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Longitudinal cortical markers of persistence and remission of pediatric PTSD

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A B S T R A C T

Background: Previous studies have identified structural brain abnormalities in pediatric PTSD. However, little is known about what structural brain substrates may confer recovery versus persistence of PTSD in the context of the developing brain.

Methods: This naturalistic longitudinal study used T1-weighted MRI to evaluate cortical thickness and surface area in youth with a PTSD diagnosis (n = 28) and typically developing healthy youth (TD; n = 27) at baseline and one-year follow-up. Of the PTSD group, 10 youth were remitters at one-year follow up while 18 had persistent PTSD. Whole-brain estimates of cortical thickness and surface area were extracted to identify differences in cortical architecture associated with PTSD remission and persistence as compared to typical development.

Results: Youth who achieved PTSD remission entered the study with significantly lower trauma exposure and reduced symptom severity as compared to nonremitters. PTSD persistence was associated with decreased surface area over time in the ventrolateral prefrontal cortex (vlPFC) as compared to both remitters and TD youth. In contrast, PTSD remission was associated with expansion of frontal pole surface area and ventromedial PFC (vmPFC) thickness over time. Across clinical groups, vmPFC thickness was further inversely associated with symptom severity.

Conclusions: To our knowledge, these findings represent the first report of cortical substrates underlying persistence versus remission in pediatric PTSD. Together, these findings suggest active structural developmental processes unique to both remission and nonremission in youth with PTSD. In particular, expansion of prefrontal regions implicated in emotion regulation may facilitate recovery from PTSD in youth and would warrant further study.

1. Introduction

Pediatric posttraumatic stress disorder (pPTSD) is a highly prevalent disorder afflicting an estimated 5% of all youth by the age of 18 (McLaughlin et al., 2013) and is characterized by anxiety, negative affect, increased arousal, and re-experiencing symptoms (American Psychiatric Association, 2013). While some youth demonstrate remission after a few months, if left untreated, approximately one-third of youth will exhibit sustained psychopathology (McLaughlin et al., 2013). However, the neurobiological correlates that differentiate youth who continue to experience active trauma-related psychopathology from those who remit have yet to be investigated. Identifying such biomarkers has the potential to inform clinical care in multiple ways, including prediction of illness course and treatment response, and their potential to serve as novel therapeutic targets (Michopoulos et al., 2015).

The body of evidence characterizing aberrant disease states using structural neuroimaging in youth with PTSD is steadily growing (Herringa, 2017). Cross-sectional voxel-based morphometry (VBM) studies of gray matter volume (GMV) in pPTSD suggest abnormal structure in key cortical and subcortical brain regions involved in threat processing and emotion regulation. More specifically, in cortical structures, pediatric PTSD has been associated with decreased volume in the ventromedial prefrontal cortex (vmPFC) as compared to trauma-exposed and non-traumatized typically developing (TD) youth (Heyn et al., 2019; Keding and Herringa, 2015; Morey et al., 2016) [though see (Carrion et al., 2009)], decreased volume in the anterior cingulate cortex (ACC) (Ahmed et al., 2012; Rinne-Albers et al., 2017), decreased superior temporal gyrus volume (De Bellis et al., 2002), and decreased hippocampal volume with cross-sectional age (Keding and Herringa, 2015).

These previous studies importantly characterized snapshots of pPTSD at a single moment in time and suggest altered brain structure in youth with PTSD history as a group. However, due to the dynamic nature of neurodevelopment throughout adolescence, longitudinal studies of pPTSD are warranted to illuminate mechanisms of disease progression. Following two early pilot investigations of structural brain development in pPTSD (Carrion et al., 2007; De Bellis et al., 2001), our recent longitudinal VBM study of pPTSD was the first to find sustained GMV reductions in PFC and precentral gyrus, as well as atypical longitudinal development in GMV in the dorsolateral (dl)PFC (Heyn et al., 2019). While this prior study implicates both trait-like and

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neurodevelopmental gray matter changes in pediatric PTSD, it did not characterize how gray matter change may differ in persistent versus remitted PTSD. Furthermore, little is known about the cortical characteristics underlying pPTSD and how these may diverge from typical development with persistence or remission of illness.

While useful as a broad structural brain measure, VBM outputs are limited in knowledge of their more precise morphological correlates, such as cortical thickness (CT), cortical surface area (CSA), and cortical folding. The radial unit hypothesis, the predominant theory of gray matter development, posits that the number of cortical columns within a region governs CSA, while the number of cells within a cortical column dictates CT (Pontious et al., 2008; Rakic, 1988, 1995). Previous work has found that CT and CSA are uncorrelated to one another (Winkler et al., 2010), arise from discrete genetic influences (Panizzon et al., 2009; Pontious et al., 2008), and follow independent developmental trajectories throughout adolescence (Amlien et al., 2016; Raznahan et al., 2011; Tamnes et al., 2017; Wierenga et al., 2014). Specifically, CT appears to decrease linearly with age while CSA has a cubic relationship with age that peaks later than CT (Shaw et al., 2012; Wierenga et al., 2014).

Few studies have examined cortical surface morphometry in relation to either childhood trauma or pediatric PTSD. Cross-sectional studies of maltreated youth have shown reduced cortical thickness in prefrontal cortex (Busso et al., 2017; Gold et al., 2016; Kelly et al., 2013) and reduced thickness (Busso et al., 2017; Gold et al., 2016) or surface area (Kelly et al., 2013) in temporal cortex. To our knowledge, only one reported study has examined cortical morphometry in pPTSD. This study utilized a region of interest analysis for the insula, finding sex differences in insula volume and surface area in youth with PTSD (Klabunde et al., 2017). These studies have begun to shed light on how maltreatment and PTSD may alter cortical morphometry in youth. However, further work is needed to characterize brain-wide cortical morphometry in pPTSD, and which patterns distinguish PTSD persistence and remission over time.

The current study aims to expand the current knowledge on the relationship between trauma-related psychopathology and cortical development in three key ways. First, we aimed to conduct the first whole brain cortical surface analysis in pediatric PTSD, characterizing both cortical thickness and surface area to determine regional abnormalities. Second, using a naturalistic longitudinal design, we examined what developmental cortical changes differentiate persistence and remission of PTSD relative to neurodevelopment in typically developing youth. Finally, we examined to what extent these cortical abnormalities are associated with transdiagnostic symptom change over time, including symptoms of PTSD, anxiety, and depression. Based on our prior VBM study, we predicted decreased cortical thinning in the prefrontal cortex in both pPTSD groups as compared to TD youth. If delayed prefrontal thinning represents a compensatory mechanism in pPTSD, then this pattern should be accentuated in the remitted group. Alternatively, if delayed cortical thinning is a marker of ongoing illness processes, then this pattern should be accentuated in the persistent PTSD group. Complementing these specific hypotheses, this approach also allows for investigation of additional brain networks involved in recovery from, or persistence of, PTSD in youth.

2. Participants and methods

2.1. Participants

Details of the recruitment strategies employed and participant characteristics have been previously reported (Heyn et al., 2019; Keding and Herringa, 2015, 2016; Wolf and Herringa, 2016). At baseline, the Youth PTSD Study recruited a total of 96 youth between the ages of 8–18 years (TD, $n = 48$; PTSD $n = 48$). Youth with PTSD were recruited from local mental health facilities and non-traumatized TD youth matched for age and sex were recruited from the community. The longitudinal sample for this analysis was comprised of fifty-eight adolescents who returned for a follow-up assessment one year later (TD, $n = 27$; PTSD, $n = 31$). Additional information regarding reasons for attrition can be found in Supplemental Fig. 1. Of the 31 PTSD youth who completed one-year follow up, 12 were classified as PTSD remitters while 19 had persistent PTSD based upon the absence or presence of a PTSD diagnosis at the follow-up visit. Three PTSD youth were excluded due to significant motion during the scan, leaving 18 persistent PTSD, 10 remitted PTSD, and 27 TD youth in the final group analyses.

Participants were excluded before study entry if they had an IQ < 70, any history of a psychotic, bipolar, or obsessive-compulsive disorder, acute suicidality, substance abuse or dependence or psychotropic medication use in the past 4 weeks (6 weeks for fluoxetine), unstable medical condition, MRI contraindication, and/or pregnancy in females. No youth were taken off psychotropic medication for the purposes of this research study. Written informed consent from a legally acceptable representative with youth assent was obtained from all participants. All study procedures were approved by the University of Wisconsin Health Sciences IRB.

2.2. Clinical assessments

A comprehensive clinical battery was used to assess all participants for past and current psychopathology and trauma exposure through administration of the following assessment tools: Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS; (Kaufman et al., 1997)), Childhood Trauma Questionnaire (CTQ; (Bernstein et al., 1994)), Mood and Feelings Questionnaire (MFQ; (Costello and Angold, 1988)), Screen for Child Anxiety Related Emotional Disorders (SCARED; (Birmaher et al., 1997)), Stressful Life Events Schedule Adolescent Report (SLES; (Williamson et al., 2003)), and Weschler Abbreviated Scale of Intelligence-II (Wechsler, 2011) in order to assess IQ.

Within the clinical groups, presence or absence of a PTSD diagnosis was determined by DSM-IV criteria using both the KSADS and Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA; (Weathers et al., 2001)). Youth in the clinical groups also completed the UCLA PTSD Reaction Index (PTSD-RI; (Steinberg et al., 2004)) at both time points.

2.3. MRI acquisition and preprocessing

At each time point, structural MRIs were collected at the University of Wisconsin Department of Psychiatry in a 3.0T GE Discovery MR750 scanner (General Electric, Milwaukee, WI) using an 8-channel head coil. The images were acquired using a T1-weighted sequence with the following parameters: TE = 3.18 ms, TR = 8.16 ms, TI = 450 ms; flip angle = 12°, FOV = 25.6 cm, slice thickness = 1.0 mm, 156 slices, image acquisition matrix = 256 × 256, isotropic voxel size = 1 × 1 × 1 mm^3. Finally, extensive motion was assessed with the quality control measures using the Computational Anatomy (CAT12) toolbox (http://dbm.neuro.uni-jena.de/cat/) in SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) in MATLAB 8.3 (The MathWorks, Inc., Natick, MA). The covariance structure of all gray matter images was checked for homogeneity with all other images. This resulted in 3 participants being excluded from group analyses due to covariance being more than 2 SD below the mean on close inspection.

2.4. Surface-Based morphometry analyses

Surface extraction and cortical parcellation were completed using FreeSurfer image analysis suit v6.0 (Fischl and Dale, 2000). Preprocessing was carried out using default parameters (http://surfer.nmr.mgh.harvard.edu/), and technical details have been previously described (Fischl and Dale, 2000; Fischl et al., 2002, 2004). In order to

extract cortical thickness (CT) and cortical surface area (CSA), images from both time points were processed using a customized analysis stream that has been adapted from the standard longitudinal pipeline included in FreeSurfer (Reuter et al., 2012), which will be briefly summarized here. First, an unbiased within-subject template space and image (Reuter and Fischl, 2011) is created using robust, inverse consistent registration (Reuter et al., 2010). The next processing steps, including skull stripping, Talaraich transformations, spherical surface maps, and atlas-based parcellations are initialized with common information from the within-subject template, which significantly increases the reliability and statistical power (Reuter et al., 2012). The automated cortical parcellation and region of interest boundaries were performed using the Destrieux Cortical Atlas (Fischl et al., 2004), resulting in mean cortical thickness and surface area estimations for 74 regions of interest per hemisphere using the aparcstats2table function. Finally, as FreeSurfer cortical surface parcellations does not include estimations of thickness or surface area within subcortical structures, we included GMV estimations for 9 subcortical regions of interest per hemisphere using the FreeSurfer asegstats2table function as a proxy.

2.5. Primary statistical analyses

All statistical analyses were completed in R version 3.3.0 (R Core Team, 2017) and RStudio (RSTudio Team, 2012). Demographics and clinical data were analyzed using ANOVAs, independent t-tests, or χ^2 tests, where appropriate. For brain measures, group and group by time effects were identified using linear mixed-effect modeling on extracted CT, CSA, and subcortical GMV estimates, covarying for age at baseline, sex, IQ, and subject as a random effect. Models on subcortical GMV also include total intracranial volume as a covariate, as recommended by FreeSurfer documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/eTIV). All continuous variables were scaled prior to modeling (Becker et al., 1988). Normality of dependent variables was assessed through visual inspection of quantile-quantile plots using the model residuals. Across all models, the correlation coefficient for each plot (r^2) was above 0.90 for 96% of all models, with the lowest value at 0.75, indicating normal distributions of model residuals. We applied multiple-comparison correction using false discovery rate (FDR; (Benjamini and Hochberg, 1995) at $p_{FDR} < 0.05$ across CT, CSA, and subcortical GMV analyses. We report group main effects as well as group by time interactions that survive FDR correction.

2.6. Post-hoc statistical analyses

We further assessed the relationship between identified abnormal regions and symptom severity across both PTSD remitters and nonremitters (using the PTSD-RI total score, PTSD-RI B/C/D subscores, MFQ, and SCARED). Each symptom measure was evaluated using multiple linear regression separately, covaried for age at baseline, sex, and subject as a random effect. We only report symptom results that survive FDR correction ($p_{FDR} < 0.05$). Finally, we conducted regression analyses investigating the impact of the following variables on group and longitudinal differences in cortical morphology: pubertal stage (Tanner stage), age at index trauma, stressful life events (SLES), childhood maltreatment load (CTQ), previous use of psychotropic medication, or history of therapy.

3. Results

3.1. Participant characteristics

Participant demographic characteristics and trauma variables are summarized in Table 1, while clinical characteristics such as co-morbid diagnoses, history of medication, and history of therapy are summarized in Table 2. At baseline, the three groups did not significantly differ on age ($F(2,54) = 0.43$, $p = 0.67$) or pubertal stage ($F(2,54) = 0.88$, $p = 0.42$). Within the clinical groups, PTSD remitters and nonremitters did not significantly differ on race (χ^2 (3, $N = 28$) $= 0.12$, $p = 0.99$) or highest level of parental education (χ^2 (4, $N = 28$) $= 5.71$, $p = 0.22$). Youth with PTSD, regardless of future remittance, began the study with comparable trauma load (as measured by number of KSADS trauma types; $t(26) = -1.13$, $p = 0.27$), stressful life events ($t(20) = 0.03$, $p = 0.98$), age of index trauma ($t(26) = 0.84$, $p = 0.41$), anxiety symptom severity ($t(26) = -1.51$, $p = 0.14$), presence of comorbid disorders (χ^2 (1, $N = 28$) $= 0.23$, $p = 0.63$), and history of psychiatric medication (χ^2 (1, $N = 28$) $= 0.08$, $p = 0.78$) or therapy (χ^2 (1, $N = 28$) $= 0.56$,

$p = 0.45$). However, nonremitters had marginally higher PTSD severity on the CAPS ($t(21) =$ -2.0, $p = 0.06$), higher levels of childhood maltreatment experiences (CTQ; $t(26) = -2.15$, $p = 0.04$) and higher depression symptom severity (MFQ; $t(26) = -2.26$, $p = 0.03$) at the time of study enrollment.

At one-year follow-up, as expected, clinical symptom severity was greater in nonremitters compared to remitters. Nonremitters had significantly greater PTSD severity on the CAPS ($t(26) = -2.15$, $p < 0.01$), higher depression symptoms (MFQ; $t(26) = -2.24$, $p = 0.03$), marginally higher anxiety symptoms (SCARED; $t(26) = -1.83$, $p = 0.08$) and interim childhood maltreatment severity (CTQ; $t(26) = -1.86$, $p = 0.07$) as compared to remitters. However, remitters and nonremitters did not differ on interim trauma load (number of new KSADS trauma types; $t(26) = -0.29$, $p = 0.77$). There were no significant group differences in those that either had or had not used psychiatric medication (χ^2 (1, $N = 28$) $= 2.27$, $p = 0.13$) or psychotherapy ($\chi^2(1, N = 28) = 0.08$, $p = 0.78$) during the interim.

3.2. Sustained cortical abnormalities in pediatric PTSD regardless of remission status

Results from all whole-brain analyses are summarized in Table 3. We identified a significant group main effect in left posterior cingulate cortex cortical surface area (PCC; Destrieux ROI 71; $F(2,50) = 5.87$, $p_{FDR} = 0.048$). On average, youth with PTSD regardless of remission status exhibited reduced CSA across time points as compared to TD youth (Remitter < TD, $t(50) = -2.61$, $p = 0.005$; Nonremitter < TD, $t(50) = -2.90$, $p = 0.002$). We did not detect group main effect differences in CT or subcortical GMV. Across the entire clinical sample, PCC CSA was not significantly associated with depression, anxiety, or PTSD symptom severity. Next, we report significant group by time interactions, dividing results into those where youth with persistent PTSD showed unique developmental effects, followed by unique effects for PTSD remission.

3.3. Longitudinal markers of PTSD persistence

A summary of longitudinal markers of PTSD persistence can be found in Fig. 1. Group by time interactions revealed unique correlates of PTSD nonremitters for cortical surface area in the left ventrolateral prefrontal cortex (vlPFC; Destrieux ROI 24; $F(2,50) = 7.54$, $p_{FDR} = 0.019$), left supramarginal gyrus (Destrieux ROI 26; $F(2,50) = 5.57$, $p_{FDR} = 0.045$), left occipital pole (Destrieux ROI 42; $F(2,50) = 8.89$, $p_{FDR} = 0.010$), right superior parietal gyrus (Destrieux ROI 27; $F(2,50) = 7.16$, $p_{FDR} = 0.023$), and right precentral gyrus (Destrieux ROI 29; $F(2,50) = 6.43$, $p_{FDR} = 0.035$). In all cases, PTSD nonremitters showed decreased CSA with time (vlPFC, $t(50) = -3.19$, $p = 0.002$; Supramarginal gyrus, $t(50) = -3.31$, $p = 0.002$; Superior parietal, $t(50) = -3.45$, $p = 0.001$), Precentral gyrus, $t(50) = -2.91$, $p = 0.005$) while remitters and TD youth did not exhibit this effect. In the occipital pole, the PTSD nonremitters showed significant longitudinal decreases in occipital pole CSA, ($t(50) = -2.81$, $p = 0.007$) while remitters showed longitudinal increases ($t(50) = 2.08$, $p = 0.042$) as compared to TD youth. We did not detect group by time effects of nonremission in CT or subcortical GMV. None of these effects

Table 1
Participant demographics.

		Typically Developing	PTSD Remitter	PTSD Nonremitter	PTSD Group Comparisons
Basic Demographic Variables					
N		27	10	18	
Sex (Female)		21	5	12	χ^2 (1, N = 28) = 0.75, p = 0.39
Age	Baseline	14.16 (2.70)	13.28 (3.45)	14.21 (2.46)	t(26) = −0.83, p = 0.41
	Follow-up	15.42 (2.72)	14.37 (3.44)	15.51 (2.53)	
Tanner	Baseline	3.2 (1.3)	2.6 (1.5)	3.2 (1.3)	t(26) = −1.13, p = 0.27
	Follow-up	3.89 (1.15)	2.9 (1.3)	3.9 (1.2)	
IQ	Baseline	109.81 (11.86)	101.60 (13.28)	99.24 (10.8)	t(26) = 0.9, p = 0.38
	Follow-up	111.11 (11.15)	103.9 (16.06)	98.17 (11.76)	
Race	Non-Hispanic White	20	5	10	χ^2 (3, N = 28) = 0.12, p = 0.99
	Hispanic or Latino	0	2	3	
	African American	0	2	3	
	Not Provided	6	1	2	
Highest Level Parental Income	Some High School	1	0	1	χ^2 (4, N = 28) = 5.71, p = 0.22
	High School Degree	1	0	6	
	Some College	5	5	7	
	College Degree	7	2	2	
	Graduate Degree	13	3	2	
Trauma Variables					
Index Trauma Type	Witnessing Violence	–	3	4	χ^2 (3, N = 28) = 3.04, p = 0.39
	Traumatic News	–	3	4	
	Traumatic Accident	–	2	1	
	Interpersonal Violence	–	2	9	
KSADS # of Trauma Types	Baseline		3.40 (1.58)	4.17 (1.79)	t(26) = −1.13, p = 0.27
	Follow-up	–	0.90 (1.52)	1.11 (2.03)	t(26) = −0.29, p = 0.77
Age of Index Trauma		–	8.53 (5.76)	6.97 (4.03)	t(28) = 0.84, p = 0.41
CTQ	Baseline	30.85 (4.97)	42.00 (13.40)	55.44 (16.96)	**t(26) = −2.15, p = 0.04***
	Follow-up	34.45 (7.79)	41.40 (11.49)	56.67 (24.28)	t(26) = −1.86, p = 0.07
SLES	Baseline	21.30 (14.12)	69.22 (59.45)	68.62 (42.47)	t(20) = 0.03, p = 0.98
	Follow-up	9.35 (8.89)	36.78 (37.63)	37.77 (30.06)	t(20) = −0.07, p = 0.94
CAPS-CA	Baseline	–	62.88 (22.2)	79.07 (16.29)	t(21) = −2.0, p = 0.06
	Follow-up	–	28.70 (22.09)	64.22 (20.52)	**t(26) = −4.27, p < 0.01**
PTSD-RI	Baseline	–	46.60 (12.55)	50.61 (10.83)	t(26) = −0.89, p = 0.38
	Follow-up	–	31.30 (12.88)	37.22 (17.09)	t(26) = 0.95, p = 0.35
MFQ	Baseline	2.39 (1.81)	17.20 (11.50)	30.17 (15.94)	**t(26) = −2.26, p = 0.03**
	Follow-up	3.61 (4.84)	13.60 (10.31)	27.00 (17.18)	**t(26) = −2.24, p = 0.03**
SCARED	Baseline	6.19 (3.84)	29.40 (13.78)	38.72 (16.56)	t(26) = −1.51, p = 0.14
	Follow-up	7.31 (6.29)	20.90 (19.10)	33.78 (17.11)	t(26) = −1.83, p = 0.08

The PTSD remitter and nonremitter groups did not differ significantly in sex, baseline age/Tanner/IQ, index trauma type, age at index trauma, number of trauma types, PTSD symptoms (PTSD-RI), or anxiety symptoms (SCARED). PTSD nonremitters had significantly higher childhood maltreatment load (CTQ) and depression symptom severity (MFQ) than PTSD remitter at baseline. The CAPS-CA score was not obtained for five PTSD youth. Numbers in parentheses represent standard deviation. Bolded group comparisons represent significant differences between PTSD groups (p < 0.05).
Abbreviations: PTSD, Posttraumatic Stress Disorder; CTQ, Childhood Trauma Questionnaire; SLES, Stressful Life Events Screening; CAPS-CA, Clinician-Administered Child-Adolescent PTSD Scale; PTSD-RI, PTSD-Reaction Index; MFQ, Mood and Feelings Questionnaire; SCARED, Screen for Child Anxiety-Related Mood Disorders; ADHD, Attention-Deficit Hyperactivity Disorder.

exhibited a significant relationship with symptom severity across the entire sample or within the PTSD groups.

3.4. Longitudinal markers of PTSD remission

A summary of longitudinal markers of PTSD remission can be found in Fig. 2. PTSD remission by follow-up was associated with differential longitudinal increases in cortical surface area in the left frontal pole (Destrieux ROI 5; F(2,50) = 7.85, p_{FDR} = 0.017) as well as cortical thickness of the right vmPFC (Destrieux ROI 70; F(2,50) = 5.30, p_{FDR} = 0.05). In each of these regions, PTSD remitters exhibit significant increases in CSA or CT between baseline and one-year follow-up (Frontal pole CSA, t(50) = 3.57, p < 0.001; vmPFC CT, t(52) = 3.07, p = 0.003). We did not detect group by time effects of remitted PTSD in subcortical GMV. Finally, longitudinal increases in vmPFC CT with time were associated with decreased anxiety symptom severity across both clinical groups and time points (SCARED; Fig. 2; F(1,34) = 10.47, p_{FDR} = 0.039).

3.5. Post-hoc analyses

Individual regression analyses were run to test whether or not the following variables were significant predictors of surface morphology in all regions exhibiting a significant group main effect or group by time interaction: pubertal stage (Tanner stage), age at index trauma, stressful life events (SLES), childhood maltreatment load (CTQ), previous use of psychotropic medication, or history of therapy. In all regions, the group main effect or group by time interaction remained significant following adjustment for all of the above variables (Left PCC CSA: F(2,50) = 6.39, p = 0.003; left frontal pole CSA: F(2,46) = 6.47, p = 0.003; right vmPFC CT: F(2,46) = 9.52, p < 0.001; left vlPFC CSA: F(2,46) = 6.29, p = 0.004; left supramarginal gyrus CSA: F(2,44) = 7.06, p = 0.002; left occipital pole CSA: F(2,45) = 10.09, p < 0.001; right superior parietal gyrus CSA: F(2,45) = 7.88, p = 0.001; right precentral gyrus CSA: F(2,45) = 6.68, p = 0.003).

4. Discussion

To the best of our knowledge, this study is the first to identify longitudinal changes in cortical architecture unique to persistent pathology versus recovery in pediatric PTSD. To do so, we characterized sustained and longitudinal cortical markers of pPTSD progression through the direct comparison of youth with persistent pPTSD, remitted pPTSD, and TD youth using a whole-brain approach. Remarkably, only

Table 2
Diagnostic and clinical variables within PTSD groups.

		Time Point	PTSD Remitter	PTSD Nonremitter	Group Comparisons
Co-Morbid Diagnoses	1 or more comorbid disorders	Baseline	9	18	χ^2 (1, N = 28) = 0.23, p = 0.63
		Follow-up	5	14	χ^2(1, N = 28) = 2.27, p = 0.13
	Generalized Anxiety Disorder	Baseline	0	6	
		Follow-up	0	7	
	Major Depression Disorder	Baseline	3	15	
		Follow-up	1	8	
	Separation/Social Anxiety Disorder	Baseline	4	10	
		Follow-up	1	7	
	ADHD	Baseline	3	9	
		Follow-up	3	6	
	Other*	Baseline	0	2	
		Follow-up	1	6	
Psychiatric Medication	1 or more medications	Baseline	5	8	χ^2 (1, N = 28) = 0.08, p = 0.78
		Follow-up	5	8	χ^2 (1, N = 28) = 0.08, p = 0.78
	Stimulant	Baseline	3	7	
		Follow-up	2	5	
	SSRI/SNRI	Baseline	1	6	
		Follow-up	3	6	
	Benzodiazepine	Baseline	2	1	
		Follow-up	1	0	
	Atypical Antipsychotic	Baseline	2	1	
		Follow-up	1	1	
	Other$^+$	Baseline	2	1	
		Follow-up	7	6	
Therapy	Any Therapy	Baseline	2	6	χ^2 (1, N = 28) = 0.56, p = 0.45
		Follow-up	6	7	χ^2 (1, N = 28) = 1.15, p = 0.28
	Individual Therapy	Baseline	2	6	
		Follow-up	5	7	
	Group Therapy	Baseline	1	1	
		Follow-up	0	1	
	Inpatient	Baseline	0	0	
		Follow-up	1	2	

The PTSD remitters and nonremitters did not differ on the proportion of participants with comorbid disorders, history of psychiatric medication, or history of therapy at baseline or in the study interim. The outlined boxes indicate overall numbers, while the subsequent rows break each into specific categories.
*Including phobias, panic disorders, past substance use disorder, and oppositional defiant disorder.
$^+$Including anxiolytics, adrenergic agonists, antihypertensives, and antihistamines.
Abbreviations: PTSD, Posttraumatic Stress Disorder; ADHD, Attention-Deficit Hyperactivity Disorder; SSRI, Selective Serotonin-Reuptake Inhibitor; SNRI, Selective Norepinephrine Reuptake.

the PCC CSA showed trait-like, sustained differences in cortical architecture in youth with a lifetime PTSD diagnosis regardless of recovery status. In contrast, we identified a number of cortical brain regions showing differential development as a function of PTSD recovery. Here, PTSD nonremitters showed longitudinal decreases in CSA in the vlPFC, parietal, and occipital lobe. In contrast, remitters showed longitudinal increases in thickness or surface area in the vmPFC and frontal pole. These findings point to an active neural process of recovery from PTSD in canonical prefrontal regions implicated in cognitive-emotional control, and which deviate from the typical neurodevelopmental trajectory in this age range. Furthermore, these findings suggest that the persistence of pPTSD over time is not a static process but rather is characterized by active cortical contraction in numerous regions of the brain. In the following discussion, we expand further on the potential functional role of differential neurodevelopment in the progression of pediatric PTSD.

Youth who remitted from PTSD over the course of the study showed longitudinal increases in thickness and surface area in the frontal pole and vmPFC, respectively. Notably, prior VBM analyses, including our own, point to reduced vmPFC and frontal pole GMV in pediatric PTSD (Heyn et al., 2019; Keding and Herringa, 2015; Morey et al., 2016) [though see (Carrion et al., 2009)]. These regions are notable for their roles in stimulus valuation, attentional control, and emotion regulation including the extinction of threat memories (reviewed in Hiser and

Table 3
Sustained and longitudinal differences in cortical architecture.

Effect	Cortical Measure	Region	Laterality	Destrieux ROI	F	p_{FDR}
Main Effect of Group						
TD > Nonremitter + Remitter	Surface Area	PCC	L	71	5.87	0.048
Group x Time Interactions						
Remitter > Nonremitter + TD	Surface Area	Frontal Pole	L	5	7.853	0.017
	Thickness	vmPFC	R	70	5.301	0.050
Remitter + TD > Nonremitter	Surface Area	vlPFC	L	24	7.542	0.019
	Surface Area	Supramarginal	L	26	5.566	0.045
	Surface Area	Occipital Pole	L	42	8.894	0.010
	Surface Area	Superior Parietal	R	27	7.158	0.023
	Surface Area	Precentral Gyrus	R	29	6.429	0.035

Regions shown survived whole-brain FDR correction (correct $p < 0.05$). All analyses included age at baseline, sex, IQ, and subject as a random effect as covariates.
Abbreviations: TD, typically developing; PCC, posterior cingulate gyrus; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex.

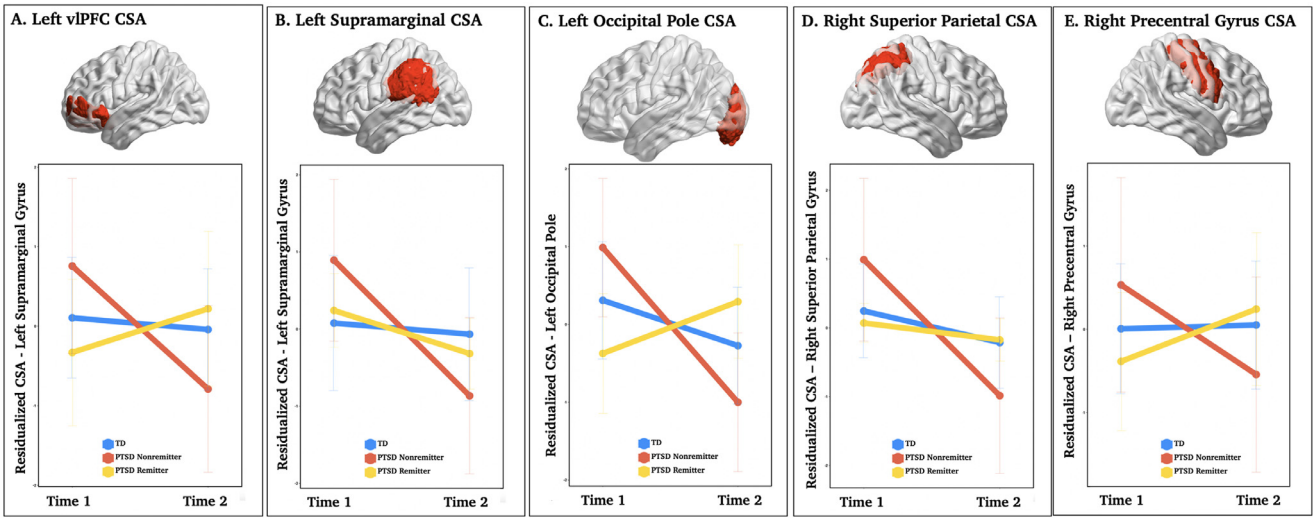

Fig. 1. Longitudinal decreases in cortical surface area associated with sustained PTSD psychopathology. Longitudinal decreases in cortical surface area were observed in (A) left vlPFC ($p = 0.019$), (B) left supramarginal gyrus ($p = 0.045$), (C) right occipital pole ($p = 0.010$), (D) right superior parietal gyrus ($p = 0.023$), and (E) right superior precentral gyrus ($p = 0.035$). In each case, youth with PTSD at both baseline and follow-up showed decreasing surface area with time as compared to those went into remission and typically developing youth. All models included baseline age, sex, IQ, and subject as a random effect, and all group by time effects survived whole-brain FDR correction ($p_{FDR} < 0.05$). Abbreviations: CSA, cortical surface area; vlPFC, ventrolateral PFC; PTSD, posttraumatic stress disorder.

Koenigs, 2018 and Tsujimoto et al., 2011). The frontal pole, also known as the anterior PFC, is largely confined to Brodmann Area 10 and represents an anatomically and functionally distinct cortical substrate with unique cytoarchitecture (Ramnani and Owen, 2004). In humans, the frontal pole encompasses is significantly larger proportion of the cortex than in other mammals (Semendeferi et al., 2001). In fact, some have argued that the human frontal pole should be divided into three separate divisions, one representing the canonical frontal pole (region 10p) while the other two occupy the regions of the vmPFC (Öngür et al., 2003). The frontal pole is a thick and highly granular cortex (Öngür et al., 2003), and has projections to the anterior hypothalamus and periaqueductal gray (An et al., 1998). Together these findings suggest the frontal pole to be intimately involved in a "viscero-motor" or "emoto-motor" system, thought to regulate autonomic activity in the presence of emotionally salient stimuli (Öngür and Price, 2000; Öngür et al., 2003). In line with this hypothesis, a recent study in adult PTSD showed that prolonged exposure therapy increased activation in frontopolar cortex in an emotion regulation task, as well as connectivity between the frontopolar cortex and the vmPFC (Fonzo et al., 2017), suggesting that this network may also play an active role in pediatric PTSD recovery via effective affective regulation.

Additionally, a recent cortical structural network analysis in pediatric PTSD found that maltreated youth resilient to PTSD showed increased centrality in the frontal pole (Sun et al., 2018). Given that PTSD remitters showed longitudinal increases in frontopolar surface area and vmPFC thickness, while nonremitters and TD youth did not, we speculate that prefrontal cortical expansion may represent part of an active recovery process in youth with PTSD that differs from normative development via compensatory addition of increased prefrontal resources for emotion regulation and cognitive flexibility, and which may reflect patterns present in youth who are initially resilient to trauma. This hypothesis is further supported by the negative association between vmPFC CT and anxiety symptoms. Such findings are particularly promising given their implicated role in therapy for adult PTSD. Thus, altered neurodevelopment in these prefrontal regions could represent key biomarkers and/or novel treatment targets for youth suffering from PTSD. Future studies characterizing the functional role of these regions in pediatric PTSD recovery processes would be warranted to examine these possibilities.

In contrast to the putative active neural recovery process in

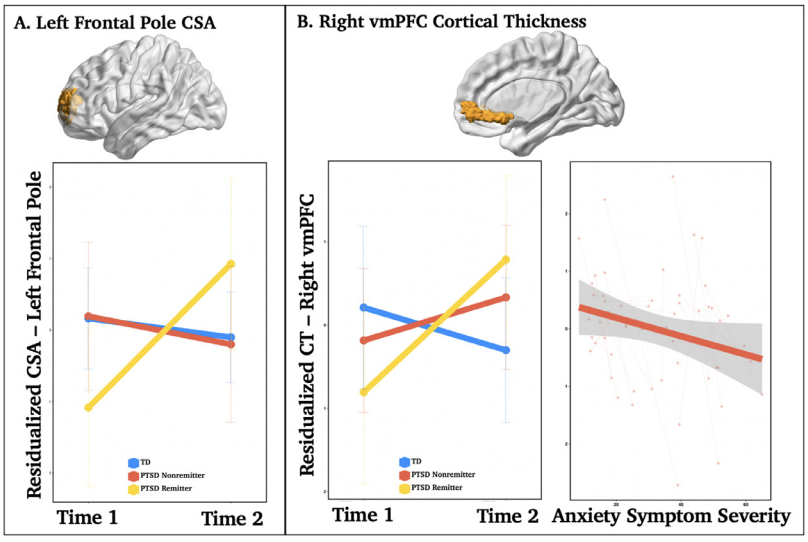

Fig. 2. Longitudinal increases in cortical architecture associated with PTSD remission. Group by time interactions were identified in (A) frontal pole cortical surface area ($p = 0.017$) and (B) right ventromedial prefrontal cortex cortical thickness ($p = 0.050$). In each case, youth with remitted PTSD at follow-up showed longitudinal increases in cortical thickness/surface area as compared to nonremitters and typically developing youth. Post-hoc testing of extracted CSA estimates in the vmPFC across both PTSD remitters and nonremitters revealed a significant negative correlation with anxiety symptom severity, as measured by the SCARED ($p = 0.039$). All models included baseline age, sex, IQ, and subject as a random effect, and all group by time effects survived whole-brain FDR correction ($p_{FDR} < 0.05$). Abbreviations: CSA, cortical surface area; CT, cortical thickness; vmPFC, ventromedial prefrontal cortex; PTSD, posttraumatic stress disorder; SCARED, Screen for Child Anxiety Related Disorders.

remitters, PTSD nonremitters also showed unique patterns of neurodevelopment suggesting an ongoing pathological process. Here, youth with persistent PTSD pathology showed longitudinal decreases in vlPFC, precentral gyrus, supramarginal gyrus, superior parietal gyrus, and occipital pole surface area as compared to both remitted PTSD and TD youth. Many meta-analyses of emotion regulation have implicated the vlPFC as a critical region for these processes (Buhle et al., 2014; Kohn et al., 2014), especially during the regulation of negative emotions (Zilverstand et al., 2017). Furthermore, amygdala modulation by the vlPFC during reappraisal of negative emotion appears to become stronger with age and is moderated by Silvers et al. (2016). Finally, activation of the vlPFC during an emotion regulation task using transcranial direct current stimulation (tDCS) was shown to enhance reappraisal of negative emotions (He et al., 2018). Thus, longitudinal decreases in vlPFC surface area could represent a general decrease or loss of modulatory influence over the negative emotional stimuli encountered by the youth with PTSD which contributes to the active pathological process of PTSD and inability to recover.

Surprisingly, we did not find any developmental effect of PTSD remission on dlPFC cortical architecture, despite our previous longitudinal findings in dlPFC gray matter volume in the PTSD group as a whole (Heyn et al., 2019). In order to explore this previously identified relationship, we independently extracted and evaluated left dlPFC GMV (Destrieux ROI 52). These analyses reproduced the significant two-group by time interaction where TD youth exhibited normative decreases in dlPFC GMV while youth with PTSD did not ($F = 3.85$, $p = 0.05$). However, in the three-group model, the group by time interaction was not significant ($F = 1.76$, $p = 0.18$). Here, both PTSD remitters and non-remitters tended to show less decrease in dlPFC GMV over time as compared to TD youth, with similar patterns between the PTSD groups. Together, these exploratory analyses suggest that attenuated decreases in dlPFC GMV, but not CSA or CT individually, may represent a general developmental cortical marker in youth with a lifetime history of PTSD (Supplemental Fig. 2). However, further study employing behavioral tasks coupled with neuroimaging and/or neuromodulation will be needed to better understand whether attenuated dlPFC GMV decreases represent an adaptive or pathological process.

Finally, our study design allowed us to analyze patterns of risk and protective factors unique to youth that will remit versus youth that will continue to experience PTSD across time. Generally speaking, the PTSD nonremitters in our study did not differ from the remitters demographically or in cortical architecture at the time of study enrollment. At the time of study enrollment, as compared to nonremitters, PTSD remitters had lower levels of PTSD, depression, and anxiety symptoms, and lower levels of maltreatment experiences. Future recovery was not significantly associated with the use psychiatric medication or therapy nor the additional experience of a KSADS trauma in the study interim. Therefore, pPTSD nonremission was unlikely related to treatment usage (lifetime or interim) but instead may reflect illness that is characterized by greater severity, comorbidity, and trauma exposure. An intriguing possibility, also raised by others (Teicher and Samson, 2013), is that maltreatment exposure may induce a unique biotype of resistant PTSD in youth that is instantiated, in this case, by both a lack of prefrontal expansion as well as cortical contraction in additional brain regions.

Although this study is a novel and first investigation into the naturalistic progression of cortical architecture in pPTSD across time, there are important limitations to consider. First, the sample size is modest. Results should thus be considered preliminary and would warrant replication in larger samples in future studies. However, we were still able to detect a number of phenotype-specific developmental abnormalities following stringent multiple comparison correction. Second, our analyses are limited to two time points. Thus, we are not able to infer causality (at least statistically) between cortical surface changes over time and persistence or remission of PTSD in youth. An alternative possibility for the cortical changes identified may be that they represent cortical adaptations to illness that then fade with remission. Future studies will require additional timepoints which would allow for statistical modeling of brain-symptom relationships in a cross-lagged manner. Third, this is a naturalistic study of illness outcome. While we examined a number of additional variables to explain the current findings, we cannot exclude the possibility of other factors associated with PTSD remission that may better account for cortical changes among the three groups. Future studies employing a randomized treatment protocol would help to more specifically model the neurobiological correlates of recovery and treatment effects, and to what extent these processes overlap. Finally, the addition of a trauma-exposed comparison group would enhance our ability to differentiate the effects of development, childhood trauma, and trauma-related psychopathology and provide support for our hypothesized model of disease progression.

Despite these limitations, this study is an important addition to the current neurobiological understanding of illness course in pediatric PTSD. To our knowledge, this is the first study to map neurodevelopmental changes in pediatric PTSD longitudinally through illness persistence and recovery processes. Our previous longitudinal investigation of pediatric PTSD first identified biomarkers of the presence of pediatric PTSD at baseline (Heyn et al., 2019). Here, we found sustained volumetric reductions in the vlPFC, vmPFC, PCC, and precentral gyrus. As an important replication, we identified all of these regions in the current study. However, we were able to detect differential development related to either remission or nonremission. Frontal pole cortical expansion is uniquely related to the active recovery process from pediatric PTSD, perhaps through the compensatory addition of cognitive flexibility and autonomic regulation of affective stimuli. Furthermore, we identified that structural development of the vlPFC may differentiate youth with persistent pathology, reflecting continued loss of prefrontal control over affective regulation. Together, these findings suggest potential new biomarkers which could be used in future studies to predict illness course, and which could reflect novel biological targets for current and novel treatment modalities. mmc.1 mmc.2

Declaration of Competing Interest

The authors of this study declare no conflict of interest.

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