criteria previously developed to denote compulsive addiction in rodent models (Deroche-Gamonet *et al*, 2004). Specifically, the cluster analysis identified a subset of 'addicted' mice (~19%) that exhibited intense operant-reinforced attack behavior, decreased likelihood to select an alternative palatable food reward over aggression, heightened relapse vulnerability and progressive ratio responding, and resilience to punishment-induced suppression of aggression-reinforced operant responding. Our studies suggest that preclinical addiction models can be used to identify the neural mechanisms controlling appetitive aggression and relapse, as well as pathological or compulsive manifestations of aggression (for an in-depth discussion of both the limitations and extensions of our studies, see Golden *et al* (2017a,b)).

In conclusion, we propose that appetitive aggression can be viewed within the context of compulsive behaviors, and that neurobiological and behavioral tools used to study compulsive drug seeking and relapse should be used to study brain mechanisms of this type of aggression, both preclinically and clinically. Finally, an appetitively motivated compulsion toward aggression might be an important endophenotype to include in dimensional formulations of psychopathology such as the National Institute of Mental Health's Research Domain Criteria (RDoC), where aggression is currently mentioned only within the domain called negative-valence systems. We suggest that these conceptualizations of aggression are fundamentally incomplete and that some forms of aggression may be best understood as strong appetitive rewards, carrying the attendant risks of compulsive behavior.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The research was supported by the Intramural Research Program of NIDA (YS) and a National Institute of General Medical Sciences Postdoctoral Research Associate Grant 1FI2GM117583-01 (SAG).

Sam A Golden[1] and Yavin Shaham[1]
[1]Behavioral Neuroscience Branch, Intramural Research Program, NIDA—NIH, Baltimore, MD 21224, USA
E-mail: sam.golden@nih.gov or yshaham@intra.nida.nih.gov

Deroche-Gamonet V, Belin D, Piazza PV (2004). Evidence for addiction-like behavior in the rat. *Science* **305**: 1014–1017.

Fish EW, De Bold JF, Miczek KA (2002). Aggressive behavior as a reinforcer in mice: activation by allopregnanolone. *Psychopharmacology* **163**: 459–466.

Golden SA, Aleyasin H, Heins R, Flanigan M, Heshmati M, Takahashi A *et al* (2017a). Persistent conditioned place preference to aggression experience in adult male sexually-experienced CD-1 mice. *Genes Brain Behav* **16**: 44–55.

Golden SA, Heins C, Venniro M, Caprioli D, Zhang M, Epstein DH *et al* (2017b). Compulsive addiction-like aggressive behavior in mice. *Biol Psychiatr* **82**: 239–248.

Golden SA, Heshmati M, Flanigan M, Christoffel DJ, Guise K, Pfau ML *et al* (2016). Basal forebrain projections to the lateral habenula modulate aggression reward. *Nature* **534**: 688–692.

Venniro M, Caprioli D, Shaham Y (2016). Animal models of drug relapse and craving: from drug priming-induced reinstatement to incubation of craving after voluntary abstinence. *Prog Brain Res* **224**: 25–52.

Neuropsychopharmacology Reviews (2018) **43,** 224–225. doi:10.1038/npp.2017.173

Computational Approaches to Behavior Analysis in Psychiatry

There is an ongoing revolution in computational behavioral analysis in business and government. Automated analysis of text is used to screen job applicants and score essays, and is applied to social media to influence individuals' purchasing and voting choices. Automated face and emotion recognition is used for both surveillance and to supplement polygraph testing. Wearables are used to collect physiological data from athletes and astronauts, and increasingly for medical purposes.

Only recently have these computational approaches been applied in psychiatry to study disturbances in thought, emotion, and behavior, which traditionally have been assessed using only expert human appraisal, codified in standardized interviews and ratings, but labor-intensive and error-prone. Herein, we review a sample of ongoing lines of research, in respect to language, emotional expression and physiological parameters.

Automated speech analysis can characterize intoxication by different drugs of abuse with increased verbosity induced by methamphetamine, and increased semantic proximity to words such as friendship/rapport/support/intimacy characterizing intoxication from MDMA or 'ecstasy' (Bedi *et al*, 2014); acoustic features of speech are similarly discriminative (Agurto *et al*, 2017). This behavioral readout in speech of drug effects has implications for diagnosis, care and clinical trials, as well as for investigations of neural mechanisms of intoxication.

We have also used automated speech analysis to characterize the subtle language disturbance that precedes psychosis onset in schizophrenia (Bedi *et al*, 2015), identifying a highly accurate predictor of psychosis that comprises both decrease in sentence-level semantic coherence (indexing tangentiality), and decrease in syntactic complexity (indexing concreteness). Further, we have used automated metaphor identification to show a significantly higher rate of metaphor usage across stages of schizophrenia, including putative prodromal stages (Gutierrez *et al*, 2017). This technology is portable, inexpensive, and easy to implement, and can improve prognosis and understanding of mechanisms of thought disorder in schizophrenia.

Beyond words themselves, voice and face expression also provide important data. At the ACNP Annual Meeting in 2016, Dr Satrajit Ghosh presented data showing that voice acoustic features can be used to predict severity of depression and Parkinson's disease (Ghosh, 2016). He introduced VoiceUp, his open source mobile platform for collection and analysis of voice data, a sensor into mental health feasible to track over time. In the same ACNP panel, Dr Justin Baker presented data on 'face action units,'

which comprise specific movements of the mouth, cheeks, and eyes, as collected by video and analyzed using the OpenFace mobile platform (Baker, 2016). Specific face action unit abnormalities were associated with symptom severity, as was the extent of mutual gaze and vowel space in speech.

The smartphones in our pockets provide complex longitudinal *in vivo* data, much of it passively obtained, including spatial trajectories (GPS), physical movement, and sleep (accelerometer), and social networks and dynamics (phone communication logs); these 'big data' at the level of the individual can be used to promote precision psychiatry (Onnela and Rauch, 2016). Smartphones can record sleep patterns, respiration, and heart rate variability. Physiological data, along with language and facial data, can provide accurate and nuanced real-time readout in telepsychiatry, and lead to deep phenotyping that can be integrated with genetic and neuroimaging data.

FUNDING AND DISCLOSURE

This research is funded by grants from the NIMH: R01MH107558 and R03MH108933. The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to acknowledge the work of Drs Gillinder Bedi, Satrajit Ghosh, and Justin T Baker.

Cheryl M Corcoran[1] and Guillermo A Cecchi[2]

[1]Department of Psychiatry, Division of Experimental Therapeutics, New York State Psychiatric Institute at Columbia University, New York, NY, USA; [2]Computational Biology Center-Neuroscience, IBM TJ Watson Research Center, Ossining, NY, USA
E-mail: cheryl.corcoran@nyspi.columbia.edu

Agurto C, Norel R, Ostrand R, Bedi G, Cecchi GA (2017). Phonological markers of oxytocin and MDMA ingestion. Interspeech.

Baker JT (2016). Panel on computational approaches to behavior analysis in psychiatry. *55th Annual Meeting of the American College of Neuropsychopharmacology*; 8 December.

Bedi G, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB *et al* (2015). Automated analysis of free speech predicts psychosis onset in high-risk youths. *NPJ Schizophr*, article number 15030 **10**.

Bedi G, Cecchi GA, Slezak DF, Carrillo F, Sigman M, de Wit H (2014). A window into the intoxicated mind? Speech as an index of psychoactive drug effects. *Neuropsychopharmacology* **39**: 2340–2348.

Ghosh S (2016). Panel on computational approaches to behavior analysis in psychiatry. *55th Annual Meeting of the American College of Neuropsychopharmacology*; 8 December.

Gutierrez ED, Corlett PR, Corcoran CM, Cecchi GA (2017). Using automated metaphor identification to aid in detection and prediction of first-episode schizophrenia. Empirical methods in natural language processing (EMNLP).

Onnela JP, Rauch SL (2016). Harnessing smartphone-based digital phenotyping to enhance behavioral and mental health. *Neuropsychopharmacology* **41**: 1691–1696.

Neuropsychopharmacology Reviews (2018) **43,** 225–226. doi:10.1038/npp.2017.188

Cannabinoid Receptor 1 Positive Allosteric Modulators for Posttraumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a severe psychiatric disorder that develops in a subset of people following a traumatic event. Exposure-based psychological treatments and antidepressants are the current first-line treatments for PTSD symptoms. However, many patients fail to receive effective treatments, drop out treatments, or are non-responsive to existing treatments (Watts *et al*, 2013), highlighting an urgent unmet need to develop novel therapeutics. Part of the challenge in developing effective therapies has been the biological heterogeneity in PTSD pathophysiology. 'Broad-spectrum' therapies such as antidepressants and standardized exposure therapies may not account for the biological diversity of the underlying deficits in neurotransmitter mechanisms, stress resiliency, and learning deficits.

One of the novel targets that has emerged as being involved in PTSD with strong preclinical and human data is the endocannabinoid system. The endocannabinoid system includes two principal cannabinoid receptors (CB1R and CB2R), their several endogenous ligands, including the two key ligands anandamide and 2- arachidonoylglycerol (2-AG), and enzymes responsible for endocannabinoid biosynthesis and inactivation. Although there are some conflicting findings, perhaps due to differences in experimental conditions, preclinical studies of fear disorder models generally support the concept that selective agonists of CB1R facilitate fear extinction. Subjects with PTSD are reported to have significantly lower CB1R availability and reduced peripheral concentration of anandamide (Pietrzak *et al*, 2014; Neumeister *et al*, 2015) and appears to be associated with threat processing in trauma survivors (Pietrzak *et al*, 2014). These data suggest that low anandamide levels and upregulation of endocannabinoid receptors in the amygdale-hippocampal-corticostriatal circuitry could result in the enhanced reactivity to threat stimuli, and endogenous cannabinoid would ameliorate such responses (Neumeister *et al*, 2015).

Despite this strong mechanistic rationale, utilizing direct agonists of CB1R receptors has several disadvantages. The CB1 receptors regulate many opposing functions in brain, especially in the regulation of fear regulation circuitry and downregulation of receptors are seen after chronic exposure to agonists. Agonists could also have adverse effects from off-target CB1 activation. Therefore, alternative approaches to augment endocannabinoid signaling need to be explored. One such promising approach is through inhibition of fatty acid amide hydrolase (FAAH) involved in endocannabinoid catabolism that would increase the availability of endogenously generated endocannabinoids (Gunduz-Cinar *et al*, 2013).

A second approach is to utilize positive allosteric modulators (PAMs) that selectively increase the CB1R effects. CB1R has allosteric sites spatially distinct from the orthosteric ligand-binding pocket, and engagement of CB1R by allosteric modulators induce a conformational change in the receptor that may be difficult to achieve with orthosteric ligands alone