Neuroimaging the Infant: The Application of Modern Neurobiological Methods to the Neurodevelopmental Hypothesis of Schizophrenia

In the study reported in this issue, Gilmore et al. (1) demonstrated that neuroimaging the brain in infants at risk for schizophrenia is feasible. This work may lead to advances in understanding the neurobiological underpinnings of the neurodevelopmental hypothesis of schizophrenia.

This hypothesis proposes that the onset of psychotic symptoms is the end result of decades of interaction between genetic and environmental factors. Two critical windows have been suggested: a fetal and early infancy period, during which vulnerability is established, and a later, often adolescent or young adult period, during which conversion from vulnerability to psychosis occurs. Brain changes during the perinatal window are not deterministic in that the majority of individuals born with vulnerability will never develop the full clinical disorder. Similarly, in less vulnerable individuals, genetic and environmental factors present during the second critical window appear to have minimal effect and are not associated with an increased risk for psychosis.

The adolescent/young adult critical development period received a significant amount of scientific attention for over 120 years (2). The last two decades have seen a focus on subjects with early signs of psychosis, a group that appears to have about a 30% risk for developing a psychotic illness. A number of techniques, including neuroimaging (3), physiological measures (4), and neuropsychological tests (5), have been used to explore the neural underpinnings of the conversion to psychosis as well as the impact of prevention strategies. Although larger randomized trials have not yet identified any clearly successful prevention strategies, early efforts are suggesting strategies for future evaluation (6). Although a significant amount of work remains to be completed, there is a clear ongoing effort to analyze individuals during the adolescent/young adult critical window and to use that information to rationally design and test prevention efforts.

The concept of an earlier, perinatal critical window was first suggested by Laura Bender in the 1950s (7). The idea was initially based on peripheral motor and behavioral assessments of infants (see review by Watt [8]) and later supported by neurobiological studies of adults (see review by Weinberger [9]) and epidemiological studies that identified correlations between adult disease state and perinatal environmental risk factors (10, 11). These results have provided strong but very indirect support for a perinatal critical window. Perinatal brain form and function have not been directly assessed. The application of modern neurobiological techniques directly to the study of fetuses and infants is necessary to develop an understanding of brain changes associated with vulnerability to later schizophrenia.

The obstacles to studying fetal and infant precursors of psychosis are many, and they include low ability to predict which infants will later develop schizophrenia, difficulties in identifying and retaining high-risk pregnant women and their infants, and lack of normative fetal or infant data for most outcomes relevant to schizophrenia.
Methodological difficulties range from the inability of fetuses and infants to follow verbal instruction to the lack of myelin, which confounds imaging analysis. What is exciting about the report of Gilmore and colleagues is that they have solved at least some of the methodological issues, allowing them to directly examine the fetal and infant brain.

Gilmore and colleagues used magnetic resonance imaging (MRI) (both structural and diffusion tensor imaging) to study brain structure in 52 infants: 26 infants who were at higher risk for schizophrenia because of a maternal history of psychosis and a 26-infant matched comparison group. A subset of these infants also had prenatal neuroimaging utilizing ultrasound in the second and third trimesters. For male infants, having a mother with psychosis was associated with a larger intracranial volume, larger total gray matter, higher total CSF, and larger lateral ventricular volumes. No significant differences were seen for female infants nor in any prenatal neuroimaging measure for either gender. The authors conclude that schizophrenia-associated brain alterations may be detectable at birth.

Larger intracranial volume is also associated with autism, and the authors suggest this macrocephaly may reflect environmental etiologies common to both illnesses. Conversely, the greater ventricular volume may reflect genetic etiological factors. Interpretation of this study is complicated by the presence of several confounding factors, including increased exposure to neuroleptics and maternal smoking in the group whose mothers had psychosis. The group was also underpowered to detect differences at the levels often seen in adults, and important differences between groups may have been missed.Replication of this effort with larger study groups is necessary before one can be confident of the interpretation.

However, the importance of this study is not in the results, but in the success of the methods. Identifying ways to conduct neuroimaging with a population that is unable to respond to requests to “lie still” is an important advance. Standard procedures for differentiating white from gray matter are ineffective when the component that makes brain matter white (the myelin) is not yet fully developed, and new analytic models had to be developed. Neonatal brains are developing very rapidly, and the window to successfully obtain a scan is only days to a few weeks long, as compared to the months or even years when studying older children or adults. In addition, pregnancy is a time of rapidly changing and often unstable social support systems, particularly for pregnant women with psychosis, and attrition from studies is expected to be high. When the short participation window is combined with the high attrition rate, recruitment and retention of pregnant psychotic mothers-to-be can be a major obstacle. The report by Gilmore et al. appears to be the first on brain imaging in fetuses and infants that are vulnerable to psychosis, and it reflects successful solutions to several methodological hurdles and gives hope that further investigation will provide additional information on the neurobiological substrate of psychosis vulnerability.

Identifying and intervening with adolescents and young adults in the early stages of conversion to psychosis is a critical direction for the field. However, even if conversion to psychosis never occurs, the “vulnerability” established during the perinatal period is associated with significant psychopathology and lifelong cognitive deficits, affective instability, social isolation, and school and work dysfunction (12). Despite its relevance, methodological constraints have limited direct assessment of the perinatal brain and limited our understanding of the associated neurobiological underpinnings. The work presented in this issue by Gilmore and colleagues demonstrates that the use of modern neurobiological techniques to directly assess the perinatal brain is feasible and will identify differences between groups when such differences are present. Additional work in this area has the potential to help our understanding of this critical brain development window—an important first step toward novel primary prevention strategies.
References
2. Clouston TS: The Neuroses of Development. Edinburgh, Oliver and Boyd, 1891

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