Understanding What Causes Schizophrenia: A Developmental Perspective

Understanding what causes schizophrenia is becoming harder and harder. We know that schizophrenia has genetic causes, since the most significant risk factor is having a first-degree relative with schizophrenia. However, most people with schizophrenia do not have an affected relative, and while the overall genetic contribution to schizophrenia may be large, the contribution of specific genes is very small. Candidate gene studies and more recent genome-wide association studies have had inconsistent results and indicate, at best, individual genes increase risk by less than 2 times—from an average population rate of 1 in 100 to 1.5 in 100. Pre- and perinatal complications and environmental exposures appear to have somewhat stronger effects than individual genes, as prenatal exposure to infection or hypoxia increases risk of schizophrenia from 1 in 100 to 2–4 in 100 (1). Schizophrenia is likely the result of an interaction between genetic risk and environmental exposures, and recent studies have attempted to describe that interaction.

In this issue, Mäki and colleagues (2) studied the interaction of genetic risk (having a parent with schizophrenia) with an environmental risk—that of maternal depression during pregnancy. They found that maternal depression during pregnancy significantly increases the risk of schizophrenia in offspring if one of the parents has a psychotic disorder. If a child had one parent with psychosis, their risk of schizophrenia increased 2.6 times. Maternal depression by itself did not increase rates of schizophrenia. However, if the genetic risk of having a parent with schizophrenia was combined with the environmental risk of maternal depression, schizophrenia was more than 9 times more likely. The combination of genetic risk with an environmental exposure interacted to increase rates of schizophrenia more than that would be expected by simply adding risk from each.

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This report is the latest of several recent studies describing gene-environment interactions relevant to risk for schizophrenia, including interactions between genetic liability and prenatal exposure to infection (3), urban birth (4), as well as between cannabis use and a catechol-*O*-methyltransferase polymorphism (5). Mäki and colleagues argue that their results are an indication of a gene-environment interaction between genetic liability and prenatal exposure to depression and/or stress. There is ample evidence, both in clinical and preclinical studies, that stress can have a variety of effects on brain development that could increase risk for schizophrenia. For example, prenatal exposure to maternal stress results in reduced hippocampal volume and reduced neurogenesis in rhesus monkeys (6). An alternative interpretation that the authors acknowledge would be one of additive genetic effects—genes that confer risk of depression may be additive with those that confer risk for schizophrenia. There is increasing evidence of nonspecificity of many risk genes and in overlap of risk genes for schizophrenia and bipolar disorder (7).

Currently, it is thought that genetic risk for schizophrenia emerges in two basic ways—the first being the polygenic interaction of multiple common variants of probably thousands of genes, each with very small individual effects (8). The second are rare but highly penetrant genetic events such as deletions or duplications—copy number variations (9). Of the environmental causes of schizophrenia, most studies have focused on pre-

and perinatal environmental risk factors; three of the gene-environment studies relevant to schizophrenia focus on these—infection, depression/stress, and urban birth.

What causes schizophrenia? The short answer may be "nothing" or more precisely "no one thing." In most cases, schizophrenia is an end result of a complex interaction between thousands of genes and multiple environmental risk factors—none of which on their own causes schizophrenia. Daniel Weinberger, in his classic paper on brain development and schizophrenia (10), entertained the "unlikely" possibility that schizophrenia is "not the result of a discrete event or illness process at all, but rather one end of the developmental spectrum that for genetic and/or other reasons 0.5% of the population will fall into." Over 20 years later, this unlikely scenario is looking more realistic. Schizophrenia is increasingly considered a subtle neurodevelopmental disorder of brain connectivity, of how the functional circuits in our brains are wired. Schizophrenia may in fact be the tail end of a distribution of how the estimated 20 billion neurons and their trillions of synaptic connections in our brains are generated, eliminated, and maintained. Schizophrenia may be the uniquely human price we pay as a species for the complexity of our brain; in the end, more or less by genetic and environmental chance, some of us get wired for psychosis.

Where does that leave us those of us who want to treat schizophrenia better, or even prevent it? The studies to date do give us a few toeholds in the heterogeneity and complexity that is schizophrenia. One strategy, the focus of many current studies, is to better understand the roles that risk genes play in brain development. A parallel approach is the study of how environmental risk factors impact the developing brain. These environmental risk factors may ultimately provide the best chance at prevention, as they are potentially preventable, while genetic risk factors are not. Clearly more studies of gene-environment interaction, in both clinical samples and in preclinical models are critical.

But even these strategies reveal enormous complexity. While many risk genes play a role in synapse development and plasticity, they also act at multiple times in brain development and participate in multiple developmental processes. Identifying the mechanisms critical for schizophrenia may prove very difficult. Environmental risk factors also likely have multiple effects on the developing brain. Prenatal infection can act directly on developing synapses and circuits; it might also cause subtle changes in neuron migration and placement, which would ultimately result in abnormal connections. Prenatal exposure to infection or stress can also permanently alter immune and/or stress responses, making someone more sensitive to subsequent environmental stressors, culminating over the course of development in a brain with abnormal connections.

Schizophrenia is likely the result of an abnormal developmental trajectory of synapse and circuit formation that ultimately leads to a miswired brain and clinical symptoms. This abnormal developmental trajectory is contributed to by the interaction of thousands of risk genes and multiple environmental risk factors. Perhaps the best hope to understand and prevent schizophrenia is to focus not so much on the genes or risk factors but rather on the developmental trajectory itself, the final common pathway(s) to schizophrenia. We must understand the periods of human brain development that are important for synapse and circuit development. When do abnormalities in brain wiring actually occur in children at risk for schizophrenia? How do the known environmental and genetic risk factors alter normal developmental trajectories? What are the key transition periods in human brain development? Can we modify developmental trajectories during periods of enhanced plasticity? These and other issues critical to understanding schizophrenia and other psychiatric disorders are discussed in a recent report from the National Institutes of Mental Health: *Transformative Neurodevelopmental Research in Mental Illness* (11). This approach signifies a bit of a paradigm shift, especially for adult psychiatrists, as it requires a new concentration of efforts on childhood brain development. Only by focusing our research on understanding human developmental trajectories can we develop interventions that recognize and modify, either with pharma-

cologic or cognitive/behavioral approaches, abnormal developmental trajectories that lead to schizophrenia.

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