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.

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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

and thus one can 'fine-tune' the pharmacological activity of the endogenous ligand. Such compounds could offer not only enhanced CB1R selectivity, but also reduced receptor down-regulation and inter-receptor promiscuity (Kulkarni *et al*, 2016). One such compound GAT211 increases CB1R effects, demonstrates good efficacy in rodent models of chronic pain without demonstrating acute tolerance, rewarding properties or dependence (Slivicki *et al*, 2017). Our preliminary data show that GAT211 also enhances fear extinction in auditory cue-induced fear conditioning model and could potentially provide a novel approach to PTSD drug development.

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Integrating 'Omics' Approaches to Prioritize New Pathogenetic Mechanisms for Mental Disorders

Neuropsychopharmacology research is between a rock and a hard place. The rock is the historical, but slow, hypothesis-driven approach, where discovery occurs by testing candidate mechanisms in already well-known biological models. The hard place is the innovative, but overwhelming, hypothesis-free approach, where 'omics' analyses of everything that is analyzable generates a deluge of data implicating hitherto unknown mechanisms. So, either we have little data on things we already know, or too much data and cannot find the needle in a haystack. One solution is to mix apples and oranges: integrating cross-species and cross-tissues 'omics' data to find mechanisms that recur across different experimental and clinical models. The idea has been used with remarkable success. And yes, we will finish with the proverbs now.

Niculescu *et al* (2000) first developed and used such an approach, which they called convergent functional genomics. More recently, the approach has been used by them to help prioritize genes from genome-wide association studies (GWAS) of bipolar disorder (Patel *et al,* 2010), integrating GWAS findings, transcriptomics data on postmortem human brain and blood, and studies in animal models, to identify top-genes supported by all approaches. They identified six genes (*ARNTL*, *MBP*, *BDNF*, *NRG1*, *RORB*, and *DISC1*), which are involved in relevant biological processes, such as circadian rhythm, connectivity, and neuroplasticity. They used a similar strategy for schizophrenia (Ayalew *et al*, 2012). Interestingly, this strategy could be done with publically available data rather than being based on novel experimental findings.

In 2013, we studied transcriptomics data from the hippocampus of adult prenatally stressed rats (an established animal model of depression with high glucocorticoid levels) and from a human neuronal stem cell line (that we treated with a concentration of cortisol that reduces neurogenesis) (Anacker *et al*, 2013). We found that TGFβ-SMAD2/3 and Hedgehog signaling are reduced in both models: TGFβ-SMAD2/3 promotes neurogenesis (and has been found to be reduced in depressed patients), whereas Hedgehog promotes neuronal differentiation (and has not been studied in depressed patients yet). Similarly, Malki *et al* (2016) studied transcriptomics from the prefrontal cortex of mice bred for high aggressive behavior and from the brain of zebrafish exposed to aggressive social encounters. They identified seven genes shared in both datasets, including HDAC4, which has genetic variants associated with aggressive behavior in mental retardation, and it is targeted by valproic acid, a pharmacological treatment for aggressive behavior. Finally, Luoni *et al* (2016) studied methylome analyses performed in multiple models of early life stress: rats exposed to prenatal stress (prefrontal cortex); human newborns exposed to stress in pregnancy (cells from the umbilical cord); and rhesus monkeys exposed to stressful rearing conditions (peripheral blood and prefrontal cortex). Their top gene was *Ank3*, a gene with a strong association for psychiatric disorders; and they also demonstrated an interaction between functional genetic variants within *Ank3* gene and obstetric complications on working memory in humans. Although these studies are predominantly 'comparative' in their nature, this cross-species and cross-tissues approach can be used to produce 'integrative' findings when it generates