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White matter microstructure in trauma-exposed children: Associations with pubertal stage

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Abstract

Puberty represents a critical period in maturation during which major changes in neural architecture emerge; these changes are shaped, in part, by environmental experiences, including exposure to psychological trauma. However, little is known about how trauma exposure affects white matter microstructure across pubertal stages. This was the goal of the present cross-sectional study. Forty-one male and female African-American children between ages 8–13 were recruited as part of a study of developmental trauma and received assessments of trauma exposure, including violence, and pubertal development as well as diffusion tensor imaging (DTI). Significant interactions of pubertal stage and violent trauma exposure were observed in association with a marker of white matter integrity (mean diffusivity, MD) in the corpus callosum, cingulum bundle and uncinate fasciculus. Greater violent trauma exposure was associated with lower MD in the hippocampal cingulum and uncinate fasciculus in girls, but not boys. These data from a sample of trauma-exposed children may reflect a pattern of accelerated maturation in pathways that are critical for emotion regulation as well as attention and memory processes. It appears that fronto-limbic and callosal connections are particularly sensitive to the effects of violent trauma, revealing a potential pathway through which trauma creates vulnerability for later psychiatric and neurological disorders.

KEYWORDS
accelerated maturation, children, puberty, trauma, violence, white matter

Puberty is a developmental period that is characterized by major structural changes in the brain (Casey et al., 2008; Sisk & Foster, 2004) that accompany dramatic physical and emotional maturation (Blakemore & Mills, 2014; Forbes & Dahl, 2010). Gray matter volume and cortical thickness show an inverted U-shaped pattern of development, with increases evident until a "peak" period in childhood (peaks differ by brain region; reviewed in Walhovd et al., 2017) after which time a significant loss of gray matter occurs in association with synaptic pruning (Ducharme et al., 2016; Giedd et al., 1999; Sowell et al., 2003; Walhovd et al., 2017). In contrast, white matter (WM) volume appears to show a more consistently linear trajectory of growth throughout childhood/adolescence into adulthood (age 35–40; Giedd et al., 1999; Koolschijn & Crone, 2013; Paus et al., 1999; Sowell et al., 2002). Protracted increases in myelination and axonal caliber are thought to contribute to this volume change (Benes, 1989; Williamson & Lyons, 2018). These patterns follow a posterior to anterior progression, with myelination initiating in projection fibers, continuing on to commissural and association fibers (Schmithorst & Yuan, 2010). White matter volume in temporal regions (and around the hippocampus more specifically) increases even more steeply during the pubertal time period (Benes et al., 1994).

During puberty, endocrine events mediate changes in brain structure, including white matter volume and microstructure (reviewed in Herting & Sowell, 2017). Activation of the adrenal glands and gonads trigger increased production of pubertal hormones such as estradiol and testosterone. Adrenal activation results in rising levels of adrenal

androgens, including dehydroepiandrosterone, which drives development of the hypothalamic-pituitary-adrenal (HPA) axis, the stress response system (Romeo, 2010). Adrenarche begins around 6–8 years of age in girls and approximately 1 year later in boys, and is the first phase of puberty. The second puberty phase, gonadarche, involves maturation of the hypothalamic-pituitary-gonadal (HPG) axis. Production of gonadal hormones (estradiol and progesterone in girls and testosterone in boys) increases, leading to maturation of reproductive systems.

In adolescence, WM maturation is shaped by these endocrine events (reviewed in Goddings et al., 2019; Vijayakumar et al., 2018). Pubertal status has been associated with increases in WM volume (Lenroot et al., 2007; Perrin et al., 2009) and *microstructural integrity* of WM throughout the brain, but findings have been mixed on sex differences in these trajectories, as well as on rates of increase for the different types of WM pathways (i.e., commissional vs. association fibers; Bava et al., 2010; Ben Bashat et al., 2005; Chiang et al., 2009; Hasan et al., 2007; Klingberg et al., 1999; Schneiderman et al., 2007; Uda et al., 2015). Fractional anisotropy (FA) is a diffusion tensor imaging metric that reflects the extent to which water diffusion is directional, or anisotropic; mean diffusivity (MD) reflects the magnitude of water diffusion, representing the mean of the three eigenvalues of the diffusion tensor. Both FA and MD indices are considered indirect measures of white matter microstructure, markers that provide information on the integrity of white matter pathways. FA has not only been related to myelination, but also to organization and density of fiber bundles, as well as axonal diameter (Beaulieu, 2002; Madler et al., 2008). There are data to suggest steady increases in markers of WM microstructure (including FA and MD) across pubertal stages, with increases in these WM markers persisting into early adulthood (e.g., age 21–35) (Bava et al., 2010; Ben Bashat et al., 2005; Hasan et al., 2007; Klingberg et al., 1999; Uda et al., 2015) with some studies showing sex differences in trajectories of development in fronto-limbic (cingulum bundle, CB) and commissural (corpus callosum, CC) white matter pathways (Chiang et al., 2009; Schneiderman et al., 2007). Among the regions that appear to show the most protracted and linear development are the CB and uncinate fasciculus (UF), two major fronto-limbic pathways.

Stressful or traumatic events occurring in development (age 8–13) can have a significant impact on neural development, particularly during sensitive periods of development, such as the peri-pubertal period. Increasingly, empirical evidence indicates that early life adversity, including trauma, impacts the timing of normative developmental processes in the brain and body, with data to suggest that it accelerates biological aging (Callaghan & Tottenham, 2016; Gur et al., 2019; Jovanovic et al., 2009; Jovanovic et al., 2017; Sumner et al., 2019; Zannas et al., 2015). These findings have focused on somewhat large-scale differences in development as a function of adversity (e.g., how adult- or child-like the brain is, per machine learning classification; accelerated biological aging as measured by DNA methylation or telomere length). Fewer studies, however, have examined how the timing of trauma, including trauma that occurred during peri-pubertal periods, affects developmental trajectories of brain development.

Research highlights

- Little is known about how adverse environmental experiences influence white matter microstructure in children during puberty, a sensitive developmental period
- This study examined how different types of trauma exposure associated with white matter integrity in a sample of peri-pubertal children
- Increased violence exposure associated with greater integrity of white matter tracts connecting the prefrontal and limbic cortices across advancing pubertal stages
- Findings show a link between violence exposure and accelerated maturation of fronto-limbic white matter tracts, which may enhance risk for adverse future health outcomes

Adverse experiences such as maltreatment or psychosocial deprivation have been previously associated with disruptions in white matter integrity (Bick & Nelson, 2016). Converging evidence in humans (De Bellis et al., 2002; Jackowski et al., 2008; Rinne-Albers et al., 2016) and non-human primates (Sanchez et al., 1998) has repeatedly implicated the CC, the largest white matter structure of the brain, which connects the two hemispheres and supports global integration of cognitive processes. In adolescence (age 12–18), in the absence of major social/environmental adversity, increased FA and decreased MD is typically observed in the CC (Schmithorst & Yuan, 2010). However, adversity impacts white matter development in animals and humans. In non-human primates, reductions in CC size have been observed in maternally-deprived adolescents (Sanchez et al., 1998). In humans, maltreatment-related PTSD has been associated with lower FA in the CC in adolescents compared to healthy controls (De Bellis et al., 2002; Jackowski et al., 2008; Rinne-Albers et al., 2016). Compromised CC integrity has been consistently associated with psychiatric pathology in children and adolescents (Daniels et al., 2013; Riem et al., 2019; Rinne-Albers et al., 2013).

Increased FA has also been observed in the CC, corona radiata, CB and superior longitudinal fasciculus in children with attention deficit hyperactivity disorder (ADHD) and trauma histories as compared to children with ADHD and no trauma (Park et al., 2016). Greater white matter volume in prefrontal and cingulate regions has also been observed in physically abused versus non-abused children (Hanson et al., 2010), and greater hippocampal white matter volume has been observed in maltreatment-related PTSD compared to non-maltreated controls (Tupler & De Bellis, 2006). Greater gray matter volume in the superior and inferior PFC (Carrion et al., 2009; Richert et al., 2006) has been associated with maltreated children versus non-traumatized controls, but no differences were observed in white matter volume. Some researchers have hypothesized that this may reflect an acute response to trauma, which may be observed in later stages of development as deterioration/shrinkage (Bick & Nelson, 2016).

Earlier studies of maltreatment-related trauma and white matter in children have focused on the CB, and CC, as well as the fornix and the UF (Choi et al., 2009; De Bellis et al., 2002; Jackowski et al., 2008; McCarthy-Jones et al., 2018; Rinne-Albers et al., 2013). However, prior research has not examined how these relationships may differ at various stages of puberty, as well as how trauma type (e.g., violent vs. non-violent trauma) influences these relationships. Additionally, little is known about how trauma exposure may be differentially associated with white matter integrity between peri-pubertal male and females. In the present study, we examined associations between microstructure of these tracts with trauma exposure and pubertal stage in children aged 8–13 years. We examined relationships between markers of white matter microstructure (FA and MD) and different types of trauma exposure, including violence and maltreatment, among early, middle and late pubertal stages. We hypothesized that trauma exposure would be inversely associated with white matter structural integrity in these regions, and that gradual decreases in FA and increases in MD across pubertal stages would be particularly evident in fronto-limbic tracts (CB, UF) in accordance with higher trauma exposure across advancing pubertal stage. Secondarily, we explored the interaction of sex with trauma exposure on microstructural integrity of these white matter regions. We examined adrenal markers of puberty, which may be best suited for detecting pubertal acceleration, given that they are first to increase (Witchel & Topaloglu, 2019).

1 | METHODS

1.1 | Participants

Participants for this study were 48 African-American children (23 male, 25 female) between ages 8–13 (range = 8.1-13.3 years; SD = 1.5 years). The children and their caregivers were participants in a cross-sectional study of developmental trauma and were recruited from the Grady Trauma Project (GTP) cohort in Atlanta, Georgia. GTP participants are recruited from primary care, obstetrical/gynecological or diabetes care clinics in a publicly-funded urban hospital, as described previously (Fani et al., 2015; Gillespie et al., 2009). During the study visit, children and parents were interviewed separately (assessments have been detailed in prior publications (Stenson et al., 2020; van Rooij et al., 2020), and self-report measures were administered verbally to address any potential literacy issues. We included data from children who had complete DTI data. Inclusion criteria were: 1) age between 8 and 13 years; 2) willing to participate. Exclusion criteria for children were: diagnosed autism spectrum disorder, bipolar or psychotic disorder, cognitive compromise or disability. All procedures were approved by the Emory University Institutional Review Board and Grady Research Oversight Committee. Demographic and clinical characteristics of this sample, divided by males and females, are described in Table 1. As noted in prior publications with this sample (Stenson et al., 2020; van Rooij et al., 2020), rates of posttraumatic stress disorder (PTSD) and other psychopathology were low [e.g., mean score for UCLA PTSD Reaction Index (Steinberg et al., 2013) = 14.7, SD = 11.5; UCLA PTSD Reaction Index cutoff for PTSD diagnosis = 35].

1.2 | Clinical assessments

1.2.1 | Puberty development

The Pubertal Development Scale (PDS) was used to measure participants' pubertal status (Petersen, Crockett, Richards, & Boxer, 1988). This 5-item scale has female and male versions. The PDS was completed by the child during a joint parent-child interview, so that the parent could assist the child if needed; PDS data was available for 41 participants. Median internal consistency was good, $\alpha = 0.77$ (range: 0.68–0.83). We utilized a coding system to convert the PDS to a 5-point scale that parallels the Tanner stages, which range from 1 (no development) to 5 (adult development) (Shirtcliff et al., 2009; Tanner, 1962). This scale has demonstrated good reliability, with high correlations with health-care professionals' ratings; it also can be used to derive separate scores for adrenarche and gonadarche (Schmitz et al., 2004; Shirtcliff et al., 2009). The adrenarche scores from the PDS were used for the primary analyses of this study, given that adrenal markers of puberty increase earliest (Witchel & Topaloglu, 2019); however, we repeated analyses with significant findings with gonadal PDS scores to assess generalizability to other aspects of puberty; gonadal PDS was significantly correlated with adrenal PDS in this sample ($r = 0.46$, $\rho = 0.003$). Given the small number of participants in later stages of puberty (adrenal PDS score of 3 or more), participants were divided into three pubertal development groups for data analyses (PDS = 1, PDS = 2, and PDS≥3). Approximately 44% (n = 18) of participants had adrenal PDS of 1, representing pre-puberty; 27% (n = 11) had adrenal PDS of 2, indicating early to middle stages of puberty, and 29% (n = 12) had adrenal PDS = 3 or above, indicating middle-late puberty. With respect to ages represented among the three groups, all ages were represented in each group with the exception of the pre-puberty group, where no participants were age 11.

1.2.2 | Violence exposure scale for children-revised

(VEX-R; Fox & Leavitt, 1995) is a 22-item self-report assessment of the child's exposure to community violence, including the home, school and neighborhood. This measure includes drawings that accompany questions about experiences, alongside a thermometer-like scale: "Chris sees a person point a knife or a real gun at another person. How many times have you seen a person point a knife or a gun at another person?" A summed score representing number of trauma types experienced was used in analyses as a measure of violence exposure, as in prior studies (Stenson et al., 2020). In the entire sample, violence type scores ranged from 1–15, with a mean of 7.9 (SD = 3.3).

1.2.3 | Traumatic events screening inventory

(Child report) is a 24-item assessment of exposure to a variety of potential traumatic events, such as injuries and physical and sexual abuse; response options are yes/no. This measure has been validated in

TABLE 1 Demographic and clinical characteristics

	Male (n = 23)	Female (n = 25)	
	Mean (SD)	Mean (SD)	F
Age (years)	11.2 (1.9)	10.8 (1.4)	.76
Age (months)	134.3 (22.7)	129.3 (16.8)	.76
Pubertal Development Scale (PDS)			
Range	1-4	1-4	
	N (%)	N (%)	Fisher's exact = 7.14
1	13 (65)	5 (24)	
2	3 (15)	8 (38)	
3	2 (10)	5 (24)	
4	2 (10)	3 (14)	
5	0	0	
VEXR Type	7.3 (3.4)	8.4 (3.2)	.3
VEXR Frequency	11.7 (6.4)	13.9 (6.2)	.2
TESI Total	5.7 (3.2)	6 (3.6)	.1
			Mann-Whitney U
Education (mother)*	N (%)	N (%)	.25
Some high school	5 (22.7)	2 (8.7)	
High school graduate/GED	8 (36.4)	8 (34.7)	
Associate's degree/some college	6 (24.9)	9 (39.1)	
Bachelor's degree	1 (4.5)	4 (17.4)	
Master's degree or higher	2 (9.1)	0	

*data missing for 3 participants.

separate versions for children (Ribbe, 1996) and parents (Ippen et al., 2002). A summed score of types of events was used in analyses.

1.3 | DTI data acquisition

Scanning took place on a research-dedicated Siemens 3-Tesla TIM-Trio scanner using a 32-channel head coil. Diffusion-weighted images were acquired in two different phase-encoding directions with the following parameters: 66 × 2.0 mm thick axial slices, matrix = 106 × 106, field of view = 212 × 180 mm, voxel size = 2 × 2 × 2 mm, TR = 3292 ms, TE = 96 ms. The diffusion weighting was isotropically distributed along 138 directions using a b-value of 1000 s/mm^2. For each scan, six normalization images, with no diffusion encoding (b = 0), were acquired and averaged for each direction using linear rigid body registration (FLIRT; Jenkinson and Smith, 2001). All image processing and analysis was conducted using FMRIB Software Library (FSL version 4.1; www.fmrib.ax.ac.uk/fsl; Smith et al., 2004). Data preprocessing and correction for head motion and eddy current distortion was conducted with TOPUP and EDDY toolkits in FSL (www.fsl.fmrib.ox.ac.uk/fsl). Normalization images were skull-stripped using the FSL brain extraction tool (Smith, 2002). DTIfit in the FMRIB Diffusion Toolbox was used to fit a tensor model at each voxel and produce FA and MD maps. Voxel-wise differences in DTI scalar indices were assessed using TBSS (version 1.2) (Smith et al., 2006). All participants' FA maps were co-registered using the non-linear registration to the most 'typical' participant's FA, then affine transformed into 1 × 1 × 1 mm MNI space. All transformed FA images were averaged to create a mean FA image, then thresholded by FA of 0.2 to ensure that gray matter regions would be excluded from these analyses. These transformations were applied to MD images as well, in accordance with published TBSS steps. Voxel values of each subject's FA and MD maps were projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton. To analyze tracts of interest, skeletoned FA and MD maps were overlaid with atlas masks of the corpus callosum (CC), uncinate fasciculus (UF), cingulum bundle (CB, body and hippocampal segments) and fornix, derived from Johns Hopkins University (JHU) ICBM-DTI-81 white matter atlas provided by FSL (Hua et al., 2008). FA and MD values were extracted from these regions using FSLmaths to examine potential associations with pubertal stage, trauma exposure and sex.

1.4 | Statistical analyses

For DTI analyses, we focused on the UF, CB, CC and fornix as in prior studies of childhood trauma; we examined anterior (body) and

hippocampal segments of the CB separately given earlier study findings indicating trauma-specific effects for anterior versus posterior segments (Choi et al., 2009; De Bellis et al., 2002; McCarthy-Jones et al., 2018; Rinne-Albers et al., 2013). Given that no prior studies have examined associations of trauma and white matter integrity across different pubertal stages in children, we first examined interactions of trauma and pubertal stage (PDS) with white matter indices (FA and MD) using non-parametric (Spearman's ρ) correlational analyses. For these analyses (with FA and MD considered separate families of statistical tests), statistical significance was set at a Bonferroni-corrected p-value of 0.01, accounting for the number of selected tracts. Significant findings were used to guide subsequent linear regression analyses examining potential interactions of trauma exposure with sex (hierarchical linear regression, enter method) after accounting for age; main effects of sex and age and the interaction of sex and trauma exposure were examined as predictors of FA or MD for these specific tracts; statistical significance was set at $p < 0.05$ for these analyses.

2 | RESULTS

2.1 | Age, pubertal stage, and trauma

As expected, age (in months) was significantly associated with pubertal stage (PDS, $\rho = 0.47$, $p = 0.002$). Although somewhat stronger associations of age and pubertal stage were observed in females ($\rho = 0.6$, $p = .004$) compared to males ($\rho = 0.45$, $p = 0.04$), there was no significant interaction of sex and pubertal stage with age ($F_{1,35} = 1.06$, $p = 0.36$). There was a significant association between age (in months) and trauma exposure as assessed by the TESI (r = 0.43, p = .002), with no significant sex differences observed ($p > .05$). There were also no sex differences in pubertal stage (Fisher's exact value = 7.14, $p = 0.06$). Age was not significantly associated with violent trauma exposure (VEX-R; r = 0.32, p = 0.05). Level of trauma exposure (VEX-R and TESI) did not significantly differ by sex. No significant associations were observed between pubertal stage and trauma exposure (VEX-R or TESI), $ps > 0.05$.

2.2 | Age, pubertal stage, trauma exposure and markers of white matter integrity

Age was significantly correlated with FA in the right UF (r = 0.36, $p = 0.012$), and left UF (r = 0.36, $p = 0.011$). These associations were not significantly different between sexes. Age was negatively correlated with MD in the right UF (r = −0.39, $p = 0.006$). Sex differences were similarly not observed for age and MD associations. No significant correlations were observed between pubertal stage (PDS) and FA for any white matter tracts (all $ps > 0.05$); correlations were similarly non-significant when split by sex or when age was covaried in partial correlational analyses. However, PDS was significantly correlated with MD values in the CC ($\rho = -.39$, $p = .01$), left CB ($\rho = -.41$, $p = .009$), right CB ($\rho = -.4$, $p = .01$), right hippocampal CB ($\rho = -.41$, p = .009), and right UF ($\rho = -.46$, p = .003).

Given that there were no sex differences in age, pubertal stage, or trauma exposure, analyses of interactions between pubertal stage and trauma exposure with FA and MD values were conducted with both sexes, combined. There was no significant interaction of PDS and violent trauma exposure (VEXR) with FA in any region. However, significant interactions of PDS and VEXR were observed for MD values in the CC ($\rho = -0.43$, $p = .005$), left CB ($\rho = -0.42$, $p = 0.007$), right CB ($\rho = -0.43$, $p = 0.005$), right hippocampal CB ($\rho = -0.52$, p = 0.001), and right UF ($\rho = -0.56$, $p < 0.001$). Gonadal PDS interactions with VEXR were similarly observed for these tracts; CC ($\rho = -0.52$, $p = .001$), left CB ($\rho = -0.47$, $p = 0.002$), right CB ($\rho = -0.49$, $p = 0.002$), right hippocampal CB ($\rho = -0.61$, $p < 0.001$), and right UF ($\rho = -0.52$, $p = 0.001$). Figure 1a illustrates associations of adrenal PDS and violent trauma exposure with right hippocampal CB, in which the strongest effects were observed. When separated by pubertal stages, the association of VEXR with MD for the right hippocampal CB was significant for early puberty (r = −0.79, $p = 0.004$), but not pre-puberty (r = −0.20, $p = 0.43$) and middle to late puberty (r = −0.51, $p = 0.09$) stages (Figure 1b). The association of VEXR with MD for the right UF was significant for middle to late puberty stages (r = −0.71, $p = 0.009$), but not pre-puberty (r = 0.06, $p = 0.82$) and early puberty (r = −0.63, $p = 0.037$) stages. TESI scores did not correlate with FA or MD of any white matter tract (all $ps > 0.01$). Next, we covaried age to better isolate effects of puberty and trauma exposure on MD in these white matter pathways; the interaction of adrenal PDS and VEXR remained significantly associated with MD of the right hippocampal CB ($\rho = -0.46$, $p = 0.003$), and right UF ($\rho = -0.41$, p = 0.009); findings were similar for gonadal PDS and VEXR with MD of the right hippocampal CB ($\rho = -0.56$, $p < 0.001$) and right UF ($\rho = -0.41$, $p = 0.01$) after covarying age.

2.3 | Sex, trauma exposure and markers of white matter integrity

Linear regression analysis was conducted to examine potential interactions of sex with violent trauma exposure (VEX-R) after accounting for age and main effects of trauma exposure on MD. We examined associations within tracts within which significant interactions of PDS and VEXR were observed: the CC, CB (body and hippocampal regions) and UF.

Regression models were not significant for CC MD ($F_{1,45} = 1.75$, p = 0.17, $R^2 = 0.11$), left CB MD ($F_{1,45} = 1.2$, $p = 0.32$, $R^2 = 0.08$), right CB MD ($F_{1,45} = 3.11$, $p = 0.04$, $R^2 = 0.12$) and left UF MD ($F_{1,45} = 3.22$, $p = 0.03$, $R^2 = 0.18$). The model was significant for the left hippocampal CB MD ($F_{1,45} = 3.05$, $p = 0.03$, $R^2 = 0.22$), right hippocampal CB MD ($F_{1,45} = 7.77$, $p < 0.001$, $R^2 = 0.42$), and right UF MD ($F_{1,45} = 5.73$, $p = 0.001$, $R^2 = 0.35$). Although the overall models for the left and right hippocampal CB MD were significant, none of the individual predictors were significant for left hippocampal CB and only age emerged as a significant predictor for the right hippocampal CB, as shown in Tables 2a and 2b.

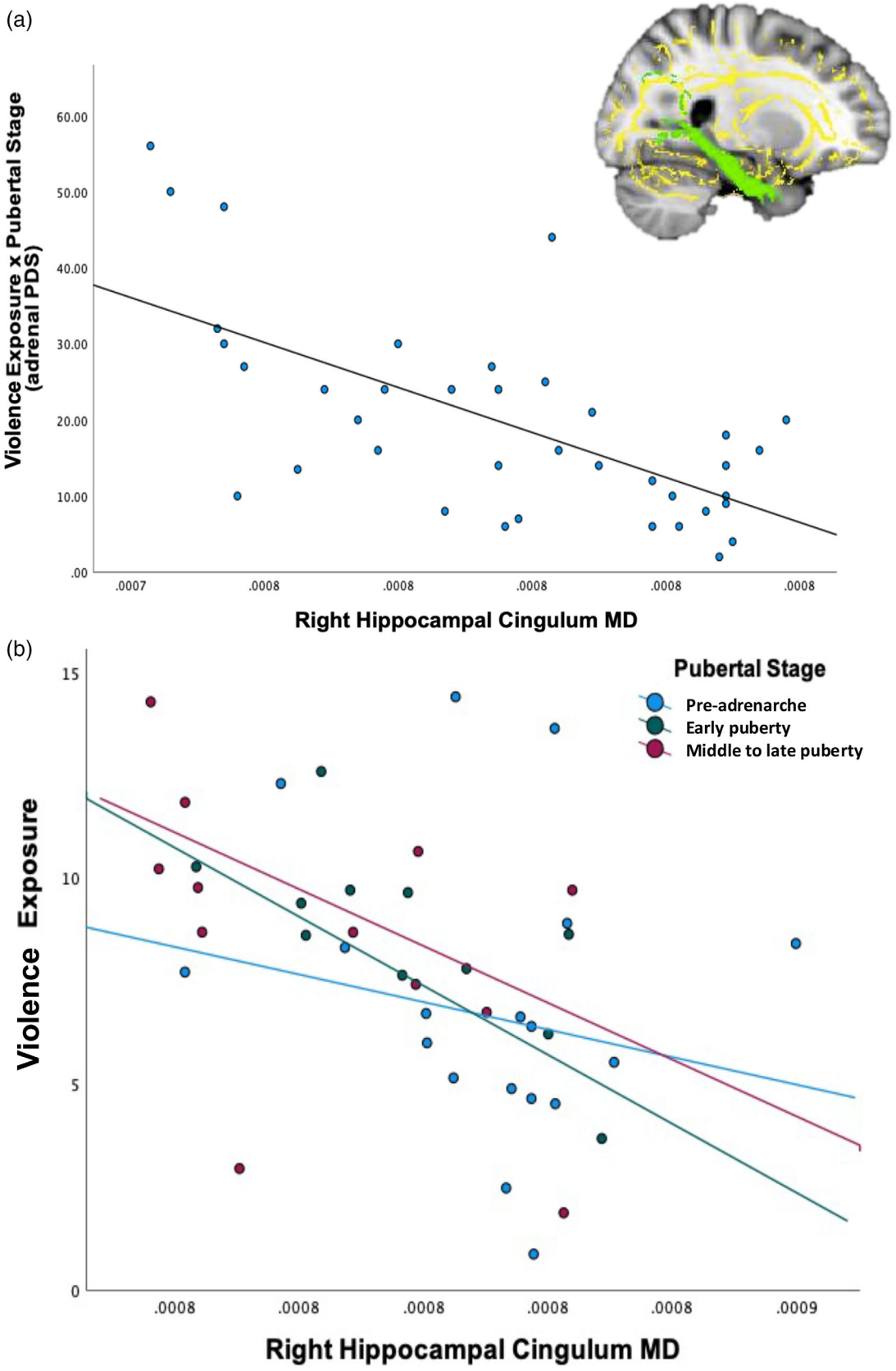

FIGURE 1 (a) Interaction of violence exposure and pubertal stage (adrenal PDS) is associated with decreased mean diffusivity (MD) of the right hippocampal cingulum (highlighted in green, right panel). (b) Associations of violence exposure and right hippocampal cingulum MD for each pubertal stage

TABLE 2A Predictors of left hippocampal cingulum MD

	B	SE	β	t	p
Sex	-8.92×10^{-6}	0.000	−0.172	−0.485	0.630
Age	-2.86×10^{-7}	0.000	−0.216	−1.505	0.140
VEX-R	-9.61×10^{-7}	0.000	−0.121	−0.599	0.552
VEX-R x sex interaction	-1.08×10^{-6}	0.000	−0.198	−0.495	0.623

TABLE 2B Predictors of right hippocampal cingulum MD

	B	SE	β	t	p
Sex	9.02×10^{-7}	0.000	0.016	0.051	0.960
Age	-4.74×10^{-7}	0.000	−0.322	−2.593	**0.013***
VEX-R	-1.02×10^{-6}	0.000	−0.115	−0.656	0.515
VEX-R x sex interaction	-3.07×10^{-6}	0.000	−0.506	−1.464	0.151

For the right UF MD regression model there was a significant effect of age and an interaction of sex with violent trauma exposure for the right UF (Table 2c). Upon further examination, a strong negative correlation between violent trauma exposure and right UF FA was observed in females ($r = -0.60$, $p = 0.002$) but not males ($r = -0.07$, $p = 0.76$; Figure 2b) for right UF MD.

3 | DISCUSSION

In this study we examined associations between pubertal stage, trauma exposure and markers of white matter microstructure in a sample of children who were assessed within a peri-pubertal period. Contrary to our hypothesis, we found that trauma exposure (specifically, violent trauma exposure) was *negatively* correlated with mean diffusivity in the CC and fronto-limbic tracts, including the hippocampal CB and UF, indicating that higher violence exposure was associated with greater white matter integrity in these pathways. An interaction of pubertal stage and violent trauma exposure was observed for the CC, hippocampal CB and UF; after accounting for the effects of age, these associations remained significant for the UF and hippocampal CB. Further, associations between violence exposure and MD of the right UF were present in females but not males, even after accounting for age.

TABLE 2C Predictors of Right Uncinate Fasciculus MD

	B	SE	β	t	P
Sex	2.33×10^{-5}	0.000	0.293	1.24	0.222
Age	-6.03×10^{-7}	0.000	−0.386	−3.11	**0.003****
VEX-R	9.27×10^{-7}	0.000	0.105	0.566	0.574
VEX-R x sex interaction	-4.96×10^{-6}	0.000	−0.671	−2.23	**0.031***

VEXR = Violence Exposure Scale for Children-Revised.
FA = fractional anisotropy.
*$p < .05$.
**$p < .01$.

Our finding of an interaction of pubertal development stage and violence exposure, and *greater integrity* of fronto-limbic white matter tracts and the CC in association with greater violence exposure, was unexpected, yet consistent with stress acceleration hypotheses (Callaghan & Tottenham, 2016). The peri-pubertal period is a unique window of neuroplasticity, characterized by neuronal pruning and increases in myelination that are shaped by hormonal fluctuations as well as adverse developmental experiences. Increased myelination in frontal brain regions may reflect the accelerated maturation of pathways that are essential to higher-order functions, including executive control and emotion regulation. Early life adversity, particularly threat-related experiences (such as violent trauma), may accelerate the onset of puberty (Chisholm et al., 2005; Mendle et al., 2016; Sumner et al., 2019), with increasing evidence showing that these effects are reflected in higher structural connectivity in white matter tracts with most protracted period of development, namely the CB and UF (Lebel et al., 2012). A recent large-scale study (N > 1000) observed higher FA in these fronto-limbic pathways in maltreated versus non-maltreated children, and found that extent of trauma exposure corresponded with early puberty (Gur et al., 2019). This echoes earlier findings of higher posterior cingulum and orbitofrontal white matter volume in physically abused versus non-traumatized children (Hanson et al., 2010) and recent findings of greater CB and UF microstructural integrity in maltreated versus non-maltreated children with prenatal alcohol exposure (Andre et al., 2020). In the present study sample of peri-pubertal children, higher levels of violent trauma exposure have been associated with relatively greater amygdala-brainstem connectivity (van Rooij et al., 2020). Relative elevations in markers of white matter microstructure have also been observed in developmental pathology, including ADHD (Davenport et al., 2016), and are particularly apparent in fronto-limbic paths (i.e., CB) in *traumatized* children with ADHD (Park et al., 2016). Longitudinal studies indicate that, among all white matter tracts, integrity of the hippocampal cingulum in maltreated adolescents specifically predicted later onset of substance use disorder (Huang et al., 2012). Further, in the Grady Trauma Project population, alterations in the integrity of these pathways have characterized PTSD and anhedonia, as well as dysregulated fear inhibition (Fani et al., 2012, 2015, 2016, 2019). As such, the present findings in trauma-exposed children from this population may indicate a pathway through which trauma exposure, particularly violence, may enhance risk for adverse psychiatric outcomes via accelerated maturation of these white matter tracts during the pubertal time period.

Accelerated maturation, or aging, caused by early life trauma exposure has been shown to increase risk for adverse health outcomes, from poor cardiovascular health to cognitive decline. (Marioni et al., 2018) Conceptual models suggest that the accelerated maturation in association with trauma exposure may reflect adaptations to stress (Boyce & Ellis, 2005; Callaghan & Tottenham, 2016; Ellis & Del Giudice, 2019), such that the increased connectivity in fronto-limbic emotion regulation pathways in highly-traumatized children emerges to manage the expectation of further traumatic events. As such, the data

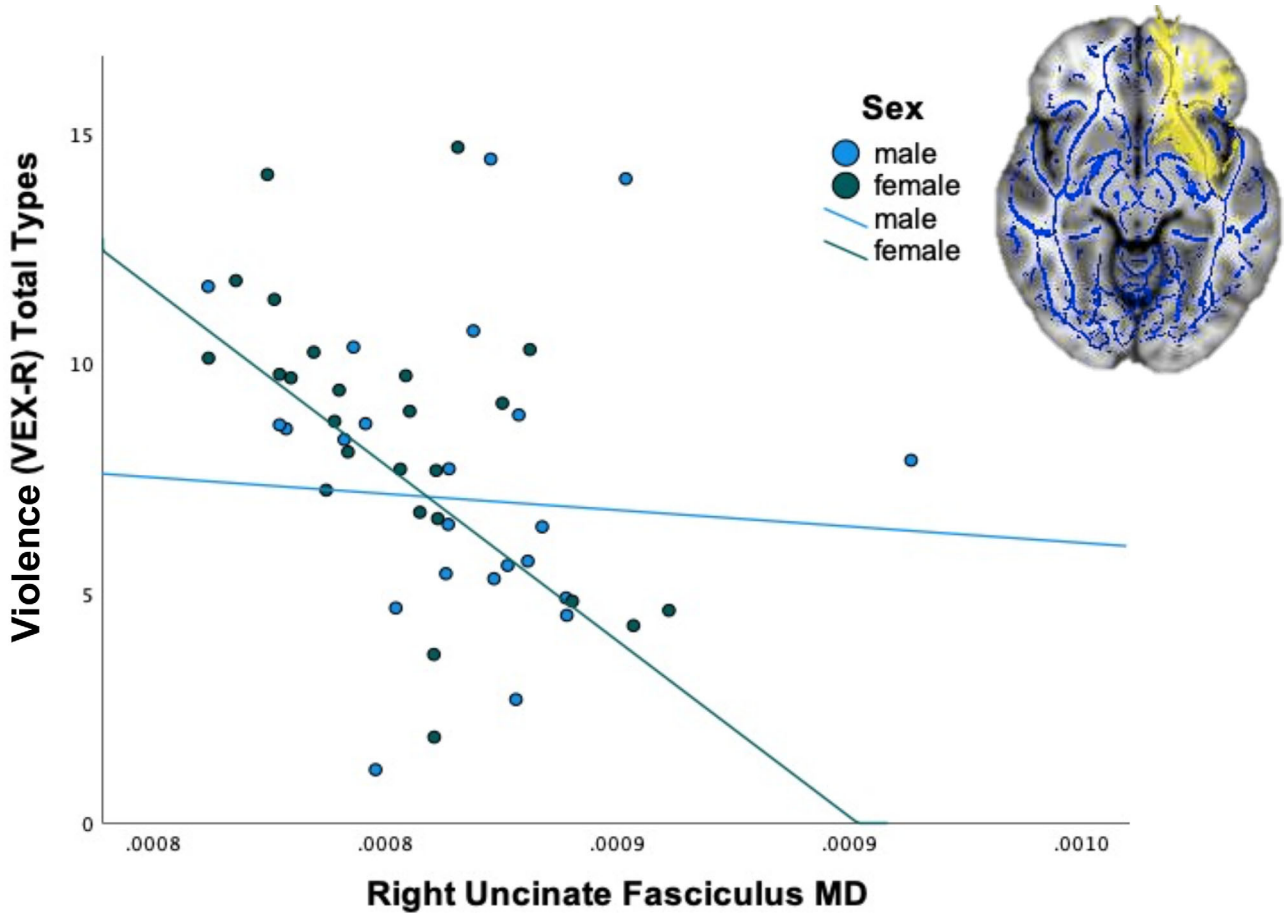

FIGURE 2 Violence exposure is negatively associated with mean diffusivity (MD) of the right uncinate fasciculus in females but not males

shown here support the stress acceleration hypothesis of development, which could have different implications for later psychological outcomes. Increased connectivity in these fronto-limbic pathways may be advantageous in the context of continued high levels of stress, conferring the needed regulatory abilities to navigate complex social situations and function adequately under unstable environmental circumstances, which has been posited by some developmental theorists (Frankenhuis & de Weerth, 2013). There is also reason to suggest that this pattern of connectivity may represent vulnerability for the later development of psychiatric disorders; for example, increased fronto-striatal connectivity in youth has been found to predict the later onset of depressive symptomatology (Hanson et al., 2018). Other data suggests that heightened learned fear responses during pubertal periods predict future anxiety symptoms (Stenson et al., 2020). However, given that we did not assess relationships with psychopathology and the cross-sectional nature of this study, we cannot make inferences regarding whether these associations represent risk or resilience for later psychopathology.

Notably, the effects of violence exposure on MD in the right UF were present for girls, but not boys. This could suggest that trauma-related acceleration in the maturation of this limbic-prefrontal circuit is most prominent in females. This relationship may be mediated by changes in hormonal exposure. Circulating levels of estrogen and progesterone during puberty affect the proliferation of neurons in the hippocampus (reviewed in McEwen, 2001), and the hippocampus and amygdala show the highest concentrations of progesterone receptors (Brinton et al., 2008). Estrogen as well as testosterone shape the myelination of white matter tracts (Herting et al., 2012). Women bear disproportionate amount of risk for trauma and stress-related disorders, which in turn exponentially increase risk for subsequent neurodegenerative disease, as shown in a large-scale (N > 100K) retrospective study (Song et al., 2020). Given that rates of myelination in fronto-limbic tracts are relatively slower in girls compared to boys during adolescence (Giedd et al., 1999; Lenroot et al., 2007), the lower MD values observed in this tract in association with greater trauma exposure may reflect disproportionately greater effects of accelerated maturation in this sample of girls. This effect may be mediated by levels of estrogen or testosterone, but we were unable to assess these effects in the current study. Although our findings reflect markers of white matter integrity and are not direct measures of myelination, it is possible that the effects of trauma exposure on white matter myelination may be most concentrated in girls, which may bear consequences in terms of risk for trauma and stress-related disorders.

We must acknowledge several limitations for this study. We did not assess the onset of trauma exposure or hormone levels, which

precluded our ability to explore how timing of trauma and related hormone levels affected the trajectory of these associations. This would also permit investigation of how trauma onset impacts pubertal timing and consequently, changes in neural architecture. A longitudinal assessment of these children could reveal the actual consequences of trauma and related white matter changes into adulthood, including trauma-related psychopathology. We plan to re-contact our study participants in the future to assess these relationships. Although we did not observe sex differences in pubertal stage and trauma exposure in our sample, a larger study sample would provide the statistical power for a more thorough interrogation of interactions between sex and trauma exposure with white matter microstructural integrity. In addition, we relied on indirect measures of microstructural integrity, including FA and MD; given that multiple factors influence FA and MD values, including crossing fibers within voxels and partial voluming (Jones et al., 2013), these findings cannot be interpreted as a direct reflection of WM integrity, but rather indirect metrics that have associations with WM integrity. In addition, the upper end of the age range of our participants was 13, and given that puberty continues past this age, we were unable to explore relationships of trauma exposure with white matter microstructure at the latest stages of puberty. Further, our participants were a trauma-exposed sample of African-American children living in inner-city Atlanta; prior research in this population has indicated relatively higher rates of trauma exposure and psychopathology (Gillespie et al., 2009). Although this could limit generalizability of findings to some degree, we believe that this work brings attention to an understudied, marginalized population that is at higher risk for later physiological and mental health difficulties.

In conclusion, we observed that violence exposure interacted with pubertal stage in this sample, with increases in violence exposure corresponding with greater microstructural integrity in fronto-limbic white matter pathways. Further, the relationship between violent trauma exposure and white matter microstructure in the UF was present in girls but not boys, indicating sex-specific effects. This reflects a pattern of accelerated maturation in pathways that are critical for emotion regulation as well as basic attention and memory processes. As such, our findings indicate that these fronto-limbic connections are sensitive to the effects of violent trauma, and illustrate a potential pathway through which trauma creates vulnerability for later psychiatric and neurological disorders.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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