

novel lists of overlapping or functionally related genes through statistical or bioinformatic analysis.

With the collapse of R&D in mental health by pharmaceutical companies, convergent/integrative 'omics' approach represents a unique opportunity for the scientific community to mine existing datasets as well as data from experimental and clinical models, to prioritize targets for the psychotropic medications of the future.

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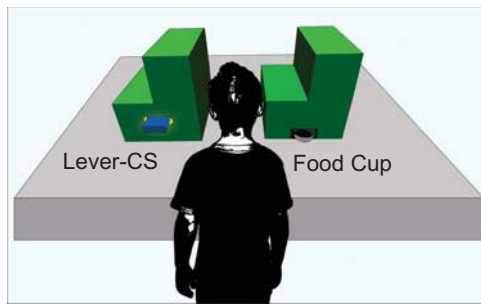
## A Translational Model to Assess Sign-Tracking and Goal-Tracking Behavior in Children

Cues or stimuli in the environment can guide behavior in adaptive ways, bringing one in close proximity to valuable resources (for example, food). For some individuals, however, environmental stimuli may acquire inordinate control over behavior and elicit maladaptive tendencies or intrusive thoughts. Thus, the way an individual responds to cues in the environment may be a key determinant of psychopathology. For example, in addiction, relapse is most often triggered by exposure to stimuli (for example, paraphernalia or places) previously associated with the drug-taking experience, and people suffering from post-traumatic stress disorder (PTSD) experience extreme anxiety or flashbacks upon exposure to stimuli reminiscent

of a traumatic event. Furthermore, in patients with schizophrenia, psychosis is believed to result from aberrant attribution of motivational salience to environmental stimuli (Kapur, 2003). Such stimuli are able to elicit complex emotional and motivational states via Pavlovian learning, and in recent years we have come to rely on an animal model to better understand these processes (for review see Robinson *et al*, 2014).

When exposed to a Pavlovian conditioning paradigm wherein the presentation of a lever (conditioned stimulus, CS) is followed by delivery of a food reward (unconditioned stimulus, US), some rats, termed 'goal-trackers' (GT), attribute *predictive value* to the lever-cue and go to the location of food delivery upon cue presentation. Others, termed 'sign-trackers' (ST), also attribute *incentive salience* to the lever-cue, as evidenced by their approach towards the cue and the ability of the cue alone to act as a reinforcer (for review see Robinson *et al*, 2014). That is, for ST the reward cue attains excessive incentive motivational value and gains inordinate control, leading to maladaptive behaviors. Indeed, relative to GT, ST have also been shown to be more impulsive, more likely to exhibit cue-induced relapse to drug-seeking behavior after relatively little drug exposure, and more susceptible to abnormal fear responses upon exposure to aversive stimuli (for review see Robinson *et al*, 2014). Thus, examining the translational relevance of the sign-tracker/goal-tracker model may prove critical to our understanding of a number of cue-motivated psychopathologies, including impulse control disorders, addiction and post-traumatic stress disorder.

To-date, little research has directly examined sign- and goal-tracking behavior in humans (Garfalo and di Pellegrino, 2015), and, to our knowledge, none with children. Due to the delayed development of the prefrontal cortex (Casey *et al*, 2000), children may be more likely to exhibit sign-tracking behavior. Indeed, the lack of cortical control and associated attentional deficits and impulsive behavior



**Figure 1.** Pavlovian conditioning apparatus and resultant behavior. The Pavlovian conditioning apparatus consists of two child-friendly plastic Lego boxes. The CS box (left) contains a lever, which illuminates and extends from the box. The US box (right) contains a small metal tray into which candy is dispensed. The boxes are powered using an Arduino program controlled by a researcher on a laptop using MATLAB. For each trial, the lever-CS illuminates and extends for 8 s, then darkens and retracts back into the box. Immediately upon CS retraction, the US box dispenses one piece of candy. Subjects are exposed to 4 blocks of 10 trials each. Following each trial is an intertrial interval (ITI) period, lasting 8, 16, 24 or 32 s (randomly chosen). The number of contacts with the lever-CS and US food cup, and the latency with which these occur during CS presentation are all recorded by the MATLAB program. Responses during the ITI are also recorded. Upon completion of each block the children are given a 45-second break.

evident in children is akin to that characteristic of sign-trackers in the animal literature (for review see Fligel and Robinson, 2017; see also Koshy Cherian *et al*, 2017). Capturing individual variation in cue-motivated behaviors in children may therefore provide a means to identify risk profiles for psychopathology early in life and thus offer earlier opportunities for intervention. In this regard, we have developed a novel apparatus to investigate sign-tracking and goal-tracking behaviors in children. The Pavlovian conditioning paradigm that we utilize is similar to that used in rodents (Figure 1) and consists of paired presentations of a lever (CS) with the delivery of candy (US). As in the animal paradigm, the children are allowed to freely move and manipulate the apparatus, and interaction with the lever-CS and candy tray are recorded. Using this paradigm, we have been able to observe both sign- and goal-tracking behavior (data not shown; to be published in a full-length manuscript). Ongoing studies are optimizing the behavioral output measures being assessed and examining the relationship between the propensity to exhibit a sign- or goal-tracking response and the development of psychopathology, including substance abuse and overeating. It is hoped that this translational model will prove invaluable for parsing

the myriad of factors (for example, developmental, genetic, environmental, neurobiological) that render an individual more susceptible to cue-motivated psychopathologies and lead to novel therapeutic interventions.

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## The Role of Mitochondrial Glutamate Metabolism in Cognitive Development and Disease

Glutamate metabolism serves a critical role in a variety of processes that regulate cognition, including excitatory synaptic transmission, energetics, and biosynthesis. We and others have recently identified a new genetic disorder of human cognitive development that involves a mitochondrial enzyme with a role in glutamate metabolism (Celis *et al*, 2015; Lobo-Prada *et al*, 2017; Ouyang *et al*, 2016). Investigation of this new neurogenetic disease promises valuable insight into the multiple functions of mitochondria and glutamate metabolism in brain development and cognition.

Through linkage mapping to chromosome 16 and high-throughput sequencing, mutations in a mitochondrial enzyme, glutamate pyruvate transaminase 2 (GPT2), have been identified in pedigrees affected by intellectual disability and postnatal microcephaly (Celis *et al*, 2015; Lobo-Prada *et al*, 2017; Ouyang *et al*, 2016). Also, a subset of patients has a progressive motor dysfunction, termed spastic paraplegia (Ouyang *et al*, 2016).