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Commentary

Maternal Depression and Structural Covariance of the Amygdala in Early Childhood

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There is growing interest in the impact of stress and depression during pregnancy on the developing fetal and infant brain. The amygdala has been a focus of recent research, given its relatively early maturation and its important role in multiple brain networks that support emotion and motivation. Human neuroimaging studies have shown that maternal depression during pregnancy can influence many aspects of amygdala structure and function in the developing brain. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Lee *et al.* (1) extend this body of work to the structural covariance of amygdala volume and cortical thickness across the entire cortex in two rather large cohorts of young children imaged after birth and at 4.5 years. Female neonates exposed to maternal depression—defined as mothers with depressive symptom scores higher than the group median during pregnancy—had significant positive relationships between left amygdala volume and cortical thickness in a region of the left insula. At 4.5 years of age, female offspring with mothers who had high depressive symptoms evidenced a significant negative relationship between right amygdala volume and cortical thickness in a region of the left inferior frontal cortex, while those with mothers who had lower than median scores had a significant positive relationship. These findings were sex specific and were not observed in male offspring.

There are several aspects of the study that deserve consideration. The first is the concept of structural covariance—what is it and what does it mean? Structural covariance is present when the volume, cortical thickness, or some other structural aspect of a brain region is significantly associated with or covaries with structure in another region. Networks of structural covariance, mainly of cortical thickness, have been described across the cortex; these networks are altered in a variety of psychiatric and degenerative brain disorders. There is some evidence that structural covariance reflects functional and structural (i.e., white matter) connectivity between brain regions (2), but more study is required to confirm this.

Little is known about how structural covariance develops in the human brain, though one study in the first 2 years of life found that resting-state functional networks were in place before cortical thickness structural covariance networks, suggesting that structural covariance may result from functional connectivity shaping and fine-tuning cortical thickness across the cortex (3). The observed difference in significant amygdala structural covariance in neonates and 4.5-year-olds in the Lee *et al.* study (1) may be due to changing functional connectivity of the amygdala in childhood development. In neonates, both the left and right amygdala have significant positive functional connectivity with the insula bilaterally, the strength of which decreases by 1 year of age (4), perhaps consistent with the loss of significant structural covariance in the 4.5-year-olds. In general, there is not a strong functional connection between the amygdala and the frontal cortex during the first 5 years of life (4,5), making the amygdala–inferior frontal cortex findings in 4.5-year-olds more difficult to interpret.

The use of imaging to understand psychiatric disease and risk is fraught with many difficulties (6), some of which are illustrated by Lee *et al.* (1). There is great heterogeneity in the construct studied—that of maternal depressive symptoms. It is not readily apparent what having an above-the-median score on an assessment of depressive symptoms at one point during pregnancy represents. Maternal depressive symptoms can represent many nonoptimal prenatal environment influences on the developing brain, including stress, immune, nutrition, and medication exposure, as well as comorbid disorders and substance and environmental toxin exposures. Another study in this cohort found that maternal anxiety was related to hippocampal development (7); it would be interesting to see how anxiety and depressive symptoms are related in this cohort and how they interact to influence fetal brain development. It is also unclear how the environment after birth influenced the results in 4.5-year-olds—do maternal depressive symptoms persist and alter early childhood brain development?

Studies have found that maternal cortisol and interleukin-6 levels during pregnancy influence amygdala structure and function in offspring (8,9), implicating stress and inflammatory pathways. Maternal depressive symptoms may also represent genetic risk factors. Polygenic risk for depression was found to modulate neonatal right amygdala volume in this Asian cohort; interestingly, the opposite effect was found in a white cohort [Qui *et al.* (10)]. This shows that risk genes can have variable effects in different populations with different genetic backgrounds. Future studies need to assess as many sources of heterogeneity as possible so that meaningful conclusions can be drawn from the results and so that generalizability of the findings can be determined.

Another limitation of imaging studies is that many aspects of psychiatric and behavioral disorders are widely distributed in circuits and networks throughout the brain (10). Focusing on a single region or structure, such as the amygdala, may fail to detect important differences in other parts of the brain and lead to a false sense of specificity of effect. For example, depression and stress also alter hippocampal structure and function.

The human brain is staggeringly complex, and the environmental and genetic factors that influence its development and function are equally complex. The analysis of structural covariance is one approach to better understand the complexity of the brain and the relationships between different structures and regions. Lee *et al.* (1) take an important step in

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understanding the impact of maternal depression on the developing brain and challenge us all to develop and apply methods that will allow us to meaningfully address the complexity inherent in this line of investigation.

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Article Information

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