Commentary

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The Translational Utility of Circuit-Based Manipulations in Preclinical Models

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In the current issue of *Biological Psychiatry: Global Open Science*, Tranter *et al.* (1) provide a recent example of the insights being generated from preclinical models of complex neuropsychiatric disorders. Their study focuses on the well-described neonatal phencyclidine (PCP) rat model and highlights how glutamatergic projection neurons in the ventromedial orbitofrontal cortex (vmOFC) mediate specific changes in reversal learning. They replicate established reversal learning impairments in this model; however, they show that inhibiting activity of vmOFC glutamatergic neurons can ameliorate PCP-induced dysfunction. Conversely, activation of these same neurons in saline-treated rats produces a similar phenotype to PCP-treated rats. Having shown that modulation of vmOFC activity can both induce and reverse cognitive deficits, the authors state that "pharmacological or neuromodulatory strategies aimed at normalizing vmOFC activity represent a potential therapeutic target for disrupted cognitive flexibility in adults with schizophrenia."

A strength of this study is the sophisticated behavioral approach, complemented by computational analysis, to determine exactly where the deficits lie and what cognitive processes are impacted. This approach not only puts cognitive functions under the microscope but enhances the capacity for direct comparisons with changes observed in patients. Paired with specific neural manipulations, this design gives us insight into exactly which neural processes drive these changes. In this case, Tranter *et al.* (1) not only show that they can replicate the PCP-induced deficit in control animals but that they can also rescue function with the inverse treatment. This powerful demonstration shines a spotlight on the vmOFC as the center of both PCP-related changes and a region that is critical for optimal cognitive flexibility, even in healthy animals.

There are, however, a multitude of practical limitations to achieve positive clinical endpoints. With regard to preclinical studies using rodent models, there are many remaining unknowns. For example, it is not clear if disrupting and/or restoring glutamatergic activity is causative or is a downstream consequence of upstream pathology. Other studies in this model suggest that dysfunction in the GABAergic (gamma-aminobutyric acidergic) interneuron control of glutamatergic outputs may be causative, which the authors also support. Optimally, interventions should aim to target the causative pathology, and therefore future studies should determine if manipulation of the OFC GABAergic systems in this model would be sufficient to replicate the observed effects. Second, advancing this work further will require identifying which vmOFC projections are driving these outcomes. The vmOFC includes two distinct subregions of the OFC (2), with the functional roles of these subregions being distinct (2). For example, studies inactivating the medial portion of the OFC have shown loss-specific outcomes (3,4), with reward learning more influenced by ventrolateral subareas of the OFC (4). Both the medial and ventral OFC subregions are known to project widely throughout the brain (5), including to striatal areas fundamentally involved in decision-making processes and schizophrenia [i.e., the dorsomedial striatum and nucleus accumbens (6)]. Together, this suggests that potentially the less well studied ventral portion of the OFC may be an area of particular interest moving forward.

The outcomes of this study continue to advance our understanding of developmental manipulations and their potential role in schizophrenia. However, it is important to consider the heterogeneity and complexity of schizophrenia when considering the relevance of our models. For example, the neonatal PCP rat model is induced using an NMDA receptor antagonist. Although PCP is far from selective, developmental deviations are likely to derive from alterations in glutamatergic transmission. Therefore, the findings of Tranter *et al.* (1), showing that altering glutamatergic transmission can be beneficial, are not necessarily surprising. It would be interesting to determine if manipulations of this same neuronal population can ameliorate other behavioral differences observed in the PCP model, such as impairments in delayed spatial alternation (7). Nevertheless, a more important translational outcome would be for this same approach to demonstrate positive outcomes in other models of schizophrenia (e.g., ones derived from altering differing processes or transmitter systems). Establishing convergent pathologies across models would increase the likelihood that beneficial outcomes can be realized in heterogeneous clinical populations.

In the context of driving positive outcomes for people with schizophrenia, preclinical approaches remain the bedrock of discovery science. Tranter *et al.* (1) identified a clear region of interest that may underlie the deficits in reversal learning and win-stay commonly observed in schizophrenia (8). There are a few things to consider moving forward. First, the temporally controlled fashion in which optogenetic manipulations are conducted is limited in its capacity for direct translation. In this study, inhibition was applied after informative feedback was provided. Any treatment targeting this area in people would favor sustained effects. It would be interesting to see if inhibiting the area preceding choice or even for longer blocks of time can successfully improve performance (or at least does not impair it). Second, whether restoring vmOFC function alleviates cognitive problems more broadly given the specific and nuanced approach of preclinical cognitive testing is important. If this outcome is so specific as to not significantly impact daily functioning for these individuals, then it is unlikely to realize

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clinical success. More importantly, any potential intervention would need to show that it does not further impair cognition in other domains, regardless of efficacy on one cognitive function. Finally, the clinical progression of these deficits in schizophrenia is complex. For example, deficits in reversal learning and win-stay behavior may not be present early in the disorder, or at least are less severe (8,9). As with all preclinical advances, the translational gap is large. However, research such as this study from Tranter *et al.* brings us a step closer to understanding the complex interactions between cognitive deficits associated with developmental perturbations and specific neural interventions that can rescue function in adults.

In conclusion, although researchers need to remain aware of the caveats and limitations of preclinical models of disorders such as schizophrenia, the ever-increasing tools available in rodents are helping us to untangle and dissect the neural processes behind cognitive deficits. Future studies using these tools will be able to build on this research by targeting different neuronal populations (e.g., GABAergic interneurons), specific output pathways (e.g., dorsal and ventral striatum), and examining different temporal windows. Together, these approaches hold the key to facilitating the leaps forward in our understanding of the brain and severe mental illnesses that are necessary to discover efficacious approaches in the clinic.

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Article Information

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