Zeroing In on Early Cognitive Development in Schizophrenia

Thoughts about the role of development in schizophrenia have evolved in recent decades. Early formulations of the "neurodevelopmental hypothesis" suggested mechanisms whereby "probably congenital and static" neurophysiological insults might remain for the most part silent, behaviorally, until the onset of schizophrenia in late adolescence or early adulthood (1). Recent versions reflect a more dynamic view of the densely interacting effects of biology and environment on behavior over the course of development (2). They also emphasize the now extensive evidence that some children who will later have schizophrenia show marked abnormalities in motor, cognitive, emotional, and social development years before the onset of psychotic symptoms (3). Among these developmental manifestations, an increasing lag in intellectual development during childhood may show some specificity in prediction of later psychosis (4), while motor, emotional, and social problems seem to be nonspecific risk factors for a variety of adult neuropsychiatric outcomes (3).

The field continues to struggle toward more convincing models of the etiology of schizophrenia. The challenge is compounded by the diversity of trajectories preceding acute illness and the vast heterogeneity of adult clinical presentation.

At the heart of the literature on cognitive predictors of later schizophrenia (for reviews, see references 5, 6) are a number of longitudinal studies of population-based birth cohorts, including the Dunedin Multidisciplinary Health and Development Study (7). The cohort comprises 1,037 individuals born between 1972 and 1973 in Dunedin, New Zealand (91% of eligible births), who have undergone repeated assessments of health, cognition, and behavior, with the first follow-up at age 3 and the most recent at age 38. In this issue of the *Journal*, Meier et al. (8) describe new Dunedin cohort analyses, extending an earlier round of analyses described by Reichenberg et al. (9) in these pages in 2010. Both studies found that childhood IQ was lower, by approximately 0.5 standard deviations relative to healthy peers, in cohort members who were later diagnosed with schizophrenia. However, for both reports, the central aims were to unpack this overall finding in order to address lingering questions about schizophrenia-related cognitive development: 1) What course does cognitive development follow in people who will have this disorder—during childhood, and from premorbid to postonset time frames? 2) Is developmental course similar across domains of cognitive performance? 3) Is there a particular pattern of cognitive development that shows specificity for the development of schizophrenia?

Reichenberg et al. explored these questions using Dunedin data from four IQ assessments completed by age 13 (9). Across a number of IQ battery subtests, there were two distinct patterns of performance in 35 individuals from the cohort who met rigorous criteria for schizophrenia by age 32: an early deficit in verbal and visual knowledge acquisition and simple reasoning that persisted, but did not

worsen, across childhood assessments (which the authors labeled "static deficit"); and a lag in development for speeded performance, working memory, and more complex problem solving that emerged after age 7 and worsened by age 13 ("dynamic deficit"). This divided pattern was not apparent in cohort controls or cohort members with persistent depression. Interestingly, within the schizophrenia group, impairment on the static deficit measures was strongly correlated with lag on the dynamic deficit measures.

Meier et al. (8) have refined and extended these findings. Their analyses incorporated cognitive assessments completed by Dunedin cohort members at age 38 that were not available to Reichenberg et al. and examined additional comparison groups. The investigators report that the substantial childhood IQ impairment in cohort members who developed schizophrenia increased significantly (by ~6 IQ points) between ages 13 and 38. The divergence in IQ performance was driven by speeded, nonverbal IQ subtests and was paralleled by declines of similar magnitude in non-IQ-battery measures of learning, processing speed, and motor speed. Notably, Meier et al. added evidence that a widening lag in cognitive development was specific to schizophrenia—finding little or no evidence of IQ subtest or neuropsychological change from age 13 to 38 among cohort controls, cohort members with depression, those who showed mild cognitive impairment as children, or individuals matched on childhood risk factors for schizophrenia (family history, socioeconomic status, cognitive impairment) who did not develop the disorder as adults.

In sum, the Meier and Reichenberg studies suggest that two main facets of the broad adult cognitive impairment in schizophrenia (10) follow distinct developmental progressions up to and after the onset of illness. Members of the Dunedin cohort who developed schizophrenia showed very early impairment on IQ subtests tapping verbal and visual knowledge and simple reasoning that were "static" through the early teenage years and well into adulthood (9). In contrast, deficits in speeded performance and more demanding learning and problem solving were "dynamic," emerging after age 7, worsening by age 13, and lagging further relative to unaffected peers by age 38. There was very little evidence of this divided pattern of cognitive development in comparison groups.

As Meier et al. suggest (8), this division of measures into static and dynamic deficit groupings aligns generally with the division of cognitive performance into more "crystallized" and more "fluid" dimensions (11, 12). Crystallized operations make use of general knowledge and experience, for example, in correctly pronouncing irregular words or identifying drawings of common objects. Developmentally—although knowledge accumulates throughout life—the neural systems that support crystallized operations mature fairly early and are thought to be resistant to aging and later brain dysfunction, which has given rise to the practice of estimating "premorbid" cognitive ability through measures of crystallized ability (13). Fluid performance depends on the abilities to work quickly, think abstractly, and solve novel problems, independent of acquired knowledge. Fluid abilities are thought to develop gradually to a peak in young adulthood and decline gradually thereafter (14). The Dunedin studies frame the question of whether dissociated or interrelated pathophysiological processes underlie the two trajectories of cognitive development in schizophrenia but do not pursue it at length.

By now, however, it probably should be a corollary of the neurodevelopmental hypothesis of schizophrenia that strong dissociations among higher-order cognitive processes are unlikely. The "neurodevelopmental disorder" label presupposes

that the cognitive impairment seen in adults arises from atypical interactions and compensatory responses across the range of cognitive processes (crystallized/fluid; static/dynamic; more impaired/less impaired) throughout development (15). The strong associations between performance on static deficit measures and dynamic deficit measures reported by Reichenberg et al. (9) probably reflect these interdependencies. Likewise, adult pathophysiology is doubtless the product of complex interactions and compensations over developmental time. Clearly, genes encode protein building blocks rather than integrated behaviors, and their impact on cognition most likely comes very gradually through low-level and widely acting mechanisms (e.g., neuronal migration and synaptic plasticity) (15) interacting with environmental (16) and random influences.

The field continues to struggle toward more convincing models of the etiology of schizophrenia. The challenge is compounded by the diversity of trajectories preceding acute illness (17, 18) and the vast heterogeneity of adult clinical presentation (19). The Dunedin study and similar longitudinal designs provide much-needed detail about behavioral development in schizophrenia. Cross-disciplinary efforts to link these behavioral patterns with atypical development of molecular, cellular, and neural systems are another critical step. But we are still at an early stage in the evolution of the neurodevelopmental hypothesis.

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