Toward Mapping Altered Trajectories of Brain Development in Depression

Two principles in the conceptualization of mental disorders relevant to future directions in research have recently been emphasized. One is that mental disorders, a product of both genetic and environmental influences, are fundamentally brain based. The second is that many disorders take root during childhood and are developmental in origin. These principles, while neither new nor surprising, form the basis of proposed paradigm shifts in psychiatric research (1). They would seem to have clear applicability to investigations of brain-behavior relationships in depression, where cross-sectional studies of alterations in the structure and function of regions and circuits involved in emotion processing have been under way for decades (2). Notably, despite this substantial body of research and the progress we have made in understanding how brain structure and function are altered in depression, there have been surprisingly few longitudinal studies of brain development in depressive disorders. In this issue, Whittle et al. (3) make an important step in this direction by investigating structural brain change in a sample of adolescents at high risk for depression.

Despite significant progress in understanding structural and functional alterations in the brain in depression over the past two decades, the literature has been limited by a cross-sectional view.

As a part of a longitudinal study of risk and protective factors for adolescent depression, Whittle et al. studied 86 adolescents screened from the community for key affective features that are thought to confer risk for or resilience to depression. Between ages 12 and 18, the study subjects participated in four assessment waves addressing mental health and medical and developmental status; waves 1 and 3 included structural neuroimaging. During the study period, 30 participants experienced a new onset of major depression, allowing the authors to investigate the predictors of adolescent depression. In this first neuroimaging study to use a longitudinal design to inform risk for adolescent depression, gender differences in brain development associated with later depression were found. For boys, attenuation of growth of the hippocampus, putamen, and amygdala between ages 12 and 16 were detected, and for girls, increased growth of the amygdala and decreased growth of the nucleus accumbens were found. The authors speculate that the development of these regions, known to be involved in the modulation of stress and emotion reactivity, may become altered in high-risk individuals by either a process of neuronal damage or a disruption of neurogenesis. In contrast, they speculate that attenuation of the decrease in putamen volume in depressed adolescents may be due to a deficit in synaptic pruning or myelination, processes that are active in gray matter development during adolescence. Based on their design, the authors conclude that this altered pattern of development represents a

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biomarker of vulnerability rather than a result of the disorder, since it was evident before the onset of depression.

Studies of normative brain development in childhood have shown that age by volume and thickness trajectories are more predictive of key developmental outcomes (e.g., IQ) than cross-sectional morphometry even in adulthood (4). These findings illustrate the potential power of mapping developmental brain change and underscore "the importance of the journey rather than the destination" in investigations of the brain basis of mental disorders (5). Longitudinal studies of structural brain development in childhood have shown particular promise in disorders such as attention deficit hyperactivity disorder, in which a developmental delay of cortical thickness trajectories in the frontal lobes has been identified and appears to be correlated with treatment response (6). Unique alterations in the trajectory of childhood brain development have also been identified in autism and schizophrenia (7).

Despite significant progress in understanding structural and functional alterations in the brain in depression over the past two decades, the literature has been limited by a cross-sectional view. The wide variation in individual brain morphometry by age adds to the difficulty in interpreting cross-sectional data, a limitation that is further amplified in child samples. As underscored by the findings of Whittle et al., not only age but also gender (and potentially pubertal status) have an impact on the trajectory of brain development and therefore must be taken into account in longitudinal studies of children.

The rapid advances in imaging technology also present unique methodological challenges for longitudinal neuroimaging studies. As Whittle et al. discuss in relation to the data they present, which were obtained by different scanners at the two scan waves, rapid changes in imaging technology must be addressed to combine data obtained years apart using evolving hardware and software. It is yet another challenge to obtain serial scans in child populations who may be resistant to participating in multiple scan sessions and who frequently undergo orthodontic care, a contraindication to MR imaging. Study designs that target younger children have to address higher rates of data loss due to greater movement artifact, an issue most relevant to studies of brain function. Despite these hurdles, it would seem that longitudinal imaging studies that start young and ascertain populations at high risk for depression would be a critical next step to understanding the developmental psychopathology of depression. When samples are followed through adolescence, careful measures of puberty are indicated, most optimally including hormonal measures.

A future focus on longitudinal neuroimaging designs in studies of the developmental psychopathology of depression would also benefit from a sharp turn to investigations in younger age groups. Given that depression has been shown to arise very early in development, and that the human brain achieves 95% of its peak volume by age 6 (5), the search for alterations in the development of key emotion-processing regions during early childhood may be particularly important. There is an emerging body of neuroimaging data demonstrating changes in the structure and function of brain emotion systems related to a preschool-onset episode of depression (8, 9). Moreover, alterations in amygdala activation in response to negative emotions have been demonstrated in acutely depressed preschoolers between ages 4 and 6 (10). This body of work suggests that brain change is already evident as early as the preschool period of development, suggesting that studies of brain development should begin at the earliest possible developmental point. Whittle

et al. provide novel evidence for unique alterations by gender in the trajectory of change in the developing brain in children at risk for depression. This innovative work, based on only two structural scans in late childhood and early adolescence, may be a prelude to a rich and fruitful exploration once multiple serial scans can be obtained from early childhood through late adolescence. Longitudinal data of this kind are necessary to connect the dots, allowing for detailed mapping of the neurodevelopmental course that leads to depression.

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