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REVIEW

NEURAL CIRCUIT DYSFUNCTION IN SCHIZOPHRENIA: INSIGHTS FROM ANIMAL MODELS

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Abstract—Despite decades of research, the neural circuit abnormalities underlying schizophrenia remain elusive. Although studies on schizophrenia patients have yielded important insights they have not been able to fully reveal the details of how neural circuits are disrupted in the disease, which is essential for understanding its pathophysiology and developing new treatment strategies. Animal models of schizophrenia are likely to play an important role in this effort. Such models allow neural circuit dysfunction to be investigated in detail and the role of risk factors and pathophysiological mechanisms to be experimentally assessed. The goal of this review is to summarize what we have learned from electrophysiological studies that have examined neural circuit function in animal models of schizophrenia. Although these studies have revealed diverse manifestations of neural circuit dysfunction spanning multiple levels of analysis, common themes have nevertheless emerged across different studies and animal models, revealing a core set of neural circuit abnormalities. These include an imbalance between excitation and inhibition, deficits in synaptic plasticity, disruptions in local and long-range synchrony and abnormalities in dopaminergic signaling. The relevance of these findings to the pathophysiology of the disease is discussed, as well as outstanding questions for future research.

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Key words: schizophrenia, neural circuits, animal models, electrophysiology, synchrony, synaptic plasticity.

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INTRODUCTION

Schizophrenia is one of the more devastating psychiatric illnesses, with a lifetime prevalence of roughly 1% and age of onset between 18 and 25 years. The symptomatology of the disease is complex and heterogeneous, consisting of positive symptoms (hallucinations and delusions, disorganized speech and behavior), negative symptoms (flattened affect, social withdrawal, avolition and anhedonia) as well as cognitive deficits (including impaired attention, working memory, executive function and verbal memory; see Mesholam-Gately et al. (2009)). Although the positive and negative symptoms form the core diagnostic features of the disease, the cognitive deficits are increasingly seen as critical to daily life functioning. However, whereas the

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Abbreviations: ASSR, auditory steady-state response; DA, dopaminergic; DISC1, disrupted in schizophrenia-1; GD, gestational day; LFP, local field potential; LTP, long-term potentiation; MAM, methylazoxymethanol acetate; MD, mediodorsal thalamus; MEG, magnetoencephalography; MIA, maternal immune activation; MMN, mismatch negativity; NMDAR, N-methyl-D-aspartate receptor; NRG1, neuregulin 1; NVHL, neonatal ventral hippocampal lesion; PPI, prepulse inhibition; PV, parvalbumin; SWRs, sharp-wave-ripple events; SWS, slow-wave sleep; vHPC, ventral hippocampus; VTA, ventral tegmental area.

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positive symptoms can be treated with antipsychotics, the negative symptoms and cognitive deficits have proven more resistant to treatment. As a result the disease places an enormous burden on patients, their families and society as a whole. Developing new treatment strategies for schizophrenia will require a detailed understanding of the pathophysiology of the disease. Although subtle structural abnormalities can be detected in the brains of schizophrenia patients, no obvious pathology has been identified as, for example, in many neurodegenerative diseases (Harrison, 1999). Rather, it is becoming increasingly clear that schizophrenia is the result of abnormal neural development (Lewis and Levitt, 2002), likely culminating in the failure of neural circuits to form and function appropriately. However, despite important insights from patient studies, the nature of the neural circuit abnormalities underlying schizophrenia remains elusive. Efforts to further our understanding will likely benefit from studying animal models of the disease (Nestler and Hyman, 2010). A number of experimental techniques can be used in animal models that allow neural circuit function to be examined in much greater detail than is possible in patient studies. Animal models can also help examine the effects of identified risk factors for the disease, such as genetic mutations, on neural circuits or test specific hypotheses about the pathophysiology of the disease.

A number of different animal models of schizophrenia have been developed over the years, reflecting the various genetic and environmental risk factors and pathophysiological mechanisms that have been associated with the disease (Jones et al., 2011; Kvajo et al., 2012). All of these models have been characterized behaviorally and found to show disturbances reminiscent of the disease symptoms in some way (discussed in more detail below). In order to understand possible underlying mechanisms of these behavioral disturbances, many animal models have also been characterized in terms of neurochemistry as well as brain structure, both at the level of gross anatomy and neuronal morphology. Although such studies have yielded many important insights it is not always obvious how alterations in neurochemistry and structure will affect the *functioning* of a neural circuit, that is how it transmits and processes information and ultimately controls behavior. Neural circuit dysfunction is likely the proximal cause for behavioral abnormalities in animal models as well as disease symptoms in patients. For this reason, studies have also attempted to characterize neural circuit function in animal models of schizophrenia using various electrophysiological methods. The goal of this review is to summarize and discuss what has been learned from these studies. I will begin with a general introduction discussing the rationale for using animal models to study neural circuit dysfunction in schizophrenia and some practical considerations regarding the application of this approach. Findings from different schizophrenia models will then be summarized. Although the focus will be on electrophysiological studies, results from studies examining behavioral or structural abnormalities will also be included where appropriate. Finally, I will conclude by identifying some of the common themes emerging from these studies and discuss open questions for future research.

The role of animal models in schizophrenia research

The role of animal models in schizophrenia research can best be appreciated against the background of current knowledge about the causes of the disease. We know that both environmental and genetic risk factors, many of which have been identified, contribute to increased risk for developing the illness. It has also become clear that schizophrenia is a neurodevelopmental disorder (as opposed to a neurodegenerative one) that ultimately leads to dysfunctional neural circuits in adulthood (Lewis and Levitt, 2002; Fatemi and Folsom, 2009). The exact nature of this neural circuit dysfunction, however, is less clear. Anatomical studies have revealed subtle changes in gross brain structure in patients, including enlarged ventricles and reduced cortical thickness, as well as alterations in cellular structure (Harrison, 1999; Volk and Lewis, 2010). Functional imaging studies have also revealed abnormalities in the activation of widely distributed brain networks both during rest and task performance (Barch and Ceaser, 2012; Uhlhaas and Singer, 2012); these have in many cases been directly correlated with the severity of disease symptoms. Nevertheless, these findings do not paint a complete picture of how neural circuits are disrupted in schizophrenia. We do not know, for example, whether and how the activity of individual neurons, or their interactions within and across brain regions, is affected in patients. This is in large part due to the fact that the available techniques to examine the structure and function of the human brain lack sufficient spatial and temporal resolution to examine neural circuits in detail. Yet such a detailed level of analysis will likely prove critical for fully understanding the pathophysiology of the disease as well as for developing new therapeutic strategies.

A major advantage of animal models is that they allow neural circuits to be examined in much greater detail than is possible in patient studies. Advanced imaging techniques have made it possible to reveal the fine structure of neurons and their synaptic connections. The activity of individual neurons or large neuronal populations can also be measured using standard electrophysiological methods or increasingly sophisticated imaging approaches. Importantly, these methods can be used to examine neural activity *in vivo* in the intact brain, including in behaving animals, thus allowing the function of neural circuits to be directly correlated with behavioral output. Optogenetic methods also make it possible to precisely manipulate neural activity in a temporally precise and cell-specific manner and thus gain a causal understanding of the contribution of neural circuits to behavior. All of these techniques, many of which have been developed over the last decade (Yizhar et al., 2011a,b; Deisseroth and Schnitzer, 2013; Berényi et al., 2014) have already led to major advances in our understanding of how various neural circuits mediate cognition and behavior. These methods are similarly poised to help unravel neural circuit