to psychoses such as schizophrenia as well as to autism (reviewed in Sokolov *et al* (2017)). Moreover, the cerebellum is widely connected with multiple cognitive regions of the neocortex (eg, Strick *et al* (2009)), with lateral cerebellar regions preferentially connected to frontal neocortical areas, both of which are expanded in the primate lineage. Despite this evidence, little is known about the putative cognitive signals that reach the cerebellum at the cellular physiological level.

In particular, the cerebellar input layer that receives external information consists of granule cells. Cerebellar granule cells receive only a few inputs that can arise from a multitude of places throughout the brain and sensory periphery, indicating they may be well positioned to receive and transmit an array of non-sensorimotor signals to the cerebellum. Because of the longstanding technical difficulties arising from their small size and dense packing, however, granule cell responses have not been recorded during cognitive tasks.

We recently performed two-photon calcium imaging in ensembles of individual cerebellar granule cells during conditioning tasks where mice learned to expect upcoming rewards (Wagner *et al*, 2017). In one such task, thirsty mice used their forepaw to move a small handle forward for delayed receipt of a water reward. Surprisingly, some granule cells preferentially responded to expected or unexpected rewards, or to the omission of expected rewards. Other cells selectively encoded the cognitive state of expectant waiting for an upcoming reward. Multiple experiments and analyses indicated that these reward signals were unexplained by motor signals such as licking or body movement. Granule cell reward signals were present in multiple different reward-related behavioral tasks, and emerged over the course of task learning.

These results raise a host of new questions. Foremost, it will be critical to understand the origin of reward-related signaling in the cerebellum. Anatomical tracing did not reveal direct input to the cerebellar cortex from midbrain dopamine cells like those of the ventral tegmental area that are known to convey reward signals (Cohen *et al*, 2012). On the other hand, the cerebellar regions we studied received robust input from the pontine nuclei, which relay projections to cerebellum from many regions of the neocortex (Strick *et al*, 2009), which is a prime candidate for further study. As important for future work will be determining how the cerebellum uses cognitive signals in its own computations, and what role any cerebellar cognitive output has in downstream circuits like those of the cortex. This would help determine whether cerebellar output could be a translational target for schizophrenia or psychosis. Integrating cerebellar circuits into the brain's broader reward-related computations may help to shed light on the mechanisms of cerebellar involvement in cognitive processes.

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The Promise of Genome Editing for Modeling Psychiatric Disorders

A sizeable fraction of the risk for psychiatric illness can be attributed to the genes that we inherit (Polderman *et al*, 2015). The challenge of identifying gene variants that influence vulnerability to psychiatric illness, which often operate only after interacting with environmental risk factors, is daunting. Nevertheless, advances in genomics are yielding new insights into these risk-modifying gene variants.

A major breakthrough that will facilitate our understanding in this area is the development of CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats) (Cong *et al*, 2013; Jinek *et al*, 2013); Heidenreich and Zhang, 2016). CRISPR technology utilizes a bacterial borne RNA-guided DNA nuclease defense mechanism to elicit specific gene mutations. Scientists have exploited the mechanism by which bacteriophages transcribe part of a pathogenic genome into guide RNAs (gRNAs) that, as their name implies, serve to guide the endonuclease, Cas9, to cut the DNA of the invading pathogen. The resulting DNA breaks are repaired by either non-homologous end joining (NHEJ) or homology-directed repair (HDR). The NHEJ pathway efficiently ligates broken ends of DNA strands, but often introduces nucleotide insertions or deletions resulting in frameshift mutations that can disrupt expression of the repaired gene. The less efficient but higher fidelity HDR pathway includes a specific DNA sequence to be inserted at the break site.

Using CRISPR-mediated NHEJ, mutations in genes of interest can be generated efficiently, thus reducing the time between gene discovery and investigation of mechanisms of action. Delivery of the CRISPR components (gRNA, tracrRNA, and Cas9) to cells or model organisms is efficient and can, for example, be accomplished through the transfection of mRNA or delivery via adeno-associated viruses

(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