. Here, we examined the role of interleukin 1 (IL-1) and tumor necrosis factor- α (TNF-α) in regulation of voluntary alcohol consumption, alcohol reward and stress-induced drinking.
Methods: Voluntary alcohol consumption was measured with a standard two bottle free choice (TBC) procedure using increasing concentrations of alcohol or water. Alcohol reward was evaluated in the conditioned place preference (CPP) paradigm using an unbiased design and a reinforcing dose of 2g/kg was administered during conditioning. Social defeat stress is well established to induce depressive like behaviors, closely linked to alcohol addiction. Here, we used the model to evaluate mice previously trained to drink in a TBC procedure and measure potentiation of alcohol consumption after 10 days of social defeat stress exposure.
Results: Deletion of the IL-1 receptor I gene (IL-1RI) in mice resulted in modestly decreased alcohol consumption, but affected neither the rewarding properties of alcohol, measured by conditioned place preference, nor escalation of drinking induced by social defeat stress. Because TNF-α signaling can compensate for phenotypic consequences of IL1-RI deletion, we then assessed double knockout (KO) mice lacking both IL-1RI and TNF-1 receptors (TNF-1R). Double KOs consumed significantly less alcohol than control mice over a range of alcohol concentrations. The

combined deletion of TNF-1R and IL-1RI did not influence alcohol reward as measured by CPP, but did prevent escalation of alcohol consumption resulting from exposure to repeated bouts of social defeat stress.
Conclusions: Taken together, these data indicate that signaling events downstream of IL-1RI and TNF-1R contribute to regulation of stress-induced, negatively reinforced drinking, while leaving rewarding properties of alcohol largely unaffected.
Keywords: alcohol, cytokines, social defeat stress, KO mice.
Disclosure: Nothing to Disclose.

M72. Buprenorphine Produces Antidepressant-like and Anxiolytic Responses in Mice Exposed to Chronic Models of Depressive-like Behavior

Edgardo Falcon, Rachel Sweeney, Vanessa Fleites, Rosa Leon, Olivier Berton, Irwin Lucki*

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Buprenorphine (BPN) is broadly used for the treatment of opiate dependence and chronic pain. Several small clinical trials have reported positive effects for BPN in treatment-resistant depression. BPN produces complex pharmacological actions at multiple opioid receptors, but is most potent as a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist. We have previously reported that acute BPN produced behavioral effects in the forced swim test and novelty-induced hypophagia test, behavioral tests in rodents that measure the responses of antidepressant and anxiolytic drugs. In this study, we set out to investigate the effects of chronic BPN treatment given for 7-14 days to mice in two models of depressive-like behavior, the Chronic Mild Stress (CMS) procedure and Chronic Social Defeat Stress (CSDS). These models ordinarily demonstrate the effects of chronic antidepressant treatments only following chronic administration for 4 weeks or longer.
Methods: In the CMS study, male C57BL/6J mice were exposed daily to three mild stressors for two weeks. Mice were then treated with BPN (0.25 mg/kg) for 7-14 d before subjected to several behavioral tests, such as sucrose preference (anhedonia), the splash test, light/dark test, the elevated zero maze, novelty suppressed feeding, and the forced swim test. In the CSDS study, male C57BL/6J mice were subjected to daily 5-min exposures to aggressive CD-1 mice for 10 days, which caused an episode of fighting and defeat, followed by continued exposure to the aggressor behind a barrier. Following the aggressive encounters, mice were evaluated for social avoidance with a social interaction test. Mice that developed social avoidance after the CSDS were treated with saline or BPN (0.25 mg/kg) for 7 days and retested in the social interaction test.
Results: The CMS procedure caused reduced weight gain and decreased sucrose preference after two weeks of exposure to stress. Stressed mice treated with BPN developed a pattern of behavioral responses supporting antidepressant and anxiolytic effects. These effects included a reversal of deficient sucrose preference, an increase in the time spent grooming in the splash test, increased time spent in the light side of the light/dark chamber, increased time in the open arm of the elevated zero maze, and decreased immobility in the forced swim test when compared to stressed mice treated with saline. No significant changes were observed in the novelty suppressed feeding test. After CSDS, BPN-treated mice showed a significant increase in social interaction when compared to saline-treated mice, measured as an increase in the time spent in the interaction zone and a decrease in the time spent in the corner zones. BPN did not alter social interaction in nonstressed mice.
Conclusions: Taken together, these studies demonstrated that BPN is effective at reversing behavioral deficits in two mouse models of chronic depressive-like behavior. BPN was effective in tests measuring anhedonia, behavioral despair and anxiety. Furthermore, the emergence of BPN activity after only 7 days of treatment in these particular tests suggests that BPN may be more rapidly acting clinically than comparable effects with conventional antidepressants.
Keywords: chronic mild stress, chronic social defeat, opioids, depression.
Disclosure: IL was a consultant to Alkermes. No other disclosures.

M73. Blockade of Presynaptic and Postsynaptic Adenosine A2A Receptors Produce Bi-directional Effects on Cocaine Seeking

Ryan Bachtell*, Casey O'Neill, Sophia Levis, Madeline Winkler, Jacob Stafford, Drew Schreiner

University of Colorado, Boulder, Colorado

Background: Repeated cocaine administration produces perturbations in dopamine and glutamate neurotransmission that contribute to the reinstatement of extinguished cocaine seeking. Postsynaptic adenosine A2A receptors co-localize with dopamine D2 receptors in nucleus accumbens neurons, while presynaptic adenosine A2A receptors co-localize with adenosine A1 receptors on glutamate terminals. The synaptic localization of adenosine A2A receptors represent targets for altering the dopamine and glutamate systems to effect the expression of behaviors associated with relapse. The goal of these studies was to determine the effects of presynaptic or postsynaptic adenosine A2A receptor antagonism on the reinstatement of cocaine seeking.
Methods: Male Sprague-Dawley rats self-administered cocaine in 10 daily self-administration sessions on a fixed-ratio 1 schedule. Lever pressing was extinguished in 6 daily extinction sessions. We first tested whether presynaptic and postsynaptic A2A receptor antagonism (SCH 442416 and KW 6002, respectively) was sufficient to reinstate cocaine seeking. We next tested the effects of SCH 442416 and KW 6002 on cocaine seeking induced by a systemic cocaine prime. Lastly, the effects of SCH 442416 and KW 6002 were tested on cocaine seeking induced by AMPA glutamate receptor stimulation in the prefrontal cortex.
Results: Administration of the postsynaptic adenosine A2A receptor antagonist, KW 6002, dose-dependently reinstated cocaine seeking and facilitated reinstatement induced by cocaine or prefrontal cortical stimulation. Administration of the presynaptic adenosine A2A receptor antagonist, SCH 442416, did not induce cocaine seeking when administered

alone, but impaired reinstatement of cocaine seeking induced by either cocaine or prefrontal cortical stimulation.
Conclusions: These findings highlight the importance of synaptic locations of adenosine A2A receptors in regulating cocaine seeking. Antagonism of postsynaptic A2A receptors facilitates cocaine seeking, perhaps by enabling postsynaptic dopamine D2 receptor signaling. Antagonism of presynaptic A2A receptors, on the other hand, impairs cocaine seeking, perhaps by enabling presynaptic adenosine A1 receptor signaling and inhibition of glutamate transmission.
Keywords: relapse.
Disclosure: Nothing to Disclose.

M74. Sleep Regulates Incubation of Cocaine Craving

Bo Chen, Yao Wang, Xiaodong Liu, Zheng Liu, Yan Dong, Yanhua Huang*

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Cumulative clinical studies suggest that the objective sleep quality deteriorates during long-term abstinence from repeated use of addictive drugs such as cocaine (Matuskey et al., 2011; Angarita et al., 2014). This poor sleep quality has been speculated to contribute to relapse of drug use, mainly based on correlation analysis in humans and sleep deprivation studies in animals (Teplin et al., 2006; Malcolm et al., 2007; Puhl et al., 2011; 2013). However, sleep deprivation is different from insomnia - thus it remains not clear if poor-quality sleep as a consequence to drug use indeed exacerbates addiction related behaviors during abstinence, and whether interventions of sleep could alleviate the symptoms. Incubation of cocaine craving following learned self-administration is an animal model of drug relapse and craving, which depicts the progressive increase in cue-induced cocaine seeking after withdrawal from the drug (Grimm et al., 2001). Previous studies have revealed a critical role of glutamatergic transmission within the nucleus accumbens in mediating the effect, and specifically the time-dependent up-regulation of calcium-permeable AMPARs in the principal neurons after long-term withdrawal (Conrad et al., 2008; Loweth et al., 2014). Here we examined the sleep effects on incubation of cocaine craving and the accompanying changes of glutamatergic transmission within the nucleus accumbens. We use a multi-disciplinary approach including in vivo EEG recordings, sleep interventions, behavioral tests, and in vitro brain slice electrophysiology.
Methods: Following cocaine self-administration (SA) training (2 hr/d x 5 d) in young adult rats (P42-56 at start of training), the rats were randomly assigned to one of the following 5 groups as they underwent withdrawal: (1) normal sleep, (2) – (5) sleep interventions for 1, 2, 3, or 6 weeks. Incubation of cocaine craving was tested on withdrawal day 1 and 45 for 30 min each, during which the cue-induced responding for cocaine ("seeking") was recorded without actual drug delivery. From before cocaine exposure to the end of withdrawal, the EEG and EMG signals were recorded every other day. To enhance the consolidated sleep in the light phase, a custom-made treadmill system was used to sleep deprive (SD) the rats during the dark phase without engaging significant exercise (dark-phase SD). Conversely, in a separate experiment assessing worsened sleep on cue-induced cocaine seeking, the rats were randomly assigned to one of the 4 groups following cocaine SA training: (1)-(2) normal sleep, (3)-(4) sleep fragmentation (SF) at 3 or 6 weeks following withdrawal, and incubation of cocaine craving was tested on withdrawal day 1, 21 or 45. All animals were trained and tested during the dark phase, and allowed at least 3 days free of sleep manipulations before test for incubation of craving or electrophysiological recordings. Accumbens recordings were performed in vitro using acute brain slices, and the synaptic content of calcium-permeable AMPA receptors (CP-AMPARs) was assessed in nucleus accumbens principal neurons using the selective CP-AMPAR antagonist Naspm (100 μM).
Results: In cocaine SA animals (group 1), compared to EEG baselines (recorded prior to cocaine exposure), a reduction in total REM but not NREM sleep was observed beyond withdrawal week (wk) 3 ($73 \pm 9\%$ of baseline by wk 3; $n = 4$; $p < 0.05$), and a trend of recovery was observed by wk 6. The REM sleep average episode duration was also reduced in the light phase during withdrawal ($75 \pm 10\%$ of baseline by wk 3; $n = 4$; $p < 0.05$). In control animals (group 1), cue-induced cocaine seeking was significantly enhanced on withdrawal day 45 compared to day 1 ($164 \pm 12\%$ of day 1, $n = 8$, $p < 0.001$), suggesting incubation of cocaine craving. By contrast, 6- or 3-wk dark-phase SD significantly reduced incubation of cocaine craving on withdrawal day 45 ($F(2, 21) = 7.756$, $p < 0.01$). Natural reward-associated learning, as assessed by sucrose self-administration at the end of 45-day withdrawal, was not altered by such sleep interventions. EEG recordings revealed that 3-wk dark-phase SD between withdrawal wk 4-6 significantly enhanced REM sleep during the light phase (by wk 6, control: $94 \pm 3\%$ of baseline, $n = 4$; SD: $121 \pm 14\%$, $n = 4$, $p < 0.05$), as well as enhanced the REM sleep average episode duration during the light phase (by wk 6, control: $81 \pm 11\%$ of baseline, $n = 4$; SD: $102 \pm 9\%$, $n = 4$). Electrophysiological recordings in in vitro brain slices revealed that the 3-wk dark-phase SD significantly reduced the synaptic content of CP-AMPARs in nucleus accumbens medium spiny neurons (%Naspm inhibition, control: $20.7 \pm 2\%$, $n = 22$; SD: $11.6 \pm 2\%$, $n = 25$, $p < 0.01$). On the contrary, one week of sleep fragmentation (SF) before withdrawal day 21 (but not day 45) significantly enhanced the synaptic level of CP-AMPARs (%Naspm inhibition, control: $6.4 \pm 1.7\%$, $n = 20$; SF: $19.7 \pm 3.4\%$, $n = 20$, $p < 0.01$), as well as enhanced incubation of cocaine craving (compared to day 1, control: $106 \pm 17\%$, $n = 8$; SF: $153 \pm 15\%$, $n = 8$; $p < 0.05$). Thus, repeated cocaine SA in rats leads to persistent reduction in REM sleep during long-term withdrawal; enhancing REM sleep in the light phase during the same period can lead to reduced synaptic CP-AMPAR content in the nucleus accumbens principal neurons and reduced cue-induced cocaine craving.
Conclusions: In summary, sleep could bi-directionally regulate addiction-associated behaviors during cocaine abstinence with corresponding changes in glutamatergic transmission within the nucleus accumbens.
Keywords: cocaine addiction, sleep, accumbens, calcium-permeable AMPA receptors.
Disclosure: Nothing to Disclose.

M75. Effects of Controllable and Uncontrollable Stress in an Animal Model of Gambling Behaviour

Daniela Lobo*, Parisa Hedayatmofidi, Jose Nobrega

Centre for Addiction and Mental Health, Toronto, Canada

Background: Depression is a well-known risk factor for the development of addictive disorders. Neurobiological research supports the characterization of gambling disorder (GD) as a behavioral addiction and it is estimated to affect over 2% of the population in the United States and Canada. DG and major depression (MD) are comorbid in 60-80% of cases. On the other hand, the prevalence of DG has been found to be 12.5% in MD patients, which is at least 10 times higher than the prevalence of PG in the general population. A recent epidemiological study reports that a diagnosis of MD predicted the subsequent onset and persistence of DG with an odds ratio of 6.6. Studies suggest that a shared underlying mechanism may render a group of individuals with MD more susceptible to the development of DG (or other addictions). Our overarching hypothesis is that individuals with higher baseline depressive symptoms will be more vulnerable to the development of a behavioral addiction (GD) through an increase in impulsive decision-making. We appreciate that this hypothesis can only be fully tested in humans through large longitudinal studies. We suggest however that pre-clinical studies could provide important clues concerning causal associations among these conditions. Thus, we aimed to investigate the relationship between depression and gambling-like behavior in rodents by evaluating their performances on a rat gambling task (rGT) coupled with an animal model of depression (Learned-Helplessness task - LH). We hypothesized that stressful experiences leading to depressive-like behavior would lead to higher levels of gambling-like behavior in rats.
Methods: We evaluated the rats' baseline gambling-like behavior using the rat gambling task (rGT), which is a task analogous to the Iowa Gambling Task used to assess decision-making under uncertainty in humans. The rGT was conducted in commercial five-choice chambers (Med Associates, St. Albans, VT) as described previously. Each rGT option (P1-P4) was calculated as a percent of total trials per session, and an impulsive choice ratio was determined for each animal (high-risk P4 choices divided by optimal P2 choices). A high rGT impulsive choice ratio reflects persistent choice of high-risk options, which are linked to larger rewards, but ultimately result in fewer pellets earned per session objective of maximizing net food gain. Depressive-like behavior was modeled using the learned helplessness task (LH) where rats are first exposed to inescapable foot shocks and then to escapable foot shocks. The experimental design was conducted in the following order: 1) all rats ($N = 45$) were trained on the rGT and their baseline performance was obtained; 2) rats were randomly distributed in three groups ($n = 15$ per group) - Group I (LH): rats underwent the Learned Helpless task (uncontrollable and controllable stress) which induces depressive-like behavior; Group II (learned-control - LC): rats were exposed only to escapable shocks (controllable stress), and Group III (cage-control - CC) who were not exposed to any stress; 3) all rats had their performance on the rGT re-evaluated after being exposed to the aforementioned stress conditions. Statistical analysis was conducted using paired t-tests.
Results: Exposure to uncontrollable/inescapable stress significantly impaired the LH rats' performance on the rGT ($t = -2.38, p < .001$), compared to both LC ($t = -2.61, p = .028$) and CC ($t = .616, p = .557$) rats. Rats that developed depressive-like behavior (LH rats) showed a significantly higher preference for the high-risk option (P4), thus presenting a higher impulsive-choice ratio. Conversely, exposure to controllable/escapable stress (LC rats) resulted in improved performance on the rGT by shifting their choice preference from the risky to the optimal option ($t = -2.49$, $p = .034$).
Conclusions: The rGT is considered both as a model of gambling behavior and a decision-making task. It is clear that the rGT cannot address the full complexity of gambling behaviors in humans, however decision-making deficits in the human Iowa Gambling Task have been consistently associated with DG. Rats exposed to an animal model of depression (LH task) developed increased risky behavior, whereas rats who were exposed only to controllable stress performed significantly better on the rGT. Our results suggest that: (1) depression (uncontrollable stress) may increase the vulnerability to addictive behaviors (GD) by increasing impulsive decision-making, and (2) controllable stress may improve decision-making, possibly by decreasing impulsive behavior. We believe that the coupling of animal models of depression and gambling can be a useful tool to identify pharmacological treatments that could potentially result in better outcomes for individuals who develop addictive behaviors secondary to depressive and/or stress-related disorders.
Keywords: addiction, depression, animal models.
Disclosure: Nothing to Disclose.

M76. Relationship Between Frontal Cortical Brain Volume and Motivation to Self-administer Cocaine in Rhesus Monkeys

Hank Jedema*, Alexandra Bonner, Jessica N. Porter, Howard J. Aizenstein, Charles W. Bradberry

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Abnormalities in the activity and structure of the orbitofrontal cortex (OFC), which plays an important role in value-based decision making, have been frequently implicated in drug addiction. For example, reduced OFC gray matter volumes in cocaine users have been repeatedly observed in human neuroimaging studies. It is not clear however, whether these observed reductions are the result of years of chronic cocaine use or reflects pre-existing differences that could mediate greater vulnerability to cocaine addiction.
Methods: Based on the similarity in brain structure between humans and non-human primates as well as their response to drugs of abuse, we compared the relative gray matter size of predefined regions of interest of rhesus macaques before and after a 12 month period of intravenous cocaine self-administration (up to 6 infusions of 0.5 mg/kg per day, 4 days a week) using magnetic resonance imaging and

atlas-based morphometry. This longitudinal assessment of regional brain volume enabled us to distinguish morphological changes induced by chronic cocaine use from pre-existing differences in regional brain volume. In addition, we evaluated the correlation between gray matter volume and the motivation to self-administer cocaine which was defined as the average time for each infusion.
Results: We observed that OFC volume in cocaine subjects ($n = 8$) increased over the period of self-administration in a similar manner as in matched control subjects ($n = 6$). In addition, the size of the OFC prior to self-administration was correlated with the rate of cocaine self-administration. A smaller OFC volume prior to cocaine exposure was associated with a faster rate of self-administration. These results suggest that smaller OFC volumes could mediate an increased vulnerability to drug addiction by increasing cocaine consumption whereas larger OFC volumes may be associated with satiation of drug administration, and limiting its use.
Conclusions: The present data underscore the importance of the OFC in the etiology of drug addiction as well as the essential role of non-human primate models in drug addiction research. Furthermore, these results suggest that the structural differences in OFC volume observed clinically may reflect a pre-existing condition rather than a consequence of cocaine exposure. Supported by: DA025636 and VA BLR&D 1IO1BX000782.
Keywords: morphometry, MRI, addiction.
Disclosure: Nothing to Disclose.

M77. Effects of a Neutral CB1 Antagonist on Nicotine Taking and Reinstatement of Nicotine-seeking in Rats

Aliou Gueye, Yaroslaw Pryslawsky, Jose M. Trigo, Kiran Vemuri, Alexandros Makriyannis, Bernard Le Foll*

Centre for Addiction and Mental Health, Toronto, Canada

Background: Tobacco smoking and its second-hand effects are a major health issue in the world. According to a 2013 World Health Organization report, six million deaths worldwide per year can be attributed directly to tobacco consumption, and by 2030 it is expected to reach eight million. Nicotine is the principal component of tobacco smoke that leads to addiction in humans, and can initiate and maintain drug self-administration behavior. A large body of congruent data supports the idea that the endocannabinoid system plays a key role in brain mechanisms underlying the motivational effects of nicotine. Indeed, CB1 receptor blockade decreases nicotine-induced conditioned place preference and nicotine intravenous self-administration (IVSA). In addition, blockade of the CB1 receptor also reduces cue-induced reinstatement of nicotine seeking. The early success of the inverse agonist rimonabant (SR141716; Acomplia, Sanofi-Aventis) as a smoking cessation aid was hindered by the occurrence of side effects which included depressive disorders, anxiety, insomnia, and thoughts of suicide. Current pharmacotherapies have shown limited efficacy in preventing relapse. Therefore, the development and validation of novel treatments absent of psychiatric side effects is compulsory. In the present study we explored the ability of AM4113, a neutral CB1 antagonist, to modify the rewarding/reinforcing effects of nicotine. Using behavioral approaches, first, we studied the effects of AM4113 on the motivation to self-administer nicotine under fixed and progressive ratio schedules of reinforcement. Secondarily, we investigated the effects of AM4113 on the reinstatement of nicotine-seeking. Various stimuli (presentation of cues, nicotine priming or stress induced by Yohimbine) were evaluated.
Methods: Long Evans rats were initially trained to self-administer nicotine (0.03 mg/kg/infusion). Once the response was stable, the effects of the acute administration of AM4113 (0, 0.3, 1, 3 or 10 mg/kg, i.p.) under fixed ratio 5 (FR5) or progressive ratio (PR) were tested. In a separate group of Sprague Dawley rats, after the acquisition phase, rats underwent an extinction phase (where lever presses had no consequences; no nicotine injection and no cue), and once the responses were stable on extinction rats were tested for reinstatement of nicotine-seeking using nicotine priming (0.15 mg/kg, s.c.), presentation of nicotine-associated cues, or a pharmacological stressor drug (yohimbine 2.5mg/kg, s.c.).
Results: We found that rats pre-treated with AM4113 (0-10 mg/kg) dose-dependently reduced the number of nicotine infusions earned under a fixed [$F(4, 7) = 13.68$, $P < 0.0001$] and progressive [$F(5, 8) = 10.77$, $P < 0.0001$] ratio schedules of reinforcement. After extinction all, the reintroduction of the cues previously paired with nicotine infusion, a priming injection of nicotine (0.15 mg/kg, s.c.) or stress induced by yohimbine, reinstated nicotine-seeking behavior ($p < 0.001$ vs. baseline). AM4113 (0-10 mg/kg) dose-dependently decreased cue, priming, and stress induced reinstatement ($P < 0.05$-0.001).
Conclusions: Data in this study suggest that acute AM4113 is effective in reducing the reinforcing effects of nicotine as evaluated in the IVSA paradigm. The absence of unwanted psychiatric side effects for AM4113 will support a clear advantage over rimonabant for the treatment of tobacco smoking and relapse. We are presently exploring in our laboratory the presence/absence of anxiety and depressive like behaviors from AM4113 administration. We expect that blocking the CB1 receptors with neutral antagonists will retain efficacy for the treatment of nicotine intake and relapse with lesser side effects.
Keywords: nicotine, endocannabinoid, neutral cb1, rimonabant.
Disclosure: Nothing to Disclose.

M78. Whole Genome and Exome Sequencing in Domestic Animals to Identify Genes Contributing to Aggressive Behavior

Carlos Driscoll*, Sonia Razaquar, David Roberson, Clay Stephens, Stephen Lindell, Kevin Blackistone, Jessica Clemente, Qiaoping Yuan, David Goldman, Anna Kukekova, Meredith Yeager, Christina Barr

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland

Background: Aggression is a behavioral trait that appears to be under selection, as it facilitates access to resources and

mating opportunities across mammals, including in domestic species. However, in humans, exaggerated aggression is known to be a hallmark of a number of psychiatric and personality disorders. One approach that could be used to determine the genetic factors that contribute to variation in aggression is the study of the genetics of domestication. At its most basic, domestication is a suite of heritable traits affecting behavior. Among most domestic animal species, there is diminution in aggression and an ability to coexist with humans. The domesticated fox (Vulpes vulpes) and the house cat (Felis silvestris catus) may be good candidates for modeling how genetic variation contributes to aggressive behavior in humans. The house cat manifests a suite of heritable behaviors characteristic of domesticates relative to wildcats, and the commercially abundant silver fox is being increasingly recognized as a superior model of domestication. However, few studies have attempted to identify intra- or inter-specific variation among these species. Here, we explore a draft whole genome sequence of a domestic cat, a wild Asian leopard cat (Prionailurus bengalensis) and interspecies hybrid offspring differing in their levels of tameness (ALC X DC). We also explore genetic variation in two selected fox lines that are distinguished by marked differences in reactivity and temperament (tame vs. aggressive).
Methods: We whole genome sequenced, at approximately 15X coverage, one domestic cat (DC), one Asian leopard cat (ALC) and interspecies hybrid offspring (ALC X DC). Tame-selected (N = 12), aggressive selected (N = 12), and unselected farm (N = 12) foxes from the Institute of Cytology and Genetics, Novosibersk, Russia and twelve wild caught foxes from Maryland, were characterized for genome-wide protein-coding variation. Exploiting the phylogenetically close relationship between the domestic dog (Canis familiaris) and fox, we used a canine (dog) -based exon assay (Agilent) on the Ion Proton platform.
Results: In ALC – DC comparisons, SNPs, some of which are predicted to be potentially deleterious by in silico analysis, were found in the transcribed region of 1400 genes and in the coding region of 158 of those. Dog-on-fox exon pulldown and sequencing resulted in ~80% on-target capture with ~70% of the targets covered at least by 20X coverage successfully resolving > 90% of the sequences expected from a dog-on-dog assay. After filtering (depth of coverage > 20; Qscore > 100), approximately 500,000 SNPs (Single Nucleotide Polymorphisms) were called in fox as compared to CanFam2.0, the Broad dog assembly. Filtering dog vs. fox differences, ~50,000 SNPs were novel in fox, as compared to the 2.5 X 10 6 SNPs reported for dog in the BROAD database.
Conclusions: In general, domestic animals have lower levels of aggression than do their non-domesticated ancestors. Systems permissive of domestication and underlying a "tame" phenotype range from those involving fear and impulse control to those driving reward and sociality. Between tame and aggressive animals, we identified damaging SNPs in gene systems influencing anxiety-like behavior, transcription control, DNA repair, epigenetic processes, synaptic plasticity/transmission, reward, and circadian rhythms. As these systems can contribute to vulnerability to or resilience to human psychiatric disorders, identification of genetic variation among domesticated animals with exaggerated differences in their degrees of tameness may inform us of the human condition and aid in identifying appropriate models for examining treatment response to compounds being developed for the treatment of various psychiatric disorders.
Keywords: SNP, domesticate, aggression, fox.
Disclosure: Nothing to Disclose.

M79. DNA Methylation, Neurodevelopment, and Risk for Anxiety and Depression in Model Rats

Sarah Clinton*, Chelsea McCoy, Phyllis Pugh, Huda Akil

University of Alabama at Birmingham, Birmingham, Alabama

Background: Post-mortem brain samples from psychiatric patients show signs of abnormal DNA methylation and other epigenetic markers, and environment and experience can alter neural epigenetic patterns in humans and model animals. Far less is known about naturally-occurring inter-individual epigenetic differences that shape brain function and vulnerability (or resilience) to stress and emotional dysfunction. Therefore, it is unknown whether epigenetic abnormalities occurring in psychiatric illnesses are primary lesions and drivers of the disease, whether the changes are secondary to environmental/experiential factors, or a combination of both. To test this idea, we are using our rat model of individual differences in emotionality to interrogate inborn methylome differences in the developing and adult brain that may drive distinct emotional behavior phenotypes.
Methods: To elucidate molecular and neuroanatomical changes in the developing brain that produce a highly fearful, anxious, and stress-vulnerable phenotype, we selectively-bred rats for differences in emotional reactivity and combined this with molecular and epigenetic profiling. Our High-Responder (HR) rats vigorously explore novel environments and exhibit greater impulsivity, aggression, and risk-taking vs. Low-Responder (LR) rats, which are very inhibited and show high levels of spontaneous anxiety and depressive-like behavior (i.e. immobility in the Forced Swim Test (FST), diminished sexual interest, and anhedonia). The LR/HR phenotypes are highly predictable across generations and emerge as early as the second week of life. Brains were collected from developing LR/HR pups at three early developmental time points (postnatal days (P)7, 14, and 21). The hippocampus, amygdala, and prefrontal cortex were dissected, and RNA and DNA were extracted for genome-wide expression profiling and DNA methylation assays, respectively. A final study manipulated DNA methylation in adult LR males via altering methyl content in their diet (i.e. supplementing or depleting DNA methyl donors from the diet) and tested its effect on anxiety- and depression-like behavior.
Results: The microarray study revealed dramatic gene expression differences in the developing hippocampus and amygdala (but not prefrontal cortex) of HR vs. LR rats, including changes in gene families involved in metabolism, synaptogenesis, and neuroplasticity. The global DNA methylation assay revealed increased DNA methylation in the amygdala of LR (vs. HR) rats specifically at P7 –an

epigenetic change that may contribute to widespread HR/LR differences in gene expression and behavior. We are currently using next generation sequencing techniques to map and compare the neural methyome architecture in the LR vs. HR amygdala, in part to identify specific genes that are differentially methylated in HR/LR brains. Finally, the behavioral study showed that increasing or decreasing DNA methylation in adult LR rats effectively changed their behavior in opposite ways. Methyl-depletion significantly worsened LRs' depression-like behavior (immobility in the FST). The methyl-supplemented diet improved LRs' FST performance and subtly improved LRs' anxiety-like behavior in the Open Field and Social Interaction test. These data are generally consistent with findings in depressed patients showing that treatment with agents that promote DNA methylation (i.e. S-adenosyl-L-methionine (SAMe) or L-methylfolate) improves depressive symptoms.
Conclusions: Our microarray studies identified distinct "molecular signatures" within the hippocampus and amygdala of developing LR vs. HR rats. The DNA methylation studies revealed increased global DNA methylation in the P7 amygdala of LR vs. HR rats, and ongoing next-generation sequencing analyses seek to identify "methylome signatures" that may contribute to distinct patterns of neurodevelopment, gene expression, and subsequent stress sensitivity and behavior. Our diet-manipulation results suggest that HR/LR DNA methylation differences persist into adulthood and may be functionally important since manipulating DNA methylation levels through increasing or decreasing methyl donors in the diet impacts their behavior. Overall this body of work aims to provide insight into the possible genesis of individual differences in emotionality and related risks for the emergence of emotional disorders (e.g. the anxiety/depression-prone nature of LRs or aggression, impulsivity and drug addiction proclivity of HRs), and delineate the role of epigenetic processes in these phenomena.
Keywords: neurodevelopment, DNA methylation, anxiety, depression.
Disclosure: Nothing to Disclose.

M80. Inborn Stress Reactivity Shapes Adult Behavioral Consequences of Early-life Maternal Separation Stress

Ilan Kerman*, Samir Rana, Nateka Jackson, Chelsea McCoy, Sara Stringfellow, Sarah Clinton

University of Alabama at Birmingham, Birmingham, Alabama

Background: It is generally accepted that early-life stress exposure heightens depressive- and anxiety-like behaviors in adult offspring. However, emerging evidence suggests that early-life stress may actually be protective in certain individuals. The present study utilized maternal separation to test the hypothesis that stress during the early postnatal period produces contrasting behavioral consequences in rats that are stress susceptible (Wistar-Kyoto rats) vs. stress resilient (Wistar rats).
Methods: Pups were subjected to either 180-min daily maternal separation or 15-min separation (neonatal handling) during the first two postnatal weeks; depressive- and anxiety- like behaviors were assessed in adult offspring.
Results: In Wistar rats, maternal separation enhanced anxiety-like behaviors, reducing exploration in the Open Field (OF), increasing latency to enter the OF center, and decreasing social interaction. In contrast, maternal separation decreased anxiety- and depressive- like behaviors in Wistar-Kyoto offspring, leading to increased OF exploration, decreased latency to obtain food in the novelty suppressed feeding test, enhanced social interaction, and diminished Forced Swim Test immobility. Maternally-separated Wistar-Kyoto rats also showed: decreased resting heart rate, increased heart rate variability, and increased whole genome methylation in the hippocampus as compared to their neonatally-handled counterparts.
Conclusions: Since Wistar-Kyoto rats exhibit heightened stress susceptibility, our findings are consistent with the match/mismatch theory of disease and the predictive adaptive response triggered by early-life stress exposure to confer resilience later in life. Future studies will be required to elucidate the neurobiological underpinnings of these contrasting behavioral effects.
Keywords: rat, depression, cardiovascular, anxiety.
Disclosure: Nothing to Disclose.

M81. Cuprizone Short-term Exposure as a Potential Model for Psychosis-related Brain Changes

Mari Kondo*, Daisuke Fukudome, Catherine Foss, Jennifer Coughlin, Martin Pomper, Akira Sawa

Johns Hopkins University School of Medicine, Baltimore, Maryland

Background: Recent studies have suggested inflammatory processes in the onset and pathophysiology of schizophrenia (SZ) and mood disorders, but its mechanism remains elusive. The maternal immune activation model is a valuable tools for understanding disease pathology, however, we sought an alternative, higher throughput model. Here we propose the new "cuprizone short-exposure" (CSE) mouse model that manifests immune/inflammatory and glial changes in parallel with neurochemical and behavioural endophenotypes associated with psychosis (1).
Methods: The CSE mouse model uses short exposure to the copper chelator, cuprizone, in young adult (8 weeks old) C57BL/6J male mice. For 1 week, mice were fed either a diet containing 0.2% cuprizone, or a control diet consisting of standard mouse chow. Ex vivo autoradiography for TSPO, a marker of activated glia and immune cells, was conducted using the clinical radioligand, DPA-713. Neurochemical, histological, and behavioral assays are as described (1, 2).
Results: Four to eight weeks of cuprizone exposure has traditionally been used as a model of multiple sclerosis to study demyelination and remyelination. Importantly, we have confirmed by electron microscopy and black-gold staining that our 1-week exposure model (CSE) displays no robust demyelination. In addition to increased IL-6 expression in GFAP-positive cells, autoradiography revealed increased binding of TSPO. Behavioural testing uncovered a deficit in working and short-term memory. More complex memory tests are underway to assess cognitive flexibility

and specifically examine the connectivity between prefrontal cortex and hippocampus. Amphetamine elicited hyperlocomotion and a delay in return to baseline in the CSE mice. In vivo microdialysis highlighted a corresponding increase in dopamine in the nucleus accumbens.
Conclusions: The novel "cuprizone short-exposure" (CSE) mouse model will allow us to study the link between inflammation, dopaminergic neurotransmission, deficits in functional connectivity, and behavioural changes. References: 1) Tezuka et al., 2013 (Neurobiol Dis) 2) Niwa et al., 2013 (Science) # denotes equal contribution.
Keywords: inflammation, mouse model, cuprizone short-exposure, psychosis.
Disclosure: Nothing to Disclose.

M82. Clarifying the Role of α4β2 and α7 Nicotinic Acetylcholine Receptors for the Ability of Lurasidone to Restore Novel Object Recognition in Sub-chronic Phencyclidine-treated Rats

Masanori Miyauchi*, Herbert Meltzer, Lakshmi Rajagopal, Mei Huang, Yoshihiro Oyamada

Northwestern University Feinberg School of Medicine, Chicago, Illinois

Background: Acetylcholine (ACh) is a major contributor to cognitive decline in Alzheimer's disease as well as normal aging and schizophrenia. Nicotinic ACh receptors (nAChRs), especially α4β2 and α7 nAChRs, along with muscarinic ACh receptors (mAChRs), M1 and M4 mAChRs, have been targets to treat the cognitive impairment in schizophrenia (CIS). We have shown that lurasidone, an atypical antipsychotic drug increases both ACh and DA release in mouse medial prefrontal cortex (mPFC) (Huang et al., 2014). We also reported that lurasidone improved the deficit in novel object recognition (NOR), an analogue of human declarative memory, induced by sub-chronic phencyclidine (scPCP), an N-methyl-D-aspartate (NMDA) receptor antagonist in rats (Horiguchi et al., 2011). Recently, we reported that the effect of lurasidone to restore NOR in rats was blocked by mecamylamine, a non-selective nAChR antagonist, but not by scopolamine, a non-selective mAChRs antagonist (Miyauchi et al., SfN, 2014). The aim of this study was to further investigate the contribution of α4 nAChR and α7 nAChR to the ability of lurasidone to improve the scPCP induced NOR deficit in rats.
Methods: Female Long-Evans rats received vehicle or PCP (2 mg/kg, b.i.d.) for 7 days, followed by a 7-day washout. Control rats were administered dihydro-β-erythroidine hydrobromide (DHβE), an α4 nAChR antagonist, or methyllycaconitine (MLA), an α7 nAChR antagonist. The scPCP-treated rats received DHβE or MLA 15 min before they were treated with an effective dose of lurasidone to restore NOR. We also tested single doses of the α4β2 partial agonist, varenicline and α4β2 agonist, A-85380, acutely in scPCP-treated rats alone and sub-effective doses (SED) in combination with SED lurasidone in the scPCP-treated rats. The NOR procedure has been described elsewhere (Horiguchi et al., 2011; Snigdha et al., 2010).
Results: Acute administration of DHβE and MLA prior to acquisition trial did not induce an NOR-deficit in normal rats. Pre-treatment with DHβE or MLA alone or in combination also did not block the ameliorating effect of lurasidone in scPCP-treated rats. However, varenicline (1 mg/kg) or A-85380 (0.3 mg/kg) alone acutely reversed the scPCP-induced NOR deficit. And the SEDs of varenicline (0.3 mg/kg) and A-85380 (0.1 mg/kg) co-administered with SED lurasidone (0.03 mg/kg), acutely reversed the NOR deficit.
Conclusions: This study demonstrates that neither an α4 nAChR antagonist, DHβE, nor an α7 nAChR antagonist, MLA alone blocks NOR in naïve rats nor do they, alone, or in combination, block the effect of lurasidone to restore NOR in scPCP-treated rats. However, the combination of α4β2 nAChR partial agonist, varenicline, or the α4β2 nAChR agonist, A-85380 with SED lurasidone, restored NOR in the scPCP-treated rats, indicating α4β2 nAChR agonism contributes to the efficacy of lurasidone in this model. Data regarding the role of α7 nAChR stimulation on NOR will be presented at the Meeting. In summary, these results suggest that the ACh efflux in mPFC induced by lurasidone improves cognition, in part, through α4β2 nAChR. However, other effects of lurasidone are able to restore the NOR deficit even when α4 and α7 are blocked. Future studies will clarify the contribution of nAChRs to the efficacy of lurasidone.
Keywords: novel object recognition, acetylcholine, atypical antipsychotic drug.
Disclosure: Dr. Meltzer has been consulting and receives research fundings form Sumitomo Dainippon. Dr. Oyamada and Dr. Miyauchi are employees of Sumitomo Dainippon Pharma.

M83. ALK in the Ventral Tegmental Area Regulates Binge-like Ethanol Consumption, Ethanol Reward and Dopamine Receptor Sensitivity in Mice

Amy Lasek*, John Dutton, Hu Chen, Chang You, Mark Brodie

University of Illinois at Chicago, Chicago, Illinois

Background: Binge drinking is a pattern of excessive alcohol consumption exhibited by 18% of adults in the United States. Binge drinking is responsible for over half of the 80,000 deaths associated with excessive alcohol use and is attributed to several adverse health outcomes. We previously found that polymorphisms in human ALK are associated with variations in ethanol sensitivity and that mouse ALK regulates binge-like ethanol consumption. ALK is a receptor tyrosine kinase expressed in the nervous system that is oncogenic when mutated. Small-molecule inhibitors targeting ALK have been developed for cancer therapy. Here, we tested whether acute inhibition of ALK would alter binge-like ethanol consumption and ethanol reward in mice. We also examined whether Alk acts in the ventral tegmental area (VTA) to regulate these behaviors, since the VTA is a key brain region involved in the rewarding and reinforcing effects of ethanol. Finally, we tested whether inhibition of ALK can affect the firing properties of putative dopamine (pDA) neurons in the VTA.
Methods: Mice were treated systemically with the ALK inhibitor, TAE684, and tested for binge-like drinking using

the drinking in the dark (DID) protocol and ethanol reward using conditioned place preference (CPP). To determine if ALK expression in the VTA is important for binge-like ethanol consumption and reward, a lentiviral-delivered short hairpin RNA (shRNA) targeting Alk or a non-targeting control shRNA was delivered into the VTA and mice were tested for DID and CPP. We performed extracellular recordings of pDA neurons in the VTA in brain slices treated with TAE684 or in slices from mice infected with Alk shRNA.
Results: Mice treated with TAE684 or with Alk shRNA in the VTA drank less ethanol than controls and showed reduced ethanol CPP. Treatment of VTA slices with TAE684 or downregulation of ALK in the VTA with Alk shRNA did not affect the baseline or ethanol-stimulated firing of pDA neurons. However, TAE684 treatment or Alk shRNA attenuated dopamine D2 autoreceptor desensitization in pDA neurons. Interestingly, we found that ethanol consumption in the DID protocol also reduced D2 receptor desensitization in pDA neurons in the VTA.
Conclusions: These data suggest that ALK activity in the VTA promotes binge-like ethanol consumption and ethanol reward. A potential mechanism for the ability of ALK to regulate behavioral responses to ethanol is through the desensitization of dopamine D2 receptors in the VTA. We hypothesize that the normal function of ALK is to facilitate the trafficking of dopamine D2 receptors. Finally, these data support the possibility that ALK could be a novel therapeutic target for the development of small molecule inhibitors used to reduce excessive alcohol consumption.
Keywords: binge drinking, reward, ALK, dopamine.
Disclosure: Nothing to Disclose.

M84. Electroconvulsive Seizures Require Adult Neurogenesis to Rescue Behavior in a Model of Stress-induced Depression

Robert Schloesser, Dennisse Jimenez, Sophie Orvoen, Nicholas Hardy, Kristen Maynard, Mahima Sukumar, Alain Gardier, Denis David, Keri Martinowich*

Lieber Institute for Brain Development, Baltimore, Maryland

Background: Neurogenesis continues throughout life in the dentate gyrus of the hippocampus. Hippocampal neurogenesis is positively influenced by antidepressant treatments, but negatively influenced by exposure to stress and elevated glucocorticoids. Adult hippocampal neurogenesis has been identified as a partial mediator of the effects of various antidepressant treatments. Electroconvulsive seizure (ECS) therapy, a highly effective treatment for depression, robustly stimulates hippocampal neurogenesis. However, whether ECS requires newborn neurons for its behavioral effects is not known.
Methods: We utilized immunohistochemistry and animal behavior studies to assess the effects of ECS on hippocampal neurogenesis in a model of chronic corticosterone-induced anxiety/depression. We first analyzed the effects of ECS on newborn neuron formation, dendritogenesis and maturation in response to corticosterone administration. We then tested the effects of ECS on corticosterone induced anxiety/depressive-like behavior in wild-type mice as well as mice in which adult neurogenesis was conditionally ablated.
Results: First, we show that ECS increases new neuron formation as well as the dendritogenesis and maturation of newly born neurons. Moreover, ECS treatment rescues the deleterious effects of chronic corticosterone on newborn neuron formation and reverses corticosterone-induced anxiety/depressive-like behavior in wild-type mice. Finally, we show that ECS is ineffective in rescuing corticosterone-induced anxiety/depressive-like behaviors in mice lacking neurogenesis.
Conclusions: ECS is capable of reversing the deleterious effects of chronic corticosterone on newborn neuron formation and anxiety/depressive behavior. The behavioral effects of ECS in this model of anxiety/depression depend on the presence of newly born neurons.
Keywords: neurogenesis, hippocampus, ECT, depression.
Disclosure: Nothing to Disclose.

M85. Effects of Early Methylphenidate Exposure on CP-55,940-induced Conditioned Place Preference in Young Adult Male Rats

Cynthia Crawford*, Christopher Plant, Michelle Stone

California State University, San Bernardino, California

Background: Longitudinal studies show that a childhood diagnosis of ADHD is correlated with increased cocaine usage during adolescence or early adulthood. While these studies do not assess the role of psychostimulant treatment in later cocaine use, preclinical data for our laboratory and others suggest that treatment with methylphenidate during childhood and adolescence could contribute to this increase in drug intake. In addition, clinical studies show that individuals with a childhood ADHD diagnosis are more likely to abuse a number of drugs including, alcohol, tobacco, and cannabis. In particular, a diagnosis of ADHD during childhood is strongly related to later cannabis use. Thus, the goal of the present study was to determine whether early methylphenidate exposure alters the rewarding properties of the cannabinoid agonist, CP 55,940. To this end we exposed rats to methylphenidate during the late childhood period and later assessed CP-55,940-induced conditioned place preference (CPP) in adulthood.
Methods: Male Sprague-Dawley rats were injected with methylphenidate (0, 0.5, 2, or 5 mg/kg, ip) twice daily for 10 consecutive days beginning on postnatal day (PD) 21. Injections were separated by 6 hrs. Starting on PD 60, CP-55,940-induced CPP was assessed using a 14-day biased CPP procedure, consisting of one preconditioning day, 10 conditioning days, one test day and two rest days. The first rest day was after preconditioning and the second rest day was after the last conditioning trial. Rats were pre-exposed to CP-55,940 (0, 10, 20, or 30 μg/mg, ip) 30 minutes after the preconditioning session. The rats were pre-exposed to the same dose of CP 55,940 as they received in the conditioning phase. The preconditioning and test sessions were 15 min long while conditioning sessions lasted 30 min. Data for all sessions were recorded using Noldus EthoVision XT 9 video and animal tracking software.

Results: CP-55,940 had a dose-dependent effect on time spent in the drug-paired room. Specifically, rats given the 20 μg dose of CP-55.940 showed a preference for the drug paired room (i.e., the rats spent more time on the test day in the drug paired room than on the preconditioning day), while rats given the 10 or 30 μg doses did not differ in the time spent in the drug paired room from vehicle treated rats. Pre-exposure to methylphenidate did not significantly alter the preference for the drug paired room although there was a non-significant ($p < 0.9$) trend for rats treated with the (0.5 or 2 mg/kg) dose to have higher preference scores as compared to vehicle treated rats. Interestingly, early treatment with methylphenidate (5 mg/kg) also increased the time spent in the white room on the preconditioning day as compared to vehicle-treated rats.
Conclusions: As expected, we found that young adult male rats developed a preference for the compartment paired with the cannabinoid, CP-55,940. This preference, however, was not significantly altered by early methylphenidate treatment. Methylphenidate did have some long-term effects as rats treated with the high dose (5 mg/kg) showed a reduction in the normal preference for the black compartment. It is possible the increased time spent in the white compartment indicates a reduced level of anxiety in methylphenidate-treated rats.
Keywords: CPP, methylphenidate, cannabinoid, reward.
Disclosure: Nothing to Disclose.

M86. Social Stress Disrupts Reward Responsiveness in Rats

Andre Der-Avakian*, Manoranjan D'Souza, Diego Pizzagalli, Athina Markou

University of California at San Diego, La Jolla, California

Background: Stress can precipitate the onset of many neuropsychiatric disorders, particularly those that are characterized by reward deficits. For example, reward responsiveness, defined as the propensity to modulate behavioral choices as a function of prior reinforcement experience, is disrupted in humans with major depression and bipolar disorder, and the severity of reward responsiveness deficits predicts treatment outcome. We recently demonstrated that reward responsiveness can be assessed in rats using a translational behavioral task that is analogous to the task used in humans (Der-Avakian et al., Translational Psychiatry 2013). The aim of the present study was to determine whether social defeat in rats, a form of social subordination stress, would produce reward responsiveness deficits.
Methods: Male Wistar rats were trained in a signal detection task to discriminate two tones varying in duration. Correct identification of each tone was reinforced with a food pellet until rats were able to reliably differentiate between both tones. Rats were then exposed to either repeated social defeat for three days ($n = 19$) or no stress ($n = 20$), followed by a reward responsiveness test 24 hr later. A probabilistic reinforcement schedule was introduced during the test session such that one tone (rich) was reinforced three times more frequently than the other tone (lean). Increased reward responsiveness was defined as an increased response bias for the rich stimulus irrespective of which stimulus was presented. Discriminability, a measure of how well rats differentiated the two tones, and accuracy were also measured.
Results: In the non-stressed control group, rats developed a response bias for the more frequently reinforced rich stimulus, reflecting increased reward responsiveness. Conversely, social defeat blunted response bias for the rich stimulus, reflecting decreased reward responsiveness. There was no effect of social defeat on discriminability, suggesting that stressor exposure did not affect the rats' ability to discriminate the two tones. Control rats were more accurate in identifying the rich vs. lean stimulus, whereas socially defeated rats were equally accurate in identifying both rich and lean stimuli. Control rats were also more accurate than socially defeated rats in identifying the rich stimulus.
Conclusions: The lack of response bias toward rewards and the equal responding for more (rich) and less (lean) frequent reinforcement in socially defeated rats suggests that exposure to the stressor disrupted reward responsiveness. This disruption in reward responsiveness in rats is similar to that observed in humans with major depression and bipolar disorder and in healthy humans exposed to stress. Thus, stress-induced disruption of reward responsiveness may contribute to the development of reward deficits commonly observed in neuropsychiatric disorders. Moreover, these results provide a translational framework to further investigate the neurobiological mechanisms underlying stress-induced reward responsiveness deficits in parallel between rats and humans.
Keywords: stress, reward, depression, anhedonia.
Disclosure: Dr. Markou has received contract research support from Astra-Zeneca, Bristol-Myers Squibb Co., and Forest Laboratories and honoraria/consulting fees from AbbVie for studies unrelated to this project over the past 2 yrs. Dr. Pizzagalli has received contract research support from Advanced Neurotechnology North America and Pfizer and honoraria/consulting fees from Advanced Neurotechnology North America, AstraZeneca, Ono Pharma USA, Servier and Shire for studies unrelated to this project over the past 2 yrs.

M87. Effects of Analgesic Drugs in an Operant Assay of Nociception

Jack Bergman*, Brian Kangas

McLean Hospital, Belmont, Massachusetts

Background: The effective management of pain is a longstanding public health concern. Morphine-like opioids have long been front-line analgesics, but produce undesirable side effects that can limit their application. Slow progress in the introduction of improved medications for pain management over the last 5 decades has prompted a call for innovative translational research, including new preclinical assays. Most current in vivo procedures (e.g., tail flick, hot plate, warm water tail withdrawal) assay the effects of nociceptive stimuli on simple spinal reflexes or unconditioned behavioral reactions. However, clinical treatment goals may include the restoration of previous

behavioral activities, which can be limited by medication-related side-effects that are not measured in such procedures. The present studies validate an apparatus and procedure to study the disruptive effects of nociceptive stimuli on voluntary behavior in nonhuman primates, and the ability of drugs to restore such behavior through their analgesic actions.
Methods: Squirrel monkeys were trained to respond for a highly palatable food reinforcer by pulling down a cylindrical thermode. Next, experiments were conducted in which the temperature of the thermode was increased stepwise until responding stopped. Determinations of nociceptive thresholds were conducted across varying parameters of the response requirement. Finally, tests with the opioids morphine and buprenorphine, the NOP agonist SCH 221510, the cannabinoid Δ9-tetrahydrocannabinol (Δ9-THC), the sedative pentobarbital, and the psychomotor stimulant d-amphetamine were conducted to assess their antinociceptive effects under these conditions. In addition, morphine and SCH 221510 were further studied following pretreatment with respectively, the antagonists naltrexone and J-113397.
Results: A reliable and orderly decrease in thermal threshold was observed as a function of increased pull duration requirements. The μ-opioid agonist morphine, the mixed action μ-opioid partial agonist/κ-opioid antagonist buprenorphine, and the NOP agonist SCH 221510 produced dose-related and significant increases in thermal threshold values. In contrast, Δ9-THC, pentobarbital, and d-amphetamine produced no significant antinociceptive effects in the present studies. Tests with the antagonists naltrexone and J-113397 verified that the antinociceptive effects of morphine and SCH 221510 were due to, respectively, opioid and NOP receptor-mediated actions. In addition, the pKB values of naltrexone + morphine and J-113397 + SCH 221510 were similar to those obtained in the warm water tail withdrawal assay with nonhuman primates.
Conclusions: In the present studies, the nociceptive effects of the thermal stimulus were evident by the disruption of ongoing behavior, permitting antinociception to be defined by its restoration. This assay yielded highly replicable thermal thresholds and, as expected, the μ-opioids morphine and buprenorphine produced dose-related anti-nociceptive effects. However, the dose range and magnitude of effects were likely limited by competing sedative and stuporific effects that precluded responding at doses below those used in other procedures. The NOP agonist SCH 221510 displayed anti-nociceptive actions comparable to, or exceeding, those of morphine, perhaps reflecting its greater behavioral selectivity as well as the contribution of its documented anxiolytic effects. The absence of effects with Δ9-THC, pentobarbital, and d-amphetamine, which do not typically produce anti-nociception, further validate the utility of the present assay procedures. In summary, results of the present studies illustrate the application of operant procedures to evaluate nociception and the anti-nociceptive effects of centrally active analgesics.
Keywords: morphine-like opioids, operant antinociception, NOP agonists, analgesics.
Disclosure: Nothing to Disclose.

M88. Electrophysiological Properties of Locus Coeruleus-Prefrontal Cortical Projection Neurons in Normal and Inattentive Rats

Barry Waterhouse*, Daniel Chandler, Eric Prouty, Wen-Jun Gao

Drexel University College of Medicine, Philadelphia, Pennsylvania

Background: The noradrenergic nucleus locus coeruleus (LC) is the primary source of norepinephrine (NE) to the neocortex and has traditionally been considered to operate as a homogenous regulator of forebrain activity. We have recently demonstrated that molecularly and electrophysiologically distinct assemblies of LC-cortical projection neurons differentially innervate medial prefrontal cortex (mPFC) and primary motor cortex (M1) in the Sprague-Dawley rat (SD) such that those that project to mPFC are more spontaneously active and electrically excitable (Chandler et al, PNAS, 2014). Because of the distinct roles that these cortical regions maintain in executive versus motor operations, and the robust actions of NE on PFC function and its associated behaviors, we hypothesized that the properties of these cortical projection neurons may vary in animal strains that display behavioral abnormalities.
Methods: To test this hypothesis, we performed whole-cell patch clamp recordings of retrogradely labeled LC neurons which project to either mPFC or M1 in animal models expressing features that are characteristic of combined and inattentive subtypes of attention deficit hyperactivity disorder, the spontaneously hypertensive rat (SHR; combined subtype) and Charles River Wistar Kyoto rat (WKY-CR; inattentive subtype).
Results: The data show that both the resting membrane potential and action potential threshold of mPFC and M1 projection neurons are more hyperpolarized in the WKY-CR strain than in the SHR. In both strains, the spontaneous firing rate of mPFC projection neurons was greater than that of M1 projection neurons, but they displayed similar levels of discharge in response to current injection. Importantly, the spontaneous firing rate of mPFC and M1 projection cells in both strains was greater than those seen in the SD rat.
Conclusions: These findings suggest that under baseline waking conditions, more NE may be released into the mPFC than M1 of these animal models of inattention, but during activation of the nucleus as would occur during arousal and vigilance, more uniform concentrations of NE may be achieved across LC projection fields. This is in contrast to the LC of the SD rat whose projection patterns and firing properties suggest differential release of NE in cortical projection fields that are associated with executive function and motor control across all phases of wakefulness. These strain-specific differences may have implications for the behavioral abnormalities displayed by the SHR and WKY-CR and allude to a potential mechanism for the efficacy of psychostimulants such as methylphenidate that target the noradrenergic system and and impact executive functions mediated by the PFC.
Keywords: noradrenergic, locus coeruleus, prefrontal cortex, spontaneously hypertensive rat.
Disclosure: Nothing to Disclose.

M89. Ventral Tegmental Area Cholinergic Mechanisms Mediate Depression-related Behavior in the Forced Swim Test

Nii Addy*, Eric Nunes, Robert Wickham

Yale University School of Medicine, New Haven, Connecticut

Background: Recent studies have revealed a causal role for midbrain dopamine (DA) activity in the manifestation of both pro-depressive and antidepressant-like behavioral phenotypes in preclinical rodent models of depression. These findings raise the possibility that processes which function to regulate phasic DA activity may mediate depression-related behavior. Recent data from our laboratory and others' has shown that midbrain cholinergic receptors in the ventral tegmental area (VTA) powerfully regulate phasic DA neuronal activity and phasic DA release. Evidence from both human and animal studies strongly suggest that dopaminergic and cholinergic mechanisms likely play important roles in the pathogenesis of depression. However, the role of VTA cholinergic regulation of depression-related behavior is currently unclear. In this study, we used a preclinical rat model to: 1) examine the role of VTA cholinergic mechanisms in depression-related behavior, and 2) to identify the class of VTA acetylcholine receptors (AChRs) that mediate these behaviors. Such work is important to delineate the critical neuronal circuits that mediate depression and to identify specific receptors that may serve as effective therapeutic targets for treating depression.
Methods: Examination of pro-depressive and antidepressant-like behavioral phenotypes was examined using the forced swim test (FST) in male Sprague-Dawley rats. A subset of subjects underwent intracranial cannulation surgery to allow for subsequent site-specific administration of cholinergic drugs to activate or block AChRs in the ventral tegmental area (VTA). On test day, subjects received VTA infusion of specific cholinergic drugs immediately prior to FST. Each FST session was video recorded and subjects' immobility time was subsequently scored by an investigator blind to the experimental condition.
Results: Either systemic or VTA-specific administration of the acetylcholinesterase inhibitor, physostigmine (systemic doses: 0, 0.06, or 0.125 mg/kg, VTA doses: 0, 1 or 2 microgram/side) led to a dose-dependent increase in immobility time in FST (one-way ANOVA, $p<0.001$ for systemic, $p<0.05$ for VTA), indicative of a pro-depressive behavioral response. Importantly, systemic or VTA-specific administration of physostigmine did not alter locomotor activity in locomotor control experiments. In addition, the pro-depressive effect of VTA physostigmine infusion was site-specific, as infusion at a site 2 mm dorsal to the VTA had no significant effect on immobility in FST ($p>0.05$). In contrast to physostigmine, VTA infusion of the nicotinic AChR antagonist, mecamylamine (0, 3 or 30 microgram/side), or the muscarinic AChR antagonist, scopolamine (0, 2.4 or 24 microgram/side), decreased immobility time in FST (one-way ANOVA, $p<0.05$ for mecamylamine, $p<0.001$ for scopolamine) reflective of an antidepressant-like behavioral response. Given the opposing effects of physostigmine and AChR antagonist administration in FST, we sought to determine whether AChR antagonists could reverse the pro-depressive effects of physostigmine. Data from our co-administration experiments revealed that the pro-depressive effects of VTA physostigmine were reversed by co-infusion of scopolamine, but unaltered by co-administration of mecamylamine.
Conclusions: Our results show that increasing VTA cholinergic tone or blocking VTA AChRs has opposing effects in FST and provides strong evidence for a role of VTA cholinergic mechanisms in depression-related behavior. Given the recent evidence for a causal role of VTA phasic DA activity in depressive-like behavior and the ability of VTA AChR blockade to reduce downstream phasic DA release, it is possible that the observed effect of VTA AChR antagonists may be mediated by their ability to decrease VTA phasic DA activity. However, future experiments are required to examine this potential mechanism. Importantly, the results of our reversal experiment specifically point to VTA muscarinic AChRs, and not nicotinic AChRs, as the critical AChR class that mediated the pro-depressive effect of VTA physostigmine. In future experiments, we will use additional preclinical models of depression to further determine the role of VTA cholinergic activity and downstream intracellular signaling targets in mediating pro-depressive behavioral responses to acute and chronic stress.
Keywords: depression, acetylcholine, ventral tegmental area, forced swim test.
Disclosure: Nothing to Disclose.

M90. Functional and Behavioral Characterization of a Constitutively Active Mutant (V175D) Form of the Human 5-HT2A Receptor

Susan Powell*, Adam Halberstadt, Caitlin McOmish, Victoria Risbrough, Mark Geyer, Jay Gingrich, Ethan Burstein

University of California at San Diego, La Jolla, California

Background: The serotonin 5-HT2A receptor plays a role in several psychiatric disorders and is targeted by serotonergic hallucinogens and by atypical antipsychotics such as clozapine. Interestingly, several antipsychotic drugs have been found to act as inverse agonists at the 5-HT2A receptor, and the selective 5-HT2A inverse agonist pimavanserin has shown promise in treating psychosis associated with Parkinson's disease (Cummings et al., Lancet 383[9916]:533-40, 2014). Similar to other G-protein coupled receptors, structural mutations can render the 5-HT2A receptor constitutively active. For example, a single mutation of amino acid 322 can increase the constitutive activity of the receptor (Egan et al, J Pharmacol Exp Ther 286:85, 1998), and preliminary studies have indicated that aspartate substitution at Val175 of the 5-HT2A receptor (V175D) can also increase the level of constitutive activity.
Methods: We investigated the functional and behavioral effects of the V175D substitution in vitro and in vivo in mice. The effect of the mutation on the activity of

the human 5-HT2A (h5-HT2A) receptor in vitro was assessed using the Receptor Selection and Amplification functional assay (RSAT; Weiner et al., J Pharmacol Exp Ther 299:268, 2001). NIH3T3 cells were transfected with h5-HT2A -V175D (constitutively active mutant or CAM) or native wild-type (WT) h5-HT2A plasmid DNA. Homologous recombination was used to insert the h5-HT2A -V175D receptor into the mouse endogenous 5-HT2A gene locus under the control of the mouse 5-HT2A promoter. 5-HT2A CAM mice were then evaluated for acoustic startle and prepulse inhibition, basal and 5-HT2A agonist-induced head twitch response (HTR), and conditioned fear learning. Startle and PPI testing were performed in SR-LAB startle chambers, using an experimental session that was specified previously (Toth et al. 2014; Neuropsychopharmacol. 39:1409-1419). HTR was measured as described previously (Halberstadt et al., J Psychopharmacol 25:1548, 2011). Mice were treated IP with vehicle or 1 mg/kg of the 5-HT2A agonist 2,5-dimethoxy-4-iodoamphetamine HCl (DOI), and behavior was assessed for 10 min. Fear conditioning was performed using the Video Freeze system from MedAssociates. Briefly, mice were presented with 3 tone-shock pairings of a tone (CS: 20 sec, 75 dB, 4 kHz) that coterminated with a foot shock (US: 2 sec, 0.5 mA) with an inter-trial interval (ITI) of 40 s. Subjects were tested on 3 subsequent days for context fear retention (Day 2), retention of auditory fear (cued retention test) combined with extinction training (Day 3), and extinction recall (Day 4).

Results: Depending upon the amount of DNA transfected, the level of basal activity displayed by the V175D mutant receptor was up to 3-fold greater than the WT receptor. Concentration-response studies demonstrated that there was a leftward-shift in the 5-HT dose-response, whereas the pIC50 of ritanserin (a 5-HT2A inverse agonist) was not altered by the mutation. Mice expressing the h5-HT2A -V175D receptor heterozygously (5-HT2A CAM mice) showed increased acoustic startle responses (gene effect: $F(1,36) = 18.59$, $p = 0.0001$) but no change in prepulse inhibition of startle. 5-HT2A CAM mice showed increased basal and DOI-induced HTR (gene effect: $F(1,19) = 6.03$, $p < 0.03$). Additionally, 5-HT2A CAM mice showed decreased cued fear learning as assessed by conditioned freezing (gene effect: $F(1,37) = 6.84$, $p < 0.02$).

Conclusions: These findings confirm that mutation of amino acid 175 can render the 5-HT2A receptor constitutively active, and demonstrate that high levels of 5-HT2A receptor constitutive activity can produce behavioral alterations in mice. Deficits in fear learning may indicate abnormalities in 5-HT2A receptor function in hippocampus and amygdala. Mice with constitutively active 5-HT2A receptors offer a novel approach for drug discovery and an increased understanding of the contribution of 5-HT2A receptors to psychosis and hallucinogen action.

Keywords: serotonin receptor, hallucinogen, psychosis, constitutive activity.

Disclosure: S. Powell has had a service contract with Servier Pharmaceuticals. M. Geyer holds an equity interest in San Diego Instruments. E. Burstein is an employee of ACADIA Pharmaceuticals.

M91. Cortisol Patterns of Response to Stress, Dexamethasone, and ACTH Predict Extremes in Temperament that are Related to Future Psychopathology: A Nonhuman Primate Model

J. Dee Higley*, Claudia Gonzales, John Capitanio

Brigham Young University, Provo, Utah

Background: One of the most replicated findings in depression is abnormal HPA Axis functioning. These studies often show high cortisol response to stress and altered response to ACTH stimulation in depression. As a consequence the dexamethasone suppression test was developed and once used as a test for depression. Studies showed, however, that while feedback was aberrant in depressives, it was also altered in other forms of psychopathology, limiting its utility as a biological test of depression. Likewise, high stress-induced cortisol and response to ACTH are also altered in other forms of psychopathology and in many cases even in individuals showing no psychopathology. Few studies have assessed patterns of cortisol response across these different measures or developed standardized set of tests to measure patterns of response across different measures. Using a nonhuman primate model designed to test temperament and cortisol response patterns to prolonged acute stress, dexamethasone suppression, and ACTH stimulation, we tested a large sample of infant macaques for aberrant patterns of cortisol response and extremes in temperament. Recent studies show that macaque infant temperament categories parallel those seen in human infants and like humans, are related to adult psychopathology.

Methods: Subjects for this study were 1753, three-four-month-old infant rhesus macaques. They were separated from their mothers for 25 hours and tested in a bio-behavioral assessment paradigm, during which 4 blood samples were obtained and later assayed for plasma cortisol levels. Cortisol Testing - Over the course of the 25 hours, four blood samples were obtained via femoral venipuncture while the subjects were manually restrained and awake. The first two samples were obtained following the stressor of separation and exposure to novel environments. The first blood sample was obtained 2 h after the infants were separated from their mothers and placed in a novel environment. The second blood sample was obtained 5 h later. Immediately after the second blood sample, infants were injected intramuscularly with 500 mg/kg of dexamethasone. A third blood sample was then obtained the next morning at 0830, immediately after which 2.5 IU of ACTH was injected intramuscularly. The final blood sample was obtained 30 minutes later. Temperament - During this period, infants were given a battery of tests to assess behavioral reactivity. This battery included assessment of behavioral responses to the separation and relocation; interactions with novel stimuli; responses to a human intruder; and responses to video playback of social. Data Analysis - The average pattern of change from A.) stress-induced cortisol sample 1 to stress-induced cortisol sample 2, B.) stress sample 2 to dexamethasone-elicited cortisol sample 3, and C.) dexamethasone-elicited sample 3 to ACTH-induced cortisol sample 4 was first established.

Based on the average pattern and the theoretical expected trajectory of change, 14 cortisol response patterns showed a sufficient sample size for analyses. ANOVAs were used with cortisol response pattern across the four samples as the independent (grouping) variable, sex as a covariate, and the dependent variable was temperament factor score. ANOVAs were followed by latent class analyses, to assess for statistical correctness of the a priori grouping.
Results: Pearson correlations showed no correlation between any of the four individual cortisol samples and factor scores for temperament. However, ANOVA showed a significant group difference between aberrant cortisol patterns of response and extremes in reactive temperament ($p < 0.01$). Latent class modeling showed a replicable, 4-Class pattern of response solution, with the most deviant class showing a highly significant classification in temperamental extremes, identifying extremes in temperamental measures of nervousness and composure ($p < 0.00009$).
Conclusions: While traditional measures of deviant HPA Axis functioning that utilize measures of high vs low cortisol were unable to discriminate temperamental extremes, this unique method of using cortisol response patterns across repeated tests showed a strong relationship with temperamental extremes. This suggests that cortisol patterns of response to a variety of tests may provide a more accurate window of aberrant HPA Axis functioning. Kagan's studies of human children with highly reactive temperament show that early temperament is predictive of adult anxiety disorders and affective psychopathology. Recent studies from our laboratory show parallel temperamental dimensions between rhesus and human temperamental dimensions, and a recent review concludes that like human children, early extremes in reactive temperament lead to psychopathological outcomes in rhesus. To the extent that our findings generalize to humans, our results suggest the potential to use this pattern of response to potentially more accurately classify and predict psychopathology in humans.
Keywords: cortisol, Developmental Psychopathology, non-human primate model, depression.
Disclosure: Nothing to Disclose.

M92. Variables in Rat Chronic Mild Stress Models Can Induce Differential Hypothalamic-Pituitary-Adrenal Axis Dysfunction Profiles

Catherine Sweatman, Anne-Katherine Zell, Tobias Hildebrandt, Katrin Fundel-Clemens, Rene Fuertig, Kelly Allers*

Boehringer-Ingelheim, Biberach, Germany

Background: Chronic mild stress, as with other chronic stress models, is thought to be a suitable method for studying stress-related psychiatric disease. To this end, chronic stress models demonstrate a variety of phenotypes, including behavioral and physiological changes induced by stress. The hypothalamic-pituitary-adrenal (HPA) axis is responsible for the glucocorticoid stress response and many psychiatric patients show altered (dysfunctional) HPA responses, either basal levels or stimulated. Likewise, many chronic stress animal models demonstrate altered HPA function. In this series of studies we demonstrate that by altering the age of the animals at the start of stress, and altering the type and duration of stressors can substantially change the phenotype observed, including a shift of HPA dysregulation from hypercortisolemia to hypocortisolemia. These data suggest a continuum of dysregulated responses determined by the duration of stress, type of stress, or age of stress experience.
Methods: The basic stress protocol to induce hypercortisolemia (GROUP I) was typical to published literature. In brief, animals received two stressors per day including noise, reduced cage space, wet bedding, and periods of food and water deprivation, and single housing from approximately 4 months of age. Group I animals underwent 13 weeks of the stress protocol. The protocol which induced hypocortisolemia (GROUP II) included 2-4 stressors per day, variable light cycles at weekends, and single housing from 7 weeks of age. Group II animals underwent 10 weeks of stress. The animals were single housed upon arrival, and the stress protocol began when all animals reached 300g (approx. 5-6 weeks). Faecal pellets were retrieved directly from all animals weekly at 10am for assessment with a faecal corticosterone assay. All methods were approved by the Animal Ethics committee, Regierungspraesidium Tuebingen, Germany.
Results: Corticosterone levels in Group I reached a peak of 200% of baseline values at week 5, followed by a steady decline to near control group levels by study end. These animals also gained weight at a faster rate, had increased adrenal weight at study end, and deregulated genes in prefrontal cortex and hippocampus showed an enrichment of genes regulated by glucocorticoid response elements. Behavioral testing (sucrose preference and consumption, open field, novelty suppressed feeding, forced swim test, elevated plus maze) showed inconsistent effects and did not correlate with physiological parameters. Group II animals had a steady decline in faecal corticosterone levels, prompting the assessment of corticosterone secretion circadian rhythm. These animals, compared to controls, had a complete loss of corticosterone awakening response, remaining at the same relatively low level through a 24 hour period. In addition, these animals gained weight at a slower rate, but shared an increased adrenal weight with Group I animals.
Conclusions: The results from these studies suggest that chronic stress models could be manipulated to mimic different kinds of HPA dysfunction. Furthermore, variables such as single housing from a young age, an increase from 2 to 4 stressors per day, or variable light cycles at weekends can induce a completely different corticosterone profile compared to the standard chronic mild stress protocol. The impact of this research is two-fold: Firstly, it suggests the possibility to study HPA dysfunction profiles observed in stress-related psychiatric disease, from induction to treatment. Secondly, it suggests stress induced HPA dysfunction may be a continuum, with milder chronic stress inducing a hypercortisolemia state, and somewhat more severe chronic stress resulting in hypocortisolemia. The mechanisms behind this continuum warrant further study.
Keywords: HPA, corticosterone, stress.
Disclosure: All authors are employed by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

M93. The Importance of 5-HT7 Receptor Blockade for Cognitive Enhancement and Antipsychotic Drug Action

Mei Huang, Lakshmi Rajagopal, Sunoh Kwon, Eric Michael, Herbert Meltzer*

Northwestern University Feinberg School of Medicine, Chicago, Illinois

Background: The role of the serotonin 7 receptor (5-HT7R) in cognition and treatment of positive symptoms of schizophrenia is controversial with some studies suggesting its stimulation has a negative, and others a positive, effect on cognition. There are also mixed results for control of positive symptoms. We have reported that in rats, the selective 5-HT7R antagonist, SB-269970, the atypical antipsychotic drugs (APDs), lurasidone, and amisulpride, which are potent 5-HT7R antagonists, improve the deficit in novel object recognition (NOR) induced by sub-chronic administration(sc) of the NMDA receptor antagonist, phencyclidine (PCP) through a 5-HT7R-dependent mechanism. The purpose of this study was to further explore the effects of 5-HT7Rs in cognition and psychosis with 5-HT7R antagonists in C57BL/6 wild type (WT) mice and parallel studies in constitutive 5-HT7R knockout (KO) mice using behavioral and microdialysis methods.
Methods: The effects of SB-269970 and PCP on open field locomotor activity (LMA) and the ability of JNJ18038683, a novel 5-HT7R antagonist, to block the NOR deficit produced by acute PCP or scPCP was studied in WT mice. We also examined the ability of co-administration of SB269970 to prevent the effect of scPCP to produce the NOR deficit. Further, the efflux of multiple neurotransmitters using mass spectroscopy in medial prefrontal cortex (mPFC) and dorsal striatum (dSTR) by microdialysis following PCP with and without pretreatment with SB269970 in WT mice and following PCP 10 mg/kg in KO mice was studied.
Results: The acute PCP-induced increase in LMA was significantly blunted by pretreatment with SB269970 in WT mice and in the 5-HT7R KO mice, supporting the role of 5-HT7R blockade in the antipsychotic action of lurasidone and other antipsychotic drugs. SB269970 and JNJ18038683 both acutely reversed the deficit in NOR produced by scPCP. Co-administration of higher doses of SB269970 with scPCP prevented the development of the NOR deficit after withdrawal of scPCP. The effect of acute PCP treatment to increase DA, NE, and 5-HT efflux in mPFC of WT mice was not affected by SB269970 pretreatment but the increased glutamate (Glu) efflux was blunted. Similar results were obtained in the 5-HT7R KO mice. The effect of acute PCP treatment to increase Glu, 5-HT and NE, but not DA in the dSTR was diminished by SB269970 in WT mice. The PCP-induced increase in Glu and 5-HT, but not DA or NE, in the dSTR was blunted in the 5-HT7R KO mice.
Conclusions: These findings suggest that 5-HT7R blockade is an important target for improving cognitive impairment and reducing psychotic symptoms. 5-HT7R antagonists may have promise for preventing the onset of cognitive impairment in schizophrenia. The reduced LMA and NOR deficit induced by PCP after 5-HT7R blockade or in 5-HT7R KO mice, may be due to modulation of glutamatergic or serotonergic neurotransmission, or both.

Keywords: NOR, 5-HT7, serotonin, cognition.
Disclosure: Grant support from Sumitomo Dainippon, SUnovion and Janssen Pharmaceuicals. Consultant to Forum, Lundbeck, Reviva, Forest, Eli Lilly.

M94. Algorithm-Enabled RNA Signatures Functionally Discriminate among Discrete Regions of the Fronto-limbic Circuit in Primate Brain

Clifton L. Dalgard, David M. Jacobowitz, Vijay Singh, Kadharbatcha S. Saleem, Robert J. Ursano, Harvey B. Pollard*

Uniformed Services University of the Health Sciences, Bethesda, Maryland

Background: The fronto-limbic circuit in primate brain is responsible for important psychiatric and neurological disorders, and subserves mechanisms responsible for executive function and emotional control. The molecular basis is poorly understood for functional contributions of different parts of this circuit to psychiatric and neurological diseases including PTSD, autism spectrum disorder, schizophrenia, major depressive depression, and dementias such as Alzheimer's and Parkinson's disease. Our hypothesis is that RNA signatures of different discrete regions from this circuit may provide insights into function.
Methods: To test this hypothesis we have developed a new Jacobowitz Brain Block□ for use with frozen non-human primate (NHP) brains. Using a novel knife strategy to prepare thin slices of frozen brain, we then deployed the Saleem Rhesus macaque atlas to assist dissection, and used the micropunch technique, to purify RNA from Brodmann Area 25, amygdala, anterior cingulate cortex and hippocampus. We then analyzed RNA components by comprehensive transcription profiling on an Illumina GIIx platform, and aligned the reads with the Rhesus macaque reference genome. An algorithm was written to distinguish RNAs that were significantly elevated in one of the four regions compared to the other three. This strategy was iterated for all regions, and region-specific RNA signatures were thereby identified.
Results: We find that the new method yields high quality RNA, and up to ca. 8,000 unique RNAs with FKPM's of >1/million reads in each brain region. We also find that fronto-limbic brain regions from 2 different NHPs of similar age yield quantitatively identical levels of different RNAs, with an r-value of 0.9. Finally, we find that RNA signatures can be identified that individually distinguish Brodmann Area 25, amygdala, anterior cingulate cortex and hippocampus from the other three, respectively. We developed a novel bioinformatic strategy to reduce numbers of RNAs in region-specific signatures to less than 25 RNAs each. We then used IPA and manual search protocols to test whether the region-specific RNA signatures had functional significance. We find that this novel bioinformatics strategy "automatically" identifies region-specific functional mechanisms. For example, the algorithm-enabled RNA signature for Brodmann Area 25 includes mRNAs for dopamine receptors 2 and 5 (DRD2 & DRD5). The algorithm-enabled RNA signature for the amygdala includes mRNAs for semaphorin signaling, a basic requirement for assembly and

patterning in the amygdala. The algorithm-enabled RNA signature for the hippocampus includes hippocalcin, a calcium-binding protein directly associated with long term potentiation (LTP, a learning paradigm), and other mRNAs and RNAs associated with schizophrenia, bipolar depression and temporal lobe epilepsy.
Conclusions: We conclude that the new dissection method, and the novel bioinformatics strategies applied here to the non-human primate brain, primate provide unique RNA signatures in four different discrete regions of the fronto-limbic circuit that "automatically" provide insights into function. We suggest that this new approach will provide a useful strategy for identifying changes in fronto-limbic systems biology underlying normal development, aging and disease in the human brain.
Keywords: non-human primate, Brodmann Area 25, Amygdala, Hippocampus.
Disclosure: Nothing to Disclose.

M95. Loss of a Pair-bond Partner and Reward Extinction in Prairie Voles

M. Katherine Shear*, Zoe Donaldson, Sarrana Rotgard, Harry Shair, Myron Hofer

Columbia University, New York, New York

Background: Bereavement is a highly disruptive experience that requires a period of adaptation. Yet despite its universal occurrence, adaptation to loss is virtually unstudied at a biological level. Current thinking about grief conflates it with depression, a view that fails to consider the central importance of yearning. Our multidisciplinary team reconceptualizes grief as involving not just stress-response and mood regulation systems, but also learning processes and modulation of reward circuits. Yearning during acute grief bears similarities to craving after drug withdrawal and is best understood as a manifestation of reward system activation. We posit that acute grief comprises a separation response with a strong urge for contact with the absent partner and that adaptation to a loss requires remodeling of reward processes. However, study of acute grief in humans requires intrusion into a deeply private and intensely emotional experience that many consider offensive and even unethical. Prairie voles provide a promising alternative. These socially monogamous rodents form selective pair bonds, and disruption of this bond presents a unique opportunity to investigate the neurobiology of acute grief and adaptation to loss. The neurobiology of pair bonding behavior is relatively well understood, and involves both social learning and reward systems. After bond formation, prairie voles show selective affiliative behavior towards their mate and aggression towards other conspecifics. Upon loss of their partner, they exhibit behavioral and physiological markers of distress, supporting face validity as a model of grief. However, questions remain. Does the urge for contact with the partner continue after separation? If so, does it attenuate with time? We conducted a study of conditioned place preference (CPP) examining its onset, extinction, and reinstatement. We also examined selective affiliative behavior towards the partner following extinction.
Methods: Using a conditioned place preference paradigm (CPP), male prairie voles ($n = 8$) were trained to associate a particular chamber with their mated partner. We examined preference to spend time in that chamber during pair-bonding and over a one month period following removal of the established pair-bond partner. We wished to investigate 1) occurrence and time course of CPP extinction and 2) reinstatement of CPP following extinction. We further investigated selective preference to spend time with the pair-bond partner compared to a stranger during the initial bonding period and following extinction.
Results: We found CPP was maintained in the initial period following partner loss (3 days; ($F(2) = 4.689$; $p = 0.027$) but showed evidence of extinction by 15 days ($F(3) = 1.695$; $p = 0.199$). Correspondingly, we also found that animals displayed a significant preference to spend time in contact with their mate compared with a novel female during pairing ($t(7) = 4.6$, $p = 0.002$) but that this selective preference was not present after extinction (29 days post separation) ($t(7) = 0.376$, $p = 0.718$). Further, brief, 3 hour re-exposure to the pair-bond partner after extinction reinstated CPP ($F(1) = 9.236$; $p = 0.019$), similar to the cue-induced re-instatement observed with drugs of abuse.
Conclusions: Our experiments were designed to identify reward and learning-based mechanisms related to adaptation to loss. These results support the hypothesis that reward extinction is involved in adaptation to loss of a pair-bond partner. Our results have potential implications for the time course of social reward remodeling following loss of a pair-bond in voles and provide an important time frame for studying underlying neural changes associated with adaptation to loss. Future work will address neurobiological processes that accompany these behavioral changes and test hypotheses about processes that may interfere with extinction. This work could shed light on the process of attenuation of yearning and longing seen over time among bereaved people and inform our thinking about complicated grief when such attenuation does not occur.
Keywords: partner loss, reward system, prairie voles, conditioned place preference.
Disclosure: Nothing to Disclose.

M96. Developmental Regulation of Human Cortex Transcription at Base-pair Resolution

Andrew Jaffe*, Jooheon Shin, Leonardo Collado-Torres, Jeffrey Leek, Ran Tao, Chao Li, Yuan Gao, Yankai Jia, Brady Maher, Thomas Hyde, Joel Kleinman, Daniel Weinberger

Lieber Institute for Brain Development, Baltimore, Maryland

Background: The transcriptome of the human brain changes dramatically across development and aging, with the largest gene expression changes occurring during fetal life, tapering into infancy (Colantuoni 2011, Kang 2011). Previous transcriptome characterizations used primarily microarray technologies based on pre-defined probe sequences that capture only a limited proportion of transcriptome diversity. The technological advances of RNA sequencing (RNAseq) now permit a flexible and potentially

unbiased characterization of the transcriptome at high resolution and coverage (Trapnell 2010).
Methods: We have implemented a method for RNAseq analysis at single base resolution to more fully characterize transcription dynamics. We performed deep coverage sequencing of the transcriptomes of 72 human dorsolateral prefrontal cortex (DLPFC) samples across 6 important life stages – fetal (2nd trimester), infant, child, teen, adult and elderly (n = 6 per group) – and implemented an annotation-agnostic differential expression analysis called "derfinder" to leverage the power of RNAseq without the difficulties in transcript assembly.
Results: We identified 50,650 differentially expression regions (DERs) agnostic of annotation, with significant and replicated expression changes across fetal and postnatal development. While many DERs annotated to non-exonic sequence, they were validated in cytosolic mRNA, suggesting that they are not nuclear pre-mRNAs. We found similar expression profiles of these DERs across 16 diverse human brain regions and within the developing mouse cortex, and observed expression among subsets of non-exonic DERs in diverse cell and tissue types. These DERs are enriched for active chromatin marks and schizophrenia-associated genetic loci. Lastly, we demonstrate that many expression changes are driven by changing neuronal phenotype related to differentiation and maturation.
Conclusions: These data highlight conserved molecular signatures of transcriptional dynamics across brain development, as well as the incomplete annotation of the human brain transcriptome.
Keywords: RNA sequencing, postmortem human brain, gene expression, brain development.
Disclosure: Nothing to Disclose.

M97. nNOS-expressing Interneurons in the Nucleus Accumbens Core Are a Novel Portal for Cortical Regulation of Cocaine Seeking

Alex Smith*, Michael Scofield, Peter Kalivas

Medical University of South Carolina, Charleston, South Carolina

Background: Chronic cocaine exposure produces neuroplasticity within the nucleus accumbens core (NAcore) that leads to increased vulnerability to relapse, even after protracted abstinence. Matrix metalloproteinases (MMPs) are pro-plasticity enzymes that degrade the extracellular matrix in order to promote synaptic growth and reorganization. Previous data from our lab show that both MMP-2 and MMP-9 are required for cue-induced reinstatement of cocaine seeking. Following extinction of cocaine self-administration there is a constitutive upregulation of MMP-2 in the NAcore, which produces a persistent potentiation of synapses on medium spiny neurons (MSNs; as measured by dendritic spine head diameter and AMPA:NMDA ratio). Additionally, when cocaine-conditioned cues are presented to reinstate cocaine-seeking behavior, there is a transient induction of MMP-9 activity that mediates a transient synaptic potentiation in MSNs. However, it is unknown how either of these two enzymatic inductions occurs. MMPs are secreted in an inactive pro-form, in which a critical Zn2 + molecule is positioned between a single cysteine residue in the pro-domain, and 3 cysteine residues in the enzyme active site. The enzyme is activated when Zn2 + interaction with the pro-domain cysteine is disrupted, allowing Zn2 + to fully coordinate within the active site. One process by which this occurs is S-nitrosylation of the pro-domain cysteine by nitric oxide. We hypothesized that cocaine exposure induces neuronal nitric oxide synthase (nNOS) activity that in turn increases activity of both MMP-2 and MMP-9 through S-nitrosylation. Nitric oxide is produced in the NAcore by neuronal nitric oxide synthase, inside a subpopulation of interneurons that constitutes approximately 1% of neurons in the striatum. Additionally, we hypothesize that nNOS-expressing interneurons in NAcore receive input from the prefrontal cortex (PFC), ventral tegmental area (VTA), and the dorsal raphe nucleus (DRN).
Methods: Male Sprague-Dawley rats were trained to self-administer cocaine in the presence of conditioning light/tone cues, and then this behavior was extinguished. Relapse was induced by representation of conditioned cues that reinstate drug-seeking behavior. In order to assess the effects of nNOS activity on relapse behavior, the nNOS inhibitor NPLA was microinjected into the NAcore 10 minutes prior to initiating reinstatement. In order to assess the role of NO in activating MMP-2/9, NPLA was injected 10 minutes prior to infusing a FITC-quenched gelatin peptide that fluoresces when proteolytically unquenched by either MMP, and animals were perfused 15 minutes later for analysis of fluorescence. In order to directly measure the nitrosylation state of MMP-2/9, we immunoprecipitated MMP-2 or 9 from a whole cell lysate, and used an antibody against S-nitrosocysteine to measure total protein nitrosylation in the precipitated extract. Finally, we utilized NOS1-Cre transgenic mice to selectively label afferent connections of nNOS-expressing interneurons in the accumbens. In order to to this we utilized a two-virus system; the first virus was AAV2-pEF1a-FLEX-GTB, which transduces a rabies receptor protein, a rabies glycoprotein, and eGFP. The second virus was EnvA-ΔG-Rab-mCherry. Using these two viruses, only Cre-containing neurons will express the machinery to complement the G-deleted rabies, and thus only afferents from these neurons will be infected by mCherry-expressing rabies.
Results: We have shown that inhibition of nNOS reduces both constitutive and cue-induced inductions of MMP activity, measured by in vivo zymography. Furthermore, by immunoprecipitating each MMP and probing for S-NO-cysteine, we were able to verify increased S-nitrosylation of these enzymes following extinction and reinstatement. nNOS inhibition was also found to block cue-induced reinstatement. Taken together, these findings indicate that S-nitrosylation of metalloproteinases is a novel pathway mediating synaptic potentiation following repeated cocaine exposure. We have also confirmed that the nNOS-expressing interneurons receive input from the PFC, VTA, and DRN, but not the basolateral amygdala (BLA).
Conclusions: These data show, for the first time, that nNOS activity is required for cue-induced reinstatement of cocaine seeking, and that this occurs by S-nitrosylation of MMPs, which is necessary for the transient synaptic potentiation in

MSNs underpinning reinstated cocaine seeking. Additionally, we discovered that nNOS-expressing interneurons receive heavy input from the prelimbic cortex, and smaller inputs from the VTA and DRN, with no input from the BLA. Together these data indicate that nNOS interneurons may be a "master switch" by which 1% of cells can control plasticity in the majority of neurons in NAcore.
Keywords: cocaine, reinstatement, relapse, extracellular matrix.
Disclosure: Nothing to Disclose.

M98. Dopamine D2 Receptors in Indirect Pathway Striatal Neurons Depress Gabaergic Transmission to Disinhibit Direct Pathway Striatal Neurons and Sustain Locomotion

Julia Lemos*, Alanna Kaplan, Danielle Friend, Jung Hoon Shin, Marcelo Rubinstein, Alexxai Kravitz, Veronica Alvarez

National Institute on Alcohol Abuse & Alcoholism, National Institutes of Health, Rockville, Maryland

Background: The direct and indirect pathways are the two main outputs from the striatum that control motor output in complementary and sometimes opposite ways. GABAergic medium spiny neurons that express D1 receptors form the direct pathway (dMSNs) and those expressing D2 receptors (D2Rs) form the indirect pathway (iMSNs). It has been postulated that D2Rs are activated by low levels of DA like those generated by tonic firing of midbrain DA neurons that project to the striatum and NAc. As such, D2Rs on iMSNs have the potential to play a critical role in regulating basal striatal circuit function and motor behavior. Testing these hypotheses have been difficult using conventional pharmacological techniques because D2Rs are present on several different cell types within the striatum. We generated a cell-specific D2R knockout mice that lacks D2R selectively in iMSNs, referred to here as iMSN-D2 KO mice (Drd2loxP/loxP;A2a-cre + /-).
Methods: Animals: Experiments used Drd2loxP/loxP;Adora2a-cre-/- (WT) and Drd2loxP/loxP;Adora2a-cre + /- mice (MSN-D2 KO). To differentiate between D1R- and D2R-MSN during recordings, we crossed our iMSN-D2 KO and Drd2loxP/loxP animals with a D1R-tdTomato reporter line. For ChR2 experiments Adora2A-cre + /- mice were the control group. Stereotaxic surgeries: Mice (6-8 weeks old) were given bilateral injections (300 nl per side) of AAV-EF1a-DIO-ChR2 (AV3468)-mCherry into the NAc core, AAV-DIO-hM4Di-mCherry or the mCherry were injected into the NAc core or dorsal stratium. Fast Scan Cyclic Voltammetry: 240 μm sagittal sections were prepared and maintained in ACSF, 31-33°C. Carbon fiber electrodes (working electrodes) were hand cut to approximately 100-150 μm past the capillary tip. The potential at a carbon-fiber electrode was held at -0.4 V versus Ag/AgCl, ramped to + 1.2 V and back to -0.4 V (400V/s) every 100 ms using pClamp 10.2 (with a modified headstage) and Master-8. A single monophasic electrical pulse (0.2 ms, 300μA) was applied to the slice to evoke dopamine release. Electrophysiology: (In Vitro): 240 μm sagittal sections were prepared and maintained in ACSF at 31-33°C while recording. Whole cell patch clamp recordings were made from dMSNs and iMSN using K-based internal solution when measuring AP firing. For recordings of mIPSCs, a Cs-based internal solution was used andslices were incubated in a cocktail of NBQX, CPG55845, TTX and CPP. (In Vivo): Animals were implanted unilaterally in dorsal striatum with a 32 microwire array (Omninetics). Signals were sampled, digitized, time-stamped, and stored for offline analysis using a Plexon recording system (Plexon, inc.). Single units were identified and average firing rates were determined using Offline Sorter (Plexon, inc.) and Neuroexplorer (Nex Technologies). Behavior: Animals were placed in a novel open field for 30 mins, placed back in their homecage for 5 mins and then placed back in the open field in the presence of a novel object. In another set of experiments, animals were placed in a circular open field with or without water for 15 mins across two days in counterbalanced fashion.
Results: iMSN-D2 KO mice display reduced locomotor activity in the homecage as well in an open field. Moreover, iMSN-D2 KOs showed impaired performance on a motor skill task as assayed by the rotarod test. This motor impairment was not apparent in animals placed in a forced swim test suggesting that these mice are capable of movement in certain contexts. While these animals demonstrate reduced locomotor activity, they concurrently show enhanced responsivity to novelty. This behavioral phenotype was not due to decreased evoked dopamine release in the striatum as shown by fast scan cyclic voltammetry. The observed motor deficits were rescued by selective activation of Gi coupled DREADD receptors (hM4Di) expressed in iMSNs demonstrating that activation of the Gi signaling pathway in iMSNs in critical for facilitating sustained locomotion. In vivo recordings made in the dorsal striatum of awake behaving KO mice revealed a decreased firing rate of MSNs. In an ex vivo slice preparation, we observed an increase in mIPSC frequency and amplitude in both the dorsal and ventral striatum as well as an enhanced tonic GABA current. These results suggest enhanced GABAergic tramission in the KO mice. We further showed that GABAergic collateral transmission from iMSNs to dMNS can shunt the excitability of dMSNs. This collateral transmission is reduced by the D2 agonist quinpirole in WT mice and this D2R mediated effects of absent in iMSN-D2 KOs, demonstrating function loss of D2R.
Conclusions: The results of this study provide evidence that activation of D2Rs on indirect pathway neurons are critical for sustaining locomotor activity during periods with less environmental arousal. Moreover, we show a synaptic mechanism by which D2Rs in iMSNs relieve collateral GABAergic transmission onto neighboring dMSNs to disinhibit direct pathway neurons. Thus one main conclusion of the study is that the indirect and direct pathway are intimately connected and can affect the activity of neighboring MSNs through GABAergic collateral transmission. This study underscores the importance of this intimate collateral connectivity largely underappreciated until recently and its modulation by D2R which exerts a strong influence on GABAergic transmission.
Keywords: Dopamine, D2 receptor, Striatum, GABA.
Disclosure: Nothing to Disclose.

M99. Progesterone Treatment for Postpartum Cocaine Users

Ariadna Forray*, Mehmet Sofuoglu, Kathleen Carroll, Kimberly Yonkers

Yale University School of Medicine, New Haven, Connecticut

Background: Cocaine-using women frequently abstain or reduce use during pregnancy, but most women relapse or resume pre-pregnancy use following delivery. Many attribute the decrease of substance use in pregnancy to a woman's motivation to minimize her offspring's exposure to drugs. However, biological factors may also play a role. Progesterone modulates multiple brain functions implicated in the pathogenesis of drug addiction, and production in pregnancy increases by a factor of 8. In animals, progesterone diminishes a number of cocaine-enhanced behavioral responses including ambulation, rearing activity, conditioned placement preference, cocaine seeking and seizures. Human data, although limited, are largely consistent with preclinical studies in that there is an inverse relationship between endogenous progesterone levels and cocaine craving and use. Direct administration of progesterone to women diminishes cocaine-induced euphoria and cue-induced craving in laboratory settings. The current study tested the efficacy of postpartum progesterone replacement in reducing cocaine use in postpartum women with cocaine use disorder.
Methods: This was a 12-week, double-blind, parallel, randomized, placebo-controlled pilot trial with a 3-month post trial follow-up. We recruited 50 postpartum women who used cocaine either during the 6 months before or during pregnancy. Postpartum participants were randomized to receive either oral micronized progesterone (100 mg twice daily) or placebo for 12 weeks. Each week we collected a substance use calendar and urine for cocaine metabolite analysis. Attrition was 18% and the analysis included all 50 participants. Outcomes were self-reported days of cocaine use and positive urine toxicology assays for cocaine metabolites.
Results: The median age for participants was 31 years, 56% were white, 32% black and 12% Hispanic. Retention was at least 80% at each postpartum visit. Women randomized to progesterone compared to placebo had a greater reduction in cocaine use per week (RR = 1.19; 95% confidence interval (CI) = 1.05 to 1.36; $p < 0.01$). At the three-month post trial visit the difference between groups was not significant (Likelihood Ratio X2 = 5.16; $p = 0.08$). There were no group differences in rates of submission of a positive urine test. A post hoc analysis showed a higher rate of relapse for participants randomized to placebo (HR = 4.71; 95% CI = 1.09 to 20.5; $p = 0.05$). We did not observe groups differences in the rate of adverse events.
Conclusions: These preliminary findings support the promise of progesterone treatment in postpartum women with cocaine use disorder and could constitute a therapeutic breakthrough. If the positive results found in this study are replicated in a larger cohort, this may constitute a viable treatment option for postpartum cocaine users.
Keywords: cocaine, progesterone, postpartum, women.
Disclosure: Nothing to Disclose.

M100. Adolescent Cannabis Use Trajectory Predicts Functional Connectivity in Reward Circuitry at Age 20

Samuel Musselman, Daniel Shaw, Stephanie Sitnick, Emily Russell, Erika Forbes*

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Cannabis use has become increasingly common among adolescents, with many adolescents believing that cannabis is benign or even beneficial. Despite the focus of addiction theories on disrupted reward processing, there has been little investigation of the association between adolescent cannabis use and later functioning in reward circuitry. Late adolescence is an important developmental period for addressing the influence of cannabis use, since reward-seeking behavior remains high, development of neural reward systems is still underway, and it is the peak age of cannabis use problems. Age of initiation of use is particularly important, as earlier use is related to higher likelihood of use-related problems. We hypothesized that trajectory of cannabis use across adolescence will be related to altered function in neural reward circuitry at age 20, with particular disruption in adolescents who were heavy users and also had an early age of initiation of use. As low educational attainment has been consistently found to be a negative psychosocial outcome in heavy cannabis users, we also tested whether functional connectivity in reward circuitry that was relevant to adolescent cannabis use trajectory predicted education level at age 22.
Methods: Participants were 165 male late adolescents (51% European American, 39% African American) who have been followed in the Pitt Mother & Child Project, a longitudinal study of high-risk, urban boys. At age 20, participants completed detailed interviews about their history of substance use and underwent functional magnetic resonance imaging on a 3T Siemens TIM Trio scanner during a monetary reward task. To determine developmental trajectories based on frequency of cannabis use (days/month) from age 14-20, a semi-parametric, group-based approach was applied using PROC TRAJ in SAS. Functional connectivity with bilateral nucleus accumbens as seed was computed using psychophysiological interaction in SPM8. Given the conceptual emphasis on altered appetitive motivation during the process of addiction, functional connectivity analyses focused on reward anticipation versus loss anticipation. AlphaSim at $p < .05$ was applied to correct imaging results for multiple comparisons. At age 22, participants reported their highest education to date and their current status as students.
Results: Four cannabis use trajectory groups emerged. Group 1 (51.5% of participants) contained young men who reported no or limited cannabis use. Group 2 (14.5%) contained young men who with consistently low-frequency use. Group 3 (11.5%) contained young men with early initiation of cannabis use and consistently high frequency of use. Group 4 (22.4%) contained young men who initiated use at a typical age and increased to high levels of use by their late teens. Groups differed in negative functional connectivity between the nucleus accumbens and the dorsolateral prefrontal cortex (589 voxels, F = 7.65), medial prefrontal cortex (242 voxels, F = 5.70), and anterior cingulate cortex (111 voxels, F = 4.37). Post hoc Bonferroni analyses indicated that findings were generally due to

greater negative functional connectivity in Group 3. Further, higher negative functional connectivity was associated with lower likelihood of being a student at age 22.
Conclusions: Stronger negative connectivity between the nucleus accumbens and the ACC and prefrontal regions in those who were early-initiating, high-frequency cannabis uses during adolescence could suggest a pattern of altered development in reward circuitry from adolescence to adulthood. With early and consistent exposure to cannabis, regions implicated in self-regulation could develop a pattern of disengaged coordination with basic reward-focused regions in the presence of a potential reward. These findings are consistent with postulated hypofrontality, which is thought to underlie compulsive drug use. This pattern of altered coordination between ventral striatum and frontal/ACC regions could also be a stable characteristic of those who are vulnerable to developing heavy use, and prospective longitudinal studies are needed to investigate this possibility. The association of altered coordination with lower likelihood of being in college or trade school suggests a potential mechanism of the association of cannabis use with psychosocial functioning. In all, these findings can help to elucidate the developmental influence of cannabis use and guide prevention efforts.
Keywords: reward, adolescent development, cannabis use, fMRI.
Disclosure: Nothing to Disclose.

M101. Validation of Mismatch Negativity and P3a for Use in Multi-site Studies of Schizophrenia: Characterization of Demographic, Clinical, Cognitive, and Functional Correlates in COGS-2

Gregory Light*, Neal Swerdlow, Michael Thomas, The COGS Investigators, David Braff, Bruce Turetsky

University of California at San Diego/San Diego VA Healthcare System, La Jolla, California

Background: Mismatch negativity (MMN) and P3a are auditory event-related potential (ERP) components that show robust deficits in schizophrenia (SZ) patients and exhibit qualities of endophenotypes, including substantial heritability, test-retest reliability, and trait-like stability. These measures also fulfill criteria for use as cognition and function-linked biomarkers in outcome studies, but have not yet been validated for use in large-scale multi-site clinical studies. This study tested the feasibility of adding MMN and P3a to the ongoing Consortium on the Genetics of Schizophrenia (COGS) study. The extent to which demographic, clinical, cognitive, and functional characteristics contribute to variability in MMN and P3a amplitudes was also examined.
Methods: Participants (HCS n = 824, SZ n = 966) underwent testing at 5 geographically distributed COGS laboratories. Valid ERP data was obtained from 91% of HCS and 91% of SZ patients.
Results: Highly significant MMN (d = 0.96) and P3a (d = 0.93) amplitude reductions were observed in SZ patients, comparable in magnitude to those observed in single-lab studies with no appreciable differences across laboratories. Demographic characteristics accounted for 26% and 18% of the variance in MMN and P3a amplitudes, respectively. Significant relationships were observed among demographically-adjusted MMN and P3a measures and medication status as well as several clinical, cognitive, and functional characteristics of the SZ patients.
Conclusions: This study demonstrates that MMN and P3a ERP biomarkers can be feasibly used in multi-site clinical studies. As with many clinical tests of brain function, demographic factors contribute to MMN and P3a amplitudes and should be carefully considered in future biomarker-informed clinical studies.
Keywords: Schizophrenia, cognition, EEG biomarkers, endophenotypes.
Disclosure: Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd.

M102. Effects of Apoe ε4 Allele on Abstinence-induced Alterations in Working Memory Function in Healthy Smokers

Rebecca Ashare*, Caryn Lerman, Kosha Ruparel, Wen Cao, Mary Falcone, Leah La Prate, Ruben Gur, James Loughead

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Background: Deficits in working memory during smoking abstinence are associated with decreased activity in brain regions important in executive cognitive control and reduced suppression of activation in regions in the default mode network (DMN). Importantly, deficits in working memory are also predictive of smoking relapse. Variation in genes important to executive cognitive function, including working memory, may contribute to risk of relapse. A relatively common variant in the Apolipoprotein E (APOE) gene, widely studied for its role in cognitive aging and risk of developing Alzheimer's disease, may also be a plausible candidate. The goal of the present analysis was to examine whether APOE ε4 genotype moderates abstinence-induced alterations in working memory and related brain activity, using data from a prior neuroimaging study of smokers (Lerman et al., 2014; Falcone et al., 2013) We predicted that during abstinence, compared to smoking as usual, smokers carrying at least one ε4 allele would exhibit poorer task performance, reduced BOLD signal in task-positive regions, and less suppression of task-negative regions, compared to ε4 non-carriers.
Methods: Seventy eight smokers (26 ε4 carriers and 53 ε4 noncarriers) performed a visual N-back task while undergoing blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) on two separate occasions: following 24 h of confirmed abstinence and during smoking as usual. APOE ε2, ε3 and ε4 alleles were determined from allelic variants of two SNPs (NCBI SNPs rs429358 and rs7412). A whole-brain APOE ε4 carrier status by session (abstinent vs. smoking) repeated measures ANOVA was performed on the effect of task. Resulting Z (Gaussianised F) statistic image of the interaction was thresholded using a whole-brain family-wise error correction of $p < 0.05$ (equivalent to $Z > 4.69$). Anatomic assignment of all clusters was determined by visual inspection and using the FSL atlas tool and pertinent anatomic templates (MNI atlas, Talairach atlas,

and Harvard-Oxford cortical and subcortical structural atlases). Mean percent BOLD signal change was examined using random effects maximum likelihood regression. Models included terms for APOE ε4 carrier status (ε4 noncarrier vs. ε4 carrier), session (abstinent vs. smoking as usual), back level (0, 1, 2, and 3), and relevant covariates (age, sex, race, Shipley IQ score, and baseline FTND score). Behavioral performance measures (accuracy and reaction time) were tested as described above.

Results: APOE genotypes were in Hardy-Weinberg equilibrium ($p = 0.78$). There were no significant differences by ε4 carrier status on demographics. For reaction time (RT), participants were slower during abstinence compared to smoking as usual ($p = 0.036$). There were no main or interacting effects (with session) of APOE ε4 carrier status on RT or true positives. The whole brain analysis revealed significant interactions in the cingulate gyrus, lingual gyrus, bilateral occipital lobe, left hippocampus, posterior cingulate cortex (PCC), right insula, and ventromedial prefrontal cortex (vmPFC). For the ε4 carriers, smoking suppressed activation (or increased deactivation), relative to abstinence, in the hippocampus ($p = 0.015$), visual cortex ($p = 0.04$), PCC ($p = 0.001$), insula ($p = 0.04$), and vmPFC ($p = 0.04$). This pattern was reversed in the vmPFC ($p < 0.001$) and cingulate gyrus ($p = 0.005$) among ε4 noncarriers. There were no significant session effects among ε4 noncarriers in the hippocampus or insula.

Conclusions: This is the first study that we know of to show that the effects of smoking abstinence on working-memory related brain activation in healthy smokers may be moderated by APOE ε4 carrier status. The ε4 carriers had more difficulty suppressing activation in task-negative regions (PCC and vmPFC) during abstinence, compared to smoking, whereas this pattern was reversed in the vmPFC among ε4 noncarriers. In the hippocampus, we observed increased activation during abstinence, compared to smoking, in ε4 carriers, but not the ε4 noncarriers. Because the hippocampus is not typically thought of as part of the working-memory network, this may reflect an inability to recruit sufficient resources from task-active regions (e.g., dorsolateral prefrontal cortex). Similarly, smoking, compared to abstinence, suppressed insula activation in the ε4 carriers, but not in the ε4 noncarriers. Based on our work suggesting that older ε4 carriers were more likely to relapse to smoking, we propose that difficulty suppressing abstinence-induced activation in task-negative regions may contribute to increased relapse risk in ε4 carriers.

Keywords: Cognition, fMRI, nicotine, APOE.

Disclosure: Nothing to Disclose.

M103. Amphetamine Effects on Acoustic Startle and Prepulse Inhibition in 90 Healthy Adults: Physiological and Genetic Predictors

Neal Swerdlow*, Savita Bhakta, Hsun-Hua Chou, Sarah Lamb, Bryan Balvaneda, Brinda Rana, Jo Talledo

University of California at San Diego School of Medicine, La Jolla, California

Background: The psychostimulant, amphetamine, is known to have potent effects on both neurocognition and sensorimotor gating, the latter measured via changes in prepulse inhibition of acoustic startle (PPI). For example, amphetamine enhances attention and vigilance (A/V) in healthy subjects (HS), and we have reported these effects to be most robust among subjects with low basal A/V performance. In HS, amphetamine has been reported to have variable effects on PPI; our laboratory reported PPI-enhancing effects of amphetamine in healthy women, and particularly those with specific physiological and personality traits (Talledo et al. 2009), including low basal PPI levels. We are now completing a 5-year study of biomarker-predictors of amphetamine effects on neurocognition and PPI in HS, in advance of trials in patients with schizophrenia; we previously reported neurocognitive data from the first 60 subjects (Chou et al. 2013) and now report findings of acoustic startle and PPI in the full cohort of 90 healthy men and women, which will also be used to test the moderating impact of 14 single nucleotide polymorphisms (SNPs) on these amphetamine effects.

Methods: 90 clinically healthy generally non-smoking, right-handed young adults (M:F = 56:34; age range 18-35) completed an initial telephone screen and three laboratory visits. HS were carefully screened for current and past medical and psychiatric history, medication and recreational drug use, family history of psychosis, structured personality traits and hearing threshold; women were tested within 72 hours of menses onset, and men were approximately "yoked" to this schedule. On visits 2 and 3, the effects of 20 mg amphetamine (po) on acoustic startle and PPI with 10-120 ms intervals were assessed in a double-blind, placebo-controlled crossover design; measures of neurocognitive performance were also collected but will be reported separately. DNA extracted from saliva and/or blood was used to test for 14 SNPs reported to regulate PPI or amphetamine sensitivity, including genes associated with dopamine, glutamate and nicotinic systems. Preliminary analyses focused on behavioral effects of amphetamine as moderated by sex, basal PPI level and status of SNP rs4680 of catechol-O-methyl transferase (COMT). Additional data with the remaining 13 SNPs will be presented.

Results: ANOVA of screening PPI revealed significant main effects of sex (M > F; $F = 3.97$, df 1,88, $p < 0.05$) and prepulse interval ($p < 0.0001$), but no interactions. Of the 90 subjects, startle magnitude in 7 individuals declined to negligible levels with repeated testing. In the remaining 83 subjects, ANOVA of startle magnitude revealed no significant effects of sex or amphetamine dose (placebo vs. 20 mg), or any interaction. ANOVA of PPI revealed a significant interaction of dose x sex x interval ($F = 2.73$, df 4,316, $p < 0.03$); AMPH increased PPI in women, particularly at longer prepulse intervals (60-120 ms) (dose x interval: $F = 2.48$, df 4,120, $p < 0.05$), and particularly among those with a Val/Val genotype for rs4680. When subjects were divided into low vs. high basal PPI groups (median split of placebo PPI levels), amphetamine significantly enhanced PPI among "low-gating" subjects ($F = 22.46$, df 1,38, $p < 0.0001$), independent of sex or prepulse interval; for women, but not men, this effect was again most robust among those carrying the Val/Val rs4680 genotype. Moderating effects of personality traits and 13 other SNPs will be reported, as will drug and gene effects on other startle measures, including reflex latency.

Conclusions: These results confirm previous findings that: 1) amphetamine enhances PPI in HS (Talledo et al. 2009; Chitty et al. 2013); 2) under the present testing conditions, these effects are most robust in women, and among low-gating individuals independent of sex; 3) these effects on PPI are independent of changes in startle magnitude on pulse-alone trials. These results extend previous findings by suggesting that in women overall and particularly low-gating women, these amphetamine effects appear to be moderated by rs4680. Additional moderating effects of physiological and personality traits, and genotype, will be presented. More generally, these results support a model whereby HS might be used to identify biomarkers predicting pro-cognitive and pro-gating drug effects, particularly in patient populations with low basal performance levels.
Keywords: Amphetamine, Schizophrenia, Prepulse Inhibition, Neurocognition.
Disclosure: Nothing to Disclose.

M104. Effects of Early Cannabis Use on Frontal Cortical Gamma Oscillations in First Episode Psychosis

Nicola Polizzotto, Chris Walker, Srihari Bangalore, Debra Montrose, David Lewis, Raymond Cho*

University of Texas Health Science Center at Houston, Houston, Texas

Background: The impact of cognitive disturbances on functional outcome in schizophrenia encouraged a rethinking of the condition as a cognitive disorder, stimulating a prolific investigation of its specificities and determinants. For instance cognitive control – a system that modulates the operation of other cognitive in the service of goal-directed behavior – is held as a core deficit in the disorder and its association with frontal cortical gamma oscillatory disturbances suggests a way to integrate molecular findings and models of cognition. However, our understanding is still determined primarily by observations in chronic patients with potential confounding factors and comorbid conditions that co-vary with the disorder and interact with its presentation and possibly genesis in complex ways. Here we present data from first break patients and address the role of concurrent cannabis usage in cognitive control impairments and its neurophysiological markers.
Methods: Sixty two healthy controls were compared to 101 first break patients in the Preparing to Overcome Prepotency (POP) task, a cued stimulus-response reversal task. During this task compromised cognitive control in chronic schizophrenic patients has been shown to be indexed by reduced engagement of prefrontal gamma activity. Psychosis subjects included patients with schizophrenia, schizoaffective disorder as well as other psychosis spectrum disorders, and had a variable history of cannabis usage. During task performance high-density EEG was acquired participants' activity was compared after time-frequency analysis.
Results: Patients showed impaired performance and complex spectral alterations of EEG activity. This included reduction of gamma activity in the frontal electrodes during high-control trials. However in the patient group, significant variability was explained by cannabis usage history. In particular a greater gamma power impairment was observed for subjects who had greater lifetime cannabis usage and heavy earlier cannabis use (<16 years old) appeared to exert a more deleterious effect than later use or more minimal use.
Conclusions: The findings of this study suggest that the presence and time course of cannabis use history in first episode psychosis has a significant deleterious impact on frontal cortical gamma oscillations in the context of a cognitive control task. Cannabis effects during development are recognized as a critical area in psychosis research, possibly implicated in the genesis, presentation of the disorder and/or serving as an important confounding factor. The present data highlights how the development of specific and accurate models of cognitive impairment in psychosis needs to address and be informed by complex interactions with cannabis usage.
Keywords: psychosis, cannabis, gamma oscillation, first-episode.
Disclosure: Nothing to Disclose.

M105. Reactivity and Habituation to Fearful Face Stimuli in Body Dysmorphic Disorder and Anorexia Nervosa

Nathan Hutcheson, Katherine Lawrence, Teena Moody, Sahib Khalsa, Michael Strober, Jamie Feusner*

UCLA Semel Institute for Neuroscience & Human Behavior, Los Angeles, California

Background: Body dysmorphic disorder (BDD) and anorexia nervosa (AN) both involve distorted perception of appearance and, frequently, anxiety. Little is known about the neurobiology underlying anxiety or fear processing in either BDD or AN. The primary goal of this fMRI study was to investigate limbic reactivity, and habituation over time, in response to viewing fearful faces. We hypothesized that: a) BDD would show abnormally low activation in limbic structures when viewing fearful faces (as has been observed in obsessive-compulsive disorder); b) AN would show abnormally high limbic activity (as has been observed in anxiety disorders such as panic disorder and social phobia); and c) there would be reduced habituation in AN but not BDD. We used linear and non-linear models for habituation, to test for decreases in activation and for reinstatement, respectively.
Methods: Participants: Participants included a total of 98 individuals, aged 14-38 years, in three groups: BDD ($n=35$), weight restored AN ($n=26$), and healthy controls ($n=37$) of equivalent age and sex. fMRI data acquisition and fearful faces task: We acquired fMRI data using a Siemens 3T scanner and a T2*-weighted EPI while participants viewed fearful faces (F), neutral faces (N), or scrambled faces (S) as a control. Stimuli appeared for 4 seconds with an interstimulus interval of 500ms. Region of interest analyses: Functional data were processed using fMRIB Software Library (FSL). For the reactivity analyses, we extracted percentage signal change from bilateral amygdala, superficial amygdala subregion, hippocampus, and anterior insula. We tested for differences among groups using ANCOVA, covarying for age. For habituation we

derived eigenvalues from the superficial amygdala and analyzed them with linear and non-linear mixed models. All analyses were controlled for age. Whole-brain analyses: For the reactivity experiments, contrasts included: F vs. N, F vs. S, and N vs. S. For the habituation experiments the contrast F vs. S was modeled with negative linear and positive quadratic modulation, using F-tests for group effects with follow up pairwise t-tests. The significance criteria was set to $Z > 2.0$ with a corrected cluster significance threshold of $p = 0.05$; all experiments were controlled for age.
Results: Reactivity ROI analysis: There was a significant effect of group in the amygdala and superficial nucleus of the amygdala for F vs. N ($F(2\ 91) = 4.98$, $p = .01$; and $F(2\ 92) = 4.73$, $p = .01$) respectively. Post-hoc pairwise tests indicated a significantly higher percentage signal change in CON than BDD for amygdala ($F(1\ 69) = 8.17$, $p = .006$) and superficial amygdala ($F(1\ 69) = 7.98$, $p = .006$). No other differences reached significance. Reactivity whole brain: The BDD group displayed decreased right insula activity compared with CON for F vs. N. The BDD group had greater activation compared with CON in the ventral visual stream (VVS) for F vs. S. The BDD group had greater activation than AN in occipital regions for F vs. S and in VVS and occipital regions for N vs. S. The AN group had significantly greater right frontal pole and bilateral lateral occipital cortex activation than CON, and greater middle frontal gyrus and superior frontal gyri activity than BDD for F vs. N. AN showed significantly greater activity than CON in the left frontal pole, bilateral caudate, and thalamus for F vs. S. Habituation ROI analysis: There was a significant difference among groups in habituation in the superficial amygdala, using the nonlinear model ($F(2\ 2250.21) = 4.33$, $p = .013$). Both the BDD group ($F(1\ 1653.16) = 7.06$, $p = .008$) and the AN group ($F(1\ 1447.12) = 5.46$, $p = .020$) had significantly lesser habituation with repeated stimuli than CON. There were no significant differences between BDD and AN. Habituation whole brain: The negative linear model revealed that BDD had lesser habituation than both CON and AN in the left angular gyrus.
Conclusions: As predicted, individuals with BDD showed abnormally low amygdala reactivity to fearful faces, which further supports its relationship with obsessive-compulsive disorder. We did not find evidence in AN of abnormal limbic reactivity, but instead found heightened frontal and striatal reactivity. Abnormal insula reactivity to neutral faces in those with BDD may be a reflection of emotional face misinterpretation, as has been found in other studies, or could indicate discomfort with uncertainty of emotional expression. As the VVS plays an important role in detail-oriented visual processing, the heightened VVS activity in BDD for neutral and fearful faces suggests that they may preferentially use detail-oriented regions when processing faces, regardless of emotion. The most notable similarity in aberrant responses in BDD and AN is reduced habituation – their amygdalae activity did not diminish normally over time with repeated stimuli. These results have implications for understanding shared and unique phenotypes across these disorders, and may have implications for treatments involving emotion processing.
Keywords: anorexia nervosa, body dysmorphic disorder, fear processing, amygdala.
Disclosure: Nothing to Disclose.

M106. Integrity of Frontal Fasciculi in Antipsychotic-Naïve First-episode Schizophrenia Patients before and after Antipsychotic Monotherapy

Bjørn Ebdrup*, Jayachandra M. Raghava, Mette Ø. Nielsen, Egill Rostrup, Birte Y. Glenthøj

CNSR & CINS, Psychiatric Center Glostrup, Glostrup, Denmark

Background: Positive psychotic symptoms are core clinical features of schizophrenia. A recent hypothesis proposes that psychotic symptoms stem from irregularities in myelination of white matter (WM) tracts projecting into the frontal cortex. We investigated WM integrity in first-episode antipsychotic-naïve schizophrenia patients and healthy controls before and after selective dopamine D2/3 receptor blockade.
Methods: Thirty-eight patients (25.9 ± 6.5 years) and 38 matched controls (25.8 ± 6.4 years) underwent baseline examination with 3T MRI diffusion tensor imaging and clinical assessments. Voxelwise group differences of fractional anisotropy (FA) were assessed using tract-based spatial statistics (TBSS). Subsequently, patients underwent 6 weeks of antipsychotic monotherapy with amisulpride (mean dose: 262 ± 177 mg). Twenty-eight patients and 28 healthy controls were re-examined.
Results: At baseline, positive symptoms were significantly associated with FA of frontal fasciculi, specifically right arcuate fasciculus and right superior longitudinal fasciculus. Whole brain TBSS analyses revealed lower FA in patients in right anterior thalamic radiation (ATR), right cingulum, right inferior longitudinal fasciculus and right corticospinal tract (CT). FA in right ATR correlated positively with positive symptoms. At re-examination, all correlations between positive symptoms and frontal fasciculi (including ATR) had resolved. FA in ATR increased significantly more in patients than in controls. Amisulpride dose correlated positively with FA changes in right CT.
Conclusions: As predicted, psychotic symptoms appeared specifically associated with the integrity of frontal fasciculi in antipsychotic-naïve schizophrenia patients. Moreover, patients displayed subtle deficits in WM integrity. Six weeks of dopamine D2/3 receptor antagonism normalized WM integrity possibly by remyelination. Further research of frontal fasciculi and psychosis is encouraged.
Keywords: Antipsychotic-naïve first-episode schizophrenia, Diffusion tensor imaging, Antipsychotic monotherapy, Psychosis.
Disclosure: The Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS was funded by a Lundbeck Foundation grant (R25-A2701).

M107. Reduced Cortical Thickness in Gambling Disorder: A Morphometric MRI Study

Jon Grant*, Samuel Chamberlain

University of Chicago, Chicago, Illinois

Background: In many countries, including the United States and United Kingdom, gambling is now undertaken by the majority of the adult population. In a minority of gamblers,

symptoms become repetitive and functionally impairing, leading to a diagnosis of gambling disorder. Gambling disorder can be conceptualized from a neurobiological perspective in terms of diminished top-down control from prefrontal cortical regions, coupled with excessive drive from subcortical regions involved in reward processing, especially the ventral striatum. Whether or not gambling disorder is associated with structural as opposed to functional brain abnormalities has received little research attention to date. Given the relative paucity of structural imaging studies conducted in gambling disorder, the current study compared cortical thickness between individuals with gambling disorder and healthy volunteers; volumes of selected sub-cortical regions were also examined. Our hypothesis was that gambling disorder would be associated with reduced cortical thickness in neural regions germane to top-down executive control especially the right frontal cortex.

Methods: Subjects meeting DSM-5 criteria for gambling disorder, free from axis-I comorbidities, were recruited via media advertisements and a psychiatric clinic. Healthy controls were recruited via media advertisements on the basis of no lifetime or current psychiatric disorders. Participants undertook high resolution structural imaging using a 3 Tesla Philips Achieva Quasar Dual 16 Ch system. Three-dimensional MPRAGE scan was obtained with imaging parameters: slab orientation = sagittal, FOV 256x224x176, voxel size 1x1x1 mm3, inversion delay time TI = 900 ms, TR/TE = 8.9/3.7 ms, flip angle = 8 degree. MRI scans for each subject were converted to FreeSurfer format and non-brain tissue was extracted using automated algorithms; these images were then transformed to standard space, segmented, and normalized. After reconstruction, cortical thickness was compared between the two study groups using permutation cluster analysis with stringent correction for multiple comparisons (cluster-forming threshold of $p < 0.001$, and cluster-wise p value $p < 0.05$, two-tailed).

Results: Individuals with gambling disorder had symptoms consistent with moderate disease severity. The groups did not differ significantly in terms of age, gender, or education. Permutation analysis identified eight clusters in which cortical thickness differed significantly between the two study groups; in all cases, this was due to patients showing significant reductions in cortical thickness compared to controls. Gambling disorder was associated with reduced cortical thickness in predominantly right frontal regions, but also – to a lesser degree – in the right supra-marginal gyrus, right post-central gyrus, and left inferior-parietal cortex. The mean cortical thickness reduction in gambling disorder compared to controls was of the order 15.8-19.9%. Cortical thickness in these identified clusters did not correlate significantly with symptom severity in gambling disorder, nor did it differ as a function of gender. Individuals with gambling disorder and controls did not differ significantly in terms of subcortical volumes of left caudate, left putamen, left accumbens, right caudate, right putamen, or right accumbens.

Conclusions: This study investigated cortical thickness in individuals with gambling disorder and healthy control subjects. Consistent with our a priori hypotheses, gambling disorder subjects showed relatively reduced cortical thickness in neural regions implicated in top-down executive control, particularly the right frontal cortex. In addition, the mean cortical thickness reduction in gambling disorder compared to controls was of the order 15.8-19.9%, which is significantly larger than the findings for many other mental health problems. Individuals with gambling disorder report being unable to control their behavior despite the financial, health, and personal ruin that often ensues. In addition, they exhibit deficits in aspects of inhibition, working memory, planning, and cognitive flexibility, and these clinical and cognitive characteristics are consistent with abnormalities of the frontal cortex. These data support neurobiological models of the disorder emphasizing deficiency of cortical regions governing top-down control and executive function.

Keywords: addiction, imaging, morphology.
Disclosure: This research was supported by a grant from the National Center for Responsible Gaming to Dr. Grant. Dr. Chamberlain's part in this work was funded by a grant from the Academy of Medical Sciences.

M108. Striatal Hyper-sensitivity During Stress in Remitted Individuals with Recurrent Depression

Roee Admon*, Laura Holsen, Harlyn Aizley, Anne Remington, Susan Whtifield-Gabrieli, Jill Goldstein, Diego Pizzagalli

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: Increased sensitivity to stress and dysfunctional reward processing are two primary characteristics of Major Depressive Disorder (MDD) that may persist following remission. Preclinical work has established the pivotal role of the striatum in mediating both stress and reward responses. Human neuroimaging studies have corroborated these preclinical findings and highlighted striatal dysfunction in MDD in response to reward, but have yet to investigate striatal function during stress, in particular in individuals with recurrent depression.

Methods: Thirty three remitted individuals with a history of recurrent MDD (rMDD) and 35 matched healthy controls underwent a validated mild psychological stress task involving viewing of negative stimuli during fMRI. Cortisol and anxiety levels were assessed throughout scanning. Stress-related activation was investigated in three striatal regions: caudate, nucleus accumbens (Nacc), and putamen. Psychophysiological interaction (PPI) analyses probed connectivity of those regions with central structures of the neural stress circuitry, the amygdala and hippocampus.

Results: The task increased cortisol and anxiety levels, although to a greater extent in rMDD than healthy controls. rMDD individuals, but not controls, also exhibited significantly potentiated caudate, Nacc, and putamen activations, as well as increased caudate-amygdala and caudate-hippocampus connectivity, in response to the negative stimuli.

Conclusions: Findings highlight striatal hyper-sensitivity in response to a mild psychological stress in rMDD, as manifested by hyper-activation and hyper-connectivity with the amygdala and hippocampus. Striatal hyper-sensitivity

during stress might thus constitute a trait mark of depression, providing a potential neural substrate for the interaction between stress and reward dysfunction in MDD.
Keywords: Depression, Stress, Reward, fMRI.
Disclosure: Nothing to Disclose.

M109. What Do Gray Matter Volume Biomarkers Tell Us about the Psychosis Dimension? Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes

Elena Ivleva*, Anup Bidesi, Shashwath Meda, Bradley Witte, Gaurav Poudyal, Brett Clementz, Godfrey Pearlson, John Sweeney, Matcheri Keshavan, Carol Tamminga

University of Texas Southwestern Medical Center, Dallas, Texas

Background: Categorization of psychotic illness is based entirely on clinical phenomenology and lacks biological definitions. Resulting diagnoses [e.g., schizophrenia (SZ) or bipolar disorder (BD)] show substantial clinical heterogeneity and do not map on emerging biomarker constructs. Targeting disease dimensions, i.e. psychosis, may capture more homogenous groups of cases and provide more direct cues towards underlying disease neurobiology. Here, we contrast regional gray matter volume (GMV) characteristics across two disease constructs: (1) DSM diagnosis and (2) psychosis dimension capturing probands and relatives with and without lifetime psychosis manifestations independent of their categorical diagnoses. We examine whether GMV outcomes may serve as a dimensional biomarker for psychosis capturing groups of cases characterized by unique brain structure phenotypes.
Methods: 3T structural MRI data from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) sample were analyzed using whole brain voxel-based morphometry (SPM8/VBM8/DARTEL). To test GMV biomarkers, the probands/relatives sample was sliced two-ways: based on DSM diagnoses [n = 1,681 including 261 probands with SZ (SZP), 168 with schizoaffective disorder (SADP), and 212 with psychotic BD, type I (BDP); 266 relatives of SZP (SZR), 183 SADR, 235 BDR; and 356 healthy control subjects (HC)] and psychosis dimension based on lifetime psychosis manifestations [n = 1,672 including 641 psychosis probands (SZP, SADP and BDP, combined), 80 relatives with Axis I psychosis, 48 relatives with Axis II psychosis, 303 relatives with non-psychotic Axis I-II diagnoses, and 244 unaffected relatives, contrasted with 356 HC].
Results: The diagnosis-based outcomes revealed extensive and overlapping GMV reductions in numerous cortical/subcortical regions in SZP and SADP, compared to HC. BDP had largely normal GMV, with small clusters of reduction in fronto-temporal, cingulate, and insular cortices. SZR and SADR showed GMV reductions similar in distribution to their probands but less extensive; BDR had normal GMV. The psychosis dimension outcomes revealed diffuse GMV reductions in the probands and relatives with lifetime psychosis. Notably, relatives with AxisI proband-like psychosis (n = 50) and AxisII psychosis (n = 48; schizotypal, schizoid, paranoid personality disorders) had more extensive and diffusely distributed GMV reductions than relatives with other psychoses (n = 17; psychotic MDD, psychosis due to GMC, etc.) who showed smaller localized reductions in frontal and anterior/middle cingulate regions. Relatives with non-psychotic AxisI-II diagnoses showed overall normal GMV; however, post-hoc analyses revealed GMV reductions in the subgroup of relatives with lifetime substance use disorders (n = 48), primarily clustered over temporal regions. Unaffected relatives had normal GM structure.
Conclusions: Our findings from DSM diagnosis approach suggest partially divergent brain structure biomarkers for SZ/SAD (i.e., diffuse cortical/subcortical GMV loss) and psychotic BD (i.e., smaller localized volume reductions in fronto-temporal and anterior limbic regions), consistent across probands and their relatives. The alternative dimensional approach supports a link between GMV reductions and lifetime psychosis burden, with measurable volume loss in probands and psychotic relatives but normal brain structure in unaffected relatives. Chronic psychosis phenotypes (SZ/SAD/BD and cluster A/psychosis spectrum disorders) are associated with more severe and diffuse GMV alterations, while episodic psychosis is characterized by smaller localized reductions primarily distributed over frontal regions. Psychosis construct defined dimensionally captures more homogenous groups of proband and relative cases characterized by unique structural biomarkers, possibly reflecting lifetime psychosis burden. These findings support the dimensional conceptualization of severe mental illness as a useful approach for studies targeting disease neurobiology.
Keywords: Schizophrenia, Bipolar Disorder, Structural MRI, Biomarker.
Disclosure: Nothing to Disclose.

M110. Altered Default Mode Network Connectivity in Patients with Late Life Depression

Helen Lavretsky*, Hongue Yang, Amber Leaver, Katherine Narr

University of California Los Angeles, Semel Institute for Neuroscience & Human Behavior, Los Angeles, California

Background: This study was designed to map the pathophysiology of resting state functional connectivity in elderly participants with depression.
Methods: Ten older adults with depression (age 60 years and older) and 18 age-, sex-, and race-similar healthy controls were studied. Brain connectivity during resting state was assessed with functional magnetic resonance imaging (fMRI) data using independent component analysis (ICA), as implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components), part of the FMRIB Software Library (FSL). Demographic and clinical measurements were assessed by standardized interviews.
Results: Diagnostic groups were similar for age, education, vascular and medical burden. Compared with the controls, patients reported higher depressive symptoms as measured

with the Hamilton Depression Rating Scale (HAMD), t(1, 25) = 10.75, p < 0.001, controls (mean ± SD): 4.24 ± 3.38, patients:18.4 ± 3.17; the Geriatric Depression Scale (GDS), t(1, 24) = 2.73, p = 0.012), controls: 10.56 ± 7.68, patients:18.70 ± 6.88. OOf the resting state networks identified across subjects, one resting state network showed regional hypoconnectivity in the depression group relative to the controls, (p < 0.05, Threshold-Free Cluster Enhancement (TFCE) corrected). Results remain significant both with and without including age, sex, and education as covariates in the statistical model. Specifically, the connectivity of the pregenual anterior cingulate cortex (pregenual ACC, X = 2, Y = 38, Z = -4, maximum p = 0.016) differentiated the depression participants from the controls in the default mode network (DMN, Figure 1). However, associations between functional connectivity in this region and clinical measures remained below the threshold of significance in the depressed group.

Conclusions: Elderly depression participants showed lower DMN connectivity during resting state, which suggest cerebral functional deficiency in late life depression. The diminished function of the pregenual ACC in default mode network illustrates a fragile interface, which may be identified as a key malleable area to pharmacological intervention for late life depression.

Keywords: Depression, geriatric, fMRI, brain connectivity.
Disclosure: Grant funding from the NIMH, Forest Research Institute, and Alzheimer's Research and Prevention Foundation.

M111. Resting State Functional Connectivity of the Locus Coeruleus in Humans: In Comparison to the Ventral Tegmental Area/Substantia Nigra Pars Compacta and the Effects of Age

Chiang-shan Li*, Sheng Zhang, Sien Hu, Herta Chao

Yale University School of Medicine, New Haven, Connecticut

Background: Noradrenergic systems play an important role in the etiologies of mood, anxiety and substance use disorders. The locus coeruleus (LC) provides the primary noradrenergic inputs to the cerebral cortex. Activity of LC neurons is known to support arousal and orienting responses to salient stimuli and, through noradrenergic modulation, to broadly influence cognitive functions. However, despite numerous animal studies documenting the functional roles of the LC, research in humans is hampered by the small volume of this midbrain nucleus. Ample evidence supports connectivity analysis of resting state (rs) fMRI data as a useful approach to characterizing functional architecture of a brain region, with low frequency BOLD signal fluctuations reflecting connectivity between functionally related brain regions. Here, we took advantage of a probabilistic template and explored the cerebral functional connectivity of the LC with rsfMRI data. We compared cerebral connectivity of LC and ventral tegmental area/substantia nigra pars compacta (VTA/SNc), which provides dopaminergic inputs to the cerebral cortex, and examined the effects of age on the pattern of LC connectivity.

Methods: Resting-state fMRI scans (3T; eyes closed; 4.5 to 10 minutes) were pooled from the 1000 Functional Connectomes Project (n = 144; Biswal et al., 2010) and studies in our laboratory (n = 106). Individual subjects' images were viewed one by one to ensure that the whole brain was covered. A total of 250 healthy subjects' resting state data (18-49 years of age; 104 men) were included in this study. Brain imaging data were preprocessed using Statistical Parametric Mapping. Additional preprocessing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity. We applied a temporal band-pass filter (0.009 Hz < f < 0.08 Hz) to the time course in order to obtain low-frequency fluctuations, as in previous work. We used a "scrubbing" method to remove time points affected by head motion (Power et al., 2012). The BOLD time courses were averaged spatially over each of the two seed regions (Hammers et al., 2003; Keren et al., 2009). For individual subjects, we computed the correlation coefficient between the averaged time course of each seed region and the time courses of all other brain voxels. To assess and compare the resting state "correlograms," we converted these image maps, which were not normally distributed, to z score maps by Fisher's z transform. The Z maps were used in group random effect analyses. We performed one-sample t test each on the Z maps of LC and VTA/SNc and paired-sample t test comparing the two Z maps. We performed a simple regression of the Z maps against age, each for the LC and VTA/SNc, to identify age-related changes of functional connectivity in the two structures. To examine gender differences, we compared men and women with age as a covariate in an analysis of variance, each for the LC and VTA/SNc. All results were reported for a corrected threshold. In an additional analysis, we identified brain regions with shared LC and VTA/SNc connectivity and examined whether these connectivities correlate significantly across subjects.

Results: The results showed positive LC connectivity to bilateral superior frontal gyri, primary motor cortices, inferior parietal cortices, posterior insulae, putamen, pallidum, ventrolateral thalamus, midbrain and large areas of the cerebellum. LC showed negative connectivity to a large region of bilateral visual cortices, temporal cortices, precuneus, posterior cingulate cortex, parahippocampual gyri, frontopolar cortex, caudate nucleus and medial thalamus. The VTA/SNc showed positive connectivity with the dorsomedial prefrontal cortex including the supplementary motor area (SMA), pre-SMA, and dorsal anterior cingulate cortex (ACC), as well as the rostral, perigenural and perigenual ACC, thalamus, putamen, pallidum, insula, inferior temporal cortex and temporal pole, midbrain and large areas of the cerebellum. The VTA/SNc showed negative connectivity with bilateral visual cortices, posterior parietal cortex, precuneus, posterior cingulate cortex, precentral cortex, temporal cortex, frontopolar cortex and caudate head. Compared to the VTA/SNc, LC showed greater connectivity to bilateral visual, parietal and motor cortices, as well as midline cerebellar structures and less connectivity to dorsomedial prefrontal cortex, middle and posterior cingulate cortices, ventromedial prefrontal cortex, inferior temporal cortex, anterior insula, thalamus, and the midbrrain. In a simple regression, LC connectivity to the angular gyrus, middle frontal gyrus as well as cerebellum

showed positive correlations with age and LC connectivity to the calcarine and lingual gyrus showed negative correlations with age. The LC and VTA/SNc shared positive connectivity with the bilateral superior frontal gyri, putamen, pallidum, posterior insula, ventrolateral thalamus, midbrain and large areas of the cerebellum. The LC and VTA/SNc shared negative connectivity with the bilateral visual cortices, temporal cortices, precuneus, posterior cingulate cortex, caudate nucleus and medial thalamus. For all of these shared regions, LC and VTA/SNc connectivity (positive or negative) showed a significant positive correlation across subjects (corrected for multiple comparison, $p < 0.05/1540$).

Conclusions: Together, the distinct cerebral functional connectivities support the role of the LC in arousal, saliency responses and cognitive motor control. Both LC and VTA/SNc showed significant positive correlation with bilateral superior frontal gyri, putamen, pallidum, posterior insulae, ventrolateral thalamus, midbrain and large areas of the cerebellum, suggesting that these structures may respond to orienting stimulus and prediction error, each mediated by noradrenergic and dopaminergic signaling. Future work may determine whether this is mediated by genetic factors that modulate metabolic pathways common to the noradrenergic and dopaminergic systems. The LC and VTA/SNc shared negative connectivity with the bilateral visual cortices, temporal cortices, precuneus, posterior cingulate cortex, caudate nucleus and medial thalamus, supporting a role of the precuneus and posterior cingulate cortex, as part of the default mode network, in responding to salient environmental stimulus. Age-related changes in LC and VTA/SNc connectivity may broadly impact behavioral and cognitive manifestations in healthy and disordered aging.

Keywords: noradrenergic, locus coeruleus, connectivity, midbrain.

Disclosure: Nothing to Disclose.

M112. Neural Circuitry of Masked Emotional Face Processing in Youth with Severe Mood Dysregulation

Melissa Brotman*, Wan-Ling Tseng, Laura Thomas, Daniel Pine, Ellen Leibenluft

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: Youth with severe, non-episodic irritability (severe mood dysregulation, SMD) show deficits in face emotion labeling and aberrant neural responses when processing emotional faces. This work has primarily focused on consciously perceived (i.e., "aware") face emotions. Few studies have probed automatic, unconscious (i.e., "non-aware") face emotion processing (Thomas et al., 2014). Affective priming incorporates backwards masking, where a prime stimulus (e.g., emotional face) is presented too quickly to reach awareness, followed by a target stimulus shown long enough to be consciously processed. Using an affective priming task, Thomas et al. (2014) found SMD hyperactivation in several brain regions while processing angry and happy, but not fearful faces; SMD also demonstrated increased activation in non-aware vs. aware conditions relative to healthy comparisons (HC). Abnormal automatic processing of angry and happy faces may contribute to the mood dysregulation and interpersonal difficulties in SMD youth. Here, we modified the task used by Thomas et al. (2014) by increasing the number of angry and happy face trials and excluding fearful faces.

Methods: Functional magnetic resonance imaging (fMRI) data were acquired from 37 participants (9-19 years old), including 17 SMD and 20 HC youth. In two awareness conditions (aware and non-aware), participants rated how much they liked an abstract shape presented for 3000 ms. In the aware condition, a fixation point and a face (or blank oval) was presented before the shape for 187 ms. In the non-aware condition, a fixation point and a face (or blank oval) was presented for 17 ms, followed by a scrambled face mask for 170 ms, then the abstract shape. We performed repeated measures analyses of variance (ANOVAs) to compare between-group differences in ratings and reaction time (RT). At the whole-brain level, we conducted a 2 (diagnosis: SMD vs. HC) x 4 (emotion: happy, angry, neutral, no face) x 2 (awareness: aware, non-aware) ANOVA. Significance threshold was $p < 0.005$, $k > 20$ (Lieberman and Cunningham, 2009). We also performed a region of interest analysis in the right and left amygdala. Two tasks were administered immediately after scanning to assess whether the awareness manipulation was successful.

Results: Groups did not differ on age, IQ, or sex distribution. There were no between-group differences in behavioral ratings or RT. There were no significant three-way interactions. Whole-brain analysis revealed several Diagnosis x Emotion interactions. In the parahippocampal gyrus (PHG, $k = 59$, uncorrected $p = 0.005$), SMD youth showed hyperactivation during angry faces ($p = 0.014$), but hypoactivation when viewing happy faces ($p = 0.026$). During angry face processing, SMD also showed hyperactivation relative to HC ($p = 0.044$) in the superior temporal gyrus (STG, $k = 34$, uncorrected $p = 0.005$). However, when processing happy faces, SMD demonstrated hypoactivation compared to HC youth ($p = 0.04$) in the insula ($k = 187$, uncorrected $p = 0.005$) and thalamus ($k = 42$, uncorrected $p = 0.005$). There was also a Diagnosis x Condition interaction ($p < 0.001$) in the ventromedial prefrontal cortex (vmPFC; Brodmann area 32; $k = 65$, uncorrected $p = 0.005$). During the non-aware condition, SMD showed hyperactivation relative to HC ($p = 0.002$); during the aware condition, SMD showed hypoactivation relative to HC at the trend level ($p = 0.07$). There were no significant interactions or main effects involving diagnosis in the amygdala ROI analyses. In both the left and right amygdala, there were main effects of emotion (angry, happy, neutral > no face, $ps < 0.05$). Post-task procedures suggest that participants were unaware of the emotional face prime.

Conclusions: Using an affective priming task, we compared the neural correlates of non-aware vs. aware processing of angry and happy faces in SMD and HC youth. We found hyperactivation in SMD when viewing angry faces in the PHG and STG, but hypoactivation in the PHG, insula and thalamus when perceiving happy faces. The PHG and STG are involved in emotional face processing and social cognition; indeed, SMD STG dysfunction is consistent with prior work using a modified version of this task (Thomas et al., 2014). Given the severe levels of irritability and anger observed in SMD youth, it is noteworthy that these patients

exhibited increased activity during angry, but decreased activity during happy faces. We also observed SMD hyperactivation in the non-aware condition in the vmPFC, an area associated with emotion regulation. Future work is needed to understand the pathophysiological correlates of severe irritability. Moreover, future studies should include larger samples, longitudinal designs, and dimensional measures of irritability.
Keywords: fMRI, irritability, affective priming, face emotion.
Disclosure: Nothing to Disclose.

M113. CB1 Receptor Availability and Threat Processing in Trauma Survivors

Alexander Neumeister*, Robert Pietrzak, Henry Huang, Stefani Corsi-Travali, Ming-Qiang Zheng, Shu-fei Lin, Shannan Henry, Marc Potenza, Daniele Piomelli, Richard Carson

New York University Medical School, New York, New York

Background: Attentional bias to threat is a key endophenotype that contributes to the chronicity of trauma-related psychopathology. However, little is known about the neurobiology of this endophenotype and no known in vivo molecular imaging study has been conducted to evaluate candidate receptor systems that may be implicated in this endophenotype or the phenotypic expression of trauma-related psychopathology, which is comprised of threat (i.e., re-experiencing, avoidance, and hyperarousal) and loss (i.e., emotional numbing, depression/dysphoria, generalized anxiety) symptomatology.
Methods: Using the radioligand [11C]OMAR and positron emission tomography (PET), we evaluated the relationship between in vivo cannabinoid receptor type 1 (CB1) receptor availability in the amygdala, and performance on a dot-probe measure of attentional bias to threat, and clinician interview-based measures of trauma-related psychopathology. The sample was comprised of adults (N = 20, 11F, age 33 years, range 21-50) presenting with a broad spectrum of trauma-related psychopathology (CAPS 0-110), ranging from non-trauma-exposed, psychiatrically healthy adults to trauma-exposed adults with severe trauma-related psychopathology.
Results: Increased CB1 receptor availability in the amygdala was associated with increased attentional bias to threat, as well as increased severity of threat, but not loss, symptomatology; greater peripheral anandamide levels were associated with decreased attentional bias to threat. A mediation analysis further suggested that attentional bias to threat mediated the relationship between CB1 receptor availability in the amygdala and severity of threat symptomatology.
Conclusions: These data implicate the amygdala CB1 receptor system as a key neurobiological underpinning of this endophenotype and its concomitant phenotypic expression of trauma-related threat symptomatology, particularly hyperarousal symptoms. They further suggest that attentional bias to threat may mediate the association between CB1 receptor availability in the amygdala and threat symptomatology, with greater CB1 receptor availability being linked to greater attentional bias to threat, which is in turn linked to greater severity of threat symptomatology. The data provide further support to examine the efficacy of candidate pharmacotherapies that target the anandamide-CB1 receptor system in mitigating both the endophenotypic and phenotypic expression of threat symptomatology in symptomatic trauma survivors.
Keywords: PTSD, CB1 receptor, positron emission tomography, anxiety.
Disclosure: Nothing to Disclose.

M114. Neuro-Correlates of Maltreated Youth with and Resilient to Posttraumatic Stress Disorder

Rajendra Morey, Courtney Haswell, Stephen Hooper, Michael De Bellis*

Duke University Medical Center, Durham, North Carolina

Background: Child maltreatment causes posttraumatic stress disorder (PTSD). Amygdala, hippocampus, anterior cingulate cortex (ACC), and ventral medial prefrontal cortex (vmPFC), which mediates the extinction response, are involved in PTSD neurobiology. In PTSD, one fails to learn fear extinction, elicited by traumatic reminders. Effective regulation of the amygdala by ACC and vmPFC leads to successful extinction in response to trauma cues. We examined amygdala, hippocampus, ACC, and vmPFC volumes in 3 groups of medically healthy youth: maltreated youth with PTSD; maltreated youth resilient to PTSD; and non-maltreated youth. The inverted U-shaped model predicts that stress is adaptive through processes that promote increased dendritic and apical spines, learning, and larger brain structures; and that chronic stress can lead to neural damage and smaller brain structures. We hypothesized that maltreated youth with PTSD would show smaller vmPFC and ACC volumes compared to healthy volunteers and youth resilient to PTSD and that maltreated youth resilient to PTSD would show larger amygdala and hippocampus compared to non-maltreated healthy volunteers and PTSD youth.
Methods: In this study, we investigated these brain structural volumes in maltreated youth with PTSD (N = 31), resilient to PTSD (N = 32), and in non-maltreated healthy volunteers (n = 57) using magnetic resonance imaging and FreeSurfer image analysis. The maltreated groups were defined by a positive forensic investigation conducted by North Carolina Child Protective Services (CPS) that indicated physical, sexual, abuse and/or neglect. Maltreated participants were recruited through statewide advertisements targeted at CPS agencies. To reduce bias, the study was advertised to CPS statewide. All participants underwent extensive assessments for DSM-IV disorders. Non-maltreated healthy volunteers, with no history of DSM-IV Axis I disorders or Type A traumas, were recruited from schools and other community settings and had a negative maltreatment and other type A trauma screen on initial telephone interview upon study entry. Intensive research interviews for any positive history of participant or participant sibling maltreatment, or positive review of pediatric and birth medical records that met or would have

met state CPS maltreatment criteria, excluded a potential healthy volunteer. The two maltreated groups had similar Full Scale IQ and socioeconomic status. Exclusion criteria were: IQ < 70; medical illness; daily prescription medication; head injury; neurological disorder; schizophrenia; anorexia nervosa; pervasive developmental disorder; obsessive compulsive disorder, bipolar I disorder or mania; birth weight < 5 lbs.; and severe prenatal (fetal alcohol and/or drug exposure) or perinatal compromise with NICU stay; current or lifetime nicotine dependence/alcohol/substance use disorder; Axis I disorder or report of maltreatment that warranted CPS investigation in non-maltreated controls; and contraindications for safe MRI scan. Written informed consent/assent were obtained to undertake IRB committee approved study.

Results: We used general linear models (GLM) to examine the influence of PTSD diagnosis on amygdala, hippocampus, ACC, and vmPFC volumes. GLM analysis included the following covariates: intracranial volume, age, gender, SES, IQ, and their interactions with group status. If covariates demonstrated $p \geq .1$, they were dropped from the model. The two maltreatment groups were clinically distinct from the non-maltreated group and from each other, with the PTSD group showing the greatest degree of emotional and behavioral symptoms and lowest levels of global function than the other two groups. Post-hoc pairwise group differences revealed that the PTSD group had smaller right vmPFC volumes than both the non-maltreated control ($p < .05$) and resilient youth ($p < .05$). We saw no differences between groups in the ACC. Post-hoc pairwise group differences revealed that resilient youth had greater left amygdala and right hippocampal volumes than non-maltreated control and PTSD youth. Post-hoc pairwise group differences revealed that resilient youth showed greater total amygdala and hippocampal volumes compared to PTSD youth and a trend for greater volumes than controls in the amygdala ($p = .08$) and hippocampus ($p = .09$). Intracranial volume and age were significantly correlated with all ROIs (all p-values $< .001$). In the maltreated sample, PTSD symptoms significantly and negatively and moderately correlated with right (Spearman's rho $= -.37$, $p < .008$), left (Spearman's rho $= -.32$, $p < .03$) and total hippocampal (Spearman's rho $= -.36$, $p = .01$) volumes and left amygdala volumes (Spearman's rho $= -.32$, $p < .03$). The youth's total number of maltreatment types experienced significantly and negatively and weakly correlated with right (Spearman's rho $= -.19$, $p < .04$), left (Spearman's rho $= -.18$, $p = .05$) and total hippocampal (Spearman's rho $= -.19$, $p < .04$) volumes, left amygdala (Spearman's rho $= -.18$, $p < .04$), and left (Spearman's rho $= -.19$, $p = .04$), right (Spearman's rho $= -.19$, $p < .04$) and total vmPFC (Spearman's rho $= -.18$, $p = .05$), and total ACC volumes (Spearman's rho $= -.18$, $p < .05$).

Conclusions: Our study examined the regional volumes of amygdala, hippocampus, ACC, and vmPFC that are important structures in the neurobiology of PTSD and those resilient to PTSD. Maltreated youth with PTSD were clinically distinct from resilient youth having suffered greater numbers of Axis I disorders, degree of psychopathology, and trauma load, and lower levels of global function. Maltreated youth with PTSD were neurobiologically different from resilient youth and non-maltreated controls demonstrating smaller right vmPFC volumes, a structure that mediates associative fear learning and extinction learning. According to behavioral models of PTSD, individuals who suffer from PTSD learn to broadly generalize fear, exhibit failure of extinction retention, and exhibit anxiety-related behaviors (i.e., conditioned responses), based on previous trauma, to traumatic reminders. The vmPFC tracks predictions of stimuli associated with safety and danger. Dysregulation of the vmPFC can lead to failure in learning extinction of traumatic reminders and PTSD. Smaller vmPFC may be a developmentally shared mechanism that leads to vmPFC dysregulation, PTSD and its common co-morbidities.

Keywords: Child abuse and neglect, PTSD, brain imaging, stress.

Disclosure: Nothing to Disclose.

M115. 3,4-Methylenedioxypyrovalerone (MDPV), A Major Bath Salt Drug, Produces a Powerful Reduction in Functional Connectivity

Luis Colon-Perez, Kelvin Tran, Khalil Thompson, Kenneth Blum, Bruce Goldberger, Mark Gold, Adriaan Bruijnzeel, Barry Setlow, Lewis Baxter, Marcelo Febo*

The McKnight Brain Institute, Gainesville, Florida

Background: Synthetic cathinones represent an emergent hazard to public health. These are sold on the streets as bath salts or legal highs. Bath salts are potent stimulant and hallucinogenic drugs and their abuse has the potential to impair mental health. Chemical ingredients of bath salts have been shown to share molecular features, biochemical actions, and behavioral effects with a range of other illegal stimulants such as cocaine, methamphetamine and methylenedioxymethamphetamine (MDMA, or 'Ecstacy'). Among the bath salts, 3,4-methylenedioxypyrovalerone (MDPV) has been reported to exert powerful cocaine-like effects in rats (Baumann et al., Neuropsychopharmacology, 2012). MDPV produces strong craving and euphoria within a few minutes of intake. Importantly, it also leads to a strong crash within hours of intake with a varying degree of severity in terms of the negative affective outcomes. During this time, users can experience paranoia, delirium, depression, anxiety and panic attacks. In many reported cases MDPV may also exert violent aggressive behavior and suicidal thoughts that may last several weeks after initial initial intake.

Methods: Despite a growing number of studies reporting the stimulant and reinforcing actions of bath salts there is still a knowledge gap with regard to their sites of action within the CNS and their effects on functional connectivity between brain regions. The present study was designed to investigate the dose dependent pharmacological actions of MDPV (in mg kg-1: 0.0, 0.3, 1.0, 3.0, i.p.) on BOLD activation across a number of corticostriatal, mesolimbic, frontal cortical and limbic subcortical circuits. Rats were imaged at 4.7 Tesla under medetomidine sedation and low (0.5%) isoflurane anesthesia at the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility of

the University of Florida. Animals were administered an i.p. injection of MDPV or saline and imaged 1 hour later. Functional MRI scans were collected with a quadrature transmit/receive 1H radiofrequency coil (200 MHz). A spin echo planar echo planar imaging scan with an echo time of 50 ms and repetition time of 2000 ms was used (field of view = 32.5x32.5, slice thickness = 1.5 mm, 12 slices). Scans were individually skull stripped, registered to a segmented atlas of the rat brain, and motion and drift corrected. Images were band pass filtered (0.01-0.1 Hz) and individual seed regions of interest (ROI) were chosen a priori from the brain reward system and other regions. Individual time series signals were extracted and used for correlating with the rest of the brain on a voxel-by-voxel basis using Analysis of Functional NeuroImages AFNI http://afni.nimh.nih.gov/afni/. Resultant maps of Pearson's correlation coefficients were Fisher's z-transformed and the final images are group analyzed using a two way ANOVA ($p < 0.05$, FDR corrected). AFNI's AlphaSim program is used to determine an adequate cluster size for a given uncorrected p value.

Results: Our results show that with the 0.3 mg kg-1 dose of MDPV there is virtually no change in resting state functional connectivity in comparison to saline controls. MDPV doses of 1 and 3 mg kg-1, on the other hand, dramatically reduced functional connectivity. This was observed as a reduction in Fisher's transformed correlation values between various frontal cortical, striatal, sensory and motor cortical, thalamic areas. The origins of the intrinsic oscillations in BOLD signal have yet to be explained. However, the observed reduction in functional connectivity could be associated with a strong desynchronization as a result of the high affinity binding of MDPV to the dopamine transporter protein. At the highest dose (3 mg kg-1) we observed an unexpected effect of MDPV on functional connectivity. Connectivity was only increased between orbital frontal cortex and subregions of the amygdala. This was observed in spite of the globally reduced connectivity. Thus, a greater synchrony in spontaneous BOLD oscillations between amygdala and this prefrontal cortical region could underlie part of the negative affective states elicited by binge consumption, especially at a high dose. In order to further examine the effects of MDPV on resting state functional connectivity following MDPV administration we also carried out model free group independent components analysis (ICA). We observed that the saline treated animals and the low 0.3 mg kg-1 dose of MDPV resulted in similar network components, most of which are well known regions that are part of the default mode network. Higher doses of MDPV severely disrupted network interactions, observed as a dramatically reduced organization of individual components into identifiable networks.

Conclusions: A major finding at this time is that MDPV given at high doses severely disrupt the brains intrinsic network connectivity. Using seed based connectivity analysis we observed that 1-3 mg kg-1 MDPV reduces connectivity globally in a manner reminiscent of the reported patterns of connectivity observed in schizophrenia. Indeed, similar functional connectivity changes have been reported in schizophrenia and have been linked with severity of cognitive dysfunction, hallucinations and negative affective states. This might represent an important signature of MDPV's mechanism of action in the CNS. It will be important to determine the neurophysiological mechanisms underlying this phenomenon and whether it is associated directly or indirectly with the behavioral effects observed in users.

Keywords: MDPV, functional connectivity, psychosis, bath salts.

Disclosure: Nothing to Disclose.

M116. GABA Assessed by Magnetic Resonance Spectroscopy in Visual Cortex in Schizophrenia

Yvonne Yang*, Junghee Lee, Katherine Narr, Amber Leaver, Ana Ceci Myers, Michael Green

VA Greater Los Angeles Healthcare System/University of California at Los Angeles, Los Angeles, California

Background: Visual perceptual deficits in schizophrenia are pervasive, measurable, and correlate with poor functional outcome. In functional magnetic resonance imaging (fMRI) studies, patients with schizophrenia show abnormal activation in a key visual processing area, the lateral occipital cortex (LO). One feature of the neurons in LO is that they selectively respond to specific objects more than others (called neural tuning). Preliminary evidence from our group shows that subjects with schizophrenia have neurons in LO that are less precisely tuned for objects than those in healthy control subjects. GABA is known to be involved in visual neural tuning. It is often found to be dysregulated in schizophrenia, including in the visual cortex, although it has not been specifically studied in LO. This study examined relative levels of GABA in schizophrenia subjects (SZ) compared to healthy control subjects (HC), in LO and in primary visual cortex (V1), using magnetic resonance spectroscopy (MRS). We expected subjects with schizophrenia to have lower levels of GABA in both regions compared with healthy controls.

Methods: Subjects: So far in this study, 4 schizophrenia subjects and 4 healthy controls have been recruited from UCLA outpatient clinics, and mental health clinics of the VA Greater Los Angeles Healthcare System. Selection criteria for all subjects included age 18-60 years, sufficient understanding of English to comprehend procedures, no clinically significant neurological disease, no history of serious head injury, no sedatives within 12 hours of participation, no positive urine toxicology screen on day of assessment, and willingness to participate in scanning. Subjects underwent the Structured Interview for DSM-IV to ensure they met diagnostic criteria. MR Data Acquisition: 1H-MRS scans were performed in 45-minute sessions on a Magnetom Trio 3T scanner (Siemens, Inc., Malvern, PA), using a 32-channel head coil, at the UCLA Staglin Center for Cognitive Neuroscience. Magnetic resonance imaging localizing scans were first acquired and landmarks therein used to localize two lateral voxels encompassing bilateral area LO, and one medial visual cortex voxel encompassing V1 (both voxels 30 mm x 40 mm x 25 mm). MR spectra were generated using the Siemens single voxel spectroscopy spin-echo sequence, a work-in-progress (WIP) protocol designed to increase the signal to noise ratio for GABA using a variant of a J-difference editing method. A total of 128

spectral averages were acquired for each voxel. Scanning parameters were as follows: TR = 2000 msec; TE = 68 ms; edit pulse frequency = 1.9 ppm; edit pulse bandwith = 44 Hz; delta frequency = -1.7 ppm; acquisition time = approximately 9 min. MRS Data Analysis: Software package LCModel was used to estimate GABA concentration with the J-edited Mescher-Garwood (MEGA) point-resolved spectroscopy (PRESS), or MEGA-PRESS, sequence. This software package was also used to estimate the error using the Cramer-Rao lower bounds (CRLB) algorithm. Spectra with error of greater than 20% were excluded.
Results: Data collection for this study is ongoing; at this time we will present preliminary data from 4 patients and 4 controls. More data will be available at the time of the conference. First, we evaluated the data quality. For 21 out of 24 voxels examined, GABA absolute concentration was detected with adequate signal-to-noise ratio. Cramer-Rao Lower Bound standard deviations ranged from 4% to 10% in those cases, well below the standard cut-off of 20%. Preliminary inspection of the data indicates that the groups did not differ notably in overall GABA levels across visual areas. The GABA levels for the controls were similar between LO and V1. The GABA levels for the patients were in the direction of lower GABA in LO. The specific values for GABA (mM) were: V1: HC 2.05 (SD 0.58), SZ 2.48 (SD 1.08); bilateral LO: HC 2.04 (SD 0.31), SZ 1.92 (SD 0.87) (SD = standard deviation).
Conclusions: In this preliminary study with n = 4 in each group, we demonstrated feasibility of measuring GABA concentrations in V1 as well as bilateral LO cortex using MRS in both healthy control subjects and schizophrenia subjects. Concentrations of GABA were consistent with published values for GABA in the visual cortex. The small n in this study precludes tests of statistical significance, but preliminary data suggest a possible lower GABA concentration in bilateral LO compared to V1 in subjects with schizophrenia, but not healthy controls. This finding could help explain the deficit in neural tuning previously measured by our group in area LO in schizophrenia. It also may demonstrate increased importance for GABA in area LO for neural tuning as compared to V1. As we increase the number of participants in the study, we will correlate GABA levels in areas LO and V1 with degree of neural tuning as indicated by level of steady state adaptation, measured with EEG. We hypothesize the degree of correlation will be greater in LO than in V1, and that this degree of correlation will be less in schizophrenia subjects than in control subjects.
Keywords: magnetic resonance spectroscopy, schizophrenia, GABA, visual cortex.
Disclosure: Nothing to Disclose.

M117. Cortical GABA Concentrations in Postpartum Depression: An Interim Analysis

Kristina Deligiannidis*, Elif Sikoglu, Nina Jaitly, Janet Hall, Blaise Frederick, Richard Edden, Constance Moore, Anthony Rothschild

University of Massachusetts Medical School, Worcester, Massachusetts

Background: Postpartum depression (PPD) affects 1 in 8 mothers. The transition from pregnancy to the postpartum period is characterized by marked physiological fluctuations in sex steroids which may contribute to the development of PPD. Sex steroids, including neuroactive steroids are among the most rapid and potent allosteric modulators of GABA A receptor (GABAAR) function. The GABAergic system, evidenced by abnormal cortical magnetic resonance spectroscopy (MRS) concentrations, has been implicated in the pathogenesis of both depression and the hormonally-modulated premenstrual dysphoric disorder. Studies in the occipital cortex suggest that reductions in cortical GABA in the postpartum period may be a risk factor for PPD development. This ongoing study tests the hypotheses: (1) PPD will be associated with lower GABA/Creatine (GABA/Cr) ratios in both the anterior cingulate (ACC) and occipital (OCC) cortices compared to healthy postpartum subjects and (2) GABA/Cr ratios will be correlated to the total Edinburgh Postnatal Depression Scale (EPDS) score.
Methods: A prospective observational cohort study evaluated 64 subjects of 18-40 yrs. of age twice between 26-36 weeks gestation and thrice up to 10 weeks postpartum. Serial mood assessments were completed at each of 5 study visits. A subgroup of 30 postpartum women comprised of healthy comparison (HCS) (n = 14, mean age: 30.35 ± 4.09) and medication-free subjects who developed unipolar PPD (PPD) (n = 16, mean age: 30.14 ± 4.29) within 10 weeks postpartum (HCS: 54.14 ± 14.31 and PPD: 42.81 ± 17.87 postpartum days at the time of the scan) were examined cross-sectionally using 1H-MRS. MRS data was acquired with 3.0T Philips Achevia whole-body MR system using phased-array receiver SENSE Head coil (Philips HealthCare, the Netherlands). Diagnostic high resolution anatomical brain MRI was performed on all subjects to exclude the existence of any pathology and to be used for MRS voxel localizations. Edited MRS spectra were acquired using MEscher-GArwood Point-REsolved Spectroscopy Sequence (MEGA-PRESS) (TE = 68 msec and TR = 2000 msec). This frequency selective technique enabled us to detect the GABA peak of the spectra by eliminating the signal due to Creatine (Cr). Two MRS runs were performed with each subject: Voxels positioned at the ACC (3.0 cm X 3.0 cm X 2.0 cm) or at the OCC (3.0 cm X 3.0 cm X 3.0 cm) regions. The data processing and spectral fitting were done by using Matlab (The Mathworks, MA, USA). We did an outlier analysis to exclude data that was 2 or more standard deviations farther than the group average data. We performed univariate ANOVA to compare GABA/Cr ratios between HCS (n = 13) and subjects who developed PPD (n = 15) as well as demographic and clinical measures between groups. We performed nonparametric Spearman correlation analysis to investigate the relationship between the GABA/Cr ratios and total EPDS score.
Results: There were no significant differences between cohorts in age (p = ns) or days since delivery to the day of MRI (p = ns). At the time of MRI, 75% (12/16) of subjects who developed PPD and 71% (10/14) of HCS were fully or partially breastfeeding. 87.5% of subjects who developed PPD had a history of depression. ACC GABA was significantly higher in PPD group when compared with HCS group ($F(1,26) = 14.505$, $p = 0.001$). There was no statistically significant difference in OCC GABA levels between HCS and PPD ($F(1,26) = 0.464$, p = ns); however

the grey (gm) and white matter (wm) and CSF GABA content was not different among two groups for either of the voxels (p = ns for all gm, wm and CSF comparisons). There was a significant relationship between EPDS total score and ACC GABA levels, when we included all subjects within our analysis (Spearman rho = 0.536, p = 0.003, n = 28). In the women with PPD, we observed a trend level increase in ACC GABA levels as days since delivery to day of MRI progressed (Spearman rho = 0.432, p = 0.108, n = 15).
Conclusions: The present investigation is the first to report ACC GABA/Cr in healthy postpartum subjects and subjects who developed unipolar PPD. Previous studies in non-puerperal unipolar depression have reported reduced GABA levels in the OCC and ACC, especially in melancholic depression. We report a novel finding of increased GABA/Cr in the ACC in PPD in an interim analysis of this NIH-funded study. Abnormally elevated ACC GABA levels in PPD may be related to differences in neuroactive steroid levels or in GABAergic receptor sensitivity to neuroactive steroids, or an affective state dependent change in ACC GABA.
Keywords: postpartum, neuroimaging, magnetic, GABA.
Disclosure: Nothing to Disclose.

M118. Brain Dopamine Responses to the Expectation of Methylphenidate in Active Cocaine Dependent Subjects

Gene-Jack Wang*, Elena Shumay, Dardo Tomasi, Jean Logan, Christopher Wong, Millard Jayne, Joanna Fowler, Nora Volkow

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland

Background: The response to drugs of abuse is affected by expectation. This is modulated in part by dopamine, which is a neurotransmitter involved with reward and expectation of reward. Here we assessed the effect of expectation on methylphenidate induced striatal dopamine changes in active cocaine dependent subjects and non-drug abusing control subjects and compared their responses between expected and unexpected conditions.
Methods: Twenty-five active cocaine dependent subjects (45 ± 4 y/o) and 23 non-drug abusing subject were evaluated with 4 PET scans and [C-11] raclopride with placebo and the stimulant drug methylphenidate (0.5 mg/kg, i.v.). Brain dopamine D2/3 receptor availability (non-displaceable binding potential, BPND) was measured under four randomly ordered conditions: (1) expecting placebo and receiving placebo (baseline); (2) expecting placebo and receiving methylphenidate; (3) expecting methylphenidate and receiving methylphenidate; (4) expecting methylphenidate and receiving placebo. D2/3 receptor (D2R) availability was analyzed with statistical parameter mapping (SPM) method. SPM significance was set at $p < 0.05$, small volume correction 100 voxels. Self-report ratings (1-low to 10-high) of methylphenidate effect were recorded.
Results: The maximal self-report ratings of anxiety after methylphenidate in cocaine subjects was delayed as compared to controls ($p < 0.001$). The timing of response in high and rush was dependent on expectation in controls ($p = 0.01$, $p = 0.001$, respectively), but not in CS. The timing of response across traits was modulated by diagnosis ($p < 0.001$). SPM revealed that methylphenidate-induced dopamine release in striatum in controls ($p < 0.001$, $T = 11.8$) is much greater than that in cocaine subjects ($p = 0.002$, $T = 4.78$). Expectation of methylphenidate did not affect D2R levels in controls but significantly reduced those in right caudate in cocaine subjects ($p = 0.046$, $T = 2.72$).
Conclusions: These results in active cocaine dependent subjects expanded prior findings of decreased striatal dopamine responses in detoxified cocaine dependent subjects. They also identify expectation responses in striatal region, which are consistent with disrupted mesocortical dopamine function in drug dependent subjects. These findings provide further evidence of dopamine's involvement in processing expectation for uncertainty about a drug's effects.
Keywords: cocaine, methylphenidate, PET, expectation.
Disclosure: Nothing to Disclose.

M119. Connectome-wide Association Study Reveals Multifocal Patterns of Dysconnectivity in Youth with Psychosis-spectrum Symptoms

Theodore Satterthwaite*, Simon Vandekar, Zarrar Shehzad, Danielle Bassett, Cameron Craddock, Daniel Wolf, Russell Shinohara, Kosha Ruparel, Mark Elliott, Monica Calkins, Ruben Gur, Michael Milham, Raquel Gur

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Dysconnectivity is a prominent finding in psychotic disorders including schizophrenia, but it is unclear when dysconnectivity emerges in the disease process. As psychotic disorders including schizophrenia typically begin in adolescence or young adulthood and are increasingly conceptualized as aberrations of neurodevelopment, it is critical to understand how dysconnectivity develops during youth. Here we conducted a connectome-wide association study (CWAS) to explore complex multivariate patterns of dysconnectivity in a large sample of youth with psychosis-spectrum symptoms studied as part of the Philadelphia Neurodevelopmental Cohort (PNC).
Methods: Subjects included 392 youth ages 8-22 imaged as part of the PNC; including 187 youth with psychosis-spectrum (PS) symptoms and 205 typically developing (TD) youth. All subjects completed a resting-state fMRI acquisition (124 volumes, $TR = 3s$, 3mm isotropic voxels) on the same scanner (Siemens Tim Trio 3 Tesla) and had adequate data quality (motion: relative mean displacement < 0.3 mm). Resting-state images were preprocessed with slice-time correction, band-pass filtering (0.01-0.08 Hz), and confound regression using a 36-parameter model. Subject-level timeseries were co-registered to the T1 image using BBR with distortion correction and normalized to the template using ANTs. CWAS was conducted using multivariate distance matrix regression (MDMR) implemented within R; the group level design matrix included group, sex, age, race, and in-scanner motion (mean relative displacement). Significant clusters ($z > 1.64$, $p < 0.05$) identified as

part of the CWAS were further evaluated with follow-up seed-based analyses.
Results: CWAS revealed multiple regions with abnormal patterns of connectivity between PS and TD subjects, including bilateral dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, bilateral hippocampus, bilateral auditory cortex, and right orbitofrontal cortex. Follow-up seed analyses demonstrated robust patterns of dysconnectivity in multiple brain systems, with TD > PS connectivity within functional brain networks, while PS > TD effects were seen between functional networks.
Conclusions: Here we demonstrate widespread evidence of dysconnectivity in a large sample of youth with psychosis-spectrum symptoms. Regions implicated show a remarkable concordance with frontotemporal regions impacted in adult clinical samples. These results suggest that dysconnectivity deficits are present early on, and therefore may be a useful endophenotype for prospective longitudinal studies of psychosis risk as well as trials of novel treatment interventions.
Keywords: Psychosis, Neuroimaging, Connectivity, Development.
Disclosure: Nothing to Disclose.

M120. Superior Longitudinal Fasciculus Abnormalities in Schizophrenia Assessed Using Compressed Sensing Accelerated Diffusion Spectrum Imaging

Philip Szeszko*, Ek Tan, Xiaofeng Lu, Aziz Ulug, Peter Kingsley, Delbert Robinson, Luca Marinelli, Anil Malhotra

Zucker Hillside Hospital, Glen Oaks, New York

Background: The first generation of diffusion tensor imaging studies demonstrated that putative white matter abnormalities are present in patients with psychosis early in the course of illness and prior to antipsychotic intervention. The most commonly reported metric obtained using diffusion tensor imaging, fractional anisotropy, is considered to be sensitive to white matter pathology, but highly nonspecific. Although lower fractional anisotropy has been consistently reported in psychosis, the underlying pathology and its white matter fiber organization remains largely unknown. A possible reason is that fractional anisotropy values are lower in crossing-fiber regions, as diffusion tensor imaging cannot resolve them and hence, a crossing-fiber-resolving diffusion technique is needed. In contrast to diffusion tensor imaging, an advantage of diffusion spectrum imaging is that it provides information regarding the constituent fibers and enables resolution of crossing fibers for tractography, but requires significant scanning time that is typically not feasible in clinical populations.
Methods: In the current study we implement a method to accelerate diffusion spectrum imaging using compressed sensing that can be used to improve resolution in diffusion space without increasing scan time. To accelerate the diffusion spectrum imaging acquisition (from 105-minutes to 26-minutes), four-fold-accelerated compressed sensing was applied (reducing 514 diffusion samples to 127, b = 6,000 sec/mm2, FOV = 24 cm, 128x128 matrix, slice thickness = 3 mm). Six healthy subjects (mean age = 20.8, SD = 2.9; 4M/2F), and seven patients with first-episode schizophrenia (mean age = 22.1, SD = 3.7; 4M/3F) were scanned at 3T MRI (GE Healthcare, WI, USA). An automated tractography approach was used whereby seeds are manually placed on a reference brain by a user familiar with brain anatomy. The reference image is registered to an undistorted target image, which is in turn registered to the diffusion images. The seeds are transformed to the coordinate system of the target image. A tract template defines segmented tracts as logical functions of the regions-of-interest to generate automated tractography measures, which are manually-adjusted to optimize tract visualization. Quantitative analysis was performed specifically for the superior longitudinal fasciculus that traverses several crossing-fiber regions; we focused on this tract because it has been widely implicated in the neurobiology of psychosis and concomitant neuropsychological impairments.
Results: For tractography, we constructed a whole-brain tract template with the primary analysis focused on the superior longitudinal fasciculus, which was defined using 3 spherical regions-of-interest per hemisphere. Results indicated a significant increase in track length following manual adjustment of regions-of-interest. Manual adjustment of regions-of-interest was also associated with greater anisotropy and lower fiber direction count. Compared to healthy subjects, patients had significantly ($p < .05$) shorter left superior longitudinal fasciculus tract length and an absence of normal asymmetry in superior longitudinal fasciculus fiber direction count.
Conclusions: We present a robust seeding approach using diffusion spectrum imaging that resolves crossing-fibers in the superior longitudinal fasciculus to increase accuracy of brain tractography in this region. Our findings suggest involvement of the superior longitudinal fasciculus in the neurobiology of schizophrenia early in the course of illness compared to healthy volunteers while resolving crossing fibers with other tracts. Our study also demonstrates the feasibility of conducting diffusion spectrum imaging studies in patients experiencing a first-episode of psychosis.
Keywords: schizophrenia, diffusion spectrum imaging, white matter, diffusion tensor imaging.
Disclosure: None.

M121. Attenuated Hippocampal Activation During Fear Extinction is Related to Public Speaking Anxiety

Tali Ball*, Martin Paulus, Murray Stein

San Diego State University/University of California, San Diego, La Jolla, California

Background: Fear extinction, or learning that a previously aversive stimulus is no longer aversive, has been hypothesized as a central deficit in individuals with anxiety disorders. Moreover, enhancement of fear extinction learning is considered an essential component of exposure therapy. However, the neural basis and processes contributing to individual differences in fear extinction are poorly understood. Delineating these processes has important implications for identifying individuals at risk for anxiety disorders and determining whether exposure therapy would be effective for a particular individual.

Methods: 24 adults with high public speaking anxiety participated in a fear conditioning task involving fear acquisition and extinction while undergoing functional magnetic resonance imaging. Conditioned stimuli were two neutral, abstract images, one of which (CS+) was associated with a loud scream in 25% of fear acquisition trials, whereas the other (CS-) was never associated. Extinction involved repeated presentation of the CS+ and CS- without any aversive stimulus. Robust regression analyses were used to uncover neural bases of fear extinction (CS+ versus CS-) that were associated with (1) self-reported valence ratings of the CS+ versus the CS-, and (2) baseline public speaking anxiety severity, assessed by the Personal Report of Confidence as a Speaker.
Results: Individuals reported significant changes in valence ratings during acquisition and extinction, demonstrating a condition (baseline, acquisition, extinction) by stimulus (CS+, CS-) interaction ($p<.01$). Individual differences in valence ratings were correlated with neural activation in the amygdala and anterior insula during both acquisition and extinction ($p<.05$). Importantly, those individuals who reported the greatest public speaking anxiety severity also exhibited the least activation in the right hippocampus during the first half of extinction ($p<.05$).
Conclusions: The results support the hypothesis that individuals with public speaking anxiety have deficits in fear extinction learning. Moreover, the involvement of the hippocampus further emphasizes that an altered ability to encode new information, particularly the fact that a previously aversive stimulus is no longer aversive, may be dysfunctional in these individuals. Future work should examine whether individual differences in extinction related activation are associated with treatment outcomes.
Keywords: Fear extinction, fMRI, Anxiety.
Disclosure: Nothing to Disclose.

M122. Connectome-wide Analysis Implicates Ventral Striatum Dysconnectivity in Major Depression

Ted Satterthwaite, Danielle Bassett, Mathew Weber, Brian Avants, Phillip Cook , Michael Milham, Yvette Sheline*

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Major depression is increasingly conceptualized as a syndrome of dysconnectivity of specific brain circuits. Large-scale networks implicated by prior work include the default mode network and the cognitive control system. Additionally, task based fMRI studies of depression highlight decreases in functional activity of the reward system, but changes in functional connectivity are less well described. Notably, prior studies have examined functional connectivity on a hypothesis-driven regional basis (using seed analyses) or within specific brain networks. Given the wide range of findings in prior reports of depression-related dysconnectivity, here we conducted a comprehensive connectome-wide association study using a previously-validated multivariate distance matrix regression approach.
Methods: Subjects included 47 adults with MDD (mean age 32.6; 39 F) with baseline HRDS score >18 and 22 healthy adults (mean age 30.2; 18 F). All subjects had been off all medication with CNS effects for at least 3 weeks (or 5 weeks for fluoxetine). Each subject completed resting-state fMRI at 3T (412 volumes over two concatenated runs, TR = 2.2s, 4mm isotropic voxels) and had adequate data quality (motion: relative mean displacement <0.3 mm). Resting-state images were preprocessed with spatial smoothing (6mm FWHM), band-pass filtering (0.01-0.08 Hz), and confound regression using a 36-parameter model. Subject-level timeseries were co-registered to the T1 image using boundary-based registration and normalized to a study-specific template using ANTs. CWAS was conducted using multivariate distance matrix regression (MDMR) implemented within R; the group level design matrix included group, sex, age, and in-scanner motion (mean relative displacement). Significant clusters ($z>2.3$, $p<0.01$) identified as part of the CWAS were further evaluated with follow-up seed-based analyses using the same covariates.
Results: CWAS revealed that the multivariate pattern of connectivity was abnormal in the right ventral striatum of depressed subjects (peak Z = 3.04, 1,216 cubic mm). Follow-up seed based connectivity analysis from this location demonstrated robust patterns of dysconnectivity in depression between the ventral striatum and both cognitive control regions as well as the default mode network. Specifically, depressed subjects demonstrated diminished connectivity between the ventral striatum and regions implicated in cognitive control, including bilateral anterior insula and the dorsal anterior cingulate. In contrast, depressed subjects showed elevated connectivity with regions within the default mode network, including most prominently bilateral posterior cingulate cortex.
Conclusions: Here we used a novel multivariate approach to reveal marked dysconnectivity of the ventral striatum in major depression. Specifically, ventral striatum connectivity with cognitive control regions was reduced, whereas connectivity with default mode regions was abnormally enhanced. While speculative, this may reflect a misallocation of reward system coupling towards a dysregulated internal milieu. These results underline the central importance of the reward system in the pathophysiology of depression, and highlight the importance of future studies relating reward system connectivity to dimensional measures of psychopathology such as anhedonia.
Keywords: resting state fMRI, reward system, cognitive control, default mode network.
Disclosure: Nothing to Disclose.

M123. Neural Mechanisms of Irritability in Youth Across Diagnoses: Dimensional and Categorical Approaches

Wan-Ling Tseng*, Melissa Brotman, Christen Deveney, Laura Machlin, Elizabeth Moroney, Kenneth Towbin, Danniel Pine, Ellen Leibenluft

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: Severe, chronic irritability is a core feature of disruptive mood dysregulation disorder (DMDD) and severe mood dysregulation (SMD). Irritability also represents a stable trait distributed continuously in the population and commonly co-occurring in many other disorders,

such as attention-deficit hyperactivity disorder (ADHD), anxiety, and depression (Leibenluft, 2011). This trait-like and cross-disorders feature makes irritability a suitable construct to be studied under the Research Domain Criteria (RDoC) framework. Despite the impairing nature of irritability, little is known regarding its pathophysiology. Frustration paradigms provide an effective means to probe irritability as irritable youth tend to have a low threshold for frustration. One fMRI study used such paradigm in youth with SMD, who also met DMDD criteria, and reported hypoactivation in SMD youth, relative to healthy controls (HC), in the amygdala, striatum, and parietal cortex during frustrating but not non-frustrating conditions (Deveney et al., 2013). Here, we extend this research by examining neural correlates of youth irritability using both categorical and dimensional approaches.

Methods: This study included 75 youth across diagnostic groups including 18 DMDD, 14 ADHD, 20 ANX, and 23 HC (Mean age = 12.91 years; 53.3% girls). Participants completed a revised affective Posner cued-attention task (Deveney et al., 2013) during which they had to identify a target's location after seeing a cue, while their fMRI data were acquired on a 3T scanner. The cue was in the same location as the target on 75% of trials (valid trials) and was in the opposite location of the target on 25% of trials (invalid trials). Frustration was induced by providing participants rigged feedback. Participants self-reported valence and frustration at several points during the task using a 9-point Liker scale (1 = "happy or not at all frustrated" to 9 = "unhappy/sad or extremely frustrated"). The parent report of the Affective Reactivity Index scale (Stringaris et al., 2012) was used as a dimensional measure of irritability. We used the SPSS to analyze the behavioral data and the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) to analyze the fMRI data. For the behavioral analyses, we conducted analysis of variance (ANOVA) to compare the parent-reported irritability between groups and repeated-measures ANOVA to examine between-group differences in accuracy and reaction time, as well as self-rated valence and frustration during the task. For the fMRI analyses, taking an RDoC approach, we conducted a whole-brain analysis of covariance (ANCOVA) to examine the association between parent-reported irritability and blood-oxygen-level-dependent (BOLD) signal changes on the positive vs. rigged feedback contrast (i.e., non-frustrating vs. frustrating conditions) across diagnoses. Taking a traditional categorical approach, we also conducted a whole-brain ANOVA to examine between-group differences in BOLD signal on the positive vs. rigged feedback contrast. Clusters surpassing a threshold of $p < .005$ and $k >= 20$ voxels were considered significant (Lieberman & Cunningham, 2009).

Results: Groups differed on the parent-reported irritability ($p < .001$). Specifically, youth with DMDD had more irritability, compared to all other groups (i.e., ANX, ADHD, and HC; $p <= .002$). Relative to the HC group, the ANX and ADHD groups also had more irritability ($p <= .01$), but the two groups did not differ from each other ($p = .37$). In terms of task performance, groups differed on the accuracy during valid trials under non-frustrating conditions ($p = .04$); that is, youth with ADHD were less accurate, compared to youth with ANX or HC ($ps <= .03$). Groups also differed, at a trend level, on the reaction time during non-frustrating conditions ($p = .06$), i.e., youth with DMDD were faster to respond, compared to youth with ADHD ($p = .01$). There were no between-group differences in self-rated valence and frustration during non-frustrating or frustrating conditions ($p >= .19$). However, all of the participants were significantly more unhappy and frustrated during the frustrating conditions than during the non-frustrating conditions ($ps < .001$), indicating that the task was effective in eliciting frustration in youth, disordered or not. Whole-brain analyses revealed a positive correlation between parent-reported irritability and neural activation across diagnoses in the left superior temporal gyrus (STG) at a trend level ($r = .22$, $p = .06$) when participants were frustrated. In addition, there were between-group differences in neural activation in the left claustrum, left STG, and right putamen during frustrating conditions ($ps <= .05$). Specifically, youth with DMDD, relative to all other groups (i.e., ANX, ADHD, and HC), showed hyperactivation in the left claustrum and left STG when frustrated ($ps <= .05$). Youth with DMDD, compared to the ANX and HC groups, also showed hyperactivation in the right putamen when frustrated ($ps <= .02$). There were no between-group differences in neural activation during non-frustrating conditions ($ps >= .65$).

Conclusions: In this first fMRI study on DMDD, we found that youth with DMDD, for which severe irritability is a prominent symptom, showed hyperactivation in the STG, compared to all other groups (i.e., ANX, ADHD, HC) when frustrated. Interestingly, this finding is consistent with the finding from a dimensional approach. That is, across diagnostic groups, i.e., DMDD, ANX, ADHD, HC, who varied along the dimension of irritability, higher irritability was associated with greater neural activation in the same region (i.e., STG; at a trend level). The STG has been implicated in social cognition and processing of social stimuli (Ruby & Decety, 2004), as well as self-monitoring and reappraisal of behavior (Adolphs, 2003). Our data provide preliminary evidence to suggest that neural dysfunction in this region may mediate irritability across disorders. In addition, findings from a categorical approach showed that youth with DMDD displayed hyperactivation in putamen and claustrum, areas involved in reward processing. Together, these findings suggest that abnormal neural activation in regions implicated in social cognition and reward processing may mediate irritability in youth.

Keywords: irritability, fMRI, categorical, dimensional.

Disclosure: Nothing to Disclose.

M124. Dopamine Efflux in Response to Ultraviolet Radiation in Addicted Sunbed Users

Bryon Adinoff*, Pamela Aubert, Julianne Price, Thomas Harris, Heidi Jacobe, Francesca Filbey, Michael Devous, John Seibyl

VA North Texas Health Care System/University of Texas Southwestern Medical Center, Dallas, Texas

Background: The World Health Organization reports a global incidence of over two million non-melanoma skin cancers, 200,000 malignant melanomas, and 60,000

melanoma-related deaths each year. The incidence of malignant melanoma continues to rise in correlation with the frequency of recreational sun exposure and intermittent exposure to ultraviolet radiation (UVR) and sunbed use. Nevertheless, voluntary exposure to sunlight continues unabated. About 40-50% of frequent tanners display evidence of behaviors associated with other addictive disorders ("tanning addiction"). Many frequent tanners also report tanning to "feel good" and "to relax" and recent preclinical studies reveal UVR increases plasma endorphin in rodents (Fell et al. 2014). In the first study to explore neural responses to UVR, we observed that addicted sunbed uses exposed to UVR, relative to sham UVR, increased regional cerebral blood flow (rCBF) in the left dorsal striatum (Harrington et al., 2012), a brain region involved in the experience and monitoring of reward. As rewards associated with addicted behaviors increase striatal dopamine efflux and many addictive disorders have been associated with decreased striatal D2/D3 receptor binding, this study was designed to assess (1) basal striatal D2/D3 receptor binding and (2) striatal dopamine efflux in addicted and infrequent sunbed tanners. We predicted that, similar to substance use disorders, both basal dopamine receptor binding and dopamine efflux (in response to UVR) would be higher in non-addicted relative to addicted tanners.

Methods: Ten participants meeting modified DSM-5 criteria for active sunbed use disorder and ten age-, sex-, race- and skin-phototype matched infrequent tanners were studied. Participants were administered UVR under two conditions on two separate days. UVR was administered from a commercially available tanning during one session or under the same canopy with a UVR-filter in place ("sham UVR"). The filter allowed the visible spectrum of light and heat to come through but blocked UVA/UVB. Basal D2/D3 receptor density and UVR-induced dopamine efflux in the caudate head was assessed using 123I-iodobenzamide (IBZM) and single photon emission computerized tomography (SPECT) to calculate striatal binding potential (BPnd). Basal receptor binding was assessed prior to active or sham UVR exposure. Dopamine efflux (BPnd change from baseline) was then assessed for 30 minutes during and following UVR administration. Whole brain scans were obtained every 5 minutes over 60 minutes; three scans were combined into 15-minute intervals for comparisons over time. Length of UVR administration was adjusted depending on recent tanning exposure.

Results: Addicted tanners reported 1851 ± 1420 (mean $\pm$ SD) (range 365-4557) lifetime sunbed exposures and met 5.7 ± 1.9 DSM-5 criteria (of 11 total) compared to 542 ± 710 (range 11-2095) lifetime sunbed exposures and 0.5 ± 0.5 criteria in infrequent tanners. UVR was administered for 8.6 ± 2.3 min (mean $\pm$ SD) (range 4-10 min) in addicted tanners and for 5.0 ± 1.0 min (range 4-6 min) in infrequent tanners. Basal dopamine receptor binding did not significantly differ between addicted and infrequent tanners. BPnd, normalized to basal receptor binding, in the bilateral caudate significantly increased during/following UVR administration only in the addicted tanners. BPnd, normalized to basal receptor binding, significantly decreased during the 5-20 min interval relative to the 0-15 min interval (reflecting increased dopamine efflux) in the addicted tanners during the UVR, but not the sham UVR, session. BPnd returned to basal levels during the subsequent 10-25 min interval. BPnd did not significantly change in the infrequent tanners during either session. ΔBPnd between the first (0-15 min) and second (2-15 min) interval during the UVR session was significantly correlated with tanning severity (lifetime sunbed episodes/years tanning) in the addicted ($r = -0.752$, $p = 0.01$) but not infrequent ($r = -0.05$, $p = 0.9$) tanners. ΔBPnd in the addicted tanners during UVR was primarily driven by the left caudate.

Conclusions: Striatal dopamine efflux is increased in response to UVR, but not sham UVR, in addicted tanners. Changes in dopamine efflux were not apparent in infrequent tanners, nor were differences in basal receptor binding observed between groups. The increase in ΔBPnd in left, relative to the right, caudate mirror those we previously observed using rCBF. While these findings are not consistent with those observed in substance use disorders, the increased dopamine efflux observed in the addicted, but not non-addicted, group are similar to those reported in pathological vs. non-pathological gamblers during amphetamine administration (Joutsa et al. 2012) and in Parkinson's patients with pathological gambling during a gambling task vs. Parkinson's patients without pathological gambling (Steeves et al. 2009). These findings suggest dopaminergic responses in individuals with behavioral addictions may differ from those with substance use disorders. The strong relationship between tanning severity and dopamine efflux supports a skin-brain connection driving excessive sunbed use. Funding was provided by NIAMS R21AR063018.

Keywords: addiction, dopamine, striatum, reward.

Disclosure: JS is a consultant to GE Healthcare, Piramal Imaging, and Navidea Biopharmaceuticals and has equity in Molecular Neuroimaging, LLC. MD has been a consultant Avid Radiopharmaceuticals (exceeding $10,000), Eli Lilly (exceeding $10,000), GE Healthcare, Piramal, Navidea, and Bayer. MD has received grants from Avid Radiopharmaceuticals, Eli Lilly and GE Healthcare that exceeded $10,000. He is presently a full time employee of Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly. Consulting contracts (JS and MD) and grants (MD) were for projects unrelated to this research.

M125. Oxytocin Facilitates Pavlovian Extinction in Humans

Monika Eckstein, Benjamin Becker, Dirk Scheele, Valery Grinevich, Katrin Preckel, Thomas Schlaepfer, Wolfgang Maier, Rene Hurlemann*

University of Bonn, Bonn, Germany

Background: Anxiety disorders are common diseases with a lifetime prevalence of up to 25%. Current perspectives on the neurobiology of anxiety disorders posit a lack of inhibitory tone in the amygdala during acquisition of Pavlovian fear responses and deficient encoding of extinction responses in amygdala-medial prefrontal cortex (mPFC) circuits. Competition between these two responses often results in a preponderance of the former, thus limiting the potentially beneficial outcomes of treatments of anxiety

disorders. One intriguing possibility is that a pharmacological strategy aimed at reducing amygdala activity and simultaneously augmenting mPFC function would facilitate the extinction of conditioned fear.
Methods: Key among the endogenous inhibitors of amygdala activity in response to social fear signals is the hypothalamic peptide oxytocin. To address the question whether oxytocin can strengthen Pavlovian extinction beyond its role in controlling social fear, we conducted a functional MRI (fMRI) experiment involving 62 healthy male participants in a randomized, double-blind, parallel group, placebo-controlled design. Specifically, subjects were exposed to a Pavlovian fear conditioning paradigm before receiving a nasal dose (24 IU) of synthetic oxytocin or placebo.
Results: We found that oxytocin, when administered intranasally after Pavlovian fear conditioning, facilitated subsequent fear extinction via enhancement of mPFC signals and simultaneous inhibition of both amygdalar and electrodermal responses to conditioned fear.
Conclusions: Taken together, our findings identify oxytocin as a differentially acting modulator of neural hubs involved in Pavlovian extinction. This specific profile of oxytocin suggests it could be very useful as an adjunct to extinction-based treatments of anxiety disorders.
Keywords: Oxytocin, Fear, Extinction, fMRI.
Disclosure: Nothing to Disclose.

M126. Abnormal Structure of Fear Circuitry in Pediatric Post-traumatic Stress Disorder

Taylor Keding, Ryan Herringa*

University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Background: Structural brain studies of adult PTSD show reduced gray matter volume (GMV) in fear regulatory areas including the ventromedial prefrontal cortex (vmPFC) and hippocampus. Surprisingly, neither finding has been reported in pediatric PTSD. One possibility is that they represent delayed developmental effects that are not fully apparent until adulthood. Alternatively, lower resolution MRI and image processing techniques in prior studies may have limited detection of such differences. Here we examine fear circuitry GMV, including age-related differences, using higher resolution MRI in pediatric PTSD vs. healthy youth.
Methods: Using a cross-sectional design, 3T anatomical brain MRI was acquired in 27 medication-free youth with PTSD and 27 healthy non-traumatized youth of comparable age, sex, and IQ. Images were processed in SPM8 using linear and nonlinear (DARTEL) transformations with output images corrected for total GMV. Voxel-based morphometry was used to compare GMV in a priori regions including the medial prefrontal cortex and amygdala/hippocampus, with family-wise error correction. Primary analyses examined group and group X age differences, as well as PTSD symptom cluster relationships to GMV within the PTSD group.
Results: PTSD youth had reduced GMV but no age-related differences in anterior vmPFC (BA 10/11, $Z = 4.5$), which inversely correlated with PTSD duration. In contrast, while there was no overall group difference in hippocampal volume, a group X age interaction ($Z = 3.6$) was present in the right anterior hippocampus. Here, age positively predicted hippocampal volume in healthy youth but negatively predicted volume in PTSD youth. Within the PTSD group, re-experiencing symptoms inversely correlated with subgenual cingulate (sgACC, $Z = 3.7$) and right anterior hippocampus ($Z = 3.5$) GMV. Post-hoc analyses revealed that these findings were not associated with trauma exposure per se.
Conclusions: Pediatric PTSD is associated with abnormal structure of the vmPFC and age-related differences in the hippocampus, regions important in the extinction and contextual gating of fear. Reduced anterior vmPFC volume may confer impaired recovery from illness, consistent with its role in the allocation of attentional resources. In contrast, individual differences in sgACC volume were associated with re-experiencing symptoms, consistent with the role of the sgACC in fear extinction. The negative relationship between age and hippocampal volume in youth with PTSD suggests an ongoing neurotoxic process over development, which further contributes to illness expression. Future studies employing a longitudinal design would be merited to further explore these possibilities.
Keywords: pediatric PTSD, structural MRI, vmPFC, hippocampus.
Disclosure: Nothing to Disclose.

M127. Cognitive Control Brain Network Function in Alcohol Use Disorder Before and During Treatment with Lorazepam

Claire Wilcox*, Andrew Mayer, Michael Bogenschutz, Josef Ling, Dekonenko Charlene, Bigelow Rose

University of New Mexico, Placitas, New Mexico

Background: In individuals with alcohol use disorder (AUD), impairments in cognitive control may contribute to difficulty maintaining abstinence. Functional brain changes associated with deficits in cognitive control in AUD are not clear. Benzodiazepines are being explored (in combination with disulfiram) for relapse prevention in individuals with co-occurring anxiety and AUD (clinicaltrials.gov identifier: NCT00721526). The effects of benzodiazepines on the cognitive control network in AUD is not known. The two aims of this study were to compare functional brain changes in brain networks mediating cognitive control in AUD relative to healthy controls (HC), and to explore the effects of treatment with a combination of a benzodiazepine (lorazepam) and disulfiram on these brain networks.
Methods: Seven AUD with anxiety from an open-label trial of disulfiram plus lorazepam performed a multisensory Stroop task and a resting state task during fMRI (both pre and 5-7 days post initiation of medication treatment). Nine HC performed the tasks during fMRI at baseline only. A 2 x 2 mixed-measures ANOVA [Group (AUD vs HC) x Condition (Congruent vs. Incongruent)] and a 2x2 repeated measures ANOVA [Time (Scan 1 vs. Scan 2) x Condition (Congruent vs. Incongruent)] were conducted on median response time data for the Stroop task. In addition, evoked

BOLD signal during the Stroop task and resting state functional connectivity using apriori seeds were compared focusing on Group (HC vs. AUD) and Time (Scan 1 vs. Scan 2 for AUD) effects. The Analysis of Functional NeuroImages (AFNI) software package was used to generate functional images using standard pre-processing techniques (time-slice correction, motion correction, 6 mm Gaussian full-width half-maximum spatial filter, and spatial normalization to Talairach space). For evoked fMRI analyses, voxel-wise 2 x 2 [Group (AUD vs. HC) x Condition (Congruent vs. Incongruent)] mixed-measures ANOVA were performed on the spatially normalized percent signal change measures. In addition, voxelwise 2 x 2 [Time (Scan 1 vs. Scan 2) x Condition (Congruent vs. Incongruent)] repeated measures ANOVA were performed in AUD only. For seed-based resting state connectivity analyses, we chose to focus on three regions which are known to be recruited during cognitive control, and which also demonstrated group differences in evoked activation during the multi-sensory Stroop task: bilateral caudate, left DLPFC, and left ACC. For connectivity analyses, paired samples t-tests were performed to examine the group and longitudinal differences (Scan 1 to Scan 2) in intrinsic activity for each of these seeds. For all evoked task-associated findings, false positives were corrected at $z > 2.3$ (input Z-stat volume voxel-wise threshold) and $p < 0.05$ (p threshold for clusters) based on the Gaussian Random Fields theory as implemented in FSL (http://www.fmrib.ox.ac.uk/fsl/feat5/programs.html) using a whole brain mask. For all resting state connectivity results, false positives were corrected at $z > 2.6$ (input Z-stat volume voxel-wise threshold) and $p < 0.05$ (p threshold for clusters); a higher z threshold was used for connectivity results, as multiple seeds were tested.

Results: AUD demonstrated significantly slower reaction time during the task compared to HC, but otherwise there were no performance differences between groups or from Scan 1 to Scan 2. Although there were no significant Group (AUD vs. HC) X Condition (Incongruent vs. Congruent) or Time (Scan 1 vs. Scan 2) X Condition interactions, AUD participants demonstrated greater activation than HC (overall Group effect) in a variety of brain regions known to be involved in cognitive control including insula, parietal lobe, DLPFC, orbitofrontal cortex (OFC), supplementary motor area (SMA), dorsal ACC, basal ganglia and thalamus. HC demonstrated increased connectivity between the bilateral caudate seed and a variety of regions involved in top down cognitive control (bilateral cingulate gyrus, PCC, precuneus) compared to AUD. AUD demonstrated increased connectivity between bilateral caudate and brainstem and caudate and limbic regions (hippocampus, middle temporal gyrus, amygdala) compared to HC. Increased anticorrelation between bilateral caudate and left inferior parietal lobe (IPL) was observed for Scan 2 relative to Scan 1 for AUD. None of the changes from Scan 1 to Scan 2 occurred in areas where there were differences between HC and AUD for either evoked or resting state analyses, providing no evidence of normalization or deterioration of brain function in the cognitive control network with treatment.

Conclusions: In summary, AUD demonstrated a variety of functional brain changes in the cognitive control network. Treatment with a combination of disulfiram and lorazepam neither resulted in a significant normalization of these brain changes, nor did it appear to worsen related brain function.

Keywords: alcohol use disorder, benzodiazepine, fMRI, cognitive control.

Disclosure: Nothing to Disclose.

M128. Callosal Tract Geometry in Non-psychotic Familial High-risk Subjects- DTI Study

Marek Kubicki*, Peter Savadjiev, Lynn DeLisi, Larry Seidman, Martha Shenton

Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts

Background: Cumulative evidence suggests that the etiology of schizophrenia includes both neurodevelopmental and neurodegenerative components, as well as genetic risk. Involvement of white matter is also clear, however currently available measures obtained from neuroimaging methods, such as DTI, do not differentiate changes in white matter architecture (related to brain development), from those related to inflammation and demyelination (related to brain degeneration). In order to characterize the neurodevelopmental aspects of brain alterations observed in white matter related to schizophrenia, we focus on white matter geometry. Our previous study (Savadjiev et al., 2013) demonstrated, for the first time, sex specific differences in white matter geometry of the corpus callosum in patients with schizophrenia. Here, we apply the same methods and measures to a cohort of nonpsychotic subjects at high familial risk to develop schizophrenia (HFR), to investigate whether callosal changes in geometry can be considered a biomarker for abnormal brain development, and thus risk for schizophrenia.

Methods: 29 HFR subjects (with one first-degree relative and at least one other relative suffering from schizophrenia), and 27 controls, low risk subjects (with no family history of schizophrenia or other psychotic illness) were scanned using a DTI sequence on a 3T scanner. Tract-based Spatial Statistics (TBSS) whole brain group analysis was conducted, which was followed by a detailed corpus callosum ROI analysis. Fractional Anisotropy, a nonspecific measure of white matter integrity and fiber dispersion, purported to be a measure of tract geometry, were compared between groups and across sexes.

Results: TBSS results revealed no FA changes in high-risk subjects, when compared to the low risk control population. Whole brain fiber dispersion analysis, however, demonstrated a main gender effect, and in follow up analyses, sex by risk interactions were observed, suggesting that the normal sexual dimorphism observed in the control population was reversed in high-risk subjects.

Conclusions: A reversal of normal sexual dimorphism, which mimics recent results in adolescent onset schizophrenia, may indicate an error in neurogenesis and a possible trait marker of schizophrenia Future studies need to focus on the role of gender in the neurodevelopment of the geometry of the corpus callosum in schizophrenia spectrum disorders.

Keywords: familial risk, schizophrenia, white matter geometry, diffusion.

Disclosure: Nothing to Disclose.

M129. Neural Processing of a Behavioral Inhibition Task among Offspring Exposed to Prenatal Smoking

Ardesheer Talati*, Ardesheer Talati, Zhishun Wang, Jonathan Posner, Virginia Warner, Myrna Weissman

Columbia University/New York State Psychiatric Institute, New York, New York

Background: Despite declines in smoking over the last several decades, 10-15% of women in the US continue to smoke during pregnancy today. Doing so impacts both maternal and fetal well-being, and a number of studies have found offspring exposed in utero to tobacco to have higher rates of pregnancy-related and neonatal complications, delayed developmental milestones, and mild to moderate cognitive impairments that can persist into adolescence. The causal mechanisms remain unclear. However, because offspring exposed to maternal smoking at other times but not during pregnancy do not exhibit the same adverse trajectories, it is presumed that at least some of the adverse outcomes are direct teratogenic effects of tobacco exposure. Examining neurobiological antecedents of these adverse outcomes may help us not only to understand mechanisms of psychopathology but also to help identify offspring who may be at greatest risk so that they can be targeted for early intervention. The current study seeks to identify brain circuit abnormalities related to behavioral inhibition among offspring exposed to prenatal smoking.
Methods: Sample: One hundred and seventeen participants from a longitudinal three generational study of families at high versus low familial risk for major depression were included in this analysis. Pregnancy history (which included data on smoking) was collected directly from the mother. Offspring were assessed longitudinally across six waves spanning up to 30 years using the age appropriate version of the Schedule for Affective Disorders (SADS/Kiddie-SADS). Exposure: Smoke exposure was defined as a categorical variable based on whether or not the mother smoked 10 or more cigarettes per day, nearly every day, while pregnant (similar findings were obtained when using a continuous count). Imaging Paradigm: Participants were imaged on a 1.5 Tesla GE scanner while performing the standard Simon Spatial Incompatibility Task, a non-verbal MRI-compatible analog of the Stroop task, that requires participants to inhibit a more pre-potent, naturally occurring response (low conflict trial, LC) in favor of a less naturalistic one (high conflict, HC). Doing so requires mobilization of attentional resources, resolution of cognitive conflict, and engagement of regulatory control. The difference between the two trials (HC – LC) indexes the representation of behavioral conflict, and forms the primary outcome measure for this analysis. Analysis: Two approaches were used to examine differences in behavioral conflict between the exposed and unexposed offspring. In the first, all exposed offspring ($N = 28$) were contrasted to all unexposed offspring ($N = 89$), adjusting for age, gender, and familial risk status. In the second, a computer algorithm was used to generate a set of 28 controls that best matched the 28 exposed cases on the aforementioned demographic variables. The two methods produced virtually indistinguishable results, and those based on the latter method are presented here.
Results: Among exposed offspring, behavioral inhibition (HC – LC) was associated with reduced bilateral activation through broad regions of the cerebral cortex, including those involved in response selection and higher-order decision making (e.g., anterior cingulate cortex, inferior frontal/orbitofrontal gyrus) emotional salience (insula, temporal cortex), and higher-ordered visual processing (middle occipital, cuneus). The superior and inferior parietal lobules, in contrast, showed greater activity in the exposed offspring. To further examine the implications of the reductions in activation seen above, we plotted the contrast estimates (i.e., the HC - LC betas) for each participant within the peak voxels for each of the above clusters. Two patterns emerged: for regions that were overall more activated during the high conflict trials ($HC > LC$), the exposed offspring showed lower activation than their unexposed counterparts. For regions that were less active during the higher conflict trial ($LC > HC$), the exposed offspring showed greater deactivation. The findings were not attributable to differences in performance as only correctly responded to trials were included in the analysis, and response time did not vary significantly across groups.
Conclusions: The overall patterns of reduced activity during behavioral inhibition tasks among offspring exposed to prenatal smoking are consistent with both (1) the greater rates of impulsivity and externalizing spectrum disorders observed among these offspring; and (2) with structural deficits previously identified by us and other groups within these regions. The patterns suggest that exposed offspring have an altered cortical representation of behavioral inhibition that involves both a failure to sufficiently activate regions required to be active during conflict, and over-suppression of regions required to be deactivated during conflict. Future work will involve testing whether these variations in neurobiological circuits are related to onset of psychopathology.
Keywords: prenatal, smoking, impulsivity, fMRI.
Disclosure: Nothing to Disclose.

M130. Utility of fMRI BOLD Signals to Stratify Responders to the Satiating Effects of the 5-HT2C Receptor Agonist Meta-Chlorophenylpiperazine (mCPP) on Consumption of High Calorie Food

Colin Dourish*, Jason Thomas, Jeremy Tomlinson, Zaki Hassan-Smith, Peter Hansen, Suzanne Higgs

P1vital Ltd., Wallingford, Oxfordshire, United Kingdom

Background: There are considerable individual differences in response to drugs used to treat obesity whereby some patients experience substantial reductions in appetite and body weight whereas others show little or no response. The 5-HT2C receptor agonist meta-chlorophenylpiperazine (mCPP) decreases food intake in lean and obese volunteers. In studies using a universal eating monitor (UEM) to measure meal microstructure we showed that mCPP had a more pronounced effect on the intake of a palatable high calorie snack (cookies) than on the consumption of a low calorie pasta lunch. Using fMRI we showed that changes in the ventrolateral prefrontal cortex and the orbitofrontal cortex were positively correlated with the amount of cookies

consumed suggesting that these brain regions could mediate the selective hedonic effects observed. Differences in brain responses to food stimuli between drug responders and non-responders could help to identify factors that influence individual responses to appetite suppressant drug therapy. The present study investigated this hypothesis by examining individual responses to mCPP on the consumption of a high calorie food using a UEM and fMRI.

Methods: Twenty four healthy female volunteers with a mean age of 23 years (SEM = 1.4) and a mean Body Mass Index of 21.8 kg/m2 (SEM = 0.3) participated in the study. The participants were dosed orally in a counterbalanced order with either placebo or 30mg mCPP on separate test days one week apart in a double-blind cross-over design. On each test day, participants were scanned twice using fMRI at baseline and after dosing and viewed images of high calorie foods or control (non-food) items. Images were displayed for 2500ms and participants were asked to imagine eating the foods they viewed. After the second scan participants were provided with a pasta lunch and allowed to eat until satiated. Twenty minutes later participants were offered chocolate chip cookies and were again allowed to eat until satiated. Food consumption and meal microstructure was recorded using a UEM. The UEM comprises a concealed weighing system and computer software to enable detailed collection and analysis of human eating behaviour and continuously monitors food intake in parallel with measures of appetite and satiety. Twenty participants completed testing and were classified either as responders if they showed a $>10\%$ decrease in cookie consumption after mCPP compared to placebo (12 participants) or as non-responders if they showed a <10 % decrease in cookie consumption after mCPP compared to placebo (8 participants).

Results: mCPP significantly decreased the cookie consumption of responders by 64% ($p<0.001$) and significantly increased the cookie consumption of non-responders by 16% ($p<0.05$). Analysis of ratings of cookie pleasantness during cookie consumption showed that the non-responders rated the cookies as significantly more pleasant than the responders ($p<0.05$), in the absence of any differences in hunger ($p>0.05$) or any differences in the amount of pasta consumed during lunch ($p>0.05$). After subtracting placebo scans, a whole-brain cluster-corrected analysis revealed a significant interaction between group (responders compared to non-responders) and time (before and after mCPP administration). Analysis of local maxima revealed that, at baseline, the non-responders exhibited greater BOLD activity than the responders in key reward and motivational areas including the midbrain (bilaterally), pons, amygdala, parahippocampal gyrus, putamen, posterior cingulate cortex, orbitofrontal cortex and dorsomedial prefrontal cortex (all significant at $p<0.001$ and FWE corrected at $p<0.05$) to the sight of high calorie food images. In contrast, the responders showed a significant increase in BOLD activity compared to the non-responders only in the ventromedial prefrontal cortex and a decrease in the BOLD signal in the midbrain after mCPP (both significant at $p<0.001$ and FWE corrected at $p<0.05$).

Conclusions: It was possible to classify participants into two groups (drug responders and non-responders) based on their cookie intake after being given mCPP. The results show for the first time that non-responders to the satiating effects of mCPP show a greater fMRI BOLD response to high calorie food in key brain reward regions. This elevated baseline response to high calorie food was not attenuated by mCPP and may be responsible for the enhanced rating of cookie pleasantness by mCPP non-responders. These results support the novel hypothesis that administration of an appetite suppressant to individuals who show enhanced reward responses to food stimuli may be associated with a blunted satiating effect and in some participants increased food intake. Our findings could explain the large individual variability in responses to serotonergic anti-obesity drugs. Furthermore, it may be possible in future clinical trials of novel serotonergic compounds and for prescribing of approved drugs such as the 5-HT2C receptor agonist lorcaserin to identify individuals who are more likely to respond to certain types of medication, leading to stratified and more effective treatments.

Keywords: 5-HT2C, eating, fMRI, stratification.

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M131. Evidence from Diffusion Tensor Imaging for Frontotemporal Deficits in Subclinical Psychosis

Pamela DeRosse*, Tossi Ikuta, Bart Peters, Katherine Karlsgodt, Philip Szeszko, Anil Malhotra

Zucker Hillside Hospital, Glen Oaks, New York

Background: In recent years, schizophrenia (SZ) has increasingly been viewed as a disorder of dysconnectivity in which decreased connections between brain areas is associated with frank psychosis. This view is consistent with findings of reductions in white matter (WM) integrity, particularly in frontotemporal regions, in patients with SZ. Recent examination of patients with schizotypal personality disorder (SPD), however, have revealed a similar pattern of WM abnormalities suggesting that frontotemporal lobe dysfunction may represent a core component of a more general psychosis phenotype. To date, few studies have examined whether WM integrity is associated with subclinical psychotic symptoms in adults who do not meet criteria for a psychiatric illness and even fewer studies have examined this relationship in typically developing adolescents.

Methods: We administered diffusion tensor imaging (DTI) exams to a sample of healthy adolescents (N = 57) between the ages of 8 and 18 and a sample of healthy adults (N = 138) between the ages of 18 and 68. All participants were recruited from the community and characterized on measures of subclinical psychotic symptoms. Fractional anisotropy (FA), a measure broadly associated with WM integrity, was examined in relation to severity of subclinical psychotic symptoms with particular focus on 5 association tracts traversing the frontal and temporal lobes including the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), cingulum bundle, superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF).

Results: In the adult sample, we found an association between subclinical psychotic symptoms and FA in the IFOF ($F(1,133) = 4.90$, $p = .029$) such that individuals characterized as high in subclinical symptoms had lower FA than those characterized as low in subclinical symptoms. In addition, there was a significant group x hemisphere interaction for the UF ($F(1,133) = 6.29$, 133, $p = .013$) such that those characterized as high in subclinical symptoms had greater asymmetry ($R > L$) than those characterized as low in subclinical symptoms ($t(136) = -2.78$, $p = .006$). In the adolescent sample, examination of tract-based spatial statistics revealed a significant association ($pFWE < .05$) between overall levels of subclinical psychotic symptoms and FA within a cluster comprising the SLF and IFOF. Tractography analyses confirmed these results and suggested that increasing levels of subclinical psychosis were associated with reductions in FA in the SLF ($t = 3.55$; $p = .001$) across adolescence.
Conclusions: These findings are broadly consistent with data derived from the study of patients with SZ and SPD and suggest that frontotemporal lobe dysfunction may represent a core component of the psychosis phenotype. These data add to the growing evidence that psychosis should not be viewed as a dichotomous category but rather, a dimensional construct.
Keywords: Subclinical psychosis, DTI.
Disclosure: Nothing to Disclose.

M132. Ventral Striatal Dopamine Synthesis Correlates with Neural Activity during Reward Anticipation

Catherine Hegarty*, Daniel P. Eisenberg, Philip Kohn, Jean-Claude Dreher, Joseph Masdeu, Angela M. Ianni, Nicholas Turner, Michael D. Gregory, Karen F. Berman

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: Dysfunction of neural circuitry subserving dopamine (DA)-related reward processing has been theorized to be an important contributor to a range of neuropsychiatric illnesses. Electrophysiological work in monkeys (Schultz et al. 1997, Fiorillo et al. 2003) reveals that dopaminergic neurons encode distinct statistical properties of reward processing, and studies in humans using [11C]raclopride displacement paradigms have suggested that presynaptic dopaminergic function has a facilitating role for BOLD-measured activity in the ventral striatum (VS) during reward anticipation (Schott et al. 2008 and Urban et al. 2012). On the other hand, one recent report identified an inverse relationship between prediction-error-related VS activation and presynaptic DA synthesis capacity measured with a different PET tracer, [18F]DOPA (Schlagenhauf et al. 2013). Whether the relationship between presynaptic dopamine and BOLD signal in the VS is specific to the tracer used or to cognitive context remains untested. Previous findings from our group using an fMRI slow-event-related design, modeled after the work by Fiorillo et al. (2003), suggest that distinct functional brain networks code for transient and sustained activities, with VS activity particularly responsive to sustained reward uncertainty (Dreher et al. 2006). We have previously reported that prefrontal cortical response to reward anticipation is linked to midbrain DA synthesis in an age-dependent manner (Dreher et al. 2008), but whether the amplitude of VS activation to reward anticipation might be guided by VS dopaminergic tone has not been specifically addressed. By employing this same fMRI reward paradigm and [18F]DOPA PET imaging to measure DA synthesis levels at rest, we tested for the relationship between presynaptic DA levels and VS activation during reward anticipation, hypothesizing that increased basal levels of DA synthesis would positively correlate with BOLD signal in the VS during reward anticipation.
Methods: Eighteen healthy subjects (mean age: 28.2, stdev: 7.7 years; 5 female) underwent fMRI scanning on a 3T GE Scanner while engaged in a reward paradigm, previously shown to elicit VS activity during reward anticipation (Dreher et al. 2006, 2008, 2009). fMRI data were preprocessed in a standard fashion, which consisted of skull stripping a mean structural image for each subject using ANTS (http://picsl.upenn.edu/software/ants/), intensity nonuniformity correction using NITRC's N3, registering the skull stripped structural scan to template space and then applying the same transform to align the fMRI image to template space (the template was a mean of 240 subjects in MNI space generated using SPM's DARTEL) before using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) to apply a Gaussian smoothing operation to the data. A VS region of interest (ROI) was generated from the registered T1 structural image using Freesurfer (http://surfer.nmr.mgh.harvard.edu/) segmentation and hand edited, and then T2*-weighted BOLD maps were analyzed using SPM5. First-level contrast maps of anticipation during maximal uncertainty of winning (50% chance of $20) vs. anticipation during the condition with lowest uncertainty (100% chance of $0) were generated, from which average VS activation for each subject was calculated. The same 18 subjects were also studied with the [18F]DOPA PET technique for measuring presynaptic DA synthesis and storage. One hour prior to the PET scan, volunteers were administered carbidopa (200 mg) by mouth to decrease peripheral tracer decarboxylation. [18F]DOPA (8-17 mCi) was then administered intravenously, and a 90-minute dynamic emission scan on a GE Advance PET scanner was performed. A hand-edited cerebellar reference region was also generated from each subject's T1 image and, along with the bilateral VS ROI, was used to generate average time-activity data for each individual. Striatum-specific uptake levels (Ki) of [18F]DOPA were calculated using the Patlak-Gjedde method. The VS activation and Ki values were then tested with a two-tailed Pearson's correlation analysis.
Results: A significant positive correlation ($r = 0.536$, $p = 0.022$) was found between BOLD signal and mean VS Ki. This relationship remained significant when tested with partial correlations controlling for age or sex. Upon examining VS in each hemisphere separately, correlation was strongest in the left VS ($r = 0.509$, $p = 0.030$), while the right VS reached trend level significance ($r = 0.461$, $p = 0.054$). Post-hoc exploration of associations using dorsal putamen and caudate were not significant ($p > 0.2$ for all regions), suggesting regional specificity of this effect.

Conclusions: Our results suggest a positive relationship between presynaptic DA tone and the VS response to uncertain reward anticipation, in line with past raclopride displacement studies. To the extent that past work has suggested an inverse relationship during components of reward processing, this suggests that VS presynaptic synthetic capacity may differentially bias VS neural responses in a context-dependent fashion, which is in keeping with the original work in non-human primates. Future studies should be aimed at understanding these relationships in patients with DA-related neuropsychiatric disorders.

Keywords: Ventral Striatum, fMRI, Reward, PET.
Disclosure: Nothing to Disclose.

M133. Emotional Cues Influence Reward-related Decision-making in Teens and Young Adults with Borderline Personality Symptoms

Michael Hallquist*, Alexandre Dombrovski, Michael Frank, Tae Kim, Beatriz Luna

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Background: Emotion dysregulation and impulsivity are two prominent and impairing features of borderline personality disorder (BPD). During intense negative emotional states, individuals with BPD frequently engage in impulsive behaviors, including self-injury, suicide attempts, substance abuse, and reactive aggression. Symptoms of BPD often emerge in early adolescence or young adulthood, yet neurodevelopmental precursors are largely unknown. Growing research on BPD in adults has identified abnormalities in a primary circuit supporting the regulation of emotion, impulsive aggression, and reward processing that includes subgenual anterior cingulate cortex (sgACC, BA 25), ventromedial prefrontal cortex (vmPFC; BA 10–12), and the amygdala, which are highly interconnected. To date, however, no studies have characterized fronto-striatal-limbic circuitry in adolescents and young adults with BPD symptoms. This is a crucial gap because major neuroanatomical reorganization of sgACC/vmPFC-amygdala fibers occurs during this period, enhancing the regulation of emotion and aggression and facilitating the mature integration of emotion with motivated behavior. The primary aim of our study was to characterize the influence of emotion on decision-making in adolescents and young adults with BPD symptoms. We were especially interested in abnormality in fronto-striatial-limbic circuitry that may underlie emotion dysregulation and impulsivity in adolescents with BPD and be associated with persistent symptoms in adults.

Methods: Participants were 18 adolescents and young adults (M age = 20.77, range = 14–26), 9 healthy controls with no history of psychopathology and 9 of whom reported clinical levels of emotion dysregulation and impulsivity on the Personality Assessment Inventory–Borderline features subscale. BPD symptoms were confirmed by structured clinical interview (Structured Interview for DSM-IV Personality), and BPD participants met at least 3 of 9 diagnostic criteria. The control and BPD groups were similar in age, IQ, and sex ratio. Participants completed self-report questionnaires measuring borderline symptoms, interpersonal problems, and personality, as well as structured clinical interviews for psychopathology and personality disorders. fMRI Study. Participants completed a functional magnetic resonance imaging (fMRI) study of emotion and reward-related decision-making. Functional images were acquired on a Siemens Tim Trio 3T scanner using a multi-band echo-planar sequence sensitive to BOLD contrast: TR = 1.0s, TE = 30 ms, MB factor = 5, flip angle = 55̊, voxel size = 2.4 x 2.4 x 2.3 mm. The experimental paradigm consisted of eight runs of 50 trials each in which participants were instructed to win as many points as possible by learning when to stop a ball that revolved around the screen over 4 seconds. The probabilistic reward contingency varied by block, with expected value increasing, decreasing, or staying constant over the four-second trial. For each block, the ball revolved around a central stimulus, which was a fearful face, happy face, or phase-scrambled face sampled from controlled facial stimuli. Facial stimuli were unrelated to the reward contingency, but participants not aware of this design feature.

Results: Analytic approach. Behavioral data during the fMRI scan were fit using two reinforcement learning models: a Rescorla-Wagner (R-W) model that tracked trial-wise expected value and reward prediction errors, and a time-clock (T-C) model that fit trial-wise reaction times in part as a function of mean differences and uncertainty in expected value for fast versus slow responses. In the R-W model, separate learning rate parameters were used to fit positive versus negative prediction errors. Trial-wise estimates of learning parameters for both models were convolved with a canonical double-gamma hemodynamic response function to generate model-predicted regressors for fMRI analysis. General linear model analyses of single-subject and group fMRI data were conducted using FSL v5.0.6. BPD and control participants did not significantly differ in the total number of points awarded for fearful ($p = .50$), happy ($p = .22$), or scrambled ($p = .36$) trials. Notably, however, R-W-derived expected value was significantly higher for BPD participants than controls during fear blocks ($t = 2.21$, $p = .04$), but not happy or scrambled blocks ($ps > .10$), suggesting that fearful faces may have differentially enhanced reward-related learning in BPD. In addition, BPD participants showed less facilitation of reaction times by positive prediction errors than controls ($t = 2.37$, $p = .03$), which has previously been linked to faster motor responding via the nigrostriatal pathway. Preliminary region-of-interest fMRI analyses based on the R-W model indicated that negative prediction errors during fearful blocks of the task were associated with greater neural activation in the amygdala in BPD participants relative to controls (small volume-corrected $p < .05$), whereas ventral striatum activation due to positive prediction errors was stronger in controls than BPD participants during happy blocks (small volume-corrected $p < .05$). Additional planned analyses of fMRI data will be presented, including 1) using the T-C model to characterize group fMRI differences in strategic exploration, 2) characterization of developmental differences in learning between groups, and 3) whole-brain analyses of fMRI data using both R-W and T-C learning models.

Conclusions: Extending prior research on threat processing in BPD, we found that the presence of fearful faces enhanced reward-related learning in BPD participants. Fear-related stimuli may be especially salient to individuals with BPD symptoms, which may increase sensitivity to outcomes. Nevertheless, at extreme levels of emotional arousal, individuals with BPD may become relatively insensitive to feedback, and our study cannot speak directly to the influence of state-related emotion dysregulation on learning. Conversely, better than expected outcomes had a weaker influence on motor responses in BPD than controls. fMRI analyses suggested that worse than expected outcomes were associated with greater amygdala reactivity in BPD when fearful, but not happy or scrambled, faces were presented. Participants with BPD also exhibited less activation of the ventral striatum to better than expected outcomes than controls, suggesting a weaker modulation of reward-related brain networks in BPD. Our preliminary study yielded novel findings that provide additional insight into how emotional stimuli influence learning and decision-making in teens and young adults with BPD symptoms.
Keywords: Borderline personality, Adolescent development, Reinforcement learning, fMRI.
Disclosure: Nothing to Disclose.

M134. Structural Brain Imaging of Myelin in Patients with Schizophrenia and Healthy Adults Using mcDESPOT

Michael Gregory*, Stefano Marenco, Grace Hansen, Susie Kuo, Christian Meyer, Joseph H. Callicott, Daniel P. Eisenberg, Jose A. Apud, Karen F. Berman

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: A considerable body of MRI research on brain structure in schizophrenia has reported reductions in gray matter volume across a range of areas including the frontal lobes, temporal lobes, hippocampi and cerebellum. While MRI-detected changes in structure may reflect the number and morphology of neuronal and non-neuronal cells, parameters such as gray matter volume can also vary as a function of non-neuropil factors such as vascular, water, and fat content, rendering the neurobiological interpretation complex. Nonetheless, to the extent that such gray matter findings do indicate changes in neuropil, it might be expected that they could be accompanied by alterations in white matter. A number of studies have investigated this possibility, primarily with diffusion tensor imaging, but findings in schizophrenia have been inconsistent and require replication. As a new addition to the neuroimaging armamentarium for characterizing white matter, multi-component driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) allows direct imaging myelin content and produces quantitative myelin maps (Deoni et al., 2008). Although further work with multimodal, converging techniques is necessary, these maps have been shown to be reliable measures of myelin water fraction, with high inter-scan reproducibility in the same individual and low inter-individual variability (Deoni et al., 2012). Here, we utilized the mcDESPOT technique to test for altered myelin content in patients with schizophrenia compared to healthy adults via a voxel-wise analysis across the entire brain.
Methods: Fifty-seven patients with schizophrenia (mean age 30.8 + /- 9.6 years, 37 males) and 56 well-screened healthy controls (mean age 30 + /- 9.3 years, 32 males) were scanned on a 3-Tesla GE MRI scanner. An inversion-recovery SPGR (irSPGR) image and eight flip angles of both SPGR and SSFP images at phase 0 and 180 degrees were obtained. Each participant's images were coregistered and then voxel-wise myelin maps were calculated in each person's native space using the three-pool mcDESPOT algorithm (Deoni et al., 2012). A mean irSPGR template was created from the average of all participants' irSPGR images, and then each individual's irSPGR image was nonlinearly warped to this template. Resulting maps were spatially smoothed using a 6mm FWHM kernel. We compared patients to healthy adults using a voxelwise t-test, controlling for effects due to age and sex. Results were assessed with a voxel-wise threshold of $p < 0.05$, FDR-corrected for multiple comparisons.
Results: Patients with schizophrenia, relative to healthy adults, showed significantly increased myelin content throughout most of the cerebellar white matter and along the lateral margin of the hippocampus bilaterally with extension towards the anterior temporal pole on the right. Additionally, there was a small cluster of voxels in the right medial prefrontal cortex wherein patients with schizophrenia exhibited significantly lower myelin content than controls. No regions showed differential effects of either age or sex when comparing patients with schizophrenia and healthy adults.
Conclusions: The current results suggest that in schizophrenia the hippocampus and cerebellum are characterized by increased myelin content. Both of these regions have previously been implicated in the disorder, with decreased gray matter volume and altered fractional anisotropy reported with diffusion imaging. The integration of these results with those from other imaging modalities and with neuropsychological and other clinical markers of disease will allow for a better understanding these changes, as will longitudinal studies.
Keywords: schizophrenia, myelin imaging, hippocampus, cerebellum.
Disclosure: Nothing to Disclose.

M135. Endogenous Opioid, Neuroendocrine, and Behavioral Responses to Social Rejection and Acceptance in Major Depressive Disorder

David Hsu*, Benjamin Sanford, Kortni Meyers, Tiffany Love, Kathleen Hazlett, Sara Walker, Brian Mickey, Robert Koeppe, Scott Langenecker, Jon-Kar Zubieta

University of Michigan, Ann Arbor, Michigan

Background: Maladaptive emotional responses to social cues can contribute to the severity and chronicity of major depressive disorder (MDD). Increased perception and sensitivity to social rejection can worsen symptoms,

and reduced pleasure from positive social interactions can lead to further withdrawal and isolation. Animal models and indirectly human studies have shown that endogenous μ-opioid receptor (MOR) mediated neurotransmission is critical for emotional recovery during social threats and promoting positive motivation during social reward. We hypothesized that, compared to healthy controls (HCs), MDD patients would have altered affective and MOR system responses to acute social rejection and acceptance.

Methods: Subjects were 18 HCs and 17 medication-free patients diagnosed with current MDD. Prior to scanning, subjects rated online profiles of preferred-sex individuals with whom they would most like to form a close relationship. A few days later they were given feedback that they were not liked (rejection) or liked (acceptance) by their highest-rated profiles during positron emission tomography (PET) with intravenous administration of the selective MOR radiotracer [11C]carfentanil. Endogenous MOR-mediated neurotransmission was measured as acute reductions in receptor availability during rejection or acceptance compared to baseline blocks, which did not contain feedback. Affect ratings and plasma cortisol levels were measured every 2 and 10 minutes, respectively, during PET scans.

Results: Both HCs and MDD patients showed sustained negative affect in response to rejection, although only HCs showed broad MOR activation, which was found in the nucleus accumbens, amygdala, midline thalamus, and periaqueductal gray. In contrast, MDD patients showed MOR deactivation in the amygdala and also showed persistent negative affect after rejection trials had ended. In HCs but not MDD patients, the trait Ego Resiliency and cortisol levels were positively and negatively correlated with MOR activation, respectively, suggesting that MOR activation during rejection serves a protective or adaptive function that is disrupted in MDD. During acceptance, MDD patients showed greater, but short-lived, positive affect compared to HCs. In HCs, acceptance was associated with significant MOR activation in the amygdala and anterior insula and deactivation in the midline thalamus and subgenual anterior cingulate cortex. In MDD patients, acceptance was associated with MOR activation in the midline thalamus whereas deactivation was found in the nucleus accumbens. During acceptance, HCs but not MDD patients showed a positive correlation with MOR activation in the nucleus accumbens, a structure involved in reward and motivation, and increases in the desire for social interaction.

Conclusions: The results suggest that an altered MOR system plays a role in impaired regulation of social-affective functioning in MDD. These alterations were found in structures regulating stress, mood, and motivation and may play a role in sustaining negative affect following social stressors, as well as the short-lived nature of positive affective responses following positive social interactions. Altered MOR function may make it more difficult for MDD patients to navigate the social environment, potentially reinforcing depressive symptoms.

Keywords: opioid, social, stress, depression.

Disclosure: Dr. Mickey received salary support from St. Jude Medical within the past 3 years.

M136. Decreased Brain Monoamine Oxidase a Distribution Volume in Impulsive, Violent Offenders with Antisocial Personality Disorder: An [11C] Harmine Positron Emission Tomography Study

Nathan Kolla*, Alan Houle, Sylvain Wilson, Michael Bagby, Paul Links, Alexander Simpson, Amina Hussain, Jeffrey Meyer

University of Toronto, Toronto, Canada

Background: Antisocial personality disorder (ASPD) presents with high levels of impulsive, violent behavior. Abnormal neurochemistry and pathology of the orbitofrontal cortex (OFC) and ventral striatum (VS) is implicated. Monoamine oxidase-A (MAO-A) is a pro-apoptotic, oxidative enzyme that metabolizes neurotransmitters influencing the development of impulsivity and violence. Animal models, genetic association studies, and positron emission tomography (PET) investigations all suggest that low or absent brain MAO-A levels are associated with impulsive phenotypes. However, neither MAO-A levels nor activity have previously been studied in the brains of people with ASPD or clinical levels of impulsivity. We hypothesized that MAO-A binding would be lower in the OFC and VS of ASPD. We further hypothesized that greater impulsivity would be associated with lower MAO-A levels in the VS and OFC.

Methods: Eighteen adult male subjects with ASPD and 18 control subjects completed the study protocol. All participants were medication-free, non-smoking, and free of illicit substance use. ASPD subjects had no history of mood or psychotic disorders. ASPD and control participants were matched on whether they had current alcohol dependence. Control participants had no other history of psychiatric illness. Each participant was scanned once with [11C] harmine PET to measure MAO-A VT. MAO-A density is highly correlated with its activity, and [11C] harmine PET can be used to measure MAO-A VT, an index of MAO-A density that reflects total tissue binding of [11C] harmine specifically bound to MAO-A. PET images were acquired using an HRRT PET camera (in-plane resolution; full width half maximum, 3.1 mm; 207 axial sections of 1.2 mm; Siemens Molecular Imaging). A Logan model with arterial sampling was used to measure MAO-A VT. Each participant also underwent magnetic resonance imaging for the region of interest (ROI) analysis. ROIs were determined using a semi-automated method in which regions of a template MRI were transformed onto the individual MRI based on a series of transformations and deformations that matched the template image to the individual co-registered MRI, as well as segmentation of the individual MRI to select the grey matter voxels. In addition to OFC and VS, MAO-A VT was also measured in the anterior cingulate cortex, dorsal putamen, thalamus, hippocampus, and midbrain. All participants completed the NEO Personality Inventory - Revised (NEO-PI-R), a comprehensive personality inventory that includes an impulsivity scale. ASPD subjects were additionally assessed for psychopathic traits using the Psychopathy Checklist - Revised (PCL-R) and completed the computerized Iowa Gambling Task (IGT) on the PET scanning day.

Results: The main finding is that MAO-A VT was significantly reduced in ASPD versus controls, on average

by 19.3% and 18.8% in the VS and OFC, respectively (MANOVA group effect: $F2,33 = 6.8$, $p = 0.003$). Significant univariate effects were also detected in both VS and OFC ($F2,33 = 12.6$ to 12.9, p-values $= 0.001$). There was also a significant reduction in all of the main brain regions analyzed (MANOVA group effect: $F7,28 = 2.9$, $p = 0.022$), with significant univariate effects detected in all regions ($F2,33 = 4.2$ to 12.9, p-values $= 0.048$ to 0.001). VS MAO-A VT was negatively correlated with IGT performance ($r = -0.52$, $p = 0.034$). That is, lower VS MAO-A VT was associated with more risky and impulsive decision making. VS MAO-A VT also showed an inverse relationship with self-reported impulsivity on the NEO-PI-R ($r = -0.50$, $p = 0.034$). Participants rated the most impulsive on the PCL-R had the lowest VS MAO-A VT (ANOVA: $F1,16 = 7.9$, $p = 0.013$). No significant correlations were detected between OFC MAO-A VT and measures of impulsivity.

Conclusions: This is the first study to demonstrate a reduction of MAO-A levels in regions that influence impulsivity and violence in a pathological sample of men with ASPD. Rodent models suggest that decreased MAO-A during neurodevelopmental results in excessive levels of monoamine neurotransmitters that adversely interfere with CNS development, predisposing to aberrant impulsivity and aggression. Our findings support the extension of this model into pathological human impulsivity. Reduction of MAO-A in the VS suggests a mechanism to account for increased dopamine release in the nucleus accumbens among individuals with impulsive-antisocial psychopathic traits (Buckholtz et al., 2010), given the role of MAO-A in metabolizing dopamine.

Keywords: monoamine oxidase A, positron emission tomography, antisocial personality disorder, impulsivity.

Disclosure: Drs. Meyer, Wilson, and Houle have received operating grant funds for other studies from Eli-Lilly, GlaxoSmithKline, Bristol Myers Squibb, Lundbeck, and SK Life Sciences in the past 5 years. Dr. Meyer has consulted to several of these companies as well as Takeda, Sepracor, Trius, Mylan and Teva. Dr. Links received an honorarium from Lundbeck within the past 5 years. None of these companies participated in the design or execution of this study.

M137. The Paradoxical Relationship between White Matter and Psychopathology in Schizophrenia: A Diffusion Tensor and Proton Spectroscopic Imaging Study

Juan Bustillo*, Thomas Jones, Christopher Abbott, Lemke Nicholas, Jose Canive, Charles Gasparovic, Arvind Caprihan

University of New Mexico, Albuquerque, New Mexico

Background: White matter disruption has been repeatedly documented in schizophrenia consistent with microstructural disorganization (reduced fractional anisotropy, FA) and axonal dysfunction (reduced N-acetylaspartate compunds, NAAc). However, the clinical significance of these abnormalities is poorly understood. Although a few small studies have reported counterintuitive direct relationships between psychotic symptoms and FA, others have not.

Methods: Diffusion tensor and proton spectroscopic imaging (SI) at 3 Tesla where used to assess FA and supra-ventricular white matter NAAc respectively, in 64 antipsychotic treated subjects with schizophrenia and 64 healthy controls. The DTI had 30 directions, with a 2mm slice thickness, 72 slices, 128x128 matrix size, voxel size = 2 mm3, TE = 84 ms, TR = 9000 ms. FA, was calculated with FSL and along a white matter tract skeleton using TBSS. SI was performed with PRESS with and without water presaturation (TE = 40ms, TR = 1500ms, slice thickness = 15 mm, FOV = 220 × 220 mm, voxel size 2.4 cm3) above the lateral ventricles and parallel to AC-PC axis including portions of the medial frontal and parietal lobes. Group differences in FA and NAAc as well as their relationships with symptoms and cognition (MATRICS) were examined.

Results: The schizophrenia group had reduced FA across several regions compared to controls ($p = 0.05$, with multiple comparison correction, by threshold-free cluster enhancement). These regions included genu, body and splenium of corpus callosum, anterior and superior corona radiata, superior longitudinal and inferior fronto-occipital fasciculi and internal capsule. There were many more regions (47/50) where FA correlated positively with severity of positive symptoms [$r(62) = 0.6$, $p < 0.0001$]. In no regions, was FA higher in the schizophrenia group. The schizophrenia group had progressively reduced NAAc with age [$F(1,121) = 4.31$, $p = 0.04$], and NAAc correlated negatively with positive symptoms [$F[1,60] = 34.3$, $p < 0.0001$]. FA correlated positively with cognition in controls [$r(62) = 0.54$, $p < 0.0001$] but negatively in schizophrenia [$r(62) = -0.27$, $p = 0.03$]. Similarly, NAAc correlated positively with cognition in controls and negatively in schizophrenia [$F(1,113) = 72.8$, $p < 0.0001$]. Negative symptoms positively related with NAAc [$F(1,60) = 51.9$, $p < 0.0001$], but not with FA.

Conclusions: In the context of the expected reduced FA in schizophrenia, the counter-intuitive relationships found are suggestive of increased structural connectivity throughout multiple white matter bundles among the most psychotic patients. A separate set of abnormal relationships between cognition and FA as well as with NAAc, converge to suggest that in schizophrenia, white matter re-organization supports the two core illness domains: psychosis and cognitive/negative symptoms.

Keywords: Fractional-anisotropy, N-acetylaspartate, psychosis, cognition.

Disclosure: Dr Bustillo consulted for Otsuka Pharmaceuticals April 2013.

M138. Mood Dysregulation and Stress Response Circuitry Deficits: Impact of Diagnosis, Mood State, and Sex

Klara Mareckova*, Laura Holsen, Roee Admon, Susan Whitfield-Gabrieli, Jill Goldstein

Central European Institute of Technology, Masaryk University, Brno, Czech Republic

Background: Maladaptive responses to negative valence stimuli are implicated in several major psychiatric disorders, including psychosis (PSY) and major depressive

disorder (MDD). Substantial evidence suggests the pathophysiology behind PSY and MDD results in part from abnormalities in the stress response circuitry regions [periaqueductal gray (PAG), hypothalamus (HYPO), amygdala (AMYG), hippocampus (HIPP), medial and orbital prefrontal cortices (mPFC, OFC)], several of which also show sex differences in anatomy and function. A critical question in our understanding of psychiatric phenomenology is whether differences in stress response circuitry function are unique to a diagnostic group, or shared across groups (i.e., vary as a function of symptoms such as mood state), and the extent to which these potential diverging patterns vary between men and women. Here we studied functioning of the stress response circuitry in MDD, PSY and healthy (HC) individuals, and tested whether it was related to mood dysregulation across diagnostic groups and sex.

Methods: Adults ($n = 99$) were recruited from a community population of individuals with recurrent MDD (14 F, 13 M), PSY [schizophrenia (SCZ) or bipolar psychoses (BP); 15 F, 16 M), and HC (19 F, 22 M). Mood and anxiety symptoms were assessed by the Profile of Mood States and State-Trait Anxiety Inventory and factor analyzed, yielding a primary component reflecting clinical mood state symptomatology. Participants underwent functional magnetic resonance imaging (fMRI) on a 3T Siemens scanner, with a mild visual stress task presenting negative, neutral, and fixation images adapted from International Affective Picture System. fMRI data were analyzed using SPM8. Anatomically-defined masks (PAG, HYPO, AMYG, HIPP, ACC, OFC, and mPFC) were overlaid on a supergroup ($n = 99$) mean of the negative > neutral contrast with a voxel-wise FWE-corrected ($p < 0.05$) threshold. Mean BOLD responses from these intersections were extracted for each participant and exported into SAS for additional analyses: (1) Main effect of Diagnosis (MDD, PSY, HC) and Diagnostic Subtypes (MDD, SCZ, BP, HC); (2) Main effect of Mood (across all diagnoses); (3) their interactions with Sex which were followed up to examine relative functioning in males vs. females. Finally, we tested whether Diagnosis or Mood Symptoms better predicted stress response circuitry activity, with Sex added as a covariate. Similar analyses were conducted for task-related connectivity, analyzed using generalized psychophysiological interaction (gPPI).

Results: Among the 99 participants, the mild visual stress task elicited significant (FWE $p < 0.05$) BOLD response in PAG, HYPO, AMYG, HIPP, OFC, and mPFC. Connectivity between right (R) AMYG and R mPFC increased in response to negative (vs. neutral) images (FWE $p = 0.04$). Cases (MDD + PSY) had higher BOLD response in PAG ($p = 0.01$, $d = 0.49$) and higher increase in PAG – R HIPP connectivity (FWE $p = 0.02$, $d = -0.67$) than HC. MDD had higher BOLD response in HYPO than PSY ($p = 0.007$, $d = 0.74$) and particularly SCZ ($p = 0.004$, $d = 1.03$). Stress-related increase in HYPO – left (L) HIPP (FWE $p = 0.045$) connectivity was stronger in MDD ($p = 0.01$, $d = 0.69$), BP ($p = 0.003$, $d = 1.18$), and HC ($p = 0.004$, $d = 0.71$) than in SCZ. Across the whole sample, deficits in mood symptomatology were related to higher BOLD response in subcortical arousal regions (HYPO: $p = 0.02$, R AMYG: $p = 0.02$). Sex-specific analyses revealed positive relationship between Mood Symptoms and R AMYG in females ($p = 0.006$) but not males ($p = 0.71$). Stress-related connectivity between (1) R AMYG – R HIPP (FWE $p = 0.008$), (2) R AMYG – R OFC (FWE $p = 0.038$), and (3) HYPO – R OFC (FWE $p = 0.02$) also showed an interaction between Mood Symptoms and Sex. Females but not males showed a decrease in (1) R AMYG – R HIPP (F: $p < 0.0001$, $R2 = 0.37$; M: $p = 0.43$), (2) R AMYG - R OFC (F: $p < 0.0001$, $R2 = 0.42$; M: $p = 0.96$), and (3) HYPO – R OFC (F: $p = 0.006$, $R2 = 0.19$; M: $p = 0.003$, $R2 = 0.23$) connectivity as a function of Mood Symptoms. Finally, the multiple regression analyses examining specificity of mood and diagnosis in relation to BOLD response showed that Mood Symptoms related to BOLD in HYPO ($F(5,68) = 2.44$, $p = 0.04$) and Diagnosis related to BOLD in PAG ($F(5,67) = 2.33$, $p = 0.05$) and R OFC ($F(5,68) = 3.52$, $p = 0.007$). HYPO – R HIPP connectivity was higher in females than males (FWE $p = 0.02$) and increased as a function of worse Mood Symptoms (FWE $p = 0.005$) but not Diagnosis. In contrast, PAG – HYPO connectivity increased as a function of Diagnosis (FWE $p = 0.028$) but not Mood Symptoms or Sex. Posthoc analyses showed that stress-related increase in PAG – HYPO connectivity was higher in SCZ than HC ($p = 0.05$, $d = 0.55$).

Conclusions: These findings offer significant insight into the shared and unshared sex-dependent brain phenotyping associated with response to negative affective stimuli in individuals with mood dysregulation. For example, females with mood dysregulation exposed to mild visual stress showed an inability to recruit cortical circuitry inhibiting subcortical arousal. Importantly, results suggest that dysfunction in stress response circuitry is sex-dependent and crosses disorders that involve mood and anxiety components. This strategy to identify shared and unshared neurobiological features speaks to the NIMH RDoC initiative to determine biosignatures associated with regulation of arousal and response to negative valence stimuli across psychiatric disorders.

Keywords: mood dysregulation, stress response circuitry, depression, psychosis.

Disclosure: Nothing to Disclose.

M139. Blunted Activation of Insula and Medial Prefrontal Cortex During Negative Emotion Processing is Associated with Resilience in Youth at High Risk for Substance Use Disorder

Mary Heitzeg*, Jillian Hardee, Lora Cope, Davia Steinberg, Mary Soules, Robert Zucker

University of Michigan, Ann Arbor, Michigan

Background: A family history of substance use disorder (SUD; FH +) increases risk for offspring SUD, yet not all FH + youth will develop SUD. The primary aim of this study was to identify neural mechanisms that may mark resilience to SUD in youth with high levels of familial adversity. Facets of self-regulation, including negative emotionality and behavioral undercontrol, have been linked to problem substance use. In contrast, positive emotions and a capacity for self-regulation have been identified as factors underlying resilience to adversity. We hypothesized that resilient youth would show differences in brain function during emotion

processing that would, in turn, be associated with behavioral control.
Methods: Participants (n = 136) aged 16-22 (mean = 19.5) were recruited from a longitudinal study of families with a parent history of SUD (n = 108) and matched control families (n = 28). Level of familial risk was determined based on the number of affected parents and whether the parent had an alcohol use disorder (1 point), a drug use disorder (1 point) or both (2 points). Familial risk scores thus ranged from 0 (no parental SUD) to 4 (both parents had dual diagnoses). Fifty participants (37%) met criteria for SUD in their lifetime. Familial risk score showed a significant linear association with participant diagnosis ($\chi 2 = 9.4$, $p = .002$). Participants with a risk score of 4 were twice as likely to have an SUD diagnosis as those with scores of 1-3 (diagnosis by risk score: 0 - 18%; 1 – 35%; 2 – 38%; 3 – 32%; 4 – 70%). Based on these data, participants with a risk score of 0 were termed low risk, those with 1-3 were termed moderate risk and those with a score of 4 were termed high risk. High risk participants with no SUD diagnosis were considered resilient. Behavior problems were assessed with Youth Self-Report (age 16-17) or Adult Self-Report (age 18+). Positive and negative emotional words, and neutral words, were presented to participants during fMRI. One-sample t-test in SPM8 was used to determine regions activated to negative versus neutral words and positive versus neutral words for the entire sample. Effect sizes from these regions were extracted and entered into a multivariate ANOVA with familial risk and SUD diagnosis as between-subject factors. Pearson correlation was used to determine associations between brain activation and behavior problems within each risk group separately. Fisher's z-transformation was used to determine differences in correlations between risk groups.
Results: As expected, SUD diagnosis was associated with more externalizing behavior problems ($t = 4.2$, $p < .0001$). Across the entire sample, activation during negative versus neutral words was observed bilaterally in the inferior frontal gyrus, extending to the insula (IFG/insula), the middle temporal gyrus (MTG), the medial prefrontal cortex (medPFC), the ventromedial prefrontal cortex (vmPFC) and the posterior cingulate. Activation during positive versus neutral words was observed in right bilateral IFG, right MTG, vmPFC, medPFC, subgenual anterior cingulate (sgAC) and posterior cingulate. Significant interactions between risk and diagnosis were observed in IFG/insula ($F = 2.9$, $p = 0.026$) and medPFC ($F = 2.5$, $p = 0.049$) activation to negative words; the resilient group showed blunted activation of these regions compared with the low risk group, the moderate risk group, and high risk individuals with an SUD diagnosis. Blunted activation of these regions was associated with fewer externalizing problems in the high risk group (IFG/insula: $r = 0.65$, $p = 0.003$; medPFC: $r = 0.71$, $p = 0.001$), but not the low (IFG/insula: $r = -0.14$, $p = 0.47$; medPFC: $r = -0.22$, $p = 0.27$) or moderate (IFG/insula: $r = -0.03$, $p = 0.80$; medPFC: $r = 0.08$, $p = 0.47$) risk groups. Correlations between activation and externalizing problems in the high risk group were significantly different from both the low risk and moderate risk groups ($z's > 2.85$, $p's < 0.005$).
Conclusions: The insula is involved in translating physiological signals into subjective emotion. It is well-connected to brain systems involved in impulsive behavior (including the IFG) and reflection, or reappraisal (including the medPFC), and integrates the signals from these regions for adaptive behavioral responses to emotional cues. These findings indicate that blunted activation of this circuitry during negative emotion is a protective mechanism in individuals with high levels of family adversity.
Keywords: adolescents, young adults, addiction, high risk.
Disclosure: Nothing to Disclose.

M140. Cannabinoid Agonists, Functional Connectivity of the Default Mode Network, and Working Memory Performance in Patients with Schizophrenia and Cannabis Use Disorder

Adina Fischer*, Susan Whitfield-Gabrieli, Robert Roth, Alan Green

Dartmouth Medical School, Hanover, New Hampshire

Background: Cannabis is the most commonly used illicit drug in patients with schizophrenia (SCZ). Long-term cannabis use substantially worsens outcomes of patients with SCZ, resulting in symptom exacerbation, increased risk of psychotic relapse, and decreased response to antipsychotic medication. Paradoxically, while cannabis use is associated with detrimental effects on cognition in healthy participants, its use in SCZ has been associated with improved cognitive function compared to non-cannabis using patients on measures of working memory, attention, processing speed, and verbal fluency. Default mode network (DMN) resting state hyperconnectivity has been implicated in symptom severity. Moreover, the degree of anticorrelation between the DMN and regions of the task positive network (i.e., frontal parietal network) during the resting state has been shown to directly correlate with working memory performance in healthy controls. To date, neither the underlying DMN functional connectivity abnormalities in patients with SCZ and CUD nor the effects of cannabis on this network have been investigated. In the present study we examined resting state functional connectivity (rs-fc) within the DMN as well as correlations between the medial prefrontal cortex (MPFC; a component of the DMN that typically decreases during attention demanding tasks) and the dorsolateral prefrontal cortex (DLPFC; a component of the fronto-parietal control network that supports executive functions and typically increases in activation during attention demanding tasks). We then we examined the effects of smoked cannabis and oral tetrahydrocannabinol (THC) on DMN functional connectivity (both positive and negative). Lastly, we evaluated working memory performance and whether there was an association between strength of MPFC-to-DLPFC anticorrelation and working memory performance both at baseline and following cannabinoid agonist administration in the patient group as compared to healthy control subjects.
Methods: Twelve patients with SCZ and co-occurring CUD (abstinent from cannabis for > 7 days) and 12 healthy control subjects participated in the study. Patients and controls completed fMRI resting scans at baseline, and patients were assessed again one week later (in a double-blind design) after either smoking a 3.6% THC cannabis

cigarette or 15mg oral THC pill. Controls were also tested a second time, with no intervention. Plasma THC level and symptom severity (PANSS) were assessed in the patient group. Positive correlations within the DMN and the strength of the anticorrelation between the medial prefrontal cortex (MPFC) and the DLPFC were assessed using seed-to-voxel rs-fc). The relationship between changes in connectivity with smoke cannabis and oral THC and performance on the Wechsler Adult Intelligence Scale Letter Number Sequencing Test (WAIS III LNST, a measure of working memory), were also examined.

Results: DMN hyperconnectivity, as well as reduced anticorrelation between the MPFC and DLPFC was found in patients relative to controls. Both cannabis and THC significantly increased the MPFC-to-DLPFC anticorrelation. While controls performed significantly better than patients on the LNST both before and after pharmacologic intervention ($p<0.01$), there was a significant improvement in working memory performance post-intervention. A significant association was found between the strength of MPFC-to-right DLPFC anticorrelation and LNST performance in the control ($p<0.05$, $r=-0.71$) but not the patient group prior to intervention. Following cannabinoid agonist administration there was a significant association between the strength of anticorrelation and working memory performance in the patient group ($r=-0.62$, $p<0.05$).

Conclusions: Functional pathology of DMN resting state connectivity in SCZ may contribute to the inability to appropriately shift attention between internally generated thoughts and external events. Cannabinoid induced enhancement of the anticorrelation between the MPFC and DLPFC, and the association of this enhancement with working memory task performance may explain why cannabis-using patients with SCZ have improved cognition as compared to non-using patients. These preliminary findings suggest that cannabis or THC may improve working memory through augmenting the strength of anticorrelation between the DMN and task positive network.

Keywords: schizophrenia, cannabis, default mode network, resting state functional connectivity.

Disclosure: Nothing to Disclose.

M141. Interaction of Aging and Inflammation is Associated with Increased Basal Ganglia Glutamate and Reduced Motivation and Motor Activity During Inteferon-Alpha Therapy

Ebrahim Haroon*, Jennifer C Felger, Bobbi J Woolwine, Moon Young Jung, Jaimi D Patel, Xiangchuan Chen, Xiaoping P Hu, Andrew H Miller

Emory University, Atlanta, Georgia

Background: Aging has been associated with an exaggerated inflammatory response to immune stimulation in central nervous system (CNS). Phenotypically distinct, aging microglial cells referred to as "primed microglia" are believed to mediate this exaggerated CNS immune response. However, the precise mechanisms that mediate this association among aging, inflammation and behavioral change are not known. Recent studies on inflammation-induced alterations in the CNS have focused on glutamate as one potential mediators. Inflammatory cytokines have been shown to influence glutamate metabolism by blocking glutamate reuptake and increasing glutamate release. Data by our group have shown increased glutamate as measured by magnetic resonance spectroscopy (MRS) in basal ganglia and dorsal anterior cingulate cortex of patients administered the inflammatory cytokine interferon (IFN)-alpha. Given data that increasing age is associated with an exaggerated CNS inflammatory response, we examined whether older age (>55 years) would be associated with a greater IFN-alpha-induced increase in CNS glutamate, which would be associated with increased behavioral and cognitive changes.

Methods: 31 patients with hepatitis C virus (HCV) underwent MRS, blood sampling for inflammatory markers, and behavioral assessments before and after four weeks of either IFN-alpha ($n=17$) or no treatment ($n=14$). The median age of the sample (55 years) was used to divide IFN-alpha-treated and untreated subjects into "older" (age >55 years, $n=15$) and "younger" (<55 years, $n=16$) subgroups. Study assessments included the Multidimensional Fatigue Inventory (MFI), choice movement and reaction time task of the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB) and plasma tumor necrosis factor (TNF)-alpha and its soluble receptor (sTNFR)-2. An anatomical T1-MPRAGE scan was obtained using Siemens Trim Trio Scanner to enable identification of voxels. The MRS settings were: TR/TE/NS = 3000/30/128, voxel sizes = 17x30x17 mm3 in the left and right basal ganglia and 20x30x10 mm3 in the dorsal anterior cingulate cortex. Post processing was done using the LC Model. Glutamate values were normalized to creatine (Glu/Cr) for use in data analyses. A comparison of creatine (Cr) and its metabolite phosphocreatine (PCr) values revealed no significant differences between the IFN-alpha-treated and un-treated groups.

Results: Older patients treated with IFN-alpha exhibited significantly increased glutamate as reflected by the glutamate/creatine ratio (Glu/Cr) in left basal ganglia compared to older controls and younger IFN-alpha-treated and untreated subjects. In addition, increased Glu/Cr in older but not younger IFN-alpha-treated and untreated patients was associated with increased tumor necrosis factor-alpha, reduced motivation on the MFI and reduced choice movement time on CANTAB. No such associations were seen with dACC or right basal ganglia voxels.

Conclusions: Taken together, these preliminary data support the notion that older age may interact with inflammation to exaggerate effects of inflammatory stimuli on CNS glutamate and behavior. The association of basal ganglia glutamate changes with behavioral (reduced motivation) and cognitive symptoms (increased choice movement time) is consistent with previously reported findings of increased basal ganglia dysfunction in inflammatory states and aging. Glutamate neurotransmission can be effectively targeted to develop personalized treatment options for older patients with increased inflammation and behavioral changes.

Keywords: Inflammation, Glutamate, Motivation, Aging.

Disclosure: Nothing to Disclose.

M142. Reduced White Matter Microstructure and Insula Connectivity after Recovery from Anorexia Nervosa

Guido Frank*, Megan Shott, Tamara Pryor

University of Colorado, Aurora, Colorado

Background: The pathophysiology of anorexia nervosa (AN) remains poorly understood. Previous functional and structural brain imaging studies have implicated the insula in AN when ill and after recovery. That brain region plays a central role in taste and food reward processing as it receives input from the peripheral taste pathways and has strong connections to dopaminergic neurons in the basal ganglia that drive reward motivation as well as to higher order taste processing regions such as the orbitofrontal cortex. Here, we assessed white matter (WM) microstructure in women recovered from AN and controls. We hypothesized that if we found reduced white matter connections to or from the insula, then this could be an indication of altered information processing in the taste reward network and related to the pathophysiology of high food avoidance and low motivation to eat, behaviors that are most characteristic for the illness.
Methods: We examined healthy control ($n = 24$, age = 27.4 ± 6.3 years) and women recovered from restricting-type anorexia nervosa (Recovered AN, $n = 24$, age = 30.3 ± 8.1 years). Subjects were carefully screened and underwent extensive diagnostic and behavioral testing. All subjects underwent diffusion tensor imaging (DTI) to assess white matter (WM) microstructure and connectivity, and results were controlled for age effects, total brain volume, comorbidity and medication use. We first tested brain WM integrity (as measured by fractional anisotropy, FA, and mean, radial and axial diffusivity) across groups (whole brain FWE corrected). Then we used probabilistic tractography to test whether altered regional WM integrity between groups would be associated with altered connectivity within the brain taste reward circuitry. We further tested whether WM integrity was related to eating disorder or anxiety related behaviors.
Results: Recovered AN displayed lower WM integrity in the external capsule, corona radiata, midbrain and cerebellum (all $p < 0.05$, FWE corrected) in fibers tracts that include the inferior fronto-occipital fasciculus, uncinate fasciculus, corpus callosum, and corticopontine tracts. To test structural connectivity across groups, we examined the number of reconstructed WM tracts going from the WM integrity seed regions (external capsule, corona radiata, midbrain and cerebellum) to our targets of interest in the taste reward circuitry (amygdala, caudate nucleus, hypothalamus, insula, orbitofrontal cortex, and putamen) and assessed the weighted average connectivity probability between groups. The average probabilistic connectivity value was less in Recovered AN compared to Controls between the WM integrity seed mask (FA clusters CW > Recovered AN) and the insula (Controls = 91.4 ± 62.5; Recovered AN = 56.7 ± 35.6; $p < .029$). All of the other classification targets had similar mean connectivity probability to the seed mask regions between groups. The analysis of WM tract connectivity between full regions of the taste reward circuitry showed in Recovered AN reduced connectivity between the insula and the orbitofrontal cortex (Controls = 949 ± 141; Recovered AN = 849 ± 107; $p < 0.008$), but increased connectivity between insula the putamen (Controls = 624 ± 221; Recovered AN = 781 ± 257; $p < 0.029$). Controls showed the expected negative correlation between regional WM integrity and trait anxiety ($p < 0.05$), but this relationship was non-existing in the Recovered AN group.
Conclusions: This study indicates localized lower WM integrity in the external capsule, anterior corona radiate, midbrain and cerebellum in AN after recovery. Those WM tracts that included the inferior fronto-occipital fasciculus, uncinate fasciculus and corpus callosum conduct information across the brain to higher order brain regions that process taste and reward stimuli, as well as to dopaminergic neurons in the striatum. This reduced regional WM integrity in the Recovered AN group was associated with reduced anatomical connections with the insula. The direct assessment of WM connectivity between taste reward related regions indicated stronger connections between insula and putamen, but lower connectivity between insula and orbitofrontal cortex in Recovered AN. The insula is a central region in taste reward processing and altered connectivity within this system could contribute to altered food appraisal or food approach motivation in AN. This finding after long term recovery from AN could indicate a biological trait but could also be an effect from the illness and contribute to high relapse rates.
Keywords: Anorexia Nervosa, Recovery, White Matter, Insula Connectivity.
Disclosure: Nothing to Disclose.

M143. Dysregulation in the Opioid System in Pathological gambling: A [11C]carfentanil PET Study

Eugenii Rabiner*, Inge Mick, Myers Jim, Stokes Paul R. A., Erritzoe David , Colasanti Alessandro, Bowden-Jones Henrietta, Clarke Luke, Gunn Roger N., Searle Graham E., Nutt David J., Lingford-Hughes Anne R

Imanova Ltd, London, United Kingdom

Background: We previously demonstrated that the acute increase in extracellular dopamine produces a release of endogenous opioids in the human brain, detectable by [11C]carfentanil PET [1, 2]. As pathological gambling (PG) is classified as a behavioural addiction and the opioidergic system has been heavily implicated in the neurobiology of reward, impulsivity and addiction, an examination of this system in PG is timely.
Methods: Fourteen males (age 34 ± 8 years) meeting the DSM IV criteria for pathological gambling (PG), and having no history of drug abuse (other than nicotine) or Axis I diagnosis (other than past history of depression or anxiety) were enrolled. All PG were evaluated with [11C]carfentanil PET before and 3 hours after single oral dose of d-amphetamine (0.5 mg/kg). Age matched ($n = 15$, 34 ± 7 years old) healthy volunteers (HV) examined with the same paradigm served as a control group. Subjective effects of d-amphetamine were evaluated by the simplified version of the amphetamine interview rating scale (SAIRS). Carfentanil BPND were quantified in pre-selected regions of interest (ROI – putamen, caudate, ventral striatum,

thalamus, amygdala, insula, anterior cingulate, frontal cortex and cerebellum) via a simplified reference tissue model with the occipital cortex as a reference region. Within each group, the effects of d-amphetamine on regional [11C]carfentanil BPND were evaluated via paired Student's t-tests. The magnitude of regional delta-BPND (calculated as a percent change from baseline BPND) in PG was compared to of HV via Student's t-tests for each ROI.
Results: (1) D-amphetamine did not change the [11C]carfentanil BPND in 8/9 ROI in PG, while in HV 8/9 ROI demonstrated a significant reduction in delta-BPND as previously reported [2] (2) delta-BPND was significantly higher in HV compared to PG in 6/9 ROI (see Figure 1). (3) D-amphetamine led to a significant increase in the "euphoria" and "alertness" scales in HV at the start of the PET scan, while no effects were seen in the PG. (4) Regional [11C]carfentanil BPND at baseline did not differ between PG and HV in any of the ROI examined.
Conclusions: (1) We found a blunting of the amphetamine induced endogenous opioid release in PG. (2) The blunting could be the result of a dysregulation in the dopamine system, with reduced dopamine release or altered post-synaptic receptor function. Alternatively the defect could lie in theopioidergic neurotransmitter system, or both systems may be involved. A previous demonstration of increased amphetamine induced dopamine release in PG compared to HV [3] implicates a defect at the level of the post-synaptic DA receptor or the opioid neuron. (3) We did not find an elevation in baseline m-OR, as has been found for substance addiction, suggesting that the increases in m-OR seen in substance addiction may be due to the effects of substance abuse. (4) Characterization of the opioid system in the neurobiology of addictive disorders ns will increase our understanding of the pathophysiology of these states and may provide novel treatment options. 1. Colasanti, A., et al., Biological Psychiatry, 2012. 72(5): p. 371-377. 2. Mick, I., et al., The International Journal of Neuropsychopharmacology, 2014. FirstView: p. 1-6. 3. Boileau, I., et al., Molecular Psychiatry.
Keywords: Positron Emission Tomography, [11C]carfentanil, pathological gambling, endogenous opioids.
Disclosure: Consultant for AbbVie, Roche, GSK, Lightlake Therapeutics. Have equity in GSK. Primary employer is Imanova Ltd.

M144. Amygdala Activity during Autobiographical Memory in Depressed and Vulnerable Individuals: fMRI Evidence and Initial Intervention with Neurofeedback

Kymberly Young*, Greg Siegle, Jerzy Bodurka, Wayne Drevets

Laureate Institute for Brain Research, Tulsa, Oklahoma

Background: Affectively balanced autobiographical memory (AM) is central to adaptive functioning. In healthy subjects, AM recall is biased towards the positive and away from the negative, while the opposite pattern is found in depression. This bias is also evident in amygdala responses to affectively valenced faces, such that depressed individuals show exaggerated responses to negative stimuli, and attenuated responses to positive stimuli. Here we examine the extent to which a putative mechanism underlying biased autobiographical memory, amygdala activity, may be causally related to the development of depression by 1) examining its activity currently depressed subjects with major depressive disorder (MDD), and two vulnerable populations – individuals with MDD in full remission (rMDD) and healthy controls at high-risk (HR) of developing depression based on having a first-degree relative with MDD, and 2) examining effects of real-time fMRI (rtfMRI) neurofeedback training on amygdala responses to positive information in a depressed sample.
Methods: For the AM task, subjects included 60 healthy control (HCs; 30F), 27 HR (19F), 42 unmedicated MDD (25F), and 25 unmedicated rMDD (16F) individuals. Subjects underwent fMRI while recalling AMs in response to 20 positive, 20 negative, and 20 neutral cue words. Subjects were presented a cue for 12s and instructed to recall a past experience, then indicate the type of memory recalled (specific, categorical, extended, semantic, none) and the memory's valence. AM recall was compared to semantic example generation in which, to control for abstract/general knowledge retrieval, subjects generated seven examples of a given category over 12s (30 cues; 10 of each valence), then rated the ease with which they generated the examples and the number of examples generated. Following each cue/category word and rating set subjects engaged in a riser detection task involving non-word letter strings to control for visual input/attention. Structural and functional imaging was performed on a 3T GE Discovery MR750 MRI scanner with an 8-channel receive-only brain array coil. Gradient-recalled echoplanar imaging with sensitivity encoding (SENSE) was used for fMRI using the parameters: 40 axial slices, TR/TE = 2000/25 ms, SENSE acceleration = 2, flip angle = 90°, matrix = 96 x96, FOV/slices thickness/gap = 240/3/0 mm, volumes per run = 211. fMRI data were processed using AFNI. For each participant the average percent signal change was extracted from anatomically defined left and right amygdala ROIs for Positive AM Recall vs Positive Example Generation, Negative AM Recall vs Negative Example Generation, and Specific AM recall vs Example Generation. The significance threshold for detecting group differences was set at $p_{corrected} < 0.05$. To assess the potential therapeutic effect of altering amygdala responding during AM recall, we initiated a clinical trial of amygdala rtfMRI neurofeedback as an intervention for depression. Thus far we trained 3 MDD participants to upregulate amygdala activity to positive AM recall via rtfMRI neurofeedback, and compared them to 3 MDD participants who received control rtfMRI neurofeedback from a control region – the horizontal segment of the intraparietal sulcus. Participants completed two neurofeedback sessions 1 week apart.
Results: For both the left and right amygdala the nominal pattern of BOLD activity during positive AM recall was HC > rMDD > HR > MDD. During positive AM recall, MDD subjects had decreased left amygdala activity compared to all other participant groups ($ps < 0.001$), while the other groups did not differ from each other. During negative AM recall the nominal pattern of left amygdala activity was MDD > HR > rMDD > HC. HCs had less amygdala activity during negative AM recall than all other groups ($ps < 0.01$),

and the other groups did not differ from each other. In MDD subjects who completed two sessions of rtfMRI amygdala neurofeedback training, Hamilton Depression Rating Scale (HDRS-21) scores decreased a mean of 8 points and Beck Depression Inventory (BDI) scores a mean of 10 points; in the control group scores decreased a mean of 3 and 0.33 points, respectively, on HDRS and BDI.
Conclusions: This is the first study to demonstrate abnormal patterns of amygdala hemodynamic activity in MDD subjects compared to HC, HR, and rMDD subjects as they engage in AM recall. While left amygdala activity was elevated in the MDD, rMDD and HR groups relative to HCs during negative AM recall, mean activations in both left and right amygdala were lower in the MDD group compared to the other groups during positive AM recall. These results suggest that amygdala hyperactivity during negative AM is a trait-like marker of MDD, as both at risk groups showed activity similar to the MDD group, and higher than the HCs. In contrast, our results suggest amygdala hypoactivity during positive AM recall is a state marker of MDD that manifests during the active disease state, and returns to normal levels with symptom remission. Finally, training MDD patients to increase amygdala activity to positive AMs via rtfMRI neurofeedback produced significant symptom improvement. We thus propose that amygdala neurofeedback may beneficial to patients in an acute depressive episode.
Keywords: amygdala, autobiographical memory, fMRI, depression.
Disclosure: Wayne Drevets is currently an employee of Johnson & Johnson, Inc.

M145. Potential Utility of the Tau Deposit Tracer [18F]T807 (aka [18F]AV-1451) as a PET Biomarker for Neurodegeneration in Clinical Trials

Mark Mintun*, Michael Devous, Sr., Giorgio Attardo, Abhinay Joshi, Adam Schwarz, Sergey Shcherbinin, Andrew Siderowf, Yin Guo Lin, Qianwa Liang, Kelly Conway, Felipe Gomez, Michael Pontecorvo

Avid Radiopharmaceuticals, Philadelphia, Pennsylvania

Background: Neurofibrillary tangles, comprised chiefly of aggregated tau protein deposits, are a pathological hallmark of Alzheimer's Disease (AD). The density and distribution of the tau deposits are hypothesized to correspond to the degree of neurodegeneration. Pathological series have shown that Braak stage, representing extent of tau pathology, correlates with cognitive status (Riley KP Ann Neurol 2002), as does the density of neurofibrillary pathology assessed in various isocortical regions (Nelson Neuropath Exp Neurol 2007). A molecular imaging probe for tau could provide a useful biomarker for diagnosis and monitoring response to therapy. The 5H-pyrio[4,3-b] indole, [18]F-T807 (also known as [18]F-AV-1451) is a potential PET tracer for detection of tau pathology (Chien et al., 2013). In vitro autoradiography studies showed that T807 binds to tau aggregates in brain sections from the frontal lobe of AD patients (Xia 2013). Immunohistochemical staining showed co-localization with PHF-tau pathology but not with Aβ on adjacent sections. Initial clinical results with T807 from 6 subjects showed greater tracer retention in AD and MCI cases compared to controls, particularly in the hippocampus and mesial and lateral temporal lobes (Chien et al., 2013).
Methods: In this abstract, we report a series of preclinical and clinical studies to evaluate the suitability of T807 as a PET biomarker for tau deposition in neurodegeneration. This includes A) determination of affinity of T807 to brain-derived paired-helical filament (PHF) tau; B) investigation of the presence of T807 binding sites in tau deposits across multiple tauopathies using post mortem brain sections; C) characterization of human whole body distribution enabling radiation dosimetry estimates; D) examining the different patterns of brain T807 retention by PET scans in healthy subjects as well as those with cognitive and functional impairment; and E) assessment of test-retest reproducibility of T807 PET signals.
Results: A) Saturation binding assays were performed to determine the dissociation constant [Kd] for [18F]T807 binding to PHF isolated from AD cortical tissue by tau immunoaffinity column chromatography. Analysis of the Kd by nonlinear regression was consistent with a single binding site with a Kd of 0.66 ± 0.18 nM ($n = 3$). B) Autoradiography of human brain slices was done with [18F]T807 and compared with stains of the hyperphosphorylated tau-specific AT100 antibody. [18F]T807 matched that of the AT100 antibody. In AD cases with greater density of PHF-Tau, the [18F]T807 signal and antibody staining was the strongest and conversely in tau poor brains the signals were either weak or invisible. Similar data was seen in brain slices from patients with Pick's disease and Progressive Supernuclear Palsy, with [18F]T807 also matching antibody-based IHC. Furthermore, using florescent IHC studies using the T807 analogue, T557, there was co-localization of the T557 to the AT100 signal at the individual cell level. C) Sequential whole body PET scans were done for approximately 6 hours after administration of 10 mCi of [18F]T807 to healthy middle aged controls ($n = 9$; mean $\pm$ S.D for age $= 56.3 \pm 4.42$ yrs). Calculation of radiation dosimetry for standard male indicates the Effective Dose was 0.0241 ± 0.0016 mSv/MBq, or 8.92 mSv for an anticipated 370 MBq (10 mCi) administration. D) Brain PET imaging (scanning from 80 to 100 min post injection of 10 mCi [18F]T807) was done in subjects with diagnosis of AD ($n = 15$), mild cognitive impairment (MCI; $n = 13$); older cognitively normal ($n = 11$) and young cognitively normal ($n = 4$). Cerebellar gray matter was used to calculate Standardized Uptake Value ratios (SUVr). PET scans of AD patients generally showed confluent areas of increased tracer centered over gray matter in temporal, occipital, parietal and to a lesser extent the frontal lobes. Atlas based regional analysis demonstrated that tau as measured by SUVr in cortical regions and anterior mesial temporal lobe regions showed significant ($p < 0.05$) inverse correlations with Mini-Mental Status Examination scores. E) A subgroup of the above subjects ($n = 21$) had repeat imaging within 30 days of initial PET imaging. Test-retest variability of the SUVr values for cortical regions (measured by the S.D. of the % change) ranged from 4 to 5%.
Conclusions: The preclinical and clinical results support continued investigation of [18F]T807 (aka, [18F]AV-1451) as a cross-sectional and longitudinal biomarker in research

trials involving aging, Alzheimer's Disease, and other types of tauopathies.
Keywords: tau, imaging, PET, neurodegeneration.
Disclosure: Authors are employees of Avid and Eli Lilly & Co.

M146. An Examination of Rostral Anterior Cingulate Cortex Function and Neurochemistry in Obsessive-compulsive Disorder

Brian Brennan*, Olga Tkachenko, Zachary Schwab, Erin Ryan, Alison Athey, Harrison Pope, Darin Dougherty, Michael Jenike, William Killgore, James Hudson, Eric Jensen, Scott Rauch

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: The anterior cingulate cortex (ACC) is a component of the dysfunctional cortico-striatal-thalamo-cortical (CSTC) brain circuitry thought to underlie obsessive-compulsive disorder (OCD). Within the ACC, the dorsal subdivision (dACC) is thought to mediate cognitive processes, whereas the rostral subdivision (rACC) is thought to mediate affect. The rACC exhibits strong connectivity to other CSTC brain regions implicated in OCD, and functional magnetic resonance imaging (fMRI) has demonstrated abnormal rACC activation in OCD patients. However, the neurochemical substrates of rACC dysfunction in OCD remain unclear. To further elucidate functional and neurochemical abnormalities in the rACC in OCD, we combined an fMRI probe of rACC function, using an emotional counting Stroop paradigm (ecStroop), together with J-resolved proton magnetic resonance spectroscopy (1H-MRS) to measure rACC glutamate (Glu) and glutamine (Gln) levels, in patients with OCD versus individuals without OCD. Given evidence for ACC hypermetabolism in OCD, plus evidence that glutamatergic neurotransmitter activity is coupled with neuronal glucose metabolism, we hypothesized that: 1) OCD patients would demonstrate increased rACC activation compared to the non-OCD group for OCD-specific words versus neutral words on the ecStroop; 2) OCD patients would demonstrate an elevated rACC Gln/Glu ratio compared to the non-OCD group; and 3) rACC activation and Gln/Glu would be significantly correlated in OCD patients.
Methods: Thirty individuals with OCD and 29 age- and sex-matched comparison individuals without OCD underwent both functional MRI (fMRI) while performing an ecStroop task modified to include OCD-specific words and single voxel J-resolved 1H-MRS using an 8cc voxel placed in the rACC. Functional data were preprocessed using standard algorithms in SPM8. For the ecStroop paradigm, the principal contrast of interest was the OCD-specific vs. neutral word condition. Functional data were analyzed using both region of interest (ROI) analyses using small-volume correction ($P<0.05$, family wise error (FWE)-corrected) and whole brain exploratory analyses ($P<0.001$, uncorrected). 1H-MRS data were analyzed using LCModel. The relationships between metabolite levels, blood oxygenation level dependent (BOLD) signal change, Stroop interference effect, and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores were analyzed using linear regression adjusted for age and sex.
Results: Consistent with our hypothesis, participants with OCD showed rACC hyperactivation compared to non-OCD participants in response to OCD-specific words relative to neutral words (MNI coordinates: 10,50,10; $Z=4.10$; $P<0.05$, FWE-corrected; $k=12$). Extraction of signal change values relative to baseline fixation from this rACC cluster, revealed that rACC hyperactivation in participants with OCD reflected an inability to deactivate this region during OCD-specific words. Whole brain analyses revealed hyperactivation in several additional brain regions in OCD participants, including medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), precuneus, posterior inferior parietal lobule (pIPL), caudate, putamen, amygdala, and insula ($P<0.001$, uncorrected). We found no significant differences between OCD and comparison participants in rACC Gln/Glu ratio, rACC levels of Glu and Gln separately, or rACC Glu + Gln levels (a proxy measure for Glx). The peak rACC BOLD signal change for OCD words versus neutral words showed no significant associations with rACC Gln/Glu ratio, levels of Gln or Glu, Glu + Gln, Stroop interference, or total Y-BOCS scores in either group.
Conclusions: Comparing OCD patients to individuals without OCD on an OCD-modified ecStroop task, we found significantly greater rACC BOLD activation, which was not associated with abnormal rACC Gln/Glu ratios. Hyperactivation of the rACC in OCD may represent an exaggerated response aimed at resolving emotional conflict or may reflect a broader inability to disengage the default mode network when patients are exposed to self-relevant emotionally salient stimuli. Future fMRI studies combining both task-related and functional connectivity analyses are necessary to more fully understand the role of rACC hyperactivity in OCD and to examine the impact of medication and behavioral interventions on rACC hyperactivation to determine whether this is a state marker that normalizes with successful treatment.
Keywords: obsessive-compulsive disorder, fMRI, MRS, anterior cingulate.
Disclosure: Dr. Brennan has received research grant support from Eli Lilly and Transcept Pharmaceuticals. Dr. Dougherty has received research support from Medtronic, Cyberonics, Eli Lilly, and Roche; honoraria from Medtronic; and travel expenses from Roche. Dr. Hudson has received consulting fees from Genentech, HealthCore, Roche, and Shire; and research grant support from Genentech, Otsuka, and Shire. None of the other authors report any potential conflicts of interest.

M147. Shared and Unshared Brain Phenotypes Associated with Reward Circuitry Between Depression and Obesity

Laura Holsen*, Priyanka Moondra, Kara Christensen, Jill Goldstein

Harvard Medical School/Brigham and Women's Hospital, Boston, Massachusetts

Background: Evidence from population-level studies indicate increased comorbidity between major depressive

disorder (MDD) and obesity, especially amongst women. The neurobiological pathways underlying this co-occurrence remain unresolved, although abnormal patterns of activity in mesolimbic and cortical food motivation circuitry have been demonstrated independently in MDD and in obesity. Given that major depressive episodes (MDE) are typified by increases or decreases in appetite and weight, this suggests that abnormalities in shared brain regions may contribute to disruptions in the balance between mesolimbic and cortical activity regulating food intake during MDEs. However, few studies have explored the neural substrates of appetite in MDD. The aim of the current studies was to characterize shared brain circuitry between depression, body mass index (BMI) and appetitive functioning in the neural response to rewarding food stimuli during hunger. This has important clinical implications considering the high rate of diabetes among individuals with MDD, which may be associated with an elevated risk of cardiovascular disease in women.
Methods: Study 1: 4 groups of female participants [11 healthy-weight (BMI 18.5-24.9) women with recurrent Major Depressive Disorder, in remission (rMDD-HW), 11 obese (BMI > 30) women with recurrent MDD, in remission (rMDD-OB), and 11 healthy-weight (HC-HW) and 11 obese (HC-OB) control women with no MDD history] viewed high-calorie food, low-calorie food, and non-food (household objects) images while undergoing functional MRI (fMRI) scanning on a 3T Siemens Trio MR scanner following a 14-hour fast. Data analysis: fMRI data were analyzed in SPM8 (contrast of interest: high- and low-calorie food > object) using full factorial modeling to examine the main effects of case status (rMDD, HC) and BMI status (HW, OB), and the interaction between case status and BMI status. Study 2: Female participants with recurrent MDD, in remission ($n = 30$) were categorized according to appetite/weight change symptoms during their most severe past MDE, with $n = 16$ classified as "typical" rMDD (appetite and/or weight loss; TYP rMDD) and $n = 9$ as "atypical" rMDD (appetite and/or weight gain; ATYP rMDD); $n = 5$ who reported no appetite or weight change were excluded. Data analysis: fMRI data were analyzed in SPM8 (contrast: food > object) using independent sample t-tests to examine differences between groups (TYP rMDD, ATYP rMDD). Regions of interest for both studies included: ventral tegmental area (VTA), hypothalamus (HYPO), nucleus accumbens (NAcc), amygdala (AMYG), hippocampus (HIPP), insula, orbitofrontal cortex (OFC), and subgenual ACC (sgACC).
Results: Study 1: There was a main effect case status in the response to food > object stimuli largely in subcortical reward and appetite regions, including the R VTA [$t = 2.24$, p (FWE-corrected) $= 0.03$], L VTA ($t = 2.29$, $p = 0.03$), R HYPO ($t = 2.87$, $p = 0.05$), R AMYG at a trend level ($t = 2.83$, $p = 0.08$), and R anterior HIPP ($t = 3.22$, $p = 0.05$). Post-hoc contrasts determined that these group differences resulted from hypoactivity in rMDD compared to HC. Conversely, the main effect of BMI yielded significant results in the R posterior HIPP ($t = 3.78$, $p = 0.008$) and cortical regions: L insula ($t = 3.79$, $p = 0.04$), L sgACC ($t = 3.75$, $p = 0.02$), and R sgACC at a trend level ($t = 2.95$, $p = 0.08$), driven by hyperactivity in HW compared to OB women. Further, the factorial analysis revealed an interaction between case status and BMI in two regions. First, an interaction in the L VTA at a trend level ($t = 1.92$, $p = 0.07$) was driven by decreased activity in rMDD-HW compared to HC-HW ($p = 0.01$), HC-OB ($p = 0.05$), and rMDD-OB ($p = 0.05$), with no differences between the latter 3 groups. Second, an interaction in the L posterior HIPP ($t = 3.60$, $p = 0.04$) resulted from decreased activity in HC-OB compared to HC-HW ($p = 0.002$) and at a trend level vs. rMDD-HW ($p = 0.07$), with no significant differences between the remaining groups. Study 2: Relative to TYP rMDD, those with ATYP rMDD exhibited elevated activity in response to food images (at a trend level) in the L HYPO ($t = 2.85$, $p = 0.06$) and L insula ($t = 3.66$, $p = 0.09$). There were no regions in which TYP rMDD women displayed greater activity than the ATYP rMDD women.
Conclusions: This study begins to characterize the brain phenotypes shared and unshared between mood dysregulation (depression) and obesity in response to food reward. MDD was more strongly associated with mesolimbic and subcortical food motivation circuitry deficits (specifically, decreased activity), consistent with previous findings of reduced reward and limbic activation in response to positively-valenced stimuli in MDD. Agnostic of mood disturbance history, BMI was more strongly related to activity in cortical regions involved in motivational and gustatory processing. Finally, only minor differences emerged between rMDD women who reported increased vs. decreased appetite/weight during an MDE, suggesting that the neural underpinnings of these symptoms may be more related to state than trait. These findings indicate distinct neural systems related to mood dysregulation and weight which may assist in developing strategies to treat appetite- and weight-related symptoms in MDD. This is particularly important for women, given the high comorbidity of depression with cardiometabolic disturbances.
Keywords: reward, appetite, fMRI, depression.
Disclosure: Nothing to Disclose.

M148. Cannabinoid Effects on Prefrontal Activation during Regulation of Negative Affect

Christine Rabinak*, Shoko Mori, Maryssa Lyon, Mike Angstadt, K. Luan Phan

Wayne State University, Detroit, Michigan

Background: Aversive emotional experiences can be regulated by antecedent-focused strategies, such as cognitive reappraisal and response-focused strategies, such as extinction. Recent evidence suggests that activation of the cannabinoid (CB) system within brain structures important for extinction, such as the ventromedial prefrontal cortex (vmPFC), may regulate extinction learning and retention. Like extinction, cognitive reappraisal engages frontal brain regions encompassing anterior cingulate (ACC), ventro/dorsomedial prefrontal (v/dmPFC), and ventro/dorsolateral prefrontal cortex (v/dlPFC); however no studies have investigated cannabinoid system involvement during cognitive reappraisal of negative affect.
Methods: We conducted a fMRI study using a randomized, double-blind, placebo-controlled, between-subjects design ($N = 14$ /group) coupled with a reappraisal-based regulation of negative affect task and an acute pharmacological

challenge with oral THC in healthy adult volunteers. We examined the effects of THC on amygdala-PFC brain function and connectivity during cognitive reappraisal (i.e., decrease negative affect) as compared to passive viewing (i.e., maintain negative affect) of emotionally-evocative aversive images.
Results: Both groups engaged dlPFC, dmPFC, and vlPFC during attempts to regulate negative affect through reappraisal and there was no effect of drug. However, during passive viewing of aversive images the PBO group engaged the amygdala, whereas THC did not, and THC increased dlPFC activation. Moreover, THC decreased functional coupling between the amygdala and the vmPFC, specifically, and not any other PFC regions.
Conclusions: This study is the first to look at the effects of cannabinoids on explicit regulation and suggests that cannabinoids may have very localized effects within the PFC regardless of implicit or explicit emotion regulation.
Keywords: cannabinoid, emotion, reappraisal, prefrontal cortex.
Disclosure: Nothing to Disclose.

M149. Resting State Networks in the Non-psychotic Siblings of Patients with Childhood-onset Schizophrenia

Rebecca Watsky*, Stephen J. Gotts, Rebecca Berman, Harrison McAdams, Dede Greenstein, Francois Lalonde, Alex Martin, Anna Ordonez, Nitin Gogtay, Judith Rapoport

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: Childhood-onset schizophrenia (COS) is a rare, debilitating form of the disorder that may provide insight to the neurodevelopmental etiology of schizophrenia. Of particular interest has been the study of the non-psychotic siblings of COS patients, as the characterization of their neurobehavioral and genetic profiles provides an opportunity to identify shared risk or resilience factors in a younger developmental cohort. Previous magnetic resonance imaging studies from our group have shown that the altered grey matter developmental trajectories in COS are partially shared by non-psychotic siblings during early adolescence. Alterations to functional networks in COS siblings have not yet been examined. We adopted a new data-driven approach to examine large-scale functional 'resting state' networks in COS patients, and here we extend this methodology to ask whether siblings resemble COS probands.
Methods: Whole-brain echo-planar images were acquired at 3T from 19 COS patients, 22 non-psychotic siblings of COS patients (SIB), and 26 typically-developing controls (TD). Groups did not differ significantly for age, sex, handedness, or subject motion (all comparisons $p > 0.2$). Each resting state scan was five minutes in duration, during which subjects were instructed to lie quietly and fixate a centrally-located white crosshair on a black background. Preprocessing and a data-driven assessment of whole-brain covariation in fMRI signal, i.e. functional connectivity, followed the methods of Gotts et al. (2012). Areas of significant difference among the three groups (COS, SIB, TD) were identified by ANOVA, covarying for age and subject motion. Group comparisons of network correlations were done using t-tests and corrected for multiple comparisons.
Results: We first identified a total of 26 cortical and subcortical regions altered in COS, all of which had significantly lower functional connectivity in COS patients compared to TD controls (voxel-wise and cluster-corrected to $p < 0.05$). Using multidimensional scaling and k-means clustering, we found that these multiple regions could be distilled into two major networks, one somato-motor in function (13 areas including precentral and postcentral gyri, motor regions of putamen and cerebellum), and the other social-cognitive in function (15 areas including medial prefrontal, posterior cingulate, superior temporal and dorsal frontoparietal cortices). Importantly, subcomponents of these two networks were significantly and negatively correlated with one another in COS patients but not in controls, and the negative across-network correlations overlapped with locations exhibiting symptom correlations in COS for positive symptoms. COS patients also showed lower within-network connectivity for both the somato-motor and social-cognitive clusters, and decreased connectivity in the social-cognitive cluster among several pairs of regions was significantly associated with negative symptoms. Were these network interactions present in COS siblings? To address this question, we computed for each individual the average within-network correlation value for somato-motor and social-cognitive clusters, as well as the average across-network correlation. In TD controls, across-network correlation was significantly lower than within-network correlation ($p < 0.001$) but was nevertheless clearly positive (median across $r = 0.24$, median within $r = 0.39$). By contrast, the median for COS was near zero (across $r = 0.04$), significantly lower than in the TD group ($p < 0.0001$). For siblings, the median across-network correlation was 0.18, significantly greater than that of COS patients ($p < 0.0001$) and significantly lower than those of controls ($p < 0.01$). The within-network correlation for COS was significantly lower than in both siblings and TD controls (median $r = 0.32$, $p < 0.01$). The within-network correlation for siblings (median $r = 0.40$) did not differ significantly from TD controls ($p = 0.9$).
Conclusions: Siblings of COS patients appear to represent an intermediate phenotype, with whole-brain network-level alterations in functional connectivity that weakly resemble those observed in COS. Specifically, the negative interaction between sensorimotor and social-cognitive networks found in many COS patients is uncommon in siblings, but siblings nonetheless show significantly reduced across-network correlations than TD controls. The altered interactions between somato-motor and social-cognitive networks in COS is consistent with the dysfunctional integration of basic sensorimotor signals proposed to contribute to schizophrenia. The moderately shared across-network decreases in COS siblings suggest that this dysfunction may be a functional trait marker for the disease. We continue to examine the relationship between these large-scale network interactions and clinical and cognitive measures in COS siblings.
Keywords: Schizophrenia, Neuroimaging, Psychiatry, Childhood-onset schizophrenia.
Disclosure: Nothing to Disclose.

M150. Striatal Dopaminergic Reward Response Relates to Age of First Drink in At-risk Youth

Barbara Weiland*, Mary Heitzeg, Robert Zucker, Jon-Kar Zubieta

The University of Colorado Boulder, Boulder, Colorado

Background: The fronto-striatal neural system undergoes significant changes in conjunction with the transition from adolescence to early adulthood, concurrent with increased substance use. Dopamine receptor concentrations, primarily in the striatum, peak during adolescence, and is hypothesized to contribute to an imbalance between subcortical, dopamine mediated mechanisms (e.g., in the nucleus accumbens, NAcc) and prefrontal control in emerging adulthood. This developmental imbalance may bias motivation and increase risk for substance abuse. In addition, receptor positron emission tomography (PET) studies have found significant reductions in striatal dopamine D2 receptors, as well as blunted amphetamine-induced dopamine release, in the ventral striatum in alcoholics compared to healthy controls. Further, parental alcoholism is a significant risk factor for substance use disorders with genetic influence accounting for 40-60% of the variance in risk. It has been suggested that deceased D2 receptor availability and blunted dopamine release may reduce sensitivity to natural reinforcers, while drugs of abuse would still be able to activate these circuits and thus may underlie vulnerability to addiction. We interrogated this system in young adults both with (FH+) and without (FH-) a family history of alcoholism, hypothesizing that those at risk would have blunted ventral striatal response to reward.
Methods: We probed the functioning of the ventral striatum using a modified version of the monetary incentive delay (MID) task as behavioral stimulation of the dopamine reward-motivation circuitry during PET imaging with [11C]raclopride. Subjects were young males (ages 18-26) considered controls (FHN, $n = 13$) or at-risk (FHP, $n = 32$) based on parental alcohol use disorder diagnosis. NAcc regions of interest were used to extract reward-associated reductions in D2/D3 receptor availability (binding potential, BP), reflecting reward-induced dopamine release and activation of D2/3 receptors. Relationships between dopamine release and age of first drink, an early indicator of risk, were examined.
Results: A significant positive relationship was found in the FHP subjects between left NAcc dopamine reward release and age of first drink such that those with lower levels of dopamine release during the MID task had initiated drinking at a younger age. A positive trend level relationship was also found with the right NAcc in the FHP subjects. There were no significant relationships between age of first drink and NAcc dopamine release in the FHN control subjects.
Conclusions: Decreased ventral striatal dopaminergic response to reward may be a risk marker in youth considered at-risk for substance abuse based on family history. This blunted response of the dopamine system may represent vulnerability for substance abuse.
Keywords: Substance abuse, PET, dopamine, reward.
Disclosure: Nothing to Disclose.

M151. Behavioral and Brain Changes Associated with the Experimental Use of N-Acetylcysteine for Non-suicidal Self-injurious Behavior in Adolescents

Kathryn Cullen*, Lynn Eberly, Bonnie Klimes-Dougan, Bryon Mueller, Leah Jappe, Melinda Westlund, Patricia Carstedt, Katharine Nelson, Michael Miller, Kelvin Lim

University of Minnesota Medical School, Minneapolis, Minnesota

Background: Non-Suicidal Self Injury (NSSI) in adolescents is a common, serious behavioral problem with limited treatment options. N-acetylcysteine (NAC) has been shown to be effective in numerous psychiatric disorders including depression and habit-related disorders, and may have promise as a novel treatment for NSSI in adolescents. Functional magnetic resonance imaging (fMRI) is a tool that can be used to track brain changes in the context of a translational clinical trial.
Methods: We studied 25 youths aged 13-21 years with a history of NSSI and 12 controls. Clinical Assessment: Participants underwent a comprehensive clinical assessment after signing informed consent/assent. History of NSSI was assessed using the Deliberate Self Harm Inventory (Gratz, 2001). The Beck Depression Inventory-II (BDI-II) (Beck, & Brown, 1996) and the Symptoms Checklist 90 (SCL-90) (Derogatis, 1977) were administered before and after treatment. Treatment: 8-week open-labeled trial of oral NAC: 300mg twice daily weeks 1 and 2; 600mg twice daily weeks 3 and 4; 900 mg twice daily weeks 5-8. Neuroimaging: Brain imaging took place before and after the NAC trial at the UMN Center for Magnetic Resonance Research on a 3 Tesla Siemens TIM Trio scanner and a 32-channel radio-frequency head coil. fMRI data were obtained using the human connectome project multi-band echo planar imaging sequence (294 T2*-weighted whole brain volumes, 64 oblique axial slices; 2mm isotropic voxel; $TR = 1320$ ms; $TE = 30$ ms; flip angle $= 90^{\circ}$, $FOV = 212$ mm; multiband factor $= 4$). The fMRI task consisted of matching emotion faces or shapes (Hariri et al, 2002). We acquired a high-resolution anatomical scan. fMRI data pre-processing steps included motion correction, brain extraction, high pass temporal filtering, prewhitening, regression of motion parameters, spatial smoothing (4mm kernel) and registration to standard space. We regressed the task model onto the fMRI data with 2 explanatory variables (emotion and shape) and the motion parameters as covariates of no interest, removing volumes where relative motion exceeded 1.5mm. Analyses focused on the emotion > shape contrast. Baseline analysis included: a group comparison of clinical measures and brain activation including an age covariate, and correlations of clinical measures with Z scores from clusters showing significant group differences in brain activation. Longitudinal analysis included: repeated measures ANOVA for count of NSSI episodes per 2 week period during treatment, voxel-wise paired t-tests for brain activation from pre- and post-treatment imaging data, and correlations of clinical change scores with change in z scores from clusters showing significant change on the paired t-tests.
Results: Baseline Clinical and Imaging Findings: In comparison to controls, NSSI participants exhibited (a)

greater levels of global psychopathology, (b) greater activation in several areas (precuneus, posterior cingulate, insula and temporal lobes) and (c) lower left frontal activation. Within the NSSI group, superior parietal activation was linked to global psychopathology as measured by SCL-90 ($r = -.47$, $p = 0.03$). Clinical Outcome Results: To measure treatment response, we examined change over time in the number of NSSI episodes per 2 weeks over the course of the treatment, using the second week of treatment as the baseline. The dose at week 2 was still sub-therapeutic, and we had a more accurate estimate of number of episodes per 2 weeks at week 2 than the pre-treatment visit. Repeated-measures ANOVA revealed a significant effect of time ($F = 5.2$, $p = 0.009$), where NSSI episodes decreased steeply at week 4 (the first assessment on the 600mg bid dose), then increased again, and then returned to approximately the week 4 levels at the final visit. Additionally, BDI-II scores ($t = 4.2$, $p = 0.001$) and SCL-90 scores ($t = 3.1$, $p = 0.01$) decreased from pre-treatment to week 8. Neuroimaging Changes with NAC Treatment and Clinical Correlations: 18 adolescents with NSSI completed neuroimaging before and after the NAC trial. After treatment, brain activation for the emotion > shape contrast increased in bilateral frontal poles, superior parietal lobe, and precuneus, but decreased in the cerebellum. Increased frontal activation was correlated with decreased global psychopathology on the SCL-90 ($r = -.7$, $p = 0.01$) and also, at a trend level, with decreased BDI-II scores ($r = -.47$, $p = 07$).

Conclusions: We found evidence for (a) significant differences in brain activation during a negative emotion task in adolescents with NSSI compared to healthy controls, (b) effectiveness of NAC for decreasing NSSI and global psychopathology in an 8-week open-labeled trial, and (c) brain changes accompanying treatment response to NAC. While a number of brain changes were associated with treatment, the increase in frontal activation in response to negative emotion was particularly linked with symptom improvement. NAC's mechanisms of action include promoting glutathione, the brain's primary antioxidant. Thus, NAC's efficacy in reducing NSSI and general psychopathology in adolescents may include reducing oxidative stress and toxicity in the frontal lobe, facilitating the appropriate recruitment of this region in the face of negative emotion.

Keywords: self-injury, adolescence, fMRI, n-acetylcysteine.

Disclosure: Nothing to Disclose.

M152. Effort Discounting fMRI Identifies Neurobehavioral Mechanisms of Amotivation

Daniel Wolf*, Joseph Kable, Theodore Satterthwaite, Christos Davatzikos, Warren Bilker, Natalie Katchmar, Lillie Vandekar, Aylin Daldal, Brenda Li, Matthew Siegelman, Mark Elliott, Kosha Ruparel

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Motivational deficits play a central role in disability due to negative symptoms of schizophrenia, and constitute a major unmet therapeutic need. However, the pathophysiology of amotivation remains largely unknown, and progress will depend on integrating clinical assessment with quantitative behavioral and imaging phenotypes. We recently demonstrated a dimensional relationship in schizophrenia between behavioral motivation deficits on a progressive ratio task and hypofunction in the ventral striatum during an fMRI monetary reward task (Wolf et al. Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures. Schizophrenia Bulletin, 2014). Further efforts to elucidate the neurobehavioral mechanisms of amotivation will benefit from fMRI paradigms in which motivation, operationalized as willingness to exert effort, is directly assessed during the fMRI scan. Unlike progressive ratio tasks, effort discounting paradigms are easily adapted to the fMRI environment, and allow neuroeconomic decision-making approaches to be applied to understand motivation circuit function and dysfunction. Here we report preliminary results from an ongoing study applying an effort discounting task (EDT) during fMRI that quantifies motivation based on the degree to which effort requirements produce reductions in (discount) the subjective value of monetary reward.

Methods: As part of an ongoing study, to date 22 patients with schizophrenia (SCH, stable/medicated) and 23 group-matched controls (CTR) performed an effort discounting task (EDT) during fMRI (3T BOLD). In each of 200 trials in the EDT, subjects choose between higher-effort/higher-reward (HARD) and lower-effort/lower-reward options (EASY). The required effort involves repetition of easy but attention-requiring trials (choosing which of 2 numbers is larger), which is the same effort required in our progressive ratio task (PRT). The reward and effort magnitudes for the HARD option are parametrically and independently varied across trials. Importantly, 200 reward-effort tradeoff choices are made in the scanner, but the required effort itself is not exerted during the scan – a single choice is selected at random for realization after the scan. Behavioral analysis of EDT applies a quantitative neuroeconomic model that captures how the subjective value of a decision to perform an effortful task incorporates the tradeoff between monetary reward and effort costs, using the equation $SV = A\text{-}B*E$. This equation describes how the subjective value (SV) of a particular monetary reward amount (A) is reduced or "discounted" as the effort cost (E) needed to obtain it increases. Higher values of the estimated free parameter B indicate a stronger negative impact of effort on subjective value, and hence lower motivation. fMRI analysis focused on key regions in motivation circuitry based on prior human and animal literature, including ventral striatum (VS) and anterior cingulate cortex (ACC) as well as ventral midbrain and ventromedial prefrontal cortex. Exploratory whole-brain voxelwise analyses were also conducted to test for effects outside of the a priori ROIs. Additional study measures include clinical negative symptom ratings with the CAINS and SANS, out-of-scanner PRT performance, and out-of-scanner temporal discounting.

Results: There were no group differences in the median across-trial reaction times, nor in the model fits measured with adjusted R-squared or percentage of choices matching the model prediction. The percentage of HARD choices, and associated estimated beta values, ranged widely in both groups. Patients showed a trend toward higher beta parameters (lower EDT motivation; $p = .06$). Subjective Value in the EDT correlated across trials with fMRI activation in VS, ACC as well as other limbic and cortical

regions. This SV effect related primarily to reductions in activity as the effort level associated with the HARD option increased. This suggests that increased effort is being processed at least in part as a "negative reward," or cost, in the same regions known to process positive rewards. Furthermore, the strength of this parametric effect of effort varied based on the behavioral motivation of the subjects. In both groups, less motivated subjects (higher B values, choosing a smaller percentage of harder-but-more-profitable choices), showed a stronger suppression of activation in VS, ACC and other task-activated regions, as effort requirements increased (VS $r = 0.40$, AC $r = 0.54$). The effect of effort was similar across groups in VS and ACC, however SCH showed stronger effort-related reductions of activation in ventral midbrain and ventromedial prefrontal cortex.

Conclusions: Findings suggest that VS and ACC, among other brain regions, are involved in evaluating the cost of effort requirements, consistent with prior work in healthy individuals as well as animal models. These preliminary results from an ongoing study support the utility of effort discounting fMRI as a neurobehavioral probe of motivation circuit function in schizophrenia and potentially other psychiatric disorders.

Keywords: Motivation, Negative Symptoms, fMRI, Effort.

Disclosure: Nothing to Disclose.

M153. Dose-Dependent Occupancy of Fatty Acid Amide Hydrolase (FAAH) Enzyme in Human Brain by the Selective FAAH Inhibitor JNJ-42165279, as Measured by 11C-MK-3168 Positron Emission Tomography (PET)

Mark Schmidt*, Andrey Postnov, Jan de Hoon, Jean Penson, Kwinten Porters, Ann Van Hecken, Peter Zannikos, Xiaoyu Yan, Darrel Pemberton, James Palmer, Wayne Drevets, Guy Bormans, Koen Van Laere

Janssen Research and Development, Beerse, Belgium

Background: FAAH catalyzes the degradation of fatty acid amides (FAA), including endocannabinoids which are endogenous agonists of cannabinoid receptors. Preclinical data suggest that modulation of FAAH may have therapeutic benefits in anxiety, stress, and distress disorders. JNJ-42165279 is a slowly reversible inhibitor of FAAH, acting as a substrate and covalently binding to the catalytic site. Prior to conducting proof of concept studies in patients, we wished to confirm central target engagement and potential variability with JNJ-42165279 to accurately define dose range that could test the mechanism while reducing risk from unnecessary exposure.

Methods: The regional brain kinetics of 11C-MK-3168 and blocking of the retention of the radioligand by JNJ-42165279 was tested in an open-label, adaptive dose design. 11C-MK-3168 PET scans were conducted at baseline and after doses of JNJ-42165279 ranging from 2.5 to 50 mg. Dynamic scans were acquired for 90 minutes on a Siemens Hirez 16 slice LSO PET/CT and included arterial sampling, radiometabolite analysis, and PK sampling for JNJ-42165279. FAAH activity was also determined in leucocytes collected at the time of the PET scan. PET image data was segmented into volumes of interest using the Hammers atlas in PMOD v3.4. The generated regional time activities and arterial input functions were used for kinetic modeling, also in PMOD. The first part of the study measured the uptake, distribution, and clearance of 11C-MK-3168 in brain in 5 healthy male subjects and a suitable tissue kinetic model was identified. In the second part, dose-dependent reduction in 11C-MK-3168 binding to FAAH due to blocking by JNJ-42165279 was determined in 6 healthy males. The distribution volume of 11C-MK-3168 in a baseline PET scan was compared to distribution volumes of 11C-MK-3168 during scans conducted after 2 single oral doses of JNJ-42165279 (at estimated tmax) separated by at least 2 weeks. In the third part of the study, 11C-MK-3168 binding to FAAH was measured in 4 healthy males after a single dose of JNJ-42165279 predicted to result in less than or equal to 100% occupancy at estimated tmax and then 24 hours after the last of 7 daily doses, to test for occupancy at steady state trough and for evidence of accumulation. All treatment scans were compared to a baseline scan acquired prior to the first dose of JNJ-42165279.

Results: Part 1: 11C-MK-3168 was taken up rapidly into brain ($SUV > 2$) and was rapidly metabolized in the peripheral compartment. Radiometabolites appeared quickly and parent tracer was absent by 60 min post-injection. The most robust kinetic parameters were Vt for one (1T) and two tissue (2T) reversible models, and binding potential (BP) for 2T model with a fixed k1/k2. Regional differences in uptake and kinetic parameters were minimal. Part 2: Doses tested ranged from 2.5 mg to 50 mg. Complete blocking was seen after pretreatment with doses as low as 10 mg of JNJ-42165279 and saturated at higher doses. Metabolism of 11C-MK-3168 was considerably slowed by JNJ-42165279, resulting in higher parent tracer availability after pretreatment. The 2T reversible kinetic model with a fixed non-displaceable distribution volume was the most reliable. Part 3: Two doses were tested: 2.5 mg and 10 mg. 10 mg resulted in approximately 85% occupancy after single dose and 24 hours after the final dose of one week of repeat dosing in two subjects. 2.5 mg resulted in 56% occupancy after single dose that was sustained after one week in one subject while the other subject had 44% occupancy after single dose of 2.5 mg that fell to 16% the day after one week of dosing. Safety and tolerability: MK-3168 and JNJ-42165279 were both well tolerated by the subjects; no compound related adverse effects or clinical abnormalities were observed.

Conclusions: The results of this study demonstrate that JNJ-42165279 blocks FAAH in brain at doses as low as 10 mg although between-subject variability was observed. The results of Part 3 suggest that occupancy with 10 mg is sustained at trough, and throughout a dosing interval of 24 hours. This is likely related to a delay in recovery of enzyme function by de novo synthesis and/or slow hydrolysis of the fragment of JNJ-42165279 from the catalytic site. The central pharmacodynamic potency of 10 mg is currently being investigated. These data support the continued investigation of JNJ-42165279 to determine whether inhibition of FAAH is clinically beneficial in the treatment of mood and anxiety disorders. The PET occupancy study was able to confirm central target engagement by JNJ-42165279 and facilitated identification of doses that can test the mechanism of action with an acceptable safety margin for

chronic treatment. A multiple dose study in healthy subjects of JNJ-42165279 was conducted in parallel that included measurements of drug in plasma, urine, and cerebrospinal fluid (CSF); FAAH activity in leucocytes (WBCs); and anandamide (AEA), N-oleoylethanolamide (OEA),.

Keywords: FAAH inhibitor, Positron emission tomography, Clinical, Dose occupancy.

Disclosure: Mark Schmidt, Jean Penson, Peter Zannikos, Xiaoyu Yan, Darrel Pemberton, James Palmer, and Wayne Drevets are full time employees of Janssen Pharmaceuticals, the sponsor of the study and developer of the JNJ-42165279. Andrey Postnov, Jan de Hoon, Kwinten Porters, Ann Van Hecken, Guy Bormans, and Koen Van Laere are all employed by the University Hospital, University of Leuven, Belgium, and conducted the study as a Janssen sponsored trial.

M154. Relationship of Monoamine Oxidase A Distribution Volume to Postpartum Depression and Postpartum Crying

Jeffrey Meyer*, Julia Sacher, Vivien Rekkas, Alan Wilson, Sylvain Houle, Leslie Romano, Donna Stewart, Pablo Rusjan

Center for Addiction and Mental Health, Toronto, Canada

Background: Postpartum depression (PPD) has a prevalence rate of 13% and a similarly high proportion of women report a subclinical state of one or more MDE symptoms. MAO-A is an enzyme that is primarily located on the outer mitochondrial membrane of glia and monoamine releasing neurons; and increases in density and activity after estrogen decline. MAO-A has several functions including creating oxidative stress, influencing apoptosis and monoamine metabolism. The aim was to investigate whether monoamine oxidase-A (MAO-A) VT, an index of MAO-A density, is increased in the prefrontal and anterior cingulate cortex (PFC and ACC), during PPD or when a PPD spectrum symptom, greater predisposition to crying, is present.

Methods: Fifty seven women were recruited including 15 first onset, antidepressant naive, PPD subjects, 12 postpartum healthy who cry due to sad mood, 15 asymptomatic postpartum healthy women and 15 healthy women not recently pregnant. None of the subjects had a history of previous major depressive episodes. Each underwent [11C]-harmine positron emission tomography (PET) scanning to measure MAO-A VT.

Results: Both PPD, and greater predisposition to crying were associated with greater MAO-A VT in the PFC and ACC (multivariate analysis of variance (MANOVA), group effect, $F(21,135) = 1.856$; $p = 0.019$; mean combined region elevation 21% and 14% in PPD and crying groups, respectively, relative to asymptomatic postpartum). A tendency towards a similar elevation in MAO-A VT was observed in the other brain regions sampled (hippocampus, ventral striatum, dorsal striatum, thalamus and midbrain).

Conclusions: Greater MAO-A VT in the PFC and ACC represents a new biomarker in PPD, and the PPD symptom of predisposition to crying. These findings also argue for clinical trials in PPD with the newer, well-tolerated MAO-A inhibitor antidepressants. These findings also have implications for prevention, based on the following model: Substantial estrogen decline, such as the 100 fold decline in estrogens over the first few days postpartum, is normally associated with a very strong, temporary rise in MAO-A VT, MAO-A density and MAO-A activity. The present study suggests that MAO-A VT subsequently declines either to normal levels, or does not decline to normal levels, leading to three subsequent outcomes: With a full decline to normative MAO-A VT level in the PFC and ACC, a healthy mood is a likely outcome. With an inadequate decline, and ongoing elevated MAO-A VT levels in the PFC and ACC, either PPD, or, a tendency to cry due to depressed mood is likely. Novel strategies for preventing PPD (and some PPD symptoms) may be possible by avoiding environmental conditions that elevate MAO-A level and enhancing conditions that normalize MAO-A level.

Keywords: monoamine oxidase, postpartum depression, oxidative stress, monoamines.

Disclosure: Drs. Meyer, Wilson and Houle have received operating grant funding for other studies from Eli-Lilly, GlaxoSmithKline, Bristol Myers Squibb, Lundbeck, and SK Life Sciences in the past 5 years and Dr. Meyer has consulted to several of these companies as well as Sepracor, Mylan and Teva. Dr. Meyer is developing (and patenting) natural health products to treat high MAO-A states. Dr. Meyer is applying for patents to apply measures of MAO to diagnose or treat mood disorders. It is likely that companies which make medications which affect monoamine receptors or monoamine oxidase binding will seek collaborations with these investigators in the future. Dr. Stewart served on the Duloxetine Pregnancy Registry Scientific Advisory Board 2011-present, received one-time Ranbaxy Travel Support in 2012, and is an author on the fetal effects of SSRI's and the Treatment of Depression in Pregnancy for the publication, "UpToDate." Leslie Romano, and Drs. Sacher, Rekkas, Wilson, Houle and Rusjan have no additional disclosures to report. None of these companies participated in the funding, design or execution of this study.

M155. Effects of Vortioxetine on Resting-State Activity in Subjects Remitted from Depression and Healthy Controls

Gerard Dawson*, Silke Conen, Shane McKie, Richard Smallman, Jessica Smith, Michael Browning, Robin Morris, Søren Rahn Christensen , Jeppe Buchbjerg, Klaus Groes Larsen, Christina Kurre Olsen, JF William Deakin

P1vital Ltd., Wallingford, United Kingdom

Background: Major Depressive Disorder (MDD) is a common psychiatric disorder that affects an estimated 350 million people globally]. It is widely treated with antidepressant medications. Imaging studies in MDD have found alterations in resting-state signal across multiple brain networks, including the Default Mode Network (DMN). Studies suggest that antidepressant medications can decrease resting-state signal in healthy volunteers, indicating that antidepressants might work by normalizing the elevated resting-state signal seen in depressed patients

Vortioxetine is a novel, multi-modal antidepressant. In vitro studies indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of the 5-HT transporter. All of these activities are considered to be involved in its therapeutic mechanism of action, but its effects on resting-state signal have not yet been investigated. The present study was therefore designed to assess the effects of vortioxetine (20mg) on resting-state signal after repeated dosing in subjects remitted from depression and in healthy controls.

Methods: Forty-eight male and female subjects remitted from depression (HAM-D <7) who reported subjective cognitive difficulties and who had received no treatment for at least 6 weeks and 48 healthy controls participated in a 4-armed, multi-site, placebo-controlled, randomized, double-blind trial. Subjects were treated with once daily doses of vortioxetine (20 mg) or a placebo for 12 – 13 consecutive days. Resting-state functional magnetic resonance imaging (fMRI) was assessed in a 3T magnetic resonance scanner during a baseline visit (pre-treatment), and after 12-13 days of treatment (post-treatment). An independent component analysis identified the component maps of interest and these were correlated to a DMN template. The change in amplitude of low frequency fluctuations (ALFF) between pre- and post-treatment was analyzed using an ANOVA with treatment, subject group, and site as independent factors. Using the previously identified DMN component maps as a small volume correction, clusters of voxels were considered significant at a cluster size threshold of pFWEc <0.05, and a height threshold of $p<0.001$ (uncorrected). The data were analyzed using SPM 8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK).

Results: In the pre-treatment condition, significantly higher ALFFs were apparent in the healthy controls in the medial frontal gyrus ($p=0.045$) and the postcentral gyrus ($p=0.006$). In subjects remitted from depression vortioxetine significantly reduced ALFF in the anterior cingulate cortex ($p<0.001$) and increased ALFF within the angular gyri ($p<0.001$). The same pattern of results was seen when both groups were analysed together (reduction of ALFF in anterior cingulate; $p<0.001$, increase in the angular gyrus; $p=0.003$). When the healthy controls were analyzed separately a significant reduction of ALFF was observed in the anterior cingulate cortex ($p<0.001$), although there was no significant effect of vortioxetine in the angular gyri when compared to placebo.

Conclusions: Vortioxetine reduced ALFF in the anterior cingulate cortex in both, subjects remitted from depression and healthy controls. An increase in ALFF was seen in the angular gyri, although this effect appeared to be limited to the remitted group. Notably, DMN signal in both of these regions has previously been found to be altered in depression. Specifically, depressed patients exhibit increased signal within the anterior cingulate cortex and decreased signal within the precuneus and angular gyri. It has further been demonstrated that the signal within these posterior regions was inversely associated with over-general autobiographical memory, a characteristic cognitive feature of depression. In summary, vortioxetine altered the resting state signal within the DMN in the opposite direction to that seen in acute depression.

Keywords: Major Depressive Disorder, Vortioxetine, Resting state, Imaging.

Disclosure: Michael Browning is an employee of P1vital Limited Gerard R. Dawson is an employee and holds shares in P1vital Limited. JF William Deakin in the last 5 years has held grants from Servier, AstraZeneca and P1vital and given talks and/or advice for Servier, Johnson and Johnson, AstraZeneca and Lilley. Fees are paid as reimbursement for his time to the University of Manchester. Guy Goodwin has held grants from Servier, received honoraria for speaking or chairing educational meetings from Abbvie, AstraZeneca, GSK, Lilly, Lundbeck, Medscape, Servier and advised AstraZeneca, Cephalon/Teva, Lundbeck, Merck, Otsuka, P1Vital, Servier, Shire, Sunovion, and Takeda, holds shares in P1vital and acted as expert witness for Lilly. Catherine Harmer has received consultancy payments from Lundbeck, P1vital and Servier and is a shareholder in P1vital. She is a company director of Oxford Psychologists and holds shares in the same company. Rahn Christensen, Klaus Groes Larsen and Christina Kurre Olsen are employees of H. Lundbeck Jeppe Buchbjerg is a former employee of H. Lundbeck.

M156. The Influence of APOE Genotype on Aging's Effect on Brain Structure and Cognition in Younger Adults with and without Depression

Warren Taylor*, Ayman Saleh, Guy Potter, Brian Boyd, Douglas McQuoid, Kamil Kudra, Allison Ashley-Koch, James MacFall

Vanderbilt University Medical Center, Nashville, Tennessee

Background: The APOE e4 allele is a risk factor for Alzheimer's disease that is associated with cognitive deficits and regional brain atrophy in older adults. Studies of direct gene effects on cerebral morphometry and cognition in younger adult populations have had mixed findings. We sought to determine the effect of APOE genotype on brain aging and cognition in younger adults and if its effects are influenced by the presence of depression.

Methods: Fifty-eight depressed and 73 nondepressed adults (33% APOE e4 positive) between the ages of 20-50 years completed neuropsychological testing and 3T cranial MRI. Automated processes measured regional MRI volumes of temporal lobe and cingulate cortex regions. Neuropsychological test results were transformed into z-scores and combined to create summary domain scores. Statistical mixed models tested for direct effects of APOE genotype, then tested for interactions between APOE genotype and both age and diagnosis.

Results: After controlling for depression, age, sex, race, hemisphere and intracranial volume, we did not observe a direct effect of APOE genotype on regional volumes. However there was a significant interaction effect between APOE genotype and age for the bilateral entorhinal cortex ($F=6.64$, $p=0.0111$), rostral anterior cingulate cortex ($F=5.08$, $p=0.0260$), and caudal anterior cingulate cortex ($F=5.94$, $p=0.0161$). Statistically significant

interactions were observed unilaterally for the left hippocampus ($F = 5.93$, $p = 0.0163$), right parahippocampal gyrus ($F = 4.83$, $p = 0.0299$), and right amygdala ($F = 4.16$, $p = 0.0434$). In these analyses, presence of the APOE e4 allele appeared to ameliorate the effect of aging on regional brain structure. A significant APOE by age interaction was also observed for the summary score of executive function ($F = 4.23$, $p = 0.0415$), where the e4 allele again ameliorated the effect of age on executive function performance. There was no evidence for interactions between genotype and depression on MRI or cognitive measures.
Conclusions: By demonstrating that the presence of the APOE e4 allele may lessen aging's effect on executive function and structure of temporal-cingulate subregions, this study supports past work suggesting that presence of the e4 allele may provide benefit to younger adults. However, we did not observe a differential effect of APOE genotype in the presence of depression. Further work across the lifespan is needed to elucidate the relationship between depression and risk of dementia.
Keywords: Aging, APOE, MRI, Cognition.
Disclosure: Nothing to Disclose.

M157. Increased Neuroinflammation in Major Depressive Disorder and Relation to Symptom Severity

Elaine Setiawan*, Alan Wilson, Romina Mizrahi, Pablo Rusjan, Laura Miler, Grazyna Rajkowska, Ivonne Suridjan, James Kennedy, Vivien Rekkas, Sylvain Houle, Jeffrey Meyer

Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

Background: The presence of neuroinflammation in major depressive disorder (MDD) is supported by several main findings. First, activation of the immune system causes sickness behaviors that present during a major depressive episode (MDE) such as low mood, anhedonia, anorexia and weight loss, in humans and animals. Second, peripheral markers of inflammation are frequently reported in MDD. Third, neuroinflammatory illnesses are associated with high rates of MDE. However, to date, there is a paucity of evidence for brain inflammation during MDE. Translocator protein density is elevated in activated microglia, a hallmark of neuroinflammation, and may be quantified using positron emission tomography.
Methods: [18F]FEPPA positron emission tomography (PET) was applied to measure translocator protein total distribution volume (TSPO VT), an index of TSPO density, in 20 subjects with MDE secondary to MDD and 20 healthy controls. MDE subjects were medication-free for at least 6 weeks. All participants were otherwise healthy, and non-smoking.
Results: In MDE, TSPO VT was significantly elevated in the prefrontal cortex, ACC, and insula (on average 30%, multivariate analysis of variance, $P < 0.007$). In MDE, greater TSPO VT in the ACC and insula correlated with greater depression severity and lower body mass index (BMI), respectively (ACC: $r = 0.628$, $P = 0.005$; insula: $r = -0.605$, $P = 0.006$).
Conclusions: These results provide the most compelling evidence to date for neuroinflammation in MDE. The correlations between higher ACC TSPO VT with severity of MDE and higher insula TSPO VT with lower BMI are consistent with the concept that neuroinflammation in these regions may contribute to sickness behaviors which overlap with the symptoms of MDE. Therapeutics which reduce microglial activation may be promising in a subset of the clinical population with relevant symptoms.
Keywords: depression, positron emission tomography, translocator protein, neuroinflammation.
Disclosure: Nothing to Disclose.

M158. An Increase in Tobacco Craving is Associated with Enhanced Medial Prefrontal Cortex Network Coupling

Amy Janes*, Stacey Farmer, Blaise Frederick, Lisa Nickerson, Scott Lukas

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: Craving is a key aspect of nicotine dependence that is thought to motivate continued drug use. Numerous brain regions have been associated with craving, suggesting that a distributed brain network mediates the desire to smoke. A rise in craving may therefore enhance the interactions between disparate brain regions allowing for greater communication within such a network. The orbital and medial prefrontal cortex (OMPFC) may serve as a site of integration across craving-related regions as the OMPFC is not only implicated in addiction and reward, but also has rich anatomic interconnections.
Methods: To evaluate whether a rise in craving corresponds with enhanced OMPFC functional connectivity, we collected resting state functional magnetic resonance imaging (fMRI) data in 17 nicotine dependent participants. Participants included 8 men and 9 women 25.4 ± 4.6 (mean $\pm$ sd) years old with 6.7 ± 4.7 pack-years of smoking experience. Nicotine dependence was confirmed by an average Fagerstrom test for nicotine dependence (FTND) score of 6.3 ± 1.0. Resting-state fMRI and craving, evaluated by the brief questionnaire of smoking urges (QSU), were measured twice with a $\sim$1 hour delay between assessments. All fMRI data were processed using tools from the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL). First, the average OMPFC network was defined across all participants using an independent components analysis (ICA). Dual regression was then used to calculate subject specific spatial maps. To evaluate a change in functional connectivity between the two resting state acquisitions, difference maps were calculated by subtracting the individual subject spatial maps for the second minus the first resting state session. Changes in craving and expired carbon monoxide (CO) were correlated with these difference maps using non-parametric permutation testing with 5,000 permutations. Multiple comparisons were cluster threshold corrected to $Z = 2.3$, $p < 0.05$.
Results: Cigarette craving was significantly increased during the second relative to the first scan session ($p < 0.01$; pre 22 ± 8.2, post 30.2 ± 10.2) and CO levels significantly

dropped ($p < 0.01$, pre 26.9 ± 12.3 ppm, post 18.6 ± 8 ppm). Enhanced craving was associated with heightened coupling between the OMPFC network and other cortical, limbic, striatal, and visceromotor brain regions that are both anatomically interconnected with the OMPFC, and have been implicated in addiction and craving. These regions included the ventral and dorsal striatum, hippocampus, dorsal anterior cingulate cortex, and supplementary motor area. No association was found between a decrease in CO and OMPFC network coupling.
Conclusions: This is the first demonstration confirming that an increase in craving is associated with enhanced brain region interactions, which may play a role in the experience of craving.
Keywords: Nicotine, Craving, Functional Connectivity, Medial Prefrontal Cortex.
Disclosure: Nothing to Disclose.

M159. Sensitivity to Rewarding Stimuli in Young Women Prone to Weight Gain is Dependent on Hunger State: An fMRI Pilot Study

Alice Ely*, Anna Rose Childress, Kanchana Jagannathan, Michael Lowe

University of California at San Diego, San Diego, California

Background: Neuroimaging research suggests that over-eating may be linked to dysfunctional reward and inhibitory processes and that this may be evident normal weight individuals. In two fMRI studies, we explore response to reward and its relationship to hunger state in normal weight individuals with past dieting behavior, a population at risk for disinhibition and weight gain.
Methods: In the first study, 10 historical dieters (HDs) and 10 nondieters (NDs) were shown pictures of highly and moderately palatable food after an 8 hour fast and again after eating. In the second study, under the same conditions, participants were shown positively-valenced romantic images of heterosexual couples. A "fast", randomized event-related design was used and cue order was quasi-randomized. Stimuli were shown for 500 milliseconds, jittered with an inter-stimulus interval of 1.5 seconds. Data acquisition took place using a 3 Tesla Trio MR Scanner. First-level contrast maps were used for statistical testing of group or condition effects at the second level (e.g. HDs v. NDs). The contrast maps were entered to into a random effects analysis to test for a significant activation unique to rewarding versus neutral cues.
Results: There were no significant differences in BMI between NDs (22.04) and HDs (21.11), while NDs were significantly older (21.1 v. 19.1, $p = 0.028$). In a fasted state, the groups did not differ in response to food reward, but after having eaten, HDs demonstrated elevated activation compared to NDs in the anterior cingulate and dorsolateral prefrontal cortex ($k > 37$, $p < 0.002$), areas related to reward anticipation, decision-making and inhibitory processes. A similar pattern emerged when examining response to romantic images. The groups did not differ when fasted, but when fed, significantly greater activation was shown in HDs in the left middle temporal, right supramarginal and right precentral gyri ($k > 200$, $p < 0.02$), regions linked to facial emotional processes and motor function.
Conclusions: This pattern of activation suggests a both a neurophysiological vulnerability to the influence of food cues and efforts to suppress this predisposition in normal weight women that may contribute to the likelihood of weight gain. Furthermore, it appears that neurobiological response to more generally positive stimuli is also linked to hunger state this population. Those at risk for future weight gain may experience differential reward sensitivity when nutritionally replete than controls. While this sensitivity is global, it may underlie the tendency to overeat.
Keywords: Dieting, reward, eating.
Disclosure: Nothing to Disclose.

M160. Effects of an Opioid (proenkephalin) Polymorphism on Error Processing and Negative Emotionality in Health and Cocaine Addiction: Imaging Genetics Study

Scott Moeller*, Nicasia Beebe-Wang, Kristin Schneider, Anna Konova, Muhammad Parvaz, Nelly Alia-Klein, Yasmin Hurd, Rita Goldstein

Icahn School of Medicine at Mount Sinai, New York, New York

Background: Chronic exposure to cocaine and other drugs of abuse perturbs the endogenous opioid system, which plays a critical role in the development and maintenance of addictive disorders. Research has shown that opioid peptides derived from endogenous proenkephalin activate μ- and δ-opioid receptors in multiple brain areas including the striatum and participate in regulating mood and reward. While addiction-related alterations of the opioid system have been effectively probed in animal studies (e.g., via gene-knockout strains), human studies remain sparse. Recently, a single nucleotide polymorphism (SNP) of the protein-coding proenkephalin gene (PENK: rs2609997), shown to relate to PENK mRNA expression levels in the human brain, was reported to be associated with dispositional neuroticism and cannabis dependence. Here we investigated the rs2609997 C/T polymorphism in individuals with cocaine use disorder (CUD) and healthy controls (HC) for similar personality traits and also examined whether functional magnetic resonance imaging (fMRI) could provide an intermediate neurobiological phenotype of gene-personality associations.
Methods: Participants were 55 CUD and 37 HC, who provided data for the following procedures: (A) genotyping for PENK (rs2609997), ascertained with whole blood samples; (B) the Multidimensional Personality Questionnaire (MPQ). Given prior studies, we were especially interested in the higher-order trait of Negative Emotionality (NEM) (akin to Neuroticism); (C) fMRI response to task error (error > correct) during an event-related color-word Stroop task (an inhibitory control/cognitive conflict task); and (D) basic demographics including race, which was covaried in the analyses. Dependent variables (personality and fMRI) were each analyzed as a function of PENK (subgrouped as in prior research: TT genotype versus any C-allele carriers) and Diagnosis (CUD versus HC). C-allele

carriers included 21 CUD and 15 HC; TT genotype included 34 CUD and 22 HC ($\chi 2 = 0.05$, $p > 0.8$). To test our hypothesis of an intermediate neural phenotype in the striatum, we also performed analyses of indirect effects (i.e., mediation analyses).

Results: For NEM, there was a main effect of Diagnosis [$F(1,87) = 16.96$, $p < 0.001$; CUD > HC] and a Diagnosis × PENK interaction [$F(1,87) = 6.20$, $p = 0.015$]. This interaction was explained by especially low NEM in HC with the lower-risk TT genotype, such that the CUD > HC effect was observed in this genotype ($p < 0.001$), but not in C-allele carriers ($p > 0.35$). Results of the fMRI data revealed that, although there were no Diagnosis or PENK effects on Stroop task behavior (errors or reaction time), there were significant Diagnosis × PENK interactions to error (p-corrected < 0.05) in the right putamen (peak: $x = 30$, $y = -4$, $z = -8$; $T = 3.85$) and left ventromedial prefrontal cortex (vmPFC) (peak: $x = -9$, $y = 53$, $z = -2$; $T = 3.31$). These interactions were both explained by increased error-related deactivations in CUD with the higher-risk PENK C-allele, but an opposite pattern of effects in HC (i.e., increased deactivations in the TT genotype). The extracted putamen, but not vmPFC, activity further correlated with NEM across all participants: the greater the putamen deactivations, the lower the NEM ($r = 0.29$, $p = 0.006$). In follow-up analyses, when the error-related putamen activity and the Diagnosis × PENK interaction (along with the constituent Diagnosis and PENK factors) were entered into a single regression to predict NEM, the putamen activity variable remained significant ($p = 0.002$), while the Diagnosis × PENK interaction was attenuated ($p > 0.17$) (indirect effect: Sobel's $Z = 2.32$, $p = 0.020$), indicating that the Diagnosis × PENK effect on NEM was fully mediated by putamen activation. Further analyses, conducted separately by PENK to determine the interaction source of the initial mediation, revealed that the indirect effect was significant in the C-allele carriers (Sobel's $Z = 2.17$, $p = 0.039$), but not in the TT genotype (Sobel's $Z = -0.83$, $p > 0.40$). Subsequent correlation analyses, conducted separately in the four Diagnosis × PENK groups, revealed that the only significant correlation between NEM and putamen emerged in HC C-allele carriers ($r = 0.57$, $p = 0.027$) (all others: $p > 0.08$).

Conclusions: These results suggest that PENK modulated NEM through error-related activity in the putamen, especially in the higher-risk C-allele carriers. In HC, this risk allele was associated with higher putamen- and vmPFC activity, possibly marking elevated responsiveness to error, with the former in turn associated with higher NEM. Since NEM is a risk factor for psychiatric and substance use disorders, future studies of at-risk youth could examine whether these results provide a possible pathway for the initiation of problematic behaviors and substance use in C-allele carriers. The heightened deactivation of putamen and vmPFC in CUD C-allele carriers remains to be further studied, but likely does not account for the overall elevated NEM reported by all CUD. Instead, heightened deactivation in this context could be marking a compensatory response that helps this (otherwise high-risk) CUD group maintain comparable task performance to the other groups.

Keywords: cocaine addiction, PENK polymorphism, opioid neurotransmission, fMRI/imaging genetics.

Disclosure: Nothing to Disclose.

M161. Cortico-Cerebellar Dysfunctions Associated with Visuomotor Abnormalities in Autism Spectrum Disorder Vary According to the Quality of Visual Feedback

Matthew Mosconi*, David Vaillancourt, John Sweeney

University of Texas Southwestern Medical Center, Dallas, Texas

Background: Sensorimotor impairments are present in the majority of individuals with autism spectrum disorder (ASD). We recently documented increased force variability during visually guided precision gripping in ASD that scaled with the gain of visual feedback. During this task, visual feedback information about the accuracy of motor responses is processed in visual and parietal cortices and relayed to cerebellum, where it is translated into a motor command that in turn is projected to primary motor cortex. Here, we used functional MRI (fMRI) to characterize cortical and cerebellar abnormalities underlying increased visuomotor variability in ASD, and to determine whether cortico-cerebellar alterations varied in relation to the gain of visual feedback.

Methods: Twenty individuals with ASD and 23 healthy controls matched on age, IQ and handedness performed an fMRI test of visually guided precision grip force. Participants completed three task conditions: rest, grip force with visual feedback, and visual feedback only. During the force with visual feedback condition, participants pressed with their thumb and index finger on a force transducer while viewing a white FORCE bar on a screen that moved upwards with increased force toward a fixed green TARGET bar. Participants were instructed to maintain the FORCE bar at the level of the TARGET bar which was set to 15% of each individual's maximum grip force. In the visual feedback condition, subjects simply viewed the FORCE bar moving as it did during the force with visual feedback condition. The cursor moved as a 1-Hz sine wave with a small amount of white noise added at each time point. Each condition lasted 26 s, and the sequence of conditions was repeated 3 times during each run. To assess the impact of changes in visual feedback on sustained force output and brain activation, separate runs were completed at three different visual gains. Visual gain was manipulated by varying the vertical distance the FORCE bar moved per Newton of grip force. Visual gain was increased by moving the FORCE bar a greater distance for every Newton of force generated.

Results: Subjects with ASD showed increased force variability that was most severe at the lowest and highest gain levels compared to the medium gain level. Mean force levels were not different between groups. To identify brain regions specifically involved in controlling motor output, we subtracted activations during the visual feedback condition from activations during the force with visual feedback condition. At low visual gain, individuals with ASD showed reduced activation in contralateral primary motor and premotor cortices, thalamus, bilateral anterior cerebellum (lobules I-III) and ipsilateral cerebellar lobules V/VI. At the medium level of visual gain, reduced activity in ASD was seen in primary motor cortex, inferior parietal lobule and middle occipital gyrus. Individuals with ASD showed increased activity in lingual gyrus and superior temporal gyrus. When visual feedback gain was high, individuals with ASD showed

increased activation in right cuneus and precuneus, supplementary motor area, middle frontal gyri, right superior temporal gyrus, and right superior parietal lobule.
Conclusions: Our behavioral results suggest that increased grip force variability in ASD is more profound when visual gain is either highly magnified or highly degraded. Findings from the fMRI analyses indicate that increases in force variability at high and low visual gains reflect different underlying cortico-cerebellar dysfunctions. During visuomotor control, visual information is translated from posterior parietal cortex to cerebellum. The cerebellum is critically involved in transforming this visual feedback information into precise motor commands sent to the thalamus and primary motor cortex. At low visual gain, individuals with ASD show reduced activation in parietal cortex, cerebellum, thalamus and primary motor cortex indicating that failure to minimize motor variability may reflect under-responsiveness throughout the visuomotor circuit. When visual gain was high, individuals with ASD showed over-activity of extrastriate and parietal cortices suggesting increases in motor variability may reflect hyperactivity during visual processing. The brain systems involved in controlling motor output and those involved in processing visual feedback information each appear.
Keywords: autism, cerebellum, sensorimotor.
Disclosure: Dr. David Vaillancourt consults to Great Lakes NeuroTechnologies. He is co-founder of Neuroimaging Solutions, LLC. Dr. Sweeney served on advisory boards for Roche, Takeda, BMS and Lilly.

M162. Fronto-Amygdalar Alterations During Emotional Face Processing May Differentiate Children with Bipolar Disorder from those with Major Depressive Disorder: A Functional Neuroimaging Meta-Analysis

Jorge Almeida*, Ezra Wegbreit, Grace Cushman, Alexandra Weissman, Kerri Kim, Angela Laird, Daniel Dickstein

Alpert Medical School, Brown University, Providence, Rhode Island

Background: Distinguishing bipolar disorder (BD) from major depressive disorder (MDD) is often complicated in our current nosology based exclusively on symptoms, potentially leading to inadequate treatment and poor outcome. This is particularly germane to children and adolescents, given that both BD and MDD often start in childhood and data suggesting that up to 35% of BD individuals take more than 10 years to receive a correct diagnosis. Thus, there is a pressing need to elucidate how the neurobiology of BD is different from MDD among youths. While emotion dysregulation has been implicated in both disorders, only one study has directly compared the neural correlates of facial emotion processing in BD and MDD children. To address this knowledge gap, we conducted activation likelihood estimation (ALE) meta-analysis to directly compare emotional face processing functional magnetic resonance imaging (fMRI) studies of youths with either BD or MDD to one another, while factoring in typical-development via healthy controls (HC) without psychopathology. We hypothesized that BD-youths would show greater convergence of amygdala hyperactivation and prefrontal cortex (PFC) hypoactivation compared to MDD-youths.
Methods: As in prior ALE studies, we began our meta-analysis with a PubMed search on July 17, 2014, for original task-related, coordinate-based fMRI articles investigating facial emotional processing. In total, 14 pediatric studies (age <18 year old, 7 MDD-youth, 6 BD-youth, and 1 comparing both) met inclusion criteria for our activation likelihood estimation (ALE) analyses. The final sample consisted of 122 youths with BD (46.2% females, mean age 15.1 years old), 114 youths with MDD (74.6% females, mean age 14.4 years old), and 124 HCs (53.2% females, mean age 14.2 years old). Coordinates of significant between-group differences between either BD or MDD and HC were extracted from each published study (i.e. hyperactivation: BD-youth $>$ HC-youth OR MDD-youth $>$ HC-youth; hypoactivation: HC-youth $>$ BD-youth OR HC-youth $>$ MDD-youth). Recent improvements in GingerALE software were used to conduct our ALE meta-analyses directly comparing the voxel-wise convergence of hyper- or hypoactivation findings in BD-youths vs. MDD-youths. False discovery rate at $p<0.05$ was used to correct for multiple comparisons.
Results: In total, 208 coordinates were extracted from the 14 pediatric fMRI studies involving emotional face processing. BD-youths showed significantly greater convergence of right parahippocampal gyrus and amygdala hyperactivation compared to MDD-youth (i.e. [BD-youth $>$ HC-youth]-[MDD-youth $>$ HC-youth]). BD-youth showed significantly less convergence of left precuneus hyperactivation compared to MDD-youth (i.e. [MDD-youth $>$ HC-youth]-[BD-youth $>$ HC-youth]). Furthermore, BD-youth demonstrated greater convergence of hypoactivation in the anterior cingulate cortex (BA32), right ventrolateral (BA47) and left dorsolateral (BA9) PFC compared to MDD-youth (i.e. [HC-youth $>$ BD-youth]-[HC-youth $>$ MDD-youth]).
Conclusions: Our data suggest that amygdala/parahippocampal hyperactivation and anterior cingulate and PFC hypoactivation during emotional face processing may significantly differentiate BD-youth from MDD-youth. Future studies directly comparing BD and MDD youth are required to further validate the differences between BD-youths and MDD-youth identified by our ALE meta-analysis and also to determine if they are useful as brain-based diagnostic or treatment markers of mood disorder. These studies could include either longitudinal neuroimaging studies of BD-youths as they become adults or discriminating MDD-youth that might convert to BD in later age.
Keywords: bipolar disorder, major depressive disorder, meta-analysis, neuroimaging.
Disclosure: Nothing to Disclose.

M163. Impact of Acute Aerobic Exercise on Cerebral Blood Flow in Adolescents with Bipolar Disorder

Benjamin Goldstein*, David Crane, Zahra Shirzadi, Antonette Scavone, Bradley MacIntosh

Sunnybrook Health Sciences Centre, Toronto, Canada

Background: Despite accumulating evidence regarding the psychiatric benefits of aerobic exercise, little is known

regarding the neurophysiology of acute bouts of aerobic exercise among people with mood disorders. Prevailing approaches to novel therapeutics increasingly emphasize mechanisms of action and the use of an intervention as both a treatment and a physiologic probe. This study therefore examines the impact of a single bout of acute aerobic exercise, which is relevant to mood and cognition, on cerebral hemodynamics in adolescents with bipolar disorder (BD) using magnetic resonance imaging (MRI) approaches.

Methods: Participants were 28 adolescents (17 ± 1.5 years of age, 10 female) with BD. Cerebral blood flow (CBF) magnetic resonance images (MRI; 3 Tesla) were acquired using arterial spin labeling before and at 15 and 45 minutes after a single 20-minute bout of recumbent cycling. Body mass index (BMI) and endothelial function, via reactive hyperemia index (RHI), were examined as potential predictors of CBF. Cerebral venous oxygenation of the sagital sinus, a global hemodynamic measure, was included to corroborate the regional CBF analysis. CBF changes were assessed in six regions of interest (ROI), as well as voxel-wise throughout the brain.

Results: CBF decreased significantly in frontal, parietal, caudate and putamen at 15 or 45 minutes post- vs. pre-exercise ($p < 0.05$, false discovery rate-corrected). Voxel wise analysis yielded significant clusters in the precuneus, angular gyrus, lateral occipital cortex, middle cingulate and paracingulate regions and middle frontal gyrus (corrected-$p = 0.05$). Cerebral venous oxygenation decreased significantly following exercise ($68.3 \pm 3.7\%$ pre-exercise vs. $66.6 \pm 3.5\%$ post-exercise; $t = 2.02$, $p = 0.03$). Pre-exercise and exercise-related changes in CBF in the paracingulate cortex were significantly correlated with pre-exercise RHI and BMI, respectively ($t = -2.3$, $p = 0.03$; $t = -2.5$, $p = 0.019$, respectively).

Conclusions: Adolescents with BD showed decreased CBF in areas relevant to executive function after a single bout of recumbent cycling. This study demonstrates that aerobic exercise alters CBF over a short time scale and that obesity may mitigate acute exercise related CBF changes. These findings inform our understanding regarding a putative mechanism of action of aerobic exercise, and highlight a readily measured moderator that may be incorporated in future studies on this topic.

Keywords: bipolar, aerobic, vascular, adolescent.
Disclosure: Nothing to Disclose.

M164. Network of Regions Showing Stronger Connectivity During Emotion (versus identify) Working Memory Correlate with Antidepressant Response to Scopolamine

Carlos Zarate*, Allison Nugent, Jessica Ellis, Maura Furey

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: Previously, we showed that pre-treatment levels of BOLD signal in bilateral middle occipital cortex (MOC) correlated with the magnitude of subsequent clinical response to the rapid antidepressant scopolamine. The correlation was specific to BOLD signal obtained during a working memory (WM) task when attending to face emotion, with no correlation associated with attending to face identify. Here we use MOC as a seed region to investigate differences in strength of whole brain connectivity between these two WM conditions in patients with major depressive disorder (MDD), and to assess the correlation between the difference in BOLD response between WM task conditions throughout the brain with subsequent treatment response to scopolamine.

Methods: Unmedicated patients with MDD ($n = 13$) participated in an fMRI study and performed the two versions of the WM task. For each trial an image of a face was presented, followed by a 15 sec delay, followed by a second face. Subjects were instructed to attend to either face identify (I) or emotion (E) and perform a matching task. Blocks of trials alternated between E and I conditions, and were separated by 20 sec periods of fixation. BOLD signal was measured using echo planar imaging in a GE 3T scanner ($TE = 23$, $TR = 2.5$, slices $= 35$). Following scanning, patients participated in a randomized, double-blind, placebo-controlled clinical trial with scopolamine (0.4μg/kg iv infusions). Depression severity was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) prior to and after treatment with scopolamine, and treatment response was reflected by the change in MADRS score. Scans were preprocessed using AFNI and 3dDeconvolve was used to conduct multiple linear regression. The regression weights for the polynomial baseline and motion regressors were extracted, and these effects were subtracted from the raw dataset. The mean ROI time series encompassing bilateral MOC was extracted, and a psychophysiological interaction (PPI) analysis was carried out. The response in the ROI was then deconvolved with a model hemodynamic response function (HRF) to produce the neural response. Finally, the multiple linear regression was repeated with three additional regressors: the ROI time series, the Block regressor, and the ROI*Block interaction time series. The beta weight for the interaction regressor for each subject was entered into a group analysis. A one-sample t-test was used to identify regions where the interaction was significant (voxel $p < 0.005$, whole brain FDR corrected at $p < 0.05$). A correlation analysis also was conducted ($n = 12$) using the beta coefficient from the Block regressor (reflecting that magnitude of difference in BOLD signal in the two task conditions) and treatment response to scopolamine (voxel $p < 0.005$, whole brain FDR corrected at $p < 0.05$).

Results: A network of regions was identified that showed increased connectivity with the MOC during the emotion relative to the identify task, including anterior and posterior cingulate cortex, bilateral insular cortex, and regions of parietal and temporal cortices. The magnitude of difference in the BOLD signal between the emotion and identify conditions correlated negatively with the magnitude of subsequent antidepressant response to scopolamine in many of the same regions, including anterior and posterior cingulate cortex, and bilateral insula.

Conclusions: These findings identify an extensive network of brain regions retaining stronger connectivity with the MOC during emotion processing than during identify processing in patients with mood disorders, and suggest that connectivity is modulated in these areas based on the

attended facial feature during WM. Importantly, those patients with the smallest difference in BOLD response to the identity and emotion task conditions show the largest clinical improvement following scopolamine administration in areas that overlapped with those identified in the connectivity analysis. This suggests that regions where pretreatment activity reflects the potential to respond to scopolamine also show differences in the strength of connectivity with other task-relevant brain regions.
Keywords: Scopolamine, Imaging, Response, Connectivity.
Disclosure: The NIMH has filed a use-patent for the use of scopolamine in the treatment of depression, and Dr. Furey is identified as a co-inventor on this pending patent application in the US and an existing patent in Europe. Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine in depression. Dr. Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government.

M165. Should Antipsychotic Dose Be Decreased in Older Patients with Schizophrenia? Lessons from a Longitudinal Clinical PET Study

Ariel Graff*, Tarek Rajji, Mulsant Benoit, Nakajima Shinichiro, Caravaggio Fernando, Suzuki Takefumi, Uchida Hiroyuki, Gerretsen Philip, Pollock Bruce, Mamo David

Centre for Addiction and Mental Health, Toronto, Canada

Background: Patients with schizophrenia are aging. Reports suggest that older patients with schizophrenia will double by 2030 to equal the population of younger ones. Positron Emission Tomography (PET) studies in younger patients with schizophrenia have established that striatal dopamine D2/3 receptors (D2/3R) occupancy by antipsychotics between 65% and 80% is a safe therapeutic window, which has been successfully employed in predicting the clinically effective doses for antipsychotics in younger patients. Aging is associated with various peripheral and brain pharmacodynamic and pharmacokinetic changes that include decreases in the absolute number of dopaminergic neurons and in the density of D2/3R in the brain. Based on these age-related changes, consensus clinical guidelines recommend the use of lower doses of antipsychotics in patients with LLS. However, there is not empirical data available on age-specific antipsychotic dosing. Therefore, the aim of the current longitudinal study was to establish a clinically effective therapeutic window of antipsychotic occupancy at striatal dopamine D2/3R in LLS.
Methods: The current open-label prospective PET study included stable outpatients with schizophrenia (the Positive and Negative Syndrome Scale (PANSS) scores $\leq$ 3 for positive symptoms), at the age of 50 years or older, treated on the same dose of oral olanzapine or risperidone for at least 6 months. Each patient was scanned with [11C]-raclopride before and after antipsychotic's dose reduction. The patients had a gradual dose reduction of up to 40% of the baseline dose to a target dose not lower than the recommended minimal maintenance dose for olanzapine (7.5 mg/day) or risperidone (1.5 mg/day). Patients were clinically followed up for at least three months after the dose reduction was completed. Clinical data was analyzed using Generalized Estimation Equation for repeated measures. Linear or Poisson regression was used for continuous or discrete variables, respectively. Multiple comparisons were conducted with Bonferroni correction. The patient's D2/3R occupancies were estimated using age and gender corrected measures of binding potential nondisplaceable from 53 healthy controls as antipsychotic free condition.
Results: The sample included 35 patients (age = 60 ± 7 years and the BPRS total score of 42 ± 9) and 53 controls. D2/3R occupancy of the entire sample decreased by 7% after the dose reduction (67.6 ± 11.4% to 61.1 ± 11.0%). The lowest D2/3R occupancy associated with clinical stability was 45%. Extrapyramidal symptoms were more likely shown with D2/3R occupancies higher than 60%. The baseline D2/3R occupancies were lower in those with clinical deterioration (N = 5) than those that remained stable (N = 29) (55.4 ± 13.1% vs. 69.7 ± 9.9%, p = .03), and those with clinical deterioration did not experience extrapyramidal symptoms before or after dose reduction. The D2/3 occupancies after dose reduction were not different between both groups (51.1 ± 18.6 [37.4-72.3] % vs. 63.1 ± 9.2 [48.3-76.6] %). Following dose reduction, total scores for the PANSS (p = .02), Brief Psychiatric Rating Scale (p = .02), Simpson Angus Scale (p < .001), Barnes Rating Scale for Drug-Induced Akathisia (p = .03), Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (p < .001), and serum prolactin levels decreased (p < .001).
Conclusions: Our study indicates that antipsychotic dose reduction is feasible in clinically stable patients with LLS. The decrease in the D2/3R occupancy was associated with an improvement in side effects, including extrapyramidal symptoms, akathisia and hyperprolactinemia, and an unexpected reduction in clinical symptoms (PANSS and BPRS). The results suggest that the lower limit of the therapeutic D2/3R occupancy window may be lower in patients with LLS (~45%) than previously reported in younger patients (i.e. 65%). The number of patients with clinical deterioration (14%) was within the range shown in previous antipsychotic dose reduction studies in younger patients (6-16%). Our study was restricted for safety to the lowest recommended maintenance dose for olanzapine and risperidone. Further research is required with lower antipsychotic doses to establish a 'true' lower limit of the therapeutic D2/3R occupancy window with a large sample and longer follow up.
Keywords: schizophrenia, elderly, PET, dopamine.
Disclosure: Nothing to Disclose.

M166. Connectivity-based Parcellation of the Striatum in Schizophrenia Using Diffusion Weighted Imaging (DWI)

James Levitt*, Yogesh Rathi, Tammy Raviv, Robert McCarley, Martha Shenton

Harvard/VA Boston Healthcare System, Brockton, Massachusetts

Background: Frontostriatal white matter connectivity may be disrupted in schizophrenia. The striatum and frontal cortex can

be divided into limbic (L), associative (DLPFC (A1); VLPFC (A2)) and sensorimotor (SM) functional subregions, which are connected via corticostriatal white matter tracts. We hypothesized fewer connections in schizophrenia, in particular, in limbic and associative frontostriatal pathways.
Methods: We used MR DTI 2-tensor tractography to calculate frontostriatal pathway fiber counts between the cortex and striatum in 27 chronic SZs and 26 matched healthy controls (HCs). We employed a connectivity-based (CB) parcellation strategy to label surface voxels on the striatum based upon the relative proportion of inputs from the functional cortical ROIs described above. The dominant input voxels (L, A1, A2, SM) were required to receive 0.7 of their fiber counts from a single functional cortical zone; voxels receiving inputs under this threshold from a single functional cortical zone were labeled mixed (MX). We tested for group differences in number of surface voxels labeled as above.
Results: A repeated measures ANOVA with group as 'between-subjects' factor and hemisphere (left hemisphere (LH), right hemisphere (RH)) and region (L, A1, A2, SM, MX) as 'within-subjects' factors showed a main effect for group ($F(1,51) = 4.24$; $p = 0.045$), but no significant interactions. Follow-up t-tests revealed fewer LH mixed voxels in SZ subjects compared with NCs ($256.9 + 109.0$ vs $336.7 + 98.6$ voxels; $t(51) = 2.79$; $p = 0.007$), but not RH mixed voxels ($403.7 + 162.0$ vs $473.5 + 225.0$ voxels; $t(51) = 1.30$; $p = 0.2$). Results were similar when we used 0.5 and 0.9 as threshold cut-offs.
Conclusions: These results show that striatal surface volumes when defined by frontostriatal CB DWI, in contrast to being defined on the basis of anatomic landmarks, are smaller in SZ subjects compared with HCs. The mixed voxel group difference is of particular interest as such voxels may have integrative functions.
Keywords: Striatum, Diffusion Weighted Imaging, Connectivity-Based Parcellation, Schizophrenia.
Disclosure: Nothing to Disclose.

M167. Common and Unique Contributions of Depression and Conduct Symptoms to the Brain's Response to Faces in Adolescent Girls

Artha Gillis*, Kristina Gelardi, Erika Forbes, Alison E. Hipwell, Kathryn E. Keenan, Amanda E. Guyer

University of California Los Angeles, Los Angeles, California

Background: Conduct disorder (CD) is common in the clinical pediatric population (American Psychiatric Association, 2000). Depending on the definition, diagnostic criteria and sample source, approximately 3-5% of pre-adolescent boys and 6-8% of adolescent boys meet criteria for this disorder (Frick, 2006; Loeber, 2000). Hipwell et al., found that 0.5-2.8% of pre-adolescent girls and 4.9-8.9% of adolescent girls met criteria for CD in a community sample (Hipwell, 2002; Keenan, 2010). Internalizing disorders, such as depression and anxiety, are commonly comorbid with CD (Loeber, 1994; Berkout, 2011). The high rate of comorbid depression and CD in girls is particularly concerning due to the elevated risk of suicidal behavior in girls with comorbid CD and depression (Keenan, 1999). Little is known about the neural pathophysiology of CD in girls, particularly in conjunction with internalizing disorders. A review of the neuroimaging literature reveals only a few functional MRI studies examining affective neurocircuitry of children and adolescents with CD. Most studies examine boys exclusively.
Methods: Participants were drawn from the Pittsburgh Girls Study (PGS), a longitudinal study examining the development of conduct problems, depression and comorbid conditions in an urban sample of 2,451 girls, ages 5-8 (in wave 1). The PGS sample was recruited from an enumeration of 103,238 Pittsburgh households, with an oversampling of the poorest city neighborhoods (see Keenan et al., 2010 for details). Girls who screened high for depression at age 8 along with a random selection from the remaining PGS sample were included in the Pittsburgh Girls Study-Emotions (PGS-E) substudy (see Keenan et al, 2010 for details). At ages 16-17, girls underwent fMRI and performed a facial emotion encoding task while in the scanner. The Adolescent Symptom Inventory-4th edition (ASI-4; Gadow & Sprakin, 1994/1997) was also administered at ages 16-17. The current study includes fMRI and task data for 92 girls. 64% of the sample is African American, 28% is Caucasian, and 8% is multi-racial. 42% of families had past public assistance (at ages 11-12). Measures: Depressed mood and conduct symptoms were assessed using the ASI-4, which evaluates the severity of clinical symptoms consistent with DSM-IV criteria (American Psychiatric Association, 1994), scored on 4-point scales (0 = never to 3 = very often). Good psychometric properties have been reported. The Facial Emotion Encoding Task included 48 faces (12 happy, 12 sad, 12 angry, 12 neutral) that cycled through three runs of four 10-trial blocks during which participants rated faces according to two instructions. Participants were asked to rate the sadness they felt, and separately to rate the width of the nose, when viewing each face using a Likert scale ranging from 0 (not at all) to 5 (very much so). Accuracy and reaction times (RT) were recorded for the rating of each face. Analyses: Analysis of behavioral data was performed using descriptive statistics and the general linear model in SPSS v21. fMRI data was pre-processed and analyzed using SPM8 for differences in brain activation for increasing levels of depression symptoms, increasing levels of conduct symptoms, presence of comorbid conduct and depression symptoms and absence of any conduct symptoms or depression symptoms.
Results: Diagnostic data: By child report, participants reported a mean of 1.03 (SD 1.53) depressive symptoms and a mean of 0.27 (SD 0.87) conduct symptoms on the ASI-4. There were 40 girls who reported experiencing any symptoms of depression, 11 girls who reported experiencing any conduct symptoms and 8 girls who reported experiencing comorbid depressive and conduct symptoms, at ages 16-17. There were 36 girls who reported never experiencing depressive or conduct symptoms by ages 16-17. Behavioral results: For the entire sample, RT varied across emotion for experience of sadness ($F3, 267 = 99.50$, $p < 0.001$). Ratings of subjective sadness were highest when viewing sad faces (mean = 2.64, SD = 1.09) and lowest when viewing happy faces (mean = 1.31, SD = 0.53). Imaging results: In a whole brain analysis, using a minimum cluster size of thirty voxels, increasing levels of depressive symptoms, presence

of comorbid conduct and depressive symptoms and absence of any conduct and depressive symptoms were associated with activation in the (R) midcingulate (x = 18, y = -20, z = 42) and the (R) inferior parietal lobule (x = 50, y = -50, z = 48) when attending to sadness in happy faces (v. neutral faces). In contrast, increasing levels of conduct symptoms were not associated with activation in these areas. Instead, increasing levels of conduct symptoms were associated with activation in the (R) superior frontal lobule (x = 22, y = 26, z = 34). When attending to sadness in angry faces (v. neutral faces), increasing levels of depressive symptoms, increasing levels of conduct symptoms and presence of comorbid depressive and conduct symptoms were associated with activation in the (R) midcingulate (x = 2, y = 14, z = 32). Presence of comorbid symptoms was also associated with activation in the (R) anterior cingulate (x = 2, y = 22, z = 24). All conditions were associated with activation in the (L) hippocampus. When attending to sadness in sad faces (v. neutral faces), all conditions were associated with activation in the (R) inferior parietal lobule (x = 52, y = -52, z = 44), (L) medial frontal gyrus (x = -6, y = 30, z = 42) and the (R) superior temporal gyrus (x = 46, y = -54, z = 18). During each of these tasks, the key areas of (hypo) activation when assessing nose width (i.e., a non-affective task) appeared to be distinct from the key areas of activation during the facial emotion coding tasks.

Conclusions: Increasing levels of conduct symptoms may alter attention to one's feelings of sadness when viewing happy faces. Increasing conduct symptoms was associated with activation of cognitive areas of the brain, whereas increasing depressive symptoms, comorbid depressive and conduct symptoms and absence of any conduct and depressive symptoms were associated with activation of the affective areas of the brain when attending to one's feelings of sadness in happy faces. Increasing levels of depressive symptoms and increasing levels of conduct symptoms may alter attention to one's feelings of sadness when viewing angry faces. Regardless of the presence or level of symptomatology, the (L) hippocampus played a role in attention to sadness when viewing angry faces. The attention to one's feelings of sadness when viewing sad faces resulted in similar activations across conditions. For each emotion, activation when attending to sadness appears to be distinct from activation when attending to a non-emotional aspect of facial emotion processing.

Keywords: functional magnetic resonance imaging, affective neuroscience, facial emotional processing, adolescents.
Disclosure: Nothing to Disclose.

M168. Cortical Serotonin Change and Amygdala Reactivity to Aversive Emotion Processing in Humans: An Intravenous Citalopram and Combined 5-HT1A [11C]CUMI-101 PET and fMRI Study

Sudhakar Selvaraj*, Elias Mouchlianitis, Danilo Arnone, Philip Cowen, Oliver Howes, Jonathan Roiser

University of Texas Health Science Center at Houston, Houston, Texas

Background: Acute selective serotonin reuptake inhibitor (SSRI) administration is associated with altered behavioral responses – specifically enhanced startle responses and fear recognition (1, 2). Intravenous citalopram has been shown to increase amygdala reactivity to aversive emotions in a functional magnetic resonance imaging (FMRI) paradigm (3). In a previous Positron Emission Tomography (PET) displacement study using novel 5-HT1A receptor tracer [11C]-CUMI-101, we reported that citalopram (a commonly used SSRI) 10 mg intravenous infusion when compared to saline infusion increased the [11C]-CUMI-101 availability in the postsynaptic cortical areas in healthy volunteers (4). Based on evidence from animal literature, we interpreted that acute systemic administration of citalopram decreased 5-HT cell firing by its action on dorsal raphe nucleus (DRN) 5-HT1A autoreceptors and therefore the increase in cortical [11C]-CUMI-101 could be attributable to a decrease in endogenous 5-HT availability in cortical terminal regions. To investigate how acute SSRI increases fear potentiation effect in humans, we recruited the same subjects that took part in the [11C]-CUMI-101 study and investigated the effect of citalopram infusion on a well-known aversive emotion face processing task (5). The protocol of the fMRI study was designed to reproduce the PET investigation as accurately as possible. We hypothesized that the citalopram induced change in the cortical regions measured in the [11C]CUMI-101 study would correlate in this fMRI experiment with citalopram induced amygdala BOLD signal change to fear vs neutral faces.

Methods: The protocol of this experiment reproduced the [11C]-CUMI PET study (4) apart from the fMRI component; thirteen healthy men (mean age (SD) 47.95 ± 9.2 years), (10 were from the [11C]-CUMI PET study) were recruited and pseudo-randomised to receive either normal saline infusion or an intravenous infusion of citalopram of 10mg over 30 minutes in a single-blinded, random order cross-over design. There was at least a gap of one week between the scans. On each occasion, after receiving the infusion, participants underwent a face emotion processing task in the scanner. This incidental task with a block design featured happy, sad and neutral faces known to activate the amygdala (5).

Results: All faces vs baseline contrast revealed activation in a number of regions including a significant left amygdala activation (MNI coordinates: [x = −24 y = −4 z = −7], Z = 4.31, P < 0.001, small volume family-wise-error corrected). This indicated that the task reliably activated the amygdala as expected irrespective of emotional valence. After extracting contrast estimates from this voxel, we found that citalopram increased amygdala response to fearful (relative to neutral) faces, which approached significance level (N = 13; placebo mean (SD) -0.20 (0.72); Citalopram mean (SD) 0.59 (1.06); t(12) = 2.02, p = 0.06). Neural activity measured in the same voxel in the left amygdala response to fearful (relative to neutral) faces at this voxel was negatively correlated with citalopram induced cortical [11C]CUMI-101 change (N = 10; r = −0.70, r2 = −0.49, P < 0.02). This effect was emotion-specific to fearful faces as there was no other similar correlation in response to happy vs. neutral faces (p > 0.1). No significant relationship between amygdala responses to fearful or happy (relative to neutral) faces and change in DRN or amygdala availability (p > 0.1).

Conclusions: Single intravenous administration of citalopram likely decreases the dorsal raphe cell firing and thereby reduces 5-HT release in the cortical regions. Although speculative, our findings suggests that citalopram might modulate cortical 5-HT levels (i.e. higher [11C]CUMI-101 response to citalopram) leading to the measured changes in amygdala neural activity in responses to fearful facial stimuli. Further research in major depression might help clarify the contribution of this mechanism to the increase in anxiety levels reported by some patients after initiation of antidepressant treatment. Reference: 1. Browning M, Reid C, Cowen PJ, Goodwin GM, Harmer CJ (2007). J Psychopharmacol. 21:684-690. 2. Burghardt NS, Sullivan GM, McEwen BS, Gorman JM, LeDoux JE (2004). Biol Psychiatry. 55:1171-1178. 3. Bigos KL, Pollock BG, Aizenstein HJ, Fisher PM, Bies RR, Hariri AR (2008). Neuropsychopharmacology. 33:3221-3225. 4. Selvaraj S, Turkheimer F, Rosso L, Faulkner P, Mouchlianitis E, Roiser JP, et al. (2012): Mol Psychiatry. 17:1254-1260. 5. Selvaraj S, Mouchlianitis E, Faulkner P, Turkheimer F, Cowen PJ, Roiser JP, et al. (2014): Biol Psychiatry.
Keywords: Serotonin, citalopram, amygdala, emotion processing.
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M169. Serotonergic Modulation of Default Mode Network Functional Connectivity with Superior Premotor and Somatosensory Cortical Areas in Children and Adolescents with ADHD and Healthy Controls

Caroline Biskup*, Katrin Helmbold, David Baurmann, Martin Klasen, Beate Herpertz-Dahlmann, Tilman J. Gaber, Sarah Bubenzer-Busch, Gereon R. Fink, Florian D. Zepf

RWTH Aachen, Aachen, Germany

Background: The default mode network (DMN) as assessed via functional magnetic resonance imaging (fMRI) describes an interaction of brain regions that are active during random episodic silent thought (REST) in healthy humans, and that are less active during task performance (''task deactivation''). Alterations of the DMN have been described in patients with different neuropsychiatric disorders including psychotic disorders, depressive disorders and attention deficit hyperactivity disorder (ADHD). The neurotransmitter serotonin (5-HT) in particular has been suggested to influence the DMN. However, the effect of a reduced central nervous 5-HT synthesis on DMN connectivity with different brain regions in young patients with ADHD has not yet been investigated. Acute tryptophan depletion (ATD) is a neurodietary method of challenging the central nervous 5-HT system by ingesting a mixture of amino acids (AAs) lacking tryptophan (TRP), the physiological precursor AA of 5-HT. The administered AAs compete with endogenous TRP on the uptake into the central nervous system at the blood-brain-barrier, thus leading to decreased substrate availability for central nervous 5-HT synthesis, which in turn is diminished for a short period. The present work aimed to study the effects of a short-term reduction in central nervous 5-HT synthesis by means of ATD on fMRI-based resting state functional connectivity (FC) between the DMN and different brain regions in children and adolescents with ADHD and healthy controls of the same age group.
Methods: Young male patients (aged 12-17 years) with ADHD ($N = 12$) and healthy controls ($N = 10$) of the same age group were subjected to an ATD challenge and subsequently diminished central nervous 5-HT synthesis and a balanced amino acid load (BAL) serving as a control condition using a randomized double-blind within-subject repeated measures crossover-design. Approximately three hours after challenge intake (ATD/BAL) resting state fMRI scans were obtained (3 Tesla).
Results: In healthy controls, after ATD administration FC of the right superior premotor cortex (Brodmann area 6) with the DMN was increased, and this relationship was the opposite in patients with ADHD as indexed by a highly significant group-by-challenge interaction. Moreover, there was a highly significant main effect of challenge administration on FC of the left superior somatosensory cortex (Brodmann area 3) with the DMN as well as a highly significant group-by-challenge interaction. The main effect of challenge administration was driven by lowered z-values after ATD intake in both groups, but was more pronounced in controls. After BAL administration in the patient group lower FC of the left superior somatosensory cortex with the DMN was detected when compared to controls.
Conclusions: Increased FC of the right superior premotor cortex with the DMN after administration of the ATD challenge was found in healthy subjects, suggesting a serotonergic modulation of this particular area relevant for motor planning function with regard to the DMN. However, in patients with ADHD the ATD challenge led to attenuated FC of the right superior premotor cortex with the DMN, which could be relevant regarding changes in neural planning capacity for motor activity in these particular patients. ATD lowered FC of the left superior somatosensory cortex with the DMN independently of the factor group but with stronger effects in controls. Overall, with patients with ADHD showing lower FC of the left superior somatosensory cortex with the DMN after BAL administration the present pilot data could point towards an altered serotonergic modulation of FC of the DMN with this particular brain area in patients with ADHD. These results are in line with altered sensory perception in patients with ADHD as described by previous clinical research, and could hint towards an altered serotonergic modulation in these patients.
Keywords: Serotonin, ADHD, Resting state, Children and Adolescents.

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M170. Neural Correlates of Inhibitory Control in Youth at Risk for Depression

Margaret Benningfield*, Justin Theiss, Jennifer Blackford, Uma Rao

Vanderbilt University, Nashville, Tennessee

Background: Youth with major depressive disorder (MDD) show deficits in executive function tasks, including sustained and selective attention, working memory, decision-making, cognitive flexibility and motor response inhibition. Neuroimaging studies of adult patients with MDD have found abnormalities in frontostriatal, cingulate and temporal brain regions that underlie motivation and affect regulation, but also play a crucial role in cognitive control functions. However, there is minimal information on the neural correlates of cognitive control functions in pediatric MDD. An important question that is yet to be addressed is whether any neural alterations related to MDD may be evident even before the manifestation of clinical symptoms in individuals at high-risk for the illness due to family history. To address these questions, we compared brain activation in youth at high risk for depression with healthy and depressed youth while performing an inhibitory control task.

Methods: Forty-three adolescents aged 12 to 20 years completed a rapid event-related Go/No-Go task during an fMRI scan. Healthy controls ($n = 11$, mean age 14.7 ± 2.33) had no personal or family history of psychiatric illness. Youth with depression ($n = 11$, mean age 17 ± 2.67) met diagnostic criteria for current MDD episode. Youth at high-risk for depression ($n = 21$, mean age 15.2 ± 2.50) had no lifetime history of a psychiatric disorder but were at high familial risk for MDD, with at least one parent with a history of MDD. To test for group differences in BOLD activation during failed inhibitory control, we performed a whole brain analysis using a 3 (group: control, high-risk, depressed) by 2 (condition: correct go, commission error) ANOVA with voxel-wise $p < .001$, corrected to $p < .05$ using cluster extent threshold.

Results: The groups did not differ significantly with respect to age, sex, race, response time, or accuracy. BOLD signal differed significantly among groups in a large network of regions including medial prefrontal cortex, dorsal anterior cingulate cortex (ACC), rostral ACC, sub-genual ACC, inferior frontal gyrus, amygdala, cerebellum, and visual cortex. Post-hoc tests revealed that youth with depression had greater BOLD activation in each of these regions than high-risk youth and healthy controls.

Conclusions: The results indicated greater activation in brain regions associated with conflict monitoring and inhibitory control in depressed youth compared to high-risk and healthy youth. They are congruent with findings from a meta-analysis of motor response inhibition using Go/No-Go tasks which showed that right-lateralized regions including the inferior/medial frontal gyri were recruited under conditions of increased working memory demand. The observed differences in brain activation patterns between depressed and high-risk groups suggest that the differences in brain activation may be state-dependent rather than trait-like/vulnerability markers for depression.

Keywords: Major Depressive Disorder, Vulnerability, Adolescent, fMRI.

Disclosure: Nothing to Disclose.

M171. Deficits in Hippocampal Habituation Predict Social Deficits in Schizophrenia

Jennifer Blackford*, Lisa Williams, Stephan Heckers

Vanderbilt University Medical Center, Nashville, Tennessee

Background: Social deficits are prominent in schizophrenia and cause substantial impairment. Considerable research implicates hippocampal alterations in the pathophysiology of schizophrenia; for example, patients with schizophrenia show hippocampal hyperactivity and memory deficits. We propose that an underlying mechanism of both hippocampal hyperactivity and memory deficits is a failure of a fundamental learning process—habituation. In this study we tested the hypothesis that deficits in hippocampal habituation to social stimuli underlie increased hippocampal activation and memory deficits, and contribute to social impairment.

Methods: Hippocampal habituation was examined in patients with schizophrenia (n = 21) and healthy controls (n = 20). Functional magnetic resonance imaging (fMRI) was used to measure decreases in BOLD signal to a repeated neutral face and a repeated neutral object. Effects of gender (subject gender x stimulus gender) were examined and correlations between habituation, memory, and negative symptoms were performed.
Results: Patients with schizophrenia failed to show the hippocampal habituation to neutral faces that was present in healthy controls (significant clusters in bilateral posterior hippocampi, FWE corrected $p < .05$). Interestingly, this deficit was specific to social stimuli and was moderated by the match between stimulus x subject gender (significant clusters in bilateral anterior and posterior hippocampi, FWE corrected $p < .05$). When viewing same-gender faces, patients showed consistent activation across repeated presentations (habituation failure). However, when viewing opposite-gender faces, patients showed increased activation over time, or sensitization. Across all participants, faster hippocampal habituation correlated with better memory. Within patients, faster hippocampal habituation correlated with lower social withdrawal. ($p < .05$).
Conclusions: These results provide evidence that a failure of hippocampal habituation underlies schizophrenia. Importantly, habituation deficits were specific to social stimuli, moderated by stimulus gender, and associated with social functioning. Thus, habituation deficits do not reflect alterations in basic neuronal processes, but instead are dependent on complex social information. These findings further our understanding of the pathophysiology of schizophrenia and suggest novel targets for treatment.
Keywords: schizophrenia, habituation, social impairment, memory.
Disclosure: Nothing to Disclose.

M172. Childhood Poverty Predicts Adult Amygdala-Frontal Reactivity and Connectivity to Emotional Faces

Arash Javanbakht*, Anthony King, Luan Phan, Gary Evans, James Swain, Mike Angstadt, Israel Liberzon

University of Michigan Medical School, Ypsilanti, Michigan

Background: Childhood poverty negatively impacts physical and mental health in adulthood. Altered brain development in response to social and environmental factors associated with poverty likely contributes to this effect, engendering maladaptive patterns of social attribution and/or elevated physiological stress.
Methods: In this fMRI study, we examined childhood poverty and neural processing of social signals (i.e., emotional faces) in adulthood, using 53 subjects from a longitudinal prospective study recruited as children and studied at 23-25 years of age using the Emotional Faces Assessement Task (EFAT).
Results: Childhood poverty, independent of concurrent adult income, was associated with higher amygdala, medial prefrontal, and rostral anterior cingulate cortex responses to negative than to happy faces. Also, the connectivity between left amygdala and medial prefrontal cortex (angry minus happy faces contrast), was positively correlated with childhood socioeconomic status.
Conclusions: This study is among the first prospective analyses of objective childhood poverty and emotional processing, suggesting a neural mechanism underlying negative social-emotional bias. Adults who grew up poor appear to be more sensitive to social threat cues and less sensitive to positive social cues.
Keywords: poverty, neurocircuitry, amygdala, emotion.
Disclosure: Nothing to Disclose.

M173. Large Scale Brain Network Abnormalities in Unmedicated Patients with Schizophrenia and Response to Antipsychotic Treatment

Nina Kraguljac*, David White, Jennifer Hadley, Adrienne Lahti

University of Alabama at Birmingham, Birmingham, Alabama

Background: Few attempts have been made to effects of antipsychotic medication in characterize large scale functional brain networks, assessed by resting state functional MRI (fMRI), despite evidence suggesting that functional networks are sensitive to dopaminergic neuromodulation.
Methods: 34 subjects with schizophrenia who had been off antipsychotic medications for at least two weeks and 34 matched healthy controls participated in this study. Imaging was performed on a 3T Siemens/Allegra scanner. Resting state scans were obtained at baseline, after one week, and after six weeks of treatment with risperidone. The resting state scan was acquired during a five-minute gradient recalled EPI sequence. Preprocessing included slice time correction and realignment, normalization, and smoothing using DARTEL. Nuisance regressors included the six motion parameters, and components of white matter and CSF explaining 90% of signal variance identified using a principal component analysis. Following preprocessing and motion scrubbing, statistical parametric maps of four functional networks were created. Spherical seeds with 6mm radius were placed at the following MNI coordinates to define networks: (1) 1/-55/17 for the default mode network, (2) -42/34/20 and 44/36/20 for the executive control network, (3) -32/26/-14 and 38/22/-10 for the salience network, and (4) +/-25/-53/52 and 25/-57/52 for the dorsal attention network. The first eigenvariate of the BOLD time series from each region was extracted and correlated to the time series of all other voxels to produce a functional connectivity map. Maps were converted to normally distributed values using Fisher's r-to-Z transform. For networks with bilateral seeds, these were averaged to form a single connectivity map of each network. Group-level connectivity maps were obtained by performing one-sample t-tests on each group's participant-level connectivity maps. Connectivity group differences were assessed with two-sample t-tests on the groups' participant-level connectivity maps, change over time was assessed with paired sample t-tests on the groups' participant-level connectivity maps. To assess the relationship between connectivity abnormalities and symptom burden at baseline in patients with schizophrenia, we used a general linear model that

included BPRS total scores and one that included RBANS total scores. Treatment response was defined as percent change of positive symptoms between baseline and week 6. Analyses were corrected for multiple comparisons using the false disc.
Results: Patients with schizophrenia and controls did not differ in demographics. In unmedicated patients compared to controls we found increased resting state functional connectivity in the executive control network, salience network, and dorsal attention network, but no connectivity abnormalities were observed in the default mode network. Over the course of treatment, resting state connectivity attenuated only in the dorsal attention network. Baseline connectivity strength in the dorsal attention network was predictive of response to antipsychotic medication after six weeks of treatment.
Conclusions: Our findings are consistent with the concept of schizophrenia as a disorder of brain network organization and indicate that both connectivity abnormalities and effects of antipsychotic medications on connectivity vary across networks. Future studies will have to carefully control for antipsychotic medications as possible confounding factors.
Keywords: Schizophrenia, Resting State, Dorsal Attention Network, Large Scale Networks.
Disclosure: Nothing to Disclose.

M174. Alterations and Clinical Correlations of Frequency Amplitude of Low Fluctuation Frequency Changes after Venlafaxine Treatment in Unipolar Major Depression

Reza Tadayon-Nejad*, Olusola Ajilore , Brian J. Mickey, Anand Kumar, Jon-Kar Zubieta, Scott Langenecker

University of Illinois at Chicago, Chicago, Illinois

Background: Resting state fMRI (RS-fMRI) has recently been used for elucidating the treatment mechanisms of pharmacological interventions in psychiatric disorders including depression. The majority of those studies focused on the depression related changes in the BOLD signal temporal correlations between different cortical and subcortical regions (functional connectivity). This work studies the alterations and clinical correlations of change in the amplitude of regional spontaneous activity in a group of subjects with unipolar major depression after treatment with Venlafaxine.
Methods: Eye-closed RS-fMRI data was acquired in a group of subjects with depression ($n = 11$) before and after 8 weeks treatment with Venlafaxine (75mg\Daily). Imaging data was pre-processed using an SPM8 pipeline. Power spectrum was obtained by performing a fast Fourier transformation (FFT) analysis. Fractional amplitude of low-frequency fluctuation (fALFF) value for each voxel was obtained by averaging square root of power in the 0.01-0.8 Hz (lower frequency) or 0.1-0.25 Hz (higher frequency) bands for each voxel were normalized by total power across all available frequencies for that voxel (LF-fALFF and HF-fALFF). Treatment related LF- and HF-fALFF alterations were calculated using Paired t-test. Pearson's correlations were used to analyze the relationship between changes in LF- and HF-fALFF values after treatment and improvement in depression severity. For all of the above analyses, Monte Carlo simulation was applied for multiple comparisons correction (at the level of 0.05).
Results: Our results revealed significant increase in HF-fALFF values in the left middle temporal gyrus and left precuneus ($p < 0.01$, corrected) and significant decrease in the left inferior frontal gurus ($p < 0.01$, corrected). Our results also showed significant positive correlations between values of HF-fALFF change in the left precuneus ($p < 0.05$; $r = 0.73$) and depression symptoms severity improvement after Venlafaxine treatment.
Conclusions: This study shows how a pharmacological intervention (Venlafaxine) alters the higher frequency brain resting-state amplitude of regional spontaneous activity in depression. Furthermore, it was also demonstrated how those biological changes correlate meaningfully with symptoms improvement at the psychological level.
Keywords: MDD, Venlafaxine, Resting-State fMRI, ALFF.
Disclosure: Nothing to Disclose.

M175. Connectome Signatures of Neurocognitive Abnormalities in Euthymic Bipolar I Disorder

Olusola Ajilore*, Nathalie Vizueta, Liang Zhan, Alex Leow, Lori Altshuler

University of Illinois at Chicago, Chicago, Illinois

Background: Using graph theory, we have previously investigated structural connectome in euthymic bipolar subjects in a sample of 25 bipolar I and 24 gender and age matched healthy controls, and reported novel findings of inter-hemispheric integration deficits in bipolar disorder. Using an overlapping sample with additional psychometric and fMRI data, we here report the first-ever study relating structural connectome properties to cognitive performance and fMRI activations in euthymic bipolar I subjects.
Methods: The total sample consisted of 24 participants with bipolar I disorder (13 male, 11 female; age 42.5 ± 12.2) and 23 healthy controls (13 male, 11 female; age 42.7 ± 10.8). Out of the 47, 42 subjects (20 control, 22 bipolar) additionally underwent a neuropsychological battery covering domains of processing speed verbal memory, working memory, and cognitive flexibility, while 32 subjects (16 control 16 bipolar) also underwent task-based fMRI while performing the Go-NoGo task. Imaging data were acquired on a 3T Siemens Trio scanner.
Results: Bipolar participants had lower performance across all domains, but only the working memory domain reached statistical significance ($F = 4.6$, $p = .04$, $df = 1$). In the bipolar group, processing speed was significantly associated with both fractional anisotropy (FA) in the corpus callosum (CC) and inter-hemispheric network integration. Mediation models further revealed that the relationship between interhemispheric integration and processing speed was mediated by FA in the genu of CC, and processing speed mediated the relationship between FA and working memory. For Go-NoGo, reaction times for both conditions were significantly shorter in controls. Bipolar subjects had significantly decreased BA47 activations during NoGo vs. Go. Significant predictors of BA47 activations during the Go-NoGo task were determined to be its connectome nodal

path length (left) and its nodal clustering coefficient (right). Further more, nodal path length in BA47 was a significant mediator of the relationship between BA47 activation during the NoGo vs. Go trials and reaction times during the trials.
Conclusions: This study suggests that structural connectome changes underlie abnormalities in fMRI activation and cognitive performance in euthymic bipolar I subjects relative to healthy controls. Results further support that BA47 structural changes may be a trait marker for BPI. Future studies are urgently needed to determine if these "connectome signatures" may also confer a biological risk and/or serve as predictors of relapse.
Keywords: bipolar disorder, DTI, fMRI, connectome.
Disclosure: Nothing to Disclose.

M176. Effects of Fish Oil Monotherapy on Emotion-generated Cortical Activity in Depressed Bipolar Offspring: A Double-blind Placebo-controlled fMRI Study

Robert McNamara*, Jeffrey Strawn, Lauren Stahl, Wade Weber, Jeffrey Welge, Rodrigo Patino, Stephen Strakowski, Melissa DelBello

University of Cincinnati College of Medicine, Cincinnati, Ohio

Background: When offspring of parents with bipolar disorder develop major depressive disorder they are at increased risk for developing mania (and by definition bipolar I disorder). Antidepressant medications that are commonly used to treat depressive symptoms may further increase risk of developing manic symptoms. Therefore, treatments for mood symptoms in ultra-high risk youth are urgently needed to establish early intervention and ultimately prevention strategies. Long-chain omega-3 (LCn-3) fatty acids are anti-inflammatory and have neurotrophic and neuroprotective properties, and increasing LCn-3 fatty acid status with fish oil (FO) has antidepressant actions. However, the central mechanisms mediating this effect remain poorly understood. This study investigated the effects of increasing LCn-3 fatty acid status on corticolimbic activation patterns elicited by emotional images in depressed adolescent bipolar offspring by functional magnetic resonance imaging (fMRI).
Methods: Sixty medication-free youth (ages 9-20 years) with a current diagnosis of MDD or Depressive Disorder NOS and a biological parent with bipolar I disorder were randomized to 12 week treatment with FO supplements (2,100 mg/d) or placebo (olive oil). At baseline and endpoint, fMRI scans were obtained while performing a continuous performance task with emotional and neutral distractors (CPT-END). Standard event-related voxel-wise fMRI analysis was performed. Symptom ratings were performed weekly using the Children's Depression Rating Scale-Revised CDRS-R, Young Mania Rating Scale (YMRS), Clinical Global Impression-Severity Scale (CGI-S), and CGI-Improvement Scale (CGI-I). Erythrocyte fatty acid levels were obtained at baseline and endpoint.
Results: Baseline-endpoint RBC LCn-3 fatty acid (EPA + DHA) levels increased, and the ratio of arachidonic acid to EPA + DHA (AA/EPA + DHA) decreased, significantly following FO supplementation but not placebo. Both treatment groups demonstrated significant reductions over time in symptoms of depression ($p < 0.0001$) and mania ($p < 0.0001$). Response rates (mean CDRS % improvement) were 61% (FO) and 55% (Placebo) ($p = 0.39$), and remission (CDRS < 28) rates were 46% (FO) and 54% (Placebo)($p = 0.1$). The rates of CGI-I response (defined as ≤ 2, i.e., very much improved or much improved) were significantly greater in the FO group than placebo group (64% vs. 36%, $p = 0.04$). The FO group had a significantly greater CGI-S reduction than the placebo group (-1.8 vs. -1.0, $p < 0.01$). Baseline-endpoint activation in the left parahippocampal gyrus and fusiform gyrus in response to emotional images decreased, and activation in bilateral cerebellar tonsils increased, following FO supplementation but not placebo.
Conclusions: Increases in LCn-3 fatty acid status and reductions in depressive symptoms in bipolar offspring following FO supplementation are associated with reduced activation of limbic structures in response to emotional stimuli.
Keywords: Bipolar Disorder, Omega-3 Fatty Acid, fMRI, High Risk.
Disclosure: Nothing to Disclose.

M177. Amygdala Subregion Reactivity to Social Signals of Threat in Generalized Social Anxiety Disorder is Normalized "Early" in Cognitive Behavioral Therapy

Heide Klumpp*, Daniel Fitzgerald, Sheila D'Sa, Amy Kennedy, Julia Roberts, Scott Langenecker, K. Luan Phan

University of Illinois at Chicago, Chicago, Illinois

Background: Generalized social anxiety disorder ("gSAD") is a widespread, debilitating illness characterized by a threat processing bias that contributes to exaggerated fears of potential scrutiny. The pathophysiology of threat bias involves heightened neural sensitivity to threat-relevant signals as evidenced by amygdala hyper-reactivity to social signals of threat in gSAD. Cognitive Behavioral Therapy (CBT) is first-line psychotherapy for gSAD. It attempts to reduce symptoms by means of cognitive strategies (e.g., negating dysfunctional beliefs) at the beginning of therapy and subsequently focuses on facing fears via exposure techniques. In addition to decreases in symptomatology, CBT is associated with reductions in threat bias yet findings of reductions in amygdala response to threat faces after CBT have been mixed. Inconsistencies may relate to amygdala subregions, which play distinct roles in threat processing. Subregions include the basolateral amygdala (BLA), which among other functions is critical to automatic threat assessment. The superficial amygdala (SFA) is involved in processing socially relevant stimuli, and the central medial amygdala (CMA) is implicated in the expression of fear behaviors to imminent/unavoidable threat. Little is known about BLA, SFA, and CMA activation during threat processing in the context of CBT.
Methods: As part of an on-going study, 10 patients undergoing 12 weeks of individual CBT participated in functional magnetic resonance imaging (fMRI) at 3 time points: Week 0 (pre-CBT), Week 6 (end of cognitive focus/

start of fear exposures), and Week 12 (post-CBT). For comparison, 8 healthy controls (HC) also underwent fMRI at Weeks 0, 6, and 12. During fMRI all subjects completed an Emotional Face Matching Task designed to probe brain (e.g., amygdala) response to signals of threat. Faces comprised angry, fearful, and happy faces which were contrasted against simple geometric shapes. Using bilateral BLA, SFA, CMA anatomical-based regions of interest (ROI), we extracted from each subject parameter estimates of activation averaged across all voxels to Fear (>Shapes), Angry (>Shapes), and Happy (>Shapes). In SPSS, extractions for each ROI for each face type were submitted to a 2 (Group) x 2 (Laterality) x 3 (Time) Analysis of Variance with time as a repeated measure. Significant main effects for group or group-related interactions were followed-up by two-tailed t-tests (independent, paired). The clinician-administered Liebowitz Social Anxiety Scale ("LSAS") was used to examine symptom severity.
Results: Significant Group effects emerged for fearful but not for angry or happy faces. In BLA, there was a significant main effect for Time that was moderated by a Group x Time interaction. The gSAD group exhibited exaggerated bilateral amygdala reactivity to fearful faces compared to HC at Week 0 but not at Weeks 6 or 12. Within the gSAD group, BLA reactivity to fearful faces was significantly decreased by Week 6 with no further change noted at Week 12. In HC, no significant changes in BLA response over the course of time were observed. In SFA, a significant main effect for Time was moderated by a Group x Time interaction. There was also a main effect for Laterality with activation greater for right than left SFA across subjects. No Group x Time x Laterality interaction was observed. Follow-up analysis revealed a non-significant trend towards greater SFA reactivity in gSAD relative to HC at Week 0. No group differences emerged at Week 6, however, at Week 12 the gSAD group showed a significant reduction in SFA response relative to HC. Within the gSAD group, there was a significant decrease in SFA reactivity to fearful faces at Week 6 with no further decrease at Week 12. Again, in HC there were no significant changes in SFA response over time. For CMA, no group-related findings were revealed. Regarding symptom severity, LSAS was significantly reduced at Weeks 6 and 12 in gSAD. No correlations between LSAS and significant findings were observed.
Conclusions: Preliminary findings show pre-CBT exaggerated bilateral BLA and SFA reactivity to fearful faces in gSAD relative to HC. By the mid-point of treatment, activation in these amygdala nuclei in gSAD was analogous to BLA and SFA response in HC. The HC group did not show changes in response in these regions over time indicating reliable activation to fearful faces in controls. In CBT for gSAD Week 6 largely marks the end of the cognitive phase of CBT and start of systematic exposures to fears. The BLA and SFA are in general input regions for sensory information and results suggest cognitive therapy may reduce neural sensitivity to threat-relevant signals potentially by engaging prefrontal regions. Thus, future analyses will include psychophysiological interactions analyses to examine amygdala-prefrontal interactions. Also, further study is needed to rule out non-specific effects such as time spent in psychotherapy. Lastly, a lack of power may have reduced our ability to detect group effects for angry faces or correlations between significant results and symptom severity. Nevertheless, data indicate early modulation of BLA and SFA response in CBT.
Keywords: fMRI, social anxiety, threat faces, brain imaging.
Disclosure: Nothing to Disclose.

M178. Olfactory Function and Fear-related Odor Cues in Combat Veterans with and without PTSD

Bernadette Cortese*, Kimberly Leslie, Anouk Grubaugh, Qing Yang, Thomas Uhde

Medical University of South Carolina, Charleston, South Carolina

Background: Fear is processed by 2 separate but parallel pathways in the brain; the subcortical route (i.e. amygdala) that provides basic information for a quick response to potential danger and the cortical route that provides full evaluation of a potential threat (LeDoux, 1996). PTSD and other fear-related disorders are characterized by a dysfunctional brain circuit comprised of hyperactive subcortical processing (i.e. amygdala) and hypoactive cognitive control (i.e. prefrontal cortex). Odor processing in the brain parallels the 2 functional pathways of fear processing, with subcortical (i.e. odor sensitivity = lower-level processing) and cortical (i.e. odor identification = higher-level processing) components. Given this overlap, we sought to assess fear-related odor cues (i.e. trauma versus non-trauma odor cues) in combat veterans with and without PTSD.
Methods: Nineteen Operation Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) combat veterans with posttraumatic stress disorder (PTSD) and 22 healthy OEF/OIF/OND combat veterans (HV) participated in this study, which consisted of 2 phases: 1) documentation of combat history and assessment of PTSD and 2) subjective odor sensitivity ratings, objective clinical olfactory testing, and fMRI BOLD response during odor challenge testing. Both subjective sensitivity ratings (100mm visual analog scales) and fMRI BOLD response during odor challenge tests utilized neutral odors [lavender (LAV) and odorless propylene glycol (PG)] and an odor specific to traumatic combat experiences (burned rubber, BR). Clinical olfactory testing was conducted using 2 standardized tools, the Smell Threshold Test (STT) and Smell Identification Test (UPSIT, Sensonics, Inc.). The STT used phenyl ethyl alcohol (PEA), a rose-like scent, to determine odor sensitivity, a function that requires an intact 'lower-level' olfactory system (e.g. olfactory bulb, piriform cortex and amygdala). The UPSIT used a variety of common, neutral, odorants to assess odor identification, an ability that requires an intact 'higher-level' olfactory system (e.g. anterior insula, orbitofrontal cortex).
Results: Demographics: The PTSD and HV groups were nearly all male (PTSD: 18 M/1 F, HV: 21M/1 F) and of similar age [PTSD: $M = 29.6$ ($SD = 8.0$), HV: $M = 29.4$ ($SD = 6.1$)]. The groups differed significantly on the total score of the Clinician Administered PTSD Scale (CAPS) [PTSD: $M = 60.9$ ($SD = 24.0$), HV: $M = 15.8$ ($SD = 12.4$), $p < 0.05$], but did not differ with respect to the level of combat exposure [PTSD: $M = 22.9$ ($SD = 8.8$), HV: $M = 20.2$ ($SD = 10.4$), $p > 0.1$], or the number of additional traumatic events experienced during their lifetime [PTSD: $M = 2.6$ ($SD = 1.7$), HV: $M = 2.2$

(SD = 1.3), $p > 0.1$]. Subjective Odor Ratings: Odor strength ratings were acquired for trauma-related (BR) and neutral (LAV and PG) odor cues. A diagnosis by odor strength interaction was revealed ($F2,39 = 3.16$, $p < .05$), demonstrating that the PTSD group, compared to the HV, reported BR (the trauma-related odor cue), but not LAV or PG, to be significantly stronger. Objective Measures: Lower Level Olfactory Processing: The PTSD and HV groups performed similarly on the STT, indicating no significant difference in sensitivity to the neutral odorant (PEA) in combat veterans with and without PTSD. However, performance of both combat groups fell well below standardized norms (PTSD = −4.48, HV = −4.2, Norms = −5.94, 75% CI: −6.12 to −5.76). Higher Level Olfactory Processing: A significant group difference ($t39 = 2.8$, $p < .01$) was revealed for odor identification, a higher-level olfactory function. PTSD group performance on the UPSIT fell within the range of mild impairment compared to the HV who had normal odor identification performance. There was also a trend-level group difference in the number of trauma-related and neutral odor cues (BR, LAV, and PG) that were correctly identified [PTSD: M = 1.4 (SD = .84), HV: M = 1.7 (SD = .55), $p = 0.1$]. fMRI Fear-Odor Circuit: Olfactory fMRI region of interest analyses revealed a significant diagnosis by odor-elicited BOLD response in both the lower- (amygdala) and higher-level (insular cortex) olfactory pathway ($F1,35 = 5.9$, $p < .05$; $F1,35 = 3.9$, $p = .05$, respectively). In both regions, the PTSD group, but not the HV, demonstrated significantly reduced activation to BR compared to LAV.
Conclusions: While subjective ratings indicated an increased sensitivity to the trauma-related odor cue (burned rubber), our "objective" odor assessment tools actually demonstrated deficits in olfactory function (i.e. reduced odor detection and identification of common neutral odors). Explanations for this apparent dissociation between subjective ratings (i.e. increased sensitivity to burned rubber) and objective findings (i.e. reduced odor detection and identification of common neutral odors) include: 1) inadequate understanding and/or objective tools to quantify the biological correlates of increased trauma-related odor sensitivity; 2) a compensatory, adaptive, down-regulation of the relevant fear-odor circuitry in PTSD, and 3) concurrent structural changes in the olfactory system that include combat-related general damage to olfactory receptors, along with the selective up-regulation of olfactory receptors that code for specific, fear-related, odors (e.g. BR).
Keywords: PTSD, fear-odor circuit, odor cue, MRI.
Disclosure: Nothing to Disclose.

M179. Orbitofrontal Thickness as a Measure for Treatment Response Classification in Obsessive-Compulsive Disorder

Marcelo Hoexter*, Juliana Diniz, Antonio Lopes, Marcelo Batistuzzo, Roseli Shavitt, Darin Dougherty, Fabio Duran, Rodrigo Bressan, Geraldo Busatto, Euripedes Miguel, João Sato

Federal University of Sao Paulo/University of Sao Paulo Medical School, Sao Paulo, Brazil

Background: Predicting treatment response in early stages could diminish exposure to ineffective treatments and optimize medical resources. Neuroimaging techniques have been used to identify biomarkers that are predictive of future outcome. The aims of this study were twofold: 1) to investigate the orbitofrontal cortex thickness as a potential morphometric biomarker able to discriminate outcome in obsessive-compulsive disorder (OCD) and 2) to validate this algorithm in an independent cohort.
Methods: A logistic regression model based on the mean thickness of orbitofrontal cortex subregions of 29 treatment-naïve OCD patients who participated in a clinical trial was performed to classify individuals according to their probability of treatment response. Then, this algorithm was validated on an independent cohort of 12 refractory OCD patients.
Results: Measures of the orbitofrontal cortex thickness significantly differentiated treatment-naïve OCD patients in responders (n = 13) from non-responders (n = 16) (overall classification accuracy of $\cong$ 80%; sensitivity of 77% and specificity of 81%). The subregions that contained the most discriminative information were the thickness of the left and right medial orbitofrontal cortex ($p = 0.009$ and $p = 0.028$, respectively). In a second approach based on an independent cohort of refractory OCD patients, 67% of refractory patients were correctly classified as non-responders.
Conclusions: Orbitofrontal cortex thickness measures turned out to be a strong predictor of treatment response for this sample of treatment-naïve OCD patients. Although there is no reliable brain imaging biomarker for clinical practice today, our present results highlight the potential use of these measures as a tool for predicting treatment outcome in OCD.
Keywords: OCD, neuroimaging, treatment outcome, prediction.
Disclosure: Nothing to Disclose.

M180. Clinical Implications of Ventral Striatum Dopamine Receptor Binding in Major Depression

Marta Pecina*, Katie Chang, Magdalena Sikora, Erich Avery, Joseph Hefferman, Brian Mickey, Jon-Kar Zubieta

University of Michigan, Ann Arbor, Michigan

Background: Accumulating evidence supports a role for diminished dopaminergic (DA) neurotransmission in the pathophysiology of Major Depression (MD). These alterations could result from either diminished DA release from presynaptic neurons or impaired signal transduction (e.g. changes in receptor number/function) and compensatory up-regulation of DA receptors at the postsynaptic level. Results from neuroimaging studies using single photon emission computed tomography (SPECT) and the 123I-iodobenzamide (123I-IBZM) D2 receptor antagonist have been inconsistent and possibly confounded by patient medication status and differences in depression severity. Furthermore, the clinical relevance of DA deficits in MD remains poorly understood. Here, we hypothesized that compared to healthy controls, chronic DA deficits in patients with MD will result in an up-regulation of D2/3 receptors in reward regions, such as the ventral striatum

(VS),that would be associated with increased anhedonic symptoms.
Methods: Dopamine D2 receptor binding potential (BP) was assessed in 26 un-medicated subjects with MD and 24 healthy comparison subjects matched for age and sex. Because depression and anxiety disorders are frequently comorbid, we only permitted comorbid anxiety disorder diagnoses (generalized anxiety, panic, agoraphobia, social phobia, and specific phobia). Striatal BP was measured using positron emission tomography (PET) and the selective DA D2 receptor antagonist 11 C-raclopride. Personality trait and depression severity measures were also collected. Patients with MD completed 10 weeks of treatment with citalopram. Partial correlation analyses (with age as a covariate) were used to study the relationship between D2 receptor biding in the VS, depression severity and personality traits.
Results: Mean D2/3 receptor BP in the bilateral VS was significantly higher in subjects with MD than in a matched comparison healthy control group [MNI coordinates (left VS: -14, 6, 6; right VS: 14, 4 -10), FWE-corr = 0.05]. Within the MD group, DA receptor availability in the VS bilaterally was not significantly correlated with symptoms of anhedonia, as measured by the Snaith-Hamilton questionnaire or depression severity, as measured by the Hamilton Depression scale (HAM-D); Montgomery-Asberg Depression Rating Scale (MADRS); the Patient Health questionnaire (PHQ-9); and the Quick Inventory of Depressive Symptomatology questionnaire (QIDS-SR-16). Instead, DA D2/3 receptor BP in the VS was associated with increased symptoms of anxiety at baseline as reported in the Beck Anxiety Inventory (left VS: $r = 0.4$, $p = 0.04$) and the Generalized Anxiety Disorder assessment (GAD-7) (left VS: $r = 0.6$, $p = 0.002$; right VS: $r = 0.4$, $p = 0.03$). DA D2/3receptor BP at baseline was not predictive of improvements of depressive symptoms after 10 weeks of antidepressant treatment. At a trait level in both depressed and healthy control subjects, DA receptor availability was positively correlated with anxiety-related traits such as the STAI-trait (left VS: $r = 0.6, < 0.001$; right VS: $r = 0.62, < 0.001$), the Neuroticism domain of the NEO-PI-R (including the anxiety facet) (left VS: $r = 0.47$, $p = 0.003$; right VS: 0.46, $p = 0.005$) and the Neuroticism/Anxiety dimension of the Zuckerman – Kuhlman Personality Questionnaire (left VS: $r = 0.5$, $p = 0.002$; right VS: $r = 0.5$, $p = 0.001$). In addition, a negative correlation was observed between DA receptor BP at baseline and the Extraversion domain of the NEO-PI-R (left VS: $r = 0.6$, $p = < 0.001$; right VS: $r = 0.6$, $p = < 0.001$). To examine the influence of comorbid anxiety diagnosis present in 70% of our depressed sample ($n = 20$), we examined differences in D2/3 DA binding in the VS in patients with and without comorbid anxiety. Patients with comorbid anxiety diagnosis showed significantly increased DA D2/3 BP in the right VS ($F = 0.34$, $p = 0.049$).
Conclusions: Our results show that patients with MD show higher DRD2/3 BP in the VS compared to healthy controls. These differences in DRD2/3 BP might result from a compensatory up-regulation in response to chronic DA deficit in MD. Despite the role of DA neurotransmission in reward processing, differences in DRD2/3 receptor availability in the VS were not associated with anhedonic symptoms. Instead a significant association with symptoms of anxiety as well as anxiety related personality traits was observed. Furthermore, patients with comorbid anxiety showed higher levels of DRD2/3 BP. Surprisingly, it has been shown that patients with some primary anxiety disorders (social phobia), had lower striatal DRD2/3 BP compared with healthy controls. These preliminary findings suggest that DRD2/3 receptor availability in the ventral striatum might play a key role in the neurobiology of MD with comorbid anxiety symptoms, a notably treatment refractory condition, informing decisions on treatment options and guiding prognosis.
Keywords: PET, Dopamine, Major Depression, Anxiety.
Disclosure: Nothing to Disclose.

M181. Frontostriatal Neurocircuitry Alterations and the Contribution of the Arousal System in the Context of Late Life Depression

Sara Weisenbach*, Julia Rao, Michelle Kassel, Anne Weldon, Erich Avery, Emily Briceno, Helen Kales, Jon-Kar Zubieta, Robert Welsh, Scott Langenecker

University of Illinois at Chicago & Jesse Brown VA Medical Center, Chicago, Illinois

Background: Executive dysfunction is a hallmark feature of the vascular depression syndrome and a robust predictor of treatment response (Sneed et al., 2007) and course of illness (Alexopoulos, 2000) among older adults with late life depression (LLD). Although a range of executive functioning skills is observed in patient samples (see Alexopoulos et al., 2002), variability in internal motivational incentive mechanisms may play an important role in engaging the cognitive control (CC) system, given the close interconnection between those processes (Harsay et al., 2010, 2011). Specifically, individuals with lower levels of motivational arousal (i.e., higher levels of apathy) may be less able to recruit networks important for tasks of CC, such as complex attention and task switching. The aim of this study was to investigate alterations in neural networks underlying CC in LLD, and to examine how variability in internal motivational incentive modulates the CC system during challenge.
Methods: Twenty-four older adults with LLD and 23 never-depressed comparisons (NDC), ages 55-88 (M age = 66.82) completed Level 1 of the Parametric Go No-Go Task (Langenecker, 2003), requiring sustained attention and attentional switching, while undergoing fMRI. First, to investigate within group activation patterns and between group activation differences, two-sample t tests were conducted for activation during correct hits. Second, to examine the contribution of internal motivational incentive to engagement of the CC system, scores on items of the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967) assessing apathy (i.e., items reflecting energy level, lack of interest, psychomotor retardation, and lack of insight; see Marin et al., 1991, 1993) were regressed onto activation during correct hits in the LLD group, while controlling for overall depression symptom severity as measured by the HAM-D (subtracting out apathy items). AlphaSim correction (1000 iterations) was used for all fMRI analyses, balancing height ($p < .003$) and extent (264 mm3) thresholds to achieve a whole brain correction of $p < .05$.

Results: Accuracy and reaction time did not differ between groups, and amount of apathy was not associated with either performance metric in LLD (ps > .05). Both groups demonstrated activation in similar regions, with the majority of activation occurring in areas that are relevant for attention and CC (BA6, 10, 32, caudate). At the same time, LLD exhibited a more diffuse pattern of activation relative to NDC. In between-group contrasts, LLD demonstrated greater activation than NDC in regions relevant to CC (BA32, caudate) and motor control (BA6). In LLD, greater apathy was predictive of activation in BA6, relevant for complex motor control, while lesser apathy was predictive of activation of BA10, associated with cognitive functions necessary for complex attention and task switching.
Conclusions: Despite performance that was not significantly different between groups, LLD demonstrated greater and more diffuse activation in regions that are relevant to attention, CC, and motor control relative to NDC, suggesting compensation and/ or reorganization. Apathy among LLD was predictive of activation patterns in prefrontal regions, and results suggest that those with greater levels of apathy may be unable to engage regions that are especially relevant for CC. Instead, these individuals may rely on areas that are applicable to motor planning, which could be considered a more basic set of cognitive processes, relative to higher-order executive control skills. Results suggest that variability in internal motivational incentive modulates engagement of the CC system in LLD, and are relevant in the context of development of interventions for LLD that target the positive valence system, such as ENGAGE (Alexopoulos & Arean, 2014).
Keywords: fMRI, cognitive control, depression, aging.
Disclosure: Nothing to Disclose.

M182. EEG Source Localization Reveals Dissociable Neural Correlates of Three Promising Endophenotypes of Depression: Evidence from the Multi-site EMBARC Study

Christian Webb*, Daniel Dillon, Franziska Goer, Madhukar Trivedi, Maurizio Fava, Patrick McGrath, Myrna Weissman, Ramin Parsey, Phil Adams, Sarah Weyandt, Crystal Cooper, Patty Deldin, Eva Petkova, Craig Tenke, Gerard Bruder, Diego Pizzagalli

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: Major Depressive Disorder (MDD) is clinically, and likely pathophysiologically, heterogeneous. A potentially fruitful approach to parsing this heterogeneity is to focus on promising endophenotypes. Inspired by the NIMH Research Domain Criteria (RDoC) initiative, we used source localization of scalp-recorded EEG data to examine associations between three putative endophenotypes of depression - neuroticism, cognitive control deficits, and blunted reward responsiveness - and their underlying neural correlates.
Methods: Data were drawn from the ongoing multi-site EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) clinical trial of MDD. A well-validated source localization technique – low resolution brain electromagnetic tomography (LORETA) - was employed to compute resting state intracranial estimates of standard EEG bands (1.5-44 Hz) in a sample of 81 unmedicated adults with MDD. Region-of-interest and whole-brain, voxelwise correlational approaches were used to test the association between EEG current density in specific brain regions and neuroticism (NEO-Five Factor Inventory), cognitive control (Eriksen Flanker Task) and response bias towards a more frequently rewarded stimulus (Probabilistic Reward Task).
Results: Neuroticism was positively associated with resting gamma (36.5–44 Hz) and theta (6.5–8 Hz) current density in the subgenual anterior cingulate cortex (sgACC) and orbitofrontal cortex (OFC). In contrast, greater cognitive control was associated with higher resting gamma and alpha2 (10.5-12 hz) power in the left dorsolateral prefrontal cortex (dlPFC), as well as theta power in the dorsal ACC (dACC). Finally, reward responsiveness was associated with greater OFC and left dlPFC, and reduced right insula, gamma power.
Conclusions: Three putative endophenotypes of depression were examined and found to have partially dissociable resting intracranial EEG correlates. These findings may reflect different underlying neural circuitries subserving these three dimensions, which may be abnormal in depression. Overall, these findings highlight the need for additional research examining these and other plausible endophenotypes of depression in an effort to parse the heterogeneity and complexity of the disorder as currently defined.
Keywords: Depression, Endophenotype, EEG, Source Localization.
Disclosure: Madhukar H. Trivedi is or has been an advisor/ consultant to: Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals Inc.), Alkermes, AstraZeneca, Axon Advisors, Bristol-Myers Squibb Company, Cephalon, Inc., Cerecor, Concert Pharmaceuticals, Inc., Eli Lilly & Company, Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Global Services, LLC, Janssen Pharmaceutica Products, LP, Johnson & Johnson PRD, Libby, Lundbeck, Meade Johnson, MedAvante, Medtronic, Merck, Mitsubishi Tanabe Pharma Development America, Inc., Naurex, Neuronetics, Otsuka Pharmaceuticals, Pamlab, Parke-Davis Pharmaceuticals, Inc., Pfizer Inc., PgxHealth, Phoenix Marketing Solutions, Rexahn Pharmaceuticals, Ridge Diagnostics, Roche Products Ltd., Sepracor, SHIRE Development, Sierra, SK Life and Science, Sunovion, Takeda, Tal Medical/ Puretech Venture, Targacept, Transcept, VantagePoint, Vivus, and Wyeth-Ayerst Laboratories. In addition, he has received research support from: Agency for Healthcare Research and Quality (AHRQ), Corcept Therapeutics, Inc., Cyberonics, Inc., National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), and Solvay Pharmaceuticals, Inc. Dr. Fava's disclosures can be viewed on-line at http://mghcme.org/faculty/faculty-detail/maurizio_fava.

M183. Impact of Birth Outcomes and Genetic Variation on White Matter Microstructure in Neonates

Kaela Kelly, Shaili Jha, Rachel Steiner, Jessica Bullins, Kai Xia, Fei Zou, Mihye Ahn, Hongtu Zhu, Martin Styner, John Gilmore, Rebecca Knickmeyer*

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Background: Understanding how environmental factors and genetic variants affect human neurodevelopment is a key scientific question that the emerging discipline of population neuroscience endeavors to address. The objective of the current study was to determine if gestational age at birth, birthweight, gender, or common variants in psychiatric risk genes predicted individual differences in white matter microstructure in neonates. The prenatal/perinatal period represents a foundational phase of white matter development, including fiber organization into fascicles, proliferation and maturation of glial cell bodies and intracellular compartments, premyelination, and early myelination. Disrupted white matter development in this period may have long term consequences for intellectual ability and risk for neurological and psychiatric disorders.
Methods: Diffusion weighted imaging (DWI) scans were acquired from 348 neonates (167 singletons, 181 twins, 194 male, 154 female) at 2 weeks of age. Birth outcomes were identified via review of labor and delivery records. Buccal cells were genotyped using either Sequenom® iPLEX® Gold Genotyping Technology or Affymetrix Axiom Genome-Wide LAT and Exome arrays followed by imputation. The current analysis focuses specifically on rs35753505, a single nucleotide polymorphism in neuregulin-1 that has been linked to schizophrenia and altered axonal integrity in adults. We will also examine common genetic variants in disrupted-in-schizophrenia-1 (DISC1, rs821616 and rs6675281), catechol-O-methyltransferase (COMT, rs4680), apolipoprotein E (APOE; ε3ε4 vs. ε3ε3), estrogen receptor alpha (ESR1, rs9340799 and rs2234693), brain-derived neurotrophic factor (BDNF, rs6265), and glutamate decarboxylase 1 (GAD1, rs2270335). Quantitative tractography of major white matter pathways was performed using the UNC-Utah NA-MIC DTI framework adapted for our neonatal sample. For statistical analysis, we divided the subjects into two equal-sized randomly selected independent groups to serve as a discovery and a replication sample. Functional analysis of diffusion tensor tract statistics (FADTTS) was used to identify associations between the variables of interest and fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (RD) along 45 major white matter tracts.
Results: Gestational age at MRI was associated with increased FA and decreased MD, RD, and AD across fiber tracts, in keeping with the rapid maturation of white matter during the first 6 months of life. Gestational age at birth was also associated with increased FA and decreased MD, RD, and AD in many fiber tracts. Birthweight, gender, and neuregulin-1 genotype did not show consistent associations with diffusion parameters in any of the tracts examined.
Conclusions: Despite coding for a key axonal signal regulating Schwann cell proliferation, migration and myelination, and despite being associated with diffusion parameters in adults, neuregulin-1 genotype was not associated with white matter microstructure in neonates. We hypothesize that rs35753505 influences brain development and psychiatric risk in later childhood or adolescence and as such may be a particularly promising target for intervention. Regarding gestational age at birth, previous tractography studies have included only a small number of major white matter pathways, focused on extreme rather than normative variation in gestational age, and rarely disambiguating low birthweight from prematurity. The current study suggests that normative variation in gestational age at birth does impact diffusion parameters across many fiber tracts, with earlier born children demonstrating less mature white matter after adjusting for gestational age at MRI and birthweight. Longitudinal studies are needed to determine if this represents a delay in white matter development or a persistent difference in white matter microstructure with functional consequences.
Keywords: Diffusion tensor imaging, neuregulin-1, connectivity, gestational age.
Disclosure: Nothing to Disclose.

M184. Cross-Modal Maps of Functional Connectivity in Adults with a History of Childhood Attention Deficit Hyperactivity Disorder

Gustavo Sudre, Eszter Szekeley, Daniel Weingart, Wendy Sharp, Philip Shaw*

National Human Genome Research Institute, Washington, District of Columbia

Background: Attention Deficit Hyperactivity Disorder (ADHD) is increasingly conceptualized as the result of disruption to multiple neural systems. We have previously demonstrated that the adult outcome of ADHD reflects the developmental trajectories of cortical hubs of key networks and the degree of atypical structural connectivity within these networks. Thus, adults with symptoms persisting from childhood show more atypical cortical structure and greater anomalies in white matter architecture. Here, we ask whether atypical functional connectivity is also linked with the adult outcome of childhood ADHD. We thus delineated the connectivity seen within the network of brain regions which show heightened spontaneous activation during task-free periods - the default mode network (DMN). We employ both functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), allowing us to define connectivity using both hemodynamic and electromagnetic activity.
Methods: Sixty-seven adults with a history of childhood ADHD, 32 with persistent ADHD and 35 in remission, were contrasted against 58 never affected adults (mean age 24.7, SD 4.0, 46.2% female). All subjects underwent magnetoencephalography using a helmet-shaped CTF 275-channel whole head system. MEG data was acquired for a total of 4 minutes while the subjects were simply at rest in the MEG scanner. One hundred and seventeen of these subjects also completed resting state fMRI, collected on a 3T Siemens scanner (TR = 2.5s, 3.5x3.5x2.8 mm voxels). The fMRI run lasted 5.2 minutes in total and acquired 126 volumes continuously. We defined the degree of connectivity between signals observed in spatially distinct brain regions. First, in the resting state fMRI, we corrected for head motion and regressed out physiological parameters. We then extracted the BOLD time courses of two seed regions within the

default mode network: the precuneus and the medial prefrontal cortex. This was then correlated with the time course of activation in all other voxels in the brain. A T-test was used to evaluate how the Z-scored correlation maps differed between the groups (pairwise contrasts were performed). In the MEG data, the sources of magnetic activity were estimated using the Synthetic Aperture Method. Connectivity between the same seed regions and the other sources in the brain was estimated using an unbiased estimate of the Weighted Phase-Lag Index in five different frequency bands (delta, theta, alpha, beta, gamma). Finally, t-tests were used to evaluate the differences in connectivity maps between the three groups. In all analyses, we corrected for multiple comparisons by using non-parametric cluster simulations (voxel-wise $p<.01$, cluster corrected at $p<.1$).

Results: Four central findings emerged (1) In resting state fMRI, both DMN seeds showed atypical connectivity in the ADHD groups compared to the never affected group, predominately with other midline regions. Thus, there was anomalous connectivity between the two DMN seeds and between these seeds and cuneus and parahippocampal regions. (2) The connectivity anomalies defined using fMRI were more pronounced in the persistent ADHD group. (3) Functional connectivity mapped using MEG data likewise showed atypical connectivity between the DMN seeds and midline regions. (4) While the fMRI and MEG maps of atypical functional connectivity in ADHD showed many similarities, there were also several spatially distinct networks of atypical connectivity in ADHD revealed by MEG (particularly in the alpha and beta bands, incorporating dorsolateral prefrontal and angular gyrus cortical regions).

Conclusions: This is the first cross-modal study of intrinsic functional connectivity in adults with a history of childhood ADHD. We confirm previous reports of atypical functional connectivity using fMRI within the default mode network, particularly among those with symptoms persisting into adulthood. Spatially comparable maps of atypical connectivity in ADHD were defined by both fMRI and MEG thus bolstering the argument that default mode anomalies are present in adult ADHD. There were also patterns of atypical connectivity specific to MEG, suggesting that defining networks through electromagnetic activity can provide additional novel insights into the functional architecture of adult ADHD.

Keywords: Default mode network, Attention Deficit Hyperactivity Disorder.

Disclosure: Nothing to Disclose.

M185. Gray Matter Volume in Pediatric Anxiety and Mood Disorders: Regional Prefrontal Cortex Volume Differences in Anxiety, Bipolar Disorder, Severe Mood Dysregulation, and ADHD

Andrea Gold*, Sara N. Lever, Nancy E. Adleman, Daniel S. Pine, Ellen Leibenluft

National Institute of Mental Health, Bethesda, Maryland

Background: Prior pediatric and adult research links anxiety and mood disorders to structural brain abnormalities, particularly in the prefrontal cortex (PFC). Compared to healthy volunteers (HV), gray matter (GM) volume differences have been linked to anxiety disorders, bipolar disorder, severe mood dysregulation (SMD), and attention-deficit hyperactivity disorder (ADHD) in children and adolescents. However, virtually all of these findings accrue from separate studies comparing HV to one patient group. The current study directly compares GM volumes among children and adolescents with anxiety disorders, bipolar disorders, SMD, ADHD, and HVs.

Methods: Voxel-based morphometry (VBM) analysis was conducted on T1-weighted structural MRI scans acquired on a 3-Tesla scanner from 177 youths (36 anxious, 19 bipolar disorder, 52 SMD, 17 ADHD, and 53 HV). The five groups were matched on age, sex, and IQ (all $ps>.1$). We created a custom template, given the pediatric sample, and used standard procedures in the VBM8 toolbox in SPM8, including high-dimensional DARTEL normalization. Segmented GM images were modulated for non-linear effects, resulting in relative GM volume images. One-way ANOVA tested the main effect of diagnosis on GM volume using a whole-brain voxel-wise height threshold of $p<.001$ uncorrected, cluster extent ≥ 200 voxels. Post-hoc pairwise comparisons were conducted on the mean GM volume values extracted from significant clusters (using Tukey's Honestly Significant Difference [HSD] correction).

Results: Diagnosis was significantly associated with GM volume in medial and lateral PFC as predicted, including clusters in ventromedial PFC (vmPFC), dorsomedial PFC (dmPFC), and dorsolateral PFC (dlPFC). Post-hoc tests revealed that, depending on the region, differences between HVs and patients were (1) specific to bipolar disorder, (2) common among multiple disorders, or (3) specific to anxiety disorders. First, decreased GM volume compared to HVs was specific to the bipolar group in the vmPFC (peak MNI coordinates: -16, 54, -8), dmPFC (-8, 62, 21), left superior frontal gyrus (-28, 41, 34), and left precental gyrus (-46, -16, 37). Second, decreased GM volume compared to HVs was common among bipolar disorder, SMD, and ADHD in the right superior frontal gyrus (26, 27, 58). Third, decreased GM volume compared to HVs was specific to the anxiety groups in the left middle frontal gyrus (-42, 33, 22) and right parahippocampal gyrus extending to lingual gyrus (22, -51, -2).

Conclusions: GM volume differences in pediatric disorders were found. Some were specific to anxiety disorders; others specific to bipolar disorder; and a third group shared among bipolar, SMD, and ADHD. Further research should test for specificity in larger samples with more diagnostic groups. Developmental research mapping the commonalities and differences of structural brain abnormalities among pediatric disorders is needed to inform functional neuroanatomical models and developmental risk trajectories.

Keywords: anxiety disorders, bipolar disorder, prefrontal cortex, voxel-based morphometry.

Disclosure: Nothing to Disclose.

M186. Neurobiological Markers within the Olfactory System Are Associated with Heightened Clinical Risk for Schizophrenia

David Roalf*, Megan Quarmley, Kosha Ruparel, Paul Moberg, Bruce Turetsky

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Deficits in olfactory function are a hallmark of schizophrenia. These deficits are reliably observed in multiple olfactory domains, including odor detection threshold (Turetsky et al., 2009; Isseroff et al., 1987; Serby et al., 1990), identification (Kopala et al., 1989) and hedonic perception (Crespo-Facorro et al., 2001; Kamath et al., 2011). Olfactory deficits precede the onset of illness, distinguish adolescents who are developing prodromal symptoms from healthy youths, (Kamath et al., 2011; Woodberry et al., 2010) and may predict which vulnerable youths go on to develop schizophrenia (Brewer et al., 2003). Importantly, these behavioral deficits denote fundamental neuroanatomic and neurophysiologic abnormalities that are specific to the peripheral olfactory system and primary olfactory cortex (Turetsky & Moberg, 2009). Here, we extend this previous work to an investigation of structural brain measures of the olfactory system in youths at heightened clinical risk for psychosis. We believe that, as a set of neurobiological markers, abnormalities of the olfactory system are likely to aid in predicting schizophrenia risk status.
Methods: Nineteen typically developing youth (TD; age = 19.8 ± 3.3) and 20 youth at clinical risk for psychosis (CR; age = 17.2 ± 2.1) from the Philadelphia Neurodevelopment Cohort underwent follow-up 3T MRI of the olfactory system. The following scans were collected: a high resolution T1-weighted structural, a T2-weighted and diffusion weighted imaging oriented parallel to the olfactory bulb. Outcome measures included: 1) volume of the olfactory bulb, 2) volume of primary olfactory cortex, 3) depth of the olfactory sulci and 4) diffusion within the olfactory bulb and primary olfactory cortex. A subset of participants underwent 7T imaging of the olfactory cortex using a glutamate sensitive magnetization transfer technique (GluCEST; Cai et al., 2012) to quantify glutamate concentration. Modality specific image analysis was performed using standard neuroimaging tools (e.g. FreeSurfer 5.3, FSL v5.0).
Results: Left ($p < .05$) and right ($p = .01$) olfactory bulb volumes were significantly smaller in CR than LR, and comparable to previous reports in schizophrenia. Entorhinal cortex was, on average, 6.2% smaller in CR than LR, and significantly smaller in the right hemisphere ($p < .05$, one-tailed). However, volume of the medial orbitofrontal cortex and temporal pole did not differ in CR and LR (2.4% smaller and 1% larger in CR, respectively). Lengths of the olfactory sulci were nominally smaller in CR (4.2%) than LR, but this did not reach statistical significance ($p = .22$). Subtle differences were noted in diffusion measures (Trace ADC) in the olfactory bulb and primary olfactory cortex. CR individuals had lower ADCs ($p < .05$) in the olfactory bulb, but higher ADCs within regions associated with primary olfactory cortex. Glutamate concentration, as measured using GluCEST, was higher in CR than in LR in the primary olfactory cortex ($p < .05$), but not within the medial orbitofrontal cortex. Overall, our preliminary work indicates that youth at clinical risk for psychosis exhibit subtle, but significant neuroanatomical and neurochemical abnormalities of the olfactory system, similar to those found in schizophrenia.
Conclusions: Given the clinical evidence implicating abnormal neurodevelopment in the pathogenesis of schizophrenia, and the potential utility of olfactory measures to predict illness vulnerability, the olfactory system holds distinct promise for understanding neurodevelopmental contributions to schizophrenia pathophysiology. The sensitivity of the olfactory system as a vulnerability marker may be related to its developmental time course, which occurs in close coordination, embryologically, with early forebrain development during the first trimester of pregnancy (Maynard et al., 2001; Turetsky et al., 2009). Adolescence is a critical developmental risk period, during which developmental anomalies or stressors can greatly increase the subsequent risk of schizophrenia (Maynard et al., 2001). As such, early intervention requires valid and reliable methods of identifying youths at highest risk for developing psychosis. We suggest, that in addition to other metrics, neuroanatomical and neurochemical metrics of the olfactory system be considered as markers of risk.
Keywords: psychosis risk, olfaction, neuroimaging, schizophrenia.
Disclosure: Nothing to Disclose.

M187. Oxytocin Administration Modulates Mesoaccumbal Activity in Response to Non-social Reward

Tiffany Love*, Joseph Heffernan, Brian Mickey, Curtis Heisel, Marta Pecina, David Hsu, Jon-Kar Zubieta

University of Michigan, Ann Arbor, Michigan

Background: Oxytocin is widely recognized for its role in regulating social reward and behavior. However, growing evidence in animal models suggest that oxytocin also plays an important role in reward processing outside of the social context. Here, we sought to investigate whether oxytocin administration could influence activity within reward-networks in response to a non-social form of reward (i.e. money) in humans.
Methods: In a double-blind, placebo-controlled, randomized, crossover, pharmaco-fMRI study, we explored the effects of intranasal oxytocin administration (24IU, Syntocinon, Novartis, Basel, Switzerland) on brain activity elicited during the processing of monetary reward in eighteen healthy males (age: 22 ± 2, mean ± SD). Participants were scanned twice, on separate days, once following self-administration of oxytocin and once after self-administering placebo. During each of the scanning sessions, subjects were asked to perform a version of the monetary incentive delay (MID) task. Personality traits were also assessed using the Revised NEO Personality Inventory (NEO PI-R) to examine whether particular traits impacted individual responses to oxytocin.

Results: Oxytocin significantly enhanced brain activity within the left nucleus accumbens, ventral tegmental area, anterior cingulate, and left lateral orbitofrontal cortex during incentive anticipation compared with placebo. Analyses of personality revealed that low levels of extraversion predicted greater oxytocin-induced changes in neural activity within the nucleus accumbens and ventral tegmental area. These results are line with current theories that hypothesize the effects of oxytocin administration may be strongly influenced by individual trait characteristics.
Conclusions: Our results provide evidence that oxytocin administration can influence reward processes in absence of a social context. In addition, our findings suggest the degree to which exogenous oxytocin impacts these processes are dependent on trait personality characteristics. These findings are of significant interest as oxytocin is currently being considered as a therapeutic agent for the treatment of psychiatric disorders where reward system dysfunction is implicated (e.g., addiction, schizophrenia, autism).
Keywords: oxytocin, fmri, reward, nucleus accumbens.
Disclosure: Nothing to Disclose.

M188. Fronto-Striatal Brain Activation is Related to Cocaine Cue Reactivity

Liangsuo Ma, Joel Steinberg, Cunningham Kathryn, Waters Andrew, Bjork James, Lane Scott, Kosten Thomas, Narayana Ponnada, F. Gerard Moeller*

Virginia Commonwealth University, Richmond, Virginia

Background: Cocaine dependent subjects as a group show an attentional bias to cocaine related stimuli, which has been used as a measure of cocaine cue reactivity. However, not all cocaine dependent subjects show this attentional bias. This pilot study compared functional magnetic resonance imaging (fMRI) brain activation between cocaine dependent subjects who showed an attentional bias during a cocaine-Stroop task to cocaine dependent subjects without an attentional bias.
Methods: FMRI data were acquired from 16 cocaine dependent subjects (CDs, 1 female) and 11 non-drug using healthy controls (CTLs, 4 females) when they performed a cocaine-Stroop task. The cocaine-Stroop protocol is a block design, in which a block (60 sec.) of neutral words alternates with a block (60 sec.) of cocaine words. There were 8 blocks, and each block was separated by 10 sec. rest. Across subjects, it was randomly selected whether cocaine words or neutral words were the first block. During the task, the subject was asked to discriminate the color of each stimulus and to ignore the meaning of the words. The difference between reaction time (ΔRT) to cocaine related words and neutral words was used as the "attentional bias" measure. FMRI data were processed using SPM12b, including standard preprocessing steps, first level, and second level statistical analysis. Activation was defined as the linear contrast of the parameter estimates for cocaine-word blocks minus neutral-word blocks. Statistical significance was defined as false discovery rate (FDR) corrected cluster probability (p) less than 0.05 (2-tail).
Results: The difference in age between CDs ($39.0.8 \pm 7.8$ yrs) and NCs (33.2 ± 8.5 yrs) was in trend significance ($t = 1.8435$, $p = 0.0771$). During the task, nine CDs (age: 38.5 ± 6.0) had attentional bias ($\Delta RT > 0$) and the other 7 CDs (age: 39.1 ± 10.1) did not have attentional bias ($\Delta RT < 0$). Overall, there was no significant difference in brain activation between the 16 CDs and the CTLs. In addition, there was no significant difference in brain activation between the 7 CDs without attentional bias and the CTLs. However, compared to CTLs, the 9 CDs with attentional bias had significant lower activation (Cluster 1, FDR corrected $p = 0.012$) in bilateral (LR) caudate, left (L) rectus, L superior orbital frontal gyrus (g), LR olfactory, L medial orbital frontal gyrus, and R anterior cingulated cortex (ACC). Compared to the 7 CDs without attentional bias, these 9 CDs with attentional bias had significant lower activation (Cluster 2, FDR corrected $p < 0.002$) in LR caudate, LR ACC, LR medial orbital frontal gyrus, LR rectus, LR superior orbital frontal gyrus, LR olfactory, right (R) thalamus, L inferior orbital frontal gyrus, and LR superior orbital frontal gyrus. The overlap between Cluster 1 and Cluster 2 had 568 voxels, occupying 57% of Cluster 1 (995 voxels), and 23% of Cluster 2 (2509 voxels).
Conclusions: These findings indicate that during a cocaine Stroop task, fMRI brain activation is related to attentional bias in CDs, suggesting that brain related cue reactivity differs between cocaine dependent subjects who show an attentional bias and those who do not. This result suggests that attentional bias may need to be considered as a screening factor in future studies of the neurobiology of cue reactivity including studies in which cue reactivity is a target for medication development in cocaine dependence.
Keywords: fMRI, Cocaine, Cue reactivity.
Disclosure: Consultant for Boehringer Ingelheim.

M189. Impaired Context Modulation in Posttraumatic Stress Disorder: An fMRI Study

Erel Shvil*, Santiago Papini, John C. Markowitz, Mohammed R. Milad, Tor D. Wager, Yuval Neria

Columbia University/New York State Psychiatric Institute, New York, New York

Background: Contextual processing deficits have been implicated in the pathophysiology of posttraumatic stress disorder (PTSD). Furthermore, recent reviews have suggested impaired context-dependent fearful memory is an important vulnerability factor for developing PTSD. However, studies have yet to examine context modulation in PTSD. The current study assessed whether subjects with PTSD exhibit impaired context modulation and determined whether this impairment involves dysfunctional activation of the hippocampus.
Methods: Thirty-two PTSD subjects and 32 matched trauma-exposed healthy controls completed a two-day Pavlovian conditioning paradigm with functional magnetic resonance imaging (fMRI) and skin conductance response (SCR) assessments (Milad et al., 2007). On Day 1, during the conditioning phase, two different colored lights ($CS+1$ and $CS+2$) were paired with shock in the threat-context. The extinction-learning phase (for $CS+2$) began approximately one minute after the conditioning phase ended. While the $CS+1$ was not presented at this point, both

the CS + 2 and the CS- were presented without a shock in a novel context (safe-context). Twenty-four hours later, during the extinction-recall phase, all CSs were presented without reinforcement in the safe-context. Following the extinction-recall phase came the renewal phase, with all CSs presented without reinforcement in the threat-context. All fMRI images were preprocessed using standard procedures in SPM8 software. We used Neuro-Synth (Yarkoni, et al. 2011), to generate two regions of interest (ROIs) around the left and right hippocampus. We hypothesized that the change in context would not modulate SCR responses in the PTSD group. In addition, we predicted greater differential hippocampal activation between the two contexts in the control group but not in the PTSD group.

Results: a) Fear Conditioning: A significant Stimulus main effect, $F = 32.72$ $df = 1, 62$, $p < 0.007$, showed greater response to the CS + than to CS- among both the PTSD and the control groups. No significant Group main effect or Group x Stimulus interaction was found, suggesting the PTSD and control groups had similarly conditioned to the CS +. b) Extinction (Day 2): No significant main effect of Stimulus, Group or Group x Stimulus interaction (last 4 CS + vs. last 4 CS- trials) appeared, suggesting comparable extinction learning had been achieved in both groups. c) Contextual Modulation Assessment: An ANOVA (mean of the first four CS + 1 trials in threat- context during renewal phase vs. the mean of the last four trials in safe-context during Day 2 extinction phase) revealed a significant Group X Context-type interaction ($F = 4.12$, $df = 1, 62$, $p = 0.04$). Whereas the control group had significantly lower SCRs to the CS + 1 presented in safe-context compared with threat-context ($p < 0.02$), the PTSD group failed to differ in SCR between the CS + 1 presented in safe-context compared with threat-CX ($p = 0.12$). This suggests impaired contextual modulation of the CS + 1 response in the PTSD group. D) BOLD responses: Within the hippocampal ROIs, the control group showed greater activation of the left hippocampus in the safe-context compared to the threat-context relative to the PTSD group ($p < .05$ corrected). Within group and on average across the a priori ROIs, the control group showed marginally increased bilateral hippocampal activation for the CS + 1 presented in the safe-context compared to the CS + 1 presented in the threat-context (Left hippocampus: $t = 1.97$, $df = 25$, $p = 0.06$; Right hippocampus: $t = 1.88$, $df = 25$, $p = 0.07$). The PTSD group demonstrated no difference in hippocampal activation for the CS + 1 in the safe-context compared to the threat-context (Left hippocampus $t = -1.01$, $df = 30$, $p = 0.32$; Right hippocampus: $t = 0.29$, $df = 30$, $p = 0.77$).

Conclusions: Our findings link dysfunctional hippocampal activation to impaired context modulation of conditioned threat responses in PTSD, providing further evidence of hippocampal irregularities in this disorder. This impairment may underlie difficulties in effectively discriminating threat from non-threat stimuli and overgeneralization of fear in PTSD. Our findings could guide the development of psychotherapies aiming to facilitate context processing and of novel pharmacological compounds targeting hippocampal plasticity in PTSD.

Keywords: fMRI, PTSD, Context, Fear.
Disclosure: Nothing to Disclose.

M190. Subcortical Biophysical Abnormalities in Major Depression with and without Diabetes

Anand Kumar*, Shaolin Yang, Olusola Ajilore, Jamie Cohen, Melissa Lamar, Dulal Bhaumik

University of Illinois at Chicago, Chicago, Illinois

Background: Major depression (MDD) is commonly seen in patients diagnosed with Type 2 diabetes and is associated with several negative outcomes including poor compliance and more frequent complications of diabetes. Despite the clinical association, the underlying neurobiological mechanisms of depression associated with type 2 diabetes remain unknown. Magnetization transfer (MT) is a magnetic resonance imaging (MRI) based neuroimaging approach that makes it possible to examine the biophysical properties of macromolecular proteins in both gray and white matter regions of the brain. In an earlier study (Kumar, A, et al. Arch Gen Psych 66:324-330, 2009), we reported lower MT ratio (MTR; a composite measure in the gray matter of macromolecular proteins and lipids) in the head of the caudate nucleus in patients with type 2 diabetes and depression when compared with healthy control subjects and patients with diabetes without depression. The goal of our current study was to examine the biophysical integrity of the macromolecular protein pool in 'nodes' belonging to the three main frontal-subcortical circuits responsible for mediating behavior – the anterior cingulate (Ac), dorsolateral prefrontal (Df) and orbitofrontal (Orbf) circuits and their corresponding subcortical nodes (Alexander, GE, Ann Rev Neurosci 9:357-381, 1986). The regions examined, in addition to the aforementioned cortical regions, included the head of the caudate nucleus, putamen, globus pallidus, thalamus and the frontal white matter. Subjects from four groups – patients diagnosed with type 2 diabetes with ($n = 21$, aged 65.1 ± 11.6 years, 12M/9F) and without MDD ($n = 22$, aged 56.1 ± 10 years, 10M/12F); healthy control subjects ($n = 38$, aged 62.6 ± 12.1 years, 16M/22F) and patients diagnosed with MDD without diabetes ($n = 32$, aged 58.5 ± 12.6 years, 9M/23F). All participants received a comprehensive psychiatric assessment and structured clinical interview.

Methods: The MRI was performed on a Philips Achieva 3T scanner (Philips Medical Systems, Best, the Netherlands). The MT images were acquired using a three-dimensional (3D) spoiled gradient-echo sequence with multi-shot echo-planar imaging (EPI) readout and the following parameters: TR/TE = 64/15 ms, flip angle = 9°, field of view (FOV) = 24 cm, 67 axial slices, slice thickness/gap = 2.2 mm/no gap, EPI factor = 7, reconstructed voxel size = $0.83 \times 0.83 \times 2.2$ mm3, with a nonselective five-lobed Sinc-Gauss off-resonance MT prepulse (B1/Δf/duration = 10.5μT/1.5kHz/24.5ms) optimized for maximum white matter/gray matter contrast (Smith, SA, et al. Magn Reson Med 56:866-875, 2006). The image slices were parallel to the anterior commissure–posterior commissure line.

Results: T1-weighted MPRAGE images, T2-weighted FLAIR images, and the images without the off-resonance MT prepulse in the MT scan (M0) were co-registered first and the images with the off-resonance MT prepulse (Ms) were then registered to the co-registered M0. The MTR values were calculated on the voxel-by-voxel basis using

co-registered M0 and Ms with the formula MTR = (M0-Ms)/M0. The ROIs were placed at the nodes of frontoal-subcortical circuits including four subcortical regions, i.e., the head of the caudate nucleus, putamen, globus pallidus, and thalamus, and three cortical regions, i.e., Ac, Df, Orbf, in both hemispheres. For the three cortical ROIs, we used the FreeSurfer package (https://surfer.nmr.mgh.harvard.edu/) to segment out these structures. The generation of the ROIs in the images and the calculation of MTR in each ROI were performed using in-house developed programs. MTRs were compared between groups using a mixed-effects model with random subject error incorporating within-subject correlation and adjusting for fixed covariates such as age and gender. MTR was significantly lower in several subcortical nuclei/nodes in the groups with MDD when compared with the healthy control and diabetic control groups $p < 0.05$; R and L thalami, R caudate, and R and L globus pallidus. There were no differences in MTR in the cortical regions between groups. MTR in several subcortical regions correlated inversely- the expected direction -with measures of glycemic control (hemoglobin A1c), stroke risk (Framingham Scale), and the CES-D score for depression.
Conclusions: Our data demonstrate that key subcortical nodes in frontal-subcortical circuits were biophysically compromised in patients with MDD and may be relevant to the pathophysiology of mood disorders. These observations have broad implications for the underlying neurobiology of depression across categories.
Keywords: magnetization transfer, depression, diabetes.
Disclosure: Nothing to Disclose.

M191. Disconnection of Striatum, Hippocampus, and Cortex Assessed with 18F-Fallypride PET Binding in Schizophrenia

Monte Buchsbaum*, Bradley T. Christian, Brian Merrill, Douglas S. Lehrer

University of California at San Diego, San Diego, California

Background: Extra-striatal cortical and thalamic dopamine D2 receptors may be more critical to the pathophysiology of schizophrenia and antipsychotic response than the striatal dopamine D2 receptors since the behavioral function of these areas appears more closely related to the symptoms of schizophrenia. The high-affinity dopamine receptor ligand fallypride allows assessment of both cortical and subcortical brain structures.
Methods: We had acquired 18F-fallypride images on 25 unmedicated (primarily never-medicated) patients with schizophrenia and 19 age and sex-matched normal controls. Dopamine D2/D3 receptor levels were measured as binding potential (BP). MRI images in standard Talairach position and segmented into gray and white matter were coregistered to the fallypride images and the AFNI stereotaxic atlas applied. We examined the interregional correlation coefficients in the healthy and patient groups separately. To assess circuits widely reported in fMRI studies, we assessed the hippocampus, fusiform gryus, inferior and middle temporal gyri, substantia nigra, thalamus, medial dorsal nucleus, accumbens, medial geniculate, Brodmann area 5 and 10, the superior and inferior amygdala, and the dorsal and ventral caudate.
Results: Using Steiger's test implemented in R we confirmed differences between the two groups (Chi-square = 206, df = 105, p = 1.3e-08. Follow-up univariate tests revealed significantly lower ($P < 0.05$) correlations between hippocampus-temporal lobe, thalamus-amygdala, and temporal-accumbens, -thalamus, -BA05, -BA 10, -inferior amygdala, and dorsal caudate-hippocampus, -accumbens, -amygdala, and -ventral caudate regions. The mean z-transformed r values were also different by t-test. Sets of prefrontal-thalamic, prefrontal-striatal, and temporal-hippocampal-thalamic regions were further explored.
Conclusions: Central gray matter disconnection dominated the deficit pattern suggesting relatively short pathways were important in the pathology of schizophrenia.
Keywords: dopamine circuitry, positron emission tomography, basal ganglia, psychosis.
Disclosure: Nothing to Disclose.

M192. Baseline Functional Corticostriatal Circuitry Predicts Treatment Response in First Episode Schizophrenia

Deepak Sarpal*, Delbert Robinson, Todd Lencz, Miklos Argyelan, Katherine Karlsgodt, Majnu John, Gallego Juan, John Kane, Philip Szeszko, Anil Malhotra

Zucker Hillside Hospital, Glen Oaks, New York

Background: Though antipsychotic medications are the primary treatment for psychosis, many patients fail to show an adequate clinical response to standard agents, suggesting a need for prognostic biomarkers. Pre-treatment neuroimaging measures have the potential to provide prognostic information, but have not been extensively studied in the context of controlled clinical trials that differentiate response to treatment of psychosis. We have recently demonstrated that functional connectivity of several key corticostriatal networks may be influenced by antipsychotic medication (Sarpal et al., JAMA Psychiatry, in press). However, no study to date has examined whether functional corticostriatal interactions might predict treatment response. In a group of first-episode patients with schizophrenia, we tested whether baseline functional connectivity of the striatum can predict response to treatment with second-generation antipsychotic medications.
Methods: Forty-one patients experiencing their first-episode of schizophrenia were examined. Patients underwent resting state fMRI scanning and evaluation of symptomatology prior to 12-weeks of controlled treatment with a second-generation antipsychotic medication (risperidone or aripiprazole). Following a 5-minute resting-state fMRI scan, whole-brain functional connectivity maps of were derived for each subject from 12 striatal seed regions of interest (ROIs). Raters blind to treatment condition and MRI results conducted weekly assessments during the first 4 weeks, then biweekly assessments. Response criteria were stringent, requiring a Clinical Global Impressions Scale (CGI) improvement rating of much or very much improved, as well as a rating of 3 ("mild") or less on all of the following items of the BPRS-A: conceptual disorganization, grandi-

osity, hallucinatory behavior, unusual thought content. Treatment response status and number of weeks to response were entered into two sets of Cox regression analysis: first, we performed a hypothesis-driven analysis of 6 corticostriatal networks emerging from our prior work (Sarpal et al, in press); second, we performed a voxel-wise exploratory analysis to our whole-brain functional connectivity data derived from our 12 striatal seed ROIs. The hypothesis-driven analyses were Bonferroni-corrected (p-value threshold set at .05/6 = .00833. For the voxel-wise analyses, significant results were defined at $p < 0.001$, cluster corrected.

Results: Of the six a priori corticostriatal networks examined, decreased functional connectivity between the right putamen and anterior cingulate was able to separate responders from non-responders at a Bonferroni-corrected significance level ($p = 0.0027$). Additionally, voxel-wise analyses revealed that decreased connectivity between right putamen and bilateral insula strongly predicted response to treatment. Other significant corticostriatal predictors of response included a dorsal caudate-precentral gyrus circuit, as well as networks connecting nucleus accumbens with temporal lobe structures.

Conclusions: Our results provide evidence that abnormal functional corticostriatal connectivity may predict response to treatment with antipsychotic medications. In particular, lower connectivity between striatum and limbic and frontal areas including the anterior cingulate, insula, and hippocampus may be associated with more rapid response to treatment.

Keywords: Schizophrenia, Antipsychotic, striatum, connectivity.

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M193. Atypical Development of Neural Substrate for Error-processing in Pediatric Obsessive Compulsive Disorder

Kate Fitzgerald*, Yanni Liu, Robert Welsh, Gregory Hanna, Stephan Taylor

University of Michigan, Ann Arbor, Michigan

Background: Hyperactivation of dorsal anterior cingulate cortex (dACC) during error-processing has been implicated in OCD, based on functional MRI (fMRI) and electrophysiological research in child and adult patients. Hyperactive dACC response occurs with errors on simple cognitive tasks, even when OCD symptoms are not specifically evoked, leading investigators to hypothesize generalized hypersensitivity to errors as a core process underlying illness. The observation of hyperactive error response near illness onset, in pediatric patients, suggests that abnormal development of error-processing function may underlie early course of OCD. Yet, atypical development of dACC-based error-processing function remains to be documented. Moreover, it remains unclear whether increased dACC response to errors indexes a pathological source of OCD symptoms, or reflects a downstream, compensatory response that may help patients to reduce symptom severity. To address these questions, we conducted a cross-sectional fMRI study of pediatric patients with OCD compared to healthy controls, across a wide range of ages and symptom severity. We hypothesized that a) age would differentially associate with dACC response to errors in patients compared to controls and b) among patients, greater error-related dACC activation would associate with OCD severity.

Methods: Fifty-one OCD (14.2 + /- 2.8 years) and 51 healthy youth (14.1 + /- 3.2 years), ranging in age from 8 to 19 years, performed an error-eliciting interference task in a rapid, event-related design. Forty oblique T2* weighted images were acquired on a 3T GE Magnet (TR = 2000 ms, TE = 30 ms, flip angle = 90o, FOV = 20 cm, Freq = 64, 3 mm/slice). Using SPM8, contrasts between error and non-error trials during the high interference, incongruent condition were calculated at the first level, and then entered into a random effects model to test the effects of errors on brain activation across all subjects (OCD + healthy). The resulting whole brain map for error-processing was displayed at a threshold of $p(fwe) < 0.005$, revealing a large cluster of error-related activation spanning dACC into pre-supplementary motor area (-6, 29, 28; $Z = 6.37$; $k = 992$). Contrast estimates were extracted from this volume and entered into a linear regression model testing for main effects of group, age (linear and quadratic, orthogonalized), performance (error rates, response time) and interactions between these variables. Among patients, contrast estimates were also tested for correlation with scores on the Child Yale-Brown Obsessive Compulsive Scale, controlling for effects of age and performance.

Results: Linear regression modeling showed main effects of group, group interaction with both linear and quadratic age terms, response times, and group interaction with response times. Group effects were driven by greater dACC activation to errors in patients compared to controls (ß = .79, p = .05). Main effects of age were not significant (linear effect: ß = − .24, p = .10, quadratic effect: ß = .006, p = .86). However, group x age interaction terms were significant for both the linear (ß = .42, p = .02) and the quadratic (ß = − 11, p = .02) effects of age; these interactions were driven by a more positive linear effect of age (i.e., steeper increase) and a more negative quadratic effect of age (i.e., more pronounced inverted U-shape relation with age), respectively, on dACC activation in pediatric OCD compared to healthy controls. For performance regressors, there was a significant negative effect of response time (ß = − .006, p = .003), but not error rate (ß = − .062, p = .13) on dACC activation. Group x performance interactions were also

significant for response time (ß = .005, p = .03), with patients exhibiting a more positive relationship of response time on dACC activation than controls. Finally, among patients, error-related activity of the dACC was inversely associated with OCD symptom severity (r = − .30, p = .03) – an effect that remained significant after covarying for age, response time and error rates (r = -.28, p = .05).
Conclusions: Compared to healthy youth, patients with pediatric OCD exhibited increased dACC activation during error-processing, consistent with prior work. In addition, we observed steeper age-related increase of dACC response to errors in patients than controls, consistent with abnormal development of error processing function early in the courese of illness. Greater dACC response to errors associated with lower OCD severity, suggesting that greater engagement of dACC-based error-processing function may reflect a compensatory mechanism through which patients achieve better control of symptoms. Longitudinal work is needed to determine whether increasing dACC activation to errors with age predicts better outcomes in patients over time and could serve as a target for mechanism-based treatment strategies (e.g., cognitive training, transcranial magnetic resonance stimulation) to reduce OCD severity.
Keywords: dACC, errors, OCD, development.
Disclosure: Nothing to Disclose.

M194. Preterm Birth Alters Functional Rich Club Organization

Dustin Scheinost*, Soo Kwon, Xilin Shen, Cheryl Lacadie, Karen Schneider, Feng Dai, R Todd Constable, Laura Ment

Yale University School of Medicine, New Haven, Connecticut

Background: Preterm (PT) birth represents a major public health problem; 27% of survivors experience significant long-term neurodevelopmental disability. While known to disrupt neural connectivity, emerging data suggest that PT birth results in both proximate and long-lasting changes in cerebral functional organization. Rich club (RC) organization is common construct among complex systems where important (or "rich") nodes connect preferentially to other important nodes. Indeed, structural connections in the human brain shows RC organization in infancy, childhood, and adulthood. While these structural RC are largely consistent over the lifespan, functional RCs evolve during development as hubs destined for the efficient long-range transfer of information mature. Using resting-state functional magnetic resonance imaging (rs-fMRI) data, we examined alterations in neonatal RC organization as a result of preterm birth.
Methods: Since PT neonates engage alternate pathways for language and executive function, we calculated neonatal RC organization separately for preterm and term infants. Twelve PT and 25 term non-sedated neonates without evidence of brain injury underwent rs-fMRI on a 3 T Siemens TIM Trio system at term equivalent age (TEA). Images were preprocessed with standard rs-fMRI processing. Using the term neonatal data, a functional brain atlas was created using a group-wise spectral clustering algorithm resulting in a 95 node parcellation. The mean time-course for each of the 95 nodes was calculated and these mean time-courses were correlated with each other forming a 95x95 weighted connectivity matrix. Negative correlations and self-loops were removed. To quantify RC organization, all connections are ranked by their weight creating a vector of weights (R) and all nodes with degree $\leq$k are removed in an iterative procedures over a range of k values. For the resulting sub-network at each k value, the sum of all connection weights (W), the number of connections (L), the sum of the L strongest weights in R (S) are computed. The RC coefficient for any k value is the ratio of W and S. RC coefficients were calculated for each subject over a range of k values ($30 \leq k \leq 90$) resulting in a RC curve for each subject. As networks may show increasing RC coefficients in the absence of RC organization, each subject's RC curve was normalized by a set of random networks, created by randomizing the connections of the network. For each subject, 1000 random networks were created and, for each random network, RC curves were computed. Normalized RC curves were computed as a subject's RC curve divided by the mean RC curve of the subject's random networks. Permutation testing was used to compare RC organization.
Results: Rich club organization was found for both PT and term neonates. PT infants displayed significantly reduced RC organization ($p < .05$, for $40 \leq k \leq 76$). RC nodes for the term neonates were located in the posterior cingulate, portions of the temporal and inferior parietal lobes, and lateral regions of the frontal lobe mainly in the right hemisphere. PT neonates had a significantly greater number of RC nodes (#PT nodes = 34 ± 26, term nodes = 16 ± 15, $p < 0.0025$) and greater consistency of RC nodes among subjects (mean PT overlap = 40.2%, mean term overlap = 17.6%; $p < 0.001$). Regions of the highest overlap for the PT neonates were in regions similar to the RC nodes for term neonates. All regions in the term neonates RC also appeared in the PT neonates RC with the exception of two in the right frontal lobe (Brodmann area 9). Additionally, the number of RC nodes was not correlated with gestational age (GA) at birth for the PT neonates ($r = 0.41$, $p < 0.19$), suggesting a non-dose dependent effect of PT birth. Connection strength—defined for each node as the sum of connection weights divided by the number of connections—for connections between two RC nodes (RC connections), between RC nodes and non-RC nodes (feeder connections), and between two non-RC nodes (local connections) were calculated for each neonate based on individually defined rich clubs. Term neonates displayed significantly greater RC, feeder, and local connection strength ($p < 0.02$, $p < 0.003$; $p < 0.03$). Finally, we defined a group average RC as the top ten most consistent nodes from the term infant's individual RC nodes. Using this RC definition for both PT and term infants, there were no significant differences between any pair of connection weights or overall strength, suggesting that a core infrastructure is common to both groups.
Conclusions: Using a measure of whole-brain organization, these data demonstrate, for the first time, that preterm birth fundamentally alters functional RC organization in the developing brain. Comparing PT and term neonates at TEA, PT infants showed reduced RC organization, but displayed a greater number of RC nodes. For PT, the number of RC

nodes was not correlated with GA, suggesting a non-dose dependent effect of PT birth. Notably, PT appear to have the same core infrastructure as term infants. However, the PT RC comprises additional "rich" nodes not present in the term RC that appear to reduce the overall organization and connection strength between RC, feeder, and local connections. These results foreshadow altered neural networks in PT subjects at school age, adolescence and young adulthood and may reflect a delay in maturation or the engagement of auxiliary systems in the prematurely-born.
Keywords: Preterm, connectivity, resting-state, functional organization.
Disclosure: Nothing to Disclose.

M195. Resting State Amygdala Functional Connectivity and Antidepressant Treatment Response in Major Depressive Disorder

Go Okada*, Yasumasa Okamoto, Masahiro Takamura, Shigeru Toki, Tetsuya Yamamoto, Shigeto Yamawaki

Hiroshima University, Hiroshima, Japan

Background: The abnormal functional connectivity (FC) patterns have been reported in major depressive disorder (MDD), and neuroimaging studies of MDD have demonstrated enhanced amygdala reactivity to emotional stimuli relative to healthy controls (HCs). However, it is poorly understood, regarding the intrinsic FC of the amygdala in MDD and its relationships with the clinical characteristics such as an antidepressant treatment response. In this study, we investigated whether intrinsic FC of the amygdala characterizes MDD and predicts antidepressant response.
Methods: Resting-state functional magnetic resonance imaging (fMRI) was performed on 42 patients with MDD, and they were received standardized antidepressant treatment with escitalopram, a selective serotonin reuptake inhibitor (SSRI). Severity of depression was measured by the Hamilton Rating Scale of Depression, and treatment response was assessed six weeks after pharmacotherapy with escitalopram began. Forty-two age and sex matched HCs were also received the resting-state fMRI. We examined between-group difference in amygdala seed-based resting state FC, and also assessed its relationship to SSRI treatment response. The study was conducted under a protocol that was approved by the Ethics Committee of Hiroshima University. All participants gave informed consent prior to participation in the study.
Results: Relative to the HCs, the MDD group had higher level of connectivity of the right amygdala with a variety of brain regions involved in emotion processing, including the left temporal superior gyrus, right middle temporal gyrus, left inferior parietal lobule, and left middle temporal gyrus. Among the MDD, pretreatment right amygdala-subgenual anterior cingulate (sgACC) FC was positively correlated with symptom improvement after SSRI treatment.
Conclusions: These findings suggest that the enhanced resting state FC of the amygdala network may be related to altered emotion processing and regulation in MDD. Our preliminary data also implicate the sgACC-amygdala interaction in the prediction of SSRI treatment response. Further studies are needed to clarify the utility of this potential biomarker in clinical decision making to attain a better antidepressant treatment outcome.
Keywords: major depressive disorder, fMRI, functional connectivity, antidepressant.
Disclosure: Nothing to Disclose.

M196. Probing Molecular Markers of Inflammation and Oxidative Stress in Patients with Early Stage Schizophrenia: A Combined Study of CSF and PET-based Imaging

Jennifer Coughlin*, Yuchuan Wang, Teppei Tanaka, Shuangchao Ma, Lindsay Hayes, Martin Pomper, Akira Sawa

Johns Hopkins University School of Medicine, Baltimore, Maryland

Background: Interconnected oxidative stress and inflammatory pathways may underlie the pathology of schizophrenia. We have addressed this question by examining cerebrospinal fluid (CSF) biochemically. Studies have also probed this proposed mechanism using brain imaging. Results from a recent post-mortem study by Kreisl et al. using [11C]PBR28 demonstrated a 16% increase in specific binding to translocator protein (TSPO), a candidate marker of inflammatory response, in prefrontal cortex of patients with schizophrenia. Nonetheless, almost all studies are limited to one methodology and test for either markers of inflammation or of oxidative stress. Therefore, the molecular mechanisms underlying pro-oxidative and inflammatory processes in this disease remain elusive. We sought to test for in vivo tissue markers consistent with a model integrating these two processes in early stage disease using both molecular imaging and CSF analysis in parallel.
Methods: We quantified regional distribution of TSPO in vivo using [11C]DPA-713 positron emission tomography (PET)-based neuroimaging data of twelve, well-characterized patients with recent onset of schizophrenia (within five years of diagnosis) and twelve age-matched healthy controls. All subjects were genotyped for the rs6971 TSPO polymorphism to control for the effect of this common SNP on [11C]DPA-713 binding. Regional total distribution volume (VT) measurements were calculated using the Logan method for several cortical and subcortical regions from each subject's 90-min dynamic PET data and their metabolite-corrected plasma input function. In addition, markers of inflammation and oxidative stress were assessed from plasma and CSF specimens from these same patients and controls, and correlated with regional [11C]DPA-713 VT.
Results: [11C]DPA-713 brain uptake of TSPO in twelve patients with recent onset schizophrenia show a trend in altered PET signal in early stage schizophrenia after controlling for rs6971 genotype. Complementary molecular analysis of both plasma and CSF also suggest alterations in immune function and oxidative pathways in these same patients with recent onset of disease.
Conclusions: Our findings highlight the benefit of using parallel design of CSF study with PET-based neuroimaging to characterize in vivo molecular changes early in the disease process.

Keywords: schizophrenia, neuroinflammation, oxidative stress, TSPO.
Disclosure: Nothing to Disclose.

M197. Improvement of Brain Reward Abnormalities Correlate with Dopamine D2/3 Receptor Blockade: A Longitudinal Study on Initially Antipsychotic-Naïve First-episode Schizophrenia Patients

Sanne Wulff, Egill Rostrup, Mette Ø. Nielsen, Claus Svarer, Lars Thorbjørn Jensen, Lars H. Pinborg, Birte Y. Glenthøj*

Copenhagen University Hospital, Glostrup, Denmark

Background: Positive schizophrenic symptoms have been associated with abnormalities in striatal dopamine activity as well as with changes in striatal blood oxygen level dependent (BOLD) response during reward anticipation. The link between blockade of striatal D2/3 receptors and the effect of antipsychotics on positive symptoms is well-validated and we have previously demonstrated an effect of treatment with amisulpride on the disturbances in reward processing (Nielsen et al. 2012). However, a direct influence of striatal D2/3 receptor blockade on striatal brain activity during reward anticipation in antipsychotic-naïve schizophrenia patients has, to our knowledge, never previously been shown. The purpose of the present study was to examine the association between alterations in reward processing, striatal dopamine D2/3 receptor blockade and positive psychotic symptoms in a longitudinal study of initially antipsychotic-naïve first-episode schizophrenia patients.
Methods: Twenty-eight antipsychotic-naïve first-episode schizophrenia patients and 26 healthy controls matched on age, sex, and parental socioeconomic status were recruited in the Capital region of Denmark as part of a large multimodal longitudinal study on antipsychotic-naïve first-episode schizophrenia patients (the PECANS study). The patients were examined with functional Magnetic Resonance Imaging using a variant of the monetary-incentive-delay task before and after six weeks of treatment with flexible doses of the relatively selective D2/3 receptor antagonist, amisulpride. D2/3 receptors were assessed with Single Photon Emission Computed Tomography using 123-labeled-iodobenzamid. There was an overlap between patients and healthy controls included in the present study and the study described in Nielsen et al. 2012 of 9 patients and 6 controls.
Results: In agreement with previous data from our group, we found an attenuated striatal BOLD response in the patients at baseline that partly normalized after treatment. The increase in the BOLD response was correlated with the improvement of positive symptoms. In the patients, who responded to treatment, the increase was further significantly associated with D2/3 receptor occupancy. In line with this, a higher BOLD response was associated with higher D2/3 receptor occupancy at follow up.
Conclusions: To our best knowledge, the present data are the first to confirm a direct influence of striatal D2/3 receptor blockade on striatal brain activity during reward anticipation. Ref. Nielsen MØ, Rostrup, E, Wulff S, Bak N, Broberg BV, Lublin H, Kapur S, Glenthøj B. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Archives of General Psychiatry 2012 Dec;69:1195-204.
Keywords: SPECT, dopamine D2 receptors, fMRI, reward.
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M198. Corticostriatal and Glutamatergic Predictors of Adolescent Depression

Randy Auerbach*, Angela Pisoni, Poornima Kumar, Colin H. Stanton, John E. Jensen, Diego A. Pizzagalli

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: There is a dramatic increase in the prevalence of major depressive disorder (MDD) during adolescence. In particular, between the ages of 12-18, there is a 6-fold increase in rates of MDD, and at the age of 14 gender differences begin to emerge with female adolescents reporting twice as many depressive episodes as males – a difference that persists throughout adulthood (Merikangas et al., 2010). Identifying promising biological markers that contribute to the onset and maintenance of depressive symptoms during this critical developmental window is essential, and emerging evidence indicates that deficits within the mesocorticolimbic pathways (i.e., anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC); e.g., Forbes et al., 2009) and glutamatergic dysfunction (e.g., Merkl et al., 2011) may play key roles in MDD. Presently, it is unclear whether these abnormalities are a cause or consequence of MDD. Consequently, in order to identify biomarkers that may prospectively predict depressive symptoms in low- and high-risk adolescents ages 12 to 14 (i.e., a critical developmental period prior to the peak onset for MDD), the current study utilizes functional magnetic resonance imaging (fMRI) to probe neurobiological mechanisms underlying reward deficits and magnetic resonance spectroscopy (MRS) to assess glutamate and glutamine levels within the rostral ACC (rACC).
Methods: At baseline, low- and high-risk (i.e., with a maternal history of MDD) female adolescents, aged 12-14, and mothers completed diagnostic interviews to assess for current and past mental health disorders. All participating female adolescents reported no current or past history of mental illness and were matched for pubertal status. Adolescents and parents then completed questionnaires assessing adolescent depressive and anxious symptoms, anhedonic symptoms, and perceived stress. After the baseline assessment, adolescents completed an ecologically valid peer feedback task (i.e., Chatroom Task that assesses peer acceptance versus rejection) while fMRI data were collected, and additionally, MRS data assessed glutamate and glutamine levels within the rACC. After completing the

baseline assessment, adolescents and parents completed 1- and 3-month follow-up assessments pertaining to adolescent symptoms.
Results: Preliminary results (low-risk = 15; high-risk = 8) from the Chatroom Task (i.e., peer acceptance vs. rejection) indicate that relative to high-risk adolescents, low-risk youth show greater activation when contrasting acceptance versus rejection trials within the nucleus accumbens ($p < .005$ uncorrected, $x = -12$, $y = 6$, $z = -2$; $z = 3.48$; cluster = 20 voxels) and right ventral striatum ($p < .005$ uncorrected, $x = 16$, $y = 10$, $z = -10$; $z = 3.19$; cluster = 20 voxels). When examining glutamatergic dysfunction, compared to the low-risk group, the high-risk group exhibited a greater glutamatine-glutamate ratio at the trend level ($t(21) = -1.42$, $p = .117$) suggesting glutamatergic overactivity and defective neuronal-glial coupling. Data collection remains ongoing, and the target sample will include 40 adolescents (low-risk = 20, high-risk = 20) as well as prospective symptom data 1- and 3-months following the baseline assessment.
Conclusions: Overall, these preliminary data highlight that greater risk for adolescent MDD may be characterized by both corticostriatal and glutamatergic dysfunction. Together, these data provide empirical support for identifying neurobiological abnormalities that may improve our early identification of and treatment for adolescent MDD.
Keywords: Adolescent Depression, Reward, Glutamate, Glutamine.
Disclosure: Over the past three years, Dr. Pizzagalli has received consulting fees from ANT North America Inc. (Advanced Neuro Technology), AstraZeneca, Servier, and Pfizer for activities unrelated to the current research.

M199. The Impact of Birth Weight on Brain Morphology in Adolescence: A Monozygotic Twin Study and Epigenetic Mechanisms

Kevin Casey, Melissa Levesque, Elmira Ismaylova, Marie-Pier Verner, Cherine Fahim, Frank Vitaro, Mara Brendgen, Ginette Dionne, Michel Boivin, Moshe Szyf, Richard Tremblay, Linda Booij*

Queen's University, Kingston, Canada

Background: Numerous studies in humans have shown that adverse events happening in utero or short after birth could lead to mental health and cognitive problems later on. For instance, perinatal adversity (e.g. prematurity, low birth weight, gestational exposure to nicotine) has been associated with greater risk for externalizing problems or problems in executive functioning. Neuro-imaging studies have associated perinatal adversity with a variety of alterations in cortical and subcortical brain structures in childhood and adolescence. However, little is known how much of this association is confounded by gene sequence. The present study utilizes a monozygotic (MZ) twin design to investigate whether the perinatal environment affects in adolescence the morphological development of brain structures that are highly involved in the regulation emotions and cognitive processing (i.e. frontal-limbic circuitry). Since MZ twins are genetically identical, investigation of differences within MZ twin pairs controls for gene sequence. Differences in the perinatal environment were indexed by birth weight. In addition to having the same genes, MZ twins also have many perinatal environmental characteristics in common (e.g., gestational age, mother's lifestyle). Thus, differences in birth weight are likely to be related to differences in unique factors acting in utero. Hence, to the extent that birth weight is associated with outcome and within-pair birth weight discordance predicts discordance, unique in utero characteristics must be an underlying pathway accounting for this relationship. The present study tested (1) whether lower birth weight was associated with altered brain morphology and (2) whether the magnitude of within pair differences in birth weight was associated with within pair differences in brain morphology. (3) We also examined whether DNA methylation is a putative mechanism accounting for the association between the perinatal environment and brain morphology.
Methods: Fifty-three healthy MZ twin pairs (23 male pairs, 30 female pairs) from the Quebec Study of Newborn Twins, followed regularly since birth, were tested at age 15. Twin pairs had variable discordances in birth weight. Each participant underwent T1 weighted MRI. The CIVET pipeline was used to extract morphological features including cortical thickness, volume, and surface area. A saliva sample was taken to investigate DNA methylation at over 480,000 methylation sites across the genome using Illumina Infinium HumanMethylation450K BeadChip kits. We first investigated the relationships between cortical morphometry and birth weight, and then looked for patterns in methylation which might plausibly underlie them.
Results: We replicated previous observations of strong positive associations between birth weight and cortical surface area across the cortical mantle when our participants were considered as single-subjects (modeling effects of family membership, and sex). This relationsip was present in the whole brain ($Q = 0.009$), an in each of the cortical lobes. A highly similar relationship was observed between birth weight and cortical volume ($Q = 0.039$). Next, we looked for differences within the twin pairs and found that the brains of the lower birth weight members of a twin pair had reduced cortical surface area ($Q = 0.024$), relative to the higher birth weight members of a twin pair. Furthermore, the magnitude of the twins' discordance in birth weight was positively related to the discordance in cortical surface area ($Q = 0.008$) and volume ($Q < 0.001$). DNA methylation analyses of the first 37 pairs showed relatively high within-pair variability in genes associated with (brain) development, cellular mechanisms, tissue and cell morphology and various disorders. The present poster will also present results on the putative role of DNA methylation in the association between the perinatal environment and brain morphology in the full data-set.
Conclusions: Overall, these preliminary findings of our longitudinal twin study support the importance of the in utero environment for long-term brain development, while controling for gene sequence. Alterations in morphology may be a mechanism of how adverse in utero factors could increase susceptibility to psychopathology or cognitive problems.
Keywords: Brain development, Adversity, Epigenetics, Perinatal stress.
Disclosure: Nothing to Disclose.

M200. Dopaminergic Tone and Neuroleptic Mediated Hyperactivity in the Striatum of Patients with Schizophrenia

Daniel Eisenberg*, Lisa Yankowitz, Philip Kohn, Catherine Hegarty, Angela Ianni, Nicholas Turner, Michael Gregory, Joseph Masdeu, Daniel Weinberger, Jose Apud, Karen Berman

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: In schizophrenia, antipsychotic treatments enact variable, partial therapeutic responses linked to D2 receptor blockade. In the striatum, where these receptors abound, patients, on average but not uniformly, demonstrate phenotypes consistent with exuberant presynaptic dopaminergic operation, such as elevated measurements of striatal dopamine synthesis and greater striatal dopamine release in response to amphetamine challenge. The degree to which an individual with primary psychosis expresses these phenotypes may, therefore, be an important predictor of neural responses to antipsychotic medications, the mechanisms underlying which remain incompletely understood. Acute increases in striatal activity from antipsychotic administration have been observed in animals, healthy individuals, and patients and have been hypothesized to be linked to therapeutic response. In light of these data, we hypothesized that patients with greater striatal presynaptic dopaminergic tone might show greater striatal blood flow change in response to neuroleptics.
Methods: Fifteen patients (age 27.47 + /- 7.28, 6 female) with schizophrenia underwent three positron emission tomography (PET) scanning sessions while undergoing a blinded, balanced two-arm medication withdrawal protocol. Two scans were performed after at least three weeks of placebo treatment – one [18F]DOPA PET scan to measure dopamine synthesis and one [15O]water PET scan to measure regional cerebral blood flow (rCBF) – and an additional [15O]water PET scan was performed after at least 3 weeks of standard, stable antipsychotic monotherapy. For [18F]DOPA studies, a single oral dose of carbidopa was administered to limit peripheral tracer decarboxylation. After an 8-minute transmission scan for attenuation correction, intravenous injection of [18F]DOPA (13-17mCi) was followed by a 90-minute, dynamically binned emission scan on a GE Advance PET scanner. Three bilateral striatal regions of interest (ROIs; caudate, putamen, ventral striatum) and one cerebellar reference region that would serve as the input function were generated from coregistered native T1 weighted 3T MRI volumes acquired in a separate session. Calculation of Ki, the specific uptake rate constant and a measurement of dopamine synthetic capacity, utilized the Gjedde-Patlak method, as implemented in PMOD software. For each [15O]water session, two minute-long resting-state emission scans, separated by 6 minutes were obtained for each subject and were corrected for attenuation and background activity, registered, spatially normalized, scaled, smoothed, and averaged. Mean voxel values for bilateral caudate, putamen and ventral striatum ROIs were obtained as above from a corresponding, T1 weighted template, subtracted across medication condition, and entered into standard statistical association analyses using SPSS. Symptoms were rated during both medication and placebo arms with the Positive and Negative Syndrome Scale.
Results: During antipsychotic medication treatment relative to placebo, patients had on average fewer symptoms (paired $t(14) = 2.64$; $p = 0.019$) and a significant increase in regional cerebral blood flow (rCBF) in all three ROIs (caudate: $t(14) = 2.41$, $p = 0.030$; putamen: $t(14) = 3.00$, $p = 0.010$; ventral striatum: $t(14) = 3.39$, $p = 0.004$). Greater therapeutic response to medication correlated positively with rCBF increase in the putamen ($r(13) = 0.55$, $p = 0.034$) and ventral striatum ($r(13) = 0.60$, $p = 0.017$), but not in the caudate. When rCBF change and medication-free Ki were tested for association (one Pearson's test for each ROI), both putamen ($r(13) = 0.56$, $p = 0.028$) and ventral striatum ($r(13) = 0.69$, $p = 0.005$) showed significant positive correlations (greater K¬i was associated with greater medication-induced rCBF increases), but caudate did not. These results remained significant in partial correlation analyses accounting for sex, age, and chlorpromazine equivalent dose. Post-hoc correlations between Ki and blood flow during each condition separately were not significant.
Conclusions: Antipsychotic treatment, relative to placebo, induces enhanced striatal blood flow that may be therapeutically relevant. Dopaminergic tone measured in the medication-free state may selectively predict the strength of this response, an association that is unlikely explained by perfusion biases in the Ki calculation. Future work to corroborate and extend these findings will help refine understanding of the salient facets of neuroleptic therapeutic action in the service of ultimately generating novel, personalized approaches to psychiatric care.
Keywords: Schizophrenia, Dopamine, Antipsychotic, Striatum.
Disclosure: Nothing to Disclose.

M201. Imaging the Expression of Visceral and Peripheral Pain

Joseph Carrion, Rebecca Silverman, Stergiani Agorastos, Christina Veith, Giovanni Santoro, Sandra Scherrer, Yoon-Young Choi, Wynne Schiffer, Jonathan Brodie, Stephen Dewey*

Feinstein Institute for Medical Research, Manhasset, New York

Background: Opioid abuse is a major health concern making the clinical management of pain a particularly complex issue. Central modulation of pain requires both inhibitory and excitatory pathways in neocortical and subcortical structures. Additionally, there is a marked difference between males and females in their response to opioid analgesia (Mogil, et al., 2012). In an ongoing effort to better understand how opioid-mediated pain management develops into opioid abuse, we established a reproducible metabolic signature of inflammatory pain using micropositron emission tomography (microPET), 18FDG, and two distinct animal models. Specifically, we utilized the acetic acid writhing and the formalin pain assays, the former a measure of visceral pain and the latter a measure of tonic peripheral inflammatory pain. Finally, using the formalin assay, we examined sex differences with respect to behavioral responses and metabolic signatures.

Methods: For each assay, animals initially received baseline 18FDG scans (n = 8 in each group). Formalin paw assay: Animals received 0.05 ml of 5% formalin in the left rear paw 10 minutes prior to a second 18FDG scan. Behavior was recorded for 30 minutes beginning 10 minutes after formalin. Animals were scored for pain intensity (0-3 with 3 being highest) using the Dubuisson and Dennis weighted-scoring method. Acetic acid assay: Animals received 0.9% acetic acid (10ml/kg, intraperitoneal) 15 minutes after a second 18FDG injection. Behavior was recorded for 30 minutes and time-sampled using Corel software into 5-second time bins collected every 10 seconds to capture 4 observations per minute. Static images were reconstructed using ordered subset expectation maximization-maximum a posteriori (OSEM-MAP) algorithms. Images were then co-registered to a standard rat atlas (Paxinos and Watson) with PMOD (Zurich, Switzerland), and statistical comparisons between the formalin/saline and acetic acid/saline groups were conducted using the statistical parametric map (SPM5) protocol.
Results: The acetic acid group expressed an average of 12.65 ± 1.69 writhes within the observation window. Increases in 18FDG uptake occurred in the dorsolateral periaqueductal grey, retrosplenial granular cortex, and the intermediate reticular nucleus. The formalin group expressed a pain score of 2.15 ± 0.19. Increases in 18FDG uptake also occurred in the dorsolateral periaqueductal grey but in the striatum, hippocampus, cerebellum, and thalamus as well.
Conclusions: The acetic acid and formalin pain assays produced distinct and reproducible metabolic signatures. These data suggest that brain regions associated with addiction (i.e., striatum and thalamus) are selectively activated in a model of peripheral inflammatory pain but not visceral pain. Thus, it is conceivable that a pharmacologic strategy targeted at blocking brain activations in specific regions associated with the addictive liability of opioids may attenuate their abuse potential while having no effect on their analgesic properties. Males and females had similar activations in the periaqueductal grey and thalamus in both pain assays. Females, however, had significant decreases in the caudate and nucleus accumbens shell. Behaviorally, at the start of the inflammatory phase of the formalin assay, females expressed a higher pain score than males (1.5 vs. 0.5). Clinically, it is known that males and females experience pain differently. Finally, using microPET, we may begin to better understand why these differences occur and how they may be used for the development of clinically relevant, sex-specific, pain management strategies.
Keywords: Pain, Imaging, microPET, addiction.
Disclosure: Nothing to Disclose.

M202. Disrupted Functional Topography of Striatal Connections in Schizophrenia

Guillermo Horga*, Clifford Cassidy, Mark Slifstein, Holly Moore, Xiaoyan Xu, Daphna Shohamy, Anissa Abi-Dargham, Jared Van Snellenberg

Columbia University/New York State Psychiatric Institute, New York, New York

Background: Converging evidence suggests that the striatum, in particular the associative striatum, is a central site of pathology in schizophrenia. Abnormal dopamine transmission in this region is thought to mediate its effects on cognitive processes via basal ganglia-thalamo-cortical pathways that modulate cortical function. Although the functional topography of the striatum has been partially assessed in task-based and resting-state functional connectivity studies, it is unclear whether the functional topography of striatal connections as a whole (i.e., the specific pattern of connections across striatal subregions) is preserved in patients with schizophrenia. Furthermore, given that striatal-cortical connectivity is sensitive to dopamine agonism and antagonism (Cole et al., Cerebral Cortex 2013; Kelly et al. J Neurosci 2009), an assessment of functional topography in unmedicated patients is needed. Here, we tested the hypothesis that the normal functional topography of striatal connections is disrupted in unmedicated patients with schizophrenia.
Methods: We obtained functional magnetic resonance imaging (fMRI) data during an eyes-open, resting-state condition in 18 medication-free patients with schizophrenia and 24 sociodemographically matched healthy controls. Five striatal subregions (ventral striatum, pre-commissural caudate, pre-commissural putamen, post-commissural caudate and post-commissural putamen) were manually delineated on anatomical T1 scans for each participant. Following preprocessing of fMRI data, functional connectivity maps were generated in SPM8 by simultaneously regressing averaged timeseries for each of the five striatal subregions (and nuisance variables including timeseries from regions of no interest, motion parameters, and artifactual volumes) against fMRI signal in subject-level voxel-wise analyses. Univariate analyses using a linear mixed model compared within-group and between-group differences in connectivity by striatal subregion. FDR-corrected p-values at the cluster level were used to assess statistical significance. We also conducted an analysis of global brain connectivity from each striatal subregion to every voxel in the brain (excluding the striatum). To test the hypothesized differences in functional topography of the striatum as a whole, we further parcellated the connectivity maps by subregion into cortical Brodmann areas (18) and subcortical regions (9) with significant connections to any of the striatal subregions. We then used multivariate pattern analysis, specifically linear support vector machine (SVM), to test the accuracy of a binary group classification based on connectivity strength for all relevant pairs of regions (5 striatal subregions by 27 cortico-subcortical target regions, for a total of 135 features), using leave-one-out cross-validation.
Results: Univariate analyses showed that striatal subregions in healthy controls had specific patterns of functional connectivity that differed across regions. The anterior (pre-commissural) caudate had stronger global connectivity to the rest of the brain than the other striatal subregions. Specifically, the anterior caudate was more strongly connected than the other striatal subregions to ventromedial and dorsolateral prefrontal cortex, thalamus, posterior cingulate cortex, parietal and temporal regions. In turn, the posterior (post-commissural) putamen was more strongly connected than the other subregions to premotor and occipital cortices. In within-group analyses, patients had no evidence for such functional topography of striatal connec-

tions although we failed to detect significant differences between the groups. Nonetheless, the multivariate SVM classifier was able to differentiate the groups with above-chance accuracy (64% leave-one-out accuracy; $p = 0.04$, binomial test), suggesting that the specific pattern of connections across striatal subregions was indeed disrupted in patients.

Conclusions: These results suggest that the anterior caudate may have a particularly strong influence on brain-wide networks including default-mode, fronto-parietal, and executive networks. Critically, our data provide support for the notion that the functional topography of striatal connections to other cortical and subcortical regions is disrupted in schizophrenia and suggest that such disruption is not a direct consequence of antipsychotic medication. A more exact characterization of this disruption to striatal connectivity is likely to emerge in samples with enhanced statistical power. We speculate that an overall disruption in the functional topography of striatal connections may be particularly taxing on higher-order cognitive functions by affecting connectivity of the anterior caudate.

Keywords: striatum, connectivity, schizophrenia, multivariate.

Disclosure: Nothing to Disclose.

M203. Resilience and Ventromedial Prefrontal Cortex Structure in Posttraumatic Spectrum Adults

Isabelle Rosso*, Shreya Divatia, Elizabeth Olson, Scott Rauch, Lily Preer

McLean Hospital, Belmont, Massachusetts

Background: Resilience can be defined as the process of adapting well in response to significant adversity, and from a psychobiological standpoint as adaptations that reduce allostatic load. In trauma research, resilience has often been operationalized as the absence of DSM-based psychopathology, such as posttraumatic stress disorder (PTSD), among individuals who were exposed to extreme stressors. Increasingly, however, it has been noted that resilience is a dynamic and multifactorial process that may be better captured by dimensional measures than by categorical groupings that sort individuals into pathological versus resilient. Higher scores on dimensional measures of resilience have been associated with decreased likelihood of developing posttraumatic symptoms following a traumatic event and with less severe symptoms amongst individuals who meet full criteria for PTSD. Neural correlates of resilience in PTSD are not fully characterized, particularly using dimensional definitions of the construct. There is evidence from animal and human studies that neural mechanisms of resilience overlap with those involved in stress responses, which is in line with evidence from psychosocial research that the ability to regulate stress and emotions is a protective factor against adversity. The ventromedial prefrontal cortex (vmPFC) is a brain area of particular interest, having been implicated in resilience to stressors, emotion regulation, as well as the pathophysiology of PTSD. Previous imaging studies have found higher activity and grey matter density of the vmPFC in asymptomatic trauma-exposed subjects compared with PTSD patients, indicating sensitivity of these imaging measures to variance at extremes of the resilience continuum. In this study, we examined whether a dimensional measure of resilience was associated with individual differences in volumes of the vmPFC in a group of both nontraumatized and trauma-exposed adults with varying levels of posttraumatic stress symptoms.

Methods: Subjects were 36 right-handed adults (ages 20-50; 23 female), including 7 healthy nontraumatized subjects, 12 trauma-exposed subjects with subthreshold PTSD, and 17 trauma-exposed subjects who met criteria for PTSD based on the Clinician Administered PTSD Scale (CAPS). All subjects underwent magnetic resonance imaging (MRI) at 3T, and completed the 25-item Connor-Davidson Resilience Scale (CD-RISC-25). Subjects also completed the Beck Anxiety Inventory (BAI) and Beck Depression Inventory, 2nd version (BDI-II). Volumes of total vmPFC (left + right) and total intracranial volume (ICV) were derived using Freesurfer. A multiple regression analysis examined CD-RISC scores as the independent variable and total vmPFC volumes adjusted for ICV as the dependent variable, and entered as covariates the effects of age, gender and diagnostic group (nontraumatized, subthreshold PTSD, DSM-IV PTSD).

Results: CD-RISC scores were significantly lower in DSM-IV PTSD patients compared with both subthreshold PTSD and nontraumatized healthy controls ($p \leq .05$ Tukey's HSD). Within the combined group of subthreshold and DSM-IV PTSD subjects, CD-RISC scores were significantly negatively correlated with CAPS symptom scores ($r = -0.76$, $p < .0001$). In terms of demographic correlates, CD-RISC scores were numerically but not significantly higher in female compared with male participants ($t(34) = 1.56$, $p = .13$), and were not correlated with age or education. Multiple regression analysis revealed a significant positive association of CD-RISC scores with larger vmPFC volumes ($F(1,30) = 6.41$, $p = .02$), while controlling for a significant association of female gender with larger vmPFC volumes ($F(1,30) = 8.62$, $p = .01$) and nonsignificant associations of age and diagnostic group with vmPFC volumes. In follow-up analyses examining components of resilience, personal competence ($F(1,30) = 8.94$, $p = .01$) and control ($F(1,30) = 5.55$, $p = .03$) were the CD-RISC subscales significantly associated with increased vmPFC volumes. Finally, in analyses that examined possible confounds of anxiety and depression, neither BAI scores ($r = .15$, $p = .38$) nor BDI scores ($r = -.23$, $p = .16$) were significantly correlated with vmPFC volumes across the sample.

Conclusions: We found that resilience, particularly aspects that reflect an individual's sense of personal competence and control, was correlated with significantly larger volumes of the vmPFC in a group of adults comprising both nontraumatized subjects and trauma-exposed persons representing a range of posttraumatic symptom severity from asymptomatic to threshold PTSD. These preliminary findings suggest that MRI measures of vmPFC structure relate to a broad range of variability in psychological resilience. Identification of neural phenotypes of resilience may ultimately lead to the development of treatments that can enhance adaptive responses to adversity, including emotional regulation mechanisms governed by the vmPFC. Operationalizing resilience as a dimensional process may be

a particularly powerful approach for identifying its neurobiological substrates, and for developing prevention and treatment interventions that are relevant to a spectrum of stress and trauma severity.
Keywords: posttraumatic stress, resilience, prefrontal cortex, imaging.
Disclosure: Nothing to Disclose.

M204. Longitudinal Evidence of Dynamic Changes in Resting FC during Early Abstinence in Stimulant Addicts - Relationship to Craving

Jazmin Camchong*, Angus W. MacDonald III, Bryon A. Mueller, Brent Nelson, Sheila Specker, Valerie Slaymaker, Kelvin O. Lim

University of Minnesota Medical School, Minneapolis, Minnesota

Background: Neuroimaging studies have identified several neural markers of relapse vulnerability. Resting fMRI allows us to examine intrinsic connectivity without regard to task choice, providing good reliability for longitudinal studies (Shehzad et al., 2009). Rest fMRI data can focus on isolating observations due to treatment effects without having to consider potential confounds related to level of task performance, which may systematically vary across study groups. There are two studies that examined resting FC differences as predictors of relapse (McHugh et al., 2013; McHugh et al., 2014). These cross-sectional studies found lower striatal-insula FC (McHugh et al., 2013) and lower amygdala-cortical FC (McHugh et al., 2014) in individuals with cocaine use disorder (at 2-4 weeks of treatment) that subsequently relapsed within 30 days after discharge. The present study aims to explore the dynamics of FC changes across time in the same group of abstinent individuals with stimulant use disorder (SUD). Together with FC dynamics, we explored whether a time-varying component of craving known as incubation of craving (the progressive increase of craving throughout abstinence (Gawin and Kleber, 1986; Grimm et al., 2001) can be another measure that has prediction potential for subsequent relapse. This longitudinal study identified differences in resting FC changes between subsequent relapsers (vs. abstainers) that were related to stimulant craving.
Methods: We examined resting FC in 18 SUDs (8 females, age: $M = 22.05 \pm 2.64$) and 15 healthy controls (HC; 5 females, age: $M = 24.21 \pm 5.76$) at 5 weeks of abstinence. Twelve SUD were re-examined at 13 weeks of abstinence (14 HC were examined 8 weeks after study entry). With seed-based FC measures, we examined FC differences between SUD that abstained or relapsed over the subsequent 6 months. SUD completed the Cocaine Craving Questionnaire (CCQ) (Tiffany et al., 1993) to assess craving at both data collection timepoints.
Results: When examining FC change between 5 and 13 weeks of abstinence we found a significant time x group interaction. At 5 weeks of abstinence, subsequent relapsers (REL) had significantly higher NAcc FC with fronto polar cortex (FPC) and posterior cingulate cortex (PCC) than abstainers (ABS). At 13 weeks of abstinence, NAcc FC in REL had significantly dropped. REL had a larger decrease of NAcc-FPC (fronto polar cortex) and NAcc-PCC (posterior cingulate cortex) FC when compared to HC and abstainers between 5 and 13 weeks of abstinence. At 13 weeks of abstinence, the measure "anticipation of a positive outcome from stimulant use" from the CCQ was negatively correlated with change (from 5-13 weeks) in FC between NAcc and prefrontal cortex (FPC). SUD that anticipated more positive outcomes from hypothesized cocaine use at 13 weeks had the greatest drop, from 5 to 13 weeks, in strength of FC between NAcc and FPC.
Conclusions: Our pilot longitudinal data suggest that relapse status is related to progressive changes in resting brain circuitry. We hypothesize that the higher FC between NAcc and FPC found in the abstainers represents a neural compensation needed to counter craving and support abstinence. NAcc plays a role in the incubation of stimulant craving, an observation of a progressive increase in craving during the first several months of abstinence seen in rodents (Grimm et al., 2001). This effect has also been identified in humans, particularly when exposed to drug cues (Bedi et al., 2011; Gawin and Kleber, 1986). Correlates of NAcc FC provide further support of the role of NAcc's circuitry in incubation of craving. These findings will provide critical information of this potential brain biomarker to allow clinicians to select and monitor a therapeutic course of action and will help researchers to evaluate new therapeutic interventions.
Keywords: longitudinal, stimulant, craving, functional connectivity.
Disclosure: Nothing to Disclose.

M205. Reduced Striatal Response to Feedback Expectancy but Elevated Response to Receipt of Punishment in Individuals with Prior Methamphetamine Dependence

Amanda Bischoff-Grethe*, Colm Connolly, Stephan Jordan, Gregory Brown, Martin Paulus, Susan Tapert, Robert Heaton, Steven Woods, Igor Grant

University of California San Diego, La Jolla, California

Background: Individuals with amphetamine use disorder often show different outcome expectancies than non-users. One possibility is that chronic use of amphetamine affects the reward system in general, and the ventral striatum in particular, such that neural substrates that normally process reward-related stimuli show an attenuated activation pattern when expecting a reward. In addition, the anterior caudate processes performance feedback, and chronic amphetamine use may likewise impair the response to receipt of reward and punishment. The goal of this study was to examine the neural mechanisms associated with probabilistic expectancy cues and their outcomes in adults with a history of prior methamphetamine dependence (METH+) versus a non-METH healthy comparison group (METH-). We predicted that METH + would show less activation than METH- in striatal regions associated with reward expectancy and feedback.
Methods: Participants (17 METH + ; 23 METH-) performed a probabilistic feedback expectancy task during blood-oxygen level-dependent (BOLD) functional magnetic reso-

nance imaging (fMRI). Participants were presented visual cues that were probabilistically associated with monetary gain, loss, or neutral outcomes. In a separate session, participants completed self-report measures representing frontal systems behavior, including impulsivity/disinhibition, sensation-seeking, and apathy, as well as neurocognitive and neuropsychiatric assessments to permit detailed characterization of neurocognitive deficits and other conditions, including Antisocial Personality Disorder (ASPD) and Attention-Deficit/Hyperactivity Disorder (ADHD). Statistical analyses used two separate general linear models. The first model examined the BOLD response to pre-trial positive, negative and bivalent cues. The second model examined the BOLD response to trial outcome and included separate regressors for positive, negative, and neutral monetary outcomes. Anatomical regions of interest (ROIs) included the ventral striatum and separate ROIs for the anterior and posterior zones of the caudate. Associations of frontal systems behavior (specifically, apathy, impulsivity/disinhibition, and sensation-seeking) with both bilateral (i.e., mean average across hemispheres) and asymmetrical (i.e., left - right difference) brain activation were studied. We also assessed whether details of METH use history (i.e., age, days since last use, age of first use, and METH density [defined as total quantity used/total days used]) influenced our findings.

Results: METH+exhibited greater apathy ($t(22.4) = 7.26$, $p < 0.001$) and impulsivity ($t(28.17) = 5.15$, $p < 0.001$) than METH-. A significant group x trial type interaction for BOLD responses to positive and negative expectancy cues showed that METH + had lower responses to negative cues compared to METH- in the ventral striatum ($z = -3.4$, $p = 0.004$) and posterior caudate ($z = -3.2$, $p = 0.007$). METH + individuals with higher self-reported sensation-seeking showed greater BOLD response in the anterior caudate ($t = 2.4$, $p = 0.03$) to pre-trial positive cues, predominately in the right hemisphere. Higher apathy in both groups was associated with attenuated ventral striatal response to positive cues (METH +: $t = -3.1$, $p = 0.008$; METH-: $t = -2.2$, $p = 0.04$). High apathy METH + showed more anterior caudate response ($t = 2.4$, $p = 0.03$), whereas high apathy METH- showed reduced anterior caudate response ($t = -2.3$, $p = 0.03$) to negative cues. For analyses associated with trial outcome, a significant group x outcome interaction showed METH + to have an elevated BOLD response to negative outcomes relative to positive outcomes in the anterior ($z = 2.8$, $p = 0.03$) and posterior caudate ($z = 2.9$, $p = 0.02$). Only in METH + were higher sensation seeking ($t = -3.3$, $p = 0.006$) and impulsivity ($t = -2.2$, $p = 0.05$) associated with a reduced response in the ventral striatum to negative outcomes. ASPD and ADHD were not associated with striatal brain response to cues or outcomes.

Conclusions: While our findings supported the hypothesis that methamphetamine dependent individuals would show an attenuated neural response to gains and losses in areas associated with reward processing, this was not supported for feedback. Rather, METH + showed a greater response to receipt of negative relative to positive outcomes. This suggests METH + individuals may have a dissociation between expectancy and feedback; while they may be aware of negative consequences when they experience them, they may be impaired in using this experience to guide future decisions. A decreased response to cues predicting outcome, along with a greater response to negative outcomes, suggests an impaired ability to form action-outcome associations. This impaired ability to evaluate future risks and benefits based upon prior experience may underlie the altered decision-making seen in METH + individuals and increase the likelihood of risky behavior.

Keywords: methamphetamine, striatum, reward, punishment.

Disclosure: Nothing to Disclose.

M206. Abnormal Cerebellum Functional Connectivity in Schizophrenia

Ann K. Shinn*, Justin T. Baker, Kathryn E. Lewandowski, Bruce M. Cohen, Dost Ongur

Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Background: Schizophrenia (SZ) is a devastating illness associated with disturbances in multiple domains. Growing evidence suggests that cerebellar abnormalities play a major role in the pathophysiology of SZ. However, it is unclear what specific cortico-cerebellar networks are altered in SZ. Here, we systematically investigated cerebellum functional connectivity (FC) using a seed-based approach, utilizing the cortical parcellation map of Yeo et al. (J Neurophysiol. 2011 Sep;106(3):1125-65) as the basis for our FC seeds.

Methods: Participants were 44 patients with schizophrenia spectrum disorders (SZ) recruited from both inpatient and outpatient services at McLean Hospital, and 28 age- and sex-matched healthy controls (HC). Using a Siemens Trio 3-Tesla MRI scanner, we acquired a T2-weighted functional scan (interleaved EPI sequence, 42 oblique slices, flip angle 82°, TE/TR = 24/2500 ms, 3.5 mm isotropic voxels, matrix 128 x 128, 224mm2 FOV, 240 volumes over 600s). Participants were scanned at rest, and instructed to stay awake, keep their eyes open, and think of nothing in particular. We used FSL v5.0.6 for image analyses. After discarding the first 4 volumes, images were slice-time and motion corrected, smoothed with a 6mm Gaussian kernel, band-pass filtered ($0.009\,Hz < f < 0.08\,Hz$), and affine registered to standard MNI space. We used the 17 network (N) cortical parcellation map of Yeo et al. (2011) as the basis for our FC seeds. We excluded from analysis six networks that had zero or minimal (equal to or less than 30 voxels) representation in the 17 network cerebellum maps published in Buckner et al. (J Neurophysiol. 2011 Nov; 106(5):2322-45). These were the Visual Peripheral (N1), Visual Central (N2), Dorsal Attention A (N5), Control C (N11), Auditory (N14), and Default C (N15) networks. Consistent with Baker et al. (2014), we also combined N9 (temporal pole) and N10 (orbitofrontal cortex) into a single Limbic network. Thus we analyzed 10 total networks. We eroded each of the network maps by one voxel layer using a 3D kernel. The BOLD time course from each of the 10 network seeds was extracted and entered into a general linear model, with signal from white matter, CSF, whole brain, and six rigid body motion correction parameters regressed. Data from first-level analyses were entered into a mixed-effects group analysis, comparing SZ with HC. We

entered age, sex, chlorpromazine equivalents, and acquisition post-TIM scanner upgrade as covariates. Given our goal to investigate between-group FC differences in the cerebellum, we restricted our analysis to the cerebellum, using the cerebellum atlas in FSL as a pre-threshold mask. We set our voxel threshold to $p<0.01$, correcting for multiple comparisons with a $p<0.05$ cluster threshold.
Results: The combined-group cerebellum maps captured the Buckner et al (2011) cerebellar maps with 90.1% mean accuracy (range 80.0-96.0%), suggesting a relatively high degree of correspondence. We found SZ to have reduced cortico-cerebellar FC in Ventral Attention (N7), Salience (N8), Control A (N12), Control B (N13), and Default Mode A (N16) networks compared to HC. SZ showed, on the other hand, greater cortico-cerebellar FC in the Somatomotor A (N3) network. In addition, a component of the Default Mode A (N16) network also showed SZ greater than HC FC connectivity. SZ did not differ from HC in the cortico-cerebellar FC of Somatomotor B (N4), Dorsal Attention B (N6), Limbic (N9-10), and Default Mode B (N17) networks.
Conclusions: These results provide evidence for cortico-cerebellar functional connectivity abnormalities in SZ. There were reductions in connectivity in SZ in networks implicated in higher order functioning but inappropriately elevated connectivity in a somatomotor network. The default mode network in SZ appears to have elements of both increased and decreased functional connectivity, with increased connectivity in more anterior aspects of the cerebellum.
Keywords: cerebellum, connectivity, schizophrenia.
Disclosure: Nothing to Disclose.

M207. Corticotrophin-releasing Hormone Genotype Interacts with Pre-treatment Anxiety Status and Amygdala Reactivity to Predict Treatment Outcomes in Major Depressive Disorder

Andrea Goldstein-Piekarski*, Alan Schatzberg, Mayuresh Korgaonkar, Stuart Grieve, Amit Etkin, Leanne Williams

Stanford University School of Medicine, Stanford, California

Background: Previous research suggests that i) genetic variation in the corticotrophin-releasing hormone receptor 1 (CRHR1), ii) limbic reactivity (most prominently amygdala) and iii) anxiety status independently contribute to the pathophysiology of major depressive disorder (MDD) and response to antidepressants. CRH and amygdala systems are critically involved in the regulation of behavioral and neuroendocrine correlates of anxiety and are themselves highly interconnected. Despite this overlap in neural circuitry and function, it remains unknown whether the interaction of these three factors together predict antidepressant treatment outcomes. We tested this interaction in MDD patients from the International Study to Predict Optimized Treatment in Depression (iSPOT-D). We focused on the CRHR1 rs110402 allele implicated in MDD and emotion-related neural activation and assessed both symptom and functional outcomes.
Methods: 1008 MDD patients were randomized to one of three treatment arms: escitalopram, sertraline and venlafaxine-XR ($n=336$ in each). Of these, approximately 10% ($n=102$ MDD) were scanned using fMRI pre-treatment and at 8 weeks post-treatment follow up. Participants were additionally genotyped for rs110402 within the CRHR1 gene. Amygdala fear reactivity was assessed using a validated emotional face task. Pre-treatment anxiety status was determined using the Hamilton Anxiety Factor. Multiple regression analyses were utilized to test the interaction effects between rs110402 genotype (GG vs A-Carriers), amygdala fear reactivity, and pre-treatment anxiety while controlling for baseline depression severity and age, on two measures of treatment outcome: i) the precent of depression symptom improvement measured by the Hamilton Depression Rating Scale and ii) the precent of functional capacity improvement as indexed by the Social and Occupational Functioning Assessment Scale (SOFAS).
Results: As predicted, the degree of symptom improvement for GG-homozygotes was dependent on pre-treatment amygdala reactivity and anxiety status. GG-homozygotes with high amygdala reactivity, but low pre-treatment anxiety were the least likely to show symptom improvement post-treatment. In these "high amygdala-low anxiety" GG homozygotes there was only a 28.2% decrease in depressive symptoms from pre- to post-treatment. Importantly, these interaction effects were also present for outcomes in social and occupational function: "High amygdala-low anxiety" GG homozygotes also showed the least improvement in function. In contrast, rs110402 A-allele carriers improvement was present to a similar degree regardless of high/low amygdala and high/low anxiety status. Each A-carrier group showed an average improvement in depressive symptoms of at least 54.84%.
Conclusions: The general capacity to mount a response to antidepressants for GG-homozygotes was dependent on pre-treatment levels of anxiety and fear reactivity. In contrast, the CRHR1 A-allele appears to buffer the effects of pre-treatment anxiety severity and amygdala fear reactivity on treatment response. Such findings suggest that the protective effect of the A-allele on the development of depression may also extend to treatment success, both in terms of symptom remediation and functional outcomes.
Keywords: Depression, Anxiety, Corticotropin-Releasing Hormone, Antidepressant 5. Amygdala reactivity.
Disclosure: A. Goldstein-Piekarski: None L. Williams: Brain Resource (consultant) A. Schatzberg: Dr. Schatzberg has served as a consultant to BrainCells, CeNeRx, CNS Response, Eli Lilly, Forest Labs, Genetech, Gilead, GSK, Jazz, Lundbeck, Merck,Neuronetics, Novadel, Novartis, Pathway Diagnostics, Pfizer, PharmaNeuroBoost, Quintiles, Sanofi-Aventis, Sunovion, Synosia, Takeda, Xytis and Wyeth. Dr. Schatzberg has equity in Amnestix, BrainCells, CeNeRx, Corcept (co-founder), Delpor, Forest, Merck, Neurocrine, Novadel, Pfizer, PharaNeuroBoost, Somaxon, Synosis, and Titan. He is a named inventor on pharmacogenetic use patents on glucocorticoid antagonists and on prediction of antidepressantresponse. Dr. Schatzberg has also received speaking fees from Merck, GlaxoSmithKline and Roche. S. Grieve: Brain Resource (consultant) M. Korgaonkar: None A. Etkin: Brain Resource (study sponsor).

M208. Hippocampal Glutamate and Disturbance of Hippocampal-Prefrontal Effective Connectivity in Schizophrenia: Effect of Antipsychotic Medication

Adrienne Lahti*, Meredith Reid, Nathan Hutcheson, Nina Kraguljac, David White, Karthik Sreenivasan, Gopikrishna Deshpande

University of Alabama at Birmingham, Birmingham, Alabama

Background: Using MR Spectroscopy (MRS), we previously observed an increase in glutamate + glutamine (Glx) in the hippocampus in unmediated patients with schizophrenia (SZ) (Kraguljac el al., 2013). We report here on two experiments conducted to further characterize the extent, consequences, and effect of treatment on glutamatergic (Glu) abnormalities in SZ. First, in unmedicated SZ, we measured Glx in the dorsal anterior cingulate (dACC) and hippocampus, before and after treatment with an antipsychotic medication (APD). We hypothesized that Glx would decrease with treatment. Second, given our previous findings that regional cerebral blood flow (rCBF) is increased in hippocampus in unmedicated SZ (Medoff et al., 2001) and that reduction in hippocampal rCBF with APD is associated with good treatment outcome (Lahti et al., 2009), we hypothesized that known fronto-temporal functional connectivity disruption in SZ measured with fMRI might originate from abnormal hippocampal function and could be partially restored by APD.
Methods: Using MRS we compared SZ (n = 20) scanned unmedicated, and after 6 weeks of APD treatment with risperidone. Voxels were placed in the dorsal ACC (dACC) and hippocampus. Spectra were acquired using the point resolved spectroscopy sequence (PRESS; TR/TE = 2000/80 ms) and analyzed using jMRUI. In addition, with fMRI acquired using an EPI sequence (repetition time/echo time [TR/TE] = 2100/30 msec, 70° flip angle, 24 x 24 cm2 field of view, 64 x 64 matrix, 4-mm slice thickness, 1-mm gap, 26 axial slices), we measured effective connectivity (EC) accessed with multivariate autoregressive Granger causality (Deshpande et al., 2009) and obtained from latent neural signals estimated from blind deconvolution of fMRI during episodic memory retrieval (Hutcheson et al., 2012). We evaluated EC between frontal (3) and temporal (2, including hippocampus) nodes when patients were unmediated (n = 21) and after one-week of treatment with risperidone (n = 16). Matched healthy controls (HC) (n = 20) were scanned as well.
Results: After 6 weeks of treatment, there was a significant reduction in the ratio of Glx/N-acetylaspartate in the hippocampus (p = .03), but not in the dACC. In HC, the right hippocampus was identified as a major node of a fronto-temporal network with connections from the hippocampus to all bilateral frontal nodes. Compared to healthy controls, unmedicated SZ had significant EC decrease from the right hippocampus to the right medial frontal node. After 1-week of treatment SZ showed significant EC increase from the right hippocampus to all bilateral frontal nodes.
Conclusions: Our data indicate that APD modulate Glu function in a manner that is regionally specific. In addition, in unmedicated SZ, we observe a reduced hippocampal to frontal EC that is partially reestablished with treatment. Because elevated Glu levels might result from gamma-aminobutyric acid (GABA) interneuron hypofunction and hippocampal interneurons generate oscillations in the gamma frequency ranges that are thought to synchronize brain activation, their dysfunction could affect functional/effective connectivity, including fronto-temporal connectivity. Changes in functional connectivity with treatment could be a necessary intermediary step (Hadley et al., 2014) to symptomatic improvement. This work was supported by grant R01 MH081014 (ACL). Deshpande, G., LaConte, S., James, G.A., Peltier, S., Hu, X. (2009) Multivariate Granger causality analysis of fMRI data. Human Brain Mapping, 30:1361-1373. Hadley, J.A., Nenert, R., Kraguljac, N.V., Bolding, M.S., White, D.M., Skidmore, F.M., Visscher, K.M., Lahti, A.C. (2014) Ventral Tegmental Area/Midbrain Functional Connectivity and Response to Antipsychotic Medication in Schizophrenia. Neuropsychopharmacology, 39.
Keywords: schizophrenia, glutamate, brain connectivity, antipsychotic medication.
Disclosure: Janssen Pharmaceuticals, Inc. donated medication for this study.

M209. Alteration of Insular Activation: An Ultimatum Game Study in Alcohol-dependent Subjects

Claire Mann, Carlos Cortes, Karan Mathur, David George, Markus Heilig, Reza Momenan*

National Institute on Alcohol Abuse and Alchoholism, National Institutes of Health, Bethesda, Maryland

Background: The insula, an "island" of cortex located beneath the temporal lobe, plays significant role in consciousness, emotional decision-making, and homeostasis. Alcoholism is a chronic relapsing disorder associated with abnormalities in insula. Additionally, the insular cortex is susceptible to the toxic effects of alcohol. Not only does this toxic effect markedly reduce the volumes of this region (Senatorov, under review) in alcohol dependents patients (ADPs), but it also is functionally affected. For example the insular cortex of ADPs is activated during alcohol craving (Xiao et al., 2012; Claus et al., 2011; Park et al., 2007). Other studies have shown positive correlations between induced stress and alcohol craving in alcohol abusers (Nesic and Duka, 2014). The goal of this study is to determine the effect of alcohol use disorders on the functionality of insula, particularly under conflict/stress prone decision-making conditions. To that end, the current study employs a task called the Ultimatum Game (Safney et al., 2003), an economic decision making task in which participants are presented with monetary offers that are fair or unfair. Unfair offers have been shown to activate the anterior insula (Sanfey et al., 2003; Tabibnia et al., 2008). The Ultimatum Game has never before been tested on ADPs. In the present study, we used this paradigm to study altered insula activation in ADPs compared to healthy controls (HCs).
Methods: In an ongoing functional Magnetic Resonance Imaging (fMRI) study we are investigating the brain response to the Ultimatum Game in ADPs in comparison

to HCs. In this abstract we are reporting the results for 8 ADPs and 16 HCs. Subjects were scanned using a Siemens 3T Skyra MR scanner and structural images were captured with an MPRAGE sequence. Whole brain functional data were collected with a 64 x 64 x 36 matrix, TR = 2000 ms. Subject and group fMRI data analyses were carried out using AFNI (Cox, 1996) software. During the ultimatum task, participants first view the face of the proposer about to make an offer, splitting $20. While participants believe that the proposer is a real human, the offers were chosen in advance in a randomized order. In one third of the trials, the proposer's face was replaced with an image of a computer (baseline condition). Next the offer is presented, always splitting $20. In this study, offers to the participant between $1 and $5 were considered unfair offers, and offers between $6 and $10 were considered fair offers. The participant was never offered more than a $10-$10 split. Participants then chose to accept or reject the offer. Finally, feedback of the selection was shown. Participants played three 10-min rounds of the game, viewing 60 offers in total. Payment was determined by the sum of ten randomly selected trials by the participants.

Results: Behavioral data demonstrated that ADPs generally accepted unfair offers more than HCs. HCs showed an activation trend ($p < 0.05$ uncorrected) in middle frontal gyri and anterior insula and deactivation in lentiform/putamen when presented with unfair versus fair offer contrast. The same contrast showed lower activation in middle frontal gyrus, caudate and insula of ADPs in comparison to HCs.

Conclusions: Our preliminary data with few subjects indicates higher activation in anterior insula (and the middle frontal gurus) for unfair in contrast to fair offers in HCs, replicating the earlier studies using the Ultimatum Game. On the other hand, the ADPs showed a trend toward deactivation in the same regions as well as caudate and putamen when compared to HCs. ADPs may be more motivated by a smaller amount of money than the HCs and hence demonstrating less stress induced activation in the insula. This is corroborated by the behavioral data, which suggests that ADPs are more likely to accept unfair offers. Given the number of subjects, this data is very preliminary and the present results should be interpreted cautiously. More subjects are currently being enrolled in the study.

Keywords: Imaging, Insula, Alcohol, decision.

Disclosure: Nothing to Disclose.

M210. Long-range Prefrontal Cortex Dysconnectivity in Major Depressive Disorder

Chadi G. Abdallah*, Lynnette A. Averill, Paul Geha, Katherine A. Collins, Edmund Wong, Cheuk Y. Tang, Alan Anticevic, James Murrough

Yale University School of Medicine, West Haven, Connecticut

Background: Resting state functional connectivity magnetic resonance imaging (rs-fcMRI) has been successfully used previously to identify altered neural circuitry in major depressive disorder (MDD). Yet, the majority of prior studies were seed-based analyses with sample sizes approximately 10 to 20 MDD subjects. To extend previous findings and to address some of the limitations of pilot seed-based analyses, we conducted a data-driven whole-brain voxel-wise rs-fcMRI study in a relatively large sample of medication-free depressed patients compared to healthy controls. We used a recently developed rs-fcMRI measure termed weighted Global Brain Connectivity (GBC). Briefly, GBC value of each voxel is the average of the blood oxygenation level-dependent (BOLD) signal time series correlation of the voxel with all other gray matter (GM) voxels in a specific network. Based on graph theories, GBC is a measure of weighted nodal strength in a network. The aim of the current study was to identify brain regions with altered connectivity strength in MDD subjects. To gain insight into the spatial extent of altered connectivity, we performed complementary analyses of GBC restricted to the prefrontal cortex (PFC) and seed-based analyses in the default mode network (DMN), the cognitive control network (CCN), and the affective network (AN).

Methods: Total of 76 subjects (49 MDD and 27 healthy) successfully completed all imaging procedures. MDD subjects were psychotropic medication-free for at least one week prior to scanning. The clinician-rated Montgomery-Åsberg Depression Rating Scale was conducted to determine depression severity (MDD group: mean $\pm$ SD 28.3 $\pm$ 6.6). Imaging data were acquired on a 3-Tesla Philips scanner at the Mount Sinai Medical Center. High-resolution T1-weighted three-dimensional anatomical images were acquired with the following parameters: repetition time (TR), 7.6 ms; echo time (TE), 3.49 ms; flip angle, 8°; matrix, 224 x 224, 172; voxel size 1 mm3; field of view (FOV), 210. Echoplanar imaging were used to image the BOLD signal with the following parameters: TR, 2000 ms; TE, 27 ms; flip angle, 90°; FOV, 210 mm; matrix, 96 x 96 x 38; voxel size, 2.19, 2.19, 3.25 mm3; acquisition of 120 volumes. FSL, AFNI, Freesurfer, and in-house written Matlab programs were used to perform all image processing and analyses. Preprocessing included brain extraction, tissue segmentation, motion and slice timing correction, spatial smoothing (FWHM 5 mm), high-pass temporal filtering (100 s), and nonlinear registration to high-resolution T1 images. Motion parameters, and the signals of CSF, white matter, GM, and global brain were regressed out of each voxel's time series. Functional and structural images were registered to a standard Montreal Neurological Institute (MNI) template. All processing and analyses were conducted in the subject space, except for 2nd level group analyses. Permutation tests along with cluster-level type I error correction ($p < 0.05$) were performed.

Results: In the whole-brain analysis, we found an anteroposterior dissociation with reduced GBC in the frontal brain regions including: subgenual anterior cingulate (sgACC), dorsomedial PFC (DMPFC), dorsolateral PFC (DLPFC), and anterior regions of the insula, the hippocampus and the caudate (corrected $p < 0.05$). In contrast, there is increased GBC in the posterior brain regions including: posterior cingulate (PCC), precuneus, midline occipital, left lateral occipital and fusiform cortices, and cerebellum (corrected $p < 0.05$). The increased GBC in the PCC/precuneus region positively correlated with MADRS severity (corrected $p < 0.05$). In the PFC restricted GBC

analysis (r-GBC), we found increased r-GBC in the rostral ACC and DMPFC (corrected $p < 0.05$). Similarly, the seed analyses showed increased functional connectivity within the PFC (ACC-DMPFC, DLPFC-sgACC) and within the posterior regions of the brain (PCC-precuneus, PCC-dorsal-caudate, PCC-left-thalamus, PCC-cerebellum), but reduced long-range anteroposterior connectivity (ACC-PCC, PCC-insula, PCC-DMPFC, DLPFC-right-temporal cortex) (corrected $p < 0.05$).

Conclusions: In the current study we found anteroposterior dissociation with reduced prefrontal GBC but increased parietal-occipital-cerebellar GBC, which was highest in patients presenting with the highest depression scores. Follow-up analyses showed that the reduced prefrontal GBC is largely driven by long-range dysconnectivity between the PFC and other brain regions. Anteroposterior dichotomy has been previously observed in MDD using several imaging modalities (e.g. ICA fMRI, PET, or 1H-MRS) and study designs (e.g. cross-section, or longitudinal pharmaco-imaging). The current findings revealed comparable dichotomy along with paradoxical reduction in long-range but increased short-range connectivity. This network reconfiguration may explain the failure of the brain to down-regulate hyperactive regions (e.g. sgACC) leading to the previously reported excitotoxicity and neuronal atrophy. Finally, the association between altered GBC and depression severity highlights the potential utility of GBC as a diagnostic and treatment biomarker. Future longitudinal and pharmaco-imaging studies are needed to better understand the role and the mechanisms of this network reconfiguration.

Keywords: Major Depressive Disorder, fMRI, Graph-based Analysis, Prefrontal Cortex.

Disclosure: Nothing to Disclose.

M211. Trait Anger Differentially Modulates Brain Activity Underlying Negative Emotional Arousal

Rebecca Preston-Campbell*, Scott Moeller, Anna Konova, Muhammad Parvaz, Monja Froböse, Patricia Woicik, Fred d'Oleire Uquillas, Rita Goldstein, Nelly Alia-Klein

Icahn School of Medicine at Mount Sinai, New York, New York

Background: Anger is considered a high arousal negative emotional state that develops across the lifespan to adopt stable trait patterns of emotional reactivity in response to unpleasant or undesired events. Individuals who demonstrate elevated levels of trait anger are more prone than others to respond to emotional triggers with increased reactivity and aggression. However, during passive viewing of normatively threatening and violent images, those with high anger traits may exhibit blunted processing in regions associated with autonomic arousal and threat evaluation as compared to those with low anger traits due to impaired emotion regulation. Here, we employed fMRI to investigate neural reactivity to high- versus low arousal images during a passive viewing task as a function of trait anger.

Methods: Thirty-seven healthy male participants were grouped via median split on State-Trait Anger Expression Inventory (STAXI-2) trait anger scores [18 Low trait anger (LA); 19 High trait anger (HA)]. The groups were matched on age, race, education, and estimates of verbal and non-verbal intelligence. In a blocked fMRI design (4 blocks, 10 images per block), participants passively viewed International Affective Picture System (IAPS) images, selected on the extremes of positive/negative valence and high/low arousal according to published norms for healthy males. We focused on the neural response to high versus low arousal for the negatively valenced images, of greatest relevance to the aggression phenotype. Participants also completed the Multidimensional Personality Questionnaire (MPQ) and the Buss Perry Aggression Questionnaire (BPAQ). A 2 (group: LA, HA) x 2 (picture arousal: high, low, each versus fixation baseline) ANOVA was conducted in SPM8 for inspection of the main effects and interaction at the whole brain level (p-corrected < 0.05). We then correlated the extracted blood-oxygenation-level-dependent (BOLD) signals from the regions showing significant interaction effects with selected MPQ irritability and BPAQ hostility traits across all participants.

Results: Across subjects, a main effect of arousal was found in the bilateral anterior cingulate cortex (low > high; $x = 15$, $y = 47$, $z = 1$, $x = -15$, $y = 38$, $z = 16$). Between subjects, a main effect of group was found, with the HA group showed greater activation compared with the LA group in the left insula ($x = -36$, $y = -10$, $z = -1$). A group x arousal interaction was found in the left posterior thalamus (Pulvinar) ($x = -12$, $y = -22$, $z = 1$) and the right posterior insula ($x = 39$, $y = -31$, $z = 10$). These interactions were driven by differences between high and low arousal images in the HA group ($p < 0.05$) but not the LA group ($p > 0.16$) (insula: high < low; thalamus: high > low). Across all participants, these regional differences (from the main ANOVA) correlated with distinct traits: greater pulvinar activation to high versus low arousal images correlated with more BPAQ hostility ($r = 0.35$, $p = 0.036$), while lower posterior insula activation to high versus low arousal images correlated with more MPQ irritability ($r = -0.40$, $p = 0.025$).

Conclusions: Results suggest that, compared to individuals with low trait anger, individuals with high trait anger process high arousal negative images with enhanced pulvinar activation and reduced posterior insula activation. Notably, pulvinar hyperactivation was associated with hostility, and insula hypoactivation was associated increased irritability across all study subjects. Studies suggest that pulvinar activation is associated with rapid processing of visual threat, thereby modulating amygdala activation and response, whereas the mid-posterior insula relays information to the anterior insula regarding the physiological condition of the entire body for subjective evaluation of internal conditions. Thus, it appears that passive processing of negative images by individuals with high (versus low) anger traits is marked by generalized arousal (pulvinar), which may be modulated by hostility traits, yet lacking in negative appraisal, as modulated by irritability. Together, these effects may suggest a deficient somatic feedback to aversive stimuli due to a blunting of autonomic arousal. Future laboratory or naturalistic studies can test whether these collective neural responses reduce one's threshold to behave aggressively.

Keywords: trait anger, aggression, emotional arousal, brain activation.

Disclosure: Nothing to Disclose.

M212. fMRI Reveals Divergent Responses to Social Reward Among Patients with Unipolar Versus Bipolar Depression

Anup Sharma*, Theodore Satterthwaite, Lillie Vandekar, Natalie Katchmar, Brenda Li, Aylin Daldal, Kosha Ruparel, Mark Elliott, Claudia Baldassano, Michael Thase, Raquel Gur, Joseph Kable, Daniel Wolf

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Neuroimaging studies of mood disorders demonstrate abnormalities in neural circuits corresponding to reward processing, emotional processing and emotional regulation. Adopting dimensional approaches to compare reward system activity across disorders will help highlight both shared and differential aspects of reward pathology with clinical implications. Currently, there is a paucity of data investigating how social rewards affect reward circuit activity in these disorders.
Methods: 25 patients with bipolar depression, 20 patients with unipolar depression and 34 healthy controls completed a social reward task during 3T BOLD fMRI. Analysis focused on the positive versus negative affective feedback contrast, applying a voxelwise whole brain approach. Significant effects were defined as clusters with a voxel height $z > 2.33$ and cluster extent $p < 0.05$.
Results: Greater depression severity (BDI) significantly correlated with reduced VS activation to social reward in the bipolar depressed group ($p < 0.05$), but not the unipolar depressed group. In addition, decreased bilateral orbitofrontal cortical (OFC) activation associated with more severe symptoms in bipolar depression ($p < 0.05$), but not unipolar depression. A direct voxelwise group comparison of the BDI effect revealed a significantly stronger inverse relationship between BDI severity and activation to social reward in bilateral VS ($p < 0.05$) and bilateral OFC ($p < 0.05$) in bipolar depression than unipolar depression.
Conclusions: These results demonstrate that social reward processing differentiates the two disorders. Specifically, deficits in VS and OFC responsivity uniquely relate to severity of bipolar depression and not unipolar depression. This suggests that depression in bipolar disorder may be more strongly related to a failure to respond to social rewards compared to unipolar depression.
Keywords: mood disorders, neuroimaging, reward system.
Disclosure: Nothing to Disclose.

M213. Diffusion Measures of Free Water and 1H-MRS Measures of Glutathione in First Episode Patients with Schizophrenia – A Multi-modal Investigation of an Inflammatory Model for Psychosis

Tyler A. Lesh*, Richard J. Maddock, Taylor Salo, Costin Tanase, J. Daniel Ragland, Tara A. Niendam, Marjorie Solomon, Cameron S. Carter

University of California, Davis School of Medicine, Sacramento, California

Background: Evidence has been accumulating for an immune-based component to schizophrenia etiology, including genetic links to the major histocompatibility complex, maternal infection, pro-inflammatory cytokine elevations in cerebrospinal fluid and plasma, as well as evidence of microglial activation. Advancements in diffusion magnetic resonance imaging (MRI), including use of multi-shell acquisitions (i.e., Pasternak, Shenton, and Westin, 2012), has enabled estimation of extracellular free water, a putative biomarker of neuroinflammation in vivo. Furthermore, there is evidence that neuroimmune activation may alter brain levels of metabolites that can be measured non-invasively with proton magnetic resonance spectroscopy (1H-MRS). Glutathione (GSH) represents an ideal candidate inflammatory biomarker as it is depleted by oxidative stress and has been found to be reduced in several neuroinflammatory conditions (e.g., multiple sclerosis, neuroAIDS). Consequently, we sought to test the hypothesis that first episode patients with schizophrenia have increased extracellular free water and decreased glutathione levels when compared to healthy controls. Additionally, we investigated the proposed inverse relationship between these neuroinflammatory markers within both groups.
Methods: First-episode schizophrenia ($n = 14$) and healthy control ($n = 9$) participants were identified from referrals to the UC Davis Early Detection and Preventative Treatment (EDAPT) clinic using the Structured Clinical Interview for DSM-IV. Participants underwent a diffusion MRI scan on a Siemens TIM Trio 3T scanner in which multiple b-value shells were acquired to improve estimation of extracellular free water. Diffusion images were aligned to individual subject MPRAGE scans, which were segmented to provide whole-brain gray- and white-matter free water estimates. 1H-MRS was performed during the same scan and GSH/creatine ratios were calculated for voxels located in dorsolateral prefrontal cortex (DLPFC) and visual cortex. Symptom measures included the SANS, SAPS, and BPRS, which were used to calculate Poverty, Disorganization, and Reality Distortion syndrome scores. Independent samples t-tests were used to test for between-group differences and Pearson correlations were performed to test for relationships between the two MRI variables and symptom ratings. All statistical analyses were performed using SPSS 22.
Results: First-episode schizophrenia patients demonstrated significantly elevated extracellular free water in whole-brain gray matter ($p = 0.02$) but not white matter ($p = 0.21$). At the time of writing, only a subsample of 7 patients and 6 controls was available to evaluate GSH levels and there was no significant difference between groups ($p > 0.3$). Notably, even in these small subsamples, both groups showed strong inverse relationships between DLPFC GSH and gray matter free water, and patients showed a trend for a steeper slope compared to controls ($p = 0.09$). A significant positive relationship was also identified between symptoms of Reality Distortion and gray matter free water ($p = 0.03$) in the patients.
Conclusions: These data provide compelling convergent evidence for the presence of neuroinflammatory processes in first episode schizophrenia patients. In agreement with previous work using a traditional diffusion scan (Pasternak et al., 2012), we identified increased free water in whole-brain gray matter using an optimized multi b-shell acquisition. In contrast, we did not find a significant increase in free water in white matter. The identified inverse relationship between GSH in DLPFC and gray matter free

water implies a common linkage to neuroinflammatory processes that may be more pronounced in patients with schizophrenia. Furthermore, our identification of a positive relationship between psychotic symptomatology and gray matter free water suggests that increased free water levels may signal greater disease severity. However, future longitudinal designs could better identify whether this relationship holds during transient fluctuations in symptomatology. Ultimately, these data suggest that free water and GSH show promise as early stage neuroinflammatory biomarkers and provide a tractable treatment target for pharmacological intervention.
Keywords: glutathione, free water, inflammation, schizophrenia.
Disclosure: Nothing to Disclose.

M214. Anterior Cingulate Gyrus and Sulcus Thickness: A Potential Predictor of Remission following Internet-Based Cognitive Behavioral Therapy for Major Depressive Disorder

William Killgore*, Lauren Demers, Elizabeth Olson, Isabelle Rosso, Christian Webb, Scott Rauch

University of Arizona, Tucson, Arizona

Background: Functional and structural abnormalities in the medial frontal cortex have been implicated in the pathophysiology of major depressive disorder (MDD). Neuroimaging and animal lesion studies suggest the rostral anterior cingulate cortex (rACC) as a key region involved in the modulation of emotional behavior. Gray matter volume and thickness in this region is reduced in patients with MDD, and is related to depressed mood and negative affect in healthy controls. Both pretreatment hyperactivity and increased volume of the rACC have been shown to predict response to pharmacological and cognitive behavioral therapy (CBT) for depression and related disorders. To our knowledge, no study has yet investigated neuroimaging predictors of treatment response to internet CBT (iCBT). In this study, we sought to determine whether thickness of the anterior part of the cingulate cortex is associated with subsequent treatment response in a sample of subjects with MDD receiving iCBT as part of a clinical trial.
Methods: Twenty-nine adult subjects with MDD and 14 healthy controls (HC) with no history of depression have been enrolled and generated complete data to date. During a pre-treatment study visit, all participants were interviewed using the Structured Clinical Interview for DSM-IV and underwent a magnetic resonance imaging scan at 3T. After scanning, MDD subjects were randomly assigned to 10 weeks of iCBT ($n = 17$) or to the monitored attention control (MAC) condition ($n = 12$). Ten weeks later, MDD subjects returned for a post-treatment assessment visit. At both time points, patients were interviewed with the Hamilton Depression Rating Scale (HDRS) by a rater blind to treatment group. Cortical thickness measurements were derived for the rACC using FreeSurfer software version 5.3.0. Treatment effects were analyzed using a repeated measures analysis of variance on HDRS scores at the two time points with treatment group as the between-subjects factor. An independent sample t-test was conducted to determine baseline differences in average thickness of the anterior part of the cingulate gyrus and sulcus between the MDD and HC group. Thickness of the rACC was also compared in treatment remitters (post-treatment HDRS $\leq$ 7) and non-remitters using an independent sample t-test.
Results: Compared with HC subjects, MDD patients showed significantly reduced average thickness of the anterior cingulate gyrus and sulcus thickness at the pretreatment visit ($t(41) = 2.38$, $p = .02$). Of the MDD subjects, those who received iCBT showed significantly greater reductions in their HDRS scores post-treatment, compared to those in the MAC condition ($F(1,27) = 7.14$, $p = .01$). Ten of the 17 subjects who received iCBT met criteria for remission. Those who remitted had significantly greater thickness in the anterior part of the cingulate gyrus and sulcus than non-remitters ($t(15) = -2.75$, $p = .02$).
Conclusions: These preliminary results suggest that cortical thickness of the rACC region may be a marker of higher likelihood to remit from depression in response to iCBT. In this study, MDD subjects relative to healthy controls showed lesser cortical thickness in the rACC, whereas greater thickness of this region was associated with a significantly higher likelihood of subsequent clinical remission following iCBT. This is consistent with previous demonstrations that ACC structure and function predict remission of depression following pharmacological and clinician-delivered CBT. This preliminary finding therefore suggests that iCBT may have analogous neuroimaging predictors, and possibly similar mechanisms of action, as previously validated treatment approaches.
Keywords: Depression, Treatment, Internet, CBT.
Disclosure: Nothing to Disclose.

M215. Sustained Attention Associated Bold Signal Differentiates 7-Day Quit Status in Healthy Smokers

James Loughead*, Rebecca Ashare, Mary Falcone, Wen Cao, Leah LaPrate, Caryn Lerman

University of Pennsylvania, Philadelphia, Pennsylvania

Background: The neural mechanisms underlying failed attempts at behavior change are poorly understood. Brief abstinence from smoking impairs executive cognition function, which can contribute to smoking relapse. Identifying the neural substrates of abstinence-induced changes in cognitive function that differentiate successful quitters from those who relapse to smoking is a crucial step in developing neuroscience-based interventions that facilitate successful behavior change. This fMRI study examined BOLD signal change associated with sustained attention in a sample of smokers who subsequently achieved 7-day biochemically confirmed abstinence compared to a matched group of relapsers.
Methods: Eighty-one smokers completed two fMRI sessions (smoking satiety vs. 24hr abstinence challenge) followed by a quit attempt. BOLD fMRI was acquired during an event related sustained attention task (continuous performance task) with the following parameters: TR/TE = 3000/30 ms, FOV = 220 mm, matrix = 64 $\times$ 64, slice thickness/gap = 3.4/0 mm, 48 slices, effective voxel resolution of 3.4 x 3.4 x 3.4 mm. Time series preprocessing included: non-

brain removal, slice time correction, motion correction, high pass temporal filtering, smoothing and mean-based intensity normalization. Relapse during the first 7 days was biochemically confirmed by the presence of the nicotine metabolite cotinine. Eighteen participants achieved 7-day abstinence and were matched for age and sex to a subsample of those that failed the quit attempt ($n = 18$). A whole brain session (abstinent, smoking) by outcome (relapse, quit) voxel wise ANOVA was carried out and resulting statistical maps cluster-corrected at $Z > 3.09$ ($p < 0.001$) and cluster probability (family-wise error) $p < 0.05$.

Results: All participants were more accurate under the prior smoking (vs. abstinence challenge) condition ($p = 0.04$). No other differences were observed in task performance. The whole brain ANOVA of the target-foil contrast revealed a group by session interaction in the ventral medial prefrontal cortex (vmPFC) and right parietal region. For both areas, inspection of percent signal change showed greater relative deactivation under abstinence challenge for the quit group while the relapse group showed more deactivation under the smoking condition.

Conclusions: Impaired performance of goal directed sustained attention has been associated with abstinence from smoking and is predictive of relapse. In this study, participants who were able to quit successfully for 7 days showed greater deactivation in task negative regions. This effect suggests that the suppression of critical nodes in the default network while engaging in attentional tasks may represent a novel target for neuromodulation interventions to promote smoking cessation. Additionally, regions sensitive to relapse risk can guide the improvement of existing interventions and provide an early signal for the efficacy of novel tobacco dependence treatments.

Keywords: nicotine, addiction, cognition, fMRI.

Disclosure: Nothing to Disclose.

M216. Nicotinic Modulation of the Default Network of Resting Brain Function in Non-smokers

Britta Hahn*, Alexander Harvey, Bernard Fischer, William Keller, Thomas Ross, Elliot Stein

University of Maryland Medical School, Maryland Psychiatric Research Center, Baltimore, Maryland

Background: Nicotine consistently improves attentional functions; these effects may be of clinical benefit. In a previous study (Hahn et al. 2007, J Neurosci 27:3477), we showed that transdermal nicotine (21 mg/24 hrs) improved visuospatial attention in minimally deprived smokers by enhancing task-induced deactivation of the default network of resting brain function, a network that subserves task-independent thought processes such as mind-wandering. In the present study, we tested whether these effects would generalize to non-smokers tested with a smaller dose of nicotine (7 mg/24 hrs), and how these effects would compare to the nicotinic antagonist mecamylamine (7.5 mg p.o.).

Methods: Seventeen non-smokers underwent functional Magnetic Resonance Imaging on three separate days: once in the presence of nicotine, once in the presence of mecamylamine, and once with placebo. In each session, participants performed a visuospatial attention paradigm in which central cues predicted the location of a peripheral target, and a letter N-back task (0-back and 2-back). The visuospatial attention task was analyzed as a fast event-related design, the N-back task as a block design.

Results: Effects on task performance: In the visuospatial attention task, nicotine reduced reaction time (RT), omission errors, and the trial-by-trial variability of RT across task conditions. The effects of mecamylamine were restricted to a task block that was twice as long as other blocks, presumably challenging sustained attention processes, and consisted of RT slowing in trials with spatially unpredictable targets. In the N-back task, nicotine enhanced target detection across conditions, while mecamylamine slowed RT, particularly in the 2-back condition. Effects on fMRI BOLD signal: Regions of the default network were defined as task-negative regions in a previous meta-analysis of different cognitive tasks. We also probed those regions of the default network that were modulated by nicotine in our previous study. In the attention paradigm, the previously reported potentiation of cue-induced default network deactivation by nicotine was not apparent overall. However, this effect did emerge in medial prefrontal, posterior cingulate and superior frontal cortex, central regions of the default network, in task blocks with a faster event rate, similar to the one used previously. In blocks with a slower event rate and more time off task, in which default network regions were overall more active, cue-induced deactivation was more pronounced, and nicotine tended to reduce rather than enhance this deactivation. The effects of mecamylamine were not significant in the attention task. However, within the regions modulated by nicotine, the effects of mecamylamine trended into the same direction as those of nicotine. In the N-back task, deactivation of the default network was more pronounced in the 2-back than 0-back condition. Mecamylamine reduced this deactivation in the medial prefrontal cortex and angular gyrus/precuneus, particularly in the 2-back condition. Despite robust effects of nicotine on N-back task performance, no BOLD effects of nicotine were observed in this task.

Conclusions: The potentiating effects of nicotine on task-induced default network deactivation previously described appear to generalize to non-smokers, but they heavily depend on the specific task conditions and the basal level of task-induced deactivation of these regions. The pattern of activity with mecamylamine suggests that, at least in part, these effects may be mediated by nicotinic receptor desensitization. In the N-back task, the effects of mecamylamine consisted of a reduction in default network deactivation in the task condition in which the largest performance impairment was observed with mecamylamine. Nicotinic receptor tone does appear to impact default network functioning, but in a complex task-dependent manner. This work was supported by NIH grant 1R21DA027894 (B.H.), and by the Intramural Research Program of the NIH, National Institute on Drug Abuse.

Keywords: nicotine, mecamylamine, fMRI, default network.

Disclosure: Nothing to Disclose.

M217. Brodmann Area 25 Predicts Clinical Response to ECT in Depression

Miklos Argyelan*, Styliani Kaliora, Noah Weissman, Peter Kingsley, Anil Malhotra, Philip Szeszko, Georgios Petrides

Feinstein Institute for Medical Research/Zucker Hillside Hospital/Hofstra North Shore-LIJ, Glen Oaks, New York

Background: There are no reliable biomarkers of response to Electroconvulsive Therapy (ECT). Resting state fMRI (rsfMRI) is an informative method of assessment of brain functional connectivity which has been implicated in playing an important role in mood regulation. In the present study, we aimed to evaluate rsfMRI changes before and after a course of ECT and their relationship to antidepressant response.
Methods: Sixteen depressed patients (48.1 ± 12.6 yrs; 6 females) underwent rsfMRI before the first ECT(TP1), within 36 hours after the first ECT(TP2), and within 36 hours after the last or 8th ECT(TP3) (whichever occurred first). ECT was performed with bifrontal placement at 1.5 times seizure threshold. Patients' symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D). Remission was defined as two consecutive HAM-D ≤ 10. 12 patients remitted. Ten healthy controls (45.6 ± 12.0 yrs, 5 females) underwent the same fMRI protocol, at the same intervals. Fractional amplitude of low frequency fluctuations (fALFF) maps were assessed voxel-wise with statistical parametric mapping (cluster corrected $p < 0.05$); we compared TP1 versus TP3.
Results: In a whole brain voxel wise analysis, we found a significant time effect in the subgenual cingulated cortex (Brodmann area 25). No other area survived our statistical threshold. At baseline, depressed patients had higher fALFF than controls in the subgenual cingulate cortex. This difference decreased over the course of treatment, with significant effects observed following the first ECT. No changes were seen in healthy controls. In remitters versus non-remitters comparisons, we observed that decreases in fALFF were present only in remitters and only remitters had increased fALFF at baseline.
Conclusions: ECT responders showed increased resting state fALFF at the subgenual cortex that decreased with treatment, while healthy controls and non-responders showed no changes. This indicates that baseline abnormality in Brodmann area 25 is a good prognostic sign in ECT treatment. Our results are especially intriguing given that this area, also called the Mayberg area, is thought to play a central role in the neurocircuitry of depression. Therefore "normalization" of subgenual cortex fALLF activity may be a biomarker of response to ECT.
Keywords: resting state fMRI, Brodmann area 25, depression, biomarker.
Disclosure: Nothing to Disclose.

M218. Neural Mechanisms Underlying Emotion Modulation During Recovery from Acute Stress

Elizabeth Duval*, Xin Wang, Andrew Cotton, Hong Xie, Vikram Ramanujam, Shaun Ho, Kristopher Brickman, Marijo Tamburrino, Samuel McLean, Israel Liberzon

University of Michigan Health System, Ann Arbor, Michigan

Background: Acute stress and trauma can lead to the development of serious mental illness including posttraumatic stress disorder and depression. Previous findings suggest that stronger emotion modulation abilities and less threat processing are linked to recovery from acute stress. Recent studies indicate that stressful or traumatic experiences can rapidly alter brain function in the days after a traumatic event, leading to changes in emotional processing. However, little is known about the specific neural changes associated with recovery from acute stress or trauma. We address this gap by studying brain activation associated with emotional threat processing and modulation at two time points (within 10 days and at 3 months) following a motor vehicle collision (MVC). We hypothesized that brain regions involved in emotion modulation (e.g. dorsal prefrontal cortex) would become more active over time, in the context of recovery from MVC.
Methods: Thirty-six adult MVC survivors were recruited from an Emergency Department. To assess changes in brain function following acute stress, participants completed a novel task, the Shifted-Attention Emotion Appraisal Task (SEAT), to examine activation in regions associated with attention and emotion modulation of threat. During SEAT, participants viewed pictures of affective faces superimposed on buildings, and responded to one of three questions on each trial: 1) the face gender (male/female) to probe implicit emotional processing; 2) whether the scene was inside or outside to probe attention modulation of emotion; and 3) whether they liked or disliked the face to probe emotional appraisal. SEAT was completed during fMRI scanning at two time points (within 10 days and at 3 months) following MVC to examine neural changes associated with recovery from acute stress over time. Acute stress symptoms were measured with the PTSD Checklist (PCL)-Stressor version at each time point.
Results: Within 10 days after MVC, brain regions involved in threat processing (anterior cingulate cortex and insula) were activated during emotional appraisal ($ps < .05$ SVC). During emotion modulation, regions involved in regulating attention and emotional reactivity (dorsal prefrontal cortex, superior parietal cortex) were activated ($ps < .05$ SVC). Twenty participants went on to repeat SEAT three months after the MVC. PCL scores for these subjects decreased from the initial assessment (36 ± 13) to 3 months later (27 ± 12; paired t-test, $p < .05$), with no participants meeting criteria for PTSD. Changes in brain function revealed increased activation in dorsal prefrontal cortex over time during both emotion appraisal and emotion modulation tasks ($ps < .05$ SVC).
Conclusions: Results suggest that these MVC survivors modulated threat reactivity while experiencing acute traumatic stress. Moreover, activation in dorsal prefrontal cortex, a region involved in emotion modulation, increased

over time in the context of recovery from acute stress. These findings suggest that dorsal prefrontal cortex regions may play an important role in resilience and recovery from acute stress/trauma.
Keywords: Acute Stress, fMRI, Emotion Modulation.
Disclosure: Nothing to Disclose.

M219. Magnetic Resonance Imaging of Behavioral Dysregulation in Neurodevelopmental Disorders

Jean A. Frazier*, Mollie Wood, Eric Mick, Teresa Mitchell, Steven Hodge, David M. Cochran, David Kennedy

University of Massachusetts Medical School, Worcester, Massachusetts

Background: Behavioral dysregulation is a hallmark feature of many neurodevelopmental disorders. Behavioral dysregulation can be characterized by the Child Behavior Checklist-Dysregulation Profile (CBCL-DP) which consists of three subscales (anxiety/depression, attention problems, and aggression). In order to more fully determine the extent to which each of the three subscales contributes to the overall neuroimaging findings associated with the CBCL-DP, we examined the overlap between brain regions associated with the three CBCL subscale measures and brain regions that correlate with the overall dysregulation profile score.
Methods: We identified 85 subjects in our cohort, aged 6-18, who had a volumetric MRI and CBCL assessment. The cohort included neurotypical subjects, as well as subjects with ADHD, early-onset schizophrenia, or early onset bipolar disorder. The structural images were analyzed with FSL's voxel-based morphometry processing stream and reregistered to the MNI template; gray matter density was subjected to a voxelwise correlation with the various CBCL measures. These correlation maps were thresholded for regions demonstrating correlation coefficients greater than 0.23 (positive and negative). Overlap measures were then performed for the subscales relative to the overall CBCL-DP correlated brain regions. Overlap of 50% or greater was considered significant.
Results: A number of regions were identified that demonstrated significant positive and negative correlation between the total dysregulation score and gray matter density. Positive association between behavioral dysregulation and gray matter density was seen in the caudate (bilaterally) and left lingual gyrus; whereas negative association was identified in the left hippocampus, right posterior temporofusiform gyrus, precentral gyrus bilaterally, left middle temporal occipital gyrus, right central operculum, parietal opercula bilaterally, and the right planum polare. The aggression subscale of the CBCL dominates many of the brain regions demonstrating correlation with the overall dysregulation profile including the caudate and areas in the parietal and occipital cortices. In addition, the anxious/depressed subscale dominates the left parietal operculum, right planum polare, and the left middle temporal occipital gyrus; whereas the attention subscale dominates the right posterior temporofusiform gyrus.
Conclusions: Consistent with evidence in the structural analysis literature in these disorders, brain regions previously implicated in the greater learning and memory circuitry showed an association between gray matter density and behavioral dysregulation. Eight of the 12 brain regions had significant overlap with the brain regions associated with the aggression subscale alone, while three regions overlap significantly with the anxious/depressed subscale regions and with the attention problems subscale regions. These results suggest that a more detailed understanding of the relationship between these brain regions and behavioral profiles in children and adolescents with neurodevelopmental disorders is warranted to more fully inform our intervention efforts.
Keywords: Imaging, Children, Adolescents, Dysregulation.
Disclosure: Nothing to Disclose.

M220. Predicting Cognition from Brain Activity: A comparison of Task-based and Resting-state fMRI Methods

George James*, Tonisha Kearney-Ramos, Jonathan Young, Jennifer Gess, Jennifer Fausett, Clint Kilts

University of Arkansas for Medical Sciences, Psychiatric Research Institute, Little Rock, Arkansas

Background: The clinical translation of functional MRI (fMRI) into patient care is impeded by our limited understanding of how the brain encodes normative variance in cognition. Although numerous functional neuroimaging methods have been proposed for modeling brain-behavior relationships, our field lacks a direct comparison of these approaches. To address this limitation, we compare the ability of two popular neuroimaging methods, task-based general linear modeling (GLM) and resting-state functional connectivity, for predicting cognition.
Methods: Fifty-three healthy adults [mean(sd) age = 32(9.7) years, 31 (58%) females] underwent comprehensive neuropsychological testing and 11 fMRI paradigms including the n-back task, multi-source interference task (MSIT) and resting-state scans. Task-based and resting-state activity timecourses were extracted for 10 canonical resting-state networks, including a frontocingulate network. GLM identified betas describing task-related frontocingulate activity, and robust regression related participants' GLM betas to (a) task performance and (b) neuropsychological measures. Resting-state connectivity of the frontocingulate network was identified via correlation with other networks' resting timecourses; these correlations were z-transformed and also regressed to performance and cognition. All regressions controlled for participant age and years of education.
Results: Task-induced frontocingulate activity predicted both MSIT ($R2 = 0.49$, $p < 0.001$) and 2-back performance ($R2 = 0.20$, $p < 0.05$). Frontocingulate resting connectivity predicted MSIT performance ($R2 = 0.15$, $p < 0.05$) but not 2-back ($R2 = 0.06$, ns). MSIT activity ($R2 = 0.09$, $p < 0.05$) and resting connectivity ($R2 = 0.10$, $p < 0.05$) predicted attentional conflict, measured via DKEFS Color-Word test. 2-back activity ($R2 = 0.16$, $p < 0.01$) but not resting connectivity (all $R2 < 0.10$, ns) predicted working memory, measured via Digit Span Sequencing test.

Conclusions: Task-related frontocingulate activity and resting-state connectivity explained task performance, with task-related activity generally explaining more variance in performance measures. Task activity and resting connectivity variably explained neuropsychological performance, although these predictors explained less than 20% of variance observed among cognitive measures. Additionally, none of the reported resting-state predictors survived statistical correction for multiple comparisons, casting doubt upon the predictive value of resting-state connectivity analyses. Future work will further compare the ability of region-of-interest and task-related connectivity analyses for predicting brain-behavior relationships.
Keywords: individual differences, fMRI, neuropsychology, cognition.
Disclosure: Nothing to Disclose.

M221. Triangulating the Sexually Dimorphic Brain Through High-resolution Neuroimaging of Murine Sex Chromosome Aneuploidies

Armin Raznahan*, YanHe Lue, Frank Probst, Deanna Greenstein, Jay Giedd, Christina Wang, Jason Lerch, Ronald Swerdloff

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: Sex has a significant influence on risk for psychopathology: males sex is a risk factor for multiple early-onset neurodevelopmental disorders, and females sex is a risk factor for adolescent-onset affective and anxiety disorders. Thus, characterizing sex-differences in brain development, and clarifying biological contributions to these sex-differences may help to define mechanisms of risk and resilience in psychiatry. In recent years, there has been growing interest in the contribution of sex chromosome dosage to differences in brain development between females (XX) and males (XY). Sex chromosome dosage effects cannot be experimentally modeled in humans, but studies of naturally occurring sex chromosome aneuploidies (SCAs) - such as Turner (XO) and Klinfelter (XXY) syndromes - suggest that differences in X chromosome dosage may have direct effects on brain development. However, a number of factors complicate use of human SCA syndromes to examine sex chromosome gene dosage effects, including lack of control over background genetic and environmental diversity, karyotypic mosaicism, and X-chromosome parent-of-origin. Murine sex chromosome aneuploidies (SCAs) provide control over these factors while also allowing easier access to brain tissue and experimental paradigms. To date, the only existing study of brain anatomy in murine SCA has compared X-monosomic females (XO) to their karyotypically normal XX and XY littermates.
Methods: Here, building on prior work in X-monosomic (XO) mice, we use spatially non-biased high-resolution imaging to compare and contrast neuroanatomical alterations in XXY and XO mice relative to their wild-type XX and XY littermates.
Results: First, we show that carriage of a supernumerary X chromosome in XXY males (i) does not prevent normative volumetric masculinization of the bed nucleus of the stria terminalis (BNST) and medial amygdala, but (ii) causes distributed anatomical alterations relative to XY males, which show a statistically unexpected tendency to be co-localized with and reciprocal to XO-XX differences in anatomy. These overlaps identify the lateral septum, BNST, ventral group thalamic nuclei and periaqueductal gray matter as regions with replicable sensitivity to X chromosome dose across 2 SCAs. We then harness anatomical variation across all four karyotype groups in our study - XO, XX, XY and XXY - to create an agnostic data-driven segmentation of the mouse brain into five distributed clusters which (i) recover fundamental properties of brain organization with high spatial precision, (ii) define two previously uncharacterized systems of relative volume excess in females vs. males ("forebrain cholinergic" and "cerebelo-pontine-thalamo-cortical"), and (iii) adopt stereotyped spatial motifs which delineate ordered gradients of sex chromosome and gonadal influences on volumetric brain development.
Conclusions: Taken together, these data provide a new framework for the study of sexually dimorphic influences on brain development in health and disrupted brain development in SCA. First, data provide strong evidence for direct X chromosome dosage effects on the development of sexually-dimorphic brain regions that have been considered classical foci of sex-steroid dependent masculinization Also, we detect spatial gradients within the brain that bridge foci of predominant sex-steroid sensitivity and foci predominant X-dosage effects with transitional regions where both influences shape brain volume. This adds emphasis to the current movement away from "gonad-centric" mechanistic accounts for sexual dimorphism in the brain. Second, X-chromosome dosage effects appear to center on brain regions that are strongly implicated in the neurobiology of fear. This raises the hypothesis that differences in X chromosome dosage between typically developing males and females may be relevant for sex-differences in risk for anxiety disorders. Third, our study also detects two previously unrecognized sexually dimorphic brain systems where larger volume appears to segregate with the presence of ovaries above X chromosome count. These systems represent important new candidates foci of sex-steroid effect on brain development. Finally, with regards to the neurobiology of SCA, our murine findings motivate targeted studies of BNST and periaqueductal gray matter structure/functioning in both Turner and Klinefelter syndromes. Important areas for future work will be to understand the molecular bases for, and functional consequences of, the regionally-specific X chromosome effects we localize on our study.
Keywords: Brain Anatomy, Sexual Dimorphism, XO, XXY.
Disclosure: Nothing to Disclose.

M222. Analysis of Large-Scale Human Brain Functional Networks in Schizophrenia

Brent Nelson*, Jazmin Camchong, Kelvin Lim

University of Minnesota, Minneapolis, Minnesota

Background: Schizophrenia is a disease with alterations in thought, perception, emotion, and behavior. While the

fundamental cause is unknown, the leading theory, called the disconnectivity hypothesis, proposes schizophrenia is due to aberrant brain connectivity (Friston 1998). This hypothesis is supported by mounting evidence from a variety of imaging techniques including structural and functional MRI. Many studies describe network disruptions as complex and wide reaching, involving circuits connecting disparate brain regions (Volkow et al. 1988, Greicius 2003, Camchong 2011). In order to quantify these complex brain networks, an area of mathematics called graph theory has been applied to understand and describe these network differences. Our study used this technique to examine brain connectivity in a large group of subjects with schizophrenia. Our goal was to use a data driven approach to better characterize network differences at multiple levels.

Methods: Data were collected from 76 probands (56 males and 20 females with the diagnosis of schizophrenia) and 86 healthy controls (60 males and 26 females) for a total of 162 subjects. The mean age for both groups was 36 years. Magnetic resonance scans included structural (T1) and resting state functional (6min in length, TR 2s, TE 30ms) imaging. Images were preprocessed with standard pipelines. Functional images were aligned to their structural counterpart which was then registered to standard MNI 152 space. Average timecourses were extracted for 90 ROIs (AAL atlas), regressed with motion parameters, and wavelet decomposed. Motion artifacts were removed via a novel ICA approach (Kelly 2010). Level 2 wavelets were extracted for each ROI and functional connectivity matrices generated by ROI pearson correlation. This matrix was 90x90 with the cells representing the connectivity between two brain regions. Global strength, nodal strength, and edge strength measures were calculated for all subjects. Global strength was calculated as the average of all values in the connectivity matrix. Nodal strength was calculated as the average connectivity between each region and all 89 other regions. Edge strength was the cell value between two regions in the connectivity matrix. Groups were compared via student's t test at each analysis level. Random distributions were generated via permutation and significance (p values) was calculated based on these random distributions. Nodal and edge p values were then converted to q values using matlab's mafdr function. Areas of significant difference were identified for those nodes and edges with a q value < 0.05.

Results: Significant differences were seen at all levels of analysis. Global strength was found to be significantly decreased with an average difference of -0.11 ($p = 0.02$). Nodal strength was found to be significantly decreased in 85 of 90 nodes with an average difference of -0.04 ($q < 0.05$ std $= 0.01$) and increased in 3 of 90 nodes (left caudate, left thalamus, and right thalamus) with an average difference of 0.02 ($q < 0.05$ std $= 0.01$). Two nodes (left rectus and right caudate) did not show any significant between group differences. Edge strength was found to be decreased in 1767 of 4005 edges with an average difference of -0.07 ($q < 0.05$ std $= 0.02$) and increased in 51 of 4005 edges with an average difference of 0.07 ($q < 0.05$ std $= 0.01$).

Conclusions: Schizophrenia is a complex disease with a variety of symptoms including disruption of thought, behavior, and perception. Evidence continues to support the disconnection hypothesis with many observations of global network disruption. Our study adds additional evidence to this hypothesis and further demonstrates that not only are a large number of brain regions affected but also the individual connections between these regions. Our data goes further and shows both decreased and increased connectivity at the nodal and edge levels. Our large sample size combined with strong analysis methods provide us with a model to better understand the specific nature of network differences. In the future our study will examine the relationship between these network differences and clinical markers such as positive symptoms and cognition. If reliable areas of disconnectivity can be identified, methods such as non-surgical brain stimulation may be used to modulate these connections.

Keywords: functional, schizophrenia, graph.
Disclosure: Nothing to Disclose.

M223. Persistent Cannabis Use During Adolescence is Linked to Morphological Changes in the Medial Temporal Lobe and Persistent Cognitive Deficits in Late-life

Alison Burggren*, Susan Bookheimer, Edythe London

University of California Los Angeles, Los Angeles, California

Background: As advancing legislation across the United States has made marijuana (Cannabis sativa) more available, knowledge of the long-term effects of cannabis on the brain, for either medical or recreational purposes, is crucial, and has profound importance for public health policy, including messages targeted to adolescents. People who were adolescents through the 1960's and 70's, when cannabis use doubled (Robinson, "Decades of Drug Use: Data From the '60s and '70s," Gallup, 2002) are now entering senescence, a period of high risk for cognitive deficits related to aging (Schaie, Am Psychologist 1994; Grimby and Berg, Aging 1995, Hultsch et al., Psych and Aging 1992, Zarit and Berg, Journal of Gerontology 1992; Farmer et al., Annals of Epidemiology 1995). However, there is little information on the neurobiological and cognitive effects of cannabis use in adults approaching late life. Because cannabis use appears to have a primary neurotoxic effect within the hippocampus (Chan et al., J Neuro, 1998), the main structure for memory and the one affected most by age-related memory impairments and pre-clinical Alzheimer's disease (Braak and Braak, Acta Neurol Scand Suppl, 1996), we expect that the effects of chronic cannabis use in the hippocampus may be substantial in senescence. Although cognitive deficits from chronic adolescent cannabis use were shown to persist into late-life, decades after the period of usage (Meier et al., PNAS 2012), little research has addressed the long-term neurobiological effects of cannabis use, assessed in adults approaching late-life. This study investigated whether there are morphological differences late in life (average age $= 70.1$ years old) 30 subjects who used cannabis heavily or not at all during adolescence. It focused on the hippocampus, an area of the brain that is densely innervated with cannabinoid (CB)1 receptors (Burns et al., PNAS 2007)., and on cognitive performance in the memory domain.

Methods: We enrolled 30 subjects into two groups; 14 participants who used cannabis > 20x/month for at least a year during adolescence ('Cannabis + ') and 16 participants who did not use cannabis at all ('Cannabis–'). No participants were using cannabis at the time of assessment, as verified by urine test on the day of testing. Subjects provided self-reports of drug use. Endorsement of cigarette smoking (tobacco) and alcohol use were allowed in both groups; and the groups were matched on number of smokers and nicotine dependence, measured according to the Fagerström Test for Nicotine Dependence (96); light alcohol use was also allowed and matched across both groups (< 14 drinks/week for men; < 7 drinks/week for women; may not meet DSM-IV (97) criteria for alcohol dependence). The two groups also were matched according to age, IQ (using both the WTAR and NAART), gender and mother's educational attainment. In order to verify the accuracy of historical reporting, close family members or friends who were present during the period of time when the subject actively used marijuana were also interviewed. Only data form subjects whose self-reporting reached a threshold of 85% or greater cross-validation with the family member/friend's reports of marijuana use (Marijuana Smoking History Questionnaire; Bonn-Miller and Zvolensky, The Am J on Addict 2009) were included in the analysis. All subjects underwent high-resolution MRI through the long-axis of the hippocampus (3T Allegra; TR: 5200ms, in-plane resolution: 0.4 mm x 0.4 mm, 3-mm thick, skip 0) and neuropsychological testing. In order to increase visibility of the convoluted medial temporal lobe, the T2 FSE images were unfolded and flattened into a 2D map. Thickness values were calculated by taking the maximum of the distance values across all layers in the gray matter strip isolated within the MTL. For analyses, 'age at first use', 'frequency during first 10 years', and 'frequency over lifetime' were entered into regression analyses with cortical thickness and cognitive performance.
Results: Participants in the Cannabis + group had thinner cortex within the Cornu Ammonis 1,2,3 and the dentate gyrus, and thinner hippocampus averaged over all subregions. The magnitudes of these effects were significant in every region of the HC: 13.2% thinner CA23DG ($p = 5.2e-4$), 14.8% thinner CA1 ($p = 2.3e-5$) and 16.4% thinner overall hippocampal thickness averaged across all subregions ($p = 4.6e-6$). In additon, age at first use was significantly negatively correlated with Z-score in the Memory Domain. Neither 'frequency during first 10 years' nor 'frequency over lifetime' were significantly related to differences in cortical thickness or cognitive performance.
Conclusions: Our findings suggest that cannabis use has a neurotoxic effect on the adolescent brain that persists well into adulthood, and highlight the importance of public policy efforts that target adolescents. The results suggest that chronic use of cannabis in adolescence has long-lasting effects on hippocampal structure, which may underlie and exacerbate age-related cognitive decline. These results, when expanded to a larger sample size, may help to identify persons more likely to decline than their age-matched counterparts and suggest early intervention in therapies aimed at slowing cognitive decline in late-life.
Keywords: cannabis, high-resolution, hippocampus, aging.
Disclosure: Nothing to Disclose.

M224. Neural Correlates and Developmental Progression of Executive Function in Youth with Bipolar Disorder

Marguerite Reid Schneider*, Luis Rodrigo Patino, Wade Weber, James Eliassen, Caleb Adler, Stephen Strakowski, Melissa DelBello

University of Cincinnati College of Medicine, Cincinnati, Ohio

Background: Bipolar disorder (BD) is a serious psychiatric disorder that often presents during adolescence. In addition to the mood symptoms that define the illness, BD is associated with cognitive deficits, particularly in the domains of attention, verbal memory, and executive control. These neurocognitive deficits may contribute significantly to the functional impairment associated with the disorder. In particular, executive function deficits in bipolar youth have been associated with impaired academic performance and increased risk for placement in a special class, beyond the risk predicted by BD alone. In adults, cognitive impairment has been associated with poorer functional outcomes and lower quality of life than BD alone. However, little research has assessed functional activation patterns associated with executive function deficits in this population or longitudinally assessed developmental or progressive changes associated with executive functioning in youth with bipolar disorder.
Methods: Adolescents (12-17 years old) presenting with a first mixed or manic episode associated with bipolar disorder were recruited from Cincinnati Children's Hospital Medical Center (CCHMC). Demographically-matched typically developing adolescents were recruited from community advertisements. Subjects were group-matched for age, race, sex, socioeconomic status, and Tanner stage. All study participants completed scanning sessions both at baseline (during first manic/mixed episode for bipolar youth) and 1 year later. Each session consisted of a high resolution structural MRI scan and fMRI during the performance of a modified version of the Continuous Performance Task – Identical Pairs (CPT-IP) task, in which stimuli at each of three degradation levels were randomly interspersed within the active task. In addition, at each visit, a parent or legal guardian completed the parent version of the Behavior Rating Inventory of Executive Function (BRIEF), a standardized 86-item assessment of executive function. Region of interest (ROI) analysis was conducted on the fMRI data, focusing on components of the anterior limbic network. Correlations between activation patterns and BRIEF composite scores was assessed both to evaluate the relationship between regional activation and scores at baseline and to assess how longitudinal changes in activation correlated with changes in executive function performance.
Results: At baseline, BRIEF composite score was significantly associated with activation in the bilateral caudate (Right $p = 0.0068$, Left $p = 0.0078$) and the bilateral subgenual anterior cingulate cortex (Right $p < 0.0001$, Left $p = 0.016$) in both healthy youth and youth with bipolar disorder. In these regions, higher BRIEF composite scores (signifying worse executive function) were correlated with decreased activation. In addition, bipolar youth showed a

significant correlation between recruitment of Left BA 45/47 and composite BRIEF scores ($p = 0.0017$), increased activation in this region was associated with better executive function scores. This relationship was not seen in healthy youth ($p = 0.60$). Subscale analysis revealed that the relationship was strongest for the working memory subscale in bipolar youth ($p = 0.0031$). In contrast, healthy youth showed a strong correlation between activation in right BA 11/12 and BRIEF composite scores ($p = 0.0123$) that was not seen in youth with bipolar disorder ($p = 0.83$) and was strongest for the Initiate subscale ($p = 0.0065$). With regards to progressive changes, in youth with bipolar disorder, increases in activation in left BA 10 from baseline to 1 year were associated with significant worsening of BRIEF composite scores ($p = 0.0012$), a relationship that did not reach significance in healthy youth ($p = 0.07$). This relationship was strongest for the Inhibit ($p = 0.0049$) and Emotional Regulation ($p = 0.0107$) subscales.
Conclusions: Our results demonstrate that while some regions, including the caudate and subgenual anterior cingulate cortex that are associated with executive function ratings in both youth with bipolar disorder and typically developing youth, there are also regions where such relationships are strong for youth with bipolar disorder and not healthy youth, and vice versa. These differences suggest that executive function deficits in youth with bipolar disorder are associated with recruitment of a different network of regions during sustained attention, as opposed to merely altered levels of activation in the same regions recruited by healthy youth. Further research using functional connectivity and other methods to explore network level activation patterns will be necessary to further clarify this relationship.
Keywords: bipolar disorder, executive function, fMRI.
Disclosure: Nothing to Disclose.

M225. Differential Patterns of Activity and Functional Connectivity in Emotional Conflict Regulation in Adolescents with and without Suicide Attempt

Lisa Pan*, AnnaMaria Segreti, Henry Chase, Anett Gyurak, Amit Etkin, David Brent, Mary Phillipsa

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Suicide is the third leading cause of death in adolescence. Functional differences in emotion processing and regulation neural circuitry in adolescents with a history of suicide attempt with depression (ATT) relative to adolescents with depression but no history of attempt (NAT) and healthy controls (HC) have been identified. Differences in emotional conflict regulation in adolescent attempters remain unexamined.
Methods: 57 adolescents:17 ATT, 23 NAT, and 17 HC, completed a Stroop-based emotional conflict regulation task with fMRI. Conflict adaptation trials were utilized to assess neural circuitry during emotional conflict regulation based on previous task findings. Post-hoc analyses were conducted on interactions from the whole brain analyses ($p < 0.05$,corrected). Generalized psychophysiologic interaction (gPPI) analyses were undertaken utilizing a right dACG (dACG) seed.
Results: ATT showed significantly greater activity than NAT in right dACG, right posterior cingulate gyrus, and inferior parietal gyrus; and than HC in left insula, right middle temporal gyrus, and parietal areas. GPPI analyses using a right dACG seed demonstrated increased connectivity in ATT to right amygdala and left insula compared with NAT, and to left inferior frontal gyrus compared with NAT and HC. ATT showed significantly diminished right dACG to right dorsolateral prefrontal cortex (DLPFC) and right middle frontal gyrus connectivity versus HC ($p < 0.002$, corrected).
Conclusions: Inefficient recruitment of key areas in the salience and default mode network, with a pattern of diminished functional connectivity between right dACG and executive control network regions, and increased functional connectivity between right dACG and emotional and salience networks during emotional conflict regulation in ATT compared with NAT and HC may represent potential markers for suicide risk.
Keywords: suicide, adolescence, dACG, insula.
Disclosure: Nothing to Disclose.

M226. Identifying and Validating Distinct Clinical Phenotypes in Bipolar Disorders Using Neurocognitive Data, Neuroimaging Scans and Machine Learning

Benson Irungu*, Benson Mwangi, Mon-Ju Wu, Isabelle Bauer, Marsal Sanches, Giovana Zunta-Soares, Jair Soares

University of Texas Health Science Center At Houston, Houston, Texas

Background: Diagnosis and clinical management of psychiatric disorders is largely guided by the assumption that diagnostic and statistical manual defined categories align with distinctive pathophysiological mechanisms. There is general consensus within the psychiatric community that the precincts of current diagnostic categories may not effectively capture underlying pathophysiological mechanisms of dysfunction (Frangou, 2013; Insel, 2014). We report a novel approach of identifying and validating distinct and biologically meaningful clinical phenotypes of bipolar disorders using CANTAB neurocognitive tasks measurements and structural neuroimaging scan data.
Methods: Neurocognitive tasks measurements from 70 patients with bipolar disorders (age range = 18-62 years) were analyzed using an unsupervised machine learning technique and unique subgroups or clinical phenotypes identified. The Least Absolute Shrinkage and Selection Operator (LASSO) method (Tibshirani, 2011) was used to investigate the predictive validity of original or 'raw' neurocognitive measurements in predicting individual subjects' phenotypic labels. Lastly, we used voxel-based and surface-based T1-weighted scan measurements coupled with LASSO to predict individual subjects' phenotypic labels. The latter step was used to establish whether identified phenotypes were biologically distinct.
Results: The unsupervised machine learning technique identified two unique phenotypes which were labeled (1 – phenotype I, 2 – phenotype II). Neurocognitive measurements predicted individual subjects' phenotypic

labels with 94% accuracy (sensitivity = 92% and specificity = 98%, chi-square $p < 0.0005$). Voxel-based white-matter volume predicted individual subjects' phenotypic labels with 71.4% accuracy (sensitivity = 80%, specificity = 62.5%, chi-square $p < 0.0025$). In addition, surface-based Gaussian curvature which is a measure of cortical folding predicted individual subjects' phenotypic labels with 74% accuracy (sensitivity = 85%, specificity = 63%, chi-square $p < 0.0006$).

Conclusions: These results suggest that there may exist two biologically distinct clinical phenotypes in bipolar disorders. Most importantly, our results indicate that neuroimaging scan measurements can identify the two phenotypes at an individual subject level and with high accuracy. We suggest a strong clinical utility of the proposed approach in defining biologically meaningful and clinical valuable sub-classifications of major psychiatric disorders.

Keywords: Research domain criteria (RDoC), machine learning, bipolar disorders, neuroimaging.

Disclosure: JC Soares - participated in research funded by Forest, Merck, BMS, and GSK and has been a speaker for Pfizer an Abbot. All other co-authors have nothing to declare. Study supported in part by NIMH grant R01 085667 and the Pat Rutherford, Jr. Endowed Chair in Psychiatry (Jair C. Soares).

M227. From the Immune System to the Brain: Increased Levels of Soluble Receptor Ii for Tumor Necrosis Factor Are Associated with Reduced Hippocampal Volume in Humans

Aoife O'Donovan*, Linda Chao, Jennifer Paulson, Kristin Samuelson, Judy Shigenaga, Carl Grunfeld, Michael Weiner, Thomas Neylan

University of California at San Francisco, San Francisco, California

Background: The immune system has the potential to profoundly influence brain function and structure, particularly through the activities of inflammatory proteins called cytokines, and their receptors. The hippocampus, a brain area that plays a critical role in learning and memory, appears highly sensitive to inflammation. In fact, experimental non-human research indicates that inflammation has the potential to reduce hippocampal volume by blocking neurogenesis and promoting neurodegeneration. Posttraumatic stress disorder (PTSD) has been linked with reduced hippocampal volume in numerous studies and with elevated inflammation. Thus, elevated inflammation may contribute to the association between PTSD and hippocampal volume. However, only a few studies with small sample sizes have examined associations between inflammatory markers and hippocampal volume, and none have examined these associations in the context of PTSD.

Methods: In the present study, we measured morning fasting levels of the pro-inflammatory cytokine interleukin-6 (IL-6) and the soluble receptor II for the pro-inflammatory cytokine tumor necrosis factor (sTNF-RII), as well as hippocampal volume in 246 Gulf War veterans with and without current and past PTSD (85% male gender; 18% current PTSD; 17% past PTSD; mean age = 45 years). High sensitivity enzyme-linked immunosorbent assays were used to measure inflammatory markers, and 1.5 Tesla magnetic resonance imaging (MRI) and Freesurfer version 4.5 were used to quantify hippocampal volume. PTSD was diagnosed using the Clinician Administered PTSD Scale and the Structured Clinical Interview for DSM-IV was used to diagnose psychiatric disorders other than PTSD, including the exclusionary diagnoses of lifetime psychotic disorders and bipolar disorder and current substance dependence. Hierarchical linear regression models were used to examine relationships between inflammatory markers and hippocampal volume, adjusting for age, gender, and intracranial volume. Analysis of covariance models were used to examine PTSD-related group differences in IL-6 and sTNF-RII, adjusting for age and gender. In secondary analyses, we examined if significant associations were independent of potential confounding and mediating factors including PTSD status, BMI, Gulf War Illness, childhood trauma and lifetime trauma exposure.

Results: Increased sTNF-RII was significantly associated with reduced volume of the hippocampus overall ($\beta = -.128$, $p = .017$), as well as of the right ($\beta = -.14$; $p = .01$) and left ($\beta = -.12$; $p = .03$) hippocampi considered separately. In contrast, IL-6 was not significantly associated with overall hippocampal volume ($\beta = -.044$, $p = .409$) or with either left or right hippocampal volume. The relationship between sTNF-RII and hippocampal volume was independent of age, gender, PTSD status, body mass index, Gulf War Illness, and childhood and lifetime trauma exposure. We observed no significant group differences by PTSD status in either IL-6 or sTNF-RII.

Conclusions: Overall, our findings are consistent with the idea that aspects of inflammation are associated with reduced hippocampal volume, independent of PTSD status, and that peripheral inflammatory activity may act as a marker of inflammatory processes that affect brain structure. The data also highlight heterogeneity in levels of inflammation among samples of individuals with PTSD.

Keywords: Inflammation, Hippocampal volume, PTSD, Psychoneuroimmunology.

Disclosure: Nothing to Disclose.

M228. A Combined Diffusion Tensor Imaging and Magnetic Resonance Spectroscopy Study of Patients with Schizophrenia

Meredith Reid*, David White, Nina Kraguljac, Adrienne Lahti

Auburn University, Auburn, Alabama

Background: Postmortem and neuroimaging studies report white matter abnormalities in patients with schizophrenia. In vivo diffusion tensor imaging (DTI) has consistently shown global reductions in fractional anisotropy (FA), a putative marker of white matter integrity, in the major white matter tracts. The cingulum bundle, in particular, is one tract frequently implicated in schizophrenia (1,2). It facilitates communication between two important components of the cortico-limbic network: the anterior cingulate cortex (ACC) and the hippocampus. We recently reported

alterations in function, neurochemistry, and volume in the ACC and hippocampus of patients with schizophrenia (3–5). Only a few studies have attempted to combine DTI and MRS in schizophrenia. These studies focused primarily on MRS metabolite measurements in predominantly white matter regions rather than in related cortical regions. This is an important distinction because aberrant functional interactions between discrete regions could stem from isolated cortical neuronal abnormalities, from abnormal white matter connections, or from both. Thus, an important question is to determine how these alterations are related to each other. Furthermore, none of these studies reported axial diffusivity (AD) and radial (RD) diffusivity, which have been linked to axon and myelin integrity, respectively, and may better reflect underlying pathology than FA alone. In this study, we used DTI and tract-based spatial statistics (TBSS) to assess white matter integrity and proton MRS to quantify metabolites in the ACC and hippocampus. We hypothesized that patients would have reduced FA and elevated RD compared to controls. We further hypothesized that N-acetylaspartate (NAA), a putative marker of neuronal health, would positively correlate with FA and negatively correlate with RD and that glutamate + glutamine (Glx) would negatively correlate with FA and positively correlate with RD.

Methods: 29 patients with schizophrenia and 20 healthy controls were included in this study. Imaging was performed on a 3T head-only MRI scanner. Two DTI runs were acquired, each non-collinearly distributed along 30 directions [b = 1000 s/mm2, TR/TE = 9200/96 msec, field of view = 246 × 246 mm, matrix = 112 × 112, 60 slices, interleaved acquisition, 2.2 mm slice thickness with no gap (2.2 × 2.2 × 2.2 mm voxel size), bandwidth = 1396 Hz]. Analyses of the FA, AD, and RD data were performed with FSL's tract-based spatial statistics (TBSS). MRS data were acquired from the ACC (2.7 × 2.0 × 1.0 cm) of 26 patients and 18 controls and from the left hippocampus (2.7 × 1.5 × 1.0 cm) of 23 patients and 18 controls. Water-suppressed spectra were collected with the point-resolved spectroscopy sequence [PRESS; TR/TE = 2000/80 msec to optimize the glutamate signal, ACC: 256 averages (8 min 32 sec scan time), hippocampus: 640 averages (21 min 20 sec scan time)] and analyzed in jMRUI. TBSS was used to correlate MRS metabolite levels with DTI measures only within the bilateral cingulum bundle, including the cingulate and hippocampal parts.

Results: We found reductions in FA in patients in multiple tracts (including anterior thalamic radiation, corticospinal tract, cingulum, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, corpus callosum, superior corona radiate, and fornix) as well as elevations in RD in many of the same regions. In controls but not patients, we found significant negative correlations between hippocampal NAA/creatine and RD and axial diffusivity (AD) in the hippocampal part of the cingulum bundle. We did not find correlations between Glx and DTI measures.

Conclusions: In this study, we measured metabolites in regions of predominantly gray matter because we sought to relate cortical neuronal abnormalities to alterations in the white matter connecting these regions. Our findings suggest white matter abnormalities in patients with schizophrenia are driven by loss of myelin integrity as indicated by overlapping FA reductions and RD elevations. Importantly, the region of the cingulum where we observed the negative correlation between RD and NAA in controls is located near the same region where we obtained hippocampal MRS measurements. The presence of the correlation demonstrates the potential utility of this multi-modal MRI approach to help further our understanding of the relationship between white matter microstructure and neurochemistry in distinct cortical regions connected by white matter tracts. References: 1. Kubicki et al. (2007). J Psychiatr Res, 41(1-2):15-30. 2. Whitford et al (2014). Neuroimage Clin, 5:93-99. 3. Reid et al. (2010). Biol Psychiatry, 68(7):625-633. 4. Kraguljac et al. (2013). JAMA Psychiatry, 70(12): 1294-1302. 5. Hutcheson et al. (2012). Schizophr Res, 140(1-3):136-142.

Keywords: schizophrenia, diffusion tensor imaging, magnetic resonance spectroscopy, cingulum.

Disclosure: Nothing to Disclose.

M229. Insecure Attachment in At-risk Youth is Associated with Hyper-responsivity of a Parietofrontal Cortical Network Involved in Social Behavior

Tracy Barbour*, Stephanie N. DeCross, A. J. Holmes, Emily A. Boeke, Rick P. F. Wolthusen, Susanna Crowell, Ellie Beam, Garth Coombs, Maren Nyer, Roger B. H. Tootell, Maurizio Fava, Amy H. Farabaugh, Daphne J. Holt

Massachusetts General Hospital, Boston, Massachusetts

Background: Insecure attachment styles are associated with a number of psychiatric illnesses, including depression, psychotic illnesses and personality disorders. Conversely, secure attachment has been linked to high levels of resilience in the face of psychosocial adversity and low levels of psychopathology. Attachment characteristics are thought to have both intrinsic, biological antecedents (e.g., temperament) as well as environmental determinants (e.g., the quality of parent-infant interactions), with interactions between these factors. However, little work has been done to investigate the neural underpinnings of attachment characteristics in humans. Given that attachment insecurity is associated with risk for psychopathology, a better understanding of the underlying neurobiology of these characteristics in humans could provide valuable information about neural phenotype(s) that confer vulnerability to psychiatric illness. We have previously characterized a parietofrontal network in humans, initially identified in non-human primates, that is involved in monitoring stimuli in "near space" (the space immediately surrounding the head and body) (Holt et al, 2014). Evidence suggests that this network, which includes the dorsal intraparietal sulcus (DIPS) and premotor cortex (PMv), plays a role in habitual social behaviors. For the current study, we collected imaging data in young people with subclinical symptoms of depression and psychosis in order to identify neural correlates of these symptoms and poor outcomes in this population. A subset of the participants of this study filled out the Relationship Questionnaire (RQ, Bartholomew and Horowitz, 1991), which assesses dimensional levels

of four types of attachment styles: secure, insecure-anxious, insecure-avoidant/fearful, insecure-avoidant/dismissing. Based on prior evidence linking particular attachment styles to abnormalities in lower-level sensory-motor processing, we tested the hypothesis that attachment insecurity is associated with changes in function of a near-space monitoring network.

Methods: Young people attending four Boston area universities participated in on-campus screenings for depression and other symptoms. The screening involved filling out a set of standard questionnaires, including the RQ, and for those deemed at risk (based on scores on a depression or subclinical psychosis measure), also a brief clinical interview conducted by an MD or PhD level clinician. The at-risk subjects later participated in an MRI scanning session (Siemens 3T Tim Trio) which included four 3.33 minute long runs of a paradigm that recruits the near-space monitoring network. The paradigm is comprised of pictures of human faces or cars moving towards or away from the participant in randomly presented 16 second blocks (4 conditions: Approaching and Withdrawing Faces and Cars). Participants performed a simple attentional task (dot detection) to ensure that they were attending to the stimuli to an equivalent extent across all four conditions. The FreeSurfer data analysis stream (www.surfer.mgh.harvard.edu) was used to conduct the analyses. The two a priori regions-of-interest (ROI), DIPS and PMv, were delineated using an automated parcellation of each individual's anatomical T1 scan. In 48 subjects (with both RQ and high quality fMRI data), correlations between each of the attachment styles and responses to approaching versus withdrawing faces (percent signal change) within right and left DIPS and PMv were tested using Pearson's r. Correlations with DIPS and PMv responses to car stimuli were also examined in a control analysis.

Results: In the screened sample ($n = 646$), levels of anxious and avoidant/fearful attachment were positively correlated with depression, suicidality and subclinical psychotic symptoms. Consistent with this, levels of secure attachment were negatively correlated with all of these symptoms. The ROI-based fMRI analysis revealed that levels of anxious, but not avoidant or secure, attachment were significantly correlated with bilateral DIPS and PMv responses to approaching versus withdrawing faces (all $ps < .05$). In contrast, DIPS and PMv responses to approaching versus withdrawing cars did not show correlations with levels of any attachment style.

Conclusions: These data reveal that one type of attachment insecurity is associated with elevated responses of a sensory-motor network involved in social behaviors. Additional work will determine whether this type of "tuning" to approaching social stimuli in this population is associated with other behavioral or cognitive characteristics, such as changes in social spacing, affect perception or mentalizing. If confirmed, this type of objective marker of social functioning may prove useful in identifying young people who could benefit from interventions that target social/relational deficits.

Keywords: Attachment, Imaging, Social Behavior, fMRI.

Disclosure: For Maurizio Fava: Advisory Board/Consultant Abbott Laboratories; Affectis Pharmaceuticals AG; Alkermes, Inc.; AmarinPharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRxBioPharma; Cephalon, Inc.; Clinical Trials Solutions, LLC; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; Diagno-Search Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; GenOmind, LLC; GlaxoSmithKline; Grunenthal GmbH; i3 Innovus/Ingenis; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante, Inc.; Merck & Co., Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Neuronetics, Inc.; NextWave Pharmaceuticals; Novartis AG; Nutrition 21; Orexigen Therapeutics, Inc.; Organon Pharmaceuticals; Otsuka Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; PharmaStar; Pharmavite® LLC.; PharmoRx Therapeutics; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; Puretech Ventures; PsychoGenics; Psylin Neurosciences, Inc.; Rexahn Pharmaceuticals, Inc.; Ridge Diagnostics, Inc.; Roche; RCT Logic, LLC; Sanofi-Aventis US LLC.; Sepracor Inc.; Servier Laboratories; Schering-Plough Corporation; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.;Synthelabo; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; Tetragenex Pharmaceuticals, Inc.; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc. Speaking/Publishing Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; BoehringerIngelheim GmbH; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; PharmaStar; United BioSource,Corp.; Wyeth-Ayerst Laboratories Research Support: Abbott Laboratories; Alkermes, Inc.; Aspect Medical Systems; AstraZeneca; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; Cephalon, Inc.; CeNeRxBioPharma; Clinical Trials Solutions, LLC; Clintara, LLC; Covidien; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; Ganeden Biotech, Inc.; GlaxoSmithKline; Icon Clinical Research; i3 Innovus/Ingenix; Johnson & Johnson Pharmaceutical Research & Development; LichtwerPharma GmbH; Lorex Pharmaceuticals; NARSAD; NCCAM; NIDA; NIMH; Novartis AG; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmavite® LLC; Photothera; Roche; RCT Logic, LLC; Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Synthelabo; Wyeth-Ayerst Laboratories Stock/Other Financial Options: Stock/Other Financial Options:Compellis Pharmaceuticals, PsyBrain, Inc. Royalty/patent, other income: Patent for SPCD and patent application for a combination of azapirones and bupropion in MDD, copyright royalties for

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M230. Baseline [11C]raclopride Binding Potential is Inversely Related to D2/3 Receptor Stimulation by Endogenous Dopamine

Lawrence Kegeles*, Diana Martinez, Mark Slifstein, Marc Laruelle, Anissa Abi-Dargham

Columbia University/New York State Psychiatric Institute, New York, New York

Background: Many PET neuroreceptor imaging studies of the dopamine system in patients with schizophrenia and healthy subjects are single-scan baseline binding potential (BPND) measurements. In these studies, the outcome measure, baseline BPND, is sometimes used as an imaging correlate of behavioral and cognitive measures. Key to the interpretation of these single-scan studies is an understanding of how baseline BPND relates to D2/3 receptor stimulation by endogenous dopamine. Here we quantify this relationship. We use receptor occupancy by endogenous dopamine as an indicator of D2/3 receptor stimulation, as measured with a dopamine depletion 2-scan paradigm.
Methods: Thirty-three healthy volunteers participated in [11C]raclopride PET scans with the alpha-methylparatyrosine (AMPT) dopamine depletion paradigm (data previously published as healthy controls in two studies {1,2}). Each subject underwent a baseline scan followed by a 48-hour period of administration of approximately 8 gm of AMPT followed by a second [11C]raclopride PET scan. Baseline BPND was determined from the initial scan and receptor occupancy by endogenous dopamine was computed as the difference between the BPND measures of the two scans as a percent of the second (dopamine-depleted) scan BPND. Correlations between baseline BPND and its two major determinants, the receptor occupancy by endogenous dopamine and the true or unmasked BPND (BPND in the depleted state) were evaluated. The correlation between receptor occupancy and the "AMPT effect" or "baseline synaptic dopamine level" presented in prior AMPT neuroreceptor imaging studies {1-3} was also computed. The AMPT effect is defined as the difference between the BPND measures of the two scans as a percent of the baseline BPND. We examined age effects on the BPND measures and on occupancy by endogenous dopamine. All measures were also examined in a smaller sample of patients with schizophrenia ($n = 18$) who participated in the same procedures {2}.
Results: In the healthy subjects, baseline BPND showed a significant negative correlation with occupancy by endogenous dopamine ($R = -.40$, $p = .02$). There was a high positive correlation between baseline and the true or unmasked BPND ($R = .85$, $p < .0001$). Receptor occupancy by endogenous dopamine was extremely well correlated with baseline synaptic dopamine level ($R = .998$, $p < .0001$). A significant effect of age was found for BPND in the depleted state ($R = -0.40$, $p = .02$) and a trend level effect for baseline BPND ($R = -.32$, $p = .07$) but not for receptor occupancy by endogenous dopamine ($p > .05$). Similar results were found in the patients although the age effects and the relationship between BPND and receptor occupancy by dopamine occurred at trend level.
Conclusions: Baseline [11C]raclopride BPND is not a positive or direct indicator of D2/3 receptor stimulation by endogenous dopamine. While much more of the variance in baseline BPND is explained by true or unmasked BPND than by receptor occupancy by endogenous dopamine, true BPND is not available in single-scan studies. Although these findings were obtained with the radioligand [11C]raclopride, they might also hold for other D2/3 radioligands known to be displaceable by endogenous dopamine, such as [18F]fallypride. The inverse indication of D2/3 receptor stimulation provided by baseline BPND in PET scans should be taken into account when interpreting relationships of BPND to behavioral or cognitive measures.
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Keywords: dopamine, neuroreceptor, imaging, PET.
Disclosure: Lawrence Kegeles: research grant, Amgen Mark Slifstein: research grant, CHDI; consultant, Amgen Anissa Abi-Dargham: research grants, Forest and Takeda; advisory boards, Roche, Otsuka and Forum.

M231. Attenuation of Neural Activity During Emotion Processing in Unipolar and Bipolar Depression

Jay Fournier*, Henry Chase, Mary Phillips

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Background: Bipolar disorder (BD) and unipolar depression (UD) can be difficult to distinguish clinically, particularly during episodes of depression. Prior work in our group, along with work by others, has identified differences in the functioning of regions involved in emotion processing and emotion regulation in BD versus UD. To date, the majority of this work has used fMRI to examine differences in mean BOLD activation between groups during a single testing session. Little prior work has examined stability and change in neural activity during emotion processing within and between sessions in these patient samples. Given recent work highlighting the importance of articulating the temporal dynamics of emotion processing, in this study we seek to test for differences between BD, UD, and healthy control (HC) adults regarding within- and between-session attenuation of the BOLD response during implicit emotional processing.
Methods: During fMRI, HC adults ($N = 16$) and depressed adults with UD ($N = 17$) and BD ($N = 15$) performed an implicit emotional faces task in which they identified a color label superimposed on neutral faces that dynamically morphed into one of four emotional faces (angry, fearful, sad, happy). BOLD response to the faces was contrasted to BOLD response to a dynamically changing shape condition. Each participant contributed data from two scanning sessions, separated by six-months, resulting in 96 total scans. All participants were followed naturalistically during

the six-month window. Standard imaging preprocessing was performed using SPM12b. First level, within-subjects models were constructed to probe mean BOLD response during emotion processing, as well as changes in BOLD response over time. To model the latter, first- and second-order time modulators were added to the design matrix for each task condition. At the second level, separate 3(Group: BD vs UD vs HC)-by-2(Emotion: Positive vs Negative)-by-2(Time: Session 1 vs Session 2) random effects, repeated-measures models were conducted to examine each outcome of interest (mean BOLD response and linear and quadratic attenuation effects). Results were whole-brain FWE cluster corrected at $p<0.05$, with a cluster-forming threshold of $p<0.005$.

Results: Analysis of linear attenuation over time revealed a group-by-condition interaction in a large area in the right MTG, STG, and inferior parietal cortex ($k=132$, FWE <0.05, Peak Voxel: $F(2,45)=9.79$, $p<0.001$, $x=48$, $y=-34$, $z=10$). Specifically, individuals with BD demonstrated a large linear decrease in BOLD activity to negative emotional conditions across trials within testing sessions, whereas HC and UD individuals demonstrated an increase over time ($t(45)=5.30$, $p<0.001$ for BD vs HC; $t(45)=5.74$, $p<0.001$ for BD vs UD). UD and HC groups did not differ ($t(45)=0.37$, $p>.05$). We found no evidence that this effect differed across the 6-month separation between sessions (the 3-way group-x-condition-x-session interaction was not significant). The three groups did not differ regarding attenuation of the BOLD response in this region to the positive emotional conditions (all $ts(45)>1.68$, $ps>0.05$). In addition, we observed a main effect of group in the linear attenuation of the BOLD signal in a large cluster that included bilateral caudate head and which extended posteriorly on the right to include potions of the putamen and thalamus ($k=182$, FWE <0.05, Peak Voxel: $F(2,45)=10.89$, $p<0.001$, $x=27$, $y=-4$, $z=16$). In this region, the BD group demonstrated a linear decrease in BOLD response across emotional conditions compared both to the HC and UD groups ($t(45)=6.01$, $p<0.001$ for BD vs HC; $t(45)=4.47$, $p<.001$ for BD vs UD). UD and HC groups did not differ ($t(45)=1.66$, $p>.05$). No significant effects were observed for the term representing accelerated (e.g., quadratic) attenuation of the BOLD response for any comparison. Finally, we observed a group-by-condition interaction for mean BOLD activity in two regions: a large, bilateral, occipital region extending anteriorly on the left to include portions of the fusiform gyrus ($k=760$, FWE <0.05, Peak Voxel: $F(2,45)=13.88$, $p<0.001$, $x=-30$, $y=-46$, $z=-20$), and a smaller region in the left temporal lobe that spanned portions of STG, MTG, and ITG ($k=95$, FWE <0.05, Peak Voxel: $F(2,45)=11.88$, $p<0.001$, $x=-57$, $y=-31$, $z=4$). In both regions, the BD group demonstrated reduced BOLD activity to negative emotions compared to the HC and UD groups (all $ts(45)>2.77$, $ps<0.01$).

Conclusions: We observed substantial differences between those with BD and UD during processing of emotional faces. Across testing sessions separated by 6 months, individuals with BD demonstrated reduced activity in visual and visuospatial processing regions compared to those with UD. Moreover, compared with individuals with UD, those with BD demonstrated a large, linear reduction in BOLD response to emotional stimuli within each session in predominantly right-sided thalamostriatal regions as well as in right-sided tempero-parietal regions. These findings suggest that members of the BD group may either have habituated rapidly to or disengaged quickly from processing the emotional images, despite comparable task performance. Whereas reduced BOLD activity in BD is consistent with prior reports, we believe the finding of abnormal attenuation of BOLD response to be both significant and novel. Together, these patterns may represent a biomarker of illness that could reflect underlying pathophysiological processes associated with BD.

Keywords: fMRI, Bipolar Disorder, Depression, Emotion Processing.

Disclosure: Nothing to Disclose.

M232. Elevated Levels of Inflammatory Markers Are Associated with Longitudinal Changes in Regional Cerebral Blood Flow in Older Adults

Kristen Warren, Lori Beason-Held, Olga Carlson, Yang An, Josephine Egan, Susan Resnick*

National Institute on Aging, National Institutes of Health, Baltimore, Maryland

Background: Inflammatory changes in older adults are associated with a variety of adverse health outcomes, including cardiovascular disease, cancer, physical disability, and mortality. In addition, chronic inflammation has been linked to impairment in memory and other cognitive functions, as well as Alzheimer disease. Here, we investigate the association between markers of inflammation and cerebral blood flow changes during the normal aging process in older adults.

Methods: 138 cognitively normal older adult participants (mean age at baseline = 71.3) in the neuroimaging study of the Baltimore Longitudinal Study of Aging (BLSA) underwent annual 15-O water resting state PET scans over a 9-year period. Stored serum samples, collected every other year, were assayed for markers of inflammation using ELISA kits. A voxel-wise linear mixed model approach, controlling for age, sex, and regular NSAID use, was used to estimate associations between regional cerebral blood flow (rCBF) and interleukin-6 (IL-6) and C-reactive protein (CRP) markers of inflammation. Associations were examined between baseline inflammation markers and baseline rCBF, as well as longitudinal changes in rCBF over time. Effects were considered significant at $p<0.005$ and cluster size greater than 50 voxels. Region of interest (ROI) analysis was then performed to estimate the annual rates of change, direction of change, and trajectories of rCBF changes in regions that were significant in the voxel-wise analysis.

Results: Baseline IL-6 and CRP were associated significantly with both baseline rCBF and longitudinal change in rCBF. Higher baseline IL-6 was associated with significantly lower baseline rCBF in medial frontal, cingulate, precuneus, lingual gyrus, and postcental gyrus regions and significantly greater longitudinal declines in superior and orbitofrontal, superior temporal, and hippocampal regions. Higher CRP at baseline was associated with greater longitudinal decline in rCBF in cingulate and parahippocampal regions. ROI

analysis revealed linear trajectories of regional changes over time in these regions.
Conclusions: Elevated levels of inflammation are associated with longitudinal changes in rCBF in many brain areas important in learning and memory. These results, along with previous studies, suggest a role for chronic inflammation in age-related memory decline and suggest that changes in brain activity may contribute to this association.
Keywords: Inflammation, Cerebral Blood Flow, Aging, Imaging.
Disclosure: Nothing to Disclose.

M233. Cocaine-induced Functional Hyper-connectivity at Rest Between Fronto-striate Regions and Structural Hypo-connectivity Between Frontal-limbic Regions

Aysenil Belger*, Karen Grewen, Joshua Bizzell, NanKuei Chen

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Background: Cocaine exposure (CE) disrupts multiple domains of cognition and behavior, including stress and emotion regulation, decision making, and reward processing. While disruption of these systems account for poor decision-making, impulsivity, and greater risk for addiction and relapse, they have particularly devastating effects on maternal behaviors (MB) and maternal sensitivity (MS) to offspring needs. Indeed, CE during pregnancy appears to co-opt affect and stress regulation and the reward processing operations key to early parenting11-14, eliciting long-term blunting of the strong motivational and reinforcing value of mother-infant interaction. Prenatal and maternal cocaine abuse also contributes to impaired infant cognitive, affective and physical maturation, offspring substance abuse in later adolescence, further giving rise to long-term individual and societal burden. The goal of this study is to identify the effects of cocaine on maternal brain circuits, and explore the association between impaired affective processing and blunted reward processing. We present preliminary resting state functional magnetic resonance imaging and diffusion tensor imaging to quantify effects of maternal cocaine use on fronto-limbic neural circuits implicated in affect/stress regulation and F-S circuits of reward processing, critical for maternal behavior and sensitivity.
Methods: We examine node-based intrinsic resting state connectivity using fMRI, and white matter connectivity using diffusion tensor imaging (DTI) in 33 control subjects and 19 CE mothers. We focused on resting state connectivity between selected regions within the Fronto-Limbic (F-L) (Frontal –sup, mid, infer, orbit; Insula; Cingulate – anterior, mid, post; limbic-HIP, AMY, para-hippo; Temporal) and the Fronto-Striate (F-S) (Frontal, Cingulate, Parietal, Striatal, Insula, precuneus) networks. Diffusion tensor imaging results are focused on the inferior longitudinal fasciculus, linking fronto-limbic-sensory regions. Imaging was performed on a Siemens 3 Tesla MAGNETOM Trio high speed-imaging device equipped with a 32-chanel head-coil. Following a localizer scan, high-resolution T1-weighted anatomical images were acquired using Siemens' MPRAGE pulse sequence (TR, 2400 ms; TE, 3.16ms; FOV, 256mm; voxel size, 1mm3 isotropic). Whole brain functional images were acquired during an infant cry sound/infant video presentation task. using a T2* weighted echo planar (EPI) sequence sensitive to BOLD contrast (TR, 2000 ms; TE, 25 ms; voxel size, 4mm3; flip angle = 80°, 36 slices). Resting State scans were acquired at the beginning and at the end of the imaging session, with eyes open, while subjects look at a central fixation on the screen (TR, 2000 ms; TE, 32ms; voxel size, 4mm3; flip angle = 80°, 33 slices). Diffusion Weighted Imaging scans were acquired using parameters for HARDI DWI: GRAPPA, repetition time (TR) = 7200 ms; echo time (TE) = 83 ms; slice thickness = 2 mm; FOV 256 mm, in-plane resolution = 2 2 mm2, and 62 slices. 42-directions with b-value = 1000s/mm2, acquisition time 6:14. Here we report the preliminary analyses on the rs-FMRI and DTI data.
Results: Intrinsic resting state connectivity analysis (Figure 1 left panel) revealed significantly greater resting state connectivity in F-L (top row, Figure 1-left panel) and F-S (bottom row, Figure 1-left panel) regions at rest in the CE relative to CTL mothers. In contrast, connectivity between fronto-parietal nodes (bottom row, Figure 1-left panel) was significantly reduced in CE compared to CTL mothers. DTI Quantitative Tract-based statistical analysis revealed (Figure 1 right panel) significant group differences in both anterior, mid, and posterior regions along the ILF ($p < 0.05$, corrected for multiple corrections), with smaller FA values in CE compared to CTL in many subregions of the ILF. These results suggest that cocaine significantly alters dopaminergic projections both in F-S and in F-L circuits, potentially leading to an inability to recruit these systems during task performance. Mothers were assessed for maternal characteristics, including environmental and psychiatric/medical history, neurocognitive function, drug use, and a broad array of psychosocial factors.
Conclusions: These results suggest both a hyperconnectivity at rest between dopaminergic regions of the brain, and a reduced structural connectivity between frontal and limbic areas. A convergence of dysruptions in front-limbic and fronto-striate systems may be necessary to disrupt maternal behavior and sensitivity. Ongoing cluster and contingency analyses are exploring seeded functional connectivity during task-based fMRI to further understand the impact of resting state and DTI connectivity abnormalities on both regional activation and functional neural circuitry.
Keywords: cocaine, maternal sensitivity, maternal behavior, neuroanatomy.
Disclosure: Nothing to Disclose.

M234. Connectivity Strength Changes after a Course of ECT for Depression. Pilot Data from a Resting-state fMRI Study

Georgios Petrides*, Styliani Kaliora, Peter Kingsley, Philip Szeszko, Anil Malhotra, Noah Weissman, Miklos Argyelan

Northshore-LIJ Health System, Glen Oaks, New York

Background: The biological underpinnings of the mechanisms of action of Electroconvulsive Therapy (ECT) are not fully understood. The last decade several fMRI studies have

shown neurocircuitry changes after ECT for severe depression and there is indication that ECT exerts its effects at network -wide level . Newer neuroimaging techniques such as resting-state fMRI can assess not only individual brain areas but also the interplay among them and therefore evaluate the strength of such functional connectivities among brain regions. In this pilot analysis we sought to characterize changes after a course of ECT by using a novel technique to calculate overall Connectivity Strength.
Methods: Ten healthy controls (age: 45.6 ± 12.0, 5 females) and sixteen patients (age 48.1 ± 12.6, 6 females) who received ECT for a major depressive episode were included in the study. All patients underwent resting-state fMRI sessions at baseline (TP1), within 36 hours of the patient's first ECT(TP2), and a third session (TP3) within 36 hours of the last ECT or after the 8th ECT if they had not remitted by then . ECT was performed with bifrontal placement. Seizure thereshold was determined at the first session and the following treatments were performed at 50% above seizure threshold. Healthy individuals underwent the same imaging protocol, at approximately the same time intervals. We calculated Pearson correlations of low frequency BOLD fluctuations (0.1-0.01 Hz) among 266 nodes in the brain and used correlation coefficient as a measure for functional connectivity strength among brain regions. We averaged correlations across regions and called it Connectivity Strength (CS). We then compared CS with repeated measures ANOVA, with between-subjects factor of time. We used the data from the healthy controls for comparisons. We used $p < 0.05$ threshold to report significance.
Results: We found that at baseline depressed patients had a significantly lower Connectivity Strength (0.075 ± 0.026) compared to healthy individuals (0.123 ± 0.039). We observed a significant main effect of time in overall CS in the within-subject-comparisons in the ECT subjects. At baseline, during the course of ECT the Connectivity Strength increased incrementally, with a smaller increase after the first ECT (0.085 ± 0.026) and higher increases after the last ECT (0.119 ± 0.037). Connectivity Strength of the ECT patients did not differ from that of the healthy controls after the last ECT.
Conclusions: We found decreased Connectivity Strength among brain regions in depressed patients compared to healthy controls. A course of ECT normalized Connectivity Strength among brain regions. Further research is needed to determine whether these changes correlate to treatment outcomes.
Keywords: Resting-state fMRI, ECT, Connectivity strength, Depression.
Disclosure: Nothing to Disclose.

M235. Changes in Cortical Thickness in Youth Offspring of Parents with Bipolar Disorder Type I before and after Developing Their First Mood Episode

Fabiano Nery*, Wade Weber, James Eliassen, Matthew Norris, Tiffany Robles, Anna Wilson, Michelle Durling, Stephen Strakowski, Caleb Adler, Melissa DelBello

University of Cincinnati, Cincinnati, Ohio

Background: The objective of this study is to identify the clinical characteristics and structural abnormalities associated with illness progression in youth offspring of parents with bipolar disorder (BD) type I. Offspring of parents with BD I are at increased risk of developing mood disorders. We will present findings from a prospective evaluation of youth offspring of BD I parents who were evaluated before and after developing their first mood episode. We hypothesized that: 1) youth offspring of parents with BD I who develop a mood episode present more baseline psychiatric comorbidities and subthreshold mood symptoms than youth offspring of parents with BD I who do not develop a mood episode; 2) youth offspring of parents with BD I who develop a mood episode exhibit smaller cortical thickness in ventrolateral prefrontal cortex (VLPFC), as compared with healthy offspring of healthy parents (HC) at baseline; 3) youth offspring of parents with BD I who develop a mood episode exhibit longitudinal acceleration of cortical thinning in VLPFC after developing their first mood episode compared with HC.
Methods: This is a subsample of a larger prospective study evaluating clinical and neurobiological aspects of youth offspring of BD I parents. None of the offspring of BD I parents had a mood episode prior to entering the study. DSM-IV diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for children and the Structured Clinical Interview for DSM-IV Diagnoses (SCID) for parents. Mood symptoms were rated with Hamilton Depression Rating Scale (HamD) and Young Mania Rating Scale (YMRS). Conversion was defined as the development of a full mood episode (either major depressive or manic) during follow up. Offspring of BD I parents are evaluated at least every 4 months until they present a full mood episode. For the neuroimaging analysis, we compared 15 offspring of BD I parents (mean age ± SD: 13.4 ± 2.0; male: 26.3%) to 15 HC (mean age ± SD: 13.9 ± 3.0; male: 26.3%), matched for age, gender, and interval between scans. All 30 subjects underwent MRI scanning twice (offspring of BD I parents at baseline and after conversion). HC, who were matched for age, sex, race and duration between scans in at risk youth, were also scanned twice. Regional cortical thickness measures will be extracted from T1-weight structural MRIs using FreeSurfer v5.1. Differences in regional cortical thickness between both groups at baseline and after conversion, and longitudinal within-group comparisons will be evaluated using repeated measures ANOVA.
Results: Out of 122 youth offspring of BD I parents, 85 had at least one assessment post baseline, and 37 were lost to follow up. Out of 85 with post-baseline assessment, 17 became converters and 68 were non-converters (mean age ± SD: 13 ± 2 vs. 14 ± 3 years old, respectively, $p = 0.4$; males: 29.4% versus 54.5%, respectively, $p = 0.07$). Among the 17 converters, 6 (35.3%) had depressive disorder NOS, 5 (29.4%) had anxiety disorder NOS, 4 (23.5%) had ADHD, and 1 (5.9%) had BD NOS at baseline. Among the 68 non-converters, 23 (33.8%) had ADHD, 11 (16.2%) had depressive disorder NOS, 7 (10.3%) had anxiety disorders, and 1 (1.5%) had BD NOS at baseline. There were no statistical differences in baseline psychiatric diagnoses between the 2 groups (p values ranging from 0.06 to 0.41). Baseline HamD scores were 11.9 ± 5.5 for converters and 6.4 ± 6.2 for non-converters ($p < 0.01$). Baseline YMRS scores were 8.9 ± 5.2 for converters and 7.2 ± 6.1 for non-

converters ($p = 0.11$). Among the converters, 12 developed a full major depressive episode and 5 developed a manic episode, and mean ± SD time for conversion was 487 ± 321 days. For 15 converters, one HC was recruited for a second scan to match time for conversion, and their neuroimaging data will be presented. For these subjects, mean time between 1st and 2nd scan were 468 ± 325 days for offspring of BD I parents and 496 ± 328 days for HC. Comparisons of regional cortical thickness measures for both groups at baseline and after conversion will be presented.

Conclusions: Presence of subthreshold depressive symptoms, female gender, and comorbid anxiety disorders at baseline may characterize offspring of BD I parents that later present a first mood episode. Cortical thickness changes after developing a first mood episode in youth offspring of BD I parents may help to identify patterns of brain structural changes related to early progression of mood disorders. Longitudinal acceleration of cortical thinning may suggest that there is a gray matter loss early in the course of illness.

Keywords: bipolar disorder, child offspring, neuroprogression, cortical thickness.

Disclosure: Dr. Fabiano Nery held a position of Associate Medical Advisor in Eli Lilly and Company from 2012 to 2013. His wife is a currently employee of Eli Lilly and Company. Dr. Stephen Strakowski chairs DSMBs for Sunovion and is a consultant to Procter & Gamble. Dr. Caleb Adler has received research support from AstraZeneca, Amylin, Eli Lilly, GlaxoSmithKline, Lundbeck, Martek, Merck, Novartis, Otsuka, Pfizer, Takeda, and Shire. He has been on the lecture bureau for Merck and Sunovion, for which he has received honoraria. Dr. Melissa DelBello has received research support from AstraZeneca, Amylin, Eli Lilly, Pfizer, Otsuka, GlaxoSmithKline, Merck, Martek, Novartis, Lundlbeck and Shire, and is also on the lecture bureau for Otsuka, Merck and Bristol-Meyers Squibb. She has received Consulting/Advisory Board/Honoraria/Travel from Merck, Pfizer, Dey, Lundlbeck, Sunovian and Otsuka. The remaining authors reported no conflicts of interests.

M236. Abnormal Amygdala Functional Connectivity in Youth with Subclinical Delusions

Daphne Holt*, Stephanie DeCross, Avram Holmes, Emily Boeke, Rick Wolthusen, Elizabeth Beam, Garth Coombs, Maren Nyer, Randy Buckner, Maurizio Fava, Amy Farabaugh

Harvard Medical School/Massachusetts General Hospital, Charlestown, Massachusetts

Background: Abnormalities in gating information flow through the striatum, hippocampus and brainstem have been postulated to underlie psychotic symptoms. Evidence from electrophysiological studies conducted in rodents suggests that the amygdala plays a role in this gating. However, investigations of the neural mechanisms of psychosis have been hindered to some extent by the challenges associated with the confounding effects of antipsychotic medications on brain structure and function. In recent years, evidence from large epidemiological studies and detailed studies of first degree relatives of schizophrenic patients has suggested that subclinical delusions represent a clinical phenotype that, in a subset of people, is biologically related to clinical psychosis. Thus, an overall goal of this research was to identify neuroimaging markers that could contribute to distinguishing, among young people with mild subclinical symptoms, those who are at true risk for psychopathology from those with transient, non-impairing, delusion-like experiences.

Methods: Young people attending four Boston area universities participated in on-campus screenings for depression and other symptoms. The screening involved filling out a set of standard questionnaires, and for those deemed at risk, also a brief clinical interview conducted by an MD or PhD level clinician. Subjects were considered to be at some risk for psychopathology if one of three criteria were met: having a score > 5 on the Beck Depression Inventory (BDI), a measure of depression; a score > 7 on the Peters et al. Delusions Inventory (PDI), a measure of delusional thinking and other unusual experiences which has been validated for use in the general population; or a score > 0 on the suicidality item of the BDI. Those found to be at-risk, plus a small number of healthy controls and clinically depressed subjects (total $n = 125$) participated in an MRI scanning session (3T Siemens TIM Trio), which included one 6 minute long resting-state blood oxygenation level dependent (BOLD) scan. A seed-based functional connectivity analysis was conducted using an independently-defined, atlas-based amygdala seed, with customized software and SPM 8. Pearson's coefficients representing correlations in low frequency fluctuations in the BOLD signal were extracted and z-transformed. Based on prior studies using the PDI, in the analysis, the sample was divided into: 1) those with high levels of subclinical delusions (SD) (high SD, total PDI score > 7, $n = 66$) and 2) those with low-to-moderate levels of subclinical delusions (low SD, total PDI score ≤ 7, $n = 59$). Group averages and between-group comparisons of voxel-wise maps of amygdala connectivity were constructed (whole brain corrected, False Discovery Rate $p < .05$). Also, a whole brain voxel-wise regression was conducted in the full sample, using PDI score as a regressor.

Results: Both the high and low SD groups showed the expected pattern of amygdala connectivity, with strong functional coupling of the amygdala with the medial prefrontal cortex, anterior-mid cingulate gyrus, striatum, and brainstem. The between-group comparison revealed that there was significantly stronger amygdala-striatal connectivity bilaterally in the low SD group compared to the high SD group. In addition, the high SD group showed significantly greater amygdala connectivity with lower-level visual processing areas (BA18 and 19), compared to the low SD group. Lastly, the whole brain regression analysis showed that PDI score was positively correlated with amygdala-visual cortex connectivity.

Conclusions: These findings indicate that the presence of odd or erroneous beliefs in young people, which in some may represent a harbinger of future serious psychopathology, is associated with disrupted functional interactions between the amygdala and striatum. Moreover, consistent with recent findings in patients with schizophrenia and sensory models of psychosis, subclinical delusions are associated with excessive coupling between the amygdala

and visual cortices. These results suggest that a "pre-prodromal" state, characterized by a combination of mild psychotic symptoms and neural connectivity changes, may be detectable in a population of vulnerable youth with modifiable risk.
Keywords: psychosis, connectivity, amygdala, risk.
Disclosure: Nothing to Disclose.

M237. Serotonin Transporter Binding after Recovery from Eating Disorders

Ursula Bailer*, Monte Buchsbaum, Kishore Kotta, Daria Orlowska, Alex DeCastro, Carl Hoh, David Vera, Walter Kaye

University of California San Diego, San Diego, California

Background: It is well known that 5-HT alterations occur in people who are ill with anorexia nervosa (AN) and bulimia nervosa (BN) and persist after recovery from the eating disorder (ED). How 5-HT function contributes to symptoms in AN and BN is not well understood. Recovered (REC) AN and REC BN have differences in 5-HTT function that, in turn, might contribute to extremes of impulse control or inhibition of feeding behaviors and could affect medication response. We have previously reported that REC AN had significantly increased 5-HTT binding, measured with positron emission tomography (PET) and [11C]McN5652 compared to REC AN-BN for the dorsal raphe and anteroventral striatum (Bailer et al. 2007). However, neither group was different from healthy control women (CW). No other studies assessing 5-HTT binding have been done in REC AN. More recently we have shown that REC BN had significantly lower [11C]DASB binding in midbrain, superior and inferior cingulate and significantly higher [11C]DASB binding in anterior cingulate and superior temporal gyrus compared to CW (Pichika et al., 2012). The current study aimed to further elucidate 5-HTT binding across REC ED subtypes using [11C]DASB and PET in a new and independent sample.
Methods: A total of 23 female REC ED participants (8 REC AN, 7 REC AN-BN, 8 REC BN) and 15 CW were scanned with PET and [11C]DASB. This is part of an ongoing study so results should be considered preliminary as sample sizes will further increase. Logan graphical analysis was applied and parametric binding potential (BPND) images were generated. A Region of Interest analysis was conducted using AFNI regions. The dorsal raphe was modified from the red nucleus to be more lateral. The caudate was divided into an inferior, middle and superior region and other regions were taken directly from the standard set. Following the statistical design of our earlier study with [11C]McN5652, we entered the previous five regions of interest (dorsal raphe, middle caudate, mediodorsal thalamus, ventromedial caudate, subgenual cingulate) into a three-way repeated measures MANOVA with diagnosis as a group dimension and brain region and hemisphere as repeated measures dimensions.
Results: The brain region by group interaction was confirmed as significant (Wilks lambda 0.52, $F = 2.00$, $df = 12, 84$, $p = 0.03$). REC AN-BN tended to show greater differences in comparison with CW, having lower BPND values in the raphe (REC AN-BN: $2.52 + 0.56$; CW: $3.11 + 0.37$), and higher BPND in the ventromedial caudate (REC AN-BN: $1.17 + 0.17$; CW: $0.84 + 0.11$) and mediodorsal thalamus (REC AN-BN: $2.23 + 0.31$; CW: $1.76 + 0.21$). REC AN showed a similar pattern with less marked change except for the mediodorsal thalamus where they exhibited lower values ($1.46 + 0.29$) than CW ($1.76 + 0.21$). REC BN alone showed somewhat less difference in comparison to CW except in the subgenual cingulate where they showed greater values (REC BN: $1.54 + 0.29$; CW: $1.28 + 0.20$). Univariate Fisher exact tests revealed REC AN-BN differed ($p < 0.05$) from CW for the raphe. REC AN differed from REC AN-BN in the mediodorsal thalamus.
Conclusions: In summary, these preliminary data confirm differences in 5-HTT binding after recovery from EDs using a more specific radioligand for assessment of 5-HTT binding, consistent with our previous report showing a marked decrease of 5-HTT binding in REC AN-BN compared to REC AN in the raphe region, and points in the same direction of increased binding of REC BN compared to CW in the subgenual cingulate. These results potentially further help clarifying whether SSRIs are effective in subgroups of AN individuals after recovery. Our clinical experience and data (Kaye, Nagata et al., 2001; Kaye, Weltzin et al., 1991; Walsh, Kaplan et al., 2006) suggest that individuals with pure AN respond better to fluoxetine than do those with AN-BN. Decreased 5-HTT function may be related to poor response to SSRI medication, whereas individuals with increased 5-HTT activity may respond to higher SSRI doses.
Keywords: anorexia nervosa, bulimia nervosa, serotonin transporter, positron emission tomography.
Disclosure: Nothing to Disclose.

M238. Cocaine Cue-induced Dopamine Release in the Human Prefrontal Cortex

Michele Milella*, Aryandokht Fotros, Paul Gravel, Kevin Casey, Kevin Larcher, Jeroen Verhaeghe, Sylvia Cox, Andrew Reader, Alain Dagher, Chawki Benkelfat, Marco Leyton

McGill University, Montreal, Canada

Background: Altered mesocortical dopamine (DA) pathway activity has been proposed to influence multiple facets of addiction, including impaired decision-making, perturbed valuation of reward-paired cues, and craving. While accumulating neuroimaging studies suggest that drug related cues can induce DA release in the striatum of substance abusers, the tools to test whether they provoke DA release in the cortex have become available only recently. Here, we used [18F]fallypride with high-resolution PET to investigate whether exposure to drug-related stimuli would induce both cortical and striatal DA release in cocaine dependent individuals.
Methods: Volunteers with current cocaine dependence ($n = 12$) underwent two PET scans with a high-resolution research tomograph (HRRT) and [18F]fallypride on separate days: on Day 1, they were exposed to neutral cues; on Day 2 they were exposed to cocaine-related cues, including manipulation of drug paraphernalia and watching cocaine-

themed videos before and during the PET scan. The percent difference between D2/D3 receptor availability in the presence vs. absence of drug cues was taken as a measure of DA release in cortical and striatal regions. Drug craving and subjective mood states were assessed using visual analog scales (VAS).
Results: Nine of the 12 subjects (75%) had a craving response to the cocaine cues. Among these subjects, cocaine cue exposure significantly decreased BPND values in the medial orbitofrontal cortex (20% magnitude of [18F]fallypride displacement) and striatum (7 to 10% displacement), with a threshold response in the anterior cingulate (11%). In all 12 subjects, individual differences in the magnitude of craving correlated with [18F]fallypride displacement in the medial orbitofrontal cortex ($r = 0.71$, $p = 0.009$), dorsolateral prefrontal cortex ($r = 0.64$, $p = 0.026$), anterior cingulate ($r = 0.58$, $p = 0.046$), and striatum ($r = 0.75$, $p = 0.005$). Consistent with the presence of autoreceptors on mesostriatal but not mesocortical DA cell bodies, midbrain D2 levels were significantly correlated with [18F]fallypride displacement in the striatum but not the cortex. The lower the midbrain D2 receptor levels, the higher the striatal [18F]fallypride displacement and craving. Path modeling analyses indicated that the midbrain D2 – craving association was mediated by DA release in the sensorimotor striatum.
Conclusions: The study suggests that drug associated cues can induce craving related DA release in the limbic prefrontal cortex and striatum. In people with severe cocaine use disorders, drug focused incentive motivational states might reflect DA release in both regions, each with separable regulatory mechanisms.
Keywords: cocaine, dopamine release, prefrontal cortex, craving.
Disclosure: Nothing to Disclose.

M239. Localized Morphological Abnormalities of the Thalamus and Symptom Correlates Across the Lifespan in Autism Spectrum Disorders

Marisa Spann*, Ish Balla, Xuejun Hao, Ravi Bansal, Bradley Peterson

Columbia College of Physicians and Surgeons/New York State Psychiatry, New Haven, Connecticut

Background: The role of the thalamus in the pathogenesis of Autism Spectrum Disorders (ASD) is poorly understood. Yet, the thalamus is the major relay station of the brain for sensorimotor and complex, higher order information processing. A large-scale study is needed to clarify thalamic abnormalities and the association of thalamic morphology with clinical symptoms. We used anatomical MRI to examine the morphology of the thalamus in children and adults with ASD and a typically developing (TD) comparison group.
Methods: We examined 92 ASD and 106 TD age- and sex-matched individuals 8—60 years of age in a cross-sectional case-control study using MRI. Measures of surface morphology of the thalamus served as the main outcome. We used linear regression at each voxel on the surface of the thalamic template to compare differences in the surfaces for ASD and TD groups. We also explored the associations of thalamic morphology with the Autism Diagnostic Observation Scale (ADOS) scores in the ASD group and Social Responsiveness Scale (SRS) scores in both groups.
Results: Maps of the thalamic surface revealed overall decrease in thalamic volume in the ASD relative to TD groups that were widespread across the thalamic surface. Significant reduction was localized to the pulvinar on the inferior surface, ventroanterior, ventrolateral, and lateral dorsal nuclei on the superior surface, and the medial dorsal nucleus of both hemispheres. The significant reductions were also localized to the surface of the left anterior nucleus and the right ventroposterior nucleus. In the ASD group, more severe ASD symptoms on the ADOS total scale correlated with a volume decrease in the lateral posterior nuclei and increase in the pulvinar nuclei of both hemispheres. The findings for the ADOS social affect and restricted - repetitive behaviors subscales were similar. Additionally, greater restricted - repetitive behaviors correlated with volume decrease in the left central nuclei and increase in the right ventral lateral nuclei. The ASD group in comparison to the TD group demonstrated significant associations in similar regions of the thalamus with the SRS total score. However, the associations were in the opposite direction. For example, higher scores on the SRS total score correlated with the anterior nucleus, lateral posterior, and ventroanterior nuclei, and pulvinar inversely in individuals with ASD and positively in individuals that are TD.
Conclusions: The findings demonstrate alterations in regional volume of the thalamus in children and adults with ASD compared to age- and sex-matched TD. The findings also demonstrate similar involvement of thalamic sub-circuits in the pathogenesis of clinical symptoms of ASD with the exception of restricted – repetitive behaviors. Furthermore, we were interested in identifying the specific deficits in social processing that correspond to differences in thalamic volume between the groups. Our findings demonstrate similar thalamic pathways with patterns of differential growth associated with social processing in ASD compared to TD. Abnormalities in the thalamus contribute to the multiple clinical symptoms and functional deficits in ASD.
Keywords: Autism, Thalamus, Brain, Social.
Disclosure: Nothing to Disclose.

M240. Pubertal Delay and Social Stress Impact Prefrontal-Amygdala Functional Connectivity in Adolescent Female Rhesus Macaques: Behavioral and Stress Correlates

J.R. Godfrey*, C. Kelly, F.X. Castellanos, M.E. Wilson, M.M. Sanchez

Emory University Yerkes National Primate Research Center, Lawrenceville, Georgia

Background: Adolescence is a period of significant brain reorganization, which increases plasticity but also susceptibility to stress, leading to increased risk for emergence of

psychopathology. Cortico-limbic regions such as prefrontal cortex (PFC) and amygdala (AMYG), which regulate emotional and stress responses, seem particularly vulnerable to stress during this period, likely due to their protracted development. Girls are more vulnerable than boys to emotional disorders during the pubertal transition, likely contributing to the higher incidence of mood disorders in women compared to men. This suggests a potential role of puberty-induced increases in estradiol (E2) on brain circuits important for emotional regulation in females. We have previously shown that experimentally delayed puberty (EDP) (via administration of Lupron, a GnRH agonist) in female macaques prevents puberty-induced increased in E2 and causes widespread brain structural and functional alterations. These include effects on PFC and AMYG volumes, as well as effects on intrinsic functional connectivity (iFC) within the cingulo-opercular network and on brain white matter tract integrity peripubertally. For this study we test the specific hypothesis that EDP-induced low E2 levels will impact the maturation of PFC-AMYG iFC of adolescent female macaques, modulating the impact of social stress during adolescence. We also examined the behavioral and stress neuroendocrine correlates of E2 exposure effects on PFC-AMYG circuits.

Methods: Naturally occurring social subordination in rhesus macaque social groups serves as an ecologically relevant model of chronic social stress and we have previously shown that subordinate females exhibit hypercortisolemia and alterations in behavioral development. As part of a longitudinal study, resting state functional MRI (rs-fMRI) scans (4x15min), socioemotional behavior and measures of stress physiology were collected from 51 socially housed juvenile female rhesus monkeys between 43-46 months of age (post-puberty). Twenty-six of these subjects received monthly injections of Lupron from 14 through 36 months of age, spanning the interval from prepuberty through post-menarche to experimentally delay the onset of puberty, which resulted in suppressed E2 exposure. Subjects were also divided as dominants ($n = 30$) and subordinates ($n = 21$), based on their relative rank within their natal social group. iFC was extracted and analyzed using a region of interest (ROI)-based analysis focused on the correlated activity between AMYG and PFC regions (dorsolateral PFC regions: Broadmann areas (BA) 46, 9; medial PFC region: BA 25; orbitofrontal: BA 11, 13). Behavior measured included (1) social behavior (aggression, submission, affiliation and play) and (2) behavioral reactivity during the Human Intruder (HI) task, designed to evoke emotional responses to an unfamiliar human (including fearful, aggressive, and submissive behaviors, as well as vocalizations). Basal and stress-induced levels of cortisol, as well as glucocorticoid negative feedback (cortisol suppression following dexamethasone administration), were also examined. Behavioral and stress physiology measures were correlated with PFC-AMYG iFC in order to examine brain-behavior relationships.

Results: In general, there were robust effects of Lupron treatment on AMYG iFC with ventromedial PFC regions, particularly BA 13 and 25, which also showed effects of social rank. AMYG- BA13 iFC was positively correlated with appeasement behavior in the HI task and stronger glucocorticoid negative feedback. Additionally, Lupron treatment increased the strength of iFC between BA25 and PFC areas with a strong role on executive cognitive function such as BA46 and BA9. However, the effects of E2 exposure during this developmental period were opposite depending on rank. BA25-BA46 iFC was negatively correlated with cortisol suppression in response to dexamethasone. Lastly, BA25-BA9 iFC was positively correlated with locomotion in the HI task and was negatively correlated with cortisol in response to dexamethasone and anxiety behavior in the HI task.

Conclusions: These data provide evidence that the hypoestrogenism caused by experimentally delayed puberty affects PFC-AMYG functional connectivity in adolescent females, with behavioral and stress neuroendocrine consequences. Thus, developmental exposure to E2 seems to have a strong impact on limbic circuits important for emotional and stress regulation and are sensitive to the effects of social stress. The findings from our study have profound implications as they suggest that history of E2 exposure is important for neurobehavioral development during the pubertal transition. These data may be particularly relevant for young girls who experience a normal delay in puberty or whose puberty is arrested by pharmacological administration of Lupron.

Keywords: Neuroimaging, Estradiol, Adolescence, Rhesus.

Disclosure: Nothing to Disclose.

M241. Measures Derived from Resting State Functional MRI and Resting State EEG Aggregate with Psychosis Biotypes More Definitively than with DSM Diagnoses: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP)

Godfrey Pearlson*, Shashwath Meda, Balaji Narayanan, Brett Clementz, Matcheri Keshavan, Carol Tamminga, John Sweeney

Yale Institute of Living, Hartford, Connecticut

Background: The traditional diagnostic categories of schizophrenia (SZ) and psychotic bipolar disorder (BDP) are likely highly heterogeneous, being based on phenomenological similarity rather than any underlying biological classification. Prior BSNIP cognitive and sensorimotor endophenotype data yielded three distinct psychosis "Biotypes" that display distinct neurobiological characteristics and cut across traditional diagnostic boundaries. Here, we examined 2 distinct BSNIP endophenotypes that were not used in the creation of the Biotypes, to examine their status as external validators.

Methods: For resting functional MRI data, we compared 70 schizophrenia and 64 psychotic bipolar probands, their respective unaffected first-degree relatives ($N = 70$ and $N = 52$, respectively) and 118 healthy subjects, all group-, age-, sex- and ethnicity-matched. Using independent component analysis (ICA) we derived loading coefficients for 7 independent resting state components. From 64-channel resting state EEG of 225 schizophrenia and 234 psychotic BP probands, their respective unaffected first-degree relatives ($N = 201$ and $N = 231$) and 200 healthy

controls, we used ICA to derive 8 independent spectral components and their associated spatial weights. Data were compared using analysis of covariance to evaluate group differences between DSM diagnoses and among Biotypes.
Results: In the case of resting state fMRI loading coefficients, there were no post-hoc differences between DSM diagnoses, although both groups differed significantly from healthy controls on multiple components; data from relatives were similar (but less marked in differences from HC) to those of probands. Biotype values also differed significantly from healthy controls, but in contrast to DSM diagnoses, 4 of the 7 component values showed significant differences among Biotypes, generally with Biotype 1 being most severely abnormal. Unaffected relatives displayed similar patterns to their corresponding Biotype probands. Mean spatial weights for ICA-derived resting state EEG components were more complex. For Delta, theta and slow alpha components, schizophrenia probands were more abnormal (augmented) than psychotic bipolars, but these abnormalities were not transmitted to relatives in either group. For fast alpha and slow beta, psychotic bipolars were more abnormal than schizophrenia probands and these abnormalities were transmitted to relatives. In contrast, all Biotype groups differed significantly from healthy controls for delta, theta and slow alpha components. Biotype 1 was the most and Biotype 3 the least abnormal; these abnormalities were transmitted to unaffected relatives. For fast alpha and slow beta, in contrast, Biotype 2 was the most significantly abnormal with a similar pattern being transmitted to relatives.
Conclusions: Resting state fMRI and resting state EEG data provide useful adjunctive external validation for Biotypes, in differing more significantly among Biotypes than between DSM diagnoses, (and in the case of fMRI showing no significant differences between DSM categories). Neither of these data types was used in creation of the Biotype categories. Biotype differences for resting state EEG fast alpha and slow beta do not support the idea of Biotypes as representing a simple gradient of severity. In fact, patterns observed for Biotype 2 are congruent with the distribution of sensorimotor pattern abnormalities observed for the originally-defined Biotypes, further underpinning the validation of this classification pattern.
Keywords: Psychosis, endophenotype, Biotype, DSM.
Disclosure: Nothing to Disclose.

M242. Using Brain Glucose Metabolism to Predict the Neural Correlates of Extinction Memory Recall Among Trauma-unexposed and Trauma-exposed Individuals

Marie-France Marin*, Huijin Song, Lindsay K. Staples-Bradley, Michael B. VanElzakker, Natasha B. Lasko, Lisa M. Shin, Mohammed R. Milad

Harvard Medical School/Massachusetts General Hospital, Charlestown, Massachusetts

Background: Fear conditioning and extinction paradigms have been used to study the processes by which individuals learn and unlearn fear. Neuroimaging investigations, in conjunction with animal data, have allowed the identification of key brain structures involved in both fear and extinction expression. Individuals suffering from post-traumatic stress disorder (PTSD) have shown to acquire and extinguish fear normally when using laboratory paradigms. They do however show a deficit in recalling the extinction memory trace when later tested for it. This higher fear is also accompanied by lower activation of the ventromedial prefrontal cortex (vmPFC) and the hippocampus along with higher activation of the dorsal anterior cingulate cortex (dACC) and the amygdala. Interestingly, resting metabolism in some of these key nodes of the fear extinction network has been shown to differ between individuals suffering from PTSD and normal controls. The relationship between the resting metabolism and functional activation has not been carefully examined. In this study, we asked if it is possible to use resting brain metabolism to predict functional activation in the fear extinction network in trauma-exposed and unexposed populations?.
Methods: Twenty individuals never exposed to trauma (Healthy Controls), twenty trauma-exposed individuals non-PTSD (TENP) and twenty-four trauma-exposed individuals with a PTSD diagnosis (PTSD) were recruited. During their first visit, all participants had a diagnostic interview. Participants were then invited for a second visit where they went through a resting PET-FDG scan. Four days later, they underwent a well-validated two-day fear conditioning and extinction protocol in the fMRI scanner. BOLD signal was used to quantify functional neural activation during extinction recall. Resting glucose metabolism values were extracted for the following regions of interest: amygdala, hippocampus, dACC and vmPFC. Resting metabolic ratios of the vmPFC/dACC and vmPFC/amygdala were also calculated and used as additional predictors of neural activation during extinction recall.
Results: When collapsing data across all three groups of interest, increased resting glucose metabolism in the right amygdala was found to predict higher vmPFC and dACC activations during extinction recall. Higher dACC resting metabolism predicted lower amygdala, hippocampus and vmPFC activation during extinction recall. Higher metabolism in the vmPFC/dACC ratios predicted higher vmPFC activation. Moreover, both resting metabolic ratios (vmPFC/amygdala and vmPFC/dACC) were inversely associated with hippocampus activation during recall.
Conclusions: Our data suggest that resting brain metabolism could be used to predict the functional activation of key brain regions involved in extinction memory recall. The finding that the vmPFC/dACC resting metabolic ratio is predictive of vmPFC activation during extinction recall (positive association) support some of our previous data showing that this same ratio also predicts psychophysiological index of fear (higher ratio associated with lower fear at recall). These data highlight the importance of taking a global perspective by integrating multiple brain structures (such as ratios), rather than examining the effects in isolation. Ongoing analyses are being conducted to test the potential link between the findings noted above and various domains pertaining to anxiety and emotion regulation.
Keywords: PET Resting Metabolism, Extinction Memory Recall, fMRI, PTSD.
Disclosure: Nothing to Disclose.

M243. Varenicline Administration Diminishes Amygdala Response and Self-reported Feelings of Acute Effects of Alcohol in Heavy Drinkers

Joshua Gowin*, Vatsalya Vatsalya, Jonathan Westman, Melanie Schwandt, Reza Momenan, Daniel Hommer, Selena Bartlett, Markus Heilig, Vijay Ramchandani

National Institute on Alcohol Abuse & Alcoholism, National Institutes of Health, Bethesda, Maryland

Background: There is considerable evidence for a role of the nicotinic system in the rewarding effects of alcohol and alcohol consumption. Further, recent clinical and pre-clinical studies have shown that varenicline, a nicotinic acetylcholine receptor partial agonist that is FDA-approved as a smoking cessation medication, can reduce heavy drinking among alcoholics. This reduction may reflect diminished motivation to consume or reduced rewarding effects of alcohol. Previous neuroimaging studies have shown that acute alcohol can reduce amygdala activation in response to fearful facial expression images, possibly serving as a reinforcing effect of alcohol consumption. Studies in rats suggest that varenicline may reduce drinking by regulating amygdalar activity. This study examined the effect of varenicline on subjective and amygdalar response to acute alcohol exposure in humans.
Methods: In this double-blind randomized study, 36 male and female heavy drinkers (20 smokers), aged 21-58 years, were randomized to receive varenicline (2 mg/day) or placebo for 3 weeks. Participants underwent a functional MRI scan two weeks after the start of dosing. During the scan, participants saw 90 images of faces with either a neutral or a fearful expression. Participants were then given an intravenous alcohol infusion that brought blood alcohol level (BAL) up to 80 mg% and clamped it at that level for the remainder of the scan. Participants then saw the same 90 images under the acute influence of alcohol. Blood-oxygen-level dependent (BOLD) response was preprocessed and analyzed with Analysis of Functional Neuroimaging (AFNI) software in a final sample of 30 participants (13 placebo, 17 varenicline). A linear mixed-effects model was used to examine the effects of facial expression (fearful versus neutral), alcohol (pre- versus post-infusion) and treatment (placebo versus varenicline). Subjects also completed the Drug Effects Questionnaire (DEQ) at the beginning of the scan, after the first run of the faces task and again after the second run of the faces task when BAL was at 80 mg%.
Results: Linear mixed-effects analysis revealed an alcohol-by-treatment interaction in the bilateral amygdala. The placebo group showed greater activation relative to baseline in the amygdala when viewing faces prior to the alcohol infusion, and this activation was attenuated by alcohol (family-wise error corrected $p<0.05$). The varenicline group, in contrast, showed no change from baseline when viewing faces prior to infusion, and alcohol failed to alter their level of activation. Further, whereas both groups reported a significant increase in 'feeling' the drug on the DEQ following alcohol compared to pre-infusion values, the placebo group showed a greater increase in feeling relative to the varenicline group, and this effect remained significant after controlling for age, smoking status and drinking history [$F(1,21)=4.31$, $p=0.05$].
Conclusions: The present results suggest that varenicline may disrupt alcohol's effects on amygdala activation during emotional cues. In addition, varenicline appeared to attenuate the subjective perception of feeling alcohol effects compared to placebo. Given previous results that reduced amygdalar activation may be part of the reinforcing effects of alcohol, the current findings support the hypothesis that varenicline may act by attenuating these reinforcing effects. These results further suggest that altered amygdala activation may be developed as a biomarker of treatment efficacy of agents being developed for the pharmacotherapy of alcohol use disorder.
Keywords: reward, alcohol, pharmacotherapy.
Disclosure: Nothing to Disclose.

M244. Fortune-telling? Heightened Ventral Striatal Activity to Brief (500 msec) Cocaine Cues Predicts Future Drug Use in Treatment-seeking Cocaine Patients

Anna Rose Childress*, Kanchana Jagannathan, Zachary Monge, Jesse Suh, Kimberly Young, Teresa Franklin, Ronald Ehrman, Ze Wang, Daniel Langleben, Michael Gawrysiak, Reagan Wetherill, Charles O'Brien

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Background: Why some addicted individuals have long drug-free periods, punctuated by relapse, while others seem unable to establish even brief abstinence, is not known – but it would of great clinical value to understand this heterogeneity. We have hypothesized that individual differences in relapse vulnerability may be traced to two, interactive, brain systems: the brain's incentive motivational ("GO!") circuitry, triggered by rewards and their signals, and brain's modulatory ("STOP!") circuitry, responsible for inhibiting and managing the pull of incentive stimuli. When encountering cues signaling a drug reward, either an over-responsive "GO!" circuit, or an under-responsive "STOP" circuit, or both, could increase the likelihood of relapse. We tested this hypothesis in a new cohort of cocaine-addicted individuals, with the goal of identifying which brain responses had the strongest predictive relationship to future drug use. Finding strong predictive relationships between motivational/modulatory circuits and future drug use would offer very concrete targets for anti-relapse interventions, and would also inform our fundamental understanding of relapse – the most painful and costly aspect of the addictions.
Methods: We studied a new cohort ($n=34$; ongoing) of cocaine-dependent patients; these patients were participants in a large ongoing study focused on brain predictors of relapse. As part of their study participation, each individual received inpatient stabilization, followed by a functional magnetic resonance imaging (fMRI) session with several probes. The inpatients were then discharged into 12 weeks of outpatient treatment, with twice weekly urine samples. For the current analyses, we examined the brain response to very brief cues administered within a "fast" event-related BOLD (Blood Oxygen-Level-Dependent) fMRI paradigm. The cues (24 unique cues per category, repeated once, for a

total of 48 presentations in each category) were cocaine-related and comparison (sexual, aversive or neutral) visual stimuli of 500 msec duration. Average interstimulus interval was 1500 msec (TR = 2 sec). Data were smoothed, normalized, realigned and batch-analyzed within SPM 8, using canonical HRF as the basis function. Pre-planned contrasts compared the brain response to evocative (e.g., cocaine, aversive, sexual) vs. neutral cues. For the correlational analyses, the percent of cocaine positive urines (of 23 opportunities) was used as a single regressor against the drug cue contrast (e.g., cocaine cue vs. neutral), and against the comparator contrasts (aversive cue vs. neutral; sexual cue vs. neutral). The resulting statistical parametric maps were thresholded at $p < 0.005$; $k = 100$ voxels, for display.
Results: Prior to conducting correlations, we confirmed that our 500 msec cues (cocaine v. neutral contrast) differentially activated the motivational circuitry (amygdala, midbrain, striatum, v. pallidum, etc). Correlations: Consistent with our general hypothesis, cocaine-addicted individuals with higher activation in the ventral striatum to cocaine cues had more cocaine positive urines during the 12 weeks of outpatient treatment. A singular supra-threshold cluster ($p < 0.001$; $k = 109$ contiguous voxels) was localized in the right ventral striatum (peak t, 4.29; peak voxel, -6, 10, 2). There were no significant brain correlates (predictors) of cocaine use in the comparison conditions.
Conclusions: These findings offer a clear demonstration that a drug cue-provoked brain state may be able to predict future relapse in addicted individuals. The results have several implications. From a mechanistic perspective, these "fortune-telling" correlations suggest that the brain response to drug cues in incentive motivational (GO!) circuits is likely to be an important relapse substrate. From a theoretical perspective, it will be useful to determine whether explicit probes for modulation (STOP!) can also function as relapse predictors for the cocaine population. From a practical perspective, the brain response to brief drug cues may be a very useful research tool, allowing us to screen candidate medications for their ability to engage relapse-relevant brain targets.
Keywords: cocaine, relapse, reward, addiction.
Disclosure: Nothing to Disclose.

M245. Polygenic Risk Profile Score of DISC1-Interactome is Associated with Diagnosis of Schizophrenia and Impacts on Prefrontal Physiology During Working Memory

Enrico D'Ambrosio*, Qiang Chen, Ena Xiao, Alessandro Bertolino, Joseph H. Callicott, Daniel R. Weinberger, Venkata S. Mattay

Lieber Institute for Brain Development, Baltimore, Maryland

Background: Schizophrenia is a complex genetic disorder affecting approximately 1% of the population. The main goal of genetics research in schizophrenia is to identify altered biological pathways relevant for pathophysiology and, therefore, potential pharmacological targets. Gene-set based analytical methods aim to define biologically meaningful sets of genes associated with a certain trait, rather than focusing on a single gene locus. Variation in DISC1 has been reported to be a risk-factor for schizophrenia in a well publicized Scottish pedigree and in various candidate gene studies as well as being implicated in modulating cognitive function. However, single loci association of DISC1 with schizophrenia has been negative in large scale population based GWAS studies. DISC1 participates in a broad Interactome complex of proteins involved in multiple processes, including neuronal migration and signaling. We hypothesized that using a gene-set strategy based on proteins in the DISC1-Interactome may be associated with schizophrenia and relevant intermediate phenotypes. To this end, we used a polygenic risk profile score approach restricted to a DISC1-Interactome gene-set, investigating the effect of this score in predicting case-control status and in modulating working memory function.
Methods: GWAS data including 671 controls and 667 patients with schizophrenia were included in our study. Among them, 263 healthy volunteers were studied with fMRI at 3T performing the N-Back working memory task. Risk profile scores (RPSs) for 116 genes in a DISC1-Interactome gene-set (created using the Entrez GENE database of interactants that is based on BIND, BioGRID and HPRD databases) were calculated. High quality ($INFO > 0.9$ and $MAF > 0.1$) independent SNPs obtained from clumping for each gene (extended half distance to neighbored genes) were picked for calculating cumulative risk profile scores for schizophrenia as the sum of the number of reference alleles weighted by the natural logarithm of the odds ratio from the PGC2 schizophrenia case control GWAS results after excluding these subjects from the PGC analysis. We used 10 p value thresholds from the PGC2 case-control analysis as arbitrary thresholds (thresholds: $p = 1$, $p = 0.5$, $p = 0.2$, $p = 0.1$, $p = 0.05$, $p = 0.01$, $p = 0.001$, $p = 1e\text{-}04$). These thresholds involved from 799 to 21 SNPs, respectively. While there were SNPs meeting P thresholds of 1e-6 and 1e-8, they were too few to merit further polygenic RPS analyses. Logistic regression was done in R to explore clinical association of these DISC1-Interactome risk profile scores with schizophrenia. Multiple regressions in SPM8 were performed to assess the correlation between the each RPS with BOLD fMRI activation of the prefrontal cortex during 2-Back working memory task.
Results: We found an association between RPSs based on the DISC1-Interactome gene-set with diagnosis of schizophrenia. In particular the more significant association values (all $p < 0.02$) were observed for RPS scores calculated with arbitrary threshold higher than $p = 0.01$ in the PGC2 case-control analysis. Moreover, we also found a positive correlation between RPS scores and BOLD fMRI activation of the prefrontal cortex during 2-Back (right Middle Frontal Gyrus, MNI coordinates $x = 39$, $y = 39$, $z = 30$; best p value < 0.001 uncorr, best Z value $= 3.18$) for the same level of performance.
Conclusions: These data support a role for a DISC1 interaction network being associated with risk for schizophrenia and phenotypes relevant to this disorder even in the absence of a positive single locus association. DISC1-Interactome polygenic scores were associated with diagnosis of schizophrenia and with inefficient activation of prefrontal cortex during working memory (a well established intermediate phenotype of schizophrenia). The

gene-set used in this study includes genes coding for proteins involved in functions that could be relevant for the etiology of schizophrenia, such as neurite outgrowth, cytoskeletal functions, intracellular transport, protein trafficking and signaling. Thus, our findings suggest further studies to investigate the role of DISC1, in the pathophysiology of schizophrenia, not as an isolated factor but as an element of a complex network.
Keywords: schizophrenia, DISC1, polygenic risk score, working memory.
Disclosure: Dr. Bertolino is a full time employee of Hoffman-La Roche, Ltd.

M246. Diminished Learning and Pursuit of Reward and Disrupted Resting State Connectivity of Reward Networks in Remitted Major Depressive Disorder (MDD)

Scott Langenecker*, Sophie DelDonno, Rachel Jacobs, Alyssa Barba, Kelly Ryan, Jennifer Gowins, Lisanne Jenkins, Natania Crane, Jon-Kar Zubieta, Robin Nusslock, Luan Phan, Stewart Shankman

University of Illinois at Chicago, Chicago, Illinois

Background: An emerging corpus of data has demonstrated the importance of reward related processes in the etiopathogenesis of major depressive disorder. These studies suggest that anhedonia, apathy, diminished reward anticipation, suppressed reward consummatory responses, and decreased reward learning may form a key substrate for a subtype of MDD. A number of key questions remain to be answered toward understanding the risk for and expression of MDD in these behavioral and functional domains: Are they state or trait features? If they are traits, how might they be effectively assessed? Are they related to dysfunction of ventral striatal connections to other nodes within the reward network or other networks?.
Methods: The study was of adults between 18 and 23, including 30 remitted MDD and 30 healthy comparison subjects (HC) who completed an individually titrated version of the monetary incentive delay (MID) task outside the scanner. The participants also underwent resting state functional connectivity scans within the fMRI scanner. Remitted MDD status included Hamilton Depression Rating scale below 8. On average, remitted MDD subjects had been well for nearly two years. Groups did not differ in verbal IQ. Dependent variables are total money earned on MID, trait measures of reward responsivity (Behavioral Activation Scale, BAS RR) and inhibition (Behavioral Inhibition Scale, BIS), and resting state functional connectivity of left and right ventral striatum.
Results: The rMDD earned significantly less money than the HC group ($F(1,41) = 4.72$, $p = .036$). Left ventral striatum (VS) was hyperconnected to amygdala and hippocampus in rMDD relative to the HC group ($p < .01$, $k > 25$ uncorrected). In contrast, the HC group exhibited hyperconnectivity of the left VS to bilateral orbital frontal cortex and lateral temporal cortex. Connectivity analyses using a right ventral striatal seed yielded similar results. Follow up analyses will investigate links between functional connectivity of VS, BAS/BIS traits, and amount of money earned.
Conclusions: Remitted MDD still exhibit diminished reward learning and pursuit. Reward circuitry remains disturbed into periods of remission. These changes reflect diminished connectivity to auto autoregulatory regions (OFC, rostral cingulate), and increased connectivity to threat regions (amygdala). The diminished reward learning is present even in the remitted state and is still related to reward responsiveness and behavioral inhibition, as is the disrupted connectivity. These effects are present early in the course of the illness, and are not related to active symptoms or to completing the task inside the fMRI scanner. Putative mechanisms of prevention include the domains of reward anticipation and the learning of reward-based contingencies.
Keywords: MDD, reward, connectivity, trait.
Disclosure: Nothing to Disclose.

M247. Analysis of Depression and the Effect of Ketamine in Depression Patients by Use of ROIs Designed from Genetic Expression Analysis

Philip Baldwin*, Tessy Lal, Kate Collins, Sanjay Mathew, James Murrough, Ramiro Salas

Baylor College of Medicine, Houston, Texas

Background: Major depressive disorder affects one in 15 adults and can be associated with pathological brain functional connectivity. Seed based functional connectivity methods, however, assume regions of interest a priori and may overlook critical regions. We use genetic expression data to ascertain key ROIs in resting state seed based analysis, and justify these choices across a two site fMRI study.
Methods: Gene Lists: Led by Fritz Henn, two lines of rats have been bred to exhibit learned helplessness (L) or exhibit resistance (N) to depression. The genetic prevalence of these lines resulted in two lists of genes. Our software finds that most (300 of 500) of the genes have a sagittal experiment associated to it in the Allen Brain Atlas. The coarse grained expression volumes for each set of these genes are then averaged; the differences between the L and N lists are subtracted and compared to normal variability to arrive at significances. This analysis indicates that Habenula (Hb), Brodmann area 25 (BA25), Medial vestibular cortex (MVC), Nucleus Accumbens (Acc) and Precentral Gyrus (PCG), and septum verum are indicated in depression. Resting state functional connectivity: We took resting state fMRI readings at two different sites in a depressed population and matched controls. At Mount Sinai: 17 controls, as well as 44 depressed subjects, with 8 of those subjects measured once before and once after administration of ketamine. At Baylor COM, 20 controls, 36 depressed, with 10 subjects scanned twice. The seed based, resting state software, CONN was employed, using as ROIs the regions suggested above as well as several areas such as dorsal raphe nucleus (DR), which have been otherwise implicated in depression.
Results: The brain ROIs that were suggested by the above genetic expression analysis figure prominently in the connectivities that most distinguish controls from the depressed cohort at each site, as well as the differences in

connectivities due to the ketamine treatment. The BA25 to medial prefrontal cortex connectivity especially changed for pre-post ketamine, although the most consistent change across sites was Putamen/Acc and contralateral Striatum/Putamen. Distinguishing controls from the depressed cohort was primarily given by the Caudate/Hb and Dor Raphe/Striatum connectivities.
Conclusions: The complimentary use of genetic expression results in the design of ROIs for seed based studies. These ROIs figure prominently in those connectivities that distinguish controls from the depressed cohort, as well as those areas affected by ketamine. We hope to develop this genetic expression analysis as use in intelligent design of ROIs.
Keywords: Human Neurimaging, Depression, Resting State Functional Connectivity.
Disclosure: Nothing to Disclose.

M248. MRI Scan-related Subjective Discomfort and Brain Metabolites in OCD Patients and Healthy Controls

Garth Terry*, Courtney Sheen, TM Lai, Jeffry Alger, Joseph O'Neill, Jamie Feusner

University of California Los Angeles, Semel Institute for Neuroscience & Human Behavior, Los Angeles, California

Background: Magnetic resonance spectroscopy (MRS) is used in longitudinal studies of brain physiology in obsessive-compulsive disorder (OCD). However, test-retest reliability of MRS metabolite levels has not been determined in OCD, nor have effects on metabolites of subjective state during the scan (e.g., anxiety or discomfort level) been assessed. The confined and uncomfortable environment of a magnetic resonance scanner may confound results of repeat scans, as anxiety may decrease with extinction or increase due to anticipation, and these changes may differ in patient vs. control groups. The goal of this study was to determine: 1) if MRS test-retest reliability was comparable between OCD and healthy subjects, 2) if scan-to-scan change in subjective indices of anxiety and discomfort differed between the two groups, 3) if changes in these indices correlated with scan-to-scan changes in metabolite levels in brain regions implicated in OCD.
Methods: We acquired proton MRS (3 T Siemens, single-voxel PRESS TR/TE = 2000/30 ms) from bilateral pregenual anterior cingulate cortex (pACC), anterior middle cingulate cortex (aMCC), and thalamus in 11 adult OCD patients and 12 age-matched healthy controls at baseline and after 4 weeks of no-treatment waitlist. Test-retest reliability was calculated as the intraclass correlation (ICC) for the metabolites tNAA, Glu, Glx, Cr, Cho, mI, in each brain region. Subjective experience while in the scanner was assessed with an exit survey consisting of Likert-type scales for items including average anxiety, feeling physically comfortable, wanting to fidget or adjust oneself, thinking about how long the scan was taking, and awareness of how one's body felt. Group-mean scan-to-scan changes in survey indices levels were tested with repeated-measures ANOVA. Correlations between changes in survey indices and changes in brain metabolites were also tested (Pearson).
Results: Scan-to-scan ICC averaged across metabolites and brain regions was relatively low but did not differ significantly between groups (OCD: 0.28, range -0.34 – 0.72; control: 0.30, -0.33 – 0.78). Controls were 74% less anxious during the second scan than during the first ($p = 0.003$); %change in this anxiety correlated negatively with %change in right thalamus mI ($r = -0.59$, $p = 0.043$). OCD subjects were equally anxious during both scans but thought 44% less about how long the scan was taking for the second scan ($p = 0.013$); %change in this endpoint correlated significantly with %change in left pACC Cho ($r = 0.76$, $p = 0.007$). Other survey indices did not differ significantly between scans. In addition, for OCD subjects, thinking about the body in scanner correlated negatively with right pACC Glx ($r = -0.79$, $p = 0.004$).
Conclusions: Scan-to-scan variability in MRS brain metabolites levels is comparable in OCD subjects and healthy controls. While healthy controls may be less anxious with a repeat MRI scan, OCD subjects may not be, though they may think less about how long the scan takes. This cautions against assumptions in longitudinal studies that scanner environment experience is equivalent between control and patient groups. These findings also correlated with changes in metabolites in at least one brain region (pACC) associated with affect and autonomic integration of emotions. State anxiety and discomfort may influence regional metabolite levels or vice versa. Additional analysis with a larger sample size is needed to better assess these potential state confounds, and to determine corrective actions for future MRS studies.
Keywords: MRS, OCD.
Disclosure: Nothing to Disclose.

M249. Interhemispheric Insular and Inferior Frontal Connectivity Are Associated with Substance Abuse in a Psychiatric Population

Ramiro Salas*, Humsini Viswanath, Kenia Velasquez, David Molfese, Kaylah Curtis, Philip Baldwin, Christopher Frueh, Christopher Fowler

Baylor College of Medicine, Houston, Texas

Background: Substance abuse is highly comorbid with other major psychiatric disorders. While the neural underpinnings of drug abuse have been studied extensively, most existing studies compare drug users with healthy, non-user controls. Thus, prior studies do not generalize well to the typical person with a substance abuse disorder. Therefore, we studied a population of psychiatric inpatients ($n = 159$) with several mental illnesses treated at a private psychiatric hospital.
Methods: Psychiatric disorders were diagnosed via structured diagnostic interviews, with 65% of patients meeting criteria for at least one substance use disorder. Patients were recruited for resting state functional connectivity (RSFC) and diffusion tensor imaging (DTI) experiments to examine the interhemispheric connectivity in several brain regions hypothesized to be involved in drug addiction, namely the inferior, medial, and superior frontal gyri; insula; and anterior cingulate cortex. The WHOA questionnaire was used to further assess drug use.
Results: We observed an association between tobacco, alcohol, cocaine, sedatives, and hallucinogens with insular interhemispheric connectivity. In addition inferior frontal gyrus inter-connectivity was associated with amphetamine and inhalant use.

Conclusions: Our results suggest that increased inter-hemispheric insula connectivity is associated with the use several drugs of abuse. Importantly, we used psychiatric inpatients without history of drug use as controls, thereby controlling for non-drug-related variables. Thus, our comparisons may be more ecologically valid than the traditional comparison of "mentally ill vs. healthy control" populations. We suggest that the insula and, to a lesser extent the inferior frontal gyrus, are important for drug abuse-related brain activity in psychiatric populations.
Keywords: Substance abuse, Resting state functional connectivity, Diffusion Tensor Imaging.
Disclosure: Nothing to Disclose.

M250. Abnormal Functional Connectivity of the Salience and Default Mode Networks in Youths with Bipolar Disorder

Melissa Lopez-Larson*, Lubdha Shah, Deborah Yurgelun-Todd, Jeff Anderson

University of Utah, Salt Lake City, Utah

Background: Over the past few years, there has been an increased interest in the application of functional resting-state neuroimaging methods in the study of brain networks in several neuropsychiatric disorders including bipolar disorder (BD). For example, in adults with BD, abnormalities in the default mode network (DMN) and salience/ventral attention network in BD have been reported (1,2). In youths with BD, a paucity of resting-state connectivity studies have been done and the few that have been performed have focused on a priori regions of interest (ROIs). Therefore, the current study examined whether differences in functional connectivity could be detected in large-scale brain, i.e. DMN and salience networks, in youths with BD as compared to healthy controls (HC).
Methods: Eighty subjects, including 32 youths with Bipolar Disorder, currently euthymic (12 males; 15.0 ± 2.0 years old) and 48 healthy controls (HC) (27 males; 14.5 ± 2.4 years old) received MRI scans using a 3T Siemens Trio scanner with a 12-channel head coil. In addition, 8 minute resting BOLD images were obtained for each subject. BOLD echoplanar images ($TR = 2.0$ s, $TE = 28$ ms, GRAPPA parallel acquisition with acceleration factor $= 2$, 40 slices at 3 mm slice thickness, 64 x 64 matrix) were obtained during the resting state, where subjects were instructed to, "Keep your eyes open and remain awake and try to let thoughts pass through your mind without focusing on any particular mental activity." Preprocessing steps included motion correction coregistration to MPRAGE, segmentation of MPRAGE, and normalization of MPRAGE and BOLD to MNI template. Phase-shifted soft tissue correction (PSTCor) method (3) was used to regress physiological waveforms as well as regressors obtained from subject motion parameters, degraded white matter, degraded CSF, and soft tissues of the face and calvarium. No regression of the global signal was performed to avoid contamination of gray matter sources. Brains were then parcellated into 7266 ROIs that covered the cortical and subcortical gray matter at 5 mm resolution. Connectivity between each pair of ROIs was calculated using Fisher-transformed Pearson correlation coefficients. Correlations that were greater than the mean plus one standard deviation among ROIs were plotted on brain slices to show which ROIs most frequently participated in abnormal connections in BPD compared to HC. Nodes from the brain regions that had the highest number of abnormal connections were subsequently extracted. For each pair of nodes, Fisher-transformed correlation coefficients were calculated and partial correlation was performed between these values and diagnosis, age, sex, and IQ across the 80-subject sample. An acceptable false discovery rate $q < 0.05$ over all pairs of connections was used to denote significant partial correlation with diagnosis.
Results: Of the 7266 ROIs, abnormal connections were predominately found in anterior insula, anterior cingulate (ACC), medial prefrontal (MPF), and posterior cingulate (PCC) cortex in BD as compared to HC ($p < 0.05$, uncorrected for PBPD vs. TD). Analyses of the partial correlation between each of these 6 nodes (ACC, anterior insula, MPF, PCC) while accounting for age, sex, and IQ, revealed that youths with BD had several abnormal functional connections as compared to HC between the DMN and salience hubs, with higher correlation found between each pair of nodes.
Conclusions: The current study found increased functional connectivity in youths with BD in key nodes of the salience and default mode networks, such as the ACC, anterior insula, MPF and PCC. Our findings extend the previous reports in adult studies that have also reported abnormalities in these 2 key networks (1,2) and suggest abnormalities in critical nodes of the DMN and salience network are present early in the course of BD illness. Further studies examining the relationship between the DMN and salience networks in mood regulation, cognitive functioning and impulsivity is needed in both adult and youths with BD.
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Keywords: bipolar, functional connectivity, adolescents.
Disclosure: Nothing to Disclose.

M251. Mismatch Negativity Deficits Are Associated with Inflammation, Increased Cortisol, and Prefrontal Gray Matter Decline in Clinical High Risk Youth Who Convert to Psychosis

Daniel Mathalon*, Diana Perkins, Elaine Walker, Jean Addington, Carrie Bearden, Kristin Cadenhead, Barbara Cornblatt, Thomas McGlashan, Larry Seidman, Ming Tsuang, Scott Woods, Tyrone Cannon, NAPLS Electrophysiology Task Force

University of California San Francisco, San Francisco, California

Background: Synaptic over-pruning during adolescence remains a largely untested candidate pathogenic mechanism

underlying the transition from clinical high-risk (CHR) states to frank psychosis and has been posited to contribute to the MRI-based cortical gray matter volume deficits and post-mortem neuropil and dendritic spine reduction observed in schizophrenia. Synaptic pruning targets weak synapses and is mediated by microglial activation. Synapses are strengthened with experience via mechanisms of synaptic plasticity, including NMDA receptor (NMDAr)-dependent short-term and long-term potentiation (LTP). Mismatch negativity (MMN), an ERP component that reflects NMDAr-dependent short-term plasticity in the auditory system, is reduced in schizophrenia and predicts transition to psychosis in CHR individuals. In addition, life stress, which has been implicated in the onset of psychosis, activates the HPA-axis, resulting in increased levels of cortisol and inflammatory cytokines that, in turn, trigger microglial activation and neuroinflammation. Stress, cortisol, and neuroinflammation interfere with NMDAr-dependent mechanisms of synaptic plasticity such as LTP, and therefore, may contribute to synaptic over-pruning as part of the pathogenic cascade underlying the transition to psychosis. Here, data from the North American Prodromal Longitudinal Study (NAPLS) are examined from the perspective of this pathogenic model.
Methods: Individuals at CHR for psychosis ($n = 598$), including a subgroup who converted to psychosis (CHR-C; $n = 72$) and a subgroup who did not transition during a 24-month follow-up period (CHR-NC; $n = 199$), as well as healthy comparison subjects (HC; $n = 242$), were recruited from 8 NAPLS consortium sites. Measures included: 1) MRI-based cortical gray matter and ventricular volumes at baseline and 12-months (or post-transition to psychosis), 2) EEG-based baseline duration- and pitch-deviant MMN, 3) A plasma-based baseline inflammatory cytokine index (TNF-α, IL-2, IL-6, interferon-γ), and 4) baseline salivary cortisol.
Results: CHR-C subjects, relative to CHR-NC and HC subjects, showed greater rates of right prefrontal cortical thinning and third ventricle expansion ($p < .01$, FDR cluster corrected), smaller MMN amplitudes ($p < .05$), and higher cortisol levels ($p < .05$). Reduced MMN was associated with higher inflammatory cytokine ($r = .48$, $p < .01$, $n = 29$) and cortisol ($r = .34$, $p < .01$, $n = 58$) levels in CHR-C, but not CHR-NC ($n = 39$ and $n = 162$, respectively), subjects. Reduced MMN predicted greater rates of prefrontal cortical thinning ($r = -.36$, $p < .05$, $n = 32$) and third ventricular expansion ($r = .41$, $p < .05$, $n = 32$) in CHR-C, but not CHR-NC ($n = 154$), subjects.
Conclusions: Transition from prodromal symptoms to full-blown psychosis involves cortical thinning and third ventricle expansion that are predicted by baseline deficiency in NMDAr-dependent short-term plasticity (MMN), consistent with a pathogenic model in which deficient NMDAr-dependent synaptic plasticity leads to an excess of weak synapses that are then subject to over-pruning during adolescent brain maturation. Baseline increases in cortisol and inflammatory cytokines are associated with MMN amplitude deficits in CHR-T subjects, consistent with their well-established deleterious effects on mechanisms of NMDAr-dependent plasticity such as LTP. Deficient NMDAr-dependent plasticity, exacerbated by stress-mediated hypercortisolemia and inflammation, may provide the pathogenic pathway for synaptic over-pruning during the transition to psychosis, producing the gray matter deficits, neuropil reduction, and neural dysconnectivity that constitute core pathophysiological features of schizophrenia.
Keywords: Psychosis, Plasticity, Inflammation, Cortisol.
Disclosure: Nothing to Disclose.

M252. What Goes Up, Can Come Down: Continuous Theta Burst Stimulation to the Medial Prefrontal Cortex Decreases Craving and Nucleus Accumbens Activity in Cocaine Users

Colleen Hanlon*, Logan Dowdle, William DeVries, Bashar Badran, Mark Geroge

Medical University of South Carolina, Charleston, South Carolina

Background: Vulnerability to drug related cues is one of the leading causes for continued use and relapse among substance dependent individuals. Using drugs in the face of cues may be associated with dysfunction in at least 2 neural circuits: 1) elevated activity in frontal-striatal circuits that govern limbic arousal (including the medial prefrontal cortex (MPFC) and ventral striatum) or 2) depressed activity in frontal-striatal circuits that govern cognitive control (including the dorsolateral prefrontal cortex (DLPFC) and dorsal striatum). Transcranial magnetic stimulation (TMS) is emerging as a promising new tool for the attenuation of craving among multiple substance dependent populations. To date however nearly all rTMS studies in addiction have focused on amplifying activity in frontal-striatal circuits that govern cognitive control.
Methods: In this sham-controlled crossover study of 11 cocaine dependent individuals and 12 alcohol dependent individuals, functional connectivity between the medial prefrontal cortex and the striatum was measured before and after a single dose of continuous theta burst stimulation to the left medial prefrontal cortex/frontal pole (FP1). FUnctional connectivity was measures via interleaved TMS/BOLD imaging procedures in which a series of TMS pulses were applied to the medial prefrontal cortex.
Results: Following LTD-like TMS stimulation (continuous theta burst) there was a significant decrease in BOLD signal in, and only in, the ventral striatum/nucleus accumbens and the medial prefrontal cortex/orbitofrontal cortex.
Conclusions: These data suggest that, it is possibly to selectively modulate the MPFC and its downstream striatal targets with LTD-like theta burst stimulation to the MPFC. Additionally while most TMS studies have focused on applying LTP-like stimulation to the DLPFC, the MPFC might be a new, efficacious, and treatable target for craving in cocaine dependent individuals.
Keywords: addiction, brain stimulation, striatum, craving.
Disclosure: Nothing to Disclose.

M253. Risk for Posttraumatic Stress Disorder in the Early Aftermath of Interpersonal Violence

Matt Morris*, Natalie Hellman, Uma Rao

Meharry Medical College, Nashville, Tennessee

Background: While many women develop some symptoms of posttraumatic stress disorder (PTSD) following a

traumatic event, most recover within several months. Although individuals with PTSD report greater use of maladaptive coping strategies and exhibit alterations in sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) function, it remains unclear whether these coping and neuroendocrine factors contribute to increased risk for developing PTSD during the acute post-trauma phase. In the present study, coping was defined as follows: primary control coping involves attempts to change stressful circumstances (e.g., problem solving), secondary control coping involves attempts to adapt to a stressful situation (e.g., acceptance), and disengagement coping involves attempts to withdraw from a stressor (e.g., avoidance). The present study reports preliminary data from a larger, ongoing study examining risk for PTSD over a 6-month interval.

Methods: Participants were 30 women who experienced an incident of interpersonal violence (IPV) within a month of their baseline assessment (but did not meet diagnostic criteria for PTSD) and 17 women with no history of IPV or lifetime psychopathology (NTC group). IPV events included physical or sexual assault as well as intimidation or harassment. Mean age of participants at baseline was 27.9 years (SD = 5.4). Psychiatric interviews (Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinician-Administered PTSD Scale), a self-report coping measure (Responses to Stress Questionnaire), and diurnal saliva sampling on two consecutive days to determine cortisol (an indicator of HPA function) and alpha-amylase levels (sAA; an indicator of SNS function) were completed at baseline and again at 3-month follow-up. Overall daily cortisol and sAA output were obtained by taking the mean area under the curve with respect to ground (AUCg) across the two days of saliva collection. Awakening responses were calculated by subtracting each participant's cortisol/sAA levels immediately after awakening from their cortisol/sAA levels 30 minutes after awakening.

Results: The IPV group reported lesser use of primary control ($t = 3.85$, $p < .001$) and secondary control coping strategies ($t = 3.58$, $p = .001$) and greater use of disengagement coping ($t = 3.95$, $p < .001$) than the NTC group at baseline. The IPV group also exhibited lower sAA AUCg ($t = 2.30$, $p = .027$) than the NTC group; however, the IPV and NTC groups did not differ in cortisol AUCg ($t = .31$, $p = .76$), cortisol awakening response ($t = .47$, $p = .64$), or sAA awakening response ($t = .57$, $p = .57$). Within the IPV group, neither history of PTSD ($t = 1.03$, $p = .31$) nor major depressive disorder ($t = 1.32$, $p = .20$) was associated with baseline PTSD severity scores. Multiple regression tested whether coping and neuroendocrine factors predicted PTSD severity scores at 3 months within the IPV group, controlling for baseline PTSD severity scores. Results revealed that greater PTSD severity at 3 months was predicted by lower baseline sAA awakening responses ($\beta = -.55$, $t = 2.63$, $p = .021$) and lesser use of primary control coping strategies at baseline ($\beta = -.37$, $t = 2.43$, $p = .030$).

Conclusions: The present findings suggest that lower sAA awakening responses in the early aftermath of trauma may be an indicator of risk for greater PTSD severity prospectively. Our results conflict with cross-sectional studies showing sAA awakening increases in individuals with PTSD. One possible explanation for the discrepancy between the present findings and prior studies of individuals with more chronic forms of PTSD is that SNS awakening responses in at-risk individuals are lower in the acute post-trauma phase but increase over time following trauma-exposure. In the present study, although IPV exposure was linked to lesser use of adaptive coping (i.e., primary and secondary control coping) and greater use of maladaptive coping (i.e., disengagement coping) at baseline, only primary coping strategies predicted change in PTSD severity over time. Early intervention programs for women at increased risk for developing PTSD following IPV should target primary coping strategies such as problem-solving and emotion modulation.

Keywords: posttraumatic stress disorder, interpersonal violence, hypothalamic-pituitary-adrenal axis, coping.

Disclosure: Nothing to Disclose.

M254. Corticotropin Releasing Factor (CRF) Impairs Sustained Attention in Male and Female Rats

Debra Bangasser*, Yushi Kawasumi, Robert Cole, Gerald Van Buskirk, Vinay Parikh

Temple University, Philadelphia, Pennsylvania

Background: Stress can disrupt a variety of cognitive processes, including attention. Moreover, patients with stress-related psychiatric disorders, such as depression, often report difficulty in sustaining attention. Despite these well documented effects, the neurobiological basis for stress regulation of attentional processes remains underexplored. During a stressful event, corticotropin releasing factor (CRF) is released centrally to modulate cognitive and behavioral stress responses. Previous research identified sex differences in the CRF1 receptor that increase neuronal sensitivity to CRF in female compared to male rats. The present study was designed to examine whether CRF alters sustained attention—a subject's ability to monitor a situation for a prolonged period of time in order to respond to rare and unpredictable events—and, if so, whether there are sex differences in this effect.

Methods: Adult male and female Sprague-Dawley rats were trained on an operant Sustained Attention Task (SAT) in which they had to discriminate trials with visual signals from non-signaled trials. After attaining criterion (70% correct responses on signal and non-signal trials and < 20% omissions), rats were surgically implanted with a cannula aimed at the lateral ventricle. Following recovery and reacquisition of baseline criterion, one of three doses of CRF (100 ng, 500 ng, and 1 μg) or vehicle (artificial cerebral spinal fluid) were administered intracerebroventricularly 20-min prior to the task onset. The doses were administered in a counterbalanced fashion using a within-subjects design (successive infusions were separated by at least a week). Performance measures included average response accuracies (i.e., hits), a vigilance index (a measure of overall attentional performance), and omissions.

Results: Mixed factor ANOVAs revealed that CRF in a dose-dependent manner impaired accuracy [$F(3,33) = 9.64$, $p < 0.001$] and vigilance [$F(3,33) = 19.11$, $p < 0.001$] similarly in both male and female rats. There were no main

effects of sex or interactions for these measures. Although the number of omissions increased with the CRF dose in both males and females [$F(3,33) = 20.82$, $p < 0.001$], female rats omitted more trials [$F(1,11) = 7.57$, $p < 0.05$]. Interestingly, at the 500 ng dose, SAT performance in males remained stable throughout the session, while in females accuracy [$F(2,22) = 4.29$, $p < 0.05$] and vigilance [$F(2,22) = 3.56$, $p < 0.05$] decreased, but omissions [$F(2,22) = 4.45$, $p < 0.05$] increased across the session.
Conclusions: Together the results reveal for the first time that central CRF administration disrupts sustained attention in both males and female rats. Interestingly, female rats omitted more trials, presumably reflecting a lower motivation to perform under "stressful" conditions than males. At the 500 ng dose, females, but not males, showed a deficit in vigilance over time, an effect that may be linked to sex differences in CRF1 receptors. Clinically, these findings suggest that CRF antagonists represent a viable therapeutic option to treat attentional deficits that characterize certain stress-related psychiatric disorders.
Keywords: stress, attention, cognition, sex difference.
Disclosure: Nothing to Disclose.

M255. Association of Testosterone Levels and Future Suicide Attempts in Women with Bipolar Disorder: A Prospective Study

Leo Sher*, Michael Grunebaum, Gregory Sullivan, Ainsley Burke, Thomas Cooper, J. John Mann, Maria Oquendo

Icahn School of Medicine at Mount Sinai, Bronx, New York

Background: Considerable evidence suggests that testosterone may play a role in the pathophysiology of mood disorders in females. This is the first prospective study to examine whether blood testosterone levels predict suicide attempts in females with bipolar disorder. We hypothesized that testosterone may be related to the course of bipolar illness and suicidal behavior in women with bipolar disorder based on observations that testosterone may affect mood and suicidality. We examined whether testosterone is related to the course of illness at baseline and whether blood testosterone levels predict suicide attempts on follow-up.
Methods: Females with a DSM-IV diagnosis of a bipolar disorder in a depressive or mixed episode with at least one past suicide attempt were enrolled. We limited this study to previous suicide attempters in order to have a higher risk group for suicide attempt on follow-up and thus sufficient power to allow detection of a relationship to testosterone and clinical variables. Demographic and clinical parameters were assessed and recorded. Plasma testosterone was assayed using a double antibody radioimmunoassay procedure. Patients were followed up prospectively for up to 2.5 years. The SPSS 19 statistical program was used to perform statistical analyses.
Results: At baseline, testosterone levels positively correlated with the number of past major depressive episodes ($r = 0.353$, $p = 0.014$) and suicide attempts ($r = 0.408$, $p = 0.003$) but negatively with the Reasons for Living Scale scores ($r = -0.373$, $p = 0.014$). We did not find a correlation between testosterone levels and Brown Goodwin lifetime aggression scale scores ($r = 0.126$, $p = 0.395$), the number of manic episodes ($r = 0.077$, $p = 0.605$), current severity of suicide ideation ($r = 0.133$, $p = 0.425$), depression ($r = 0.027$, $p = 0.850$) or hopelessness ($r < 0.001$, $p = 0.997$). The Cox proportional hazards regression analysis demonstrated that higher baseline testosterone levels predicted suicide attempts during the follow up period: $HR = 169$, $Wald = 6.575$, $df = 1$, $p = 0.01$, which means an increase in the testosterone level by 0.1 ng/ml (10 ng/dl) increases the probability of suicide attempt 16.9 times.
Conclusions: This prospective study shows that testosterone levels may predict suicide attempts in women with bipolar illness. The results of this study also suggest that testosterone levels may be related to the course of bipolar disorder. Our results are consistent with observations suggesting that testosterone influences mood and behavior in females. For example, an association between blood or saliva testosterone levels and depressive symptoms in women was observed by several research groups. Possibly, depression mediates the relation between testosterone and suicidality.
Keywords: testosterone, bipolar, female, suicide.
Disclosure: Nothing to Disclose.

M256. CSF 5HIAA Reflects MAO-A Gene Expression, which is Suppressed by Testosterone; and Not TPH2 Gene Expression, which is Increased by Testosterone, in Male Macaques

Kenny Phu, Arubala P. Reddy, Sarah C. Bethea, Cynthia L. Bethea*

Oregon National Primate Research Center, Beaverton, Oregon

Background: Androgens reduce CSF concentrations of 5HIAA, the metabolite of serotonin. This has long been considered an indication of a reduction in serotonin production, which in turn has been linked to aggression in males. We recently showed that TPH2 gene expression, which codes for the rate limiting enzyme in serotonin synthesis, was significantly increased by testosterone (T) and dihydrotestosterone (DHT); and the increase was not affected by aromatase inhibition of metabolism to estradiol (E). The T-induced increase in TPH2 gene expression was accompanied by a significant elevation of serotonin in axons innervating the noradrenergic (NE) locus ceruleus, and this was blocked by aromatase inhibition. Since these observations did not agree with the majority of literature on androgens, aggression and CSF 5HIAA extrapolations, we questioned the expression of genes coding for the metabolic enzymes, MAO-A and MAO-B, and determined whether they correlated with CSF concentrations of 5HIAA, HVA and MHPC, the metabolites of serotonin, dopamine (DA) and NE, respectively.
Methods: Castrated male macaques were treated with androgen receptor (AR) agonists (T, DHT) and an antagonist (Flutamide), with and without aromatase inhibition to manipulate estrogen receptor (ER) activity ($n = 5$/group). ATD was used to inhibit aromatase. Treatments included T, placebo, DHT + ATD and FLUT + ATD for 3 months. Therefore, the brain was expected to have the

following receptor activation: + AR + ER, -AR + ER(low), + AR-ER and -AR-ER, respectively. The placebo group was assumed to have low E in the brain due to de novo synthesis. CSF samples were obtained by puncture of the cisterna magna under ketamine sedation prior to euthanasia with pentobarbital overdose. Biogenic amine metabolites were measured by liquid chromatography with tandem mass spectrometry. The midbrain was obtained for in situ examination of gene expression in the serotonergic dorsal raphe nucleus.

Results: Unlike TPH2, MAO-A gene expression was significantly suppressed by T, but this effect was lost in the presence of aromatase inhibition (ANOVA $p = 0.003$) indicating that the effect of T on MAO-A is mediated by metabolism to E. MAO-B was not different between the groups. Although CSF 5HIAA was not significantly different between groups, the trend showed lower values with T and higher values with aromatase inhibition, which were further used in correlation analyses. MAO-A positive pixel area and number of positive cells correlated with 5HIAA at $r2 = 0.78$ and 0.79, respectively. TPH2 positive pixel area and number of positive cells did not correlate with 5HIAA at $r2 = 0.19$ and 0.13, respectively. The serotonin innervation of the locus ceruleus analysis yielded positive pixels and positive varicosities that correlated with 5HIAA at $r2 = 0.66$ and 0.73, respectively. There was no difference in MAO-B or MHPG between the groups.

Conclusions: These results indicate that CSF 5HIAA concentrations depend on MAO-A expression, which is suppressed by T after aromatization to E and depends on ER activation. CSF 5HIAA concentrations do not reflect TPH2 gene expression, which is dependent on AR activation. We suggest that inferring global serotonin activity in brain from CSF 5HIAA has led to a misunderstanding of the effects of androgens on serotonin. Moreover, different compartments of the serotonin system may depend on AR or ER activation, which can produce differential regulation under experimental conditions containing aromatase inhibition.

Keywords: serotonin, testosterone, monoamine oxydase, aromatase.

Disclosure: Nothing to Disclose.

M257. Association Between Direct and Indirect Measures of Insulin Resistance and Cognition in Euthymic Adults with Histories of Major Depressive Disorder

Tonita Wroolie, Heather Kenna, Manpreet Singh, Natalie Rasgon*

Stanford University School of Medicine, Stanford, California

Background: Major depressive disorder (MDD) and type 2 diabetes (DM2), share numerous pathophysiological characteristics that suggest bidirectional links between the central nervous system (CNS) and endocrine homeostasis. Insulin resistance (IR), a subclinical state that often precedes the development of DM2, is often accompanied by depressive symptomatology and patients with mood disorders have biomarkers suggestive of high IR. While the majority of previous studies on the relationship between IR and cognitive impairment have been conducted with elderly or mixed aged individuals, increasing age is a major confounder in this association, as IR generally worsens with increasing age in the elderly. Additionally, normal and pathological brain aging reduces the ability to understand the specific negative effects of IR on cognition. We report on the relations among a direct quantitative measure of IR (steady-state plasma glucose; SSPG) and a surrogate marker of IR (BMI) with cognitive performance in euthymic adults with a history of MDD giving special consideration to younger (< 45 years) and older adult patients (> 45 years).

Methods: Subjects included men and women ages 19-71 with BMI < 40 kg/m2 with a history of a non-psychotic, non-melancholic MDD. All subjects underwent an insulin suppression test to determine Steady-State Plasma Glucose (SSPG), neuropsychological testing, and measurement of BMI. Correlations and multiple linear regressions were conducted on the whole sample and within dichotomized age groups (< 45 and > 45 years) testing two regression models: Model 1: Age, education, SSPG, and any significantly associated predictors. Model 2: Age, education, BMI, and any significantly associated predictors.

Results: Interestingly, SSPG and BMI were not significantly correlated in the whole sample or dichotomized age groups. In the sample as a whole ($N = 39$), SSPG did not predict performance on any neuropsychological variables whereas, BMI as well as lower level of educational predicted worse dominant hand fine motor abilities. In the younger group ($N = 14$), higher SSPG and lower educational attainment predicted worse cognitive flexibility whereas BMI did not significantly predict performance on any neuropsychological variables. In the older group ($N = 25$), higher BMI as well as lower educational attainment predicted lower full scale IQ (using an abbreviated measure) whereas SSPG did not significantly predict performance on any neuropsychological variables.

Conclusions: The results of this study suggest differential cognitive effects of direct and indirect measures of IR in relation to age in adults with a history of MDD. Our results suggest that the presence of IR (as measured directly by SSPG) in young adults may be detrimental to cognitive domains involving higher order abilities (cognitive flexibility/set-shifting) whereas increased BMI at an earlier age in these persons, may have no appreciable negative impact on cognition. In older adults, higher BMI is associated with a global and less specific negative impact on cognition. Findings suggests, that sole reliance on a surrogate measure of IR (BMI) in young adults may fail to detect underlying endocrine dysfunction and its associated negative impact on cognition.

Keywords: Insulin resistance, Cognition, Depression.

Disclosure: Nothing to Disclose.

M258. Do Depression and/or Childhood Maltreatment Increase the Risk for Visceral Obesity?

Li Li*, Rachel Chassan, Richard Shelton

University of Alabama at Birmingham, Mountain Brook, Alabama

Background: Depression and obesity are prevalent disorders that have been repeatedly shown to be associated

although the mechanisms underlying this association are poorly understood. Childhood maltreatment predisposes for both obesity and depression. Recent studies indicate that visceral obesity but not obesity itself is a greater risk for obesity-related disorders. Whether depression alone or combined with childhood maltreatment increases the risk for visceral obesity and obesity-related disorders is not known yet. We conducted a study to determine whether depression alone or combined with childhood maltreatment is predictive of adiposity, body composition and obesity, and the mechanisms.
Methods: Childhood maltreatment was assessed using the Childhood Trauma Questionnaire. Weight, height, waist and hip circumference were measured. Body fat including total fat mass, visceral fat mass and lean mass was measured using the Dual-energy X-ray absorptiometry. Saliva samples for each participant at awakening, 15-, 30- and 60-min post awakening were collected for the determination of the cortisol awakening response (CAR), indicating the HPA activity.
Results: Compared with controls, patients with depression have greater waist/hip ratio, total fat mass and visceral fat mass, but not BMI and lean mass. Total fat mass and visceral fat mass are even greater in depressed patients with a history of childhood maltreatment. Correlation analysis indicates that the severity of depression is positively correlation with the amount of total fat mass and visceral fat mass ($r = 0.47$ and 0.41, respectively). Serum leptin levels were measured and are slightly but not significantly elevated in depressed patients. Compared with controls, depressed patients have a blunted CAR, which is further suppressed in patients with exposure of childhood maltreatment.
Conclusions: Our current preliminary findings suggest that depression combined with childhood maltreatment increases the risk for obesity in general, and visceral obesity in particular, probably through the alterations in the HPA functioning instead of leptin resistance.
Keywords: visceral obesity, depression, childhood maltreatment, HPA axis.
Disclosure: Nothing to Disclose.

M259. Decreases in GR and MR, but Increases in FKBP5 and PTGES3 mRNA and Protein Levels in the Middle Frontal Gyrus of Autism Spectrum Disorder Subjects

Neil Patel, Anthony Ahmed, Anilkumar Pillai*

Medical College of Georgia, Augusta, Georgia

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by severe deficits in social interaction and communication, and the presence of repetitive or stereotyped behaviors. Although the neurobiological mechanism/s underlying ASD is unknown, recent studies indicate that stress plays an important role in the pathophysiology of ASD. Chronic stress is known to cause deleterious effects on neuronal functions via glucocorticoid receptor-mediated signaling pathways. However, it is not known whether glucocorticoid receptors are dysregulated in the brain of ASD subjects. We hypothesized that subjects with ASD have altered expression of glucocorticoid receptors in their prefrontal cortex.
Methods: We investigated the expression of glucocorticoid receptor (GR) isoforms (GRalpha, GRbeta, GRgamma and GRp), mineralocorticoid receptor (MR) and co-factors (FKBP5, BAG1 and PTGES3) in the middle frontal gyrus of 13 ASD and 13 control subjects (NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, Baltimore, MD). We measured mRNA levels by real-time PCR and protein levels by western blotting. A multivariate analysis of covariance (MANCOVA) model served to examine differences between the ASD and control samples in their mRNA levels.
Results: With age, post-mortem interval, storage time, sample PH, and RNA integrity number as covariates, we identified significant increases in the mRNA expression of the FKBP5 ($\sim$60%) and PTGES3 ($\sim$40%) in subjects with ASD. There were significant decreases in mRNA levels of GRalpha ($\sim$54%), GRgamma ($\sim$50%), GRp ($\sim$15%), and MR ($\sim$50%) in ASD samples. No significant changes were observed in GRbeta and BAG1 expression levels between ASD and control subjects. Western blotting analysis further confirmed the above changes at the protein level. Also, we found significant associations between the mRNA levels and ASD symptom scores.
Conclusions: This study provides the first evidence on the alterations in glucocorticoid receptors and co-factors in the brain of ASD subjects. These results suggest that coordinated GR-chaperone interaction is necessary for GR stability and function.
Keywords: autism, glucocorticoid, cortex, FKBP5.
Disclosure: Nothing to Disclose.

M260. Reduced Hypothalamic Functional Connectivity to the Subgenual Cortex is Associated with Genetic Variations in the Glucocorticoid and Mineralcorticoid Receptor Genes

Keith Sudheimer*, Jennifer Keller, Ruth O'Hara, Alan Schatzberg

Stanford University, Stanford, California

Background: Hypothalamic-Pituitary-Adrenal (HPA) axis production of cortisol is typically tightly regulated by inhibitory feedback loops. Cortisol inhibits ACTH secretion from the pituitary and CRH secretion from the hypothalamus. In addition to these inhibitory feedback loops, cortisol receptors are also located in many additional brain regions that coordinate emotional behaviors, reproductive drive, and other appetitive behaviors. Down-regulation of cortisol receptors is thought to play a key role in causing HPA axis dysregulation and producing some of the emotional/neurophysiological changes that accompany major depression. Genetic variability in cortisol receptors could increase or decrease susceptibility to such emotional and neurophysiological changes by altering the structure/sensitivity of the receptors. Our group has recently presented evidence that resting state functional connectivity between the hypothalamus and the subgenual cortex is disrupted in patients that have major depression with psychotic features and that these disruptions are associated with symptom severity.

This finding is notable because these patients frequently present with cortisol dysregulation, suggesting that cortisol receptor sensitivity could be driving both symptomology and disruptions in functional connectivity. In order to investigate whether genetic variability in specific cortisol receptors could be contributing to cortisol dysregulation susceptibility, and ultimately to disrupted functional connectivity, we collected genetics data on a subset of the same healthy and depressed participants that were previously studied to demonstrate functional connectivity changes in psychotic major depression. We hypothesized that genetic variability across the glucocorticoid receptor (GR) and mineralcorticoid receptor (MR) would be associated with changes in hypothalamic functional connectivity to the subgenual cortex and elevated cortisol during the circadian nadir.

Methods: 131 participants across 3 groups (healthy, major depression, psychotic major depression) participated in an eyes-closed resting functional magnetic resonance imaging (fMRI) scan. 31 of these participants were excluded due to motion artifacts, susceptibility artifacts, or other issues involving fMRI scanning. Of the remaining 100 participants, 74 had genetics data for 9 GR single nucleotide polymorphisms (SNP), and 14 MR SNPs. These 74 participants included 24 healthy individuals, 28 patients with major depression but no psychotic features, and 22 patients with psychotic major depression. These same participants also had their cortisol secretion measured via hourly overnight blood draws. A backwards step-wise linear regression was conducted to determine whether genetic variance in GR or MR was associated with changes in hypothalamic functional connectivity to the subgenual cingulate. The regression terms included group, age, cortisol secretion during the circadian nadir (6 pm-1 am), gender, and each of the SNPs for GR and MR in two separate linear regressions.

Results: The final regression model that included GR variance explained 36.2% of the variance in hypothalamic functional connectivity to the subgenual cortex $F(6,65) = 7.72$, $p < 0.001$. In this model higher cortisol, age, and 2 GR SNPs (rs41423247 and rs2918419) were associated with more disrupted connectivity. Variance across groups was also associated with connectivity but only at a trend level ($p = 0.066$). In addition, a single GR SNP (rs12655166) was associated with less disrupted connectivity. The regression model that included MR variance explained 21.2% of the variance in hypothalamic functional connectivity to the subgenual cortex $F(3,69) = 7.46$, $p < 0.001$. In this model, age and a single MR SNP (rs5522) were associated with disrupted connectivity. Variance across participant groups for the MR models was again trend-level significant ($p = 0.061$).

Conclusions: These results indicate that genetic variability in the GR and MR genes that affect the structure/function of the receptors could be affecting not only the regulation of the HPA axis inhibitory feedback loops but also the neurophysiological networks associated with the symptoms and severity of depression.

Keywords: Cortisol, subgenual, glucocorticoid receptor, mineralcorticoid receptor.

Disclosure: Dr. Schatzberg and Dr. Keller are both named on a provisional use patent related to using genetic variability to determine depression risk and inclusion/exclusion of clinical trials. Dr. Sudheimer and Dr. O'Hara have no relevant financial conflicts.

M261. Effects of Gonadal Steroids on Mood and Emotion Processing in Women with a History of Postpartum Depression

Crystal Schiller*, Aysenil Belger, Joshua Bizzell, Peter Schmidt, David Rubinow

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Background: Neuroendocrine factors are purported to play a role in the etiology of postpartum depression (PPD), but direct evidence for this role is lacking. We are currently investigating the effects of changes in gonadal steroid levels on emotion processing by simulating two hormonal states related to pregnancy and parturition, respectively, in euthymic women with and without a history of postpartum depression. Here we present preliminary baseline data from an ongoing pharmaco-fmri study to examine emotion processing pre-manipulation and the effects of two hormonal states related to pregnancy and parturition in women with and without a history of PPD. Data from an additional six subjects currently enrolled will be presented in December.

Methods: Functional magnetic resonance images (fMRI) were collected from euthymic women with a history of PPD ($n = 6$) and those without such a history (controls; $n = 3$) at the baseline session, which took place during the early- to mid-follicular phase. Participants performed an emotional face-matching task (Hariri et al., 2002) to probe the neural circuits implicated in social affect processing, including the amygdala and dorsomedial PFC. This block-design paradigm consisted of 4 blocks of a perceptual angry/fearful face-matching task alternating with 5 blocks of a sensorimotor (geometric shape-processing) control task. Whole brain analyses were conducted to examine group differences in percent signal change in the BOLD response during the presentation of the faces versus shapes. Analyses were conducted using FMIRB's Local Analysis of Mixed Effects (FLAME) within the fMRI Expert Analysis Tool (FEAT). Group-level activation maps were thresholded using a z score of 2.3 ($p < .01$) to define contiguous clusters of activation. For women with a history of PPD only, we examined correlations between self-reported dysphoria and clusters of activation in corticolimbic regions that distinguished those with and without a history of PPD at baseline. After the baseline fMRI session, participants received four monthly injections of leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist, to induce and maintain a hypogonadal state during the hormone protocol. The hormone protocol consisted of 4 weeks of placebo treatment, followed by 8 weeks of estradiol and progesterone addback to mimic the hormone profile of pregnancy, followed by 4 weeks of placebo treatment to mimic the rapid decline in estradiol and progesterone levels that occurs with childbirth. Women completed follow-up assessments 12 weeks after the last GnRH agonist injection. We examined self-reported dysphoria during three hormone states (early to mid-luteal phase, high dose estradiol and progesterone,

and hormone withdrawal) in women with (n = 2) and without (n = 3) a history of PPD that had completed the hormone protocol.
Results: As a result of the inclusion criterion of euthymia, there were no significant differences in self-reported symptoms of depression and anxiety between those with and without a history of PPD at baseline. At baseline, women with a history of PPD showed greater activation of the right amygdala, thalamus, hippocampus and left occipital pole when viewing angry/fearful faces versus geometric shapes compared with control women. In addition, in women with a history of PPD, the degree of amygdala activation was significantly associated with severity of self-reported dysphoria ($r = 0.68$, $p = .05$) at baseline. Self-reported dysphoria further increased during the hormonal states consistent with pregnancy and parturition (compared with baseline and follow-up) in the women with a history of PPD (r = 2), but not in the control women (r = 3); however, the sample sizes were too small to conduct statistical tests.
Conclusions: Euthymic women with a history of PPD showed increased activation of limbic regions during emotion processing, and the degree of amygdala activation was associated with self-reported dysphoria at baseline. Hyperactivation of limbic regions may reflect a trait-like vulnerability to PPD in euthymic women. Although preliminary, our data show the involvement of the reproductive hormones estrogen and progesterone in the severity of dysphoria, consistent with their role in the development of PPD, and suggest that the mood destabilizing effects of gonadal steroids in these women may result from the neuromodulatory effects of estradiol and progesterone on limbic regions.
Keywords: estradiol, postpartum, depression, neuroimaging.
Disclosure: Nothing to Disclose.

M262. Estradiol Shifts Neuronal Activity Within the Infralimbic and Prelimbic Cortices to Enhance Fear Extinction Memory Consolidation

Lisa Maeng*, Kara Cover, Aaron Landau, Siobhan Glynn, Kelimer Lebron-Milad, Mohammed Milad

Harvard Medical School/Massachusetts General Hospital, Charlestown, Massachusetts

Background: The neurocircuitry involved in fear conditioning and extinction processes is well defined. Estradiol's influence on the consolidation of extinction memory is similarly documented. However, it remains to be investigated how estradiol influences these critical brain regions to elicit its effects on fear extinction. In this study, we examine the effect of estradiol on c-fos expression within the fear extinction network. Through this analysis, we identify sites of estradiol-modulated neuronal activity and describe how these neural changes correlate with fear expression.
Methods: One day after fear conditioning, experimentally naïve female rats received subcutaneous injections of estradiol (15 ug/kg) or vehicle during the metestrus phase of the estrous cycle. 30 minutes later, all rats underwent extinction training. Half of the rats were sacrificed 60 minutes after extinction, and the other 60 minutes after the recall test on the day following extinction. Their brain tissue was collected, and c-fos expression was analyzed within the ventromedial prefrontal cortex, amygdala, and hippocampus.
Results: There was no difference in post-extinction c-fos expression in the infralimbic (IL) cortex with estradiol treatment ($p > 0.05$), but an increasing trend was observed post-recall ($p = 0.10$). While the IL to prelimbic (PL) c-fos activity ratio was not different between the vehicle and estradiol groups post-extinction ($p > 0.05$), this ratio was significantly greater post-recall ($p < 0.01$). An increasing trend was observed in the central amygdala with estradiol administration post-extinction ($p = 0.12$), but this elevation was not observed post-recall ($p > 0.05$). Expression of c-fos in the dorsal hippocampus does not appear to be altered by estradiol treatment at either time point (ps > 0.05).
Conclusions: These findings suggest that estradiol induces a shift in neuronal activity within the IL and PL during recall. The IL to PL ratio of neuronal activity is greater with estradiol treatment during recall compared to the ratio observed during extinction. These results are consistent with fMRI findings in humans: a higher ratio in activation of homologs of the rodent IL and PL correlates with better extinction recall and reduced fear expression (Milad et al., 2009). Thus, the findings of the present study help to elucidate the neural mechanisms through which estradiol facilitates extinction memory, potentially leading to new developments in the treatment of anxiety and fear-based disorders.
Keywords: estradiol, fear extinction, anxiety, infralimbic cortex.
Disclosure: Nothing to Disclose.

M263. Genome-wide Methyl-Seq Analysis of Blood-Brain Targets of Glucocorticoid Exposure

Richard Lee*, Fayaz Seifuddin, Gary Wand, Laura Moody, Olivia Cox, Xiaoju Yang, Kellie Tamashiro, Peter Zandi

Johns Hopkins University School of Medicine, Baltimore, Maryland

Background: Chronic exposure to glucocorticoids (GCs) leads to numerous health complications, including cardiovascular disease, obesity, and diabetes. The CNS is particularly vulnerable to GCs, as prolonged GC exposure is associated with cognitive decline and psychiatric disorders such as depression and bipolar disorder. However, efforts to identify neuronal processes that are targeted by GCs have been hindered by the highly inaccessible nature of the brain in patients. A tool that can assess functions of specific genes and processes in the brain through the use of peripheral tissues may be immensely useful. Previously, we have demonstrated that blood DNA methylation (DNAm) changes in the candidate mood disorder gene Fkbp5 can accurately reflect 30-day GC exposure and dose-dependent alterations in Fkbp5 DNAm and gene expression in the hippocampus.
Methods: To identify additional hippocampal genes whose epigenetic alterations may be reflected in blood, we employed a novel genome-wide, targeted capture Methyl-Seq platform to identify GC-induced, differentially methylated regions (DMRs) in mouse blood and brain tissues.

Animals were treated with GCs for 30 days, after which DNA from white blood cells and hippocampus were processed for Methyl-Seq that combines target-capture, bisulfite conversion, and next generation sequencing to provide base pair resolution DNA methylation information at more than 1.5 million CpGs. DNA extracted from another cohort was used for bisulfite pyrosequencing to replicate the genome-wide sequencing results.
Results: Of the 3,681 DMRs identified in blood, 72.6% were DMRs that lost methylation following GC treatment. Similarly, 71.5% of the 5,365 DMRs identified in the hippocampus were loss-of-methylation events. In addition, we identified 3,095 DMRs that were common to both tissues that mapped to 1,068 unique genes. Common DMRs were associated with genes involved in important neuronal processes, including those involved with WNT, insulin, circadian rhythm, and neurotrophin signaling pathways. DMRs relevant to psychiatric disorders were replicated in in the additional cohort of animals by bisulfite pyrosequencing, including those that are located within genes implicated in neuronal migration (Nav2), circadian rhythm (Nr1d1), and autism (Shank3).
Conclusions: Our results suggest the feasibility of using peripheral tissues as a surrogate for GC-induced changes in neuronal genes and warrant additional studies to examine and establish cross-tissue epigenomic and transcriptomic correlations in greater detail.
Keywords: epigenetics, blood-brain correlations, glucocorticoids, stress.
Disclosure: Nothing to Disclose.

M264. Common TSPO Polymorphism Predicts Differences in Cortisol's Diurnal Variation in Individuals with Bipolar Disorder and Alcohol Use Disorder

Alan Prossin*, Masoud Kamali, Erika Saunders, Sebastian Zoellner, Mary Heitzeg, Melvin McInnis

University of Texas Health Science Center at Houston, Houston, Texas

Background: Dysregulated HPA responses to stressful challenges have been identified in psychiatric disorders including bipolar disorder (BD), alcohol use disorders (AUD), and others. HPA-axis reactivity can be assessed by measuring stress-related changes in cortisol, the body's main steroid stress hormone. A mitochondrial transmembrane protein, the translocator protein (TSPO), permits mitochondrial entry of cholesterol in various cell types throughout the body, a rate-limiting step in steroid hormone synthesis. Given current understanding regarding its mechanism of action, structural alterations to TSPO proteins could alter steroid hormone production, potentially dysregulating HPA reactivity during times of elevated stress. The ensuing changes in cortisol production would enhance vulnerability to psychosocial stressors, particularly in illnesses associated with HPA dysregulation (i.e. BD, AUD). Structural changes to the TSPO protein are known to occur in the presence of a specific polymorphism in the TSPO gene. These changes substantially impact binding of a highly selective radiotracer, [11C]PBR-28 (G allele enhances binding). However, whether these TSPO structural changes are associated with abnormal stress reactivity and consequent clinical exacerbations is unknown. To determine whether the presence of the GG allele of this TSPO polymorphism impacted HPA reactivity in individuals with stress-related clinical vulnerability, we tested whether this TSPO polymorphism predicted differences in cortisol's diurnal variation in BD volunteers with and without comorbid AUD.
Methods: We studied 128 volunteers from the Prechter Longitudinal Study (PI: McInnis). These included 101 BD volunteers including 50 with and 50 without AUD and 27 healthy volunteers of similar age and demographic. Diagnoses were confirmed using the Diagnostic Instrument for Genetic Studies adhering to DSM-IV-TR criteria. Guided by prior evidence associating allelic variation in a common TSPO polymorphism (snp rs6971) with altered [11C]PBR-28 binding affinity (AA:low, AG:moderate, or GG:high), genetic assessments focused on the TSPO rs6971 snp as previously described. The TSPO factor was dichotomized based on the presence/absence of the GG allele and therefore the presence/absence of the high affinity binding (HAB) phenotype. Cortisol was quantified from volunteers' saliva, obtaining samples in the evening (10-15 min prior to bedtime) and morning (10-15 min after wake-up) for 3 consecutive days. Results were log normalized. Repeated measures ANOVA was used to confirm effects of time (repeated measure: morning and evening for 3 consecutive days) and impact of independent factors of interest (BD, AUD, TSPO HAB) (all dichotomous) on salivary cortisol concentration (dependent variable). Further testing determined whether the presence of the HAB phenotype was associated with inhibitory control, often impaired in BD and AUD.
Results: Results from repeated measures ANOVA confirmed significant effects of time on Cortisol ($F5,530 = 51.0$, $p < 0.001$). Significant interaction effects were also confirmed for time x BD ($F5,530 = 2.6$, $p < 0.026$) and time x AUD ($F5,530 = 2.4$, $p < 0.034$), but not for time x TSPO HAB ($p > 0.05$). However, a significant interaction was confirmed for TSPO HAB x time x BD ($F5,530 = 3.9$, $p < 0.002$) and TSPO HAB x time x Alcohol Use Disorder ($F5,530 = 2.7$, $p < 0.021$). Further testing confirmed that HAB volunteers had greater mean inhibitory control accuracy for go/nogo tasks ($T210 = 2.9$, $p = 0.004$).
Conclusions: We identified significant differences in volunteer HPA reactivity (cortisol diurnal variation) depending on presence or absence of TSPO GG homozygosity (HAB) in volunteers with either BD or AUD. That these significant interactions are associated with an abnormal HPA reactivity has wide ranging applications to research and clinical domains. For example, TSPO screening in illnesses associated with exacerbations during periods of increased psychosocial stress (i.e. BD, AUD, and others), could reveal enhanced vulnerabilities, triggering early implementation of patient oriented preventive interventions. Additionally, these findings are also likely to inform [11C]PBR-28 PET research reducing clinical confounders associated with the requisite genetic pre-screening for high affinity binders (HAB) and improving clinical translational potential of [11C]PBR-28 PET. Nevertheless, further testing in an expanded clinical sample is needed to properly validate these findings and further delineate TSPO associated behaviors.

Keywords: neuroimmune interaction, bipolar disorder, alcohol disorder, TSPO and [11C]PBR-28 PET.
Disclosure: Nothing to Disclose.

M265. New Evidence that PANDAS (Acute-onset OCD) Is a Form of Autoimmune Encephalitis (AE)

Susan Swedo*, Kyle Williams, Ashura Buckley, Rebecca Hommer, Precilla D'Souza, James Leckman

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Background: The first cases of post-infectious, acute-onset obsessive-compulsive disorder (OCD) were described over two decades ago (Allen et al., 1995). Subsequent research demonstrated that infections with Group A streptococcal (GAS) bacteria were often the triggering factor, leading to description of the PANDAS subgroup (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) (Swedo et al., 1998). For PANDAS, and its prototypical disorder, Sydenham chorea, the postulated disease mechanism involves molecular mimicry. Antigens on the GAS cell wall "mimic" host antigens (to evade detection by the immune system) and antibodies produced against the GAS epitopes then cross-react with the host antigens, provoking an autoimmune response and inflammation of the caudate, putamen and other brain regions. The pathophysiology shared by SC and PANDAS is consistent with that described for several of the autoimmune encephalitides (AE), including laboratory abnormalities and evidence of encephalopathy on PET and MRI scans, and electroencephalograms (EEG). In addition, new findings from polysomnography (PSG) document abnormalities of sleep architecture and provide further evidence of CNS disruptions in PANDAS.
Methods: Subjects: 42 children (25 males; mean age 8.2 yrs; range 3 - 12 yrs) who were participants in a double-blind placebo-controlled trial of intravenous immunoglobulin (IVIG) for PANDAS (n = 35) or a natural history study of childhood neuropsychiatric disorders (N = 7). Both protocols (11-M-0058 and 13-M-0028, respetively) were approved by the NIH CNS IRB. Parents gave informed, written consent and children who were old enough to understand study procedures provided written assent to participation. Evaluations were conducted between March 2011 and May 2014. Methods: All subjects underwent a comprehensive diagnostic evaluation, which included medical, psychiatric and family history, physical and neurological examination, structural MRI scans, blood draw and lumbar puncture. Clinical symptoms were rated with the PANS Scale (under development by Leckman et al), as well as a number of validated assessment measures, including the Y-BOCS, YGTSS, CDRS, MASC and CGI-S. Routine EEGs were obtained in all 42 children, and 14 also had a prolonged overnight EEG and full PSG with extended array (20 scalp leads) and audio-video recordings. Laboratory assays were conducted by the NIH Clinical Center Laboratory according to standard protocols. Because duration of illness was not controlled for the participants in the natural history study, we are only reporting results for the 35 participants in the IVIG trial.
Results: EEGs were abnormal in 7 of 42 children (17%). Sharp/sharp or wave epileptiform abnormalities were demonstrated in 4 (10%) children and non-specific diffuse or focal slowing in 3 cases. None of the children had seizures clinically or on EEG. Abnormal PSG's were found in 12 of the 14 (86%) of the children examined, All had complaints of PANDAS-episode related sleep disturbances, including initial insomnia, "restless" sleep and severe nightmares or recent onset of night terrors. The PSG revealed the following: Non-REM Parasomnias (n = 3); Periodic Limb Movements of Sleep (PLMS; n = 5); REM Behavior Disorder (RBD) (n = 4) [Met scoring rules of the American Academy Sleep Medicine, OR the continuation of PLMS into REM]; Nonspecific REM motor disinhibition (n = 6) [Defined as the presence of moaning, laughing, excessive aperiodic limb movements, OR stereotypies (hands and fingers) clearly evident in REM sleep. Laboratory values were abnormal in 27 of 35 children (77%), including low serum IgG levels in 5 of 35 (14%); elevated antistreptococcal antibodies (ASO or anti-DNAseB) in 13/35 (37%) and positive antinuclear antibodies (ANA) in 14/35 (40%; 6 of whom also had anti-strep Abs). Results of cross-reactive autoantibodies (including anti-dopamine D1R and D2R, tubulin and lysogangliosides) and CAM KII activation also will be presented.
Conclusions: The criteria for AE require 1) acute or subacute onset of neuropsychiatric symptoms and 2) para-clinical evidence of brain inflammation (EEG or MRI abnormalities, antineuronal antibodies, etc). Ample clinical and paraclinical evidence of AE was present in this cohort of patients with PANDAS. Overall, 3/4's had an abnormal laboratory value; 17% had an EEG abnormality, and 12 of 14 children with sleep complaints had abnormalities of sleep architecture. These results suggest that PANDAS is a form of "striatal encephalitis", requiring prompt recognition, diagnosis, and treatment. A thorough medical evaluation of children presenting with acute-onset OCD/eating disorders is imperative, including evaluations for occult infections. Anecdotal reports suggest that some children's symptoms remit completely with appropriate antibiotics treatment; others require more aggressive interventions, including immunomodulatory therapies such as intravenous steroids, intravenous immunoglobulin (IVIG) and plasmapheresis. Prompt medical treatment not only provides relief of the acute illness, but may also prevent damage to affected brain regions.
Keywords: OCD, Neuroimmune, PANDAS, Autoimmune encephalitis.
Disclosure: Grifols Laboratory provided intravenous immunoglobulin (IVIG) for use in the Yale-NIMH trial.

M266. Identification of a Novel, Highly Potent D3 Dopamine Receptor-selective Agonist

David Sibley*, Amy Moritz, R. Benjamin Free, Jennie Conroy, Warren Weiner, Elena Barnaeva, Noel Southall, Marc Ferrer, Jonathan Javitch, Jeffrey Aubé, Kevin Frankowski

National Institute of Neurological Disorders & Stroke, National Institutes of Health, Bethesda, Maryland

Background: Dopamine receptors are highly validated drug targets in neurology and psychiatry. For instance, all

receptor-based antiparkinsonian drugs work via stimulating the D2 receptor, whereas all FDA-approved antipsychotic agents are antagonists of this receptor. However, many currently available dopaminergic drugs modulate both D2 and D3 dopamine receptors due to the high structural homologies in their orthosteric binding sites. Therapeutic use of compounds lacking receptor selectivity may lead to unwanted side effects, and also provide uncertainty as to the roles that the D2 and D3 subtypes play in normal and pathological processes. As part of an overall effort to develop compounds with improved selectivity for D2 and D3 receptors, we now report the optimization of a novel, potent D3 receptor-selective agonist that may exhibit allosteric properties.

Methods: We performed a high throughput-screening (HTS) campaign to interrogate a 380,000 + small molecule library to identify novel dopamine receptor modulators. The primary HTS assay utilized a cell line expressing the D2 receptor coupled to a chimeric Gqi5 protein, thereby linking receptor activation to robust calcium mobilization. We also conducted secondary assays to measure orthogonal D2 and D3 receptor signaling activities, including stimulation of β-arrestin recruitment (non-G protein-linked). Radioligand binding assays were used to characterize direct interactions with dopamine receptor subtypes. Hit compounds were selected and optimized using standard medicinal chemistry approaches.

Results: Through the NIH-MLPCN high throughput-screening program, we initially identified a series of compounds exhibiting antagonist activity at the D2 receptor. This set of antagonist compounds was subjected to a series of orthogonal and counter-screens using D2 and D3 receptor-mediated β-arrestin recruitment assays. Importantly, the compounds were tested as both agonists and antagonists. As expected, most of these compounds were confirmed as D2 receptor antagonists and the vast majority exhibited D3 receptor antagonism as well. However, one compound "3843" exhibited agonist activity at the D3 receptor. Radioligand binding studies revealed that 3843 had minimal affinity in displacing radioligand binding to either the D2 or D3 receptor. Given this unusual pharmacological profile of having D2 antagonist and D3 agonist activities, with minimal affinity for the orthosteric binding sites, we decided to develop this compound further. Over 270 analogs were synthesized and tested to explore the structure-activity relationship of 3843 for the D2 and D3 receptors, and several compounds with a nearly 500-fold increase in D3 receptor agonist potency (EC50s in nM range) were found. At the same time, some of these compounds exhibited diminished potency and/or efficacy for inhibiting the D2 receptor (IC50s >1 μM) using the β-arrestin recruitment assay. The pharmacological profiles of two of the most promising compounds were verified using a [3H]-GTPγS binding assay and a BRET assay that measures Go activation. Importantly, dissociation kinetic radioligand binding assays suggested that these optimized compounds interact with the D3 receptor in an allosteric fashion.

Conclusions: We have currently identified a novel D3-selective agonist that appears to interact with the receptor in a unique, potentially allosteric fashion. The availability of such a highly selective agonist would be important from a therapeutic standpoint, as drugs exhibiting marginal selectivity for the D3 receptor have exhibited neuroprotective and neurorestorative properties. However, these drugs, which are most commonly used to treat Parkinson's disease, frequently exhibit side effects such as compulsive gambling and hypersexuality. Notably, the loss of impulse control-related side effects are thought to be due to over-stimulation of the D2 receptor. Therefore, more highly selective agonists for the D3 receptor, such as the compounds identified in this study, may serve as promising neuroprotective and neurorestorative agents for slowing or stopping the progressive loss of dopaminergic neurons seen in Parkinson's disease, with fewer side effects.

Keywords: Dopamine, Receptor, Allosteric, Agonist.
Disclosure: Nothing to Disclose.

M267. A Circuit Mechanism in the Bed Nucleus of Stria Terminalis for the Anxiogenic Actions of Serotonin

Catherine Marcinkiewcz*, Chris Mazzone, Cayce Dorrier, Dan Perron, Tom Kash

University of North Carolina, Chapel Hill, North Carolina

Background: Serotonin neurons originating from the dorsal raphe nucleus (DRN) innervate a variety of limbic structures involved in feeding, mood regulation, reward-related and avoidance behavior. The bed nucleus of stria terminalis (BNST) is one critical output of the dorsal raphe with a well-defined role in stress-induced relapse and anxiety associated with drug dependence and acute withdrawal states. While it has been shown that 5HT has opposing effects on BNST neurons, 5HT actions on neurochemically and anatomically defined populations and their specific behavioral outcomes has not been explored. Using a combined genetic and electrophysiological approach, we investigated how 5HT modulates distinct neural circuits in the BNST. The data from these experiments is then synthesized into a working model that informs our understanding of how 5HT orchestrates a variety of behavioral states.

Methods: We used slice electrophysiology to probe 5HT actions in the BNST. Using a SERT-cre transgenic mouse injected in the DRN with a floxed ChR2 vector (AAV5-eF1a-DIO-ChR2-eYFP), we light evoked 5HT in the BNST and recorded effects on membrane potential (MP) in BNST neurons with and without bath applied 5HT2c-R antagonists. We also recorded MP during bath application of 5HT and mCPP to CRF neurons using a CRF reporter mouse. The effects on subsets of CRF neurons were parsed out by injecting retrograde tracer beads into the VTA or LH of CRF reporters and recording from beaded and non-beaded CRF neurons. In order to map out the circuit mechanism for non-beaded ("local") CRF neurons, we injected a floxed ChR2 vector into the BNST of CRF-cre mice and retrograde tracer beads into the VTA or LH. Recording exclusively from non-CRF beaded neurons, we recorded light evoked GABA currents. We also recorded sIPSCs and mIPSCs in wild-type mice injected with retrograde tracer beads in the VTA or LH before and after bath application of 5HT. Bath

application of 5HT2c-R antagonists was used to determine 5HT2c-R dependence of these effects.
Results: Optogenetic stimulation of 5HT terminals from the DRN to BNST depolarized neurons by an average of 4 mV and was blocked in the presence of the 5HT2c-R antagonist RS 102221. Both 5HT and mCPP depolarized non-beaded ("local" CRF neurons) while 5HT hyperpolarized CRF neurons that projected to the VTA or LH. mCPP had no effect on CRF projection neurons. These data suggest that there are two distinct populations of CRF neurons; a local population that likely expresses 5HT2c-Rs and a projecting population that mostly expresses 5HT1a-Rs. Interestingly we could light-evoke GABA currents in non-CRF neurons that projected to the LH and the VTA, suggesting that some CRF neurons locally inhibit BNST outputs to these two regions. Bath applied 5HT enhances sIPSC frequency but not amplitude on VTA and LH projecting neurons, and this effect is both activity and 5HT2c-R dependent. Together with our above-mentioned results, these data suggest that 5HT is activating a population of GABAergic neurons upstream of VTA and LH outputs, presumably CRF neurons. The fact that 5HT increases GABAergic transmission via 5HT2c-Rs suggest that this cell population must express 5HT2c-Rs and be activated by 5HT, which points to local CRF as opposed to CRF projecting neurons.
Conclusions: In summary, we provide a framework for understanding how 5HT acts on a distinct population of CRF neurons in the BNST to generate anxiety-like behavior. Light evoked 5HT depolarized neurons in the BNST via a 5HT2c-R dependent mechanism. In a CRF reporter model, we find that bath applied 5HT depolarizes non-projecting CRF neurons and hyperpolarizes CRF projections to the LH and VTA, two main outputs of BNST CRF neurons. This local CRF population forms local GABAergic synapses with BNST outputs to the VTA and LH and increases inhibitory transmission when activated by 5HT. Given that BNST outputs to the VTA and LH are known anxiolytic pathways, 5HT actions in the BNST, by inhibiting these outputs in a direct and indirect fashion, would be predicted to be anxiogenic. We intend to test this model by assessing behavior after manipulating different components of this circuit using optogenetic and chemogenetic tools.
Keywords: Serotonin, BNST, anxiety, CRF.
Disclosure: Nothing to Disclose.

M268. The Gut Microbiome in Patients with Anxiety, Depression and Inflammatory Bowel Disease

Rebecca Anglin*, Josie Libertucci, Melanie Wolfe, Christine Lee, Paul Moayyedi, Michael Surette

McMaster University, Toronto, Canada

Background: The human body is home to almost 100 trillion microorganisms, most of which are located in the distal gut. The symbiotic relationship that exists between the gut microflora and body is essential for health. Recently there has been considerable interest in the bidirectional communication that exists between the gut and the brain, and the role that the gut microbiome may play in mental health. Animal studies have suggested that manipulation of the gut microbiome can alter anxiety-like behavior, raising the possibility that the gut microbiome may play a role in the pathophysiology of psychiatric disorders. At the same time, it is increasingly being recognized that patients with gastrointestinal disorders have significant psychiatric co-morbidity. This raises the possibility that there is a shared pathophysiology that may involve the gut microbiome. In this study we investigated the gut microbiome profile in patients with ulcerative colitis with and without anxiety and depression. To our knowledge this is the first study to analyze the gut microbiome in patients with anxiety and depression.
Methods: Microbiome composition was analyzed in 67 patients with ulcerative colitis by culture-independent methods. DNA from fecal samples was extracted using an in-house protocol and the bacterial composition was determined by amplification of the V3 region from the 16S rRNA gene and MiSeq Illumina sequencing. Sequences were trimmed, aligned and clustered into operational taxonomic units (OTU) and assigned taxonomy using an RDP classifier. Beta diversity was measured by transforming the OTU table to proportions and ordinated using the Bray Curtis Dissimilarity Matrix. Differential abundance testing between groups was computed using a negative binomial model (DESeq2). Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADs), with a score of ≥ 8 on either subscale used to classify patients as anxious or depressed.
Results: Twenty-three patients met criteria for anxiety and 16 for depression. Beta diversity analysis revealed no distinct clustering of UC patients with or without anxiety or depression. Patients with anxiety showed a statistically significant increase in OTU 184 classified as Collinsella (log2 fold change = 8.8; padj = 2.05E -05), OTU 455 classified as the order ML615J-28 (log2 fold change = 2.3; padj = 4.7E -07) and OTU 635, Coriobacteriales (log2 fold change = 1.82; padj = 0.00021) and decrease in OTU 131 Streptococcaceae (log2 fold change = 28.5; padj = 0.00012), OTU 173 Parabacteroides (log2 fold change = 8.37; padj = 2.71E -05) and OTU 193 an unclassified group belonging to the phylum Firmicutes (log2 fold change = 17.1; padj = 0.00013) compared to patients without anxiety. Patients with depression showed a significant increase in OTU 97, classified as Sutterella (log2 fold change = 3.10; padj = 6.00E -07) and decrease in OTUs 171 and 201 both classified as Lachnospiraceae (log2 fold change = 11.5, 9.29; padj = 1.03E -07, 1.98E -07 respectively) compared to patients without depression.
Conclusions: In patients with ulcerative colitis, we found that anxiety and depression were associated with significant alterations in gut microbiota. This suggests that the gut microbiome may play an important role in the pathophysiology of the psychiatric comorbidity of inflammatory bowel disease. It also contributes to a growing body of evidence that the gut microbiome and gut-brain interactions may play an important role in mental health and the development of psychiatric illness, which could lead to important therapeutic developments.
Keywords: Gut microbiome, Anxiety, Depression, Ulcerative Colitis.
Disclosure: Nothing to Disclose.

M269. Noradrenergic Regulation of Optimal Decision Making

Elena Vazey*, Gary Aston-Jones

Medical University of South Carolina, Charleston, South Carolina

Background: Decision making goes awry in many psychiatric disorders. Cortical function during decision processing is heavily influenced by several ascending monoamines, including norepinephrine (NE). Locus coeruleus (LC) provides the vast majority of NE to the cortex. Our lab and others have previously shown LC-NE neurons respond phasically during optimal decision processing in several cognitive tasks including two alternative forced choice (2AFC) tasks. NE release is posited to act as a temporal filter for integrating task relevant information and facilitating decision execution.
Methods: We tested a range of pharmacological compounds to identify potential mechanisms of noradrenergic influence in optimal decision performance in a 2AFC task. We trained male Long-Evans rats to perform a 2AFC task in which one of two adjacent central cue lights (red/green) illuminated on every trial to indicate which of the two laterally-located levers would be rewarded. Rats self-initiated cue presentation by nose-poking in front of the cue lights, and performed 249 trials per session with each trial a 50% probability of either cue presentation. Correct responses were rewarded with 100 μl of 15% sucrose.
Results: The α2-noradrenergic agonist guanfacine, or the noradrenergic reuptake inhibitor atomoxetine, both increased accuracy of 2AFC performance. However, this effect was restricted to animals that had $<75\%$ accuracy on vehicle, indicating a ceiling effect in the cognitive enhancement with these compounds. Guanfacine and atomoxetine also increased reaction times, possibly indicating an effect on the response criterion (β in signal detection theory). The α2 antagonist atimpamezole produced no clear effects on either accuracy or reaction time. The α1 antagonist prazosin did not alter accuracy but caused significant increases in reaction time, indicating a possible arousal or motor effect. The β noradrenergic antagonist propranolol strongly reduced accuracy in all subjects; however, propranolol caused no change in reaction time, indicating a role for β noradrenergic signaling in cognitive processing.
Conclusions: These results have implications for the development of cognitive enhancers and highlight intricacies of noradrenergic function during optimal decision processing that require further investigation.

Keywords: Locus coeruelus, Pharmacology, Attention, Cognition.
Disclosure: Nothing to Disclose.

M270. Web-based Curriculums for Teaching Psychopharmacology: Revision of the Resident and the Medical Student Curriculums

Ira Glick*

Stanford University School of Medicine, Stanford, California

Background: Started by the ACNP training committee in 1984, the ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents, medical students and primary care physicians. It has increasingly had global penetration. We present here the 8th edition of the resident curriculum and the 2nd edition for medical students – both now available online.
Methods: The ASCP Curriculum Committee composed of directors of both resident education as well as medical student education educators have developed materials related to the "what, why, and how" to teach and evaluate. In addition for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow-ups on both curriculums within the last 2 years.
Results: We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the two curriculum. Based on the follow up of both curriculum, we have revised every lecture and updated the pedagogy Depending on the size/resources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-english speaking countries as committee members work with users to adapt/translate to local conditions and teaching strategies. It has been difficult to connect with primary care training programs.
Conclusions: For residents, the curriculum is now in its 8th edition and has 88 lectures and over 4,000 slides. For teaching medical students, there has never been a generally accepted curriculum or set of teaching materials specifically designed for them. There is a great deal to teach in the four year curriculum and medical students have widely divergent career paths. This curriculum has 22 lectures. Having the curriculum web-based has improved availability although some programs globally still need a hard copy version.
Keywords: Training, schizophrenia, depression, education.
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