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REVIEW

USING HUMAN BRAIN IMAGING STUDIES AS A GUIDE TOWARD ANIMAL MODELS OF SCHIZOPHRENIA

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Abstract—Schizophrenia is a heterogeneous and poorly understood mental disorder that is presently defined solely by its behavioral symptoms. Advances in genetic, epidemiological and brain imaging techniques in the past half century, however, have significantly advanced our understanding of the underlying biology of the disorder. In spite of these advances clinical research remains limited in its power to establish the causal relationships that link etiology with pathophysiology and symptoms. In this context, animal models provide an important tool for causally testing hypotheses about biological processes postulated to be disrupted in the disorder. While animal models can exploit a variety of entry points toward the study of schizophrenia, here we describe an approach that seeks to closely approximate functional alterations observed with brain imaging techniques in patients. By modeling these intermediate pathophysiological alterations in animals, this approach offers an opportunity to (1) tightly link a single functional brain abnormality with its behavioral consequences, and (2) to determine whether a single pathophysiology can causally produce alterations in other brain areas that have been described in patients. In this review we first summarize a selection of well-replicated biological abnormalities described in the schizophrenia literature. We then provide examples of animal models that were studied in the context of patient imaging findings describing enhanced striatal dopamine D2 receptor function, alterations in thalamo-prefrontal circuit function, and metabolic hyperfunction of the hippocampus. Lastly, we discuss the implications of findings from these animal models for our present understanding of schizophrenia, and consider key unanswered questions for future research in animal models and human patients.

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Key words: schizophrenia, brain imaging, dopamine, striatum, thalamo-cortical circuit, hippocampus.

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Abbreviations: CNO, Clozapine-*N*-Oxide; D2R, dopamine D2 receptor; dlPFC, dorsolateral PFC; DTI, diffusion tensor imaging; fMRI, functional MRI; GPe, globus pallidus externa; GPi, globus pallidus interna; MD, medidorsal thalamus; MIA, maternal immune activation; MRI, magnetic resonance imaging; MSNs, medium spiny neurons; PCP, phencyclidine hydrochloride; PET, positron emission tomography; PV, protein parvalbumin; rsfMRI, resting state fMRI; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area.

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SCHIZOPHRENIA IS A MENTAL DISORDER DEFINED BY ITS SYMPTOMS

Schizophrenia is a highly heterogeneous disorder that is characterized by so-called positive, negative and cognitive symptoms. The positive symptoms – also known as psychotic symptoms – include hallucinations, delusions and disordered thought processes. The presence of positive symptoms is a prerequisite for diagnosis and as such, positive symptoms are most often the dominant characteristic generally associated with schizophrenia. However, most patients also exhibit impairments in a number of social, emotional and cognitive behaviors (Tandon et al., 2009). Such deficits are categorized as either negative symptoms (e.g. social withdrawal, anhedonia and deficits in incentive motivation), or cognitive symptoms (e.g. impairments in working memory, behavioral flexibility, verbal memory, reference memory and cognitive processing speed). Although negative and cognitive symptoms are not required elements of the diagnostic criteria, they are present in a high proportion of patients and can be particularly insidious for patient outcomes (Fenton and McGlashan, 1991; Green et al., 2000). While many patients respond to dopamine D2 receptor (D2R) blockers as a treatment for positive symptoms – albeit with the risk of profound side effects – negative and cognitive symptoms remain largely untreatable (Miyamoto et al., 2012). Moreover, normal social, emotional and cognitive processing are essential requirements for everyday functioning and success in society. These two realities largely explain the finding that the severity of cognitive and negative symptoms is more predictive of the long-term prognosis of patients than the severity of positive symptoms (Green, 1996; Green et al., 2000).

At present, the symptom-based diagnosis of schizophrenia lacks biological meaning due to limited knowledge of the underlying disease pathology. Yet understanding how schizophrenia pathology manifests itself in the symptoms of patients is essential for the development of both novel biomarkers for aiding diagnosis and for new or improved therapeutics that limit side effects. In the last 30 years, technical developments in human genetics, epidemiology, and brain imaging have provided significant advances in our knowledge of the biological processes that are affected in the disorder. In the following, we summarize the biological findings from schizophrenia patients that we found to be most reliable; propose a role for and discuss findings from translational animal models based on intermediate pathophysiological phenotypes observed in schizophrenia; and discuss the utility and future directions of such translational animal modeling approaches in illuminating the biological basis of schizophrenia.

BEYOND SYMPTOMS: THE BIOLOGY OF SCHIZOPHRENIA

Genetic studies have revealed a significant genetic component in schizophrenia

Twin studies had long been pointing to the importance of genetic factors in schizophrenia (Kallmann, 1946; Slater, 1953; Fischer et al., 1969), with findings suggesting a heritability of about 70% (Kendler and Diehl, 1993; Gottesman and Erlenmeyer-Kimling, 2001). Early behavioral genetic studies were followed up by gene association studies, which identified a variety of common allelic variants that associated with the disorder, although with very low penetrance (Rees et al., 2015). However, many of these associations could not be replicated due to low sample sizes (Tosato et al., 2005). The advent of whole genome studies using significantly larger sample sizes changed the picture by adding statistical power to some of the common variants and, in addition, by isolating rare variants with high penetrance (Stefansson et al., 2008; Schizophrenia Working Group of the Psychiatric Consortium, 2014). One well-replicated example of a rare mutation with high penetrance is the 22q11 deletion, which increases the risk for schizophrenia by about 30-fold (Karayiorgou et al., 1995). However, it is important to note that many high penetrance rare variants are not specific to schizophrenia and are also associated with phenotypes that go beyond the diagnostic symptoms of the disorder (Watson et al., 2014). The recent identification of *de novo* mutations that were isolated by studying family triads adds another level of complexity since they are genetic in origin but not inherited – although there may be a predisposition affecting the rates of *de novo* mutations (Xu et al., 2011, 2012). Nevertheless, these studies have clearly confirmed the existence of a strong genetic component to schizophrenia, and ongoing work aimed at uncovering novel gene associations and understanding the biological consequences of highly penetrant genetic mutations is an important and powerful avenue for future research.

Epidemiological studies have revealed that environmental factors also contribute to schizophrenia

Epidemiological studies have identified a number of environmental risk factors for schizophrenia, including prenatal infection, malnutrition, hypoxia, and exposure to stress or cannabis during early adolescence (Dean and Murray, 2005). Interestingly, many of these risk factors occur during development years before schizophrenia is diagnosed. These observations support the hypothesis that schizophrenia has a neurodevelopmental origin (Weinberger, 1987). One well-replicated example of a developmental risk factor is prenatal infection. Because a variety of pathogens – including influenza virus, toxoplasmosis, herpes simplex virus-2 and rubella – are capable of conferring risk, it is thought that the core risk factor is an activation of the maternal immune system (Brown, 2012; Canetta and Brown, 2012). Like other risk factors, however, prenatal infection is not specific for schizophrenia but increases risk for several other disorders, including autism, bipolar disorder and depression (Machon et al., 1997; Brown et al., 2014). In addition – as is the case with common genetic alleles – environmental risk factors only moderately increase the risk for developing schizophrenia. It is therefore thought that a combination of environmental and genetic factors is required for developing the disorder. Exploring the biological consequences