

Investigating the Cognitive Antecedents of Schizophrenia

Although premorbid cognitive deficits are well-described in individuals with schizophrenia, less is known about the cognitive developmental trajectories of children who develop schizophrenia as adults. This reflects, in part, the financial and methodological challenges inherent in implementing a prospective study that can follow, at multiple timepoints, a large, representative cohort of individuals from early childhood through young adulthood. Studies of youth at genetic high-risk for schizophrenia have provided valuable insights into the cognitive and neuropsychological antecedents of conversion to schizophrenia (1–3). However, genetic high-risk studies are not necessarily generalizable to the entire population of individuals with schizophrenia, most of whom do not have a first-degree relative with the disorder. Studies of military conscripts encompass a more representative, population-based sample, but are often limited in the number of timepoints at which participants are assessed, and may be further limited to male records.

These design challenges have been addressed, to some extent, by population-based prospective studies, which assess a birth cohort at multiple timepoints during childhood, adolescence, and young adulthood. Interestingly, however, data on the trajectory of intellectual functioning from several extant birth cohort studies do not converge. In some studies, children who eventually develop schizophrenia exhibit significant declines in intellectual skills (4), whereas in other studies, preschizophrenic children displayed static cognitive deficits during childhood (5). In this issue of the *Journal*, the article by Reichenberg and colleagues (6) takes this unresolved question head-on. Reichenberg et al. investigated the cognitive trajectories of a cohort of children born in 1972–73 in Dunedin, New Zealand, who were followed from birth to age 32. The data reported here are drawn from IQ assessments at four timepoints between the ages of 7–13 years. In order to determine the specificity of cognitive trajectories in preschizophrenic children, their development was compared to both healthy

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comparison children and children who eventually were diagnosed with recurrent depression. Whereas several other prospective cohort studies have used composite indicators of intellectual function (5), this study disaggregated IQ into multiple cognitive functions, including verbal reasoning, visuospatial problem solving, working memory, attention, and processing speed. Moreover, standardized, reliable mental health assessments were built into this cohort study, thus overcoming potential limitations of several other studies that relied on public mental health registries to identify patients on whom childhood developmental data also existed.

The authors tested three developmental models that putatively explain the cognitive trajectories of preschizophrenic children: 1) the developmental deficit model, which predicts early, stable cognitive impairments throughout childhood; 2) the developmental lag model, which predicts cognitive growth that is slower than healthy peers; and 3) the developmental deterioration model, which predicts tangible declines in cognitive functions over time. The authors report that both children who developed schizophrenia and those who developed depression exhibited diminished premorbid IQ scores

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relative to healthy comparison children. But in contrast to children who developed depression as adults, those who eventually developed schizophrenia displayed different developmental trajectories for different cognitive functions. In support of the developmental deficit model, impairments in verbal reasoning and verbal concept formation were observed very early in the elementary school years of preschizophrenic children, and persisted into adolescence. In support of the developmental lag model, the study found that skills requiring attention, processing speed, and working memory were intact in young preschizophrenic children and continued to develop into adolescence, but at a significantly slower pace than those of healthy peers. Although children who eventually developed depression also displayed deficits and lags in some functions, the changes were not as robust as in children who went on to develop schizophrenia.

These findings are in line with other prospective studies that have reported that cognitive impairments can be detected several years prior to puberty in preschizophrenic children. However, by linking specific components of cognitive function to particular developmental trajectories, this article brings new insights into the subtle complexities of cognitive development in children who eventually develop schizophrenia. These findings also support neuroimaging studies that have demonstrated that developmental trajectories of distributed neural circuits subserving fluid abilities such as attention and working memory are relatively protracted (7). Interestingly, the findings may also provide insight into the article by Dickinson and colleagues that also appears in this issue of the *Journal* (8). The study tested the benefits of a computer-assisted cognitive remediation program in patients with schizophrenia and found that although patients improved over time in their performance on the remediation tasks, they did not improve on any of the neuropsychological or functional outcome measures. This may reflect the longstanding and impenetrable roots of cognitive dysfunction in schizophrenia that are demonstrated by Reichenberg and colleagues.

As the authors point out, a limitation to the study is the absence of cognitive data during adolescence. The developmental models that the authors considered are not mutually exclusive, and it is possible that the static cognitive skills of the preschizophrenic children in this sample began to deteriorate as they moved through adolescence and began experiencing prodromal symptoms of psychosis. In addition, the sample size is smaller (9) and more racially homogenous than many other birth cohort studies, likely affecting the generalizability of the findings.

Nonetheless, these findings strongly support the notion that premorbid cognitive deficits in schizophrenia represent early and enduring genetically based vulnerabilities to the disease. However, the extent to which the findings carry clinical implications for the early identification of children who are at risk for developing schizophrenia is not clear. The authors correctly state that the assessment of multiple cognitive functions at multiple timepoints would inform our ability to detect subtle cognitive patterns that are predictive of the development of schizophrenia at the group level. Moreover, careful and consistent clinical monitoring of individual children who present with multiple risk factors might enable us to identify and intervene to avert the severity of a range of psychiatric disorders, not only schizophrenia. Since schizophrenia is relatively rare however, the specificity (10) of and power to predict from (11) the cognitive and behavioral risk factors identified in most birth cohort studies to individual cases of schizophrenia remains low.

Our ability to identify vulnerable children would be most likely be enhanced by prospective studies that incorporate genetic and physiological (e.g., neuroanatomical and neurofunctional) indicators of risk. Many birth cohort studies that have explored the antecedents of schizophrenia were initiated prior to the explosion in technology that now enable us to investigate the association between susceptibility genes and endophenotypic features of the disorder, and to explore the way in which multiple etiological factors aggregate and interact to produce risk (12). In addition, increased attention to factors (both biological and environmental) that potentially protect vulnerable children

from severe psychiatric disorder is warranted (9). Without consideration of all of these factors, our ability to translate the knowledge gained from population-based studies into specific clinical guidelines will be diminished. Accordingly, it is critical that we utilize the full range of 21st-century knowledge and technology to construct and operationalize comprehensive, multilevel models representing the etiology of and developmental trajectories toward this devastating disease.

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