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Links between Caregiver Postpartum Internalizing Symptoms and Infant Brain and Behavior Raise New Questions

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Rates of pediatric depression and anxiety disorders are steadily increasing in the United States and treatment of these disorders accounts for some of the most expensive health care costs incurred during childhood (1). Recent estimates suggest that around 8% of children aged 6 to 17 years meet diagnostic criteria for depression or anxiety, placing them at increased risk of academic underachievement, poorer social competency, and reduced occupation and income in adulthood (1). Understanding the biological and socioenvironmental mechanisms of internalizing problems in childhood is vital to design targeted, preventative interventions that reduce risks for depression and anxiety and mitigate the individual, family, and economic burden of developmental psychopathology. In the current issue of *Biological Psychiatry,* Phillips et al. (2) examines infant amygdala connectivity with large-scale brain networks as a potential neural mechanism linking caregiver mood/affective problems with infant positive and negative emotionality at age three months.

Longitudinal research suggests that the socioemotional problems implicated in the development of depression and anxiety emerge as early as infancy. For example, high levels of emotional reactivity and difficulty regulating emotions as well as increased behavioral inhibition (characterizing the difficult and slow-to-warm temperament styles, respectively) in infancy confers risk for depression and anxiety in later childhood (3). Individual differences in emotional reactivity, emotion regulation, and behavioral inhibition are thought to be relatively stable across development, thus highlighting the homotypic continuity of difficult and slow-to-warm temperaments for the prediction of internalizing disorders (4). It is no surprise, therefore, that infancy is a foundational period of socioemotional development strongly influenced by the context of the parent-infant dyad (4–6). During infancy, the caregiver acts as the infant's main source of external regulation by responding to and regulating changes in the infant's physiological and arousal states (7). As older infants become increasingly able to inhibit simple behaviors and orient attention away from distressing stimuli, infants begin to transition towards the capacity for internally-modulated emotion regulation (7). Although infancy represents a key period of socioemotional development, few studies have attempted to elucidate the neural processes that underlie

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the emergence of positive and negative emotionality within the first months of life or the extent that these neural underpinnings may be shaped by aspects of the early caregiving environment.

Infancy is an extremely sensitive period of brain development involving rapid and complex changes in brain structure and function (5,8). During the first year of life, total brain volume approximately doubles in size, white matter pathways become more organized from increased myelination and packing of axons, and intrinsic functional connectivity (fc, broadly defined as synchronous fluctuations of neural activity) between brain regions develops such that localized interhemispheric connections and proto forms of large-scale brain networks may be observed using resting state fc-MRI (6,8,9). The infant brain is also highly plastic to environmental exposures. Infant structural and functional brain connections are strengthened by repeated, enriching experiences whereas connections that are less frequently stimulated are pruned back; allowing brain connections to become fine-tuned and more efficient for adaptive functioning in the social environment (8). However, it should also be acknowledged that brain plasticity may be impaired by adverse environmental exposures (8). For example, the amygdala is a key subcortical structure involved in the processing of emotion that has been found to be particularly vulnerable to the effects of stress, overactivating the hypothalamic-pituitary-adrenal (HPA) axis and production of cortisol which has deleterious consequences for the complexity of brain structural and functional connectivity (5,6,8). The amygdala is thought to regulate emotions via dynamic interactions with the ventrolateral and dorsolateral regions of the prefrontal cortex (10). Although amygdala-cortical connections are largely in place at birth, the ways in which the amygdala interacts with large-scale brain networks in the first months of life is unclear (5,6). Thus, Phillips et al. employs a highly innovative approach by examining patterns of functional connectivity between the amygdala and the default mode network (DMN), salience network (SN), and executive control network (ECN) in relation to infant emotionality. The DMN, SN, and ECN are identifiable in infants using resting state fc-MRI, and research in older children and adults has implicated these networks in emotional processing, attention to emotionally relevant stimuli, and the top-down control of emotion regulation (2,9).

With regard to the adverse environmental exposures that alter infant brain development, the extant literature has typically focused on severe caregiving experiences such as neglect, maltreatment, and deprivation (5,6). Although normative variations in parental mood/affective problems are associated with reductions in sensitive parenting behavior and poorer infant socioemotional outcomes (3), the influence of parental mood/affective problems on infant brain functional connectivity is less clear (8). Phillips et al. addresses this critical gap in the literature by examining parental depression/anxiety symptoms in relation to infant amygdala functional connectivity with large-scale brain networks, and in turn, positive and negative emotionality at age three months. Phillips et al. explores these associations in a sample of 58 healthy, term-born infants and replicates findings in a second, independent sample of 31 infants. Both samples underwent resting state fc-MRI scans and a parent-report evaluation of infant temperament using the Infant Behavior Questionnaire-Revised. Caregivers completed the Edinburg Postnatal Depression Scale and the Spielberger State-Trait Anxiety Inventory to assess depression and anxiety symptoms, respectively.

Phillips et al. found that greater infant amygdala-SN connectivity was related to reduced infant positive emotionality, specifically lower levels of smiling. Increased connectivity between the amygdala and the ECN was associated with increased infant smiling. These findings suggest that differential patterns of connectivity between the amygdala and large-scale brain networks are an important neural correlate of rudimentary aspects of emotion signaling in the first months of life, and may also identify key brain networks to target as part of biologically-informed enrichment interventions that optimize infant brain development and support socioemotional development (5,10). In addition to the neural correlates of infant smiling, Phillips et al. found that higher levels of caregiver depression and anxiety symptoms were correlated with reduced infant smiling. These associations persisted after covariate adjustment for caregiver education (as a proxy for socioeconomic status) and quality of caregiving in the home environment. Links between caregiver anxiety and reduced infant smiling were also replicated in the second infant sample, highlighting that caregiver mood/affective problems are a consistent risk factor for early disruptions in infant socioemotional development. Most importantly, Phillips et al. found that greater amygdala-SN connectivity and reduced amygdala-ECN connectivity mediated the association between caregiver mood/affective problems and lower levels of infant smiling.

Phillips et al. primarily attributes the role of parental mood/affective problems on infant amygdala-SN and ECN connectivity, and in turn, infant smiling to the quality of caregiving in the postnatal environment. Indeed, parents with depression and/or anxiety may experience emotional blunting and miss opportunities to interact in ways that facilitate and reinforce positive, reciprocal interactions that strengthen infant brain connections underlying the early expression of positive emotionality (3,8). The link between parent mood/affective problems and decreased infant positive emotionality could also reflect heritable liabilities in emotion dysregulation that increases the propensity for internalizing problems among offspring of parents with psychiatric disorders (3). Furthermore, it is increasingly recognized that maternal mood/affective problems during pregnancy alter the prenatal environment such that increased maternal cortisol and inflammation may over-activate the developing fetal HPA axis, with deleterious consequences for emergent brain connections (8). Phillips et al. offers an extremely valuable first step in understanding how normal variations in parental mood/affective problems are cross-sectionally associated with the neural underpinnings of infant emotionality, and beckons future research to elucidate the causal consequences of parental mood/affective problems and/or the effects of prenatal programming. Future research should include measures of past or lifetime history of parental depression/anxiety to account for heritable influences independent of the current caregiving environment, as well as control groups matched for pre vs. postnatal timing of parental depression and anxiety. Larger, longitudinal research studies beginning in the prenatal period are also needed to determine whether parental mood/affective problems precede and thus shape the unfolding of infant brain fc-socioemotional development.

When taken together, the findings of Phillips et al. suggest that emerging patterns of functional connectivity between brain regions involved in emotional processing, attention to emotionally relevant stimuli, and the top-down control of emotion regulation are already being shaped by the caregiving environment in the first months of life. Additionally,

Phillips et al. provides evidence that normal variations in caregiver mental health have important impacts on the development of infant brain connectivity and positive emotionality. Addressing the full spectrum of postpartum depression and anxiety symptoms, not just those that reach clinical significance, may be important to support infant brain and socioemotional development. Finally, Phillips et al. demonstrates the usefulness of resting state fc-MRI for the identification of neural biomarkers underlying early emotion regulation problems before socioemotional impairments may be observed in later childhood. Findings may not only inform the identification of infants who may be at greatest risk for later impairments, but also infants who may benefit the most from early identification and intervention (5,6).

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