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# Case Series: Fractional Anisotropy Along the Trajectory of Selected White Matter Tracts in Adolescents Born Preterm With Ventricular Dilation

**Nathaniel J. Myall, MS[1], Kristen W. Yeom, MD[2], Jason D. Yeatman, BA[3], Shayna Gaman-Bean, MD[4], and Heidi M. Feldman, MD, PhD[4]**

## Abstract

This case series assesses white matter microstructure in 3 adolescents born preterm with nonshunted ventricular dilation secondary to intraventricular hemorrhage. Subjects (ages 12-17 years, gestational age 26-29 weeks, birth weight 825-1624 g) were compared to 3 full-term controls (13-17 years, 39-40 weeks, 3147-3345 g) and 3 adolescents born preterm without ventricular dilation (10-13 years, 26-29 weeks, 630-1673 g). Tractography using a 2 region of interest method reconstructed the following white matter tracts: superior longitudinal/arcuate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and corticospinal tract. Subjects showed increased fractional anisotropy and changes in the pattern of fractional anisotropy along the trajectory of tracts adjacent to the lateral ventricles. Tensor shape at areas of increased fractional anisotropy demonstrated increased linear anisotropy at the expense of planar and spherical anisotropy. These findings suggest increased axonal packing density and straightening of fibers secondary to ventricular enlargement.

## Keywords

prematurity, ventricular dilation, diffusion tensor imaging, tractography, fractional anisotropy, intraventricular hemorrhage, preterm

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Preterm infants born at $\leq$32 weeks' gestation are at risk for sustaining intraventricular hemorrhage, bleeding into the germinal matrix and/or ventricles.[1] Factors predisposing to intraventricular hemorrhage include immaturity of the blood brain barrier, systemic blood pressure instability, and a highly vascular germinal matrix.[1] Intraventricular hemorrhage can be complicated by progressive ventricular dilation secondary to decreased reabsorption of cerebrospinal fluid through obstructed or scarred arachnoid villi and ependyma.[2] Infants with ventricular dilation are at risk of developing cognitive impairment.[3]

Injury to the periventricular white matter in preterm infants can occur independently of intraventricular hemorrhage. Preoligodendrocytes in the developing white matter are susceptible to oxidative and excitotoxic injury, triggered by ischemia and inflammation during the neonatal period.[4] Moderate to severe white matter abnormalities persist on magnetic resonance imaging at term age and have been associated with motor delay and poor executive function skills in children born preterm.[5,6]

In vivo diffusion tensor imaging has improved the understanding of white matter injury in prematurity. Diffusion tensor imaging measures the diffusion of water molecules within the brain.[7] In areas of white matter injury characterized by loss of axonal architecture, water diffusion becomes less anisotropic, or more equal in all directions.[8] Injury can be quantified as a decrease in fractional anisotropy, a scalar ratio that describes the extent to which water diffusion is anisotropic in any given voxel. The principal direction of diffusion can also be described and is thought to represent the predominant arrangement of axon fibers within a voxel. Tractography is a method that takes advantage of this relationship to reconstruct the course of fiber groups between predefined regions of interest in the brain.

[1] Stanford University School of Medicine, Palo Alto, CA, USA
[2] Department of Radiology, Stanford University School of Medicine, Palo Alto, CA, USA
[3] Department of Psychology, Stanford University, Palo Alto, CA, USA
[4] Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA

**Corresponding Author:**
Heidi M. Feldman, MD, PhD, Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA 94303.
Email: hfeldman@stanford.edu

Comparisons of white matter tracts between preterm subjects and full-term controls have generally demonstrated a decrease in fractional anisotropy with prematurity.[9] The purpose of this case series was to assess the effect of ventricular dilation on microstructural properties of white matter tracts in 3 adolescents born preterm with nonshunted ventricular dilation secondary to intraventricular hemorrhage. The authors hypothesized that fractional anisotropy would be decreased relative to full-term controls and preterm comparisons without ventricular dilation. Because of the distortion caused by ventricular enlargement, the authors chose to examine the tracts in the native space of each subject using tractography.

## Case Series

All participants were recruited as part of a larger cohort of preterms and controls. Written consent was obtained from parents and verbal assent from participants. Three preterm subjects were incidentally found on imaging to have enlargement of the lateral ventricles. Review of neonatal records revealed a history of grade III or III-IV intraventricular hemorrhage in all subjects based on cranial ultrasound findings. Ventricular dilation had arrested spontaneously without shunting in each subject. All subjects were asymptomatic at the time of this study and scored within the normal range in intelligence quotient when assessed by the Wechsler Abbreviated Scale of Intelligence.[10] T1 scans were reviewed by an experienced neuroradiologist (KWY) to classify the extent of ventricular dilation in each subject. Subject 1 had mild symmetrical dilation, subject 2 mild to moderate dilation, and subject 3 moderate dilation (Figure S1, available at dbpresearch.stanford.edu.) Subjects 2 and 3 had asymmetric enlargement of the lateral ventricles (left > right) and irregular ventricular margins, suggestive of additional periventricular injury. Three healthy, full-term controls and 3 adolescents born preterm without ventricular dilation served as comparisons (Table 1).

Diffusion tensor imaging data was acquired on a 3 T Signa Excite (GE Medical Systems, Milwaukee, WI). Imaging parameters are described in the supplementary materials. The following association and projection fibers were tracked bilaterally in each participant using the 2 region of interest method described by Wakana et al[11]: superior longitudinal/arcuate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and corticospinal tract. A limitation of this tractography method is its inability to differentiate the superior longitudinal fasciculus and arcuate fasciculus.

Brute-force tracking of all fibers in each hemisphere was initiated from 8 equidistant seed points in voxels with fractional anisotropy > .20. Fiber tracts were estimated using a deterministic streamlines-tracking algorithm with a fourth-order Runge-Kutta path integration method.[12,13] For tracking purposes, a continuous tensor field was estimated using trilinear interpolation of the tensor elements. Tracking proceeded in all directions at a fractional anisotropy threshold of > .20 and an angle threshold of < 41°.[11] Each fiber group was reconstructed by constraining the results of the brute-force approach to those fibers passing through the 2 corresponding regions of interest. Any fibers passing through the contralateral hemisphere were eliminated using a "not" region of interest. From the tensor matrix in each voxel, eigenvalues were derived representing the rate of diffusion in different directions within that voxel. Axial diffusivity is a measure of the rate of diffusion along the main axis. Radial diffusivity is a measure of the average rate of diffusion in all other directions. Fractional anisotropy was calculated from these eigenvalues.[14]

The authors then compared patterns of fractional anisotropy along the trajectory of each tract between groups. To assure that they compared the same anatomical regions of the tracts, the tracts were clipped to include only those streamlines between the 2 defining regions of interest. The remaining fiber group was divided into 30 equidistant segments, and the weighted mean of fractional anisotropy at each segment was calculated.[15] The weighted mean of clipped tracts was highly correlated ($r^2 \geq .80$) to weighted mean of full tracts for all fiber groups except the right uncinate. Using the full or clipped right uncinate did not affect the relative differences between groups.

Tractography results in subjects with ventricular dilation reproduced some streamlines belonging to other tracts in addition to the tract of interest (Figure S2). A secondary advantage to clipping the tracts to the region between the 2 regions of interest used for tractography was that it eliminated many aberrant streamlines. Values reported are those of the clipped tracts.

Preterms with ventricular dilation tended to have equal or increased fractional anisotropy of white matter tracts compared to full-term controls (Table 2). All subjects had increased fractional anistropy in the right superior longitudinal/arcuate fasciculus and corticospinal tract. Subjects 2 and 3 also had increased fractional anisotropy in the right inferior longitudinal fasciculus. These elevations were driven by decreased radial and/or increased axial diffusivity. Similar findings were seen in the left hemisphere tracts (data not shown). There was a trend toward normal or decreased fractional anisotropy in the preterm comparisons without ventricular dilation compared to full-term controls.

Subjects with ventricular dilation demonstrated diffusely elevated fractional anisotropy along the entire superior longitudinal/arcuate fasciculus compared to full-term controls and preterms without ventricular dilation (Figure 1). The increases were associated with both increased axial and decreased radial diffusivity along the tract (Figure 2).

Two subjects demonstrated a localized elevation in fractional anisotropy near the dorsal end of the left and/or right corticospinal tract (Figure S3), the approximate location at which the tract courses around the enlarged ventricle. The pattern of fractional anisotropy along the uncinate fasciculus was similar across all 3 groups, consistent with its location anterior rather than lateral to the ventricles (Figure S4).

To describe changes in tensor shape underlying the differences in fractional anisotropy among groups, the authors calculated linear, planar, and spherical anisotropies for all participants at the points of maximally increased fractional anisotropy along the superior longitudinal/arcuate fasciculus and

**Table 1.** Characteristics of the Participants.

| | Subject 1 | Subject 2 | Subject 3 | Full-Term Control 1 | Full-Term Control 2 | Full-Term Control 3 | Preterm Comparison 1 | Preterm Comparison 2 | Preterm Comparison 3 |
|---|---|---|---|---|---|---|---|---|---|
| Gender | Male | Male | Female | Female | Male | Male | Female | Female | Female |
| Age at diffusion tensor imaging scan (years) | 12 | 17 | 17 | 15 | 13 | 17 | 13 | 12 | 10 |
| Birth weight (g) | 1624 | 997 | 825 | 3317 | 3345 | 3147 | 630 | 1192 | 1673 |
| Gestational age (wk) | 28.5 | 27.0 | 26.0 | 40.0 | 39.0 | 40.0 | 26.0 | 28.5 | 29.0 |
| Total IQ | 113 | 87 | 116 | 118 | 111 | 107 | 77 | 95 | 109 |
| Papile classification[a] | Grade III, bilateral | Grade III-IV, bilateral | Grade III | | | | | | Grade II |
| Ventricular dilation[b] | Mild | Mild-moderate | Moderate | | | | Slight prominence | | |
| Ventricular symmetry | Symmetric | Asymmetric (left > right) | Asymmetric (left > right) | Mildly asymmetric (left > right) | Mildly asymmetric (right > left) | Symmetric | Symmetric | Symmetric | Symmetric |

[a] Based on cranial ultrasound findings during the neonatal period. Severity of intraventricular hemorrhage graded according to the Papile classification system.
[b] Based on clinical assessment of T1 scans taken at the time of the study.

**Table 2.** Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity Along the Right Hemisphere Tracts in All Participants.

| Tract | | Subject 1 | Subject 2 | Subject 3 | Full-Term Control 1 | Full-Term Control 2 | Full-Term Control 3 | Preterm Comparison 1 | Preterm Comparison 2 | Preterm Comparison 3 |
|---|---|---|---|---|---|---|---|---|---|---|
| SLF/AF | FA | 0.55 | 0.56 | 0.59 | 0.49 | 0.45 | 0.47 | 0.46 | 0.42 | 0.45 |
| | RD | 0.49 | 0.51 | 0.44 | 0.57 | 0.65 | 0.54 | 0.58 | 0.65 | 0.60 |
| | AD | 1.26 | 1.36 | 1.25 | 1.25 | 1.31 | 1.19 | 1.22 | 1.29 | 1.23 |
| ILF | FA | 0.43 | 0.47 | 0.50 | 0.45 | 0.44 | 0.43 | 0.49 | 0.39 | 0.47 |
| | RD | 0.68 | 0.63 | 0.61 | 0.63 | 0.68 | 0.67 | 0.61 | 0.71 | 0.62 |
| | AD | 1.37 | 1.39 | 1.41 | 1.30 | 1.37 | 1.34 | 1.40 | 1.31 | 1.34 |
| IFOF | FA | 0.48 | 0.51 | 0.52 | 0.50 | 0.49 | 0.51 | 0.49 | 0.46 | 0.49 |
| | RD | 0.68 | 0.60 | 0.63 | 0.57 | 0.65 | 0.59 | 0.64 | 0.65 | 0.60 |
| | AD | 1.49 | 1.45 | 1.50 | 1.33 | 1.50 | 1.39 | 1.47 | 1.40 | 1.36 |
| UNC | FA | 0.46 | 0.41 | 0.42 | 0.45 | 0.40 | 0.47 | 0.41 | 0.41 | 0.43 |
| | RD | 0.59 | 0.65 | 0.66 | 0.63 | 0.73 | 0.61 | 0.67 | 0.70 | 0.66 |
| | AD | 1.29 | 1.27 | 1.30 | 1.33 | 1.42 | 1.32 | 1.33 | 1.36 | 1.32 |
| CST | FA | 0.59 | 0.65 | 0.70 | 0.53 | 0.50 | 0.57 | 0.56 | 0.50 | 0.61 |
| | RD | 0.46 | 0.41 | 0.40 | 0.53 | 0.60 | 0.47 | 0.52 | 0.57 | 0.48 |
| | AD | 1.37 | 1.44 | 1.55 | 1.33 | 1.40 | 1.33 | 1.43 | 1.35 | 1.44 |

Abbreviations: AD, axial diffusivity; CST, corticospinal tract; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; RD, radial diffusivity; SLF/AF, superior longitudinal/arcuate fasciculus; UNC, uncinate fasciculus.

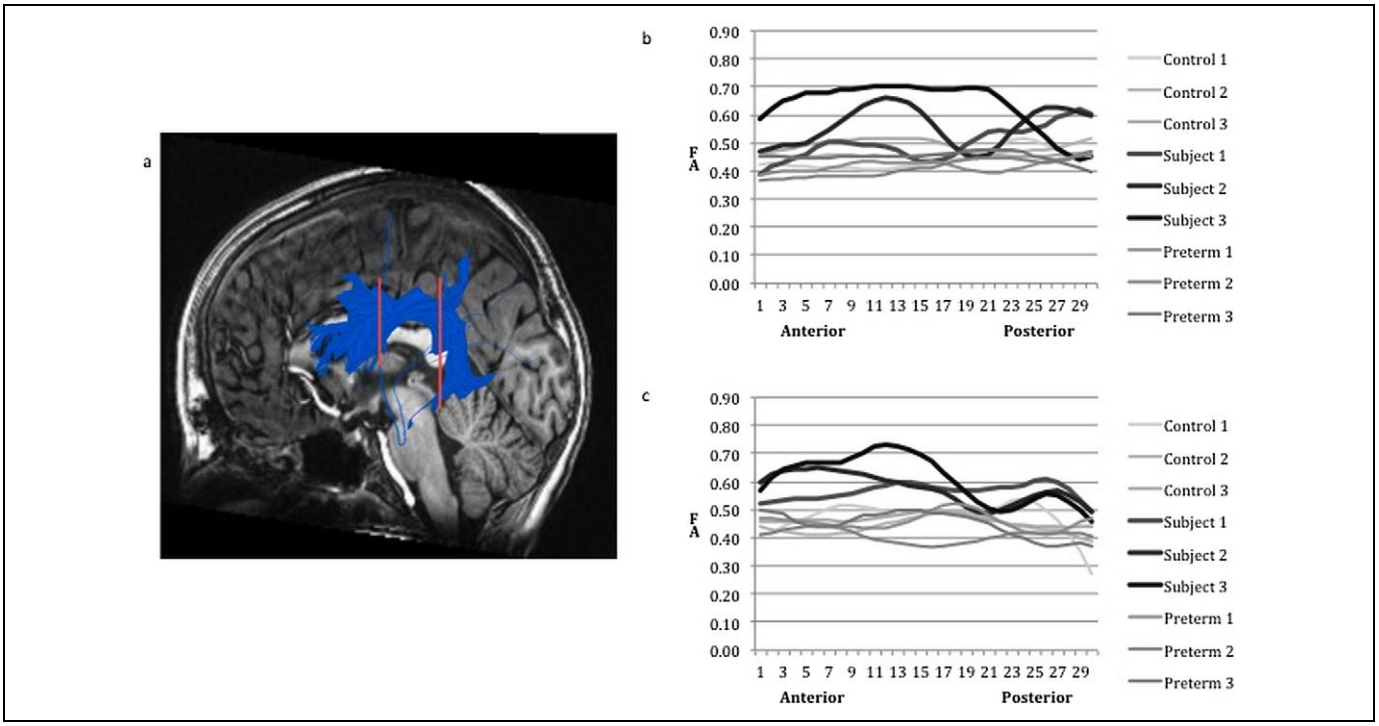


**Figure 1.** (a) The superior longitudinal/arcuate fasciculus in a full-term control visualized with QUENCH. Red markers represent the location of the 2 regions of interest used for tractography. Fractional anisotropy along the tract at 30 equidistant points is shown for the left (b) and right (c) hemispheres. Subjects with ventricular dilation demonstrate elevated fractional anisotropy at various points along the trajectory of the tract compared to full-term controls and preterm comparisons.

corticospinal tract in the subjects with ventricular dilation. Following the methods of Alexander et al[16], the authors mapped the anisotropies of each individual onto a 3-phase tensor shape diagram to visualize changes in tensor shape among the groups. Subjects with ventricular dilation demonstrated increased linear anisotropy and decreased planar and spherical anisotropy in the superior longitudinal/arcuate fasciculus (Figure 3) and corticospinal tract (Figure S5) compared to controls and preterms.

## Discussion

The authors found increased fractional anisotropy in adolescents born preterm with ventricular dilation secondary to

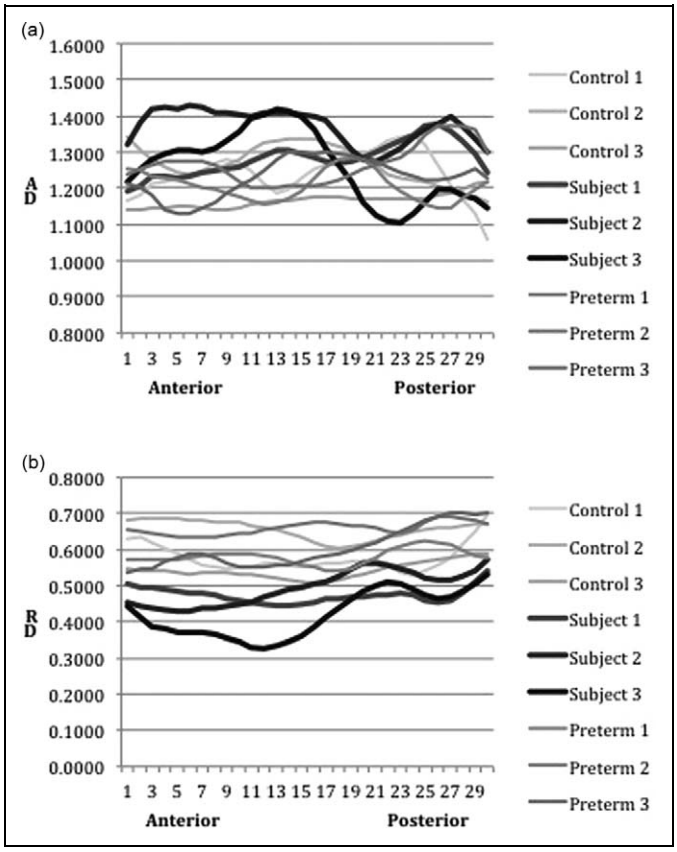


**Figure 2.** Axial (a) and radial diffusivity (b) along the trajectory of the right superior longitudinal/arcuate fasciculus. Areas of increased fractional anisotropy along the tract seen in Figure 1c are associated with both increased axial diffusivity and decreased radial diffusivity compared to full-term controls and preterm comparisons.

intraventricular hemorrhage. Diffusion tensor imaging studies of prematurity have generally demonstrated decreased fractional anisotropy in white matter that can persist into adolescence.[9] Other studies in this population have also reported positive correlations between fractional anisotropy and cognitive outcomes in various domains.[17] It is generally inferred from these results that higher fractional anisotropy is a marker of intact white matter unaffected by injury. These findings suggest that high fractional anisotropy in prematurity has different implications in the case of children born preterm with ventricular dilation.

The most likely explanation for these results is that ventricular enlargement caused changes in the organization and density of axons. Diffusion tensor imaging studies of space-occupying tumors in the brain have demonstrated increased fractional anisotropy, increased axial diffusivity, and decreased radial diffusivity in the surrounding nonedematous white matter.[18,19] The authors of these studies speculate that fiber displacement by tumor increases the alignment of surrounding axons, resulting in a greater density of fibers within a given area of white matter. In their model, the increased packing of axons limits diffusion in the perpendicular direction, producing a decrease in radial diffusivity. The pressing of the tumor mass against white matter also stretches and straightens axons, leading to increased diffusion in the parallel direction and increased axial diffusivity. Consistent with this model, the authors found changes in the tensor shape in voxels with increased fractional anisotropy in subjects with ventricular dilation. The decrease in planar and spherical anisotropy in these subjects could be suggestive of axonal straightening and increased axonal density, respectively.

This study also highlights the importance of examining fractional anisotropy along the trajectory of fiber tracts. The authors found elevations in fractional anisotropy in regions along the tracts adjacent to the lateral ventricles in subjects with ventricular dilation. Measuring the mean alone potentially misses important information about the behavior of a tract along its entire length. The method presented here has the advantage of identifying areas along tracts that are important in driving the changes in mean values.

In conclusion, the authors report an increase in fractional anisotropy in multiple white matter tracts in adolescents born preterm with ventricular dilation secondary to intraventricular hemorrhage. These results suggest that the overall effect of prematurity on white matter microstructure varies with multiple factors including enlargement of the ventricles.

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## Author Contributions

NJM was responsible for data collection, data analysis, and writing the first draft of the manuscript. KWY clinically reviewed image scans, verified placement of regions of interest in each subject, and reviewed the manuscript. JDY collected and processed all image scans and provided theoretical and methodological expertise. SGB assisted with data collection by drawing regions of interest for the corticospinal tract. HMF conceived of the study, interpreted results, provided theoretical expertise, and revised earlier drafts of the manuscript.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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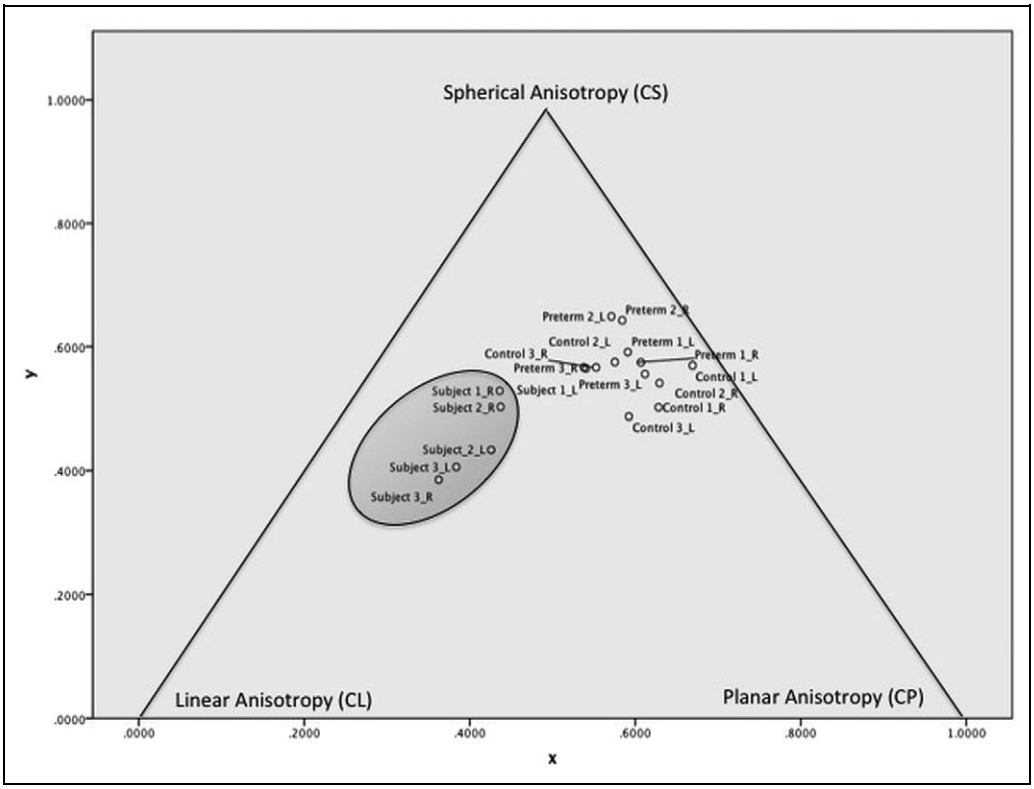


**Figure 3.** Subjects with ventricular dilation demonstrate a distinct tensor shape compared to controls and preterms. The tensor shape is represented on a 3P tensor shape diagram, with linear, planar, and spherical anisotropies mapped to coordinates $x = (1 - CL + CP)/1.732$ and $y = 1 - CL - CP$. Linear anisotropy is maximal at the left vertex of the triangle, planar anisotropy maximal at the right vertex, and spherical anisotropy maximal at the peak. Linear, planar, and spherical anisotropy were calculated in voxels at point 12 along the superior longitudinal/arcuate fasciculus where fractional anisotropy was increased in subjects with ventricular dilation. The linearity of the tensor shape is increased at this region of the tract in subjects with ventricular dilation, at the expense of both planar and spherical anisotropy.

## Ethical Approval

The protocol was approved by the Institutional Review Board of Stanford University School of Medicine and performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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