Regional Cerebral Development at Term Relates to School-Age Social–Emotional Development in Very Preterm Children

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Objective: Preterm children are at risk for social–emotional difficulties, including autism and attention-deficit/hyperactivity disorder. We assessed the relationship of regional brain development in preterm children, evaluated via magnetic resonance imaging (MRI) at term-equivalent postmenstrual age (TEA), to later social–emotional difficulties. **Method:** MR images obtained at TEA from 184 very preterm infants (gestation <30 weeks or birth weight <1,250 g) were analyzed for white matter abnormalities, hippocampal volume, and brain metrics. A total of 111 infants underwent diffusion tensor imaging, which provided values for fractional anisotropy and apparent diffusion coefficient. Social–emotional development was assessed with the Infant Toddler Social and Emotional Assessment (ITSEA) at age 2 and the Strengths and Difficulties Questionnaire (SDQ) at age 5 years. **Results:** Higher apparent diffusion coefficient in the right orbitofrontal cortex was associated with social–emotional problems at age 5 years (peer problems, $p < .01$). In females, smaller hippocampal volume was associated with increased hyperactivity ($p < .01$), peer problems ($p < .05$), and SDQ total score ($p < .01$). In males, a smaller frontal region was associated with poorer prosocial ($p < .05$) scores. Many of the hippocampal findings remained significant after adjusting for birthweight z score, intelligence, social risk, immaturity at birth, and parental mental health. These associations were present in children who had social–emotional problems in similar domains at age 2 and those who did not. **Conclusions:** Early alterations in regional cerebral development in very preterm infants relate to specific deficits in social–emotional performance by school-age. These results vary by gender. Our results provide further evidence for a neuroanatomical basis for behavioral challenges found in very preterm children. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(2):181–191. **Key Words:** preterm infant, neurodevelopment, social–emotional development, orbitofrontal cortex, hippocampus

Preterm birth is a major public health issue, principally because of the high risk for adverse developmental outcomes in survivors. Between 30% and 60% of very preterm (VPT) children (born at <30 weeks' gestation) will experience cognitive challenges and learning disabilities.[1,2] In addition, there is a growing literature reporting delays in social–emotional development with an increased prevalence of anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), and autism.[3-5] Indeed, children born <26 weeks are three times more likely to have a psychiatric diagnosis at age 11 years compared with full-term peers.[3] ADHD—inattentive type was the most common diagnosis, with rates among extremely preterm children four times higher than those of their peers. There were also significant increases in emotional disorders, anxiety disorders, and autism.

As previously published, our cohort of VPT infants had higher internalizing and dysregulation scores and lower competence scores as measured by the Infant Toddler Social and Emotional Assessment (ITSEA) at age 2 years when compared with peers born at term.[6] More recently, we have also found that early social–emotional difficulties at age 2 years predicted comparable difficulties at age 5, and we have noted increased

emotional symptoms, peer relationship difficulties, elevated hyperactivity/inattentive symptoms (Treyvaud et al., unpublished material, 2011) and overall social–emotional difficulties at age 5 as measured by the Strengths and Difficulties questionnaire (SDQ) compared with same-age peers.[7] Others have also noted similar social–emotional challenges at age 5 years.[8] Similarly, parental reports of social–emotional problems at ages 2 and 6 years were predictive of psychiatric diagnoses at age 11 years.[8]

Preterm birth is also associated with brain injury and altered cerebral development. Magnetic resonance imaging (MRI)–based studies have revealed that VPT infants commonly display a variety of white matter abnormalities, including diffuse signal abnormalities, loss of volume, enlarged ventricles, and delayed maturation.[9-12] VPT infants at term-equivalent postmenstrual age (TEA) also exhibit gray matter abnormalities, including decreased gray matter volume and delayed cortical gyration.[13-15] These alterations in brain structure by TEA are predictive of later cognitive deficits,[15-18] with some studies reporting that specific regional abnormalities are associated with particular cognitive delays, including deficits in IQ and working memory.[16,17,19]

Evidence for a relationship between altered neonatal cerebral development and later cognitive deficits is emerging in the VPT population; however, less is known about the relationship between aberrant cerebral development and social–emotional outcomes in this group. A few studies have related abnormalities in cerebral development to psychiatric symptomatology in preterm adolescents,[20,21] including a reduction in hippocampal volume in preterm adolescents with ADHD.[22] In addition, white matter abnormalities and cerebellar hemorrhage during infancy have been associated with social deficits.[6,23] Notably, a large proportion of preterm children that screened positive for autism had normal conventional MRIs, emphasizing the need for more sensitive, quantitative MRI approaches for detecting the neuroanatomical basis for social–emotional deficits in preterm infants.[24] The relative influence of aberrant neonatal cerebral development on social–emotional outcomes compared with other well-known risk factors more common among parents of preterm infants,[25-27] including parental mental illness, lower maternal education, and lower socioeconomic status,[28-30] also remains unclear.

The current study aims to address these issues by evaluating the relationship between cerebral development at TEA (determined using the MRI techniques of diffusion tensor imaging, regional brain volumes, and brain metrics) and social–emotional outcomes at age 5 in a cohort of VPT children. We assessed whether alterations of development in brain regions implicated in social–emotional development by prior research, such as the frontal lobes and orbital frontal cortex (OFC),[31] temporal cortex,[32] cerebellum,[33] and hippocampus,[34] would be associated with impaired social–emotional outcomes at age 5 years, even after adjusting for sociodemographic factors. A secondary aim was to evaluate whether any associations between the neonatal brain markers and social–emotional outcomes at age 5 varied depending on whether these behavioral problems were also noted at age 2.

METHOD

Participants

The families were recruited for this study as part of the Victorian Infant Brain Studies (VIBeS) cohort between 2001 and 2003. Entry criteria included being born at less than 30 weeks gestation or weighing less than 1,250 g at birth. The VPT infants were born at or transferred shortly after birth to the Royal Women's Hospital, Melbourne, Australia. Infants were excluded if they had a major congenital abnormality associated with early mortality. The study was approved by the Research and Ethics Committees at the Royal Children's and Women's Hospital. Informed parental consent was obtained for all participants.

Magnetic Resonance Imaging

VPT infants that underwent an MRI scan of their brain at term equivalent postmenstrual age (TEA), 37 to 43 weeks, are included in this analysis. The MRI was performed without sedation or anesthesia using a 1.5T Signa LX Echospeed system (GE Healthcare, Milwaukee, WI). The sequences that were used included a three-dimensional (3D) Fourier transform spoiled gradient recalled-echo sequence; a double-echo (proton-attenuation and T2-weighted) spin-echo sequence; and a line scan diffusion sequence, with details previously published.[35] The MR images were analyzed for the following: qualitative white matter abnormalities; hippocampal volume; brain metrics; and the diffusion parameters apparent diffusion coefficient (ADC) and fractional anisotropy (FA).

Qualitative MR Image Analysis. An established qualitative scoring system was used to classify white matter as normal, mild, moderate, or severe.[36] All