Commentary

COVID-19 and the Infant Brain: Critical Links Among Prenatal Maternal Distress, Social Support, and Neurodevelopment

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Childhood-onset behavioral and emotional problems often have their origins in infancy, where maladaptive infant emotional reactivity predicts behavioral and emotional problems later in childhood (1). Identifying in infancy objective markers of future psychopathology risk later in childhood will facilitate the early identification of vulnerability and inform interventions to help delay or even prevent these disorders prior to manifestation of symptoms. One way forward is to elucidate early multimodal neural markers of pathophysiological processes associated with emotional regulation deficits that confer risk for future psychopathology.

During infancy, there is extensive development of several prefrontal cortical–centered large-scale neural networks supporting emotional regulation (2), including the default mode network (DMN), the salience network (SN), and the central executive network (CEN). The amygdala, supporting emotion processing, is a component of the SN, allowing the SN to integrate emotional perceptual and motivational processes. Major white matter (WM) tracts connecting regions within and among these networks, including the cingulum bundle, anterior corpus callosum, and the uncinate fasciculus, also develop throughout infancy. Specifically, these tracts show significant increases in fractional anisotropy (FA) (the ratio of longitudinal versus transverse water diffusivity, reflecting the degree of longitudinal fiber alignment/collinearity of fibers) and decreases in radial diffusivity (RD) (the extent of transverse water diffusivity in WM tracts, thought to reflect noncollinearity of fibers and/or damage to myelin and axonal membranes) during the first 2 years of life. Amygdala functional connectivity (FC) with these networks also develops throughout infancy and early childhood (3).

Critically, in the first 2 years of life, important relationships evolve among large-scale neural network FC and emotional reactivity, including associations among greater amygdala–DMN, greater amygdala–SN, and lower amygdala–CEN FC and lower infant positive emotional reactivity (4) and relationships between greater amygdala–SN and greater amygdala–DMN FC and greater negative emotional reactivity (5). Together, these findings highlight the important role of developing amygdala–prefrontal cortical circuitry in shaping emotional reactivity in infancy. This neural circuitry is thus an appropriate focus for studies aiming to identify infant neural markers of future behavioral and emotional problems.

Given the highly salient role of caregiving in an infant's environment, exposure to depression and/or anxiety in infancy might especially impact infant emotional regulation and

predispose an individual to longer-term difficulties. In parallel, there are reports of significant effects of caregiver distress on infant neurodevelopment, including associations between greater caregiver depression and anxiety severity and greater infant amygdala–DMN and amygdala–SN resting-state FC and lower amygdala–CEN resting-state FC (4), and associations between greater maternal prenatal depression and anxiety and lower infant frontal WM FA (6).

Despite the growing evidence for a significant impact of caregiver distress on infant neurodevelopment, more studies are needed to elucidate these relationships, and there are many unanswered questions. In particular, while there are known effects of poverty, low socioeconomic status, and exposure to early stress/adversity on childhood neurodevelopment (7), the extent to which sociodemographic factors such as social support impact relationships among caregiver distress and infant neural circuitry is unknown. The COVID-19 pandemic, with its significant impact on mental health, especially in pregnant individuals (8), has provided a unique opportunity to examine relationships between caregiver distress, infant neural circuitry WM structure and function, and the moderating effect of sociodemographic factors on these relationships.

In a novel study in the current issue of *Biological Psychiatry*, Manning *et al.* (9) examined a subsample of 75 caregiver (mother)–infant dyads recruited from a large Canada-wide study that assessed the impact of the pandemic on individuals' physical and mental health. The authors sought to determine how elevated levels of caregiver prenatal anxiety and depression relative to prepandemic levels of these symptoms, as reported by pre-pandemic systemic reviews of perinatal anxiety and depression using the same measures, impacted amygdala–prefrontal cortical resting-state FC and associated WM in infant offspring ($n = 58$ infants with usable diffusion imaging data, and $n = 41$ infants with usable resting-state FC data). Prenatal maternal distress (measured as a factor derived from prenatal anxiety and depression scores) was elevated relative to pre-pandemic levels. There was a significant positive relationship between prenatal maternal distress and infant uncinate fasciculus FA and a significant negative relationship between prenatal maternal distress and mean diffusivity in amygdala–prefrontal WM. Interestingly, not only were there significant relationships between prenatal maternal distress and amygdala–superior orbitofrontal cortical resting-state FC and amygdala–inferior frontal gyral resting-state FC, but also significant interactions between prenatal

maternal distress and a measure of social support on these indices of amygdala resting-state FC. Here, infants of caregivers with lower-quality social support showed significant negative relationships between prenatal distress and these indices of amygdala resting-state FC, while infants of caregivers with higher-quality social support did not show these relationships (Figure 1). Furthermore, male infants showed a trend for greater negative relationships between prenatal maternal distress and amygdala resting-state FC than female infants.

The study makes a significant contribution to the growing literature showing how distress caused by the pandemic impacts mental health in pregnant individuals and, critically, demonstrates how increasing distress in the caregiver affects emotional regulation neural circuitry development in infant offspring. Furthermore, the study is the first to demonstrate how higher-quality social support buffers the otherwise deleterious impact of prenatal maternal distress on infant neurodevelopment. As Manning *et al.* (9) note, partner support might have been especially important during the pandemic, when many individuals, especially those who were pregnant, were separated from other sources of social support. Findings from the study indicate that such a buffering effect extends beyond the caregiver to the development of emotional regulation neural circuitry in the offspring, and the authors speculate that this might be via normalization of dysregulated infant hypothalamic-pituitary-adrenal axis function.

The relationships between prenatal maternal distress and infant amygdala–prefrontal WM, where greater distress was associated with higher FA and lower mean diffusivity, are somewhat counterintuitive, as previous studies report opposite patterns, although there are reports in support of Manning *et al.*'s (9) findings. The authors suggest that these findings might reflect a more mature pattern of neurodevelopment in infants exposed to higher levels of prenatal maternal distress, as FA generally increases and mean diffusivity decreases with age in childhood and adolescence. This is an intriguing possibility, and it concords with research showing that another type of environmental stressor in early childhood, maternal deprivation, is associated with earlier development of the adult pattern of amygdala–prefrontal cortical function (10).

There were limitations to this study. There was no examination of prospective relationships between prenatal maternal distress and future infant amygdala–prefrontal cortical resting-state FC and WM, and there was no measure of infant

emotional behavior. It is therefore unclear how the patterns of infant amygdala–prefrontal cortical resting-state FC and WM associated with higher levels of prenatal maternal distress were related to infant emotional reactivity and the risk for future and behavioral and emotional problems. Similarly, there was no examination of relationships among WM and resting-state FC, and thus it remains to be determined how WM shapes the functional development of amygdala–prefrontal cortical circuitry in infancy. It would also be interesting to examine WM and resting-state FC in the wider neural networks implicated in emotional regulation, including the DMN, SN, and CEN. As the authors highlight, while analyses controlled for postnatal maternal distress, many other caregiver and environmental factors might have impacted infant amygdala–prefrontal cortical circuitry development.

This is an important study, paving the way forward for future research to examine critical interrelationships among caregiver distress, caregiver social support, infant neurodevelopment, infant emotional reactivity, and the emergence of psychopathology later in childhood. The study also provides potential neural targets for monitoring the impact of interventions in infancy and, as the authors note, highlights the prenatal period as a window of opportunity for interventions to target caregiver distress and, in so doing, not only improve caregiver mental health but also facilitate healthy neurodevelopment in offspring during infancy and beyond.

Article Information

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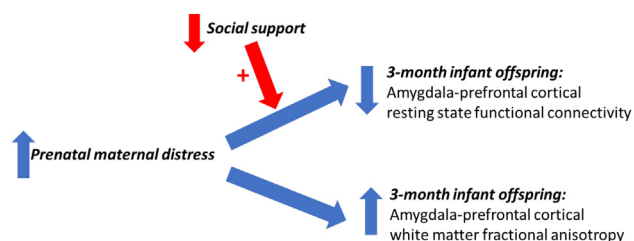Address correspondence to Mary L. Phillips, M.D., at phillipsml@upmc.edu.

Figure 1. A schematic indicating relationships between prenatal maternal distress and infant amygdala–prefrontal cortical resting-state functional connectivity and between prenatal maternal distress and infant amygdala–prefrontal white matter fractional anisotropy and the moderating effect of social support on the former relationship.

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