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Associations of behavioral problems with white matter circuits connecting to the frontal lobes in school-aged children born at term and preterm

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Abstract

Introduction: This study investigated whether internalizing and externalizing behavioral problems in children were associated with fractional anisotropy of white matter tracts connecting other brain regions to the frontal lobes. We contrasted patterns of association between children born at term (FT) and very preterm (PT: gestational age at birth =< 32 weeks).

Methods: Parents completed the Child Behavior Checklist/6–18 questionnaire to quantify behavioral problems when their children were age 8 years (N = 36 FT and 37 PT). Diffusion magnetic resonance scans were collected at the same age and analyzed using probabilistic tractography. Multiple linear regressions investigated the strength of association between age-adjusted T-scores of internalizing and externalizing problems and mean fractional anisotropy (mean-FA) of right and left uncinate, arcuate, anterior thalamic radiations, and dorsal cingulate bundle, controlling for birth group and sex.

Results: Models predicting internalizing T-scores found significant group-by-tract interactions for left and right arcuate and right uncinate. Internalizing scores were negatively associated with mean-FA of left and right arcuate only in FT children ($p_{\text{left AF}} = 0.01$, $p_{\text{right AF}} = 0.01$). Models predicting externalizing T-scores found significant group-by-tract interactions for the left

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Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data
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arcuate and right uncinate. Externalizing scores were negatively associated with mean-FA of right uncinate in FT ($p_{\text{right UF}}$ = 0.01) and positively associated in PT children ($p_{\text{right UF}}$ preterm = 0.01). Other models were not significant.

Conclusions: In children with a full range of scores on behavioral problems from normal to significantly elevated, internalizing and externalizing behavioral problems were negatively associated with mean-FA of white matter tracts connecting to frontal lobes in FT children; externalizing behavioral problems were positively associated with mean-FA of the right uncinate in PT children. The different associations by birth group suggest that the neurobiology of behavioral problems differs in the two birth groups.

Keywords

Internalizing problems; Externalizing problems; White matter; Frontal cortex; Preterm birth

1. Introduction

Mental health conditions in children and youth have become increasingly recognized as critical public health issues (Kessler et al., 2009; Patel et al., 2007; Whiteford et al., 2013). They are highly prevalent in childhood and adolescence; among children between the ages of 3–17 years, the prevalence rate is 3.2% for depression, 7.1% for anxiety, and 7.4% for conduct problems, according to the National Survey of Children's Health, (Ghandour et al., 2019). In addition, they are associated with many short-term challenges and long-term academic, occupational and social adverse outcomes (Liu et al., 2011). Parent-reported behavioral problems may be precursors to or early indicators of mental health conditions (Liu et al., 2011). Mental health conditions are likely the result of an interplay of neurobiological and environmental factors (Hatoum et al., 2018a). Few studies have asked whether behavioral problems below the threshold of a clinical mental health condition are associated with neurobiological factors (Andre et al., 2020). If studies establish that neurobiological factors correlate with the full continuum of behavioral problems prior to the diagnosis of a mental health disorder, such findings may contribute to understanding the origins of mental health conditions. In addition, the findings may inform the advisability, design, or evaluation of early treatment of behavioral problems as a strategy for prevention of serious mental health disorders.

During childhood, behavioral problems are typically divided into two categories: internalizing and externalizing problems (Liu et al., 2011; McMahon, 1994; Montoya-Castilla et al., 2018; Ollendick et al., 1994). Internalizing problems indicate internalized expressions of pain or distress, such as anxiety, fear, shyness, somatic complaints, withdrawal, and depression (Bongers et al., 2003; Ollendick et al., 1994; Wei and Lü, 2023). Externalizing problems represent outward expressions of distress, such as defiance, aggression, destructiveness, and conduct problems (McMahon, 1994; Wei and Lü, 2023). Although these behavioral problems are grouped as distinct categories, internalizing and externalizing problems often show a high degree of covariance (Hatoum et al., 2018b). It is unclear whether the neural correlates of internalizing and externalizing problems are overlapping or distinct, issues that are also relevant to understanding the conditions and for designing early treatments.

Frontal cortical regions are thought to provide top-down control over behavior, emotion, and cognition and modulate emotional and social processing (Rosch and Mostofsky, 2019). Differences in structural characteristics of the frontal lobes have been found in association with mental health conditions. For example, in anxiety disorders, an example of internalizing conditions, anomalous structure and function of prefrontal control regions, including the dorso-lateral pre-frontal cortex and the ventral-medial pre-frontal cortex (dlPFC/vmPFC) have been implicated in modulating activity in limbic regions (Rosch and Mostofsky, 2019). Among individuals with oppositional defiant disorder and conduct disorder, externalizing conditions and impaired cognitive control have been found in conjunction with structural deficits and impaired functioning of the paralimbic system, including the orbitofrontal cortex and anterior cingulate cortex (Matthys et al., 2013). Behavioral symptoms across the full continuum of scores from normal to significantly elevated have also been found to correlate with structural characteristics of the frontal lobes in children from 6 to 16 years of age (Blok et al., 2022). The orbitofrontal cortex, rostral middle frontal cortex, and the anterior cingulate cortex were associated with internalizing symptoms (Blok et al., 2022). The orbital frontal cortex, anterior cingulate cortex, amygdala, hippocampus, and striatum have been linked to externalizing symptoms (Blok et al., 2022). The frontal lobes connect to other regions of the brain through a series of white matter circuits. Characteristics of these white matter circuits have also been implicated in many mental health disorders (Fields, 2008, 2010).

The main objective of the current study was to determine if in children, internalizing and externalizing problems across the continuum of scores from normal to elevated would be associated with features of white matter circuits that connect to the frontal lobes. We focused on white matter circuits or pathways for several reasons. First, features of these structures are known to be relevant to normal psychological variation and clinical conditions (Fields, 2010). Second, white matter characteristics are sensitive to experience. For example, in the realm of mental health, measures of white matter microstructure have been shown to correlate with behavioral changes after psychological treatment of mental health conditions (Korgaonkar et al., 2021; Steiger et al., 2017). Third, previous research has found associations between the continuum of behavioral problems and white matter circuits in children and adolescents. One large study of 10-year old children found associations of white matter microstructure and a general psychopathology factor, a latent factor derived from both internalizing and externalizing problems (Neumann et al., 2020). Another study of 6–16 year olds reported internalizing and externalizing problems separately correlated with features of different white matter tracts while associations between behavioral problems and brain volumes were not significant after correction for multiple comparison (Andre et al., 2020). Given the importance of this issue, further studies are warranted.

In this study, we used diffusion MRI (dMRI) to analyze white matter circuits *in vivo*. We focused on four circuits that course to the frontal lobes: the uncinate fasciculus (UF), arcuate fasciculus (AF), anterior thalamic radiation (ATR), and dorsal or cingulate branch of the cingulum bundle. We chose these fasciculi because they have all been implicated in mental health conditions, can be reliably reconstructed in children using diffusion magnetic resonance imaging (dMRI), and represent distinctive pathways. We will briefly describe the anatomy of each pathway and results of previous studies implicating the circuit in mental health conditions.

The uncinate fasciculus (UF) connects the orbital, medial, and lateral PFC with rostral temporal areas, including the anterior temporal lobe, parahippocampal gyrus, entorhinal and perirhinal cortex, and amygdala (Koch et al., 2017). Among infants with a history of neglect and maltreatment, decreased fractional anisotropy (FA), one of the white matter metrics derived from dMRI, of the UF was associated with elevated self-reported internalizing problems (Hanson et al., 2015). Studies have also found positive correlation between mean diffusivity (MD) and reduced FA in the right UF, exacerbating anxiety scores (Ho et al., 2017; Koch et al., 2017). Other studies have found a correlation between the UF and symptoms such as flattened affect and lack of social engagement (Craig et al., 2009; Motzkin et al., 2011). These reports suggest that the microstructure of the UF may be associated with internalizing problems. Regarding externalizing disorders, adolescents with conduct disorder were found to have significantly increased FA in the left UF and a loss of the age-related changes in perpendicular diffusivity (Catani et al., 2016; Craig et al., 2009; Sarkar et al., 2013). In a different sample of children and adolescents, externalizing problems showed an age–behavior interaction in the left UF; among children with lower externalizing scores, FA was associated with age, but not among children with higher externalizing scores (Andre et al., 2020). Thus, the UF may show associations with both internalizing and externalizing problems.

The arcuate fasciculus (AF) connects the ventrolateral and dorsolateral part of the PFC with the posterior parieto-temporal regions (Nakajima et al., 2018). Patients with bipolar disorder (BD) were found to exhibit lower FA in the left AF anterior segment than did healthy controls (Sarrazin et al., 2014). In veterans, decreased FA of part of the AF was associated with aggression and anger outbursts (David et al., 2020). Again, these results suggest that the AF might be associated with both internalizing and externalizing problems.

The anterior thalamic radiation (ATR) connects the dorsolateral prefrontal cortex (DLPFC) with the thalamus through the anterior limb of the internal capsule (Deng et al., 2018). Adults and adolescents with major depressive disorder exhibit abnormal diffusion measures, mainly in the DLPFC part of the left ATR (Bessette et al., 2014; Hasan et al., 2008; Zhu et al., 2011). These findings suggest that the ATR may be associated with internalizing problems. As of this writing, we did not find studies on the ATR and externalizing problems.

The cingulum bundle forms an almost complete ring from the orbital frontal cortex along the dorsal surface of the corpus callosum to the temporal lobe. The cingulum is not a single pathway, but a collection of both long and short fibers connecting to different locations (Bubb et al., 2018). The cingulum bundle has long been recognized as part of the limbic system (Bubb et al., 2018). FA of the dorsal cingulum bundle was found to correlate with depression and healthy controls, even though group differences in cortical thickness of the anterior cingulate cortex were not found (Mertse et al., 2022). In a large, prospective study of adolescents, reduced FA within both the dorsal and ventral segments of the cingulum bundle was associated with different metrics of depression severity (Barch et al., 2022). Internalizing and externalizing problems were associated with microstructural features of the dorsal cingulum in a study correlating the full continuum of scores with white matter microstructure in a sample of adolescents (Andre et al., 2020). We analyzed the dorsal or cingulate subdivision of the cingulum bundle, coursing superior to the corpus callosum.

We recognize that other pathways also link to the frontal lobe. The superior longitudinal fasciculus (SLF) has been implicated in studies of white matter and mental health; however, using our methods many voxels and streamlines within the SLF overlap with those of the AF. The anterior segment of the inferior occipital-frontal pathway, another potential tract, shares voxels and streamlines with the UF. We limited the white matter circuits to reduce the number of analyses while evaluating distinct pathways.

Preterm birth, and in particular, very preterm birth, defined as a gestational age at birth less than 32 weeks, is associated with an increased risk for impaired neurobehavioral development (Batalle et al., 2017; Kallankari et al., 2021; Vanes et al., 2022). The degree of prematurity, as measured by birth weight or gestational age have been associated with an increased risk of developing mental health disorders in early adolescence, persisting into young adulthood (Anderson et al., 2021; Johnson and Marlow, 2011; Vanes et al., 2022). Very preterm-born children have consistently shown increases in internalizing and externalizing behaviors in childhood (Bhutta et al., 2002). Thus, this population is clinically at risk for developing internalizing and externalizing problems compared to their age-equivalent peers born at term, reflected as increased mean scores or a greater range of scores on measures of behavioral problems. Very preterm birth also has been associated with long-term changes in the microstructure of white matter. Studies on extreme preterm infants demonstrate altered structural connectivity of cortico-basal ganglia-thalamo-cortical loop connections (Fischi-Gómez et al., 2015). Prematurity-associated alterations in white matter were found in cortical and subcortical structures, affecting projection, commissural, and association fibers (Pandit et al., 2014). Additionally, adults with a history of very preterm birth have altered white matter properties (Kelly et al., 2023). However, studies differ as to whether FA values are increased or decreased when comparing individuals born preterm with peers born at term (Kelly et al., 2023; Travis et al., 2015).

A gap in the literature is whether white matter abnormalities to the frontal lobes underlie behavioral problems among children born preterm. Two previous studies have assessed the association of behavioral problems and white matter circuitry to the frontal lobe in children born at term and preterm. In a study using tract-based spatial statistics among school-aged children born at term and preterm, negative correlations between parent-reported Child Behavior Checklist (CBCL) internalizing problem scores and FA of tracts coursing to the frontal lobes, including forceps minor, inferior fronto-occipital fasciculus, and right SLF were found only in the preterm group. In addition, the same study found negative correlations only among children born preterm between parent-reported CBCL externalizing problems and FA in the forceps major and inferior fronto-occipital fasciculus (Loe et al., 2013). In another tractography study using fixel-based analysis (FBA), significant associations of both internalizing and externalizing problems were found with fiber density (FD), fiber-bundle cross-section (FC), and fiber density and cross-section (FDC) in several white matter pathways (Gilchrist et al., 2023) in 7-year-olds born both term and preterm.

Significant associations were limited to the right UF in children born at term at age 13 years. Additional research is warranted.

In this study, we assessed whether among school-aged children born at term and preterm, internalizing and/or externalizing problems would correlate with FA of four white matter tracts that connect to the frontal lobe: UF, AF, ATR and CC. We analyzed white matter circuitry using diffusion magnetic resonance imaging (dMRI) tractography. Given the increased risk of behavioral problems in children born preterm and the risk for white matter abnormalities in children born preterm, we hypothesized that behavioral problems would be greater in the preterm group. Based on the results of the study by Loe et al. (2013), we anticipated significant negative associations of FA and behavior problems within the group of children born preterm. Based on the results of the FBA analysis by Gilchrist et al. (2023), we recognized that internalizing and externalizing problems might be associated with microstructural properties of the multiple tracts, particularly the UF, in both children born at term and preterm.

2. Materials and methods

2.1. Participants

The participants were children born at term and preterm enrolled in a longitudinal study of reading skills and white matter characteristics (Bruckert et al., 2019; Dubner et al., 2020). Children were recruited from the San Francisco Bay Area from 2012 to 2015 and were followed for 2 years, from age 6–8 years. Preterm birth (PT) was defined as gestational age ≤ 32 weeks at birth. We restricted enrollment at this gestational age because we anticipated they would have elevated behavioral problems (Aarnoudse-Moens et al., 2009) and very preterm birth increases the risk for white matter injury (Larroque et al., 2003). Full-term birth (FT) was defined as gestational age ≥ 37 weeks or birth weight ≥ 2500 g. Parents reported on the race and ethnicity of the child. Exclusion criteria for all participants included hearing loss, visual impairment, history of neurological disorders, non-English speakers, genetic disorders, and IQ < 80. We decided to analyze the children at age 8-years because we would likely capture more behavioral problems at the older age than at age 6-years, given the nature and longitudinal emergence of behavioral problems (Scott et al., 2018). However, behavior problems scores were correlated across the two ages ($r_{\text{internalizing problem}} = 0.527$, $p < 0.001$; $r_{\text{externalizing problem}} = 0.587$, $p < 0.001$) in this sample. From an initial sample of 8-year olds from the two birth groups (N = 112: FT n = 51; PT n = 61), for this analysis, we included only those children whose parents completed the Child Behavior Checklist (CBCL) (n = 92, lost n = 20 as this measure was added to the protocol after initial data collection), who underwent diffusion MRI with the current protocol (n = 74, lost n = 18 due to change in imaging protocol), and whose scans were found to be free of motion artifacts and other technical problems (n = 73, lost n = 1), as described in previous studies of the sample (Bruckert et al., 2023; Hosoki et al., 2022). The final sample included 73 children from the two birth groups–36 children born FT (16 boys) and 37 children born PT (20 boys).

The experimental protocol was approved by the Stanford University Institutional Review Board (eProtocol #22233). Written consent was obtained from a parent or a legal guardian and written assent was obtained from the participant. Children were compensated for participation. We collected demographic characteristics, including child sex assigned at birth and birth group. At the time of enrollment, socioeconomic status of the family was calculated based on maternal education, maternal occupation, paternal education, and paternal occupation. Parents' education and occupation were scored using 7-point scale, 1 representing low and 7 representing high. The SES index was calculated with use of the modified four-factor Hollingshead Index (Dodson et al., 2018; Hollingshead, 1975).

2.2. Assessments conducted at age 8

Parents completed the parent-reported Child Behavior Checklist (CBCL/6–18), a questionnaire that indexes children's behavioral problems (Achenbach and Ruffle, 2000). On this scale, higher scores indicate greater number of behavioral problems or less favorable behavioral functioning. The instrument generates a total problem score, broad-band scale scores and narrow band scores. Internalizing problems is a broad band composed of three narrow bands: anxious/depressed behavior, withdrawn-depressed behavior, and somatic complaints (Achenbach and Ruffle, 2000). Externalizing problems is the second broad band score composed of two narrow band scores: aggressive behavior and rule-breaking behavior (Achenbach and Ruffle, 2000). We analyzed the T-scores of internalizing and externalizing problems. We focused on the broad bands because generally broad band scores have greater accuracy than narrow band scores. We categorized children whose T-score was at or above 60 as at risk for a clinical mental health disorder and above 70 as probable mental health condition.

2.3. Diffusion MRI acquisition and analysis

Brain MRI data were acquired at age 8 years using a 3 T scanner (GE MR750 Discovery; GE Healthcare, Waukesha, WI, USA) with a 32-channel adult head coil. All children were scanned for research purposes, without the use of sedation. MRI data analyzed in the current study included i) a high resolution T1-weighted scan using a 3D fast-spoiled gradient (FSPGR) sequence (TR = 7.24 ms; TE = 2.78 ms; FOV = 230 mm × 230 mm; acquisition matrix = 256 × 256; 0.9 mm isotropic voxels; orientation = sagittal) and ii) a diffusion MRI scan using a dual-spin echo, echo-planar imaging sequence (96 directions, b = 2500 s/mm^2, 3 b = 0 vol, voxel size = 0.8549 × 0.8549 × 2 mm^3, TR = 8300 ms, TE = 83.1 ms).

2.4. Diffusion MRI analysis

MRI data were managed and analyzed using a neuroinformatics platform (Flywheel.io) that guarantees data provenance, implements reproducible computational methods, and facilitates data sharing. The diffusion MRI analysis pipeline consisted of diffusion MRI preprocessing, whole-brain tractography, and tract segmentation. The steps were described in detail by Lerma-Usabiaga et al. (2019) and Liu et al. (2022) and are briefly summarized below.

2.5. Diffusion MRI preprocessing

Diffusion MRI data were preprocessed using a combination of tools from MRtrix3 (github.com/MRtrix3/mrtrix3), FSL (https://fsl.fmrib.ox.ac.uk/), and mrDiffusion part of VISTASOFT (http://github.com/vistalab/vistasoft) as implemented in the Reproducible Tract Profiles (RTP) pipeline (Lerma-Usabiaga et al., 2019). In brief, the steps of preprocessing included (i) denoising the data using principal component analysis (Veraart et al., 2016a, 2016b) and Gibbs ringing correction (Kellner et al., 2016), (ii) applied FSL's eddy current correction (Andersson and Sotiropoulos, 2016), (iii) resampling the data to 2 × 2 × 2 mm^3 isotropic voxels, and (iv) aligning the diffusion data to the average of the non-diffusion-weighted volumes, which were aligned to the child's high-resolution anatomical image using rigid body transformation.

2.6. Diffusion MRI tractography

The preprocessed diffusion MRI data served as the input for whole-brain tractography and tract segmentation. We used the constrained spherical deconvolution model (Tournier et al., 2007) with eight spherical harmonics (lmax = 8) to calculate fiber orientation distributions (FOD) for each voxel. These FODs were used for diffusion MRI tractography, which consisted of the following steps: (i) Ensemble Tractography (Takemura et al., 2016) to estimate the whole-brain white matter connectome. MRtrix3 (Batalle et al., 2017) was used to generate three candidate connectomes that varied in their minimum angle parameters (50°, 30°, 10°). For each candidate connectome, a probabilistic tracking algorithm (iFOD2) was used with a step size of 1 mm, a minimum length of 10 mm, a maximum length of 100, 150, and 200 mm, and an FOD stopping criterion of 0.04. (ii) Spherical-deconvolution Informed Filtering of Tractograms (SIFT) to improve the quantitative nature of the ensemble connectome by filtering the data such that the streamline densities match the FOD lobe integral. The resulting ensemble connectome retained 500,000 streamlines. (iii) Concatenation of the three candidate connectomes into one ensemble connectome. (iv) Automated Fiber Quantification (AFQ) (Yeatman et al., 2012) was used to segment the resulting whole-brain connectome of each child into our tracts of interest: bilateral UF, AF, ATR and cingulum. Tract segmentation was done using a way-point Region Of Interest (ROI) approach as described by Wakana et al. (2007). ROIs were transferred from a standard template to the native space of the participant so that tracking was done in native space. The tracts were refined by removing streamlines that were more than 5 standard deviations away from the core of the tract or that were more than 4 standard deviations above the mean streamline length (Yeatman et al., 2012).

While CSD was used to model the fibers (as it can discern crossing fibers), the diffusion tensor model (DTI), a principal and familiar dMRI method, was used to calculate FA. FA is a scalar measure that indicates the degree of directionality of water diffusion within the brain and can be used to segment presumed white matter pathways and to characterize their microstructure. FA is sensitive to many features of white matter, including axonal density, size, degree of myelination, organization of fibers within a voxel, and number of crossing fibers (Basser and Pierpaoli, 1996; Noriuchi et al., 2010). While associations of any behavioral measure and FA do not provide information on the feature of white matter associated with that function, FA is extremely sensitive to associations and a reasonable first step in establishing brain-behavior correlations.

2.7. Statistical analysis

All statistical analyses were conducted using R studio with statistical significance set at $p < 0.05$. We conducted chi-squared tests to compare the proportions of boys, race/ethnicity, and proportion of children at risk for a clinical program by birth group. We used independent samples *t*-test to compare internalizing problem T-scores, externalizing problem T-scores, SES scores and mean-tract FA of cerebral tracts by birth group. We used Welch *t*-test if there was unequal variance. To confirm we should analyze internalizing and externalizing problems separately, we ran a Pearson correlation to determine the magnitude of correlation between internalizing problem T-scores and externalizing problem T-scores, anticipating a low or moderate level of association.

We separately conducted a series of hierarchical linear regression models to assess the contribution of mean-tract FA of each of the bilateral cerebral tracts to CBCL internalizing problem T-scores and to externalizing problem T-scores at age 8. We included sex as a covariate if there was a significant difference in sex by birth group. Birth group and sex were dummy coded. First, we assessed the contribution of the birth group to internalizing and externalizing problem T-scores and included sex as the covariate. We then incorporated the contribution of the mean-tract FA of the cerebral tracts to the outcomes (main effect of tract). We computed R^2 and compared R^2 change between the model that investigated the main effect of the mean-tract FA of cerebral tracts to the model that only included covariates, to determine the contribution of mean-tract FA of the tract to the outcome. We next evaluated the interaction term to determine if the birth group moderated the association between behavioral problems and mean-tract FA of the cerebral tract. We then compared R^2 change between the model with the interaction term to the model that investigated the main effect of mean-tract FA of the cerebral tract to determine the contribution of the interaction term to the variance. We analyzed slopes of the association when the interaction term was significant.

To determine if associations of tract and behavioral problems were specific to internalizing or externalizing problems, we further evaluated those cerebral tracts in which we found a significant association between both internalizing problem T-scores and externalizing problem T-scores. If a cerebral tract demonstrated significant associations between behavioral problems as a main effect, we ran two regression models in which we considered the contribution of the mean-tract FA of the cerebral tract to internalizing problem T-scores while adjusting for covariates and externalizing problem T-scores and vice versa. If there was a cerebral tract that demonstrated associations between internalizing problem T-scores and externalizing problem T-scores respectively and the degree of association differed by birth group, we ran another model; we assessed the contribution of the mean-tract FA of the cerebral tract to externalizing problem T-scores by birth group, while adjusting for covariates and internalizing problem T-scores.

3. Results

3.1. Participant characteristics

Characteristics of participants are presented in Table 1. There were differences in the proportion of boys and girls within the birth groups; therefore, sex was included as a covariate in all linear regression models. The significant birth group differences in birth weight and gestational age were by design. While the sample was predominantly of white, approximately 1/3 identified as non-Eurpoean and approximately ¼ as Hispanic. Over half of the preterm sample were children from multiple gestation.

This sample of preterm children was relatively healthy. In terms of perinatal neurological findings, 8 children had grade 1 intraventricular hemorrhage (IVH), 2 children had grade 2 IVH, and 1 child had grade 3 IVH. No child had grade 4 IVH or periventricular leukomalacia. In terms of general health, 6 children had been diagnosed with bronchopulmonary dysplasia but none remained under treatment at the time of the study.

The sample was of high SES. The maternal occupation score and the paternal education score were both statistically higher in FT group versus PT group. Scores on T-scores on both the Internalizing and Externalizing scales were not different in the FT and PT groups. Table 1 shows that a small proportion of FT and PT children had at-risk internalizing problem T-scores, defined as T-score ≥ 60 (FT 17%; PT 16%) or externalizing problem T-score, similarly defined (FT 11%; PT 8%), and there was no difference in the proportion of at-risk population. Only 1 FT child and 1 PT child had internalizing problem T-score ≥ 70; 3 FT children and no PT children had externalizing problem T-score ≥ 70.

3.2. White matter tracts

We successfully computed mean-tract FAs for four tracts separately for right and left hemispheres for all subjects. Fig. 1 shows a representative tractography of the four tracts included in this study. As seen in Table 1, the mean-tract FA of the left UF was statistically lower in the PT compared to FT group. The mean-tract FA values of bilateral cingulum were higher in FT than PT children.

3.3. Associations of internalizing problems and mean-tract FA of cerebral tracts

Table 2 shows the results of multiple regression models for the associations of internalizing problem T-score and mean-tract FA of bilateral AF and UF. Supplementary Table 1 shows the results of multiple regression models for bilateral ATR and bilateral cingulum, none of which were significant.

The table demonstrates that birth group (FT vs PT) and sex (male vs female) did not make a significant contribution to individual differences in internalizing problem T-scores (model 1). Mean-tract FA of all of these circuits were not associated as a main effect with internalizing problem T-score (models 2a, 3a, 4a, 5a, 11a in Table 2, models 12a, 13a, 14a in Supplementary Table 1). We then investigated whether birth group-by-tract interaction would significantly increase the overall model fit after controlling for sex and birth group. We found that addition of interaction term significantly increased model fit for the left AF (model 2b) by 9% ($p = 0.011$) and right AF (model 3b) by 7% ($p = 0.030$), respectively. This finding suggests that the pattern of association was different in the FT and PT groups. Indeed, lower mean-tract FA of the left AF and the right AF were associated with higher internalizing problem T-scores only in children born FT, but not children born PT (Fig. 2A and B).

Addition of the interaction term did not increase the variance accounted for the left UF (Fig. 2C) but significantly increased the model fit for the right UF (Fig. 2D). There was a 9 %

increase in the variance ($p = 0.014$) for the model that included the interaction term for the right UF (model 5 b). Fig. 2D shows that the significant association between internalizing problem T-score and mean-tract FA of the right UF in children born FT was negative, but the association in the children born PT was trending positive ($b_{right\ UF\ Term} = -127.28$, $p_{right\ UF\ Term} = 0.050$, $b_{right\ UF\ preterm} = 85.20$, $p_{right\ UF\ preterm} = 0.080$).

3.4. Associations of externalizing problems and mean-tract FA of cerebral tracts

We then conducted the same analyses predicting externalizing problem T-score using mean-tract FA of cerebral tracts. Table 3 shows the results of multiple regressels for bilateral AF and UF, and Supplementary Table 2 shows the results of multiple regression models for bilateral ATR and bilateral cingulum, none of which were statistically significant.

Model 6 shows that sex (Male vs Female) significantly contributed to externalizing problems as a variable, but the overall model which included sex and birth group (FT vs PT) was not statistically associated with externalizing problem T-scores, accounting for 6% of the variance. None of the mean-tract FA of the circuits we investigated was statistically associated with the externalizing problem T-score as a main effect, after controlling for sex and birth group (models 7a, 8a, 9a, 10a in Table 3, models 15a,16a, 17a, 18a in Supplementary Table 2). We then investigated if birth group-by-tract interaction would significantly increase the overall model fit after controlling for sex and birth group. We found that the addition of interaction term significantly increased the model fit for the left AF (model 7b) by 5% ($p = 0.048$), and right UF (model 10b) by 16% ($p = 0.001$), indicating that the degree or direction of association differed by birth group. For the left AF, the overall model approached statistical significance ($p = 0.087$); however, the slope for each birth group was not statistically significant ($b_{left\ AF\ Term} = -72.20$, $p_{left\ AF\ Term} = 0.140$, $b_{left\ AF\ preterm} = 67.23$, $p_{left\ AF\ preterm} = 0.180$) (Fig. 3A). For the right UF, lower mean-tract FA of right UF was associated with higher externalizing T-scores in children born FT, and lower mean-tract FA of the right UF was associated with lower externalizing T-scores in children born PT ($b_{right\ UF\ Term} = -166.58$, $p_{right\ UF\ Term} = 0.01$, $b_{right\ UF\ preterm} = 115.27$, $p_{right\ UF\ preterm} = 0.01$) (Fig. 3D). The interaction term did not contribute to the strength of the model for the right AF (model 8b) or the left UF (model 9b) (Fig. 3B and ure C).

To determine if the association of the right UF and internalizing problems was driven by the shared variance of internalizing and externalizing problems, we ran a regression model that assessed contribution of the mean-tract FA and group-by-tract interaction of the right UF to externalizing problems while controlling for internalizing problem T-score, sex and birth group. The overall model was statistically significant ($p < 0.001$), and the interaction term of the right UF mean-tract FA x birth group continued to be significant ($p = 0.010$). The negative association among children born FT and positive association among children born PT continued to be statistically significant ($b_{right\ UF\ Term} = -114.11$, $p_{right\ UF\ Term} = 0.04$, $b_{right\ UF\ preterm} = 80.22$, $p_{right\ UF\ preterm} = 0.05$) (Supplementary Fig. 1). This finding suggests that the right UF is associated with both internalizing and externalizing problems and not solely based on the shared variance between them.

4. Discussion

The aim of this study was to investigate whether internalizing or externalizing problems in 8-year-old children, across the full continuum from normal to elevated scores, would be associated with measures of the microstructure of white matter circuits connecting to the frontal cortex. We also aimed to investigate if the association would differ between children born at term and children born preterm. We unexpectedly found that the T-scores on internalizing and externalizing problems did not differ in the two birth groups in this sample. Sex was associated with externalizing problems, but not internalizing problems. We found that internalizing problems were negatively associated with mean-tract FA of the right and left AF and of the right UF only in children born at term. We also found that externalizing problems were negatively associated with mean-tract FA of right UF in children born at term but positively associated with mean-tract FA of right UF in children born preterm.

4.1. Ratings of behavioral problems

In this study, we evaluated the strength of association internalizing and externalizing problems and white matter metrics across the full spectrum of behavioral problem scores from normal to elevated. The mean T-scores on the CBCL/6–18 for both children born at term and preterm were close to 50, which is the mean T-score for the general population. Few children scored in the at-risk or probable clinical condition level in either birth group.

Contrary to our initial hypothesis, the results showed no statistically significant differences in internalizing or externalizing problem scores between children born at term and very preterm. These findings differentiate our sample from other samples of children born preterm (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002). The lack of birth group differences may have been due to several factors. First, we studied a convenience sample. The full term group may have been biased toward children with learning or behavioral problems, explaining their family’s interest in participating in a study like this one. Second, the preterm group was relatively healthy. Children with severe cognitive or sensory impairments were excluded. Only a minority had medical complications of prematurity, such as bronchopulmonary dysplasia, and none had Grade IV IVH or periventricular leukomalacia. Third, both the FT and PT groups were of high SES. High SES status often confers favorable environmental circumstances, conducive to learning, cognitive development, and positive mental health (Bradley and Corwyn, 2002). By contrast, low SES status and other adverse environmental conditions can adversely impact long-term measures of prefrontal cortex development and white matter pathways (Hodel, 2018). Thus, the preterm children in this sample experienced relative biological and environmental advantage, and thereby may have followed different neurodevelopmental trajectories than those of other samples of preterm children, resulting in lower behavioral problem scores. These characteristics of the PT group may limit the generalizability of the findings to other samples of children born preterm.

4.2. Mean-tract FA in FT and PT groups

Comparing the mean-tract FA for the 8 target tracts, we found that the FT group had significantly higher FA in the right and left cingulate cingulum than the PT group but significantly lower FA in the left UF. In previous studies of this sample that used same tractography, we did not find group differences in mean-tract FA for any studied white matter pathways at age 6 (Bruckert et al., 2019). Across studies comparing FT and PT children of different ages, diffusion measures show variability as a function of the age at scanning, tracts analyzed, and methods. A meta-analysis found that FA is diffusely higher in FT than in PT infants when scanned at near-term age (Dibble et al., 2021). A longitudinal study of school aged children found no significant effect of preterm birth on diffusivity measures, despite consistent differences in brain volumes (Adrian et al., 2023). However, a tractography study of adults born preterm found no consistent FA differences across groups, although brain-behavior associations were different in the two birth groups (Kontis et al., 2009). At present, the reasons for this high variability is poorly understood and may be the result of differences in diffusion MRI acquisition and/or analysis as well as differences in the samples studied.

4.3. Results of regression models in FT and PT groups

In the children born at term, higher scores on the CBCL/6–18 scales for internalizing and externalizing problems were associated with lower mean-tract FA in two of four tracts. These results suggest that within this term group, a favorable behavioral profile was associated with increasing FA. Mean-tract FA accounted for between 13 and 23% of the variance in behavioral problem scores that ranged from normal to elevated. These results suggest that neurobiological factors may contribute to behavioral problems prior to the diagnosis of a mental health condition. We recognize that a significant association does not imply causality. In this study, we do not know if the presence of behavioral problems altered white matter microstructure, or, conversely if features of white matter microstructure represented a vulnerability that impacted the level of behavioral problems or increased vulnerability to environmental circumstances associated with the development of behavioral problems. Nonetheless, these data suggest that white matter microstructure may be an early indicator of a neurobiological contributor to behavioral problems.

The association of externalizing problems and FA of the right UF was in the opposite direction, positive, in the preterm group; children with higher number and/or severity of behavioral problems had higher FA. It is difficult to interpret which white matter properties may have contributed to positive associations of externalizing problems with FA in the preterm group. FA is a summary measure, sensitive to many different microstructural features, including density of white matter fibers, axonal diameter, fiber cohesion and number of crossing fibers (Figley et al., 2022). Different patterns of association between cognitive measures and FA in children born at term and preterm have been found in this sample of children (Bruckert et al., 2019; Dodson et al., 2018) and in other samples (Kelly et al., 2023; Travis et al., 2015). One experimental strategy to determine which microstructural features are underlying the positive association in the preterm group would be to use convergence of different advanced MRI methods, each sensitive to a distinct microstructural feature. For now, we can only say that the two birth groups differ in the underlying neurobiology of behavioral problems. Preterm birth, with its associated perinatal injury to oligodendrocyte precursors and downstream developmental effects of white matter circuits (Inder et al., 2023), may result in distinctive developmental trajectories and different brain-behavior associations.

The results we found differed from those reported by Loe et al. (2013), in which associations were found exclusively among children born preterm and in the opposite direction. We presume that the reasons for the difference were the difference in the age of the sample and in the analytic methods of white matter characterization. That study relied on Tract-Based Spatial Statistics whereas we used probabilistic tractography, a presumably more tract-specific method.

4.4. Behavioral problems and the UF

We found a significant negative association of internalizing problems and right UF in children born at term and a positive association approaching significance in children born preterm. We also found the negative association of externalizing problems and right UF in children born at term, and positive association in children born preterm. The association between externalizing problems and the right UF did not change when we controlled for scores on the scales for internalizing problems.

The UF is an association white matter tract that connects the temporal lobe with prefrontal regions associated with emotional regulation, impulsivity, and high-order cognitive skills (Andre et al., 2020; Travis et al., 2015; Von Der Heide et al., 2013). Many studies suggest that structural and functional connectivity of the UF plays a role in linking the generation of emotions (from within the limbic system) to self-regulation (controlled by the frontal cortex). For example, in children aged 9–16, diffusion-tensor imaging and functional MRI demonstrated negative associations between the UF FA and activation of the amygdala to pictures of sad and happy faces, though in that study there were no significant associations to frontal cortex (Swartz et al., 2014). In a study that evaluated white matter characteristics in children with and without autism, higher FA in the UF was associated with better self-regulation in children without autism, whereas higher FA was associated with worsening self-regulation in children with autism (Ni et al., 2020).

The association between mean-tract FA of the right UF and behavioral problems was negative in children born at term, meaning that lower T-score (indicative of fewer or less severe behavioral problems) was associated with higher FA. In this age group, behavioral problems (such as aggression or anxiety) are commonly seen in children with poor self-regulation, such as within children with impulsivity or ADHD (Reimherr et al., 2017). We were uncertain whether the same UF fibers might be serving to transfer information regarding both internalizing and externalizing characteristics and the associations were based on shared variance between the internalizing and externalizing T-scores. For that reason, we ran regression models for externalizing problems, including the scores on the internalizing problem scales. We found that the degree of association did not change substantially, suggesting that the UF is associated with both internalizing problems and with externalizing problems independently, not based on the shared variance between the scales. With our methods, we could not further dissect the UF to investigate the role of specific fibers to specific behavioral problems (internalizing problems, externalizing problems). We suggest future studies investigate UF function and connectivity in school-aged children using methods that might allow precision in the dissection of the tract.

Among children born preterm, we found that the association between mean-tract FA of the right UF and behavioral problems was positive, implicating higher behavioral problems with higher FA. The association of externalizing problems and mean-tract of the UF was not fully explained by the scores on the internalizing problem scale. The gray and white matter of children born preterm undergo altered white matter integrity (Duerden et al., 2019). One possible explanation is that UF has specific or independent roles in internalizing problems and in externalizing problems, and the complex white matter injury secondary to preterm birth and subsequent development of white matter circuits changed the direction of association. We acknowledge that previous literature demonstrates inconsistent results among children born preterm. For example, in Kanel's study (2021), the term-equivalent mean-tract FA of the right UF in children born preterm was associated with higher "emotion moderation", but not among children born at term. In Gilchrist et al.'s study that examined association between three different fiber-specific measures and concurrent behavior in 7-year-olds with and without history of preterm birth (2023), bilateral UF metrics were associated with internalizing problems and externalizing problems regardless of birth group. Among the 13-year olds, the only significant associations were between fiber density of the right UF and both internalizing and externalizing problems in the term group. Different findings may relate to the methods used to characterize white matter and to differences in the study population. However, these findings further support a role for the UF in behavioral problems. We suggest future studies in large samples using multiple advanced MRI methods to investigate the role of UF in behavioral problems in children born preterm.

4.5. Internalizing problems and the AF

In the children born at term, we found that internalizing problems were negatively associated with bilateral AF. The AF connects the frontal, parietal and temporal cortex. Emerging evidence suggests that the AF participates in attention and self-regulation. The AF, together with superior longitudinal fasciculus-III branch and inferior frontal occipital fasciculus, have been labeled a "ventral attention network" (Hattori et al., 2018; Urger et al., 2015). AF is also an important tract for language processing. Specifically, many studies find that the left AF is associated with reading and language skills (Wandell and Yeatman, 2013) and language-based working memory (Barbeau et al., 2023). It is notable that internalizing problems are commonly seen in children with attentional weaknesses, including Attention Deficit Hyperactivity Disorder and with language and/or reading problems (Bishop et al., 2019; Donolato et al., 2022; Peterson et al., 2017). One possibility is that the fibers within the AF, associated with internalizing problems, are the identical fibers engaged in transfer of information for language and reading. That would mean that the signals in both systems travel the same circuits. Alternatively, the AF may have distinct subsets of fibers that serve to transfer information about behavioral issues, attention, or language and reading. With the methods we used in this study, we could not dissect the AF with sufficient detail to determine if the same fibers would be associated with internalizing problems, attention, and reading. Future studies using different methods may be able to investigate the AF in greater detail than we could.

4.6. Behavioral problems and the ATR and the cingulum

In this study, we did not see associations between behavioral problems and either the ATR or cingulum in either birth group. Gilchrist et al. (2023) found no association between internalizing or externalizing problems and fiber density, a measurement of specific fiber population density within a voxel of the ATR. However, they found associations between internalizing and externalizing problems and fiber-bundle cross section and fiber-density-and-cross-section, measures that relate to transferring information across white matter. Loe et al. (2013) did not find association between internalizing problems and ATR in either birth group but found association between attention problems and ATR in children born at term. Future studies should verify the contribution of ATR in children.

In Gilchrist et al. (2023), there was association between internalizing problems and fiber density, fiber-bundle cross section and fiber-density-and-cross section, and externalizing problems and fiber-bundle cross section and fiber-density-and-cross section in cingulum. The Ghilchrist group analyzed the cingulum as a whole cingulum bundle, while our study only looked at the dorsal subsection of the cingulum bundle. It may be that our result was different from that of Ghilchrist's because of the different definition of the cingulum, and different methodology to characterize white matter properties. The function of the cingulum continues to be debated, and emerging evidence suggests the cingulum, particularly dorsal subsection, plays a role in working memory, executive function and social cognition (Maldonado et al., 2020). Decreased FA of cingulum-callosal bundles was associated with emotional dysregulation in children (Hung et al., 2020). In children born very preterm, increased FA of dorsal anterior portion of the cingulum bundle was associated with increased behavioral problems, including anxiety, ADHD and autistic features (Brenner et al., 2021). A few studies suggest ventral cingulum may also play a role in internalizing problems (Hu et al., 2023; Bubb et al., 2018). Loe's study (2013) did not find association between internalizing problems or externalizing problems and cingulum. Again, future studies should verify the contribution of cingulum bundle in children.

4.7. Limitations

All participants were recruited from a single site, within the San Francisco Bay Area, and the socioeconomic status of the sample was high. About 70 % of the participants identified themselves as white race. The results therefore may not generalize to samples from different geographical regions, with different racial make-up, or with a greater proportion of participants from low socioeconomic status. The collected behavioral measurements were derived from a parent-reported CBCL/6–18 from a single measure; parent-reported scores for internalizing problems may not have fully reflected the participants' internal feelings of anxiety or depression. Future studies should consider using specific self-reported instruments as well as parent reports. The children in this study had no statistically significant differences in behavioral problem scale scores between those born at term and those born preterm. The majority of children in our sample did not have behavioral problems. Hence, our findings cannot be generalized to populations with at risk/clinically significant problems.

The only metric of white matter microstructure we used in this study was FA. While FA is sensitive to cognitive and behavioral traits, it is also highly non-specific. Increasing FA may be due to one or more factors, such as higher fiber coherence, increased myelination, or decreased crossing fibers. Thus, with the use of this single metric, we cannot determine which features of white matter may be associated with behavioral problems. Future studies should use metrics of white matter that allow more specific determination of the underlying features associated with the behavioral traits and/or multiple imaging protocols each of which is sensitive to different features of white matter. In addition, we limited ourselves to four bilateral tracts. We may have missed important associations of behavioral problems and white matter microstructure by not assessing other pathways.

4.8. Future directions

While our study is distinctive as we investigated a sample that included children without elevated behavioral problems or diagnosed mental health conditions, our findings are limited due to small number of participants. A critical next step would be a replication of these findings with a larger, diverse sample. Subsequent future studies should also investigate the associations of behavioral problems and white matter metrics longitudinally. Longitudinal studies may contribute to understanding the etiology and pathogenesis of behavioral problems. To date, in a longitudinal study investigating the causal relationship of anxiety and white matter integrity in anxious preadolescent girls, higher anxiety led to decreased whole-brain white matter integrity, but without concurrent associations (Aggarwal et al., 2022). In a longitudinal study of children aged 6–10 years, presence of internalizing problems and externalizing problems predicted slow growth in whole-brain white matter integrity, but not vice versa (Muetzel et al., 2018).

Future studies should also consider how treatment of behavioral problems affects the associations of scores to white matter metrics. Adult studies have found that white matter microstructure changes after successful behavioral treatment. In a study of social anxiety disorder, a significant increase in FA was found in bilateral uncinate fasciculus and right inferior longitudinal fasciculus comparing pre- and post-treatment for social anxiety disorder (Steiger et al., 2017). In a study of post-traumatic stress disorder, FA was significantly associated with improvement in dysphoria symptoms after successful treatment (Korgaonkar et al., 2021). A potential future study could evaluate the impact of cognitive behavior therapy, the first-line treatment for children with clinically significant internalizing problems, such as anxiety and depression, on white matter microstructure. Cognitive behavioral therapy nurtures self-regulation and control through skills taught verbally (McGinn and Sanderson, 2001). White matter microstructure of the tracts to the frontal lobe may predict response to cognitive behavior therapy or may change after treatment with cognitive behavior therapy, representing adjustments in the flow of information in the brain.

4.9. Conclusion

In summary, this study found that internalizing and externalizing problems across the full spectrum from normal to elevated was associated with FA of white matter circuits connecting from other brain regions to the frontal lobe. The pattern of association was different among children born at term and preterm. Thus, white matter metrics may be an early indicator or marker of the status of a child's behavioral problems in children prior to diagnosis of a mental health condition, though the child's medical history of prematurity is essential for the interpretation of any findings. It is critical to pursue these findings in the effort to understand the origins of mental health conditions in different populations and ultimately to design appropriate early treatments to prevent progression or reduce severity of mental health conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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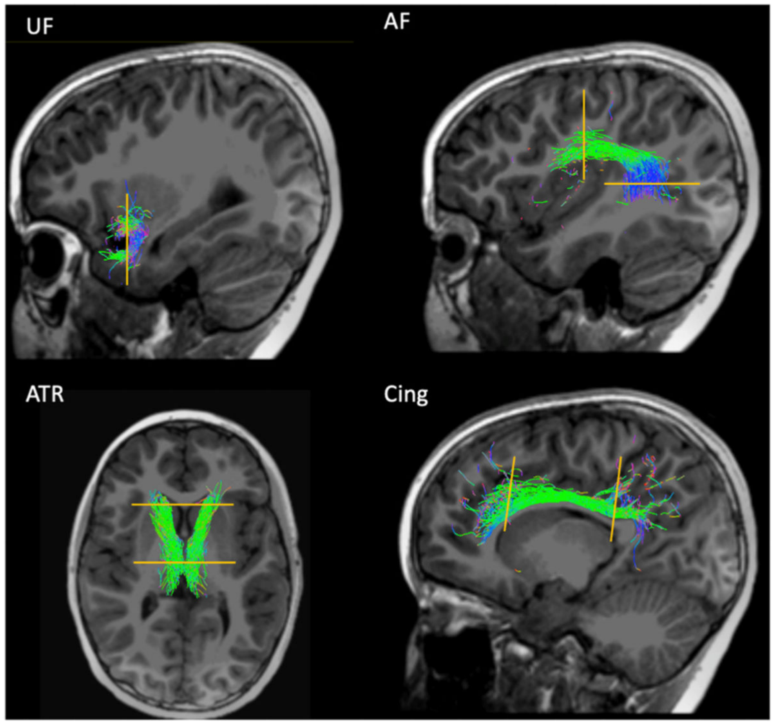

Fig. 1.

Example of results of probabilistic tractography for the four tracts included in this study presented on a typical full term participant. For each tract the portion of the tract between the two defining regions of interest are visualized. Stream line color indicates the principal direction with red for right-left, blue for dorsal-ventral, and green for anterior-posterior). The orange lines represent the defining regions of interest (ROIs) for tract dissection. UF Uncinate fasciculus; AF Arcuate fasciculus; ATR Anterior thalamic radiation; Cing Cingulum Bundle Cingulate Branch. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

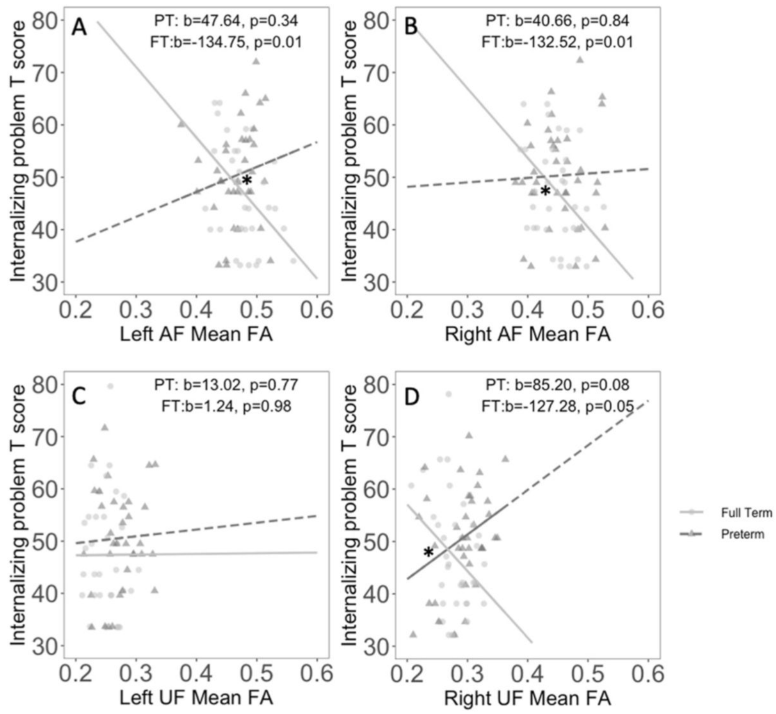

Fig. 2.

Association between mean-tract FA and internalizing problem T-score. Subplots (A, B) shows that lower mean-tract FA of the left or right AF was associated with higher internalizing problem T-score in children born at term; there was no association between mean-tract FA of the AF and internalizing problem T-score in children born preterm. Subplot C shows that there was no association between mean-tract FA of the left UF and internalizing problem T-score in either birth group. Subplot D shows that while interaction term is significant, there was negative association between the mean-tract FA of the right UF and internalizing problems in children born at term, and marginal positive association between the mean-tract FA of the right UF and internalizing problems in children born preterm. *statistically significant interaction term.

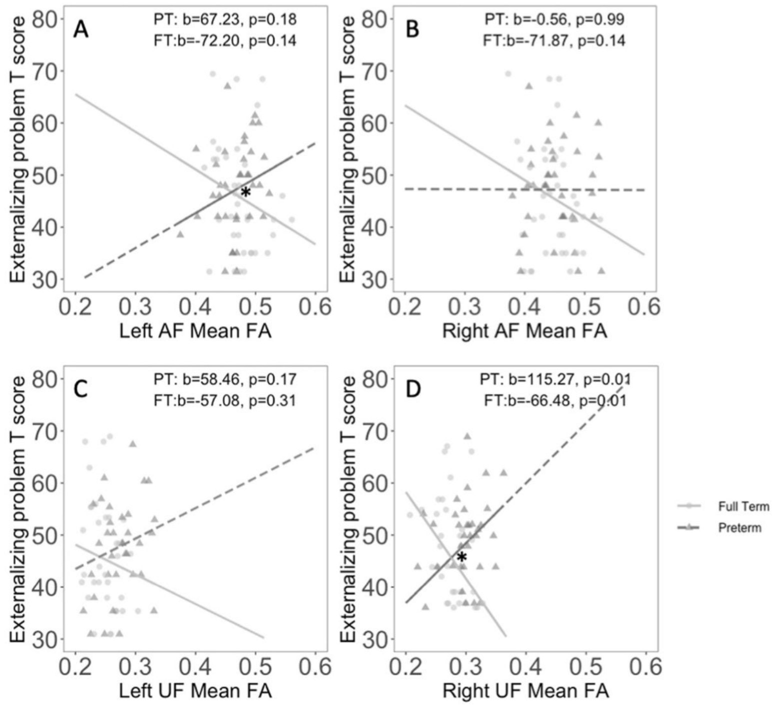

Fig. 3.

Association between mean-tract FA and externalizing problem T-score. Subplot A shows that while interaction between the mean-tract FA of the left AF and externalizing problem T-score by group is significant, there was no association between mean-tract FA of the left AF and externalizing problem T-score for each group. Subplot B and C show no association between mean-tract FA of the right AF and the left UF and externalizing problem T-score in either birth group, respectively. Subplot D shows the negative association between the mean-tract FA of the right UF and externalizing problems in children born at term, and positive association between the mean-tract FA of the right UF and externalizing problems in children born preterm when adjusting for sex and birth group. * statistically significant interaction term.

Table 1

Demographic variables, behavioral problem scores, and mean-tract fractional anisotropy (FA) values for children born at term or preterm.

	Term (n = 36) (% or SD)	Preterm (n = 37) (% or SD)	X^2 or t	*p*-value
Demographics				
Boys (%)	16 (44 %)	20 (54 %)	X^2 (1) = 3.96	**0.047**
Gestational Age (weeks)	39.6 (1.5)	29.3 (2.1)	t (64) = 24.35	**<0.001**
Birth weight (grams)	3335 (447)	1294 (442)	t (71) = 19.61	**<0.001**
Multiple gestation	3 (8 %)	21 (57 %)	X^2 (1) = 19.39	**<0.001**
Age at the test (months)	97.8 (2.0)	98.6 (2.3)	t (71) = −1.50	0.138
Non-white (%)	11 (31 %)	11 (30 %)	X^2 (1) = 0.006	0.939
Hispanic ethnicity (%)	10 (28 %)	10 (27 %)	X^2 (1)<0.005	0.943
Maternal education (1–7)[1]	6.3 (0.8)	5.9 (1.3)	t (60.9) = 1.83	0.073
Maternal occupation (1–7)[1]	6.2 (3.4)	4.3 (3.8)	t (71) = 2.24	**0.028**
Paternal education (1–7)[1]	6.6 (0.9)	6.0 (1.2)	t (68) = 2.13	**0.037**
Paternal occupation (1–7)[1]	8.0 (1.8)	7.4 (2.3)	t (68) = 1.21	0.230
SES index (8–66)[2]	58.6 (9.8)	53.5 (13.6)	t (71) = 1.82	0.072
Behavioral problem scores				
CBCL Internalizing T[3]	47.2 (11.0)	50.6 (9.6)	t (71) = −1.40	0.165
# Internalizing T[3] ≳ 60	6 (17 %)	6 (16 %)	X^2 (1) = 0.003	0.959
CBCL Externalizing T[4]	46.2 (11.2)	46.7 (9.1)	t (62.6) = −0.20	0.842
# Externalizing T[4] ≳ 60	4 (11 %)	3 (8 %)	X^2 (1) = 0.190	0.663
Mean-tract FA				
Left UF[5]	0.25 (0.03)	0.27 (0.04)	t (71) = −2.39	**0.020**
Right UF[5]	0.28 (0.03)	0.29 (0.04)	t (71) = 1.91	0.060
Left AF[6]	0.48 (0.03)	0.47 ((0.03)	t (71) = 1.05	0.300
Right AF[6]	0.45 (0.04)	0.45 (0.05)	t (71) = −0.76	0.452
Left ATR[7]	0.45 (0.04)	0.43 (0.04)	t (71) = 1.80	0.076
Right ATR[7]	0.43 (0.05)	0.42 (0.04)	t (71) = 1.60	0.114
Left Cing[8]	0.49 (0.05)	0.46 (0.05)	t (71) = 2.29	**0.025**
Right Cing[8]	0.45 (0.04)	0.42 (0.05)	t (71) = 2.20	**0.031**

Note:

[1] Score was derived from 7-point scale, from low (1) to high (7)

[2] SES index was calculated from the modified four-factor Hollingshead Index using the formula (average of maternal and paternal education score) x 3 + (average of maternal and paternal occupation score) x 5 (Dodson et al., 2018)

[3] Child Behavior Checklist Internalizing problem T-score

[4] Child Behavior Checklist Externalizing problem T-score

[5]Uncinate Fasciculus

[6]Arcuate Fasciculus

[7]Anterior Thalamic Radiation

[8]Cingulum Bundle Cingulate Branch.

Table 2

Regression analysis of internalizing problems and mean-tract FA of the Arcuate Fasciculus and the Uncinate Fasciculus.

Model	1	2a	2b	3a	3b	4a	4b	5a	5b
Birth Group	3.07	2.69	**−83.32** *	3.48	**−60.22** *	2.93	−0.04	**2.05**	**−56.74** *
Sex	−1.33	−1.25	−1.82	−1.04	−2.34	−1.17	−1.15	−1.29	1.53
Left AF[1]	–	−47.03	**−134.75** **	–	–	–	–	–	–
Left AF[1] x birth group	–	–	**182.38** *	–	–	–	–	–	–
Right AF[1]	–	–	–	−51.07	**−132.52** **	–	–	–	–
Right AF[1] x birth group	–	–	–	–	**141.03** *	–	–	–	–
Left UF[2]	–	–	–	–	–	8.78	1.24	–	–
Left UF[2] x birth group	–	–	–	–	–	–	11.77	–	–
Right UF[2]	–	–	–	–	–	–	–	8.42	−127.28
Right UF[2] x birth group	–	–	–	–	–	–	–	–	**212.47** *
R^2 change	–	0.02	**0.09** *	0.04	**0.07** *	0.00	0.00	0.00	**0.09** *
Total R^2	0.03	0.05	**0.14** *	0.07	**0.13** *	0.03	0.03	0.03	0.12

Note:

* $p < 0.05$

** $p < 0.01$.

[1] Arcuate fasciculus

[2] Uncinate fasciculus. R^2 change values reflect an increase in variance accounted for in reference to the model with covariates (model 1). For models with interaction terms, the R^2 change reflects the change in variance from adding the interaction term, after adjusting for covariates. Significant values are in bold.

Table 3

Regression analysis of externalizing problems and mean-tract FA of the Arcuate Fasciculus and the Uncinate Fasciculus.

Model	**6**	**7a**	**7b**	**8a**	**8b**	**9a**	**9b**	**10a**	**10b**
Birth Group	1.64	1.60	−64.16	1.89	−30.33	1.38	−27.77	1.46	**−77.69** **
Sex	**5.00** *	**5.01** *	4.58	**5.17** *	4.52	**5.32** *	**5.43** *	**5.07** *	**8.80** **
Left AF[1]	–	−5.14	−72.20	–	–	–	–	–	–
Left AF[1] x birth group	–	–	**139.43** *	–	–	–	–	–	–
Right AF[1]	–	–	–	−30.68	−71.88	–	–	–	–
Right AF[1] x birth group	–	–	–	–	71.39	–	–	–	–
Left UF[2]	–	–	–	–	–	16.88	−57.08	–	–
Left UF[2] x birth group	–	–	–	–	–	–	115.54	–	–
Right UF[2]	–	–	–	–	–	–	–	13.46	**−166.48** **
Right UF[2] x birth group	–	–	–	–	–	–	–	–	**281.75** **
R^2 change	–	0.00	**0.05** *	0.01	0.02	0.00	0.04	0.00	**0.16** **
Total R^2	0.06	0.06	0.11	0.07	0.09	0.06	0.10	0.06	**0.21** **

Note:

* $p < 0.05$

** $p < 0.01$.

[1] Arcuate fasciculus

[2] Uncinate fasciculus. R^2 change values reflect an increase in variance accounted for in reference to the model with covariates (model 6). For models with interaction terms, the R^2 change reflects the change in variance from adding the interaction term, after adjusting for covariates. Significant values are in bold.