Sex-based variations of prefrontal structure and longitudinal symptoms in pediatric posttraumatic stress disorder

Sara A. Heyn | Sophie Bailowitz | Justin D. Russell | Ryan J. Herringa

Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

Correspondence
Sara A. Heyn, Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI 53719, USA. Email: sheyn@wisc.edu

Funding information
Brain and Behavior Research Foundation; University of Wisconsin-Madison; National Institute of Mental Health; American Academy of Child and Adolescent Psychiatry

Abstract

Background: Pediatric posttraumatic stress disorder (pPTSD) is more than three times as likely to develop in trauma-exposed female youth than males. Despite the staggering sex differences in the prevalence rates of pPTSD and symptom expression, relatively little is known about the underlying biomarkers of these sex-based variations in pPTSD as compared to typically development.

Methods: The Youth PTSD study recruited 97 youth, ages 7 and 18, to undergo comprehensive clinical assessments and T1-weighted MRI to evaluate the extent to which sex can explain PTSD-related variations in brain structure. Whole-brain VBM as well as whole-brain estimates of cortical thickness and surface area were analyzed to identify group-by-sex interactions. Finally, we tested whether current or future symptom severity was predictive of regions exhibiting sex-based variations.

Results: Clinically, females with PTSD were significantly more likely to report exposure to and higher severity of interpersonal violence and symptoms of hyperarousal. Sex and PTSD status were predictive of gray matter across the lateral prefrontal cortex (PFC), including the ventrolateral PFC and frontal pole, where increased volume and surface area was found in PTSD females as compared to PTSD males. Interestingly, the ventrolateral prefrontal cortex and frontal pole were negatively predictive of symptoms 1 year later in only males with PTSD.

Conclusions: Together, these results establish that youth with PTSD exhibit sex-based variations in clinical and trauma characteristics and prefrontal cortical structure relative to normative development. This work demonstrates the importance of examining the role that sex may play in the behavioral and neurobiological presentation of pPTSD.

KEYWORDS
brain imaging/neuroimaging, child/adolescent, PTSD/posttraumatic stress disorder

INTRODUCTION

Recent epidemiological studies estimate that as many as two-thirds of all youth in the United States will experience a traumatic event in their childhood (Finkelhor et al., 2015), leading many to characterize this alarming rate of childhood trauma as a global public health concern (Magruder et al., 2017). While there has been much research identifying the developmental, cognitive, and emotional impact of childhood trauma exposure (Cronholm et al., 2015), one sequela of exposure in vulnerable youth is the development of pediatric posttraumatic stress disorder (pPTSD). pPTSD represents a debilitating mental illness characterized by intrusive re-experiencing of the traumatic event, avoidance of trauma-related stimuli, negative mood and cognition, and alterations in reactivity and arousal (American Psychiatric Association, 2013). Interestingly, of children who have experienced trauma, girls are more than three times more likely to...
develop PTSD than boys, with a 2.3% prevalence rate in boys and 8% in girls, irrespective to trauma type (McLaughlin et al., 2013). While these difference in prevalence rates are striking, to date, the psychobiological underpinnings of sex differences in pediatric PTSD are still understudied. This research may help to characterize more effective and individualized therapeutic targets, improve outcomes in this vulnerable population, and possibly reduce the economic burden of childhood maltreatment in the United States, recently estimated to be upwards of $2 trillion dollars annually (Peterson et al., 2018).

While few studies have investigated the unique and differential impact of sex on PTSD symptom expression in an adolescent population, some empirical data suggests that females present with differential symptom profiles than males (Garza & Jovanovic, 2017). For example, adolescent females report higher internalizing symptoms following childhood maltreatment (Herringa et al., 2013) and increased hyperarousal, depression, anxiety, and dissociative symptoms after violent injury than males (McCoy et al., 2005; Purtle et al., 2016). Sexually dimorphic symptom expression in trauma-exposed youth was further confirmed in recent network analyses of PTSD symptomatology, which found that females exhibit strongly connected symptoms of flashbacks, trauma recollections, avoidance, and detachment as compared to trauma-exposed male adolescents (Cao et al., 2019). While differential symptom profiles and risk for subsequent psychopathology are known to differ in trauma-exposed male and female youth, surprisingly little research has investigated the influence of sex on the neurobiological substrates of pPTSD.

Across the sexes, previous research has identified structural neurodevelopmental aberrations in youth with PTSD using robust, whole-brain approaches. We, and others, have cross-sectionally linked pPTSD with decreased ventromedial prefrontal cortex (vmPFC) gray matter volume (GMV) (Heyn et al., 2019; Keding & Herringa, 2015; Morey et al., 2016) and age-related decreases in hippocampal GMV (Keding & Herringa, 2015). Our preliminary longitudinal investigations further suggest increases in dorsolateral PFC (dLPFC) GMV in youth with a diagnosis of PTSD (Heyn et al., 2019), perhaps suggesting a general compensatory response in the dmPFC, implicated in explicit emotion regulation and reappraisal (Buhr et al., 2014). When we parsed PTSD remitters and nonremitters, we found notable increases in cortical thickness and surface area of the vmPFC and frontal pole predictive of pPTSD remission (Heyn & Herringa, 2019). A recent region-of-interest meta-analysis further confirmed unique structural abnormalities in pediatric PTSD, specifically in subcortical structures such as the hippocampus (Kribakaran et al., 2020). In light of increasing evidence that pubertal gonadal hormones, such as estrogen and testosterone, influence structural neurodevelopment in both male and female youth (Herting et al., 2012), we aimed to examine sexual dimorphisms in brain structure underlying pPTSD.

Throughout this paper, we will use and investigate “sex” rather than “gender” in a cohort of adolescent youth. Gender identity is an important and meaningful self-identification and representation, while sex conversely refers to underlying distribution of biological attributes that distinguish male, female, intersex, and hermaphrodite organisms (Tannenbaum et al., 2019). The analysis of sex-related variance in neuroscience research has been identified by the National Institutes of Health and others as a critical step to increasing reproducibility and generalizability of findings and enhancing the likelihood of identifying robust and meaningful effects that may have previously been masked in analyses which aggregated across sexes (NOT-OD-15-102, 2020; Tannenbaum et al., 2019). There is evidence to suggest that brain organization and structure, including GMV, may be differentially affected by the surge of pubertal hormones during adolescence based on sex (Kaczurkin et al., 2019; Vijayakumar et al., 2018), however the extent to which this process is related to childhood trauma and pPTSD is still unknown.

To our knowledge, this study is the first comprehensive assessment of the extent to which sex may explain variation in structural neurobiological biomarkers within a well-phenotyped cohort of youth with PTSD and typically developing (TD) youth. Here, we quantitatively examine clinical symptom presentation and trauma characteristics, as well as GMV, cortical thickness, and cortical surface area using a whole-brain approach. We hypothesize that many previously identified biomarkers of pPTSD, especially regions within the prefrontal cortex, may be driven by differentially by sex. While this study is unable to characterize the mechanisms underlying sex-based variations in brain structure, this initial evidence that sex may be differentially predictive of symptoms and brain structure in youth with PTSD may lead to individualized therapeutic interventions, such as targeted repetitive transcranial magnetic stimulation, which has recently shown promise in reducing fear responses (Balderton et al., 2020). For these vulnerable youth, who are more likely to experience comorbid disorders (Cohen & Scheeringa, 2009) and carry the highest risk of all mental illnesses for the first suicide attempt in adolescence (Michèle et al., 2018), improving clinical outcomes is essential.

2 | METHODS

2.1 | Participant recruitment

This cohort consisted of 97 youth (TD, n = 52; PTSD, n = 45) ages 7–17 recruited for the Youth PTSD Study baseline sample. Youth with PTSD (Male, n = 17; Female, n = 28) were recruited from local mental health facilities while age- and sex-matched TD youth (Male, n = 21; Female, n = 31) were recruited from the community using social media, flyers, Craigslist, emails, and so on. Exclusion criteria for youth study enrollment included: IQ < 70, acute suicidality, history of psychotic, bipolar, or obsessive-compulsive disorder, current or past substance abuse or dependence, unstable medical condition, MRI contraindication, pregnancy in females, or psychotropic medication use in the past 4 weeks (6 weeks for fluoxetine). No youth were taken off of psychotropic medication to enroll in 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
2.2 | Trauma and clinical assessment

All youth participants underwent a comprehensive trauma and clinical battery. First, all TD and PTSD youth were assessed for IQ using the Wechsler Abbreviated Scale of Intelligence-II (Wechsler, 2011), pubertal stage using the Tanner Sexual Maturation Scale (Marshall & Tanner, 1969), lifetime stressful life events load (SLES) (Williamson et al., 2003), childhood abuse severity using the Childhood Trauma Questionnaire abuse subscore (CTQ) (Bernstein et al., 1994), anxiety symptom severity using the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1997), and depression symptom severity using the Mood and Feelings Questionnaire (MFQ) (Costello & Angold, 1998). Parents/caregivers were also assessed for highest level of education achieved as a proxy of socioeconomic status.

Next, to assess for current and past psychopathology, youth participants and their parents/caregivers completed the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (Kaufman et al., 1997). PTSD diagnoses were made in combination with the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) (Weathers et al., 2001), and questionable cases were reviewed and confirmed by a child psychiatrist (RJH). Within the PTSD cohort, we also noted index trauma type, age of first instance of index trauma, total number of KSADS trauma types endorsed, history of psychotropic medication, history of psychotherapy, current or past comorbid disorders, and PTSD symptom severity using the UCLA PTSD Reaction Index (PTSD-RI).

2.3 | Structural MRI acquisition and quality control

T1-weighted structural MRIs were collected from all participants at the University of Wisconsin-Madison Lane Neuroimaging Center using a 3.0 T GE Discovery MR750 Scanner (General Electric, Milwaukee, WI) and an 8-channel head coil. Images were acquired using the following parameters: TE = 3.18 ms, TR = 8.16 ms, TI = 450 ms; flip angle = 12°. FOV = 256 cm, slice thickness = 1.0 mm, 156 slices, image acquisition matrix = 256 x 256, isotropic voxel size = 1 x 1 x 1 mm³.

2.4 | Voxel-based morphometry

First, we investigated group by sex differences in GMV using voxel-based morphometry (VBM). Cross-sectional processing of T1-weighted images was done using default parameters in the CAT12 toolbox (Structural Brain Mapping group, Jena University Hospital), implemented in SPM12 (Wellcome Department of Imaging Neuroscience) in MATLAB 8.3 (The MathWorks, Inc.). Briefly, images were first corrected for bias-field homogeneities, segmented into gray matter (GM), white matter, and cerebrospinal fluid, spatially normalized using the DARTEL algorithm, and smoothed using an 8 mm full-width half-maximum (FWHM) Gaussian kernel. Motion parameters and quality control measures were assessed, including the homogeneity across gray matter covariance structures. This close inspection resulted in 1 TD youth being excluded from MRI group analyses due to the covariance being >2 SD below the mean.

Sex differences in GMV in PTSD and TD youth were estimated using the Analysis of Functional NeuroImages (AFNI) tool 3dtest++. Here, 3dtest++ computes a whole-brain voxel-wise t-test for two groups of input data (males and females), with group, age, IQ, TIV, abuse severity, and index trauma type included in the covariate file. To correct for multiple comparison, whole-brain familywise error correction was performed using Monte Carlo simulation (3dClustSim, -acf option; AFNI). The individual voxel threshold of p < .005 resulted in a whole-brain cluster threshold of 557 voxels. We report results of the default group by sex interaction estimated model parameter that survive the familywise error correction at FWE < .05. Peak coordinates (x, y, z) are reported based on the Montreal Neurological Institute (MNI) atlas in left, posterior, inferior (LPI) orientation.

2.5 | Cortical surface morphometry

Sex differences across TD and PTSD youth in gray matter were then assessed using cortical surface morphometry. Cortical parcellation and extraction was completed using FreeSurfer image analysis suite v6.0 using the default parameters (Fischl & Dale, 2000). Technical details regarding the image pre-processing using default parameters are described elsewhere (Fischl & Dale, 2000; Fischl et al., 2002, 2004). Automated cortical parcellations and region of interest boundaries were performed using the Destrieux Cortical Atlas (Destrieux et al., 2010). This resulted in mean cortical thickness (CT) and cortical surface area (CSA) estimates for 74 regions of interest per hemisphere per subject extracted using the aparcstats2table function.

Whole-brain analyses were conducted in R (version 3.4.3). Group by sex effects were identified using linear modeling on extracted CT and CSA estimates. Due to identified group by sex interactions in child abuse severity and index trauma type within this cohort, as well as our previously identified relationships between IQ and cortical surface morphology (Heyn & Herringa, 2019), the following variables were included as covariates in the whole-brain models: age, IQ, childhood abuse severity (CTQ abuse subscore), and index trauma type. All dependent variables and continuous covariates were scaled before modeling, and models of CSA also included standardized total intracranial volume (TIV) as recommended by FreeSurfer documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/eTIV). Normality of dependent variables was assessed through visual assessment of quantile-quantile plots of model residuals. Model residuals were normally distributed as evidenced by correlation coefficients of each plot (r² > 0.90 for 96% of models, with the lowest value being 0.75). Due to the high number of CT and CSA models run, we applied...
multiple comparison correction using false discovery rate (FDR) at \( p_{\text{FDR}} < 0.05 \). We report only group by sex interactions that survive FDR correction. To communicate and visualize detected group by sex differences according to recent recommendations, all effects are graphed using “cat’s eye pictures” (Maney, 2016), which graph confidence intervals using error bars.

### 2.6 Predicting future symptomatology

To assess whether any significant baseline sex-based variations in brain structure may be predictive of current and longitudinal symptomatology, we ran separate multivariate regressions estimating sex by symptom severity interactions using clinical assessment data collected at the time of scan and approximately 1-year later. To account for initial symptom severity as a potential confound in longitudinal models, symptom severity totals from baseline assessments were included as a covariate in each model respectively. All models additionally covaried for baseline age and TIV in surface area and volumetric models. Anxiety and depression symptom correlates were run within the entire cohort, and PTSD symptom severity was only run within the PTSD group. To control for multiple comparisons, we extracted \( p \)-values from all estimated model parameters and implemented FDR-correction.

### 2.7 Post hoc and confound analyses

Demographic, clinical, and trauma variables were analyzed using two-tailed unpaired \( t \)-tests, \( \chi^2 \) tests, and ANOVA’s, where appropriate. Next, while whole-brain surface and GMV models described in previous sections included IQ, abuse severity, and index trauma type, there may be other characteristics that have a significant impact on brain structure. To examine whether these other possible variables may account for any main findings, we conducted additional regression analyses across the full cohort covarying for the following additional demographic and clinical variables: pubertal stage (as defined as the average Tanner score of youth and caregiver reports), age at index trauma, trauma load (defined as the total number of KSADS trauma types endorsed by the youth), stressful life event load (total youth SLES score), presence of at least one comorbid internalizing disorder, history of psychotropic medication use, and history of psychotherapy.

### 3 Results

#### 3.1 Participant demographics

Participant demographics across the entire cohort are summarized in Table 1. Briefly, male and female TD and PTSD youth did not
significantly differ on most demographics. Specifically, we did not detect any group x sex differences in age ($F_{(1,93)} = 0.36, p = .85$), IQ ($F_{(1,92)} = 0.039, p = .84$), pubertal stage ($F_{(1,93)} = 0.17, p = .68$), or underlying load of stressful life events ($F_{(1,93)} = 0.001, p = .97$). When investigating socioeconomic differences between TD and PTSD groups using the highest level of parental education, we found that youth with PTSD had significantly lower levels of education as compared to parents of TD youth ($X^2(4) = 16.63, p = .002$). Parents of males and females with PTSD did not significantly differ from each other ($X^2(4) = 3.15, p = .54$). All TD and PTSD youth were assessed for baseline depression symptom, anxiety symptom, and childhood abuse severity. We did not identify any group by sex interactions in either symptom domain (depression, MFQ, $F_{(1,92)} = 0.92, p = .34$; anxiety, SCARED, $F_{(1,92) = 0.88, p = .35}$). However, childhood abuse severity differed based upon group and sex ($F_{(1,93)} = 10.23, p = .002$). Females with PTSD report significantly higher childhood abuse than males with PTSD ($t(40) = −3.08, p = .004$), TD females ($t(29) = 5.68, p < .001$), and TD males ($t(33) = 4.85, p < .001$).

### 3.2 Clinical assessment of youth with PTSD

Next, we investigated sex differences in trauma and clinical characteristics of youth with PTSD, which are summarized in Table 2. Here, males and females with PTSD did not significantly differ (all $p$-values >.20) on any the following characteristics: presence of comorbid depression/anxiety/ADHD, history of psychotropic medication for depression/anxiety/ADHD, frequency and intensity of PTSD symptoms (CAPS score), total PTSD symptom severity (PTSD-R1 total score), reexperiencing symptoms (PTSD-R1 criterion B), avoidance symptoms (PTSD-R1 criterion C), number of KSADS trauma types endorsed, or age of index trauma. However, males and females with PTSD differed on type of index trauma ($X^2(3) = 19.72, p < .001$) and hyperarousal symptom severity ($t(26) = 26.21, p = .04$). As compared to males with PTSD, females were more likely to report sexual abuse and experience more severe symptoms of increased arousal.

#### TABLE 2 Trauma and clinical characteristics of male and female youth with PTSD

<table>
<thead>
<tr>
<th></th>
<th>All PTSD</th>
<th>Males with PTSD</th>
<th>Females with PTSD</th>
<th>Sex differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>44</td>
<td>17</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>CAPS-CA</td>
<td>63.64 ($±23.51$)</td>
<td>63.42 ($±17.13$)</td>
<td>71.19 ($±18.71$)</td>
<td>$−1.29$</td>
</tr>
<tr>
<td>PTSD-R1</td>
<td>47.04 ($±15.97$)</td>
<td>45.94 ($±16.41$)</td>
<td>51.21 ($±12.08$)</td>
<td>$−1.15$</td>
</tr>
<tr>
<td>Age of index trauma</td>
<td>8.11 ($±4.48$)</td>
<td>8.53 ($±4.29$)</td>
<td>7.90 ($±4.59$)</td>
<td>0.46</td>
</tr>
<tr>
<td>Number of KSADS trauma types</td>
<td>3.19 ($±1.92$)</td>
<td>2.76 ($±1.64$)</td>
<td>3.36 ($±2.08$)</td>
<td>$−1.82$</td>
</tr>
<tr>
<td>History of Psychotropic Medication $(n)$</td>
<td>18</td>
<td>6</td>
<td>12</td>
<td>0.035</td>
</tr>
<tr>
<td>History of Psychotherapy $(n)$</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Index trauma $(n)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>18</td>
<td>2</td>
<td>16</td>
<td>19.72</td>
</tr>
<tr>
<td>Traumatic accident</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Traumatic news</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Witness violent crime</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Comorbid disorders $(n)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>32</td>
<td>11</td>
<td>21</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>21</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Any disorder</td>
<td>41</td>
<td>15</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

Note: Sex-based variations were identified in the type of index trauma, where females with PTSD reported significantly higher rates of sexual abuse than males with PTSD. Across all columns, parentheticals represent standard deviation.

Abbreviations: CAPS-CA, Clinician-Administered Child-Adolescent PTSD Scale; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; PTSD, posttraumatic stress disorder; PTSD-R1, PTSD-Reaction Index.
3.4 | Cortical surface morphometry

Whole-brain cortical surface morphometry analyses are displayed in Figure 1a,b. We detected a significant group by sex interaction in the right frontomarginal gyrus of the frontal pole surface area (2), and the right ventrolateral prefrontal cortex surface area (3). Across all three effects, males with PTSD show significantly decreased structure as compared to females with PTSD. Orbital gyrus GMV was residualized for age and intracranial volume and graphically presented using a violin plot as a function of group and sex, where males with PTSD also show significantly decreased GMV as compared to TD males. (b) A group by sex interaction in the opposite pattern was detected in the right insula, which was driven by males with PTSD showing increased cortical thickness as compared to female youth with PTSD. Insula thickness was residualized for age and graphically presented using a violin plot as a function of group and sex. PTSD youth are depicted in red (right), while TD youth are depicted in blue (blue). *p < .05; + p < .10

3.5 | Predicting future symptomatology

Finally, we investigated whether baseline brain structure was further related to sex-based variations in baseline and longitudinal symptom severity. First, there were no significant sex by symptom interactions in models using baseline clinical symptoms (pFDR > 0.05). When predicting future symptom severity across all domains, we detected sex by symptom interactions in both GMV and CSA in the significant two frontal pole regions following FDR-correction (Figure 2). Specifically, significant sex by symptom interactions were identified in the orbital gyrus GMV (F(1,22) = 7.93, pFDR = 0.04, Figure 2a) and frontomarginal sulcus of the frontal pole CSA (F(1,49) = 7.16, pFDR = 0.04, Figure 2b) with PTSD and depression symptom severity 1 year later, respectively. Upon breaking down each interaction, we see that, for females across all four effects, baseline prefrontal structure is positively predictive of symptoms approximately 1 year later (Orbital GMV, t(13) = 2.18, p = .04), and males showed the opposite effect (Frontomarginal CSA, t(14) = −2.58, p = .02). Formal outlier analyses using the Grubbs test did not detect significant outliers in baseline orbital gyrus GMV (high, G = 2.40, p = .42; low, G = 2.06, p = .10), baseline frontomarginal gyrus CSA (high, G = 1.94, p = .10; low, G = 1.57, p = 1.0), longitudinal PTSD symptoms (high, G = 1.69, p = 1.0; low, G = 1.91, p = .79), or longitudinal depression symptoms high, G = 3.01, p = .06; low, G = 0.87, p = 1.0), altogether confirming that significant effects are not driven by outliers.

FIGURE 1  Sex-based variations in brain structure among youth with posttraumatic stress disorder (PTSD). (a) Group by sex interactions (pFDR < 0.05) were detected in the right frontal pole gray matter volume (GMV) (1), right frontomarginal gyrus of the frontal pole surface area (2), and the right ventrolateral prefrontal cortex surface area (3). Across all three effects, males with PTSD show significantly decreased structure as compared to females with PTSD. Orbital gyrus GMV was residualized for age and intracranial volume and graphically presented using a violin plot as a function of group and sex, where males with PTSD also show significantly decreased GMV as compared to TD males. (b) A group by sex interaction in the opposite pattern was detected in the right insula, which was driven by males with PTSD showing increased cortical thickness as compared to female youth with PTSD. Insula thickness was residualized for age and graphically presented using a violin plot as a function of group and sex. PTSD youth are depicted in red (right), while TD youth are depicted in blue (blue). *p < .05; + p < .10
3.6 | Post hoc and confound analyses

All detected group by sex interactions identified in cortical surface and VBM analyses remained significant after adjusting for the following potential confounds: pubertal stage, age at index trauma, trauma load, stressful life event load, presence of at least one comorbid internalizing disorder, history of psychotropic medication use, and history of psychotherapy (Frontal pole CSA, $F_{(1,76)} = 9.85$, $p = .002$; vlPFC CSA, $F_{(1,76)} = 9.46$, $p = .003$; Insula CT, $F_{(1,78)} = 4.15$, $p = .045$; Orbital gyrus GMV, $F_{(1,73)} = 7.82$, $p = .007$). Interestingly, within the insula, we also detected a significant main effect of pubertal stage, where pubertal stage was positively predictive of thickness ($F_{(1,78)} = 7.82$, $p_{FDR} = 0.007$).

4 | DISCUSSION

Despite the known differences in pPTSD prevalence in males versus females, this study represents one of the first multi-modal investigations of sex-based variations in trauma exposure, clinical symptom presentations, and neurobiology in youth with PTSD and typically developing comparison youth. Differential biomarkers of pPTSD manifestation in males and females were identified within a carefully-phenotyped sample of trauma-exposed youth using whole-brain voxel-based and surface morphometry analyses. Results highlight increased rates of exposure to sexual abuse, heightened states of arousal, elevated volume and surface area of the prefrontal cortex, and decreased insular cortical thickness in females with PTSD. While our understanding of the complex underlying neurobiology of pPTSD continues to incrementally increase, this study emphasizes the critical importance of considering sex-based influences in future investigations to translate basic neuroscientific findings to efficacious and individualized treatment modalities.

When directly measuring variations in clinical and trauma characteristics in pPTSD, females with PTSD were more likely to report sexual abuse. These findings are consistent with recent studies showing that adolescent females are 2.9 times more likely to experience sexual abuse (Gewirtz-Meydan & Finkelhor, 2020) and develop PTSD at significantly higher rates (Alisic et al., 2014) as compared to their male counterparts. Further, when looking specifically within youth exposed to interpersonal violence, approximately 17% of boys developed PTSD while 33% of girls went on to develop PTSD (Alisic et al., 2014), echoing our findings of increased rates of sexual abuse in females with pPTSD. In addition, we and others have detected more severe symptoms of hyperarousal and hypervigilance in females with pPTSD as compared to males (Cao et al., 2019).
Sex-based variations in underlying brain structures were detected in various prefrontal regions, including the ventrolateral PFC (vlPFC), frontal pole, and orbital gyri. Across the literature, the vlPFC has been consistently associated with cognitive reappraisal, emotion inhibition, and regulation (Buhr et al., 2014; He et al., 2018; Kohn et al., 2014), while the frontal pole has been linked to complex logical reasoning and regulating emotionally salient autonomic activity (Öngür & Price, 2000; Tsujimoto et al., 2011). We have previously linked structural development of the vlPFC and frontal pole with persistent PTSD pathology and remission over time, respectively (Heyn & Herringa, 2019; Heyn et al., 2019). Across these studies, we have seen that current or persistent pPTSD psychopathology is associated with decreased GMV or surface area, both cross-sectionally and longitudinally. Further, PTSD psychotherapy in adults has been associated with increased activation of the frontal pole (Fonzo et al., 2017). Altogether, these findings may suggest that PTSD psychopathology in male youth may be causally linked to symptom expression and future remission in these prefrontal regions.

However, what these previous findings cannot adequately interpret is the lack of prefrontal structural reductions in female youth with pPTSD as compared to males, particularly when considering the significantly increased hyperarousal symptoms in females and lack of sex by symptom severity interactions in current symptoms. This may be due to the fact that the vast majority of this previous work has either controlled for sex or recruited entire same-sex populations. Recent meta-analyses of adult PTSD have postulated gender and sex may differentially affect PTSD psychopathology through hormonal influences and genetic predisposition (Christiansen & Berke, 2020). In addition, a recent adult rodent study identified sex-specific behavioral responses and medial PFC activity following prolonged traumatic stress exposure (Pooley et al., 2018), suggesting that these distinct sex-based responses are further reflected in neurobiology. Our results are in line with an earlier study of maltreated youth suggesting that males with PTSD show significantly more impacts on neurodevelopment than females with PTSD, where males showed decreased PFC volume (De Bellis & Keshavan, 2003). One possible explanation may be that specific gonadal hormones, which are known to play a role in sex-related differences in brain development (Bath, 2020), released in females during puberty provide a protective factor against atypical structural reductions in the PFC. Rat models have confirmed temporal-specific changes to PFC structure via pubertal hormones (Willing & Juraska, 2015), for example, estradiol has previously been linked to delays in rates of synaptic pruning (Naftolin et al., 1990). In humans, preliminary research has linked estradiol levels to amygdala volume in adolescent females (Herling et al., 2014) and a recent review has already suggested that changes in estrogen during puberty may influence phenotypes of PTSD (Garza & Jovanovic, 2017). As our sample consisted of youth that have either begun or finished puberty by the time of assessment, this could be one potential explanation. However, the precise mechanism or direction of this interactive effect remains unknown. Further research on the interaction between pubertal hormones, trauma exposure and PTSD, and sex is crucial to disentangling this effect.

Conversely, an opposite pattern within the right insular cortex was observed, where females with PTSD exhibited decreased cortical thickness as compared to males with PTSD. Structural reductions in the insula is a common finding within pediatric and adult PTSD (Bromis et al., 2018; Herrringa et al., 2012; Kühn & Gallinat, 2013). Our findings closely resemble previously identified sex-based variations in insula structure in boys and girls exhibiting symptoms of PTSD (Klabunde et al., 2017). Specifically, Klabunde and colleagues found that boys with PTSD symptoms show larger GMV and CSA in the anterior circular sulcus of the insula when compared to TD males, while females with PTSD show decreased GMV and CSA as compared to TD females in the same insular region. Normative structural neurodevelopment is marked by global decreases in GMV over time (Wierenga et al., 2014), and females exposed to high levels of traumatic stress during childhood experience earlier puberty and accelerated cortical maturation (Boynron-Jarrett & Harville, 2012; Klabunde et al., 2017), which is additionally supported by the results of this study. Interestingly, we found that neither baseline nor longitudinal symptom severity were predictive of baseline insula CT, unlike all regions in the PFC. A recent study of pPTSD psychotherapy response found a similar pattern of insula structure and symptom changes over time, where all included youth with PTSD exhibited decreased insula GMV over time, but when investigating responders (≥50% reduction in symptoms) versus non-responders, there were no significant differences pre- or posttreatment (Zantvoord et al., 2020). Altogether, this suggests that while the insula may be a crucial node in the experience of pPTSD, it may not be an informative marker of symptom development over time naturalistically or in relation to psychotherapy.

While the current study represents a novel first step into understanding sex-based variations in clinical and trauma characteristics as well as brain structure in pPTSD, it does not come without limitations. First, this was a cross-sectional study of brain-based variations between males and females with PTSD, which limits our ability to identify changes in neurodevelopmental trajectories. Further, without the inclusion of a trauma-exposed comparison group, we are unable to postulate as to whether these neurobiological differences are related to the experience of PTSD or to the initial exposure to trauma. It may also be that variations in gray matter and cortical surface morphometry identified in the current study could be explained by hormone levels. However, this study was unable to investigate this possibility due to a lack of pubertal hormone measures. Finally, the role of epigenetics in pPTSD was also not examined in this study. Previous studies have linked pPTSD with differential DNA methylation, specifically within genes related to glucocorticoid functions (Ensink et al., 2021), it may be that sex-based variations in DNA methylation may explain sex-based neurodevelopmental variations. While the current study fundamentally cannot probe all of these possible neurobiological mechanisms, future research may benefit from the inclusion or manipulation of these variables.

In summary, the present analyses represent one of the first investigations of behavioral, environmental, and neurobiological
variations in males and females with pPTSD. While this study is unable to parse apart the mechanisms underlying sex-based variations in brain structure in pPTSD, sex is a useful proxy in these initial investigations (Maney, 2016). While the clinical significance of these findings remains unclear, future research which can directly examine these mechanisms, perhaps through the analysis of pubertal stages and hormone levels, is warranted.

ACKNOWLEDGMENTS

We owe our sincerest gratitude to the youth and families who have given their time for this study. We would like to sincerely thank Rachael Meline and Shelby Weaver for their work in the recruitment and data collection for this study. Funding for this study was provided by the National Institute of Mental Health Career Development Award (K08 MH100267, R01 MH117141, R01 MH15910, to RJH), American Academy of Child and Adolescent Psychiatry Junior Investigator Award (to RJH), NARSAD Young Investigator Grant (to RJH), University of Wisconsin Institute for Clinical and Translational Research Translational Pilot Grant Award (NIH/NCATS UL1TR000427, to RJH), University of Wisconsin Institute of Clinical and Translational TL1 Training Award (TL1TR000429, to SAH), and the University of Wisconsin School of Medicine and Public Health. None of these funding sources had a direct effect in the design, analysis, or interpretation of the study results, nor in preparation of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions collection for this study.

REFERENCES


