(AAVs). The recent generation of the Cre-inducible Cas9 mouse allowed for the delivery of a single AAV containing the gRNA, tracrRNA, and Cre. This model can be used to delete genes of interest in discrete populations of neurons in the adult brain of laboratory animals with relative ease. This model illustrated efficient knockout in their gene of interest by 80% in the prefrontal cortex (Platt *et al*, 2014). The ability of CRISPR to target more than one gene simultaneously is particularly useful for investigating the role for gene × gene interactions in psychiatric illness. In addition, CRISPR-mediated HDR, when used in combination with specifically designed DNA templates, can replicate alleles that influence the risk of psychiatric illness or, ultimately, to correct risk-modifying alleles.

CRISPR is an efficient, precise, and versatile genome editing tool. Nevertheless, the technology is still in its infancy and further maturation is necessary before its full potential is realized. For example, CRISPR-mediated HDR is inefficient in post-mitotic cells, making it difficult to insert disease-relevant mutations into the neurons of laboratory animals. Although CRISPR is highly specific, it can suffer from off-target actions, a liability that is being advanced in new iterations of the technology (Slaymaker *et al,* 2016). Nevertheless, CRISPR and other genome editing technologies are poised to markedly increase our understanding of the biological underpinnings of psychiatric illnesses and to ultimately advance therapeutic discovery.

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Aggression Addiction and Relapse: A New Frontier in Psychiatry

There is an increased risk for abnormal or pathological aggression in individuals suffering from psychiatric disorders. Aggression is commonly ethologically demarcated as either appetitive or reactive, each with its own behavioral characteristics, functionality, and neural basis that may transition from adaptive to maladaptive depending on genetic and environmental factors. One type, pathological appetitive aggression, is hypothesized to result from excessive activation of evolutionary conserved reward circuits, which also mediate the rewarding effects of addictive drugs. Indeed, inappropriate appetitive aggression shows core features of addiction: aggression is often sought despite immediate or long-term adverse consequences, and relapse (recidivism) rates among violent offenders are as high as relapse rates in drug addiction. Despite these similarities, pathological aggression seeking has not been commonly incorporated into the conceptual framework of addiction and psychiatric disorders. Such a reconceptualization may positively impact therapeutic strategies to prevent pathological aggression and decrease recidivism (relapse) rates after incarceration or inpatient treatment.

Seminal studies from the Miczek laboratory established that aggressive mice will perform operant tasks to attack subordinate intruders (Fish *et al*, 2002), in a manner akin to rodents self-administering addictive drugs. In addition, we recently adapted the conditioned place preference (CPP) procedure, commonly used to study the rewarding effects of drugs, to study aggression reward. We showed that innately aggressive male CD-1 mice form a preference to an aggression-paired context (Golden *et al*, 2016), and as with addictive drugs, this preference persists over time (Golden *et al*, 2017a). However, self-administration and CPP are also readily observed with non-drug rewards like food and water, and therefore, are not sufficient metrics to conclude that a rewarding stimulus is being sought maladaptively or compulsively. In models of compulsive drug addiction, those criteria have been operationalized as drug self-administration, despite adverse consequences, high motivation to seek the drug, and relapse to drug seeking during abstinence (Deroche-Gamonet *et al*, 2004). On the basis of this consideration, we used established animal models of drug addiction and relapse to characterize motivated aggression in a population of CD-1 male mice (Golden *et al*, 2017b).

We reported several findings: (1) ~70% of aggressive mice learned to lever-press for aggressive interactions, (2) using models of relapse after forced abstinence, punishment-induced abstinence, or choice-based voluntary abstinence (Venniro *et al*, 2016), we showed that relapse to aggression seeking persists long after the last aggressive act, and (3) cluster analysis of the aggression-related measures identified a subset of mice that met

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.

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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,'