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

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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

with schizophrenia exhibit deficient performance (Young *et al*, 2017).

Until recently, it was unclear whether attentional deficits in schizophrenia patients corresponded to altered EEG biomarkers. Early evidence suggested attentional deficits in patients with abnormal EEG markers, with the latter also seen in unaffected relatives. This effect was limited however, and focused around sensory event related potentials (ERPs; P1 and N1), perhaps as a result of using the degraded stimulus CPT that places demands on perceptual processing. In contrast to other widely used human continuous performance tasks, the 5C-CPT places less of a burden on perception or other cognitive domains. In schizophrenia patients performing the 5C-CPT, we identified decreased amplitude of N2 and frontal non-target P3 ERPs compared with healthy subjects (Young *et al*, 2017). We have also observed that poorly performing healthy subjects exhibited: (1) reduced frontal non-target P3 amplitudes; (2) had higher response disinhibition; (3) this deficit was reversible using the frontally specific dopamine degradation blocker tolcapone; which (4) reduced the response disinhibition of these subjects (Bhakta *et al*, Accepted). Hence, the reduced frontal non-target P3 of healthy humans and their response inhibition was remediated with a frontal-specific treatment. Human and animal EEG studies have identified activation decrements in similar regions within the attentional network, concurrent with regions identified via fMRI studies. Studies are currently ongoing to determine whether mice similarly exhibit frontal non-target P3 EEG measures during 5C-CPT performance.

Future studies utilizing the 5C-CPT and other novel cross-species behavioral assays (eg, (Bismark *et al*, 2017)) aim to bridge the translational gap that limits the development of CNS therapeutics. These new tests also enable cross-species assessment of the contribution of genetic disease models to the attentional and neurophysiological abnormalities observed in neuropsychiatric patients. With greater predictive validity, drugs targeting such cognitive dysfunction are likely to prove more efficacious in psychiatric conditions. Thus, the attentional/EEG work in the 5C-CPT is an example of the ability to bridge the translational pharmacotherapeutic development divide.

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