# Extreme Premature Birth is not Associated with Impaired Development of Brain Microstructure

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**Objective** To assess whether birth at <26 weeks gestation is an important predictor of brain microstructure maturation as determined by using diffusion tensor imaging.

**Study design** We performed serial magnetic resonance imaging and diffusion tensor imaging in 176 infants born at <33 weeks gestation. Diffusion parameters were calculated for white and gray matter regions. Linear regression for repeated measures was used to assess the effect of extremely premature birth on brain maturation.

**Results** In white matter, fractional anisotropy increased by 0.008 per week (95% CI, 0.007-0.009; $P < .0001$) and mean diffusivity decreased by 0.021 $mm^2$/sec per week, (95% CI, –0.24–0.018; $P < .0001$). Birth at <26 weeks was associated with lower white matter fractional anisotropy (–0.01; 95% CI, –0.018–0.003; $P = .008$), but this effect was eliminated when co-morbid conditions were added to the model. Moderate-severe brain injury was associated with decreased mean white matter fractional anisotropy (–0.012; 95% CI, –0.02–0.004; $P = .002$).

**Conclusion** Brain microstructure maturation as measured serially in premature infants is independent of extremely premature birth. Brain injury and co-morbid conditions may be the important determinants of microstructure maturation. *(J Pediatr 2010;157:726-32)*.

Advances in perinatal care have led to an increase in the survival of extremely low birthweight infants and an increase in infants born at the limits of viability.[1,2] These infants are at significant risk for motor and neurodevelopmental impairments and have the highest risk for adverse outcome.[2-4] Infants born at the limits of viability are known to be at risk for early neonatal morbidity and long-term adverse neurodevelopmental outcomes.[3-6] Although white matter injury is thought to be associated with these impairments, not all extremely premature infants have this type of injury identified on magnetic resonance imaging (MRI).[7,8] Advanced MRI techniques that can be used to study regional and global brain development include diffusion tensor imaging, tractography, spectroscopy, volumetrics, and deformation-based morphometry; these techniques may help to clarify the factors that lead to neurodevelopmental impairments.[9-13] Outcomes of these neonates are most often attributed to premature birth, with the youngest having the worst outcomes. It remains unclear, however, whether birth at an extremely young age by itself leads to abnormal brain development, white matter injury, and poor neurodevelopmental outcome or whether the perinatal complications associated with extremely premature birth are the cause.[6]

Diffusion tensor imaging is an imaging technique in which the microscopic random motion of water molecules can be used to study brain maturation in premature infants.[13] As the brain develops, brain water content decreases, extracellular spaces diminish in size, and the intracellular and intercellular microstructures become more complex and organized. The mean diffusivity of water decreases in gray and white matter structures, and the directional coherence of water diffusion, represented by fractional anisotropy, increases[14] in the developing white matter, as the premature newborn develops to term-equivalent age.[9,15-17] In our earlier work, we showed that the presence of white matter injury is associated with impaired microstructural development in preterm newborns scanned with diffusion tensor imaging early in life and again at term-equivalent age.[15] Abnormal white matter microstructure at term-equivalent age is associated with adverse neurodevelopmental (cognitive and motor) outcome.[18-21] Premature newborns without focal white matter abnormalities at term-corrected age may have microstructural abnormalities evident at two years of age that correlate with neurodevelopmental assessment scores.[22]

A major question in neonatal medicine remains whether the adverse outcomes of extremely premature neonates relate to the degree of prematurity itself or to adversities encountered by this group of newborns during their neonatal course, such as hypoxia-ischemia, infections, necrotizing enterocolitis (NEC),[23] or chronic lung disease (CLD). The impact of premature birth has been addressed in MRI measures of brain volume at term-equivalent age.[10]

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| CLD | Chronic lung disease |
| MRI | Magnetic resonance imaging |
| NEC | Necrotizing enterocolitis |
| PDA | Patent ductus arteriosus |
| UBC | Children's & Women's Health Center of British Columbia |
| UCSF | University of California, San Francisco |

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The purpose of this study is to determine the independent effect of extremely premature birth (24 to 25-6/7 weeks gestation) on the development of brain microstructure as assessed with diffusion tensor imaging in a large multicenter cohort of premature neonates studied serially.

## Methods

The study population includes infants born between 24 and 33 weeks gestation, admitted to the intensive care nurseries at University of California, San Francisco (UCSF) and the Children's & Women's Health Center of British Columbia (UBC). Exclusion criteria included evidence of congenital infections, malformations or chromosomal anomalies, and ultrasound scanning evidence of large (>2 cm) parenchymal hemorrhagic infarction. The study subjects underwent imaging twice according to study protocol, the first scan occurring as soon as the infant was deemed clinically stable by the attending neonatologist and the second before transfer to a referring institution, discharge home, or at term-equivalent age. The study was approved by the Committee on Human Research at UCSF and by the UBC Clinical Research Ethics Board. Informed consent was obtained from the parents or legal caregiver of each infant.

At both institutions, infants were transported in an MRI compatible incubator and accompanied by a physician, a team of dedicated neonatal research nurses, or both. As described previously, most scans at UCSF were obtained without the use of sedating medications.[24] No sedation was used in the cohort from UBC.

Clinical risk factors previously related to the risk of brain injury or adverse neurodevelopmental outcome were obtained prospectively and included gestational age at birth, birthweight, infant sex, mode of delivery, exposure to antenatal steroids, need for exogenous surfactant at delivery, Apgar scores, days of mechanical ventilation, presence of a patent ductus arteriosus (PDA), NEC, exposure to postnatal infection, and diagnosis of CLD (defined as the need for supplemental oxygen at 36 weeks corrected gestational age).[2,4-6,24-27] The clinical condition of the newborns at term-equivalent age was described with a neuromotor score (range, 0-5) previously found to be a means of predicting adverse neurodevelopmental outcomes (scores ≥3 considered abnormal).[24]

### Magnetic Resonance Imaging

Newborns at UCSF were scanned on a 1.5-Tesla Signa (GE Healthcare, Little Chalfont, United Kingdom) with a MRI-compatible incubator with a dedicated neonatal head coil. T1-weighted, T2-weighted, and 3-dimensional spoiled gradient echo images were acquired with sequences optimized for this scanner.[24] The diffusion tensor imaging data were acquired by using a multi-repetition, single-shot echo planar sequence with 6 gradient directions (TR 7s/TE 100ms/slice thickness of 3mm), and 3 acquisition averages with b = 600s/mm$^2$, 1 b = 0s/mm$^2$ volume, and an in-plane resolution of 1.4 x 1.4 mm. Newborns at UBC were scanned with a Siemens 1.5 Tesla Avanto with VB 13A software (Siemens, Erlangen, Germany), an MRI-compatible isolette (Lammers Medical Technology, Luebeck, Germany), and specialized neonatal head coil (Advanced Imaging Research, Cleveland, Ohio). Studies included: 3-dimensional coronal volumetric $T_1$-weighted images (TR 36 ms/TE 9.2 ms/FOV 200 mm/slice thickness 1 mm/no gap), and axial fast spin echo $T_2$-weighted images. The diffusion tensor imaging data were acquired with a multi-repetition, single-shot echo planar sequence with 12 gradient directions (TR 4900 ms/TE 104 ms/FOV 160 mm/slice thickness 3 mm/no gap), and 3 averages of 2 diffusion weightings of 600 and 700 sec/mm$^2$ (b value) and an image without diffusion weighting, and an in-plane resolution of 1.3 mm.

Two pediatric neuroradiologists at UCSF and 1 pediatric neuroradiologist at UBC who were blinded to the infants' neonatal course reviewed the images. The MRI results were scored for the presence and size of white matter injury (no white matter injury, minimal, moderate, and severe), with scores developed by our group with high reported inter- and intra-rater reliability.[24,28] Some infants were further categorized as having moderate to severe brain injury, defined a priori as the presence of moderate or severe white matter injury as aforementioned, or ventriculomegaly (>8 mm measured at the level of the glomus of the choroid plexus) or the presence of grade III/IV intraventricular hemorrhage.[24]

From the diffusion tensor imaging data, fractional anisotropy and mean diffusivity values were calculated from 5 white matter regions bilaterally, and mean diffusivity values were also obtained from 4 gray matter regions bilaterally (**Figure**).[15]

### Data Analysis

Statistical analyses were performed with Stata software version 9.2 (Stata Corporation, College Station, Texas). The

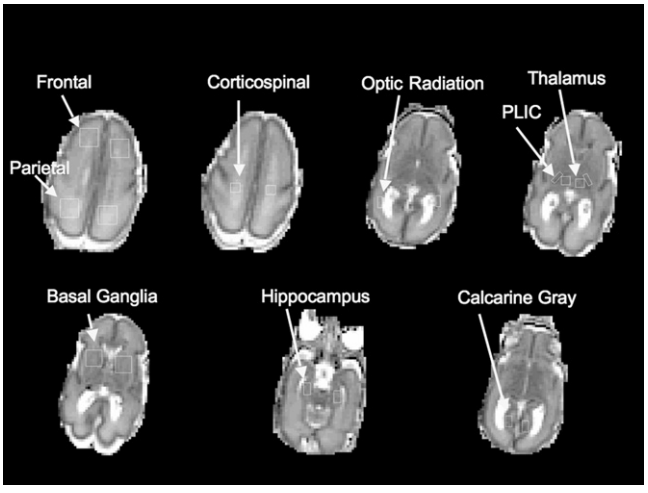


**Figure.** Regions of interest. These are the unsmoothed ADC maps that demonstrate the regions of interest in which mean diffusivity and fractional anisotropy were measured in white and gray matter regions. This infant was born at 24.5 weeks gestation and underwent imaging at 29 weeks.