

A Dynamic Relation Between Whole-Brain White Matter Microstructural Integrity and Anxiety Symptoms in Preadolescent Females with Pathological Anxiety

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Research Article

Keywords: white matter, pediatric anxiety, diffusion tensor imaging, longitudinal neuroimaging

Posted Date: August 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-842284/v1>

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Version of Record: A version of this preprint was published at Translational Psychiatry on February 8th, 2022. See the published version at <https://doi.org/10.1038/s41398-022-01827-y>.

Abstract

Pathological anxiety typically emerges during preadolescence and has been linked to alterations in white matter (WM) pathways. Because myelination is critical for efficient neuronal communication, characterizing associations between WM microstructure and symptoms may provide insights into pathophysiological mechanisms associated with childhood pathological anxiety. This longitudinal study examined 182 girls enrolled between the ages of 9–11 that were treatment-naïve at study entry: healthy controls ($n = 49$), subthreshold-anxiety disorders (AD) ($n = 82$), or meeting DSM-5 criteria for generalized, social, and/or separation ADs ($n = 51$), as determined through structured clinical interview. Anxiety severity was assessed with the Clinical Global Impression Scale and Screen for Child Anxiety and Related Emotional Disorders (SCARED). Participants ($n = 182$) underwent clinical, behavioral, and diffusion tensor imaging (DTI) assessments at study entry, and those with pathological anxiety (subthreshold-AD and AD, $n = 133$) were followed longitudinally for up to 3 additional years. Cross-sectional ANCOVAs (182 scans) examining control, subthreshold-AD, and AD participants found no significant relations between anxiety and DTI measurements. However, in longitudinal analyses of girls with pathological anxiety (343 scans), linear mixed-effects models demonstrated that increases in anxiety symptoms (SCARED scores) were associated with reductions in whole-brain fractional anisotropy, independent of age (Std. β (95% CI) = -0.06 (-0.09 to -0.03), $F(1,46.24) = 11.90$, $P = 0.001$). Using a longitudinal approach, this study identified a dynamic, within-participant relation between whole-brain WM microstructural integrity and anxiety in girls with pathological anxiety. Given the importance of WM microstructure in modulating neural communication, this finding suggests the possibility that WM development could be a viable target in the treatment of anxiety-related psychopathology.

Introduction

Anxiety is dimensional and, when extreme, becomes maladaptive and is pathological. Anxiety disorders (ADs) are among the most common childhood psychiatric illnesses, affecting up to 30% of youth [1]. In addition, numerous children have subclinical and persistent anxiety symptoms that do not meet DSM-5 criteria [2, 3]. Like children with ADs, these children also suffer considerably and are at increased risk to develop more significant stress-related psychopathology later in life [2, 4, 5]. Because anxiety is dimensional in nature, studying the full range of anxiety may provide insights into the factors that contribute to the varying degrees of distress and disability experienced by children with pathological anxiety. Understanding the factors underlying the development and expression of anxiety in young girls is of particular interest because after the transition to adolescence there is a two-fold increase in the prevalence of ADs in adolescent girls compared to boys that persists throughout the reproductive years [6–8].

White matter (WM) microstructure is highly relevant to adolescent development as adolescence is characterized by changes in WM pathways critical for effective neuronal communication [9–12]. While many studies have examined WM pathways in adults with high trait anxiety and ADs [13–23], considerably less work has examined WM in anxious youth [24–29]. Given evidence linking prefrontal-

limbic pathways to anxiety [21, 25, 30–36], our prior work focused on the uncinate fasciculus (UF), the major WM pathway linking prefrontal regions to temporal lobe structures, including the amygdala and anterior hippocampus [37, 38]. These studies demonstrated anxiety-related reductions in UF fractional anisotropy (FA), a measure of WM microstructural integrity, in adults, preadolescent children, and preadolescent non-human primates (NHPs) [21, 25, 39]. Interestingly, our findings in preadolescent children and preadolescent NHPs suggest that the relation between UF FA and anxiety is present in males but not in females [25, 39].

To more comprehensively characterize WM in anxious girls, in the current study we used a longitudinal approach to assess within-participant relations between WM parameters and anxiety symptoms in preadolescent girls (enrolled ages 9–11). Additionally, because of the dimensional nature of anxiety, we included girls with a wide range of anxiety symptoms – controls (low anxiety), subthreshold-ADs (mild-moderate anxiety), and ADs (meeting DSM-5 AD criteria for generalized, social, and/or separation ADs). We first performed cross-sectional analyses comparing WM integrity between girls with ADs, subthreshold-ADs, and controls. Next, in girls with pathological anxiety (subthreshold-AD and AD), using repeated clinical and imaging assessments over a 3-year period, we assessed the longitudinal within-participant relation between anxiety symptoms and WM microstructure. We also assessed relations between WM microstructure with age and pubertal status, which were controlled for in the anxiety-focused analyses.

Methods

Participants

Recruitment and clinical assessment

182 preadolescent girls with varying levels of anxiety were enrolled between ages 9–11 and characterized using clinical, behavioral, developmental, and neuroimaging assessments. Children were recruited from the Madison metropolitan area via community and school advertisements and mass emails. Girls were interviewed with the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL) [40], administered either directly by or under the supervision of a trained PhD-level clinical psychologist or a psychiatrist. Review of audiotapes demonstrated acceptable reliability (Cohen $\kappa > 0.80$), and tape review (by DSP) continued throughout the study to maintain interviewer fidelity. Clinicians also rated overall anxiety severity using the Clinical Global Impression Scale-Severity (CGI-S) [41]. Diagnoses and CGI-S ratings were reviewed and confirmed in group discussions with all study clinicians. Included participants had never received treatment for anxiety or other psychiatric illness, were not treatment seeking, and were eligible for an MRI scan. Major exclusion criteria included psychotropic medication use, severe psychopathology in need of immediate treatment, and diagnoses of major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, autism, bipolar disorder, or schizophrenia. Informed assent and consent were obtained from all participants and their

parents, in accordance with the Institutional Review Board of the University of Wisconsin-Madison. Individuals were compensated for their time and effort.

Based on the K-SADS and CGI-S, participants were categorized into three groups: 1) healthy controls, 2) subthreshold-AD, and 3) AD. Healthy control participants exhibited very minimal, if any, symptoms of anxiety or any other psychiatric illness (CGI-S = 1, normal/not at all ill). Subthreshold-AD participants exhibited subsyndromal but persistent levels of symptoms associated with generalized, separation, and/or social anxiety but did not meet DSM-V criteria for these disorders (CGI-S = 2, borderline mentally ill; or CGI-S = 3, mildly ill). AD participants met full DSM-5 criteria for generalized anxiety disorder, separation anxiety disorder, and/or social anxiety disorder (CGI-S > 4, moderately ill or worse). Participants in the AD group could have comorbid diagnoses of attention deficit hyperactivity disorder and oppositional defiant disorder if symptoms were less severe than the AD. The final sample (n = 182) was comprised of 49 controls, 82 subthreshold-AD, and 51 AD girls who completed the initial year of the study. Girls with pathological anxiety (subthreshold-AD and AD, n = 133) were followed longitudinally for up to 3 years with annual clinical, neuroimaging, and behavioral assessments, including the K-SADS/CGI and multimodal imaging session. 131 participants were assessed in year 1, 95 in year 2, 64 in year 3, and 53 in year 4 (Fig. 1). There were no significant differences in anxiety severity at study entry (child SCARED) among children who completed the full study (all 4 scans) vs. those who completed either 1, 2, or 3 scans (Supplementary Fig. 1).

Rating scales

Children's anxiety symptoms were rated by both the child and a parent using the Screen for Child Anxiety and Related Emotional Disorders (SCARED) [42]. Depressive symptoms and externalizing behaviors were also assessed using the Child Depression Inventory (CDI) [43] and Conners' Parent Rating Scale-Revised (CPRS-R) [44], respectively. The average interval between SCARED survey completion and MRI scan was 8.83 days (range: 0-178 days). Children's pubertal status was measured with the Tanner Staging Scale and the Pubertal Development Scale (PDS), completed by child and parent together [45]. These data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the University of Wisconsin-Madison, School of Medicine and Public Health, a secure, web-based application designed to support data capture for research studies [46, 47].

MRI Data Acquisition and Processing

DTI acquisition

All brain images were collected on a 3.0 Tesla GE MR750 scanner (GE Healthcare; Waukesha, WI) using a 32-channel head coil. Diffusion-weighted MRI scans were obtained using a two-dimensional echo planar imaging diffusion-weighted spin-echo sequence with 48 optimal non-collinear directions (see Supplementary Methods).

DTI processing and analysis

Image processing was completed using procedures described previously in Tromp et al., 2019 [25], with the exception of within-participant co-registration of tensor images prior to co-registration across participants. Deterministic tractography was performed in TrackVis [48] to delineate whole-brain WM and seven bilateral tracts of interest across the brain, including the corpus callosum (CC), cingulum (CING), inferior fronto-occipital fasciculus (IFO), internal capsule (IC), superior longitudinal fasciculus (SLF), stria terminalis/fornix (STRIA/FX), and uncinate fasciculus (UF). For each image, a weighted mean was calculated per tract for each diffusion metric (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD]) (see Supplementary Methods).

Statistical Analysis

Cross-sectional analyses assessed group differences in WM microstructure and behavioral metrics in the full initial sample of participants (controls vs. subthreshold-AD vs. AD). One-way ANCOVA models assessed between-group differences in: 1) demographic and clinical variables and 2) DTI metrics in the 7 WM tracts and whole-brain WM. Because child- and parent-rated SCARED scores were significantly correlated (see Supplementary Results), and because there is some evidence to suggest that child self-reports may be particularly relevant during this developmental period [49–51], child-rated SCARED scores were selected as the primary metric of anxiety severity. Analyses were also performed with parent-rated SCARED scores and are reported below. Linear regression models assessed the between-participant relationship between anxiety levels (child SCARED) and DTI metrics. Because age, PDS scores, and Tanner Staging scores were significantly inter-correlated (see Supplementary Results), age was used as the developmental covariate for all ANCOVA and regression models. Similar analyses substituting PDS or Tanner scores in place of age as did not change the results (Supplementary Fig. 2). All models were evaluated using both frequentist and Bayesian statistics, the latter of which affords the ability to claim evidence of absence of an effect (see Supplementary Methods) [52]. Analyses were conducted using the *stats* and *base* packages in RStudio (ver. 1.4.1106) and JASP software (ver. 0.14.1).

Across the sample of girls with pathological anxiety (subthreshold-AD and AD participants), longitudinal within-participant relationships between age, child SCARED scores, and WM microstructure were assessed using linear mixed-effects (LME) models, which allow for precise and unbiased effect estimates by accounting for repeated within-participant measures [53]. As in the cross-sectional analysis, within the longitudinal data age, PDS scores, and Tanner Staging scores were highly inter-correlated (see Supplementary Results), and age was used as the developmental covariate. Separate LME models quantified the within-participant relationship between: 1) age and child SCARED scores; and 2) child SCARED scores and WM microstructure in each tract, while controlling for age (see Supplementary Methods). LME modeling was performed using the *lme4* and *car* packages in RStudio (ver. 1.4.1106) with frequentist statistics.

All DTI analyses used a Bonferroni-adjusted P value for multiple comparison correction (8 comparisons across 7 tracts and whole-brain WM; $P_{\text{corrected}} < 0.05/8 = 0.00625$).

Results

Cross-Sectional Analysis (Controls vs. Subthreshold-AD vs. AD)

Groups did not differ in any demographic variable, except PDS scores (subthreshold-AD > control) (Table 1). As expected, groups differed on multiple clinical measures, in most cases in a stepwise manner (AD > sub-threshold-AD > control) (Table 1). For categorical (control vs. subthreshold-AD vs. AD) or dimensional (child SCARED) analyses, there were no statistically significant associations between anxiety and FA in the WM tracts of interest or in whole-brain WM after multiple comparison correction (Table 2). Bayesian analyses support the interpretation of these null effects as the absence of a relation between anxiety and FA in the CC, CING, IC, IFO, STRIA/FX, and UF ($BF_{S_{H1}} < 0.33$), and a lack of evidence for anxiety-FA relations in the SLF and whole-brain WM ($0.33 < BF_{S_{H1}} < 3$). As expected, age was associated with FA at the whole-brain level, as well as in the CING, IC, IFO, and UF, but not in the CC, SLF, or STRIA/FX (Supplementary Fig. 3 and Supplementary Table 1).

Table 1
Sample Characteristics by Cohort at Study Entry

Clinical Measure	Healthy Control (n = 49)	Subthreshold-AD (n = 82)	AD (n = 51)	One-Way ANOVA P value
Age, mean (SD), years	10.43 (0.82)	10.50 (0.85)	10.63 (0.78)	0.489
IQ (WASI), mean (SD)	113.92 (12.58)	116.77 (16.36)	113.94 (14.11)	0.449
PDS scores, mean (SD)	1.61 (0.50)	1.91 (0.55)	1.78 (0.58)	0.010 ¹
Tanner Staging scores, mean (SD)	1.64 (0.76)	1.80 (0.74)	1.82 (0.93)	0.446
Parent SCARED (Anxiety), mean (SD)	3.04 (2.98)	18.93 (9.17)	31.02 (10.50)	< 0.001 ²
Child SCARED (Anxiety), mean (SD)	6.92 (5.71)	23.65 (10.10)	33.40 (13.12)	< 0.001 ²
CGI-S (Global Impression), mean (SD)	1.00 (0.00)	2.45 (0.50)	4.16 (0.46)	< 0.001 ²
CDI (Depression), mean (SD)	40.53 (4.08)	44.74 (5.71)	50.02 (8.86)	< 0.001 ²
CPRS (ADHD), mean (SD)	45.48 (3.96)	55.25 (9.98)	58.90 (11.98)	< 0.001 ³
Abbreviations:				
WASI, Wechsler Abbreviated Scale of Intelligence; PDS, Pubertal Development Scale; SCARED, Screen for Child Anxiety Related Emotional Disorders; CGI-S, Clinical Global Impression Scale-Severity; CDI, Child Depression Inventory; CPRS-R, Conners' Parent Rating Scale-Revised.				
¹ Significant main effect of group (P < 0.05) in one-way ANOVA. Post-hoc Tukey indicates subthreshold-AD > controls (P = 0.007).				
² Significant main effect of group (P < 0.001) in one-way ANOVA. Post-hoc Tukey indicates stepwise progression (controls < subthreshold-AD < AD; all P-values < 0.001).				
³ Significant main effect of group (P < 0.001) in one-way ANOVA. Post-hoc Tukey indicates subthreshold-AD and AD groups do not differ, but both are higher than controls (P < 0.001).				

Longitudinal Analysis in Girls with Pathological Anxiety

In our longitudinal sample of girls with subthreshold-ADs or ADs (n = 133), we examined the within-participant relations between changes in the severity of anxiety symptoms and associated WM microstructural changes throughout the brain while controlling for age. Child SCARED scores exhibited a

significant negative correlation with whole-brain FA at the individual level (Std. β (95% CI)=-0.06 (-0.09 to -0.03), $F(1,46.24) = 11.90$, $P = 0.001$), such that increases in a child's anxiety level predicted decreases in her whole-brain FA (Table 3 and Fig. 2). While not statistically significant after multiple comparison correction, parallel analyses with MD and RD demonstrated consistent results (Supplementary Fig. 4 and Supplementary Table 2). Parallel analyses in each of the 7 WM tracts of interest did not reveal any statistically significant anxiety-FA associations after multiple comparison correction (Table 3). However, at the uncorrected level, multiple WM tracts – including the CC, CING, IFO, and SLF – showed reductions in FA in relation to anxiety severity (Table 3). Substituting parent SCARED scores for child SCARED scores in this analysis also revealed a negative within-participant association between anxiety and whole-brain FA but did not reach statistical significance ($P = 0.18$) (Supplementary Fig. 5). While all participants were treatment-naïve at study entry, a subset ($n = 27$) began receiving behavioral and/or pharmacological therapy in follow-up years of the study. In a supplemental analysis, excluding scans collected after treatment initiation did not alter the findings (Supplementary Fig. 6). Additionally, there was a positive within-participant relationship between age and whole-brain FA (Std. β (95% CI) = 0.08 (0.05 to 0.12), $F(1,64.90) = 24.75$, $P < 0.001$) – in line with the cross-sectional analysis – and no association between age and child SCARED scores (Supplementary Fig. 7 and Supplementary Table 3).

Discussion

This study in young females is one of the largest longitudinal neuroimaging studies of pathological anxiety, focused on understanding alterations in neural pathways relevant to the development of anxiety during childhood. The major finding from this study was derived from the longitudinal data, revealing that within participants, more severe anxiety symptoms were associated with lower whole-brain FA (Table 3 and Fig. 2). This relation manifested in treatment-naïve girls, including girls with subthreshold AD symptoms as well as girls who met criteria for ADs, independent of age and pubertal status. We also performed cross-sectional analyses with data collected at study entry, comparing WM integrity among controls, subthreshold-AD participants, and AD participants. In contrast to the longitudinal finding, this cross-sectional analysis revealed no significant relations between FA and anxiety. Taken together, these findings highlight a dynamic relation between whole-brain WM integrity and anxiety, as well as the importance of a longitudinal within-participant approach for studying developmental psychopathology.

The presence of a significant longitudinal association between anxiety and WM in the context of no significant cross-sectional association is notable (Tables 2 and 3). This suggests that within an individual, whole-brain FA and anxiety fluctuate together over time, regardless of individual differences in FA magnitude. We are unaware of other studies that have concomitantly examined the relation between anxiety symptoms and WM parameters longitudinally in children with pathological anxiety. One longitudinal DTI study in a normative sample of youth (ages 6–18) found that children with higher anxiety/depression symptoms at study intake had slower rates of WM development in multiple WM tracts [27]. Another study in a large sample of youth reported an association between initially assessed

internalizing and externalizing symptoms with reduced growth-related increases in global WM [54]. Other work examining WM alterations in relation to pediatric anxiety has been cross-sectional. Four cross-sectional DTI studies have been performed in youth (ages 6–18), examining typically developing youth with trait anxiety as well as children with ADs [25, 26, 28, 29]. Consistent with DTI studies of anxiety in adults [13, 16, 17, 19], these studies have generally reported anxiety-related WM reductions in FA in various regions, including the UF, CING, CC, and IFO. We previously reported a reduction in UF FA in boys with ADs but not girls, also using a cross-sectional approach [25]. The lack of a relation between anxiety and UF FA in girls in our previous study is consistent with the cross-sectional results reported here in preadolescent girls with pathological anxiety. These null effects should be interpreted cautiously. We note that a Bayesian analysis performed on the data from the girls in the previous study did not support evidence for the absence of an effect (see Supplemental Results), whereas a Bayesian analysis performed on the current dataset was supportive of evidence of absence for the lack of an association between UF FA and anxiety (Table 2).

The correlation between global WM microstructure and anxiety symptoms suggests the presence of a diffuse whole-brain WM effect. The consequences of this global effect could be relevant to the inter- and intra-connectivity among brain networks relevant to emotional information processing and integration, aversive stimulus detection, and the interpretation of social behavior, which is consistent with reports of whole-brain WM microstructural alterations related general psychopathology factors and cognitive abilities in youth [24, 55]. While our results suggest a dynamic relationship between WM microstructure and childhood anxiety, the mechanism underlying this association is unclear. Furthermore, it is possible that the association between WM integrity and anxiety symptoms is not causally linked, as other factors could concomitantly impact both of these measures. However, studies in both NHPs and humans suggest that stress can affect WM microstructure [56, 57]. As such, it is plausible that in our sample of girls, the experience of chronically heightened anxiety could result in altered WM microstructure. Specific mechanisms that have been implicated from preclinical studies link adversity to WM microstructure via effects on oligodendrogenesis and myelination [58, 59]. It is also conceivable that WM microstructure plays a role in directly mediating levels of anxiety. Studies manipulating oligodendrocyte function in preclinical models of anxiety could be informative in this regard. Our results provide an impetus to examine the potential utility of WM as a treatment target for early-life anxiety. In contrast to a specific tract, the data support targeting global WM microstructure. Recent work demonstrates that WM microstructure can be enhanced by lifestyle interventions such as exercise, nutrition, and sleep [60–64]. These interventions are well-suited for children and could be easily used in conjunction with pharmacological and/or psychotherapeutic treatment strategies.

Although this study included a relatively large sample, most participants were White (Supplementary Table 4). Expanding the diversity of the participants in these studies to include more BIPOC individuals will be important to enhance generalizability of the findings. Our sample did not include boys, and our longitudinal analysis did not include control participants, limiting our conclusions regarding the association between WM microstructural integrity and anxiety symptoms to only girls with pathological anxiety. While there was some attrition in the follow-up years of the study, the statistical approaches used

– linear mixed-effects models in particular – are designed to handle missing data in longitudinal datasets [53]. While we attribute the FA-anxiety relation to whole-brain reductions in FA, it is possible that there are associations between anxiety symptoms and FA in specific WM tracts that were not examined in this study.

In summary, we present one of the largest longitudinal neuroimaging studies of pediatric anxiety, demonstrating that, on an individual level in girls with pathological anxiety, worsening of anxiety symptoms is associated with a global decrease in WM microstructural integrity. Importantly, this relationship is independent of age and puberty. An extensive body of literature has shown that childhood and early adolescence are periods of significant WM growth across the brain [12, 65, 66]. Our present results demonstrate that within this overarching developmental pattern, individual variations in whole-brain WM are dynamically linked to childhood anxiety symptom severity. These findings support future studies investigating the possibility of targeting WM as a modality to aid in the prevention and treatment of childhood anxiety disorders.

Declarations

Acknowledgements

This research was supported by grant R01MH107563 (NHK) from the National Institute of Mental Health; projects ZIAMH002781 and ZIAMH002782 (DSP) from the Intramural Research Program of the National Institute of Mental Health; and training grants T32GM008692 and T32MH018931 (NA) from the National Institute of General Medical Sciences and National Institute of Mental Health. The project described was supported by the Clinical and Translational Science Award (CTSA) program, through the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS), grant UL1TR002373. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding sources had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. We thank the participants and families, as well as the staff of the HealthEmotions Research Institute at the Wisconsin Psychiatric Institute and Clinics.

Conflict of Interest

NHK reported receiving grants from the National Institute of Mental Health; consulting to CME Outfitters, the Pritzker Neuropsychiatric Disorders Research Consortium, the Skyland Trail Advisory Board, the Early Life Adversity Research External Scientific Advisory Board at the University of Texas at Austin, and Corcept Therapeutics Incorporated; and serving as editor-in-chief of The American Journal of Psychiatry during the conduct of the study. The other authors report no potential conflicts of interest.

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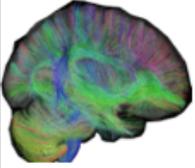
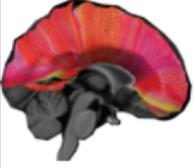
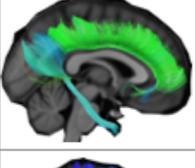
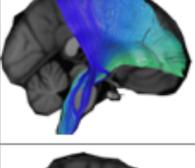
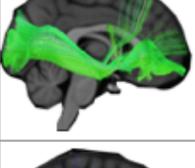
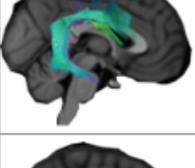
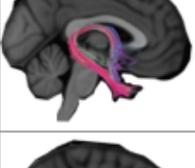
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Tables 2-3

Table 2. Group Differences in Tract FA and Dimensional Relations with SCARED Scores at Study Entry¹

		FA, mean (SD)			One-Way ANCOVA		Linear Regression - Child SCARED	
Bilateral WM Tract		Control	Risk	AD	P value	BF (H ₁)	P value	BF (H ₁)
	WB	0.358 (0.009)	0.362 (0.010)	0.363 (0.008)	0.015	2.406	0.054	1.259
	CC	0.464 (0.013)	0.466 (0.015)	0.469 (0.012)	0.249	0.190 ²	0.329	0.370
	CING	0.315 (0.018)	0.319 (0.024)	0.320 (0.016)	0.523	0.101 ²	0.260	0.375
	IC	0.450 (0.012)	0.453 (0.013)	0.455 (0.012)	0.147	0.308 ²	0.054	0.829
	IFO	0.417 (0.013)	0.420 (0.015)	0.422 (0.012)	0.343	0.143 ²	0.773	0.232 ²
	SLF	0.395 (0.016)	0.400 (0.017)	0.404 (0.016)	0.030	1.214	0.048	0.694
	STRIA/FX	0.312 (0.015)	0.314 (0.016)	0.314 (0.015)	0.776	0.072 ³	0.865	0.249 ²
	UF	0.355 (0.013)	0.360 (0.013)	0.359 (0.014)	0.186	0.254 ²	0.930	0.230 ²

Abbreviations: CC, corpus callosum; CING, cingulum; IC, internal capsule; IFO, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; STRIA/FX, stria terminalis/fornix; UF, uncinate fasciculus; WB, whole-brain WM.

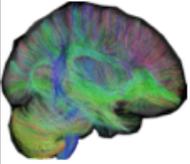
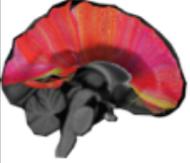
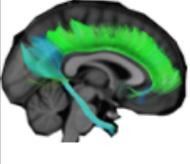
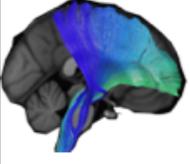
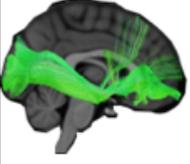
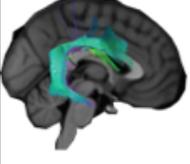
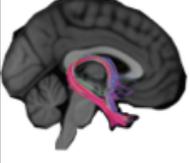
¹All analyses control for age at scan. 3-D renderings (right sagittal views) generated from deterministic tractography are shown for each WM tract of interest and whole-brain WM. Green fibers extend along

anterior-posterior axis; red fibers along the medial-lateral axis; and blue fibers along the superior-inferior axis.

²Moderate evidence of absence of an effect under the Bayesian framework ($0.1 < BF_{H1} < 0.33$).

³Strong evidence of absence of an effect under the Bayesian framework ($BF_{H1} < 0.1$).

Table 3. Average Within-Participant Associations Between SCARED Scores and Tract FA¹

Bilateral WM Tract		β_1	Std. β_1 (95% CI)	P value
	WB	-8.438E-05	-0.06 (-0.09 to -0.03)	0.001 ²
	CC	-1.057E-04	-0.05 (-0.08 to -0.02)	0.007
	CING	-1.027E-04	-0.03 (-0.06 to -0.01)	0.034
	IC	-4.460E-05	-0.02 (-0.06 to 0.01)	0.220
	IFO	-1.072E-04	-0.05 (-0.08 to -0.02)	0.007
	SLF	-7.819E-05	-0.03 (-0.07 to 0.00)	0.044
	STRIA/FX	-8.780E-05	-0.04 (-0.08 to 0.00)	0.065
	UF	-4.753E-05	-0.02 (-0.06 to 0.02)	0.345

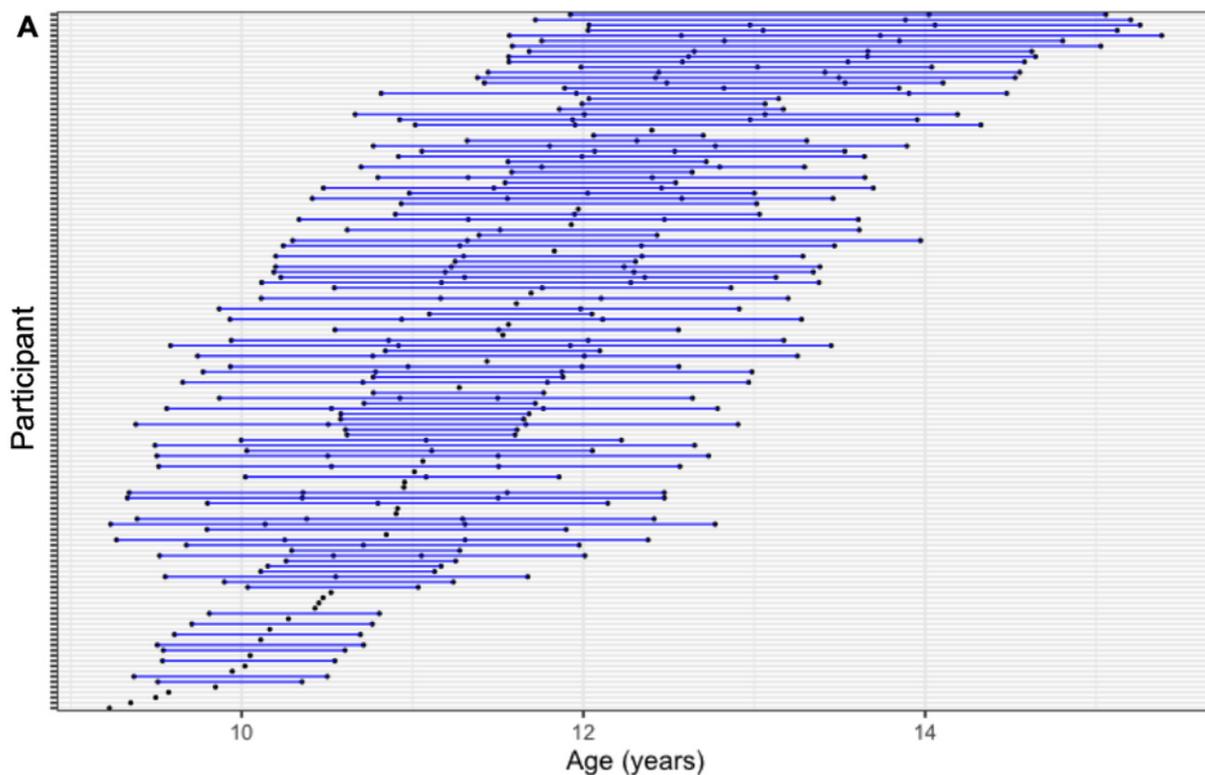
Abbreviations: CC, corpus callosum; CING, cingulum; IC, internal capsule; IFO, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; STRIA/FX, stria terminalis/fornix; UF, uncinate fasciculus; WB, whole-brain WM.

¹All analyses control for age at scan. 3-D renderings (right sagittal views) generated from deterministic tractography are shown for each WM tract of interest and whole-brain WM. Green fibers extend along

anterior-posterior axis; red fibers along the medial-lateral axis; and blue fibers along the superior-inferior axis.

²Statistically significant under the frequentist framework at a Bonferroni-corrected level ($P < 0.00625$).

Figures



B

Measure	Value
Participants, No.	133
Scans per participant, mean (SD)	2.58 (1.18)
Inter-scan interval, mean (SD), years	1.16 (0.38)
No. of participants with:	
1 scan	32
2 scans	36
3 scans	21
4 scans	44
Total no. of scans at:	
Time 1	131
Time 2	95
Time 3	64
Time 4	53

Figure 1

Depiction of the Longitudinal Study Design (A) Each blue line represents one participant; each point represents a scan for the respective participant and indicates age at scan. (B) Table with descriptive longitudinal scanning information.

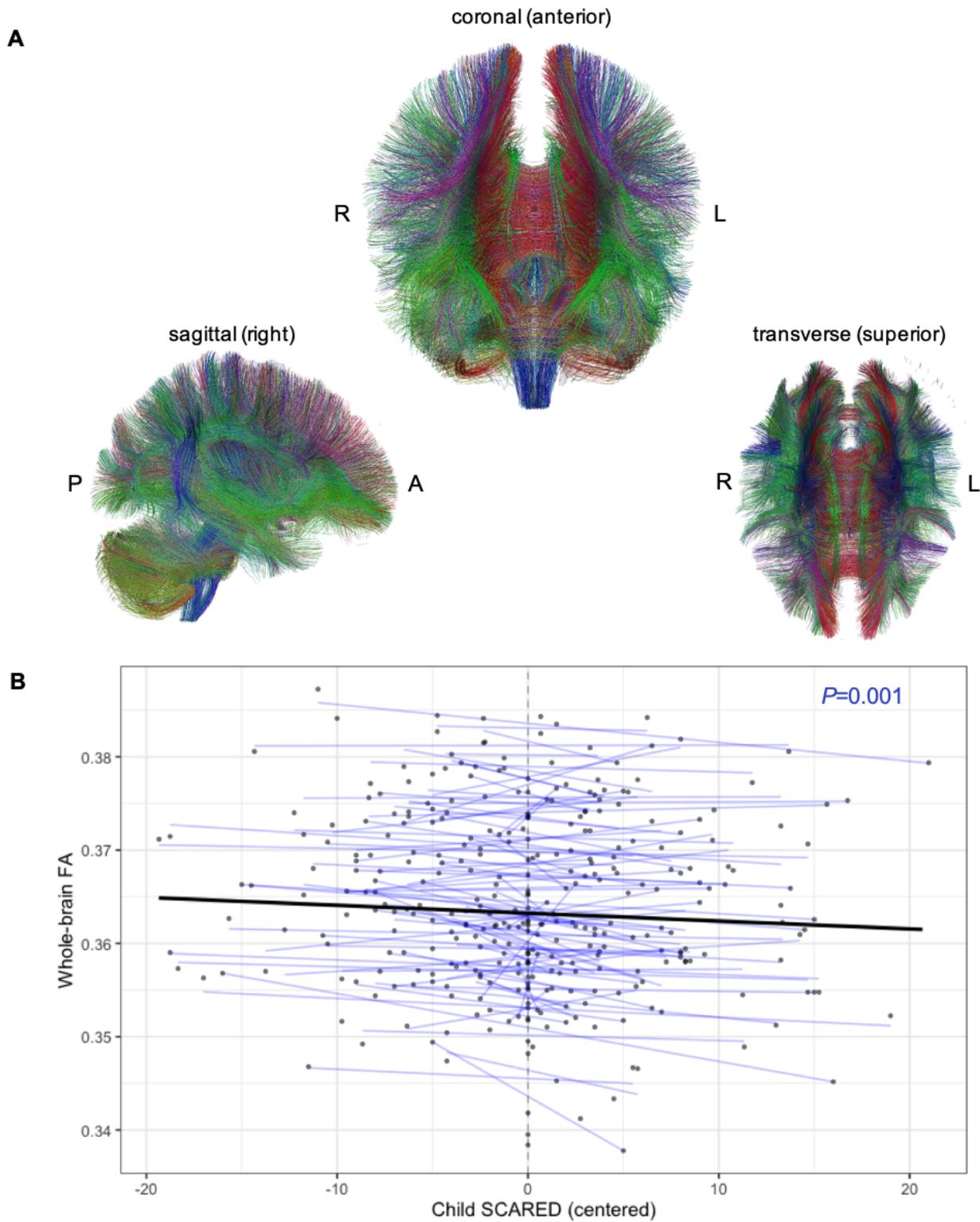


Figure 2

Longitudinal Within-Participant Association of Whole-Brain FA with Child SCARED Scores (A) Coronal, sagittal, and transverse views of a 3-D rendering of whole-brain WM tracts, as generated via deterministic tractography in TrackVis (A-P=anterior-posterior; R-L=right-left). Green fibers extend along anterior-posterior axis; red fibers along the medial-lateral axis; and blue fibers along the superior-inferior axis. (B) Within-participant relationship between whole-brain FA and child SCARED scores. Each blue line represents a participant-specific regression line predicting whole-brain FA from within-participant centered child SCARED scores, while controlling for age. Each point represents an individual scan. The bolded black line depicts the average within-participant association of whole-brain FA with child SCARED scores.

Supplementary Files

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