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ARTICLE

Pediatric PTSD is characterized by age- and sex-related abnormalities in structural connectivity

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Pediatric post-traumatic stress disorder (pPTSD) is a prevalent and pervasive form of mental illness comprising a disparate constellation of psychiatric symptoms. Emerging evidence suggests that pPTSD may be characterized by alterations in functional networks traversing the brain. Yet, little is known about pathological changes in the structural tracts underlying functional connectivity. In adults, PTSD is linked to widespread change in white matter integrity throughout the brain, yet similar studies with youth populations have yet to be conducted. Current understanding of the nature and treatment of pPTSD may be enhanced by examining alterations in white matter, while further untangling effects of age and sex. Here, we assess the microstructure of 12 major white matter tracts in a sample of well-phenotyped youth with PTSD. Measures of fractional anisotropy were derived from diffusion tensor images acquired from 82 unmediated youth (ages 8–18), of whom 39 met criteria for pPTSD. Diagnosis of pPTSD was linked to remarkable age- and sex-linked differences in the microstructure of major white matter tracts including the uncinate fasciculus, cingulum bundle, and inferior longitudinal fasciculus. In each case, youth with PTSD show an absence of increased white matter integrity with age, suggesting an altered pattern of neurodevelopment that may contribute to persistence or worsening of illness. Broadly, our results suggest abnormal white matter development in pediatric PTSD, a finding which may contribute to illness persistence, comorbidity with other disorders, and poorer prognosis across time. Critically, these findings further speak to the nature of pPTSD as a 'whole-brain' disorder.

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INTRODUCTION

Although as many as one of every three children will experience a traumatic event before reaching adulthood, most will show resilience over time [1]. However, for roughly five percent of youth, these experiences result in the development of post-traumatic stress disorder (PTSD), a debilitating constellation of cognitive, emotional, and behavioral symptoms [2]. Pediatric PTSD (pPTSD) imposes harm in the short term by imparting enormous psychological suffering, yet also in the long-term, through elevated lifetime risk of addiction, suicide, and early mortality [3, 4]. Moreover, pPTSD often acts in concert with other disorders, showing strong comorbidity with a variety of psychiatric conditions, most commonly anxiety, depression, and ADHD [5]. Yet, unlike these disorders, treatment options remain limited for pediatric PTSD. Psychotherapy appears to offer modest benefits, yet only for some, and only temporarily [6]. Advances may come from improved understanding of the neural substrates underpinning this disorder, with the aim of translating neuroscientific knowledge into new treatment options for this vulnerable population.

Though pPTSD is both prevalent and pervasive, research examining its neurological basis is still quite limited. Current knowledge of the neural underpinnings of pPTSD largely derives from adults, though the number of investigations into children and adolescents is growing [7]. Most consistently, pPTSD is linked to aberrations in the function and morphology of cortical and subcortical gray matter structures. A growing body of work further illuminates the effects of pPTSD on functional networks reflecting widespread interregional communication throughout the brain [7]. However, a remarkable paucity of research exists examining the structural pathways underlying functional transmission. Such information is critical for understanding potential disruptions in communication among regional brain nodes implicated in PTSD that subserve wider networks.

To date, investigations into white matter in pPTSD are largely limited to the corpus callosum, where studies have detected regional reductions in microstructural integrity in youth with PTSD [8]. While few studies have endeavored to examine structural changes in the broader system of interconnective white matter tracts in pPTSD, hypotheses may be informed by the larger body of work conducted with adults. Such work has frequently reported altered fractional anisotropy in the cingulum bundle, which projects to medial prefrontal regions as well as the hippocampus and amygdala [8]. Similar, though less consistent findings have been observed in the association fibers-with increased FA in the superior longitudinal and inferior fronto-occipital [9], and decreased FA in the inferior longitudinal association fibers [10]. Structural connectivity studies in pediatric anxiety and depression have identified decreased FA in the uncinate fasciculus (UNC), connecting the amygdala and orbitofrontal cortex [11]. However, no such studies have been conducted in pediatric PTSD.

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Ultimately, the nature of white matter alterations in PTSD-afflicted youth remains unclear. However, such effects may contribute to understanding a litany of research findings demonstrating differences in functional activation, connectivity, and regional volume among children with PTSD. Disturbed white matter connectivity between regions of the brain critically linked to PTSD may be a contributing or even moderating influence. Notably, it may not be reasonable to extrapolate findings from adult PTSD downward to youth, who are known to demonstrate a highly distinct variation of the disorder [12]. Moreover, youth is a time of extraordinary neurodevelopment, particularly in terms of structural connectivity [13]. Therefore, it is important to consider age as a moderator (rather than a covariate) of PTSD's effects on white matter tracts. Given previously identified sex differences in normative physiological and neural development, it is also critical to consider that disruptions in microstructural integrity may not follow the same patterns in boys and girls [13].

To our knowledge, this is the first study of tract-based abnormalities in pPTSD outside of the corpus callosum, which broadly investigates white matter integrity across twelve different white matter tracts. Drawing from the work described above, we hypothesize that youth with PTSD will show differences in fractional anisotropy (as well as three supplemental diffusion measures) among several tracts selected a priori based on prior findings: the parahippocampal (CGH) and cingulate (CGC) sections of the cingulum bundle, the inferior fronto-occipital fasciculus (IFO), the inferior (ILF) and superior (SLF) longitudinal fasciculus, and the uncinate fasciculus (UNC). Broadly, we selected these tracts due to their prominence in investigations linking white matter integrity to mental illnesses, standardized extraction protocols [14], and inclusion in a recent large-scale study of diffusion metrics in adult PTSD [15]. The microstructure of each tract is considered in terms of pPTSD diagnosis, pubertal development, age, and sex, with separate modeling for each laterality. We anticipated that pPTSD would be associated with decreased FA, generally, across tracts. We further hypothesized that these tracts would fail to show previously identified normative increases with age [13] given prior studies implicating abnormal age-related patterns in brain functional activation and connectivity in pediatric PTSD [7].

MATERIALS AND METHODS

Participants

The Youth PTSD Study recruited medication-free youth with PTSD between the ages of 8 and 18 along with age- and sex-matched non-traumatized typically developing (TD) comparison youth. The current investigation includes 39 youth with PTSD and 43 TD youth who comprised the baseline Youth PTSD cohort. Details regarding recruitment and participant characteristics are detailed elsewhere [16], but are briefly summarized here. Youth were recruited from local mental health clinics and the broader community, respectively. Exclusion criteria included: cognitive impairment (IQ < 70); history of psychosis, bipolar disorder, or obsessive-compulsive disorder; active suicidality; recent (past 4 weeks) substance abuse or dependence; recent use of psychotropic medication (past 4 weeks, or 6 weeks for fluoxetine); unstable medical condition; MRI contraindication; pregnancy in female participants. Parental consent and youth assent were obtained prior to participation, and all procedures were approved for use by a university Institutional Review Board.

Measurements

Youth clinical assessments were performed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [17]. Diagnosis of PTSD was determined using modified DSM-IV-TR criteria (as appropriate for youth) [18] ascertained using information combined from the K-SADS and the Clinician-Administered PTSD Scale for Children and Adolescents [19]. Pubertal progress was captured using the 10-item Pubertal Development Scale [20], and scores for this scale were converted to a Tanner-stage metric (PDSS) [21]. Total trauma exposure was operationalized using the Childhood Trauma Questionnaire (CTQ; total score, as well as abuse, neglect subscale scores; [22]). Depressive symptoms were assessed via the Mood and Feelings Questionnaire (MFQ; [23]), anxiety via the Screen for Child Anxiety Related Emotional Disorders (SCARED; [24]), and IQ through the Wechsler Abbreviated Scale of Intelligence-II [25].

Scan acquisition and processing

Youth underwent MRI scanning on 3.0 T GE Discovery MR750 (GE; Waukesha, WI) scanner with an eight-channel array head coil. Prior to scanning, all participants completed two mock scanning sessions that acclimated youth to the sounds and sensations of the scanner environment. Detailed description of scanning parameters and the preprocessing pipeline may be found in supplemental materials (see Supplemental Methods).

Statistical analysis

For each tract (left and right), main and interactive effects of sex, age, and PTSD diagnostic status on diffusivity indices were examined in a stepped fashion using a series of hierarchical linear regression models covarying for IQ and PDSS. The main effects of PTSD, age, and sex were tested first by entering each term into the model as an independent predictor of diffusivity. Each of the focal two-way interaction terms was added to the model in separate concurrent steps, along with the non-interactive term as a covariate (e.g., PTSD* Sex + Age; PTSD*Age + Sex), and a three-way interaction term was added last (PTSD*Age*Sex). General cognitive function is a well-studied correlate of white matter microstructure [26] and is a correlate of PTSD symptomatology [27]. Therefore, IQ was included as a covariate in all models. Similarly, given the wide range of ages in our sample, we chose to covary for underlying differences in pubertal maturation (PDSS). For each term in the hierarchical model set, multiple comparison correction was performed across lateral tracts (12 tests) using the Benjamini–Hochsberg [28] method. Regression diagnostics were performed for all models, and data points were excluded where Cook's Distance exceeded n/4, a standard threshold indicating a likelihood of distorting model parameters [29].

Post-hoc analyses were conducted to decompose significant interactions where necessary. Where interactions were significant, conditional effects of the moderator (e.g., age) were decomposed using Johnson-Neyman significance regions (tabular results provided in supplementary materials). Secondary analyses examined symptom relationships within the subset of youth with PTSD. Specifically, we investigated associations between individual symptom dimensions and FA: DSM-IV symptom severity of PTSD (PTSD-RI total and subscale scores), anxiety (SCARED), and depression (MFQ). As prior research has consistently identified a linkage between early childhood abuse and altered white matter diffusivity [30], we similarly examined the effects of abuse history on FA as measured by the CTQ abuse subscale.

RESULTS

Demographics

Eighty-two youth provided diffusion-weighted scans, of whom 39 met the criteria for PTSD diagnosis (TD, $n = 43$; Table 1). At $\alpha = 0.001$, study groups did not significantly differ by age ($p = 0.56$), sex ($p = 0.91$), or PDSS ($p = 0.38$). IQ was significantly lower in the PTSD group ($p < 0.001$). Youth with PTSD exhibited significantly higher scores on clinical scales for anxiety and depression and reported greater trauma load than TD youth (all $p < 0.001$). As expected, older youth (defined using a mean split) had greater PDSS scores, indicative of advanced pubertal maturation (no difference by sex). No sex by group or age by group interactions reached significance for clinical scales or demographics, though a marginal effect was found for trauma load, in that TD boys reported slightly higher scores than TD girls ($p = 0.03$). As reported in extant manuscripts describing this sample[31], youth were majority White (80.52%), with caregivers of TD youth more likely to have completed some higher education ($p < 0.001$).

Regression analyses

PTSD diagnosis interacted with age to account for FA in several tracts: left CGC ($\beta = -0.5817$, $t = 2.67$, $p = 0.010$), right CGH ($\beta = -0.6800$, $t = 3.04$, $p = 0.0035$), right IFO ($\beta = -0.6417$,

Table 1. Demographic and clinical characteristics of children with post-traumatic stress disorder and healthy youth [a].

	Girls						Boys					
	TD			PTSD			TD			PTSD		
	N	% Female		*N*	% Female		*N*	% Female		*N*	% Female	
	43	63		39	62		27	100		24	100	
Demographics	Mean	SD		Mean	SD		Mean	SD		Mean	SD	
Age (years)	13.95	3.03		14.32	2.81		14.20	3.17		14.41	3.06	
IQ (WASI)	110.25	11.55		101.03	11.71		109.78	11.49		99.48	12.13	
Pubertal Development (Tanner Stage)	3.18	1.32		3.44	1.33		3.52	1.17		3.64	1.16	
Measures												
Anxiety (child SCARED)	7.17	4.78		33.56	14.24		7.53	5.34		34.98	13.77	
Depression (child MFQ)	3.12	2.58		24.28	10.80		2.83	2.43		25.50	11.15	
Trauma Load (child CTQ)	31.55	5.68		48.5	15.11		29.93	4.12		51.09	16.18	
PTSD Symptoms (child PTSD-RI)	–	–		48.51	14.03		–	–		50.71	12.96	

	Boys					
	TD			PTSD		
	N	% Female		*N*	% Female	
	16	0		15	0	
	Mean	SD		Mean	SD	
	13.48	2.79		14.19	2.47	
	111.06	11.98		103.40	11.00	
	2.64	1.40		3.14	1.56	
	6.56	3.74		31.30	15.17	
	3.59	2.83		22.33	10.27	
	34.47	6.99		44.43	12.76	
	–	–		45.00	15.41	

[a] No significant differences were observed in age or pubertal development between the control and PTSD disorder groups, either overall or by sex (at $\alpha = 0.001$). IQ differed significantly across control and PTSD disorder groups overall [p (two-tailed) < 0.001), though not for boys ($p = 0.07$) or girls ($p = 0.004$) specifically. Symptom score measures and trauma load differed significantly between control and PTSD groups, both overall and by sex (all $p < 0.001$), except for among boys, where the difference was marginal ($p = 0.018$). *CTQ* childhood trauma questionnaire, *MFQ* mood and Feelings Questionnaire, *PTSD-RI* post-traumatic stress disorder–reaction index, *SCARED* screen for child anxiety related emotional disorders, *WASI* wechsler abbreviated scale of intelligence.

$t = 2.65$ $p = 0.010$), right ILF ($\beta = -0.6357$, $t = 2.85$, $p = 0.006$), left and right SLF ($\beta = -0.6737$, $t = 2.91$, $p = 0.005$; $\beta = -0.5482$, $t = 2.27$, $p = 0.027$), and right UF ($\beta = -0.5940$, $t = 2.66$, $p = 0.010$; see Figs. 1A,1B, Table 2). In each tract, decomposition of the interaction revealed that age was associated with greater FA among TD youth, but not youth with PTSD (Fig. 1A). PTSD diagnosis did not interact with sex to predict FA in any tract. However, a significant three-way interaction between PTSD diagnosis, age, and sex reached significance in the right SLF ($\beta = 1.5315$, $t = 3.22$, $p = .002$; Fig. 1C). While typically developing boys showed greater FA with age, this effect was nonsignificant among girls or youth with PTSD (Fig. 1C). This three-way interaction trended towards significance for the right IFO and right UNC but did not survive correction. The main effects of PTSD diagnosis and sex failed to reach significance, while a main effect of age was detected in the left and right ILF, with increased FA along with development.

Analyses of diffusion metrics other than FA (RD, AD, MD) generally failed to reach significance after correction with one exception. The interaction of PTSD and sex accounted for variance in AD in the right IFO, as well as RD and AD in the right ILF.

Post-hoc analyses

In decomposing the 2- and 3-way interactions, Johnson–Neyman plots revealed greater FA in youth with PTSD until early adolescence (11.6–14.5 years) broadly across all tracts, at which point the association became non-significant (Fig. 2). By late adolescence (17.4–21.5 years) (though notably, not in the left cingulate section of the cingulum), this effect was reversed, with lower FA values among youth with PTSD. The three-way interaction detected in the right SLF (PTSD × Age × Sex) was decomposed separately by sex, and revealed a non-contiguous effect of PTSD across age in boys (i.e., greater FA in childhood; non-significance in early adolescence; reduced FA versus TD youth in late adolescence) but no significant effect of PTSD among girls (Fig. 2). All tabular data for these findings are provided in Supplemental Materials for reference.

Sensitivity analyses

Finally, several additional variables were considered that could influence these results. For all youth, tract-wise main effects of comorbid symptoms were analyzed, covarying for age, sex, and pubertal development. No main effects of depression or anxiety were observed for any tract. Within youth with PTSD, we further tested for tract differences based on total PTSD symptom score as well as criterion symptom scores, for all youth total trauma exposure as well as experiences of abuse and neglect (again covarying for age, sex, IQ, and PDSS). No effects remained significant after multiple comparison corrections.

DISCUSSION

To our knowledge, this is the first study to examine white matter tract integrity in pediatric PTSD beyond the corpus callosum. Further, this work considers age and sex as moderating variables of interest, given the greater prevalence of PTSD in girls [2], and the litany of neuroscience research connecting these variables to brain development. Overall, our findings reveal a consistent pattern across tracts of interest, with expected age-related increases in FA among TD youth, but no such age relationship among youth with PTSD. A sex-specific finding emerged in the right SLF, where anticipated age-related increases in FA were observed in TD boys, but neither TD girls nor PTSD youth. Broadly, our results suggest abnormal white matter development in pediatric PTSD, a finding which may contribute to illness persistence, comorbidity with other disorders, and poorer prognosis across time.

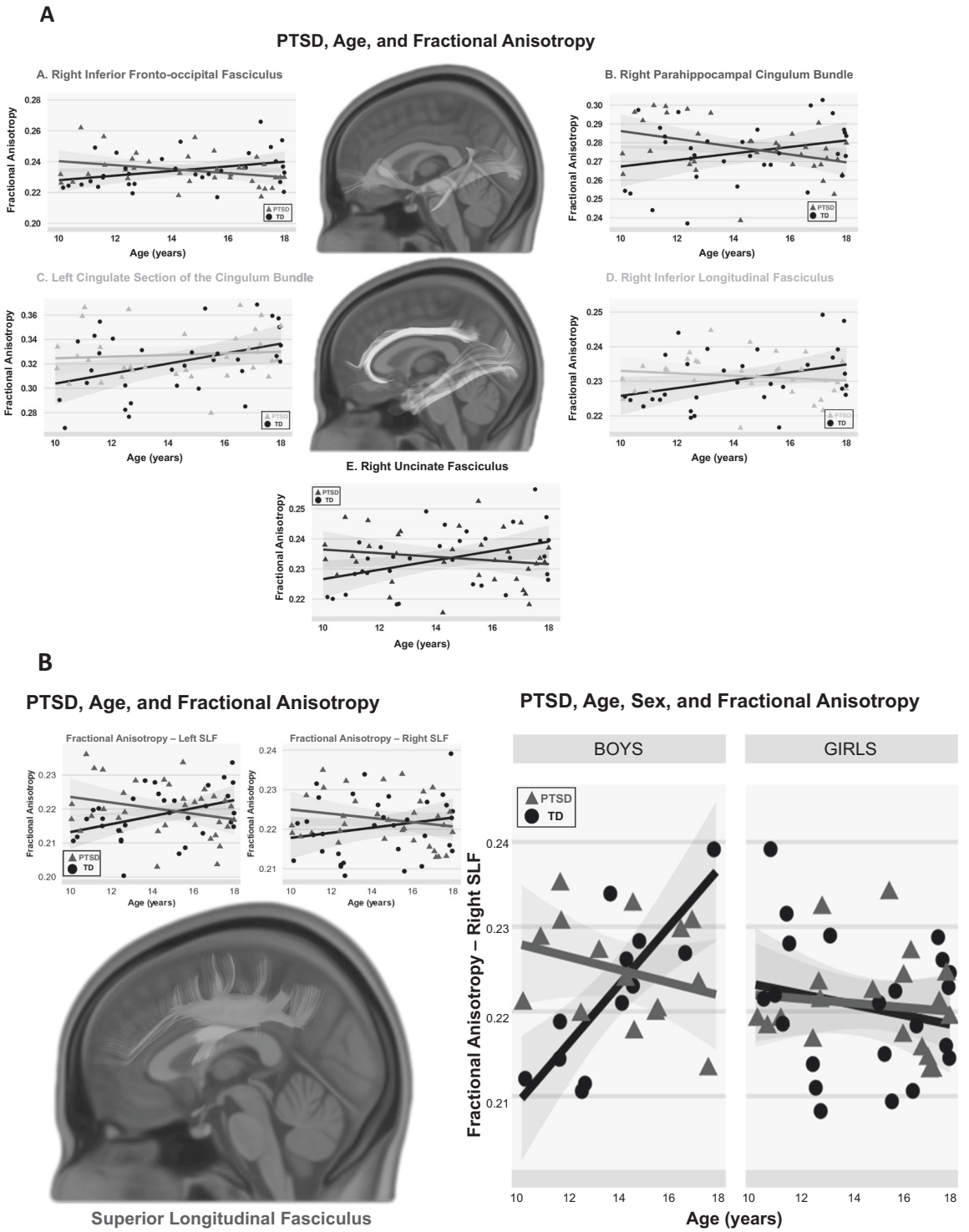

Fig. 1 Effect of pPTSD diagnosis on fractional anisotropy across age and sex. A (A) Right inferior fronto-occipital fasciculus, (B) right parahippocampal cingulum bundle, (C) left cingulate section of the cingulum bundle, (D) right inferior longitudinal fasciculus, (E) right uncinate fasciculus. **B** Effect of PTSD diagnosis on fractional anisotropy values across age in the bilateral superior longitudinal fasciculus (SLF) and differential effects of sex in the right SLF.

Briefly described, the affected tracts serve disparate functions across the brain, yet share a common link to facets of mental illness. The cingulum bundle, subdivided into cingulate (CGC) and parahippocampal (CGH) sections, is a prominent tract linking frontal, parietal, temporal, and subcortical regions [32] implicated in executive control as well as attention to emotionally-valenced stimuli [33]. The inferior fronto-occipital fasciculus (IFO) is a long tract originating in the occipital/parietal junction and terminating in the inferior frontal lobe, potentially serving as a bridge between the executive and salience functional networks, ultimately enabling goal-directed behavior in response to 'salient' environmental stimuli [34]. The nearby inferior longitudinal fasciculus (ILF) similarly originates in the occipital pole, though terminates in the temporal pole, supporting information transfer between sensory

Table 2. Interactive effect of age and PTSD diagnosis on diffusion indices.

	FA			MD			RD			AD		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
CGC–Left	−0.581716	−2.67	**0.0097**	−0.089940	−0.35	0.7242	0.030747	0.13	0.9009	−0.336676	−1.36	0.1779
CGC–Right	−0.386740	−1.62	0.1095	0.171709	0.69	0.4943	0.168042	0.68	0.4981	0.217055	0.87	0.3903
CGH–Left	−0.434387	−1.75	0.0842	−0.325380	−1.24	0.2196	−0.424424	−1.62	0.1102	−0.239025	−0.90	0.3738
CGH–Right	−0.679958	−3.04	**0.0035**	−0.333390	−1.38	0.1717	−0.047613	−0.20	0.8434	−0.509957	−2.16	*0.0349*
IFO–Left	−0.056590	−0.22	0.8245	−0.193912	−0.73	0.4680	−0.199370	−0.75	0.4559	−0.084968	−0.32	0.7489
IFO–Right	−0.641717	−2.65	**0.0101**	−0.318420	−1.27	0.2097	−0.090765	−0.35	0.7242	−0.413691	−1.65	0.1038
ILF–Left	−0.470429	−1.86	0.0687	−0.180723	−0.68	0.4988	−0.156237	−0.58	0.5610	−0.215963	−0.80	0.4284
ILF–Right	−0.635678	−2.85	**0.0060**	−0.013971	−0.05	0.9565	0.009686	0.04	0.9697	−0.053327	−0.21	0.8362
SLF–Left	−0.673650	−2.91	**0.0050**	−0.142962	−0.59	0.5544	−0.082773	−0.34	0.7330	−0.144594	−0.61	0.5443
SLF–Right	−0.548183	−2.27	**0.0268**	−0.116193	−0.47	0.6401	−0.101469	−0.41	0.6841	−0.183689	−0.73	0.4667
UF–Left	−0.223256	−0.90	0.3735	0.051470	0.21	0.8369	−0.039336	−0.16	0.8767	0.041868	0.16	0.8704
UF–Right	−0.593950	−2.66	**0.0101**	−0.008690	−0.03	0.9730	−0.015681	−0.06	0.9519	−0.053946	−0.21	0.8330

Notes. Bolded = $p_{BH} > 0.05$, *Italicized* = $p > 0.05$, *CGC* cingulate section of cingulum bundle, *CGH* parahippocampal section of cingulum bundle, *IFO* inferior fronto-occipital fasciculus, *ILF* inferior longitudinal fasciculus, *SLF* superior longitudinal fasciculus, *UF* uncinate fasciculus.

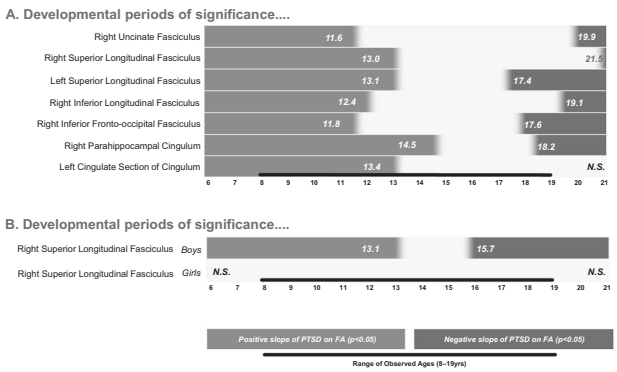

Fig. 2 Johnson-Neyman Plots of Developmental Periods of Significance. (**A**) The interactive effect of age and PTSD on fractional anisotropy across tracts, (**B**) the interactive effect of age, PTSD, and sex on fractional anisotropy in the right superior longitudinal fasciculus.

and association cortices [35]. Altered ILF integrity is observed across numerous disorders featuring disrupted information processing, a key feature of PTSD which involves insufficient suppression of sensory inputs [10]. The superior longitudinal fasciculus (SLF) extends over a wide area of the dorsal cortex, linking prefrontal, temporal, orbital, and parietal cortices. Recent work implicates the SLF in maladaptive self-referential processing (i.e., brooding), a construct common to numerous mental disorders [36]. The uncinate fasciculus is a curved tract linking temporal structures including the amygdala and parahippocampus with the inferior frontal lobe [37]. The UF is widely linked to neuropsychiatric disorders, with microstructural changes underlying a range of conditions from psychopathy to social anxiety to PTSD [11, 38, 39].

Typical development of these tracts involves substantial, though variable changes in indices such as FA associated with white matter integrity. Our findings in typically developing youth are consistent with larger studies identifying a broad developmental effect across the brain, with tracts tending to show increased FA with age [13]. Conversely, our findings with respect to pPTSD suggest potential deviation from the expected path. As illustrated in Fig. 1, youth with PTSD exhibit comparatively greater FA across numerous lateral (or bilateral, in the case of the SLF) tracts through late childhood/early adolescence, yet comparatively *reduced* FA by late adolescence/early adulthood. These results amplify the growing evidence suggesting altered development of white matter tracts among youth with PTSD at a whole-brain level, given the widespread nature of these results. Interestingly, the conglomerated results from tractography investigations in adult PTSD (as described above) would similarly suggest a global 'brain-wide' effect.

Despite the growing evidence linking pPTSD to altered neurodevelopment, the biological basis for such change remains elusive. However, several lines of research have considered potential explanations for PTSD-related change in neurocellular composition involving endocrine factors. PTSD is associated with upregulated expression of proinflammatory cytokines [40], such as interleukin-6, which are known to overstimulate cortisol production by the hypothalamic-pituitary-adrenal axis [41]. While hypercortisolism is well-linked to structural changes in limbic regions such as the amygdala and hippocampus, the effect of cortisol on white matter integrity in youth is only recent becoming clear [42]. Findings from animal models suggest that elevated glucocorticoid levels may inhibit the proliferation of astrocytes and oligodendrocytes [43], cells critically responsible for myelination of axons comprising white matter tracts. Theoretically, broad glucocorticoid-related changes in major cerebral tracts may also underlie similar, global-scale changes in functional networks known to co-occur with PTSD.

Notably, a three-way interaction was observed in the right SLF, in that the effect of PTSD on FA across age was specific to boys, not girls. The specificity of this three-way interaction to the SLF remains an open question. It may be that our analyses were underpowered to detect an interactive effect of sex in most other tracts (i.e., Type II error). Indeed, for all other tracts of interest, a three-way interaction did often trend in the same direction, and towards significance (see supplemental materials). Regarding potential mechanisms for the sex interaction, there is preliminary evidence from cellular animal models that estrogen may play a critical role in myelinogenesis [44], and attenuate damage secondary to pathology or neural injury [45]. Though research examining protective mechanisms of estrogen in humans is limited, one study has found that estrogen deficiency in girls with Turner Syndrome is linked to significant aberrations in white matter, particularly reduced FA in the SLF in comparison to TD youth [46]. Notably, a sex-specific effect of PTSD in the age-related FA of this tract is consistent with findings from functional work. As mentioned, the SLF provides a major link between parietal and

frontal lobes, and therefore may be a key component underlying the fronto-parietal or 'executive' network. Crozier et al. [47] examined executive network functioning in youth with pediatric PTSD and found altered activation in networked areas among boys, but not girls. Similar findings have been observed in other stress-related disorders. Ugwu et al. [48] found greater longitudinal diffusivity, a proxy of axonal injury, in boys with major depressive disorder exposed to childhood adversity compared to girls. Certainly, additional research is necessary to illuminate broader effects of sex on the link between PTSD and altered white matter microstructure.

The current investigation provides novel insights into the neural substrates of pediatric PTSD. However, any interpretation of the findings should be made in consideration of this study's limitations. First, this study incorporated a modest sample size, that may have limited our ability to detect complex interactive effects on white matter microstructure. Future replication or expansion of our efforts will be necessary to confirm or further clarify these findings. Second, the present study draws results from a cross-sectional design. True extrapolation of the effect of PTSD on developing microstructure and any investigation of causal mechanisms will require future studies incorporating assessments at multiple time points. Third, this study did not include a trauma-exposed control group without PTSD, precluding our ability to determine the specificity of our findings to PTSD or trauma exposure generally. Notably, however, the lack of symptom-specific findings may suggest a broader nonspecific effect for the diagnosis of trauma-related mental illness generally, as no main effects of abuse severity or trauma load were detected.

Notwithstanding these limitations, this work provides an important and novel contribution to the knowledge of PTSD's neural bases in youth. To our knowledge, this is the first study to examine white matter microstructure in pediatric PTSD beyond the corpus callosum. Beyond considering a simple main effect of diagnosis, our findings illuminate the importance of age and sex as moderators of PTSD's association with white matter, particularly in the SLF. Age-related moderation of microstructure may have important clinical relevance, as this finding could portend differential responsivity to treatment across development (e.g., poorer treatment outcomes in adolescence) as well as the changing nature of PTSD itself [49]. More broadly, global change in white matter microstructure across age may play a role in the changing patterns of comorbidity among children with PTSD through development. Definitive answers to these questions will require longitudinal research examining developmental trajectories of white matter change in pPTSD, as well as potentially altered trajectories in the persistence and reemission of PTSD in youth [50]. It will be critically important for such work to extrapolate, how the timing of PTSD-onset\stress exposure may alter white matter development indexed along with multiple metrics of time (e.g., chronological age, pubertal maturation; see [51]). Indeed, emerging evidence exists to suggest that pubertal timing in relation to exposure may play a crucial role in altering pathways of neural development [52]. In that vein, we encourage future researchers to seek out reliable data about individual traumatic experiences, such as age at onset. This work provides an important foundation upon which to build a more expansive body of research exploring how white matter, pPTSD, and development intermix to contribute to trauma-related illness in youth, as well as providing potential biomarkers or targets for intervention.

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AUTHOR CONTRIBUTIONS

JDR conceptualized the work, conducted the primary analyses, drafted and critically revised the paper. SAH acquired the data and provided critical revisions. DCD provided analytical tools, assisted in processing the data, and reviewed an initial draft of this work. RJH led the design of the original study, guided data acquisition, and interpretation, aided in analysis, and provided critical revisions to the paper. All authors provided final approval of the version published.

COMPETING INTERESTS

The authors declare no competing interests.

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