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Attention and Internalizing Behaviors in Relation to White Matter in Children Born Preterm

Irene M. Loe, MD, Eliana S. Lee, BS, and Heidi M. Feldman, MD, PhD

Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford CA 94305

Abstract

Objective—Diffusion Tensor Imaging (DTI) is a magnetic resonance imaging technique that provides quantitative characterization of white matter tracts in the brain. This study used DTI to examine the degree of association between parent-rated scores of attention, internalizing behaviors including anxiety symptoms, and externalizing behaviors and white matter fractional anisotropy (FA) in children born preterm.

Method—Participants were 9 to 16 years of age; 25 were born at less than 36 weeks gestation (mean = 28.6 weeks, birth weight = 1191 grams) and 20 were full term. We analyzed the results using Tract-Based Spatial Statistics, a technique that generates a skeleton representing the core of white matter tracts throughout the brain. We examined correlations between behavior scores and FA of (1) the whole skeleton and (2) specific regions of interest.

Results—In preterm children, scores on attention and internalizing behavior scales were each associated with whole skeleton FA and several regions of interest; unfavorable scores were consistently associated with lower FA. Externalizing behaviors were not associated with whole skeleton FA, but significant associations were found within a few regions of interest. The network of significant regions for attention and internalizing symptoms was widely distributed and overlapping. In full term children no associations of FA and behavior were significant.

Conclusions—Attention and internalizing behaviors in preterm children were associated with FA in a widely distributed, overlapping network of white matter tracts, suggesting common underlying neurobiology. DTI contributes to understanding individual differences in attention and behavior characteristics in children born preterm.

Keywords

prematurity; preterm; diffusion tensor imaging; white matter; behavior; attention; internalizing; anxiety

Preterm birth is highly prevalent, occurring in approximately 12% of all US births.¹ Many children born preterm have behavioral difficulties, including inattention and internalizing symptoms of anxiety and depression.^{2, 3} In contrast, children diagnosed with Attention-

Corresponding author: Irene M. Loe, MD, Stanford University, 750 Welch Road, Suite 315, Palo Alto, CA, 94304; Phone (650) 723-5711; Fax (650) 725-8351; iloe@stanford.edu..

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Deficit/Hyperactivity Disorder (ADHD) often have a predominance of externalizing symptoms, though some also show elevated levels of internalizing problems.⁴ A “preterm behavioral phenotype” that is characterized by symptoms and/or disorders of inattention, anxiety, and social difficulties has been proposed.²

White matter injuries are common after preterm birth.⁵⁻⁷ In the last two decades, the prevalence of cystic periventricular leukomalacia has declined, but the prevalence of diffuse, noncystic lesions remains high.⁸ Associations between emotional-behavioral regulation in school-aged children and white matter abnormalities on conventional magnetic resonance imaging (MRI) in the newborn period have been reported.⁹ However, conventional MRI provides only a qualitative impression of white matter properties.

Diffusion tensor imaging (DTI) is an MRI technique that generates quantitative measures to characterize white matter in the brain.¹⁰ Fractional anisotropy (FA) measures the degree to which diffusion is anisotropic. FA values are assumed to reflect the directional coherence of axons within a white matter tract. FA tends to increase with age, suggesting it reflects maturity;^{11, 12} however, increased FA has also been found unexpectedly in clinical populations such as Williams Syndrome, complicating the interpretation.¹³ Reduced FA in children and adolescents born preterm compared to age-matched full term children has been found in multiple brain regions, even in the absence of cystic lesions^{5, 7, 8} and has been used to infer subtle injury in those regions. However, not all studies find group differences in all tracts.^{14, 15} We previously compared preterm and full term children on DTI in a larger sample from which the current sample is drawn.¹⁶ We found no areas in which mean FA was lower in preterm compared to full term groups.

DTI studies of children and adolescents born preterm have found significant associations between white matter properties and attention within preterm samples; regions of association include the corpus callosum and bilateral internal capsules^{17, 18}, left external capsule, bilateral inferior fasciculi, left middle fasciculus, and right superior fasciculus.¹⁷ The association of internalizing symptoms and white matter integrity in children born preterm has not been previously evaluated. Skranes et al. examined hyperactivity in addition to inattention, but previous studies have not evaluated externalizing symptoms, including aggression and rule-breaking, specifically in relation to white matter properties.¹⁷

This study used DTI in children and adolescents born preterm to examine white matter properties in relation to behavioral characteristics. We hypothesized: 1) negative association between a parent-rated measure of attention and white matter properties in multiple brain regions distributed among different white matter tracts, (i.e., lower FA associated with more attention problems) based on the previous literature^{14, 17} and 2) negative associations of internalizing symptoms and white matter properties because of the known association of inattention and anxiety in the preterm group. We had no hypothesis about the association between externalizing scores and white matter properties because previous studies on externalizing problems in preterm children have been inconsistent.² Recent reports conclude that externalizing problems generally have not been elevated in preterm populations.^{2, 19}

METHODS

Participants were 9-16 year olds who underwent MRI scanning at the Stanford University site of a larger multi-site study of prematurity outcomes²⁰ (N=45). The Stanford University institutional review board approved this study. A parent provided informed consent; participants provided assent.

Preterm subjects were born at < 36 weeks gestation with birth weight < 2500 grams. Controls were community volunteers born ≥ 37 weeks. Exclusion criteria for all participants

included seizure disorder; hydrocephalus; receptive vocabulary score < 70; sensorineural hearing loss; and non-English speaker. Controls were excluded for identified language, learning, or psychiatric disorders because these conditions have been associated with abnormalities on brain imaging.^{21, 22} Given the modest sample size, we chose to focus on a healthy comparison control group, and no children in the preterm or full term groups had formal diagnoses of any behavioral disorder. Three preterm subjects who were scanned were excluded from this analysis due to extremely enlarged ventricles that altered white matter properties of selected tracts.²³ Recruitment began in 2007 and consisted of a convenience sample of children born between 1992-1999. Preterm subjects were recruited by letters sent to families of children who had been evaluated at the high-risk infant follow-up services at Lucile Packard Children's Hospital at Stanford University. Control children were recruited through local ads, school newsletters, and word of mouth. Control children were group-matched to preterm children for age, gender, and race. There were no differences in maternal education, IQ scores, or handedness. Seven preterm children were receiving special education services in school. Demographic data are presented in Table 1.

Medical complications at birth in the preterm group were: 4 of the 9 subjects on whom we had perinatal imaging results had abnormal findings on head ultrasounds or MRIs (grade 2 intraventricular hemorrhage, echodensities, or cystic lesions); 2 had mildly abnormal findings (grade 1 hemorrhage or choroid plexus cyst); 13 had respiratory distress syndrome; 5 developed bronchopulmonary dysplasia or chronic lung disease; and 2 were small for gestational age (< 3rd percentile birth weight for gestational age).

Measures of behavior

The Child Behavior Check List is a standardized parent-completed behavior questionnaire consisting of 113 items on a 3-point Likert scale.²⁴ To cover most problems in the questionnaire, we focused on the two broadband scales of Internalizing (consists of anxious/depressed, withdrawn/depressed, and somatic complaints) and Externalizing (consists of aggression and rule-breaking) Problems, and Attention Problems syndrome scores (not included in either Internalizing or Externalizing). Scores are reported as T-scores with mean of 50 and SD of 10; higher T-scores indicate more behavior problems. For the broadband scales, scores > 63 are considered clinically significant and scores of 60-63 are in the borderline range for clinical significance; for syndrome scores, scores > 70 are clinically significant and scores of 65-69 are in the borderline range.

MRI protocol

MRI data were acquired on a 3T Signa Excite (GE Medical Systems, Milwaukee, WI). Three T1 images were acquired and averaged for anatomical registration. Two high resolution IR-prep 3D FSPGR scans (FOV = 24 × 18 cm, matrix size = 260 × 192, 0.9 mm slices, TI = 300 ms, flip angle = 15 degrees, 1 NEX) and one IR-prep 3D FSPGR scan (FOV = 24 × 15.6 cm, matrix size = 256 × 192, 1.2mm slices, TI = 300 ms, flip angle = 15 degrees, 1 NEX) were collected. The three T1 images were averaged for anatomical registration. A trained experimenter manually identified the anterior and posterior commissures and mid-sagittal plane, and these points were used to put the image in a canonical orientation.

DTI Protocol

For DTI, a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence (TE = 80 ms, TR = 6500 ms, FOV = 240 mm, matrix size = 128 × 128) was used to acquire 60 slices, 2 mm thick, in 30 different diffusion directions (b = 900). The sequence was repeated 4 times, and 10 non-diffusion weighted (b = 0) volumes were collected.

DTI Processing

We used the voxel-wise “Tract Based Spatial Statistics” method from the Oxford Center for Functional MRI of the Brain (FMRIB) Diffusion Toolbox.²⁵ This method focuses on differences in white matter voxels by identifying a core white matter “skeleton” that is anatomically equivalent across subjects. Tract Based Spatial Statistics avoids spatial smoothing (averaging voxels) and minimizes partial volume effects that can occur when more than one tract goes through a voxel, thereby leading to decreases in anatomical specificity.²⁵

We analyzed fractional anisotropy (FA), a ratio from 0 to 1 that indexes the magnitude of diffusion in one direction compared to other directions. FA is elevated in white matter in comparison to gray matter and cerebral spinal fluid.

Standard preprocessing began with correction of the DTI images for eddy current distortions in the data acquisition by affine registration to a non-diffusion weighted volume. A tensor model was fit to each voxel,²⁶ and FA images were calculated. Due to variation in white matter tracts across individuals, the FA images were registered to a FA target image in standard space. The FA image of the most representative subject in the study (target) was chosen based on the minimum necessary warping, using the FMRIB Software Library's (FSL) nonlinear registration tool.²⁷ The target image was sampled to 1 mm³ resolution and aligned by affine transformation to the Montreal Neurological Institute template (MNI152), allowing us to use standard space coordinates for describing regions. Then, each subject's image was aligned to the target. We found no differences between preterm and control groups in the degree of non-linear warping using independent samples *t*-test.

The aligned FA images were averaged to create a mean FA map. We set a threshold of FA .2 to include major white matter pathways and to exclude peripheral tracts where there would be significant inter-subject variability and/or considerable mixing of grey and white matter. The mean FA image was generated and thinned to create the mean FA-skeleton, a representation of the centers or core of all major white matter tracts common to the group. Finally, for each subject, TBSS projected the highest FA on to the FA-skeleton, corresponding to the local tract core or center value. The resulting data were available for voxel-wise cross-subject statistics.

Statistical Analysis

Chi-square tests (for categorical variables and proportions), independent *t*-tests (for continuous variables), and Mann-Whitney *U* tests (for non-parametric data) were used to evaluate between-group differences on demographic variables and outcome measures.

Voxel-wise, mean FA-skeleton analysis—Analysis of the FA values of the FA-skeleton at the voxel level was conducted using a permutation-based tool for nonparametric statistical thresholding (what is called the “Randomise” function in FSL) to assess group related differences.²⁸ This method generates non-parametric, two-sample, unpaired *t*-tests of FA in subjects compared with controls. We also assessed the degree of association between behavior scores and FA of the mean skeleton within the preterm group and the control group in both the positive and negative directions. These analyses were controlled for age because of the large age range and set significance at $p < .05$ after correction for multiple comparisons using Threshold-Free Cluster Enhancement, a method which avoids using an arbitrary threshold for initial cluster-formation or identification of signal.²⁹

Regions of Interest Analysis (ROI)—Significant clusters of voxels on the FA-skeleton were visually inspected with reference to John Hopkins University DTI-based white matter

atlases³⁰ to determine their tract assignments. We selected representative clusters from major white matter tracts for region-of-interest (ROI) analyses. For clusters showing significant correlation between Attention score and FA on the mean skeleton, Attention ROIs were drawn manually. We used the following criteria to select clusters of substantial size and specificity in locations along tracts: clusters were 1) identifiable on the atlas as predominantly a single tract, 2) had a minimum of 30 voxels, 3) were continuous, and 4) mean FA of the cluster was $> .30$. Mean FA values of the clusters were described in terms of the standard space coordinates (MNI152) for the voxel with the highest average association with Attention score. Spearman correlations of Attention score and mean FA within the ROI were used to evaluate the degree of association; we also examined correlations between Internalizing and Externalizing scores within the same Attention ROIs. A negative correlation indicated that low FA was associated with more behavior problems. We repeated this process for creating Internalizing ROIs. We again examined correlations between mean FA within the Internalizing ROIs and (1) Internalizing scores, (2) Attention scores, and (3) Externalizing scores.

RESULTS

Behavior Outcomes

Mean Attention and Internalizing scores were higher for the preterm than the full-term group, whereas Externalizing scores were not different. A significantly greater proportion of preterm children had Attention scores in the borderline or clinical range compared to full term children. (Table 1) The scale scores were highly correlated: Attention and Internalizing problems scores, $r = .88$; Attention and Externalizing, $r = .72$; and Internalizing and Externalizing, $r = .73$, all $p < .001$.

Voxel-wise analysis

Comparing the preterm and full term groups, we found no areas on the mean FA-skeleton in which the preterm group had lower FA. In the preterm group, Attention and Internalizing Problems were each significantly negatively associated with the mean FA-skeleton. There were no significant positive correlations in which lower FA was associated with lower behavior scores. As behavior scores increased, FA decreased in a large and distributed network. There were no significant associations across the entire FA-skeleton in either direction for Externalizing Problems.

Figure 1 shows the multiple regions of significant association on axial views of the FA-skeleton for Attention (upper panel) and Internalizing scores (lower panel). Significant associations were found in the following bilateral tracts and regions: for Attention Problems, anterior thalamic radiation, cingulum, forceps major, forceps minor, corpus callosum, inferior fronto-occipital fasciculus/inferior longitudinal fasciculus, superior longitudinal fasciculus, fornix, and thalamus; for Internalizing Problems, the same regions and tracts were identified, with the following exceptions--no associations with anterior thalamic radiations and significant associations with bilateral corticospinal tract. Associations within the full-term group were not significant for Attention, Internalizing, or Externalizing scores in either direction.

Region of Interest (ROI) Analysis

To quantify the degree of association between behavior scores and FA, we examined correlations between Attention, Internalizing, and Externalizing scores with FA from specific ROIs identified on voxel-wise analysis. Table 2 lists the ROIs identified in major white matter tracts based on regions of association with (1) Attention scores (top half) and (2) Internalizing scores (bottom half) first identified on the mean FA-skeleton. We could not

include Externalizing ROIs because of the lack of significant clusters on the mean FA-skeleton. The tracts are listed by name and by MNI coordinates of the voxel with the highest association with the behavioral outcome. We then analyzed the degree of correlation and significance level for each behavior score (Attention, Internalizing, and Externalizing) and the FA of these ROIs. We found significant associations between the behavior outcomes of Attention and Internalizing and FA in several tracts, including forceps major, forceps minor, inferior fronto-occipital fasciculus/inferior longitudinal fasciculus, and superior longitudinal fasciculus. There were bilateral clusters on the corticospinal tract associated with Internalizing scores. Most correlations between (1) Attention scores and mean FA of Internalizing ROIs and (2) Internalizing scores and mean FA of Attention ROIs were also significant, indicating substantial overlap in the pertinent white matter network. For Externalizing scores, there were significant associations with Attention ROIs on the forceps major, forceps minor, and inferior fronto-occipital fasciculus; for Internalizing ROIs, significant associations were found only on the left forceps major and right superior longitudinal fasciculus. Representative correlations are illustrated in Figure 2 and in supplemental material, (See also Figures, Supplemental Digital Content 1, at <http://links.lww.com/JDBP/A42>). We noted one subject had an extreme score; we re-ran the analyses excluding that subject in this and subsequent analyses and found no change in statistical significance. Correlations of behavior scores and FA within these regions for the full term participants were not significant.

DISCUSSION

As hypothesized, we found that FA in multiple regions of the brain was associated with Attention and with Internalizing scores in the preterm group on voxel-wise analysis. The regions associated with both sets of symptoms occurred across a widely distributed, overlapping network. In all cases, favorable outcomes were associated with higher FA, suggesting that higher FA within the preterm group is indicative of white matter maturity and/or integrity. We also found that behavior scores from both attention and internalizing domains were significantly correlated with ROIs defined by each domain, corroborating the overlap in regions identified on voxel-wise analysis. Only a few ROIs defined by Attention and Internalizing domains showed significant correlations with Externalizing scores. The identification of an overlapping network of regions suggests that the “preterm behavioral phenotype” observed clinically may have common neurobiology underlying predominantly inattention and internalizing symptoms.

We found no areas in which FA was lower in the preterm compared to full term group, though we did find associations between FA and behavior scores within the preterm group. While these findings may seem contradictory, there are several possible explanations. First, the DTI analysis method of Tract Based Spatial Statistics is conservative in that it focuses on the centers of white matter tracts; thus, it may not detect peripheral damage in the tracts and may miss significant differences. The method is also limited in precision at the individual level due to variation in the shape of long range white matter tracts across individuals. More likely, many physiological properties contribute to FA, including white matter volume, dendritic branching or crossing fibers, and axonal size and packing.^{10, 16} It is likely that the physiological properties contributing to FA have greater variability across clinical populations than within clinical groups, making it difficult to predict the relative values of FA across groups. However, within clinical populations, it is likely that the physiological properties contributing to FA are similar, making comparisons of FA within the members of the group a meaningful index of relative health and maturity.¹⁶ We suspect that the processes affecting white matter characteristics in the preterm group are similar across individuals and therefore the sensitivity of DTI to within-group individual differences may be greater than the sensitivity to between-group factors.¹⁶

The presence of associations between mean FA and behavioral outcomes indicates that DTI may help us understand structure-function relationships in this clinical group. Our results are similar to other reports of associations between lower FA and attention problems in preterm samples.^{14, 17} The voxel-wise analysis identified the anterior thalamic radiation which connects subcortical regions to the frontal lobe. Subcortical-frontal connections are also important for attention and executive function in other studies.^{31, 32} In addition, for both attention and internalizing symptoms, voxel-wise analysis identified bilateral cingulum bundles that course from the medial temporal lobe, site of the amygdalae, to the frontal lobes. The amygdalae and frontal lobes are implicated in anxiety,²¹ and frontal regions connected by the cingulum have long been implicated in cognitive processes influencing attention.

The ROI analyses of significant regions confirmed the findings from voxel-wise correlation analyses of behavioral measures and the mean skeleton. In the ROI analysis, we found that lower FA in regions of the forceps major, forceps minor, inferior fronto-occipital fasciculus/inferior longitudinal fasciculus, and superior longitudinal fasciculus was significantly associated with attention and internalizing problems. These findings are consistent with previous DTI studies that found lower FA in preterm children with attention problems in similar specific regions.^{17, 18} The inferior fasciculi connect occipital and posterior parietal regions to the frontal lobes. These results are consistent with findings from other neuroimaging methods, such as functional MRI, that show that attention is related to posterior and anterior regions, including the dorsolateral prefrontal cortex.^{22, 31, 32} Involvement of the forceps major, extensions of white matter fibers from the corpus callosum to posterior regions, and the forceps minor, extensions of white matter fibers from the corpus callosum to anterior regions, is also consistent with the widely distributed network across anterior and posterior regions that support attention processes in typical development.

The literature on white matter microstructure in children and adolescents with ADHD is mixed. Two DTI studies of school-aged children with ADHD compared to controls found significantly reduced FA in multiple white matter areas, with differences in the regions/tracts between studies.^{33, 34} In contrast, two studies of older children and adolescents found increased FA or mixed FA findings in multiple regions compared to controls.^{35, 36} In one study, FA in the left inferior fronto-occipital fasciculus/inferior longitudinal fasciculus was significantly associated with ADHD symptom severity.³⁵ The pattern of findings on DTI in our sample differs from the patterns found in children with ADHD, suggesting that further work to investigate underlying differences in the neurobiology of inattention due to premature birth is warranted.

The association of internalizing symptoms and white matter integrity in children born preterm has not been previously demonstrated. Systematic review of structural and functional neuroimaging studies in social anxiety disorder implicates limbic, paralimbic, prefrontal, striatal, and parietal areas, providing support that tracts connecting cortical and limbic structures may be affected.²¹ Using the same Tract-Based Spatial Statistics method as in this study, a study of adults found that increased anxiety-related personality trait was associated with decreased FA in several similar major white matter tracts, including those connecting cortical and limbic areas.³⁷ A study of adults with social anxiety disorder found reduced FA and structure-function associations in the clinical group, which demonstrated a negative correlation between FA and trait anxiety, but not in the comparison group.³⁸

Limitations

The study utilized a convenience sample that included high-functioning preterm children who may not be representative of all children born preterm and a healthy comparison group

free of diagnosed behavioral disorders. The sample was small and heterogeneous in terms of the degree of premature birth and neonatal complications, limiting our ability to explore other characteristics in relation to behavior outcomes and FA. We used parent-report measures of behavioral symptoms and did not conduct diagnostic interviews. To disentangle specific effects of formally diagnosed behavior disorders and associations with white matter, a future study will require a much larger sample size with both preterm and full term children with and without diagnosed behavior disorders. In this sample, we did not have sufficient numbers of children with inattention or internalizing symptoms alone to determine if the underlying neurobiology of each condition is distinct in the pure cases. Future work should evaluate these groups using alternative methods, such as DTI tractography that allows for tracing of the continuous trajectory of white matter tracts through three-dimensional brain volumes.¹² Tractography has been validated in animals and humans and used at the individual level to identify specific locations of tracts during neurosurgery.¹²

CONCLUSIONS

We found that FA was negatively associated with the degree of attention and internalizing symptoms in preterm children. Thus, DTI helps us to understand brain-behavior relationships after preterm birth and to explain individual differences in this clinical group. The network of associated brain regions was highly overlapping, suggesting that inattention and anxiety may have a common underlying neurobiology in this population. Our next steps include using DTI tractography in native space, widely considered to be the most accurate method of DTI analysis, to replicate these findings. The clinical implications are that inattention and anxiety should both be assessed in children born preterm with behavioral difficulties. Future research should evaluate whether treatments for inattention and anxiety should vary as a function of the neurobiology of the conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
DTI	diffusion tensor imaging
FA	fractional anisotropy
FMRIB	functional magnetic resonance imaging of the brain
FSL	FMRIB Software Library
MNI	Montreal Neurological Institute
ROI	region of interest

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Figure 1. White matter regions^a (red-yellow heat map; yellow indicates higher association) on the FA-skeleton (green) of statistically significant associations between FA and attention (upper row) or internalizing (lower row) scores ($p < .05$, nonparametric permutation test, corrected for multiple comparisons) in the preterm group overlaid on axial slices of the mean FA-image (grayscale).

^aSome tracts in which significant associations were found include: a = anterior thalamic radiation; b = forceps minor; c = forceps major; d = corpus callosum; e = superior longitudinal fasciculus; f = inferior fronto-occipital fasciculus/inferior longitudinal fasciculus; g = cingulum. Abbreviations: FA, fractional anisotropy; ROI, region of interest; L = left, R = right, A = anterior, P = posterior.

Figure 2.

ROI (red-yellow heat map; yellow indicates higher association) on the forceps minor (red circle) shown on sagittal ($x = -16$), coronal ($y = 35$), and axial ($z = 11$) slices of FA-skeleton (green) overlaid on the mean FA image (grayscale). The graph shows the correlation between mean attention score and FA, $r = -.55$, $p < .05$.

Table 1

Participant demographics and behavior scores (N=45)

Participant	Preterm (n=25)		Full Term (n=20)		χ^2	p
	Number (n)	%	Number (n)	%		
Characteristics						
Boys	12	48	10	50	.894	.566
Maternal Education <	3	12	5	25	.435	.229
High School						
Nonwhite	8	32	10	50	1.5	.221
Left-handed or ambidextrous	4	16	4	20	.081	.775
Special education	7	28	0	0	6.63	.010*
	Mean (SD)	Range	Mean (SD)	Range	t	p
Age (years)	12.7 (2.1)	9.7-16.8	12.9 (2.1)	9.4-16.9	.203	.654
IQ	109 (15.8)	72-136	113 (16.1)	86-142	.759	.388
Gestational Age (weeks)	28.6 (2.5)	26-34	39.3 (1.1)	37-40	300	<.001*
Birth Weight (grams)	1191 (466)	630-2410	3171 (403)	2438-3771	226	<.001*
CBCL Outcomes	Mean (SD)	Range	Mean (SD)	Range	Z or t	p
CBCL Attention Problems ^a	59.5 (9.3)	50-80	52.5 (3.6)	50-64	-2.7	.007*
CBCL Internalizing Problems ^a	55.3 (10.1)	34-73	47.5 (10.3)	33-68	6.5	.014*
CBCL Externalizing Problems ^a	48.7 (11.7)	33-73	47.4 (7.9)	34-62	.169	.683
	Number with Borderline T-score (%)	Number with Clinical T-score (%)	Number with Borderline T-score (%)	Number with Clinical T-score (%)	χ^2	p
CBCL Attention Problems ^a	2 (8)	8 (32)	0 (0)	1 (5)	7.9	.019*
CBCL Internalizing Problems ^a	3 (12)	6 (24)	2 (10)	2 (10)	1.9	.390
CBCL Externalizing Problems ^a	1 (4)	3 (13)	2 (10)	0 (0)	3.1	.212

CBCL = Child Behavior Check List

SD = standard deviation

IQ = intelligence quotient

^a All CBCL measures are T-scores (mean of 50, SD of 10); higher T-scores indicate more problems. For Attention, a T-score of 65-69 is in the borderline range and a score 70 is in the clinically significant range; for Internalizing and Externalizing, T-scores of 60-63 are in the borderline range and scores > 63 are clinically significant.

* indicates significance at $p < .05$

Table 2

Region of Interest Analysis. The table shows nonparametric correlations between behavior scores (attention, internalizing, and externalizing) and mean FA values from regions of interest on the Tract Based Spatial Statistics mean FA skeleton. ROIs were created based on significant associations between FA on the mean skeleton and (1) attention and (2) internalizing scores. Locations of the clusters are reported in MNI coordinate system for the voxel in that cluster with the highest average association across outcomes.

Attention ROIs		Correlation with Attention Scores		Correlation with Internalizing Scores		Correlation with Externalizing Scores	
White matter tract	MNI coordinates	Correlation (r)	p	Correlation (r)	p	Correlation (r)	p
Cingulum							
Left	(-8, 15, 26)	-.220	.302	-.268	.206	-.261	.218
Forceps Major							
Left	(-22, -78, 9)	-.591	.002 [*]	-.721	<.001 [*]	-.608	.002 [*]
Forceps Minor							
Left	(-16, 35, 11)	-.548	.006 [*]	-.546	.006 [*]	-.486	.016 [*]
IFO/ILF							
Left	(-39, -42, 2)	-.377	.070 [#]	-.480	.018 [*]	-.205	.337
Right	(39, -25, -5)	-.566	.004 [*]	-.562	.004 [*]	-.323	.123
IFO							
Right	(32, 38, -1)	-.499	.013 [*]	-.567	.004 [*]	-.461	.024 [*]
SLF							
Left	(-33, -34, 28)	-.525	.008 [*]	-.553	.005 [*]	-.150	.483
Right	(35, -36, 29)	-.438	.032 [*]	-.511	.011 [*]	-.323	.123
Internalizing ROIs							
		Correlation with Internalizing Scores		Correlation with Attention Scores		Correlation with Externalizing Scores	
Cingulum							
Left	(-9, -32, 34)	-.309	.141	-.485	.016 [*]	-.331	.143
Forceps Major							
Left	(-27, -67, 16)	-.609	.002 [*]	-.498	.013 [*]	-.493	.014 [*]

Attention ROIs					
White matter tract	MNI coordinates	Correlation with Attention Scores		Correlation with Internalizing Scores	
		Correlation (r)	p	Correlation (r)	p
Right	(25, -75, 7)	-.494	.014 [*]	-.476	.019 [*]
Forceps Minor					
Right	(19, 27, 22)	-.447	.029 [*]	-.306	.147
IFO/ILF					
Left	(-33, -50, 12)	-.482	.017 [*]	-.332	.091 [#]
Right	(33, -53, 15)	-.514	.010 [*]	-.502	.012 [*]
SLF					
Left	(-44, -43, 2)	-.608	.002 [*]	-.512	.011 [*]
Right	(41, -47, 2)	-.586	.003 [*]	-.608	.002 [*]
CST					
Left	(-16, -22, -4)	-.478	.018 [*]	-.353	.091 [#]
Right	(17 -22, -6)	-.442	.031 [*]	-.343	.101

Abbreviations: IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; CST, corticospinal tract.

* indicates significance at $p < .05$

indicates trend for significance at $p < .1$