

## In Pursuit of the Pathogenesis and Pathophysiology of Schizophrenia: Where Do We Stand?

Schizophrenia is clearly a multifaceted disorder that must be considered from several perspectives (1). From the disease perspective, two central questions concern the pathogenesis and the pathophysiology of the illness. In terms of pathogenesis, what are the specific genetic and environmental factors that contribute to illness risk, and how do they act in combination to produce the biochemical and structural brain abnormalities that are characteristic of the illness? In terms of pathophysiology, how do these abnormalities alter brain function in order to give rise to the clinical syndrome that we recognize as schizophrenia? Viewed from this perspective, unraveling the pathogenesis of schizophrenia is critical for the discovery of means of prevention, and deciphering the pathophysiology of schizophrenia is essential for the identification of novel targets for therapeutic intervention. In this issue of the *Journal*, five articles highlight interesting data and innovative research strategies that address these two questions, while also revealing some of the many challenges that remain.

The pathogenesis of schizophrenia appears to involve a variety of risk factors present early in life, including maternal infection and malnutrition, place and season of birth, and labor-delivery complications (2). To this list, Brown and colleagues provide evidence that advanced paternal age at the time of birth of the offspring is a risk factor for adult schizophrenia. Their findings are consistent with several previous reports, including a recent study in a large Israeli birth cohort (3). A unique feature of the work of Brown and colleagues is their access to data from the Child Health and Development Study, which recruited a large cohort of pregnant women who received prenatal care from the Kaiser Foundation Health Plan between 1959 and 1967. The combination of this database and a rigorous research methodology contributed to the multiple strengths of this study, including offspring diagnoses obtained by standardized research interviews, the controlling of a number of potential confounders (e.g., maternal age), and the confirmation of the biological paternity of the offspring. Despite the robust nature of the findings, it is important to keep in mind that most individuals with schizophrenia are not born to fathers of advanced age, and that most offspring of older fathers do not develop schizophrenia. Although the reason for the association between advanced paternal age at birth and a higher risk for schizophrenia cannot be deduced from this study, the authors discuss several interesting possibilities, including an accumulation of de novo genetic mutations in the male germ cell line with increasing paternal age.

What are the relative contributions of these types of early life risk factors and the well-documented role of inheritance to the pathogenesis of schizophrenia? In order to address this question, van Erp and colleagues sought to determine the contributions of genetic predisposition and history of fetal hypoxia to hippocampal volume differences in patients with schizophrenia. Comparing probands with schizophrenia or schizoaffective disorder, their nonpsychotic full siblings, and a demographically similar group of healthy individuals with no family history of psychosis, van Erp et al. found that hip-

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pocampal volumes were smallest in the affected individuals, intermediate in their unaffected full siblings, and largest in the healthy comparison subjects, consistent with an inverse relationship between hippocampal volume and genetic load for schizophrenia. In addition, within the schizophrenia group, hippocampal volumes were smaller in those individuals who had experienced fetal hypoxia, whereas no such effect was found within the other two subject groups. Although this type of epidemiological study cannot directly assess pathogenetic mechanisms, the research strategy employed by the investigators does appear to exclude one possibility. Specifically, since the occurrence frequency of hypoxia-related insults was the same across all three subject groups, it seems unlikely that perinatal hypoxia is the consequence of a genetic predisposition for schizophrenia. Instead, the findings may be most consistent with an interactive “two-hit” model of genetic predisposition and fetal hypoxia. However, one limitation of the study, acknowledged by the authors, is that the relationship between hippocampal volume and history of fetal hypoxia was examined 40 years after the presumed hypoxic event took place, leaving open the possibility that other factors could account for the observed hippocampal volume differences.

Indeed, studies designed to explore the pathogenesis of brain abnormalities in schizophrenia are potentially confounded by a variety of factors that may be corollaries or consequences of the illness. Dickey et al. argue that the study of subjects with schizotypal personality disorder provides a means to circumvent these limitations. Their reasoning is that schizotypal personality disorder shares a common genetic diathesis with schizophrenia and that schizotypal personality disorder subjects exhibit some of the biological abnormalities present in individuals with schizophrenia yet generally lack exposure to psychotropic medications and other consequences of schizophrenia. Using structural magnetic resonance imaging (MRI), Dickey and colleagues examined two regions of interest in the superior temporal gyrus that are involved in auditory processing (Heschl's gyrus) and language processing (planum temporale). They observed a remarkable 21% unilateral (left-sided) gray matter volume difference in Heschl's gyrus, with no volume differences in the planum temporale in either hemisphere, in 21 male subjects with schizotypal personality disorder relative to 22 sex- and age-matched comparison subjects. The same group of investigators had previously found that first-episode subjects with schizophrenia exhibit bilateral Heschl's gyrus gray matter volume deficits and smaller left planum temporale volumes (4), perhaps providing an anatomical basis for the pathophysiological mechanisms that give rise to greater deficits in language processing in schizophrenia than in schizotypal personality disorder. However, an earlier study from the same group found that subjects with chronic schizophrenia exhibited smaller left planum temporale volumes with no Heschl's gyrus alterations in either hemisphere (5). Among the possibilities considered by the authors to explain these apparent discrepancies are methodological differences related to the reliability and sensitivity of tracing the regions of interest on MRI scans.

In order to address these types of methodological concerns, Ananth and colleagues used “optimized automated voxel-based morphometry” to examine differences in regional gray and white matter volumes in subjects with schizophrenia. The authors argue that this approach circumvents the potential problems of intra- and inter-observer bias in region of interest analyses, although the relative merits of voxel-based morphometry remain the subject of debate (6, 7). Ananth and colleagues detected significant volume differences in gray matter and CSF in subjects with schizophrenia, with the most robust differences in regional gray matter volumes observed in the mediodorsal region of the thalamus and in the occipitoparietal, premotor, medial and orbital prefrontal, and inferolateral temporal cortices. In contrast to the previous work cited in Dickey et al., Ananth and colleagues did not detect alterations in the volume of the superior temporal gyrus in the subjects with schizophrenia. A number of factors may contribute to this apparent discrepancy, including differences in methodology, the rela-

tively small size of each study, and the growing evidence that a number of factors (such as changes in body weight, alcohol intake, hormonal status, and psychotropic drug use [8]) can produce changes in MRI volume measurements. Furthermore, given the etiological heterogeneity of schizophrenia highlighted by the Brown et al. and van Erp et al. studies, and the observations by van Erp et al. that differences across individuals with schizophrenia in the presence of a particular etiological factor can affect MRI volumetric measures, different observations across studies are to be expected.

The multiple challenges that confront studies of the pathophysiology of schizophrenia may be reduced, at least somewhat, by investigations in more tractable systems, including healthy human volunteers. In this regard, Avila and colleagues found that the administration of ketamine, a noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, produced abnormalities in a smooth pursuit eye movement task that were similar to those present in individuals with schizophrenia and their relatives. Thus, the results of this study contribute to the growing body of findings in support of the hypothesis that altered NMDA receptor-mediated neurotransmission contributes to the pathophysiology of schizophrenia (9).

Together, these five articles exemplify aspects of the current state of knowledge in our pursuit of the pathogenesis and pathophysiology of schizophrenia. They also demonstrate the substantial challenges that still confront us, posed both by the complexity of the illness and the limitations of available research methods, despite the remarkable advances in the latter over the past decade. Clearly, efforts to improve our understanding of schizophrenia from the disease perspective depend upon, as illustrated in these articles, both a diversity of approaches to the study of the illness and continued improvements in the sophistication, rigor, and sensitivity of experimental designs and methods. Advances in these domains promise continued progress in the pursuit of the pathophysiology and pathogenesis of schizophrenia, progress that is critical for enhancing treatment strategies and for discovering preventive measures.

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