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Neonatal Brain Structure and Cognitively Stimulating Parenting Differentially Relate to Cognitive and Behavioral Outcomes of Children Born Very Preterm

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The survival rates of infants born very preterm (VPT) (<33 weeks' gestational age) have improved over the past 20 years, but the incidence of longer-term neurodevelopmental delays and impairments observed in these children has remained stable. One area of particular concern is cognitive development. Two recent meta-analyses suggest that VPT children and adolescents have standardized IQ scores nearly 1 standard deviation below their full-term peers (1,2). VPT children and adolescents also perform less well on neuropsychological measures of executive function and processing speed (2), indicating that VPT birth is associated with difficulties across multiple cognitive domains. In addition, both cross-sectional and longitudinal studies have reported higher levels of co-occurring anxiety, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) symptoms in VPT children compared with full-term children (3,4). This specific constellation of anxiety, ADHD, and ASD symptoms among VPT children has led to the increasing recognition of the preterm behavioral phenotype. Indeed, the behavioral phenotype is two to three times more prevalent in VPT children, with symptoms emerging in early childhood and persisting into adolescence (3,4).

As VPT birth confers risk for cognitive and socioemotional impairments (4), much attention has been devoted to understanding potentially modifiable neurobiological and socioenvironmental mechanisms that shape the developmental trajectories of VPT children. However, most longitudinal neurodevelopmental studies in this population have largely been conducted as two parallel lines of work that investigate either neonatal brain development or parenting quality in the home environment as predictors of outcome. Furthermore, most follow-up studies have included a narrow range of outcomes, limited to either cognitive or socioemotional development (4–6). In the current issue of *Biological Psychiatry: Global Open Science,* Vanes *et al.* (7) examine neonatal brain structural covariance networks (SCNs) and cognitively stimulating parenting in relation to co-occurring cognitive problems and preterm behavioral phenotype symptoms in school-age VPT children. Vanes *et al.* also investigate the additive and interactive effects of neonatal SCNs and cognitively stimulating parenting on outcomes to elucidate the modifiable aspects of the caregiving environment that may support brain–behavior development in VPT children.

VPT birth is associated with widespread alterations in neonatal structural and functional brain development, including decreased global and regional brain volumes, smaller cortical surfaces with less complex gyral and sulcal development, aberrant white matter microstructure, and reduced functional network connectivity (4,8). Neonatal reductions in frontal, temporal, parietal, and occipital brain volumes as well as smaller thalami and amygdala have been linked to neurodevelopmental and socioemotional impairments in VPT children (4,8). However, conventional structural magnetic resonance imaging (MRI) findings have only explained a modest proportion of variance in outcome. Thus, more novel approaches are needed to increase the predictive utility of neonatal structural MRI to identify VPT infants who are at greatest risk of poor outcome. As such, recent investigations have begun to leverage network-based approaches to reveal the neuropathological basis for later cognitive and behavioral impairments (4,5,8). Little is known about the ways in which VPT birth disrupts the coordinated growth of spatially distributed sets of brain regions. Furthermore, the extent to which neonatal alterations in brain structural networks precede the evolution of subsequent cognitive and socioemotional problems is unclear (5,8).

Longitudinal research suggests that the neural underpinnings of cognitive and socioemotional development in VPT children may be supported by the early caregiving environment (6,9). Early brain development is experience-expectant, such that interactions within the parent–infant dyad stimulate and strengthen brain connections and thus progressively shape the structural and functional architecture of the infant brain (5,6,10). In a recent longitudinal study of VPT children, exposure to sensitive parenting at 2 years of age was associated with greater growth of the amygdala from birth to 7 years of age, whereas intrusive parenting predicted smaller intracranial and gray matter volumes (9). Warm and nurturing parenting that meets the emotional needs of the infant is likely to support emerging self-regulation skills that are important for later mental health, and cognitively stimulating parenting provides infants with opportunities to engage in problem solving and learning activities that directly facilitate cognitive development (6). These previous findings suggest that the quality of the early caregiving environment is important for both cognitive and socioemotional outcomes (6) as well as structural brain development (9) in VPT children. The degree in which altered neonatal SCN development and exposure to cognitively stimulating parenting differentially relate to cognitive and socioemotional outcomes in VPT children is unknown.

SEE CORRESPONDING ARTICLE ON PAGE 146

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To address this important gap in the extant literature, Vanes *et al.* (7) examine neonatal SCNs and cognitively stimulating parenting in relation to cognition, executive function, and socioemotional outcomes in a longitudinal cohort of VPT children ($<$33 weeks' gestational age, born 2010–2013). At term-equivalent age, 384 VPT infants underwent structural brain MRI to assess regional brain volumes. Vanes *et al.* use an innovative, data-driven approach by analyzing the structural images with nonnegative matrix factorization to identify SCNs, which represent the coordinated maturation of regional brain volumes that vary across individuals in a consistent manner. At school age, VPT children (n = 206) underwent a standardized assessment of general cognitive ability and a comprehensive battery of parent-report questionnaires measuring executive function behaviors, ADHD symptoms, internalizing and externalizing problems, ASD traits, temperament, empathy, and prosocial behavior. To assess the quality of the caregiving environment, parents completed the Cognitively Stimulating Parenting Scale, which is based on the gold-standard Home Observation for Measurement of the Environment Inventory.

Vanes *et al.* (7) undertook a principal component analysis of measures of cognitive ability and executive and socioemotional functioning to determine the latent structure of the co-occurring impairments associated with VPT birth. Results of the principal component analysis yielded three latent components. The first component (PC1) comprised ADHD symptoms, ASD traits, and executive dysfunction. There was also some evidence that poorer cognitive ability was related to behavioral–executive problems. Importantly, the PC1 component is highly consistent with the known preterm behavioral phenotype and with previous work recognizing executive dysfunction as a transdiagnostic risk factor for developmental psychopathology. The second component (PC2) primarily represented global cognitive ability, spanning verbal and nonverbal intellectual skills, working memory, and processing speed, along with modest loadings for emotional control. The third component (PC3) comprised measures of child temperament, empathy, and prosocial behavior. Future work may consider including multi-informant perspectives on child psychopathology as well as a task-based assessment of executive function, which may capture the underlying cognitive processes involved in the top-down control of self-regulation for goal-directed behavior.

Perhaps the most intriguing finding from Vanes *et al.* (7) is that neonatal SCNs and cognitively stimulating parenting behavior were differentially related to PC1 and PC2 outcomes. While the nonnegative matrix factorization identified 15 SCNs, one particular SCN encompassing the anterior cingulate cortex, inferior frontal gyrus, insula, inferior parietal cortices, and middle occipital gyrus was important for developmental outcome. Specifically, increased volume in these brain regions was associated with higher cognitive PC2 component scores. This finding persisted after accounting for gestational age, sex, postmenstrual age at scan, and socioeconomic status. It was also present in the absence of significant brain injury. Although structural alterations in a similar set of brain regions have been linked with cognition in VPT adults (8), Vanes *et al.* show that disruptions in the coordinated growth of cingulate, frontal, insula, parietal, and occipital brain regions during the neonatal period precedes the emergence of cognitive impairments in later childhood for VPT children. Interestingly, there was no association between neonatal SCNs and the behavioral–executive PC1 component. This may suggest that white matter microstructure and/or intrinsic functional network connectivity underlies the preterm behavioral phenotype (4).

Vanes *et al.* (7) also found that exposure to more cognitively stimulating parenting was specifically associated with better behavioral–executive PC1 component scores but not cognitive PC2 component scores. Furthermore, there was no evidence of an interaction between neonatal SCNs or cognitively stimulating parenting for either PC1 or PC2 outcomes. It is possible that brain network development may mediate the link between exposure to stimulating parenting and improved cognitive and socioemotional outcomes in VPT children (9,10). Interestingly, Vanes *et al.* also found that neither neonatal SCNs nor parenting behavior predicted PC3 component scores. Because temperament is highly heritable, future work should include maternal measures of self-regulation and mental health, as these family background factors may be related to offspring socioemotional development via epigenetic processes or transmitted through parenting behavior (4,10).

The novel findings of Vanes *et al.* (7) elucidate the independent neural and socioenvironmental pathways contributing to the cognitive and preterm behavioral phenotype outcomes of school-age VPT children. These data suggest that the quality of parenting behavior in the home may be an important modifiable target to enhance resiliency and support the longer-term behavioral development of VPT children (6). Vanes *et al.* also highlight the importance of neonatal brain structural growth and development for subsequent cognitive outcomes. Thus, individual precision MRI of regional structural brain development may identify VPT infants in greatest need of close developmental surveillance, as well as those who may benefit the most from early referral to cognitively stimulating interventions (5,8).

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