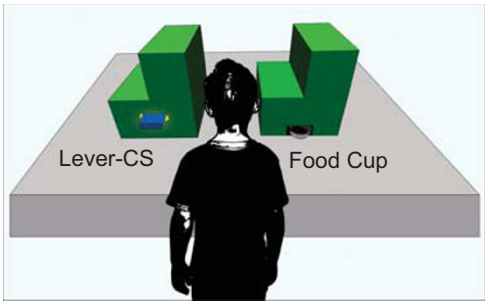

Figure 1. Pavlovian conditioning apparatus and resultant behavior. The Pavlovian conditioning apparatus consists of two child-friendly plastic Lego boxes. The CS box (left) contains a lever, which illuminates and extends from the box. The US box (right) contains a small metal tray into which candy is 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 o 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 Flagel 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).

We reported two mutations, a missense (p.Pro272Leu) and a nonsense (p.Arg404*), that lead to enzyme loss-of-function. Several other mutations have been discovered, all of which appear to be loss-of-function: p.Ser153Arg (Celis *et al*, 2015); p.Gly96Arg (Lobo-Prada *et al*, 2017); p.Arg134Cys and p.Val479Met (compound heterozygote) (Kaymakçalan Çelebiler *et al*, 2017); and p.Gly412* (Pagnamenta *et al*, 2015). Most patients present similar clinical phenotypes, including intellectual disability and postnatal microcephaly, and the inheritance pattern is autosomal recessive. As postnatal microcephaly is a condition of attenuated brain growth that is limited to the early postnatal period, the underlying causes most likely involve mechanisms of brain development such as neuronal arborization, synaptogenesis, and gliogenesis (van Dyck and Morrow, 2017).

GPT2 reversibly transfers an amino group from glutamate to pyruvate yielding alanine and α-ketoglutarate. Subcellular localization of GPT2 to mitochondria shapes its function and control over its substrates. Further, this localization suggests a prominent role in synapses, which are enriched for mitochondria. Through expression of mutated GPT2 proteins in HeLa cells, we confirmed that mutations cause loss of enzyme activity, along with reduced protein levels. We also tested for protein levels and activity in the developing mouse brain. The highest peak of expression and corresponding activity was observed postnatally, coinciding with an active time of circuit development (Ouyang *et al*, 2016).

Given the loss-of-function of the mutations, a *Gpt2*-null mouse serves as an excellent model. *Gpt2*-null mice have diminished postnatal brain growth, recapitulating microcephaly in humans. *In vitro*, dissociated primary hippocampal cultures show reductions in synapse count, suggesting defective synaptogenesis. As GPT2 is involved in several metabolic pathways, we applied metabolomics to whole-brain tissue obtained from wild-type and *Gpt2*-null mice. There was a marked decrease in alanine and several of the tricarboxylic acid cycle (TCA) intermediates, accompanied by elevated levels of several amino acids (Ouyang *et al*, 2016). The overall metabolic signature of GPT2 deficiency points to defects in biosynthesis and bioenergetics.

In conclusion, the mutations in GPT2 present new insights into neurometabolism and its relevance to mechanisms for neurological and cognitive disorders. Studies into the function of the enzyme in animal models may have broad therapeutic value and produce preventive strategies involving alteration of metabolism, such as through diet modification or co-factor supplements.

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Cross-Species Neurophysiological Biomarkers of Attentional Dysfunction in Schizophrenia: Bridging the Translational Gap

There has been a fundamental failure to translate preclinically-supported compounds into novel psychiatric treatments. That failure has been driven by a lack of suitable animal models of disease with concomitant biomarkers of neural-circuit function across species (Young and Geyer, 2015). Electroencephalographic (EEG) biomarkers of behavioral performance are direct assays of neural system functioning with compelling opportunity for cross-species translation (Featherstone *et al*, 2015). The recently developed 5-choice continuous performance test (5C-CPT) provides an example for integrating behavioral outcomes and neurophysiological biomarkers. Designed to quantify cognitive control (attention) and response inhibition in rodents and humans, the 5C-CPT has demonstrable cross-species validity including; (a) 36 h sleep deprivation-induced deficits; (b) amphetamine-induced improvement; (c) parietal requirement for performance from human fMRI and rodent lesion studies; and (d) vigilance decrement observations across time (Cope and Young, 2017). Importantly, this task is also clinically sensitive as patients