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Preterm birth and the developing brain

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Converging data suggest that preterm birth perturbs the genetically determined programme of corticogenesis in the developing brain. The number of infants delivered preterm in the USA has risen by 20% since 1990, and this increase has been accompanied by significant declines both in mortality and in neonatal morbidities that are common in premature infants.¹ By contrast, the incidence of neurodevelopmental disability in preterm populations has changed little over time. As recently reported by Larroque and colleagues² as part of the EPIPAGE study, only 61% of infants born at 24–32 weeks' gestational age were free of mild, moderate, or severe disability at 5 years of age. Consistent with other studies, the infants with the lowest gestational ages (24–28 weeks) and male neonates were most vulnerable to adverse neurodevelopmental outcomes.

Numerous MRI studies have documented the structural sequelae of preterm birth in the newborn period, in childhood, and beyond. Because neurodevelopmental outcome after preterm birth is complex, understanding of the neurobiological mechanisms that support brain development after premature birth is crucial.



Studies have shown that preterm children have decreased cerebral volumes at 7–15 years of age, and that cortical grey matter, cortical white matter, the basal ganglia, and the cerebellum have smaller volumes in preterm children than in age-matched term controls.³ Additionally, studies of children who were born prematurely suggest that different regions of the developing preterm brain are differentially vulnerable, and that the brains of male and female preterm children are affected differently. Frontotemporal and hippocampal regions seem to be most vulnerable to volumetric changes, the left hemisphere is more often affected than is the right, and premature males are more likely to experience white matter abnormalities than are females born preterm.^{4–6}

These findings have been supported by the recent introduction of voxel-based morphometry (VBM) and diffusion-tensor imaging (DTI) strategies for assessment of people born prematurely. DTI studies of fractional anisotropy, a measure of fibre tract organisation, suggest differences in neural connectivity throughout the brains of preterm children compared with term controls at 12 years of age.⁷ Similarly, studies of preterm adolescents show significant abnormalities in white matter regions through the cerebrum.⁸ Notably, both DTI and VBM measurements have been shown to correlate with cognitive outcome in people who were born prematurely, and significant correlations have been reported between changes in white matter VBM and gestational age: the lower the gestational age, the poorer the white matter integrity.^{8,9}

However, the true effect of preterm birth on the developing brain at the equivalent age to term remains largely unresolved. Studies have documented smaller cortical surface area, lower grey and white matter volumes, and widespread microstructural abnormalities in preterm infants at term-equivalent age compared with term controls,¹⁰ and Kapellou and colleagues¹¹ have suggested that the scaling relationship that determines brain growth is disrupted in children who are born prematurely. However, a more recent report showed that preterm infants with no

major neurological abnormalities do not have smaller cerebral volumes at term-equivalent age than do term controls.¹² Furthermore, both bronchopulmonary dysplasia and intraventricular haemorrhage have been identified as risk factors for impaired brain growth at term-equivalent age.^{12,13}

Functional MRI (fMRI) might offer information about neural systems in the developing preterm brain, and strategies that use auditory stimuli have been successful in the study of infants as young as 33 weeks' gestational age. Similarly, activation in response to visual stimulation can be detected in blood-oxygen-level dependent (BOLD) signals at term-equivalent ages, and might also provide useful information.

fMRI strategies are particularly useful for the study of language and memory, and fMRI studies of language in preterm children at adolescence suggest hyperfrontality of the developing brain—ie, BOLD signals traditionally recorded in the temporal regions of age-matched term and adult controls are detected in the right frontal lobes of the preterm group.¹⁴ Similarly, fMRI studies of memory, attention, and executive function suggest the engagement of alternative, right-sided neural networks in the brains of preterm children and adolescents.¹⁵

Finally, MRI studies might provide important insights into the effect of early intervention strategies, as suggested by Larroque and colleagues,² on the developing preterm brain. Als and colleagues¹⁶ used DTI strategies to document positive changes in fractional anisotropy in preterm infants randomised to early intervention before term-equivalent age. Shaywitz and colleagues¹⁷ used fMRI techniques to show greater recruitment of traditional language regions of the brain in children with reading disabilities who were exposed to an innovative school-based reading intervention compared with those in the customary school-based reading programme and those who received no intervention. The children in this study maintained both their improvement in reading skills and their fMRI BOLD signal changes 1 year after the intervention, suggesting that fMRI strategies are useful for examination of neural networks in the developing brain.

The neurobehavioural sequelae of preterm birth are a major paediatric public health problem of this decade. Emerging data suggest that MRI studies might help neonatologists, neurologists, and neuroscientists alike to identify antenatal, neonatal, and post-discharge interventions that have a positive effect on the developing preterm brain.

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