The Importance of Assessing Neural Trajectories in Pediatric Depression

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In this issue of *JAMA Psychiatry*, Luby et al[1] report neuroimaging findings from a longitudinal study of 193 youths who were carefully assessed for clinical depression since preschool and underwent neuroimaging multiple times during early adolescence. Using growth curve modeling, Luby and colleagues characterized trajectories of cortical structure as a function of depression. They found that global volume of gray matter, indexed by cortical thickness, declined more steeply in adolescents with more severe depression. Given that the age range modeled here is characterized by a decrease in volume of gray matter that is posited to reflect synaptic pruning, this finding suggests that synaptic pruning is particularly aggressive in individuals who have experienced symptoms of depression.

The research presented by Luby et al highlights the types of clinical questions that can be addressed through longitudinal neuroimaging research. We describe 3 specific ways in which such research can inform our understanding of psychiatric disorders: by revealing variability in etiologic pathways to disorder, by elucidating how external influences can alter neural trajectories and thereby either contribute to psychiatric disorders or counteract maladaptive developmental processes, and by clarifying critical changes during specific sensitive developmental periods.

Pathways to Disorder

A key objective in characterizing individual differences in trajectories of brain development is to determine when and how these trajectories deviate in people who develop depression (or other psychiatric disorders); individual differences in neural pathways to disorder may have important implications for understanding etiology and determining treatment. In this context, investigators can use growth curve modeling to characterize each individual's unique trajectory of neural development or structural equation models to elucidate the temporal association between the emergence of the particular brain pathologic findings and behavioral manifestations. Ideally, research using such analytic approaches will also incorporate and integrate measures of genetic, temperamental, social, and environmental risk

in individuals who have not yet manifested the disorder to test diathesis-stress or differential-vulnerability models of developmental psychiatric processes.

It is likely that there are many pathologic processes that lead to depression. Longitudinal neuroimaging studies can answer important questions about heterogeneity in these processes and in etiologic pathways to disorder. Thus, different trajectories of brain development may have a common behavioral end point, such as a diagnosis of major depression or the experience of anhedonia. For example, 2 adolescents with anhedonia may exhibit similarly low levels of cortical thickness and/or striatal activation, but whereas 1 exhibited these anomalies throughout childhood and adolescence, the other developed these abnormalities later and more quickly. Although the brain phenotypes of these 2 individuals are similar at adolescence, by understanding these different trajectories we gain insight into how these individuals may have differentially benefited from the process of brain development, which can enable individuals' biological characteristics to be shaped to optimally match their changing environment.

While this analytic approach requires individuals to be grouped a priori on the basis of known diagnostic (or symptomatic) subgroups, with sufficiently large samples, researchers can also use data-driven analytic approaches, such as latent growth curve modeling,[2] to identify clusters of trajectory types and, therefore, clusters of individuals who follow similar pathologic trajectories. Such approaches have already been used behaviorally to demonstrate that, whereas some individuals show sharp increases in depressive symptoms during early adolescence, others show more gradual increases in symptoms starting in childhood, and still others exhibit persistent moderate levels throughout development.[3] One way to extend this work is to examine the brain trajectories associated with these identified behavioral trajectories, which would elucidate the nature of the associations between brain-based changes and the emergence of depressive symptoms. Latent growth curve modeling also could be applied to longitudinal neuroimaging data without a priori specifications to examine whether several brain development trajectories might be associated with a single behavioral trajectory. Clarifying brain-based subgroups with distinct pathologic profiles may reveal developmental patterns that have differential implications for treatment.

Half the youths in the study by Luby et al[1] had previously experienced a depressive episode. We know that depression is recurrent. It is possible that the initial depressive episode in the participants in the study by Luby et al triggered a set of biological processes that kindled the development of subsequent depressive episodes in response to life stressors.[4] Thus, researchers could use longitudinal modeling to examine precisely how the accumulation and the timing of stressors and the experience of depressive symptoms influence brain development.

External Influences

It is also essential that we recognize that these biological processes occur in a social context. Adolescence is characterized by an increased orientation toward peers. While studies have shown that brain function is altered by the immediate presence of peers, adolescents' friendships and peer interactions also shape the brain's trajectory to maturity. At the same

time, parents continue to exert substantial influence on adolescents' daily experiences; moreover, parenting practices can influence trajectories of structural brain development.[5] Furthermore, as children enter adolescence, parents exhibit less warmth and monitoring, which can increase children's risk for the emergence of depression.[6] Understanding how parenting practices influence neural trajectories and how changes in parenting behaviors can alter these trajectories will have significant implications for intervention.

Sensitive Periods

Researchers should complement investigations of trajectories across a wide age range with studies that target inflection points and/or specific periods of accelerated change. One such sensitive period is the transition through puberty. This period is characterized by an accelerated increase in depressive symptoms, particularly in girls,[7] suggesting that it is also a time of rapid maturation in brain networks relevant to depression, such as the salience network. More important, regions within the salience network contain gonadal hormone receptors that are sensitive to changes during puberty. Studies that are designed to examine the role of gonadal hormones in shaping growth curves of various aspects of brain development can inform our understanding of the mechanisms underlying the increase in depressive symptoms during puberty. Addressing this particular question requires designs that eliminate confounders of age (eg, recruiting on pubertal status rather than age) that oversample during the pubertal transition and measure multiple aspects of pubertal development.

Similarly, it is important to examine the effects of treatment on neural trajectories in depression. There is emerging evidence that earlier interventions for depression have longer-lasting effects.[8] Furthermore, animal research and neuroimaging studies in humans indicate that antidepressant treatment changes the brain. We must extend this research to determine whether treatment alters trajectories of brain development during adolescence and whether these changes mediate improvement in depression. If so, we must then determine the optimal time to intervene to have the longest-lasting effects on trajectories of brain development.

As with all research that moves a field forward, the findings by Luby et al[1] raise additional questions. Are adolescents who differ in cortical thinning comparable before the emergence of depression disorder? How does cortical thinning unfold? Does each depressive episode alter neural trajectories and increase the likelihood of subsequent depressive episodes? Do trajectories change more markedly through puberty? How can peers, parents, and treatments counteract maladaptive developmental trajectories? We now have the analytic tools to answer these and other questions; the next few years promise to yield information that we can use to determine how best to treat and, ultimately, prevent the occurrence of brain-based disorders.

Acknowledgments

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