Original Article

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# Using Diffusion Tensor Imaging and Fiber Tracking to Characterize Diffuse Perinatal White Matter Injury: A Case Report

Jason D. Yeatman, BA, Michal Ben-Shachar, PhD, Roland Bammer, PhD, and Heidi M. Feldman, MD, PhD

Prematurity is associated with white matter injury. Diffusion tensor imaging, a new magnetic resonance imaging technique, identifies white matter fiber tracts and quantifies structural properties. We used diffusion tensor imaging fiber tracking to compare white matter characteristics in a 12-year-old born prematurely and full-term control. We divided fibers passing through the corpus callosum into 7 segments based on cortical projection zones and analyzed them for fractional anisotropy, axial diffusivity, and radial diffusivity. We also compared corticospinal and somatosensory tracts in the participant and control. The participant had decreased factional anisotropy in every callosal segment, particularly in superior and posterior parietal projections. Fractional anisotropy of the corticospinal and somatosensory tracts was not lower in the participant than control. Fiber tracking allowed precise localization and visualization of white matter injuries of the corpus callosum associated with prematurity. Quantitative measures suggested myelin deficiencies across the corpus callosum, particularly in parietal projections.

**Keywords:** white matter injury; diffusion tensor imaging; prematurity; fiber tracking

Premature birth is associated with white matter injury. Current theories attribute this damage to hypoxic/ischemic injury of developing oligodendrocytes.[1] Although focal, cystic, lesions may be apparent in T2-weighted magnetic resonance imaging (MRI), diffuse white matter abnormalities may not be detected using conventional MRI. Diffusion tensor imaging, a new MRI technique that measures the microstructural properties of white matter, is a promising method for quantifying white matter integrity and identifying regions with diffuse damage. Using diffusion tensor imaging, studies have compared the white matter integrity of groups of children born prematurely to that of children born at term and found that the corpus callosum is an area of particular vulnerability.[2-6] Diffusion measures in the corpus callosum have been found to correlate with cognitive and motor function in group analyses.[7]

A limitation in many studies using diffusion tensor imaging is that they warp individual brain images to a common template to allow for group comparisons. Warping algorithms are not designed to handle individual variation in anatomy, particularly in cases of neural injuries. Poor alignment of white matter structures may lead to errors in identification of damaged tracts.[8,9] From a clinical perspective, decisions are made at the individual level, taking into account the cognitive, behavioral, and neurological characteristics of the patient. It is therefore important to establish the contribution of diffusion tensor imaging at the individual level.

We used diffusion tensor imaging and fiber tracking methods to characterize white matter properties in a child who was born prematurely and a control born at term. We focused our analysis on the corpus callosum for 3 reasons: (1) damage to this structure in premature birth is known to be related to neuropsychological outcome[10]; (2) previous studies have developed a reliable, reproducible

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From the Departments of Pediatrics (JDY, RB, HMF) and Radiology (RB), Stanford University, School of Medicine, Stanford, California, Department of Psychology, Stanford University, Stanford, California (MB-S); and Department of Linguistics and Gonda Brain Research Center, Bar Ilan University, Ramat Gan, Israel (MB-S).

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Address correspondence to: Heidi M. Feldman, MD, PhD, Department of Pediatrics, Stanford University School of Medicine, 750 Welch Road, Suite 315, Palo Alto, CA 94304; e-mail: hfeldman@stanford.edu.

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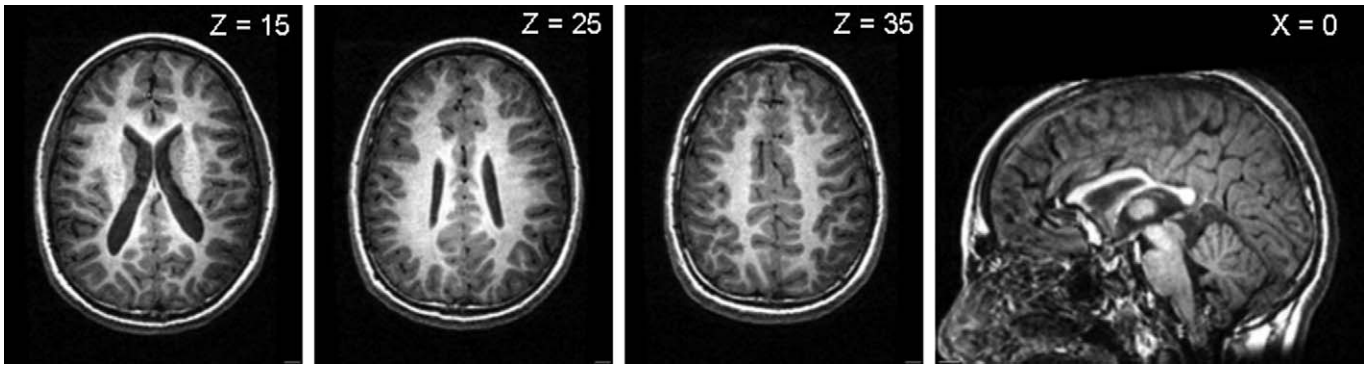


**Figure 1.** Three axial slices and 1 sagittal slice from the T1-weighted magnetic resonance imaging scan of the participant born prematurely.

method to define and segment the callosum in adult stroke patients and healthy controls; and (3) quantitative measures of diffusion in specific callosal segments have been reported for typically developing children, providing a required benchmark for comparison of the values obtained in this case study.[11,12] We included the corticospinal and somatosensory tracts as a comparison. We demonstrate that fiber tracking provides greater specificity in determining the location of injury in the corpus callosum than do volume-based methods. The technique also leads to inferences regarding the underlying neurobiological mechanisms of injury.

## Case Report

The participant of the study was a 12-year-old boy who was born at 25 weeks gestation, weighing 768 g. He required more than 1 month of mechanical ventilation and 2 months of oxygen supplementation. He developed sepsis and required surgical ligation of a patent ductus arteriosus. Three cranial ultrasounds during the neonatal period and an electroencephalogram were negative. He was discharged at 16 weeks of age. Follow-up evaluations found mild asymmetric spastic cerebral palsy, affecting the right lower leg more than the left. He attended small private schools because he showed poor attention and behavior regulation in large classrooms despite average academic achievement on individual testing. We conducted neuropsychological testing on the participant at 12 years of age. A control child was matched for age, gender, and socioeconomic status and underwent the same imaging and tractographic procedures. Neuropsychological test scores were within 1 standard deviation of the population mean for both children. Figure 1 shows 3 axial slices and 1 sagittal slice from a T1-weighted MRI of the participant's brain, demonstrating enlarged asymmetric lateral ventricles (left greater than right), a thin corpus callosum, and normal appearing parietal lobes. The T1-weighted image of the control child's brain was normal.

## Methods

The protocol was approved by the Institutional Review Board of Stanford University. Written consent was obtained from parents and verbal assent from the participants.

### Diffusion Tensor Imaging Acquisition and Preprocessing

Diffusion tensor imaging data were acquired on a 3T Signa Excite (GE Medical Systems, Milwaukee, Wis). We used a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence (echo time = 80 ms, repetition time = 8400 ms, field of view = 240 mm, matrix size = 128 × 128) to acquire sixty 2-mm thick slices (0-mm gap) in 23 different diffusion directions ($b$ = 850 s/mm$^2$) and 2 nondiffusion-weighted ($b$ = 0 s/mm$^2$) volumes. We repeated this sequence 4 times.

The data were preprocessed and analyzed using Matlab (The Mathworks, Nattick, Mass) and C++-based software tools: mrDiffusion and CINCH (available for download at http://white.stanford.edu/software). Diffusion tensor images were corrected for eddy current distortions and registered to the T1-weighted image.[13] For each voxel in the scanned volume, a tensor model was fitted and the fractional anisotropy calculated.[14] Fractional anisotropy ranges from 0 to 1; higher values indicate that water diffusion is restricted in 1 direction relative to other directions.

### Fiber Tracking and Callosal Segmentation

Our analysis is based on the protocol developed by Huang et al[11] for callosal segmentation in adult stroke patients and modified by Dougherty et al[12] for analysis of typically developing children.[12,15,16] As a first step, we tracked fibers from left hemisphere and right hemisphere masks; for each hemisphere, 8 seed points were placed at equidistant locations in all voxels where the fractional anisotropy value was greater than 0.2. Fiber tracts were estimated using a deterministic streamlines tracking algorithm with a fourth-order Runge-Kutta path integration method.[17] For tracking purposes, a continuous tensor field was estimated using trilinear interpolation of the tensor elements.

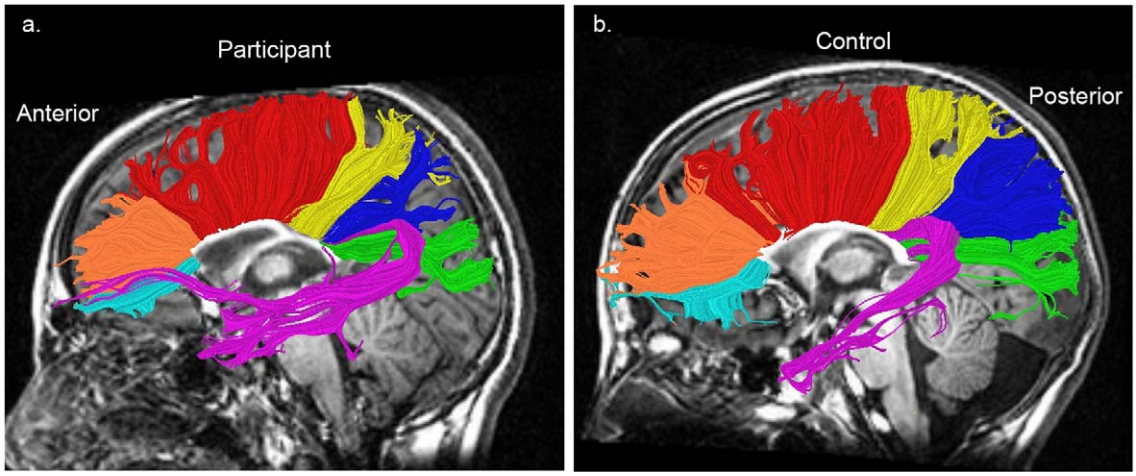


**Figure 2.** Cortical projections of the corpus callosum for the participant, a child born prematurely (A), and a control (B), based on procedures from Dougherty et al.[12] Segment (color code): occipital (green), posterior parietal (blue), superior parietal (yellow), superior frontal (red), anterior frontal (orange), orbital (cyan), and temporal (purple).

Stopping criteria for path tracing were fractional anisotropy <0.15 or turning angle >30°, because the reliability of fiber tracking is low when the tensor is near-spherical or the direction of the fiber changes abruptly. (As a reliability check, the analysis was repeated using the less restrictive stopping criterion reported by Huang et al [turning angle >50 degrees].[11] We found that the values of fractional anisotropy varied by no more than .025 and that the relative ranking of fiber groups did not change. Therefore, we present the results of the initial stopping criteria only.) We termed these global fiber groups left hemisphere group and right hemisphere group.

We conducted the analyses to callosal projections using a single region of interest approach. A callosal region of interest was defined manually on the midsagittal plane of the fractional anisotropy map. For each child, we intersected the left hemisphere and right hemisphere fiber groups with his callosal region of interest. To confine our analysis to reliable cortical projections, we excluded tracts if they met 1 or more of the following 3 criteria: (1) they crossed the midsagittal plane twice (implemented using an automated script); (2) they stopped prior to intersecting a sagittal plane 10 mm on the other side of the corpus callosum (implemented using a single region of interest approach); and (3) they projected to subcortical regions (implemented manually using CINCH, a graphical interface to identify fibers heading toward the cerebellum, thalamus, brainstem, or subcortical structures[18]).

Segmentation was conducted using regions of interest, as described by Huang et al[11] and Dougherty et al.[12] We divided the corpus callosum into 7 segments based on the cortical destinations of callosal fiber tracts following a well-described protocol used in the previous studies[11,12]: occipital, posterior parietal, superior parietal, temporal, superior frontal, anterior frontal, and orbital. The segmentations of the left hemisphere are shown in Figure 2, color-coded based on cortical destination. Although the child born prematurely had fewer callosal fiber tracts than the control, we were able to track callosal projections reliably to all 7 cortical destinations.

For purposes of quantitative measurement, callosal voxels were assigned to a particular callosal segment only if the assignment was consistent across both hemispheres. We analyzed 3 diffusion properties for each segment of the corpus callosum within a region 1 cm to either side of the midsagittal plane: (1) fractional anisotropy; (2) axial diffusivity, the rate of diffusion in the principal diffusion direction of the voxel, measured in $\times 10^{-6}$ mm$^2$/s; and (3) radial diffusivity, the rate of diffusion perpendicular to the principal diffusion direction of the voxel, measured in $\times 10^{-6}$ mm$^2$/s.

### Fiber Tracking of Corticospinal and Somatosensory Tracts

To determine the specificity of these findings, we also analyzed the diffusion properties of the right and left corticospinal and somatosensory fiber tracts. These tracts were defined following the method described by Wakana et al.[19] We used a 2-region of interest approach; left hemisphere and right hemisphere fiber groups were intersected with 2 regions of interest to define each tract. The first region of interest was drawn around the cerebral peduncle at the decussation of the superior cerebellar peduncle. The second region of interest was defined in the plane immediately superior to the bifurcation of the corticospinal tract; the corticospinal tract was defined as the white matter tract immediately anterior to the central sulcus and the somatosensory fibers were defined as the white matter tract immediately posterior to the central sulcus (Figure 3). We analyzed the properties of a segment of each tract spanning from the cerebral peduncle to the bifurcation of the corticospinal tract.

## Results

Figure 4 shows the segmentation of the corpus callosum in the midsagittal plane according to cortical projection

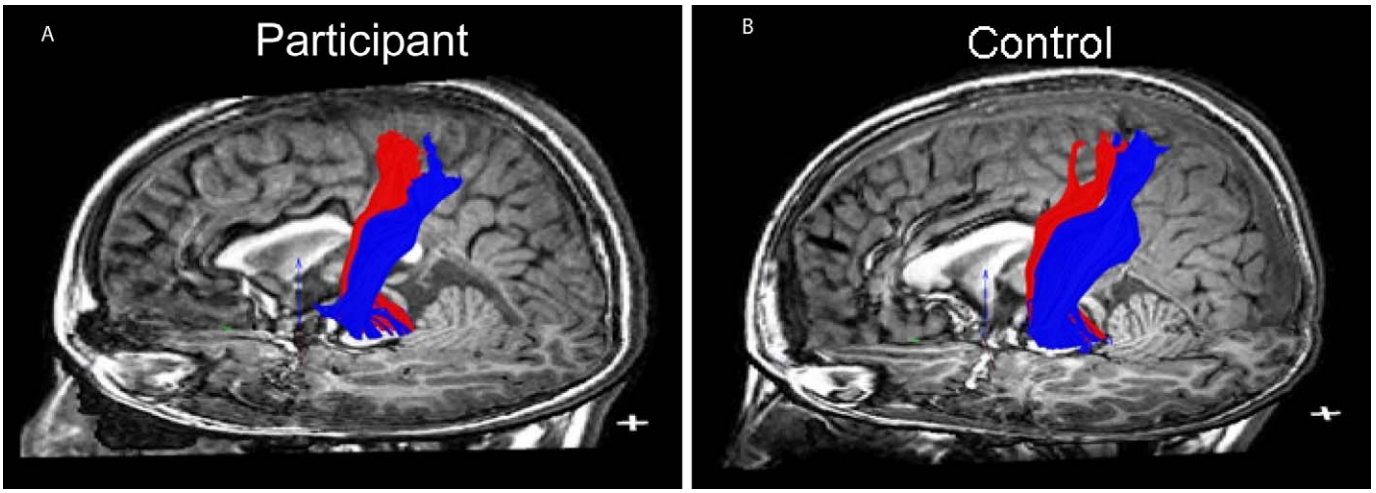


**Figure 3.** Corticospinal (red) and somatosensory (blue) tracks for the participant, a child born prematurely (A), and a control (B).

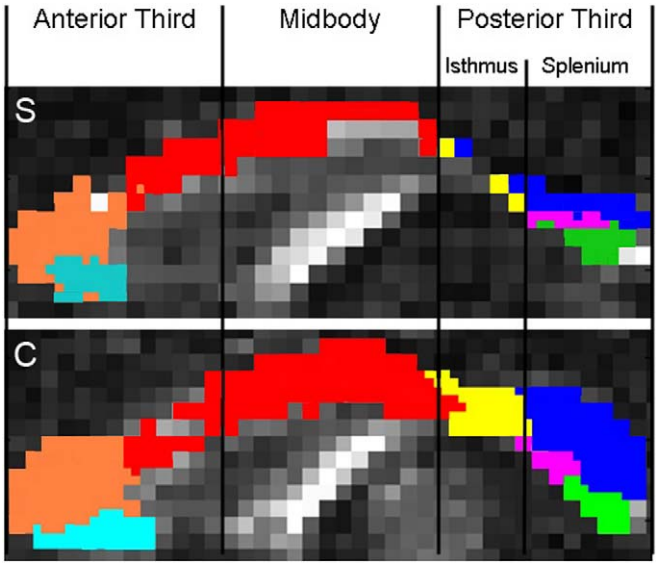


**Figure 4.** Cortical projections at the midsagittal plane of the corpus callosum for the child born prematurely (S) and the control (C). Note differences in the organization of the posterior third.

zones, restricting the analysis to those voxels that projected to the same region in each hemisphere. Vertical lines indicate division of the corpus callosum into equal thirds and division of the posterior third into the splenium (1/5 of corpus callosum length) and isthmus.[20] The figure demonstrates that the tracts to the superior parietal region are the most severely damaged. In addition, the organization of the posterior third of the corpus callosum, and particularly the isthmus, is somewhat different in the participant than in the control.

Table 1 presents mean fractional anisotropy, axial diffusivity, and radial diffusivity values within each callosal segment in each child. The mean fractional anisotropy across all the callosal segments was lower for the participant than the control, with the largest difference in posterior and superior parietal segments. The reduction in mean fractional anisotropy was associated with increased radial diffusivity in all segments in the participant. However, axial diffusivity was variable across the corpus callosum comparing participant and control.

Mean fractional anisotropy of the participant's corticospinal and somatosensory tracts was not lower in either hemisphere than the mean fractional anisotropy for the corresponding tracts of the control. Mean fractional anisotropy in the left and right corticospinal tracts were 0.678 and 0.702 for the participant and 0.568 and 0.595 for the control. Mean fractional anisotropy in the left and right somatosensory tracts were 0.667 and 0.657 for the participant and 0.628 and 0.572 for the control.

## Discussion

Diffusion tensor imaging and fiber tracking allowed visualization and quantification of the injury to the corpus callosum in a child born prematurely. The fractional anisotropy values within the corpus callosum in the control participant were within 2 standard deviations of the mean fractional anisotropy of a sample of healthy children of comparable age in all callosal segments, even though the measurements were obtained on different scanners using different protocols.[21] However, the fractional anisotropy values for the prematurely born participant were more than 2 standard deviations below the mean of that sample in 5 of 6 segments. The superior parietal segment was

Table 1. Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity of Segments of the Corpus Callosum in a Child Born Prematurely (P) and a Full Term (C)

| | Fractional Anisotropy | | Axial Diffusivity ($mm^2/s$) | | Radial Diffusivity ($mm^2/s$) | |
|---|---|---|---|---|---|---|
| Callosal Segment | P | C | P | C | P | C |
| Total | 0.574 | 0.672 | 1799 | 1841 | 665 | 511 |
| Occipital | 0.662 | 0.714 | 2284 | 2191 | 809 | 596 |
| Posterior parietal | 0.535 | 0.701 | 1566 | 1835 | 629 | 435 |
| Superior parietal | 0.431 | 0.595 | 1747 | 1922 | 894 | 641 |
| Temporal | 0.634 | 0.674 | 2268 | 2070 | 852 | 614 |
| Superior frontal | 0.607 | 0.676 | 1679 | 1825 | 549 | 512 |
| Anterior frontal | 0.586 | 0.671 | 1937 | 1865 | 677 | 520 |
| Orbital | 0.606 | 0.687 | 1959 | 1651 | 686 | 408 |

Note: P, participant; C, control.

more than 4 standard deviations below the mean of the healthy children. The quantitative measures confirm the high degree of damage, visualized by the fiber tracking methods. We did not find reductions of fractional anisotropy in the corticospinal or somatosensory tracts, supporting the specificity of the callosal damage in this participant. Future studies will determine whether reductions in fractional anisotropy are specific to the corpus callosum or characteristic of many white matter tracts in children born prematurely.

Quantitative measures of white matter were consistent with the accounts of the pathophysiology of perinatal white matter injury.[1,22-25] Developing oligodendroglial precursor cells are vulnerable to fluctuations in blood flow. Hypoxic-ischemic injury to oligodendrocytes can thereby impair myelination throughout the corpus callosum. Animal models have shown that between 24 and 32 weeks gestation, parietal and frontal regions are particularly vulnerable to hypoxic/ischemic injury because of a higher concentration of oligodendroglial precursor cells and lower blood flow compared to other regions.[22]

Fractional anisotropy values are related to a wide range of factors influencing the integrity of axonal membranes and the myelin sheath.[26,27] Animal models have found that dysmyelination is associated with increased radial diffusivity and unchanged axial diffusivity, while axonal degeneration is associated with increased radial diffusivity in conjunction with decreased axial diffusivity.[28,29] Our hypothesis is that poor myelination contributed to the low fractional anisotropy in the child born prematurely throughout the corpus callosum, yielding increased radial diffusivity. This effect is especially pronounced in posterior segments of the callosum, and particularly for fibers to the posterior and superior parietal lobe. Variable values for axial diffusivity across the regions of the corpus callosum are difficult to interpret.

Diffusion tensor imaging fiber tracking is not a direct depiction of white matter anatomy but rather an inference about the anatomy based on properties of water diffusion. A limitation of the method is that the algorithms are inaccurate in regions where there are crossing or touching fibers. The large major tracts, such as the occipitofrontal fasciculus and corona radiate, make it difficult to track fibers to lateral regions of the cortex and also result in the temporal pathways appearing to turn in an anterior direction toward the frontal lobe.[15]

In conclusion, diffusion tensor imaging fiber tracking holds promise for improving our understanding of the nature of injury in perinatal white matter injury in individual children.

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