how the brain processes contextual information. Translational research in both rodents and humans has honed in contextual processing from a psychological perspective to its core brain circuitry—the amygdala–hippocampal circuit, which appears to be conserved across species (Milad and Quirk, 2012). Structural and functional alterations of this circuit have been observed in patients with neuropsychiatric disease, and are associated with a negative emotional memory bias and a broader fear generalization gradient (Gerritsen *et al*, 2012). Translating from 'circuit neuroscience' to 'circuit neurotherapy' requires understanding of the oscillatory mechanisms controlling amygdala–hippocampal interactions during the processing of salient information. In our recent study (Zheng *et al*, 2017) using direct human intracranial recordings, we demonstrated unidirectional influence from the amygdala to the hippocampus during contextual fear processing. In addition, we showed that such modulation is mediated through coherent theta and alpha frequency oscillations between these two core brain structures.

Neuropsychiatric disorders are primarily treated with pharmacological means, targeting large swaths of brain tissue. To capture the underlying mechanistic process, a circuit-level perspective might provide a deeper understanding of neuropsychiatric disorders and improved interventions with greater efficacy and fewer side effects. A potential clinical application of our study is the modulation of oscillatory phase couplings between the amygdala and the hippocampus. Phase alignment or coupling between brain regions provides a temporal window for coordinated interregional information transfer and communication. Information transfer errors may occur due to over-coupling or under-coupling between brain structures, including failures in terminating irrelevant communication or extracting meaningful signals. These alterations in communication dynamics have been proposed to underlie neuropsychiatric disorders (Voytek and Knight, 2015). To 'break' such pathological couplings, amygdala–hippocampal network interactions could be altered with stimulation-based therapy to induce temporal phase synchronization (eg, enhanced phase alignment with phase resetting) or desynchronization (eg, reduced phase alignment with neural noises) between the two brain structures. This provides a theoretical framework for circuit-specific and stimulation-based intervention approaches, such as deep brain stimulation, transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation. Furthermore, greater specificity can also be achieved by taking individual oscillatory variation into account. For example, using tACS parameters specific to individuals' dominant theta frequency improves short-term memory capacity (Vosskuhl *et al*, 2015). Our study also showed that instead of conforming to the conventional definition of theta (4–7 Hz)/alpha (8–12 Hz) frequency rhythms, amygdala–hippocampal dynamics are contingent upon subject-specific low frequency oscillations (Zheng *et al*, 2017). Identifying such individualized electrophysiological features in patients with psychiatric disorders could enable stimulation parameters to be tailored for subject-preferred neuronal firing frequencies, leading to personalized therapeutic interventions.

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Modeling Non-Syndromic Autism with Human-Induced Pluripotent Stem Cells

Genetically, autism can broadly be segregated into syndromic and non-syndromic forms. Accounting for a small percentage of total ASD cases, syndromic ASD includes incidences of the disease with known genetic cause and unique clinical presentation, while non-syndromic ASD with unknown genetic etiology accounts for the remaining majority of ASD cases (Sztainberg and Zoghbi, 2016). The genetic underpinnings of non-syndromic ASD likely involve small effects of many genes and/or rare *de novo* mutations in a susceptible genetic background (de la Torre-Ubieta *et al*, 2016). Unfortunately, non-syndromic ASD is difficult to model precisely because of this genetic heterogeneity. The use of human-induced pluripotent stem cells (hiPSCs) offers an opportunity to uncover some of the molecular mechanisms behind non-syndromic ASD. hiPSCs possess the same genetic make-up of the individual they were derived from. Thus, hiPSCs derived from individuals with non-syndromic ASD can accurately recapitulate the heterogeneous genetics found in this form of the disease.

Recently, our laboratory and collaborators utilized hiPSCs to model non-

syndromic ASD by generating hiPSC lines from eight non-syndromic ASD males (diagnosed via behavior consistent with DSM-IV criteria) along with five healthy male control individuals (Marchetto *et al*, 2017). Known syndromic forms of ASD were ruled out in all individuals involved with this study via exome sequencing and copy-number variant analysis. On the basis of MRI scans conducted between 2–4 years of age, all ASD individuals were found to possess mild to severe macrocephaly, defined as larger than average total brain volume compared with typically developing individuals. We hypothesized that ASD individuals sharing a co-morbidity would also share disruptions in common cellular phenotypes and signaling pathways, thereby increasing our ability to detect disruptions in these processes.

Initial observations indicated that both ASD hiPSCs and neural progenitor cells (NPCs) derived from hiPSCs proliferated at a higher rate than control cells and displayed decreased Wnt signaling. Pharmacological enhancement of the Wnt pathway rescued this proliferative phenotype. Interestingly, we have also found that disrupted Wnt signaling during mouse embryonic development leads to transient brain overgrowth and behaviors analogous to human symptoms of ASD, such as aberrant social and repetitive behaviors (Belinson *et al*, 2016). This remarkable pathway conservation between species suggests that aberrant Wnt signaling might have a critical role in ASD development.

In addition to NPCs, neurons were differentiated from ASD iPSC lines and displayed decreases in synapse number, which lead to defective network properties in ASD neuronal cultures. RNA sequencing was also performed in iPSCs, NPCs, and neurons, revealing both previously described and novel misregulated genes and pathways in ASD cells, including enrichment of genes linked with brain development in NPCs, likely reflecting the previously observed brain overgrowth phenotypes. A number of genes were also found to be misregulated during differentiation of NPCs to neurons in ASD cell lines, including various cation channels that might be responsible for aberrant network connectivity.

Our study illustrates that novel pathways and physiological processes in human cells can be identified in a non-syndromic neurological disorder if classified by endophenotypes. Further exploration of the genes/pathways identified in this study and the identification of new pathways associated with neurological disease in human cells promises to aid the development of more effective clinical targets.

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Innovative Therapeutic Intervention For Opioid Use Disorder

The United States is in the grip of an opioid misuse and overdose crisis. Progression from misuse to opioid use disorder (OUD) is marked by compulsive drug-taking and clinically significant impairment. Behavioral interventions along with treatment with OUD pharmacotherapeutics, such as buprenorphine, mitigates withdrawal, reduces mortality, opioid intake, and opioid-seeking behaviors, as well as improves psychosocial functioning (Volkow *et al*, 2014). Medication-assisted treatment is an important adjunct to the proper management of OUD patients, yet additional opportunities exist to enhance the probability of extended abstinence and recovery from OUD.

Dysregulation of the limbic-corticostriatal circuitry that subserves reward and adaptive behaviors contributes to OUD development as well as the vulnerability to relapse during abstinence. Serotonin (5-HT) neurotransmission confers modulatory control over this circuitry, particularly through the 5-HT_{2C} receptor (5-HT_{2C}R) (for review) (Cunningham and Anastasio, 2014). Selective 5-HT_{2C}R agonists, which lack intrinsic abuse liability, curb self-administration of psychostimulants (eg, cocaine, nicotine) as well as associated sensitivity to drug-associated cues and impulsivity in preclinical studies (for review) (Cunningham and Anastasio, 2014). These data sparked a clinical trial that demonstrated that the FDA-approved anti-obesity medication and first-in-class 5-HT_{2C}R agonist lorcaserin (Belviq) increased abstinence from smoking (Shanahan *et al*, 2016). Furthermore, the efficacy and safety of lorcaserin for cocaine use disorder is presently under study (https://clinicaltrials.gov/ct2/show/NCT03007394). We have recently demonstrated the efficacy of lorcaserin to suppress intake of the semisynthetic opioid oxycodone as well as associated cue reactivity in both abstinence and extinction-reinstatement paradigms, effects which were blocked by the selective 5-HT_{2C}R antagonist SB242084 (Neelakantan *et al*, 2017). Lorcaserin pretreatment also decreases opioid-induced behavioral sensitization and the physical signs of naloxone-