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Circuit based interventions for the treatment of behaviors relevant to schizophrenia

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Aberrant hippocampal structure and function has been implicated in a variety of psychiatric disorders; however, the specific hippocampal circuits contributing to discrete symptom domains have not been extensively evaluated. The hippocampus has long been associated with the consolidation of declarative memory where dysfunction leads to amnesia (1); however, it is also intimately associated with emotion and stress responsivity where aberrant activity is associated with disorders such as schizophrenia and depression (2, 3). Based on anatomical connectivity and gene expression analyses, there is increasing evidence that the rodent hippocampus possesses functionally distinct subregions along its dorsal/ventral axis (analogous to anterior/posterior axis in primates) (4). Thus, the dorsal hippocampus receives multimodal sensory information from cortical regions, whereas the ventral hippocampus is connected more intimately with limbic structures, such as the prefrontal cortex, nucleus accumbens, amygdala, and the hypothalamic-pituitary-adrenal axis. To examine the contribution of these discrete circuits to behavior required advances in the field of neuroscience, such as optogenetics and Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), which allow the modulation of defined neuronal populations to examine the role of discrete brain circuits in health and disease (5).

In the current issue of *Biological Psychiatry*, Kahn et al. (6) present a comprehensive and elegant study performing circuit-based interventions to examine the involvement of discrete hippocampal regions in a mouse model of 22q11.2 deletion syndrome. Microdeletions in 22q11.2 are associated with autism-spectrum disorder and attention deficit/hyperactivity disorder in children and confer a high risk for schizophrenia in adolescence and adulthood, with ~30% of patients developing the disorder, making it one of the strongest genetic risk factors for schizophrenia (7). Based on clinical observations that impairments in social cognition dramatically alter quality of life in patients with 22q11.2, the hippocampal circuits contributing to social memory were examined (6). Using chemogenetic approaches, it was demonstrated that both activation and inhibition of the ventral hippocampus disrupted social memory in control mice. This is an important observation, consistent with similar reports demonstrating that neuronal activity in the brain is tightly regulated to permit appropriate behavioral responses. Indeed, this is likely why relatively minor imbalances in excitation/

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inhibition can lead to severe behavioral symptoms in psychiatric disorders. Moreover, it provides a powerful rationale for the use of animal models in neuroscience research where the effects of circuit-based manipulations or novel pharmacotherapies can be conducted in the context of the pathological alterations observed in these disorders. Indeed, numerous studies have demonstrated divergent and sometimes opposite effects between control animals and rodent models. For example, antipsychotic drugs have been demonstrated to increase acutely dopamine neuron activity in control rats but decrease activity in models of dopamine hyperactivity (likely due to depolarization blockade) (8). Thus, these data reinforce the importance of appropriate animal models when examining neuronal systems in the context of disease-related pathophysiology.

Given that robust deficits in social memory were observed following both activation and inhibition of the ventral hippocampus, it is important to understand the pathological alterations in ventral hippocampal activity that could underly the social memory deficit in the 22q11.2 deletion model. Using functional imaging of voltage sensitive dyes in acute brain slices, Kahn et al. present convincing data, consistent with human imaging studies in schizophrenia, demonstrating ventral hippocampal hyperexcitability in the 22q11.2 deletion model (6). These data suggest that aberrant ventral hippocampal activity may drive deficits in social memory. To confirm this directly, chemogenetics were utilized to selectively reduce activity in pyramidal neurons of the ventral hippocampus. Interestingly, reducing ventral hippocampal excitability in the 22q11.2 model was sufficient to reverse this striking behavioral deficit in social memory. In addition, a powerful approach was performed using two different inhibitory DREADDs (a muscarinic receptor-based DREADD activated by CNO and a kappa-opioid receptor DREADD activated by salvinorin b) to demonstrate divergent behavioral responses to dorsal or ventral hippocampal inactivation. Specifically, acute chemogenetic inhibition of the ventral hippocampus was able to rescue selectively deficits in social behavior, whereas inhibition of the dorsal hippocampus only affected spatial memory. This is incredibly impactful as it demonstrates that while circuit dysregulation may extend throughout the entire hippocampus, behavioral deficits are associated with discrete hippocampal subregions. Indeed, this is consistent with recent studies demonstrating that discrete behavioral alterations, observed following a developmental disruption that models aberrant hippocampal function in schizophrenia, are attributable to discrete neuronal projections from the ventral hippocampus (9). Specifically, using chemogenetics to manipulate discrete projections from the ventral hippocampus to the nucleus accumbens (NAc) or prefrontal cortex (mPFC) it was demonstrated that inhibition of the pathway to the NAc, but not the mPFC, normalized aberrant dopamine neuron activity (thought to contribute to psychosis) and deficits in reversal learning. Conversely, inhibition of the pathway to the mPFC selectively improved a higher order cognitive function, extradimensional set shifting (9). Taken together, these studies demonstrate that specific behavioral deficits in psychiatric disorders may be associated with aberrant activity within discrete hippocampal subregions or circuits. It is important to note that the neuronal control of behavior is not solely attributable to the firing rate of individual hippocampal neurons. Rather, analysis of neuronal activity across larger spatial scales has revealed crucial roles for coordinated activity throughout the nervous system (for review see (10)). Indeed, many

cognitive functions require coordinated interactions between a large number of neurons distributed within and across multiple brain regions, including the hippocampus.

To summarize, the manuscript by Kahn et al. (6) advances our understanding of the role of discrete hippocampal circuits in distinct symptom domains associated with schizophrenia, setting itself apart from earlier pioneering studies that were limited by the availability of suitable tools to target defined neuronal populations. Specifically, the demonstration that both activation and inactivation of ventral hippocampal neurons produces deficits in social memory reinforces the utility of animal models with disease-related pathophysiology. More importantly, the observation that rodent models of 22q11.2 deletion display ventral hippocampal hyperactivity provides important information suggesting that targeting aberrant hippocampal activity may be a novel therapeutic approach for social memory deficits in schizophrenia. Indeed, using advanced chemogenetic approaches, it was demonstrated that inhibition of ventral (but not dorsal) hippocampal neurons was sufficient to reverse behavioral deficits in social memory in the 22q11.2 model. This is consistent with data from other rodent models displaying circuit-based alterations and aberrant hippocampal activity (9). Taken together, this influential study significantly advances our understanding of the role of discrete hippocampal circuits in health and disease and provides information relevant to circuit-based interventions in schizophrenia.

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