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Microstructural Measures of the Inferior Longitudinal Fasciculus Predict Later Cognitive and Language Development in Infants Born with Extremely Low Birth Weight

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Abstract

Objective: Extremely preterm children are at high risk for adverse neurodevelopmental outcomes. Identifying predictors of discrete developmental outcomes early in life would allow for targeted neuroprotective therapies when neuroplasticity is at its peak. Our goal was to examine whether diffusion MRI metrics of the inferior longitudinal and uncinate fasciculi early in life could predict later cognitive and language outcomes.

Study Design: In this pilot study, 43 extremely low birth weight preterm infants were scanned using diffusion MRI at term-equivalent age. White matter tracts were assessed via diffusion tensor imaging metrics of fractional anisotropy and mean diffusivity. The Language and Cognitive subscale scores of the Bayley Scales of Infant & Toddler Development-III at 18–22 months corrected age were our outcomes of interest. Multiple linear regression models were created to assess diffusion metrics of the inferior longitudinal and uncinate fasciculi as predictors of Bayley scores. We controlled for brain injury score on structural MRI, maternal education, birth weight, and age at MRI scan.

Results: Of the 43 infants, 36 infants had high quality DTI and returned for developmental testing. The fractional anisotropy of the inferior longitudinal fasciculus was associated with Bayley-III scores in univariate analyses and was an independent predictor of Bayley-III cognitive and language development over and above known predictors in multivariable analyses.

Conclusions: Incorporating new biomarkers such as the fractional anisotropy of the inferior longitudinal fasciculus with structural MRI findings could enhance accuracy of neurodevelopment predictive models. Additional research is needed to validate our findings in a larger cohort.

Keywords

Diffusion Tensor Imaging; MRI; Neuroimaging; Cognition; Developmental Delay; Preterm

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Introduction

Survival rates for extremely low-birth-weight (ELBW; BW ≤1000 g) infants are increasing, yet 40–50% of these infants are later diagnosed with neurodevelopmental impairments that most commonly affect cognitive and language domains (1,2). To perform cognitive and language functions effectively, numerous cerebral regions must be activated concurrently (3–5). White matter tracts responsible for relaying information are as important for performance as the regions they connect. Any lesions or even a delay in the development of these tracts can result in long-term adverse outcomes (6–9).

Currently, early detection of neurodevelopmental impairments is suboptimal, with reliable diagnosis not occurring until 3 to 5 year of age (10). Earlier diagnosis of impairments would allow preventative and neuroprotective therapies for at-risk neonates when brain connectivity and growth are occurring rapidly. A meta-analysis of early development programs comprising a dozen randomized trials investigating cognitive impairments in preterm infants found that on average such programs improve cognitive performance in intervention infants up to preschool age (11). A few interventions have also shown a positive effect at or beyond school age despite being administered to all (i.e. low and high risk) preterm or low birthweight infants (12–14).

Preterm infants may exhibit white matter tracts that developed abnormally, as myelination occurs rapidly in the months between preterm birth and term-equivalent age (TEA) (15). The harsh ex-utero environment preterm infants are exposed to can interrupt this rapid myelination, resulting in overall suboptimal development (16).

Cranial ultrasound is used extensively to identify white matter abnormalities, however it exhibits poor sensitivity for the prediction of cognitive and language deficits (17,18). Unfortunately, even structural Magnetic Resonance Imaging (sMRI) has proved suboptimal for the prediction of neurodevelopmental impairments, especially cognitive and language impairments (19–21). As a result, advanced MRI has been proposed as an alternate, improved method for prediction in preterm populations (10). Diffusion-weighted MRI imaging, which is highly sensitive to the diffusion of water molecules, can be used to assess brain microstructure and white matter trajectories in vivo (22,23). The diffusion tensor (DT) model uses the measured diffusion signal to estimate underlying tissue microstructure. Fractional anisotropy (FA) indexes the degree of directionality of the white matter fibers and can be thought of as a marker of overall white matter integrity (22). Mean diffusivity (MD), on the other hand, captures the amount of diffusion in all three directions. In typical neurodevelopment, fractional anisotropy (FA) of the white matter tracts increases and MD decreases. Studies correlating neurodevelopmental impairments with white matter tract development often use FA and MD to assess white matter integrity.(23,24) Initial studies have identified these DTI metrics as promising biomarkers for neurodevelopment (2,25,26).

The uncinate and inferior longitudinal fasciculi (UNC, ILF) are white matter tracts that link frontal, temporal, and occipital regions involved in cognitive and language functions. Both tracts exhibit abnormal microstructure in ELBW infants (23,27,28). Therefore, they may serve as biomarkers for later cognitive and language development. Vollmer et al. recently

found that UNC and ILF FA values were significantly associated with cognitive flexibility, working memory, and verbal memory in 18-year-olds born with very low-birth-weight (BW<1500g) (29). Additionally, Barnett et al. discovered that reduced FA of the ILF is associated with adverse cognitive and language outcomes in preterm infants (<34 weeks gestational age) scanned at TEA (30). Additional studies of both preterm and term-born infants and adults also implicate the UNC and ILF in the ventral language pathway, which plays an important role in receptive language ability (31–35).

Despite the UNC and ILF being linked to cognitive and language outcomes in preterm infants and adolescents, in-depth analyses of their predictive value are lacking, and there is also a need to validate the link in an ELBW population (30,35–39). We hypothesized that FA and MD of the UNC and ILF at term-equivalent age could predict cognitive and language outcomes at 18–22 months corrected age.

Materials and Methods

Subjects

We examined archived data from a previous prospective cohort pilot study of 43 ELBW infants (BW ≤1000g) from the Children's Memorial Hermann Hospital neonatal intensive care unit (NICU) who were enrolled and underwent structural and diffusion MRI. Infants were excluded if they had congenital central nervous system or chromosomal defects or were too critically ill and unstable to move to the MRI scanner. Written informed consent was acquired from parents and/or legal guardians of each study participant prior to enrollment and participation in the study. The Institutional Review Board of the University of Texas Health Science Center at Houston and Children's Memorial Hermann Hospital approved the study.

MRI Acquisition

Brain MRI was performed at TEA or prior to NICU discharge, whichever came first. Patients were transported to the MRI scanner and supervised during the scan by a neonatologist, a neonatal research nurse, and a transport nurse. Prior to imaging, infants were fed and swaddled to induce natural sleep and to reduce motion during the MRI. MedVac infant vacuum splint (CFI Medical Solutions, Fenton, Michigan), Insta-Puffy Silicone Earplugs (E.A.R. Inc, Boulder, Colorado), and Natus Mini Muffs (Natus Medical, San Carlos, California) were placed on the infants to hold them in place and attenuate scanner noise. We used a 3T Achieva scanner (Philips Healthcare, Best, Netherlands) equipped with an 8-channel phased array head coil. The DTI protocol consisted of a single-shot, spin-echo planar sequence with TR/TE, 6000/61 ms; in-plane resolution, 1.6 × 1.6 mm2; field of view, 180 mm2; 112 × 112 matrix; and 2 mm contiguous slices. We used 15 directions of diffusion gradients with a b-value of 800 s/mm2.

Data Processing and Tract Segmentation

All DTI data processing for this specific cohort, including segmentation of the ILF and UNC, is detailed in our previous publication (23). Briefly, we preprocessed the data using FSL software (Analysis Group, FMRIB, Oxford, UK). We corrected for imaging

artifacts and subject motion by applying eddy current correction using the B0 image. The ILF and UNC tracts were segmented using the Fiber Assignment by Continuous Tracking (FACT) tool in DTI Studio (H. Jiang and S. Mori, Johns Hopkins University; http://cmrm.med.jhmi.edu/) with FA start/stop thresholds of 0.11/0.05 (ILF) and 0.12/ 0.12 (UNC), specified fiber turning angles (41° for ILF and 60° for UNC), and fiber selection using multiple regions of interest (ROIs). Our ROI placement for the ILF and UNC is displayed in Figures 1 and 2, respectively (see Kaur et al., 2014 for more details). ROIs were placed in the left hemisphere of the brain only to segment the left ILF and UNC. This objective method of segmentation was shown to have a high degree of reliability and repeatability. In this study, the intra-class correlation coefficients for intra-rater and inter-rater measurement error were all >0.97 for the ILF and UNC FA when measurements were repeated by two raters two weeks later for 44 infants (23). These results suggest excellent reproducibility for delineation of the ILF and UNC (23).

T1W and T2W images acquired at TEA were evaluated for moderate-to-severe structural injury by a pediatric neuroradiologist using our previously published qualitative scoring system (Slaughter et al. 2016), which is a modified version of the Inder/Woodward scoring system (18). The Inder/Woodward system was designed to assess overall brain abnormalities based on the degree of gray and white matter maturation, ventricle size, corpus callosum width, subarachnoid space size, signal abnormalities, presence of a shunt, MRI quality, degree of atrophy, and overall severity. Our definition only focused on white matter injury and determined regional structural size and atrophy based on qualitative neuroradiologist readings. Infants with white matter injury (e.g., punctate white matter lesions, cystic abnormalities) or moderate-severe tissue atrophy were coded as having moderate-to-severe structural injury.

Developmental Outcomes

We assessed all subjects using the language and cognitive subscales of the Bayley Scales of Infant & Toddler Development III (Bayley-III) at 18 to 22 months corrected age. Assessments took place at the High Risk Infant Follow-up Clinic of Children's Memorial Hermann Hospital and the University of Texas Health Science Center in Houston. For both subscales, the normative mean and standard deviation scores are 100 and 15 points, respectively, with a range from 40 to 160. The tests were administered by a certified examiner who was masked to all conventional MRI and DTI results.

Data Analysis

We collected demographical, maternal, perinatal, and neonatal medical history from each enrolled infant and entered them into a secure database. We created linear regression models of neurodevelopmental outcomes using the MD and FA of the ILF and UNC as our main experimental predictors. We added known predictors, maternal education, birth weight, and severity of injury on conventional MRI, to the models as covariates, to establish the independent predictive power of the DTI biomarkers. Additionally, postmenstrual age (PMA) was included in the model to control for age differences at MRI. Previous research indicates that fetal growth restriction, APGAR score, duration of mechanical ventilation, and parenteral nutrition are associated with FA values in the developing white matter (30).

Due to the limited statistical power of our sample, we could not include all covariates into our model simultaneously without overfitting. Thus, we tested them one at a time in a secondary sensitivity analysis, testing the inclusion of these additional covariates into a version of the final model which also included moderate-severe white matter injury on structural MRI, birth weight, and PMA at MRI scan. Two-sided p values of <0.05 were considered statistically significant. We ran diagnostics on each final multivariable linear regression model, to ensure that all assumptions of linear regression were met. STATA 15.1 (Stata Corp., College Station, TX) was used for all analyses.

Results

Of the 43 ELBW infants scanned at TEA, one patient died before 18 months corrected age, one was lost to follow-up, and three exhibited behavioral problems that prevented completion of language or cognitive testing. Segmentation of the ILF and UNC was not possible for 2 and 3 additional infants, respectively. Bilateral ventriculomegaly prevented segmentation of both tracts in one subject, and motion artifacts prevented segmentation of the ILF for one subject and the UNC for two subjects. Therefore, the final cohort consisted of 36 subjects with high-quality ILF data and 35 subjects with high-quality UNC data.

The mean (SD) gestational age at birth and BW were 25.5 (1.6) weeks and 753.2 (146) grams, respectively. 58% (N=21) of the study infants were male. Additionally, 17% (N=6) of participants showed moderate-severe WM injury on sMRI. Two of these subjects had severe intraventricular hemorrhage with periventricular infarction. The baseline characteristics of these 36 subjects was comparable to the full cohort of 43 ELBW infants (Table 1).

Patients were scanned at a mean (SD) PMA of 38.5 (2.2) weeks (Table 1). The participants were assessed with the Bayley-III subtests at a mean (SD) age of 20.0 (2.2) months corrected age. The mean (SD) Bayley-III cognitive and language scores were 87 (19) and 93 (16), respectively. The mean (SD) FA values for the ILF and UNC were 0.160 (0.032) and 0.219 (0.023), respectively. The mean (SD) MD values for the ILF and UNC were 0.00464 (0.00042) and 0.00389 (0.00025), respectively.

FA of the ILF was independently predictive of cognitive ability at 18–22 months corrected age (p=0.03) (Table 2). Our linear regression model exhibited an adjusted R2 of 0.26 (Table 2). In this model, ILF FA was positively correlated with Bayley-III cognitive score (β=181.9; 95% CI 14.5–349.2). Moderate to severe injury on sMRI was negatively correlated with Bayley-III cognitive score (p=0.02; β= −16.2; 95% CI −29.4, −3.0). In secondary sensitivity analyses, the FA of the ILF retained its significant association with cognitive scores (p<0.05) when fetal growth restriction, APGAR score, duration of mechanical ventilation, and duration of parenteral nutrition we included in the final model one at a time.

Additionally, the FA of the ILF was independently predictive of language outcome (p=0.04) (Table 2). An increase in the FA of the ILF was related to an increase in language score at 18–22 months corrected age (β=207.1; 95% CI: 14.9, 399.3) (Table 2). Our model had an adjusted R2 of 0.26 (Table 2). Similar to the relationship with cognitive outcome, injury on

sMRI was negatively correlated with language outcome (p=0.01; β=–21.4; 95% CI: –36.6, –6.2). The FA of the ILF retained its significant association with language scores ($p<0.05$) when duration of mechanical ventilation was added to the language model. It did not remain significantly associated with language scores in multivariate regression when fetal growth restriction, APGAR score, or parenteral nutrition were included as covariates, however we noted a trend towards significance for each of the three models ($p<0.1$).

The MD of the ILF was not significantly correlated with either cognitive (p= 0.59) or language (p=0.296) outcome. Additionally, the FA of the UNC was not significantly correlated with cognitive (p=0.15) or language (p=0.50) outcome, and the MD of the UNC was not significantly correlated with cognitive (p=0.69) or language (p=0.20) outcome.

Discussion

Our objective was to evaluate the prognostic value of DTI metrics of the ILF and the UNC for cognitive and language outcomes at 18–22 months corrected age in an ELBW cohort scanned at TEA. DTI metrics FA and MD were assessed as predictors while the language and cognitive subscores from the Bayley-III, administered at 2 years corrected age, were our primary outcomes of interest. We confirmed our hypothesis that the FA of the ILF is significantly associated with both cognitive and language scores, independent of other known predictors including birth weight, maternal education, and moderate to severe injury on sMRI (1,18,21,40). However, neither FA nor MD of the UNC was significantly correlated with language or cognitive outcomes. Since the FA of the ILF was found to be independently predictive of cognitive and language models shortly after birth, it could aid in early predictive models of neurodevelopmental impairments. This could facilitate earlier intervention when neuroplasticity is at its peak (10,41,42).

Recently, Vollmer et al. reported associations between executive function and the integrity of several WM tracts, including the ILF and the UNC in adolescents born with very low BW. Higher FA of the UNC was associated with improved verbal performance, working memory, and cognitive flexibility, and ILF FA was positively correlated with working memory (29). However, the specific executive functions Vollmer et al. tested cannot be assessed at 2 years of age. Despite this, we did find a similar positive association between the FA of the ILF and Bayley-III cognitive and language scores.

Barnett et al. scanned very preterm infants at TEA and used tract based spatial statistics to conclude that FA in several WM tracts, including the bilateral ILF, predicted Bayley-III cognitive score at 20 months corrected age. They also showed that the FA of the right ILF was significantly correlated with Bayley-III language score (30). Diffusion MRI measures from the UNC were not predictive of Bayley-III scores. In a similar study with a smaller cohort, Dubner et. al associated FA of the left ILF at TEA with language outcomes at two years of age but did not determine an association between the FA of the UNC and language outcomes (43). A handful of previous studies in very preterm infants using similar approaches did not find significant associations between the FA of the ILF and neurodevelopmental outcomes (8,26). These studies may have been limited by their smaller sample sizes in relation to the Barnett study. Our study corroborates the findings of Barnett

et al. and extends it using more robust tractography measures, further indicating that ILF FA is an important biomarker for cognitive and language scores.

The FA of the UNC has been associated with language function in preterm born adolescents (36,37). However, we did not find this association in our ELBW cohort, possibly because of our relatively small sample size. Additionally, the UNC is one of the slower WM tracts to develop, and our scans at TEA may have been too early to detect UNC abnormalities (28,44).

We incorporated known predictors of neurodevelopment (BW, maternal education, and abnormality on sMRI) into our linear regression models to investigate whether DTI metrics of the ILF and UNC were independently predictive of outcomes (1,18,21). Slaughter et al. showed that sMRI score exhibits high specificity (94–99%) in predicting neurodevelopmental outcomes but poor sensitivity (30–67%). Incorporating additional biomarkers with sMRI findings, such as the FA of the ILF, could lead to increased accuracy of predictive models, as suggested by our study.

Our study has several limitations. Our small sample size resulted in limited study power and may have contributed to our inability to identify a relationship between UNC microstructural measures and Bayley-III scores. Given that this was a small pilot study, we also did not correct for multiple comparisons, to decrease the likelihood of committing a type II error (45,46). Furthermore, our cohort was derived from a tertiary referral-based hospital population, and it may not be representative of all ELBW infants from the general population. Also, we assessed a limited number of diffusion directions and did not employ newer multi-compartmental models that can better resolve crossing fibers in the brain or multiple fiber populations within a single voxel (47–49). However, these models require multiple b-shells and many directions of high-angular resolution diffusion-weighted data, which is still challenging to acquire in neonates. We are addressing each of these limitations in our ongoing, multi-center study in order to validate our findings. Additionally, following our cohort until school age will allow for evaluation of more robust developmental outcomes, as some developmental outcomes are not accurate or detectable before this age (50).

In conclusion, by investigating the predictive value of DTI metrics from two important WM tracts, which are known to be involved in cognitive and language function, we demonstrated that ILF FA can help explain later cognitive and language development. The FA of the ILF was independently predictive of Bayley-III cognitive and language scores, after correction for qualitatively-defined injury on sMRI, birth weight, and maternal education. Larger studies are needed to identify additional diffusion MRI biomarkers that may allow for earlier prognosis of discrete developmental outcomes. This will facilitate earlier targeted neuroprotective therapies when neuroplasticity is maximal, leading to improved outcomes.

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Abbreviations

ELBW	Extremely Low Birth Weight
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
MD	Mean Diffusivity
ILF	Inferior Longitudinal Fasciculus
UNC	Uncinate Fasciculus
MRI	Magnetic Resonance Imaging
dMRI	Diffusion MRI
sMRI	Structural MRI
Bayley-III	Bayley Scales of Infant & Toddler Development

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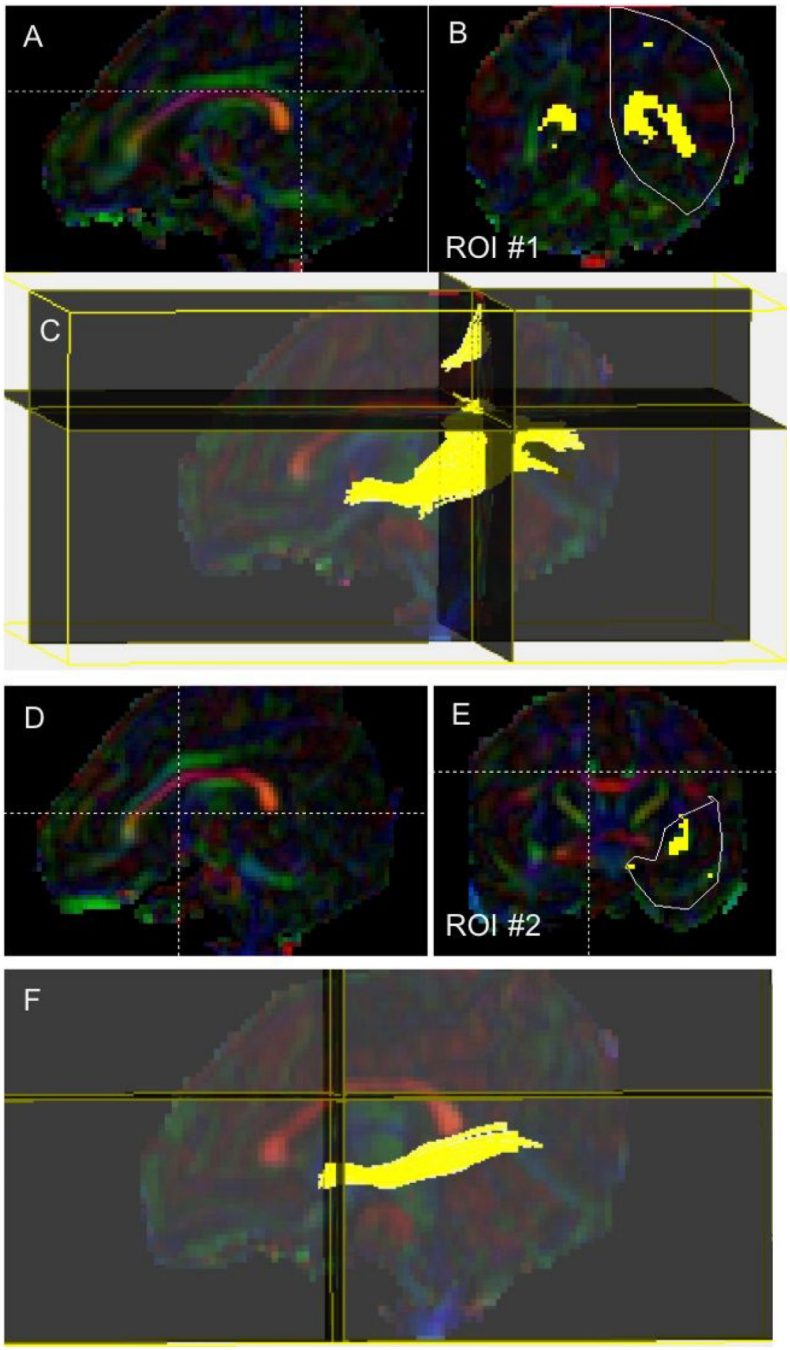

Figure 1.

Inferior longitudinal fasciculus (ILF) segmentation: (A) The sagittal color map image that was used to identify the location of the first region of interest (ROI) at the level of the posterior edge of the intensely green cingulum region in a representative ELBW infant; (B) Coronal image showing the first polygonal ROI covering the entire left hemisphere; (C) 3D sagittal view of the ILF fiber bundle after placement of the first ROI; (D) Sagittal image used to identify the second ROI at the level of the anterior third of the genu of the corpus

callosum; (E) Coronal image showing the second polygonal ROI; (F) 3D trajectory of the final IFL fibers after placement of the second ROI and fiber exclusion protocol.

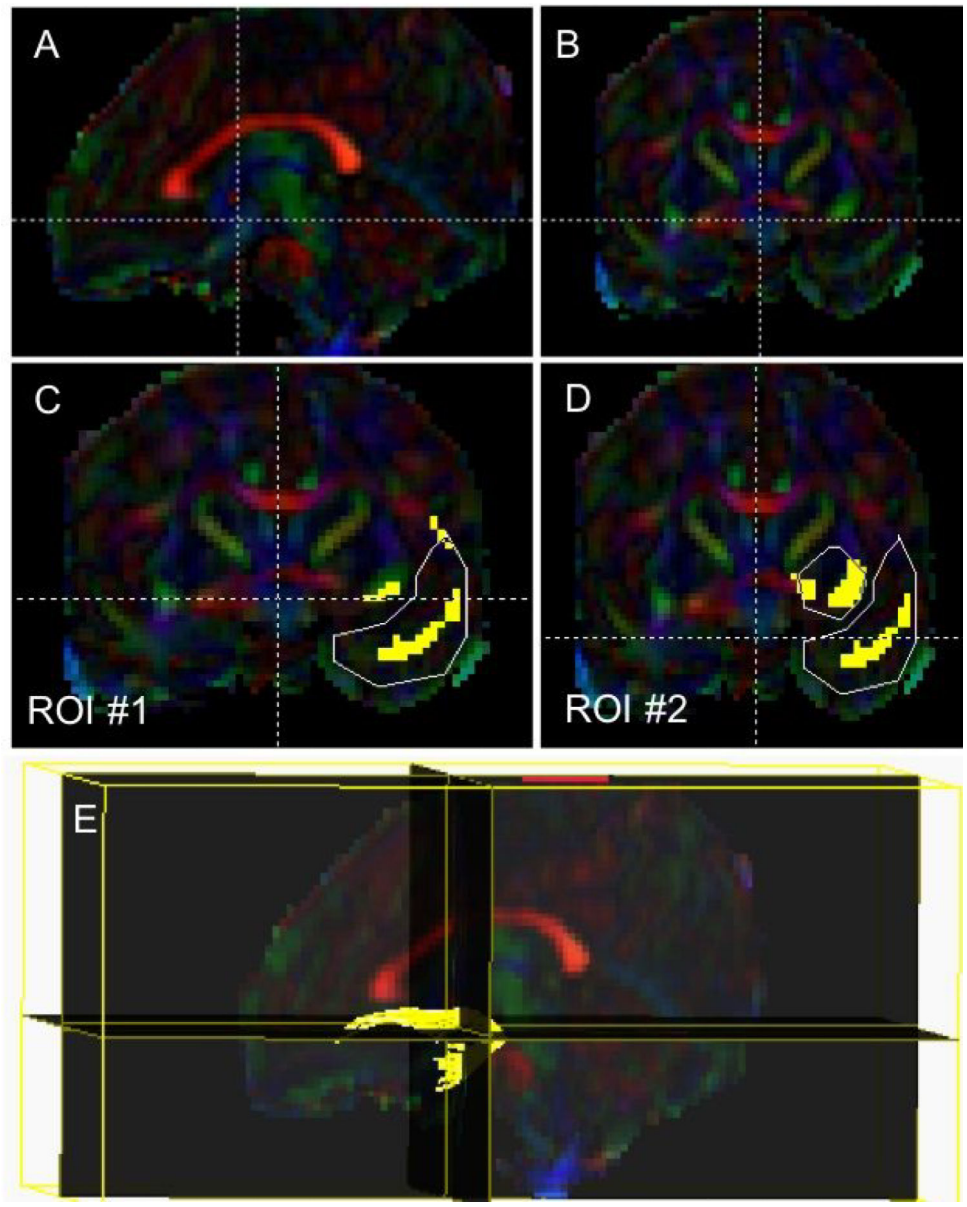

Figure 2.

Uncinate fasciculus (UNC) segmentation. (A) Sagittal color map image showing the location of the first region of interest (ROI) in a representative ELBW infant; (B) Coronal view of the first ROI; (C) Placement of the first polygonal ROI on the coronal image; (D) Second ROI placement on the same coronal image. (E) Final 3D trajectory of the UNC seen in a sagittal view after placement of the second ROI and fiber exclusion protocol.

Table 1.

Demographic and clinical characteristics of infants in the final cohort (N=36) and of all recruited infants (N=43).

Baseline Characteristic	N=36	N=43
Maternal age (years)	28.1 (5.0)	27.2 (5.2)
Gestational age at birth (weeks)	25.5 (1.6)	25.6 (1.7)
Birth weight (grams)	753.2 (146)	762.3 (143)
Male	58.3%	58.1%
Small for gestational age (<10th percentile)	11.1%	14.0%
Apgar score <5 at 5 minutes	22.2%	23.3%
Late-onset sepsis (+/− blood culture)	63.9%	65.1%
Major surgery (with general anesthesia)	5.6%	9.3%
Duration of positive pressure support (days)	47 (23,75)	47 (22, 75)
White matter injury on structural MRI *	16.7%	18.6%
Postmenstrual age at MRI (weeks)	38.5 (2.2)	38.5 (2.2)

Note: Non-percentage values are expressed as mean (SD), except for duration of positive pressure support, which is expressed as median (25th, 75th percentile)

*Defined as lesions in the white matter, including diffuse punctate lesions, cystic periventricular leukomalacia, encephalomalacia, and/or moderate/severe atrophy.

Table 2.

Multivariable models using microstructural abnormalities of the inferior longitudinal fasciculus (ILF) at term-equivalent age to predict Bayley-III cognitive and language subscale scores at 18–22 months corrected age in extremely low birth weight infants.

Clinical/DTI Variable	Coefficient (95% CI)	P
A. Cognitive score (Adjusted R^2 0.260; R^2=0.365)		
Mean Fractional Anisotropy of the ILF	181.9 (14.5, 349.2)	*0.03*
Structural Injury on MRI	−16.2 (−29.4, −3.0)	*0.02*
Postmenstrual Age at MRI scan	−1.9 (−4.6, 0.83)	0.17
Birth Weight (per 100 grams)	0.65 (−3.2, 4.5)	0.73
Maternal Education	−2.6 (−15, 9.5)	0.66
B. Language score (Adjusted R^2 0.263; R^2=0.368)		
Mean Fractional Anisotropy of the ILF	207.1 (14.9, 399.3)	*0.04*
Structural Injury on MRI	−21.4 (−36.6, −6.2)	*0.01*
Postmenstrual Age at MRI scan	−1.5 (−4.7, 1.6)	0.33
Birth Weight (per 100 grams)	2.3 (−2.1, 6.7)	0.30
Maternal Education	−7.7 (−21.6, 6.20)	0.27