Developmental Lag and Course of Cognitive Deficits From the Premorbid to Postonset Period in Schizophrenia

To the Editor: In their article published online September 13, 2013, Meier et al. (1) update earlier findings of their well-conducted population-based longitudinal study (2). Previously, the authors reported cognitive changes between ages 7 and 13 years and found that children who later developed schizophrenia had stable cognitive deficits that were already evident at age 7. The earlier report also provided evidence of change in other cognitive domains, as some children had more severe working memory and processing speed deficits at follow-up. In the present article, Meier et al. (1) extend their findings to age 38. This report has a number of strengths. It revealed that antipsychotic and illicit drug use could not explain the reported cognitive changes. It also provided some evidence of specificity to schizophrenia as no similar cognitive changes were found in clinical and healthy comparison groups.

However, there is a significant concern regarding this most recent report. The article presents the message that schizophrenia patients are losing acquired cognitive skills from the premorbid to the postonset period. The authors also suggest that decline is observed in fluid abilities but not crystallized abilities and imply that different pathophysiological mechanisms underlie these deficits. Such interpretations could be considered by many as strong support for neurodegenerative models of schizophrenia.

However, these findings should not be considered real evidence of cognitive decline in schizophrenia because of two important limitations. First, in most cognitive tests that were included, a more challenging version of the task was used at the follow-up assessment. Second, reported IQ results were based on the corrected norms. Previous studies also had the same limitations, and some studies used completely different tests at the follow-up assessment. Studies reporting follow-up data of raw scores of the same cognitive measures administered to patients with ultra-high risk to psychosis and patients with first-episode schizophrenia have not supported the idea of cognitive decline (3).

In reality, the evidence suggests that schizophrenia patients simply lag behind healthy individuals in cognitive development, and such cognitive changes are quite naturally more apparent for fluid skills than crystallized skills in adolescence and adulthood, as the development of advanced cognitive skills continues after age 13. There is no need for a different pathophysiological mechanism. In fact, the authors shyly acknowledge this in their discussion of the symbol coding findings; however, their main emphasis is cognitive decline. Cognitive deficits observed in schizophrenia can be best explained by problems in acquisition during neurodevelopment from birth to adulthood rather than by the loss of acquired abilities.

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Response to Bora

To the Editor: Schizophrenia researchers wonder if schizophrenia is a neurodevelopmental or neurodegenerative condition. Data from our life-course study suggest it may be both. We previously reported that children who later develop schizophrenia show slowed growth in fluid cognitive abilities across ages 7 to 13 years (1), consistent with a neurodevelopmental model of schizophrenia. With new data at midlife (2), we think we have documented that these same individuals show some cognitive degeneration (i.e., loss of acquired cognitive abilities) from before to after the onset of schizophrenia.

Usually, the mental abilities of an individual are interpreted against a standard of performance that is normative, where normative is defined as age typical. Childhood and adult tests tap the same abilities, but they often use age-appropriate test materials. However, the clearest evidence that neuropsychological decline in schizophrenia represents a loss of acquired cognitive abilities would be seen if the test given at follow-up precisely matched the initially administered test, as Bora (3) notes. In the Dunedin Multidisciplinary Health and Development Study, two tests given in adulthood (age 38) were identical to those given in childhood (age 13): the Grooved Pegboard Test and the Rey Auditory Verbal Learning Test. Regarding the Grooved Pegboard Test, the schizophrenia group took 4 seconds longer in adulthood than in childhood to complete the same test; thus, the schizophrenia group lost some of the motor ability they once had in childhood. (In contrast, the healthy and persistent depression groups completed the test about 2.5 seconds more quickly in adulthood than in childhood, thus showing that motor abilities normatively improve slightly from childhood to adulthood.) Regarding the Rey Auditory Verbal Learning Test, the schizophrenia group recalled seven fewer words over the four trials (Rey total recall) as adults than they had as children on the same test; thus, the schizophrenia group lost some of their ability to learn. (In contrast, the healthy and persistent depression groups recalled three fewer words as adults than they had as children, thus showing that ability to learn normatively

declines from childhood to adulthood. Individuals with schizophrenia showed accelerated decline in ability to learn.)

In summary, we previously demonstrated that in childhood, when the normative trajectory of cognitive ability is one of growth, children who later develop schizophrenia exhibit slowed growth in fluid cognitive abilities (1). Here, we demonstrate that in adulthood, when fluid cognitive abilities start to normatively decline (4), individuals with schizophrenia in our cohort exhibited early degeneration and accelerated decline. Granted, these latter findings are based on only two tests, but to us, they blur the distinction between development and degeneration. Moreover, unlike fluid abilities, deficits in crystallized abilities were apparent as early as age 7 and remained stable to age 38 years (1, 2). Fluid abilities are thought to support the acquisition of crystallized skills, with the developmental trajectory of crystallized abilities lagging behind that for fluid abilities (5). Therefore, it is somewhat surprising that deficits in crystallized abilities emerged before deficits in fluid abilities and did not worsen over time. Whether different pathophysiological mechanisms underlie cognitive deficits in fluid and crystallized abilities in schizophrenia is a key question for future research.

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Management Issues During Pregnancy in Women With Bipolar Disorder

TO THE EDITOR: We read with interest the article by Clark et al. (1) on lamotrigine dosing in pregnant patients with bipolar I disorder. The authors report on the use of lamotrigine in eight patients with bipolar disorder, six of whom received concomitant psychotropic drugs including four women who were taking antidepressant drugs. Dosage adjustments of lamotrigine were made in response to hypomanic, manic, or depressive symptoms. It is not clear whether the dosages of concomitant psychotropic drugs remained the same during pregnancy. Of the three women requiring a dosage increase to manage symptoms, two were also taking antidepressants that can increase the recurrence of bipolar mood episodes both during and after pregnancy (2). There are no data suggesting that monitoring serum levels with corresponding adjustments to lamotrigine dosing will protect against antidepressant-led mood instability. Interestingly, the authors did not report a correlation between lamotrigine concentration and scores on rating scales for depression and mania. Thus, the conclusion that women with bipolar disorder who are treated with lamotrigine experience an increase in symptoms as a result of declining concentrations of this drug is not justified.

While lamotrigine has a role in the management of bipolar disorder during pregnancy, no data on its effectiveness in the prevention of postpartum mood episodes are currently available. Moreover, lamotrigine is generally not recommended for the acute treatment of mania (3).

Finally, the statement that pregnancy is a vulnerable period for recurrence of mood episodes is true for women treated at tertiary care centers with complex and often comorbid disorders and women who discontinue mood-stabilizing drugs. However, evidence from studies using nonclinical samples, retrospective studies, and studies on psychiatric hospitalization rates is suggestive of a positive effect of pregnancy on bipolar disorder (4).

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