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Sex-dependent risk factors for PTSD: a prospective structural MRI study

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Female individuals are more likely to be diagnosed with PTSD following trauma exposure than males, potentially due, in part, to underlying neurobiological factors. Several brain regions underlying fear learning and expression have previously been associated with PTSD, with the hippocampus, amygdala, dorsal anterior cingulate cortex (dACC), and rostral ACC (rACC) showing altered volume and function in those with PTSD. However, few studies have examined how sex impacts the predictive value of subcortical volumes and cortical thickness in longitudinal PTSD studies. As part of an emergency department study completed at the Grady Trauma Project in Atlanta, GA, $N = 93$ (40 Female) participants were enrolled within 24 h following a traumatic event. Multi-echo T1-weighted MRI images were collected one-month post-trauma exposure. Bilateral amygdala and hippocampal volumes and rACC and dACC cortical thickness were segmented. To assess the longitudinal course of PTSD, the PTSD Symptom Scale (PSS) was collected 6 months post-trauma. We investigated whether regional volume/thickness interacted with sex to predict later PTSD symptom severity, controlling for PSS score at time of scan, age, race, and trauma type, as well as intracranial volume (ICV) for subcortical volumes. There was a significant interaction between sex and rACC for 6-month PSS, such that right rACC thickness was positively correlated with 6-month PSS scores in females, but not in males. In examining PTSD symptom subtypes and depression symptoms, greater rACC thickness in females predicted greater avoidance symptoms, while smaller rACC thickness in males predicted greater depression symptoms. Amygdala and hippocampus volume and dACC thickness showed no main effect or interaction with sex. The current findings provide evidence for sex-based differences in how brain volume predicts future PTSD severity and symptoms and supports the rACC as being a vital region regarding PTSD. Gender differences should be assessed in future longitudinal PTSD MRI studies for more accurate identification of future PTSD risk following trauma.

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder with known differences in occurrence between male and female individuals. Females are twice as likely as males to develop PTSD after experiencing a traumatic event [1–4], and this sex difference is not explained by differences in the type of trauma experienced nor amount of trauma exposure [2, 5, 6]. It is possible there are biological risk factors that influence the chance of developing PTSD in female individuals following trauma. Thus, it is necessary to identify potential risk factors, including neurobiological and symptom variance in females vs. males who develop PTSD post-trauma.

Neuroimaging studies suggest three main areas involved in threat neurocircuitry play an important role in PTSD - the amygdala, hippocampus, and medial prefrontal or anterior cingulate cortical areas. The amygdala is associated with emotion and fear response in both animal models and humans [7]. The hippocampus is vital for contextual memory and the contextualization of fear response, providing inhibitory signaling to the amygdala [8, 9]. Finally, several prefrontal areas play important roles in fear regulation. One is the rostral anterior cingulate cortex (rACC), which is considered to have overlap with the ventromedial prefrontal cortex (vmPFC) in functional neuroimaging studies. The rACC is important for top-down regulation of the amygdala, and is thought to be involved in emotion regulation [10–14]. A second important prefrontal area is the dorsal anterior cingulate cortex (dACC), which plays a role in conflict monitoring and salience of environmental threat cues [12, 15]. The amygdala, hippocampus, rACC, and dACC play main roles in threat response and/or salience of threat, and show functional dysregulation or changes in volume in those with PTSD.

Previous functional magnetic resonance imaging (fMRI) studies of PTSD have identified associations with amygdala hyperactivity and hippocampal and anterior cingulate/prefrontal cortex hypoactivity [13, 14, 16–18]. Regarding structural MRI data, case-control studies demonstrate an association between PTSD and smaller hippocampal volumes [19, 20]. Longitudinal studies, in which MRI scans were collected early post-trauma and participants were assessed for later PTSD symptoms, suggest correlations between the development of PTSD and reduced hippocampal volume [19, 21–25] and reduced rACC and dACC volume [26, 27]. There are mixed findings regarding amygdala structure, with either no

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correlations being seen longitudinally [26], or associations with reduced amygdala volume in case-control studies [20, 28], or differences being seen between nuclei in a case-control study [29].

However, few studies have examined the influence of sex on the relationship between PTSD and brain volumes, and early predictors of risk in females vs. males remain unknown. Animal studies, which can help inform our hypotheses regarding humans, suggests sex plays a role in the relationship between stress and dendritic spine loss, with stress increasing hippocampal dendritic spine density in males and reducing density in females [30], while having an opposite pattern in the medial prefrontal cortex (decreased in males, increased in females) [31]. Differences are shown to be influenced partially by estradiol, which increases dendritic growth between the mPFC and amygdala in females in response to stress [32, 33]. In humans, cross-sectional and developmental studies inform our current understanding, though their results are equivocal. One study saw smaller amygdala volumes in female participants with PTSD compared to male participants with PTSD [28], but another found early life trauma exposure was associated with decreased PFC, amygdala, and hippocampal gray matter in males but increased amygdala volume in females [34, 35]. Other studies do not find any strong evidence for sex differences in brain structure in those with PTSD [19, 36]. One potential reason for these discrepancies is the influence of trauma type, with females more likely to experience sexual assault and males more likely to experience non-sexual assault, accidents, or combat [1]. Differences in trauma type can influence hippocampal volume findings [37], and therefore sex differences in trauma type exposure may play a role in study results. Overall, there is little understanding regarding how sex differences impact the predictive value of brain volume for prospective PTSD across time points following trauma, with most studies focusing on both male and female participants combined with no differentiation. As there is an active attempt to understand how biological sex differences impact PTSD symptoms, it is important to determine whether differences in brain structure predict PTSD differently in females vs. males, or may predict a distinct symptom presentation in females vs. males.

In the current study, we investigated sex differences in the predictive value of brain structure for longitudinal PTSD symptoms in individuals recruited following a traumatic event in the emergency department (ED). Given previous findings implicating threat-related neurocircuitry in PTSD risk [7, 8, 10–13, 38], and the current literature regarding sex differences in brain structural alterations associated with PTSD longitudinally in adults [28, 34, 35], we hypothesized that reduced hippocampus and amygdala volumes, and rACC and dACC thickness would correlate with higher PTSD symptomology, and that we would see sex differences across these correlations. We predicted decreased dACC, rACC, and hippocampal thickness/volume in male participants, and decreased amygdala volume in female participants, based on limited prior neuroimaging findings [28, 34, 35]. Secondly, we hypothesized that sex-dependent associations might predict differences in risk for specific types of PTSD symptoms (re-experiencing, avoidance, numbing, hyperarousal) and depressive symptoms.

MATERIALS AND METHODS

Participants

Participants were recruited from a larger Emergency Department (ED) study consisting of 504 participants [39–41]. Of the 504 participants, 419 were approached regarding MRI participation. 93 participants were eligible (did not present contraindications including ferrous metal, pregnancy, pacemakers, etc.) and agreed to undergo MRI scans which were used for the current study. All subjects were ED patients at Grady Memorial Hospital in Atlanta, GA, who had experienced a traumatic event within the past 24 h of arrival to the ED. All participants were English-speaking, 18–65 years of age, experienced a criterion-A-trauma as defined by the DSM-IV-TR, and provided contact information for follow-up visits. Exclusion criteria included previous hospitalization for mental health reasons, current suicidal ideation, attempted suicide in the past 3 months, current intoxication, or altered mental status during the ED visit. 53 participants self-identified as male and 40 as female. Trauma types included 54 motor vehicle collisions, 14 pedestrian versus automobile accidents, 5 sexual assaults, 4 motorcycle crashes, 4 bike or bike versus automobile accidents, 4 industrial or home accidents, 3 non-sexual assaults, 3 gunshot wounds, 1 stabbing, and 1 animal attack. Participants provided written informed consent for all parts of the study, and study procedures were approved by the Institutional Review Boards of Emory University and Grady Memorial Hospital.

Emergency department (ED) assessment and follow-up assessments

Demographic information and trauma index information was gathered using the Standardized Trauma Interview (STI), a 41-item clinician-administered interview gathering information on relevant aspects of the trauma at baseline as well as demographic information [42]. Following the ED visit, PTSD symptoms were assessed at 1 month, 3 months, 6 months, and 12 months. PTSD symptom severity in response to the index trauma was measured utilizing the PTSD Symptom Scale (PSS) [43], a 17-item scale measuring PTSD symptom severity according to DSM-IV-TR criteria [44]. For this paper, PSS measures at 1 month (baseline) and 6 months were used, because the 6-month timepoint is critical in the recovery process when individuals who will recover spontaneously begin to clearly diverge in symptom severity from those who will maintain chronic PTSD symptoms at high levels [38, 45–47]. Table 1 displays demographics and mean scores split by sex. PSS subcategories including intrusion, avoidance, numbing, and hyperarousal were differentiated. The Beck Depression Inventory (BDI) was collected across timepoints as a measure of depression severity. The Childhood Trauma Questionnaire (CTQ) and a self-report count of prior traumas were also collected.

Structural brain imaging data acquisition

MRI sessions were completed within three weeks of the 1-month follow-up assessment. This period was targeted to account for potential injury recovery time. Brain imaging data were acquired on three Siemens 3.0-Tesla Magnetom Trio TIM MRI scanners (Siemens, Malvern, PA) using a 12-channel head coil. $N = 12$ participants were scanned on the first scanner, $N = 26$ on the second, and $N = 55$ on the third. Changes in scanner site were necessitated due to an upgrade from Trio to Prisma. For the first two MRI scanners, structural images were acquired using a gradient-echo, T1-weighted pulse sequence (TR = 2300 ms, TE = 2.78 ms; 1.2 mm × 1.3 mm × 1.3 mm voxel size). For the third MRI scanner, structural images were acquired using multi-echo T1-weighted image (176 slices, TR = 2530 ms, TE1 = 1.74 ms, TE2 = 3.6 ms, TE3 = 5.46 ms, TE4 = 7.32 ms, voxel size $1 \times 1 \times 1\ mm^3$). Images were analyzed using an automated multistep segmentation process (Freesurfer version 5.3) [48, 49]. Automated segmentation was used to compute total intracranial volume, bilateral hippocampal volume, and amygdala volume using the included FreeSurfer subcortical atlas [48]. Bilateral dACC and rACC thickness were calculated using the Desikan-Killiany Atlas with FreeSurfer [50]. Total intracranial volume (ICV) was also measured. Segmentation quality checks were performed using the ENIGMA 2 (subcortical volume) and ENIGMA 3 (cortical thickness and surface area) protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols/), designed to standardize quality control procedures and facilitate study replication [51] Table 2 displays mean regional brain volume and thickness split by sex.

We focused on cortical thickness based on an increasing number of studies that use it as a measure of cortical integrity [52–55], in addition to cortical thinning being a common finding in PTSD studies [56–58]. However, surface area for cortical areas was also recorded and included in supplemental analyses.

Statistical analysis overview

Data were analyzed and visualized using R v.4.0.3. The dplyr package [59] was used for data organization and transformation. T-tests were utilized to analyze sex differences in age, PSS scores, change in PSS score between time points (1-month PSS subtracted from 6-month PSS), BDI, CTQ, and number of traumatic events, and Chi-squared tests were performed to

Table 1. Clinical and demographic features of the sample.

	Female $N = 40$	Male $N = 53$	Effect of sex
Age, mean (SD)	34 (12.46)	37 (12.88)	$t(85.53) = 1.17$, $p = 0.25$
Race (%)			$\chi^2(3) = 3.07$, $p = 0.28$
Hispanic	1 (2.50%)	4 (7.40%)	
Non-Hispanic White	4 (10.00%)	10 (18.52%)	
Non-Hispanic Black	34 (85.00%)	37 (68.52%)	
Non-Hispanic Other	1 (2.50%)	2 (3.70%)	
Education level (%)			$\chi^2(6) = 5.24$, $p = 0.51$
Doctoral degree	0 (0.00%)	1 (1.89%)	
Master's degree	1 (2.50%)	2 (3.77%)	
Some graduate school	0 (0.00%)	1 (1.89%)	
Bachelor's degree	2 (5.00%)	8 (15.09%)	
Associate's/some college	22 (55.00%)	21 (39.62%)	
High school degree	10 (25.00%)	15 (28.30%)	
Some high school	5 (12.50%)	5 (9.43%)	
Trauma type (%)			$\chi^2(9) = 20.73$, $p = 0.01$*
Non-sexual assault	0 (0.00%)	3 (5.66%)	
Motor vehicle collision	27 (67.50%)	27 (50.94%)	
Motorcycle crash (MCC)	0 (0.00%)	4 (7.55%)	
Ped v. auto	5 (12.50%)	9 (16.98%)	
Gunshot wound	0 (0.00%)	3 (5.66%)	
Stabbing	1 (2.50%)	0 (0.00%)	
Industrial/home accident	0 (0.00%)	4 (7.54%)	
Animal bite/attack	0 (0.00%)	1 (1.89%)	
Bike accident/bike v. auto	2 (5.00%)	2 (3.77%)	
Sexual assault	5 (12.50%)	0 (0.00%)	
1-month PSS, mean (SD)	19.32 (11.09)	13.98 (11.31)	$t(84.98) = 2.28$, $p = 0.03$*
6-month PSS, mean (SD)	11.79 (9.29)	8.30 (9.36)	$t(60.00) = 1.13$, $p = 0.26$
Change in PSS score, mean (SD)	−8.69 (9.42)	−5.5 (6.56)	$t(45.14) = 1.59$, $p = 0.12$
1-month beck depression inventory (BDI), mean (SD)	16.19 (10.89)	12.57 (10.05)	$t(73.89) = 1.59$, $p = 0.12$
6-month beck depression inventory (BDI), mean (SD)	14.22 (11.41)	7.82 (7.95)	$t(41.57) = 2.56$, $p = 0.01$*
Childhood trauma questionnaire (CTQ), mean (SD)	42.91 (18.00)	36.34 (15.94)	$t(63.54) = 1.68$, $p = 0.10$
Number of prior traumatic events, mean (SD)	2.29 (1.75)	2.92 (2.01)	$t(83.14) = 1.55$, $p = 0.12$

PTSD Symptom Scale (PSS) Range: 0–40, Childhood Trauma Questionnaire (CTQ) Range: 5–125. Beck Depression Inventory (BDI) Range: 0–63.
*$p < 0.05$.

determine if race, level of education, and trauma type were significantly different between male and female participants (Table 1). Z-scores were calculated and values were winsorized if they fell outside 3 standard deviations from the mean to control for outliers. To test the hypothesis that threat neurocircuitry may show differential associations with PTSD symptoms in depending on sex, regression models were implemented with sex, region of interest (ROI), and sex*ROI effects on PTSD symptoms. Symptoms concurrent with the MRI scan (at 1-month post-trauma) and future symptoms at 6-months post-trauma were investigated in a separate regression analysis. Significant sex*ROI interaction effects were then split by sex and analyzed for correlations between ROI volume /thickness and PSS total. Spearman's rho correlations were used when data had a non-normal distribution, according to the Shapiro-Wilks test, but otherwise Pearson correlations were utilized. Variables with non-normal distributions included left dorsal ACC, right amygdala, right rostral ACC, 1-month PSS scores, 6 month PSS scores, and 6 month BDI. Correlation matrices were created using the Hmisc package [60]. The statistical threshold correcting for multiple comparisons was set at $p < 0.00625$ (bonferroni-corrected $p < 0.05$), across models for the 8 ROIs.

Statistical models of subcortical volumes included ICV as a covariate to account for significant correlations between ICV and hippocampal and amygdala volumes ($p < 0.001$). There was no significant correlation between ICV and cortical thickness ($p > 0.05$), and it was not included for cortical thickness models. Participant age, race, and education level did not differ by sex ($p > 0.05$; Table 1), but we included age and self-reported racial identity as covariates because of their established associations with PTSD risk [61–63]. Trauma type did significantly differ by sex ($p = 0.004$). Covariates therefore included total ICV (for subcortical volumes), scanner site, trauma type, age and race. An additional regression including 1-month PSS as a covariate was conducted to account for PSS at time of scan. Exploratory analyses of regions outside this set of ROIs were conducted using the same statistical models with Bonferroni correction. To further examine the significant relationships between brain volume and PTSD symptom severity, PSS avoidance, numbing, hyperarousal, and intrusive subscales based on the DSM-IV were analyzed in regression models to examine the influence of specific PTSD symptoms. Avoidance and numbing scores were separated according to a prior confirmatory factor analysis [64]. BDI was analyzed to examine the relationship between depression symptoms and brain volume. Additionally, two separate models including CTQ and number of prior traumas were performed to analyze the influence of prior trauma on results. The ggplot2 package [65] was used to visualize data.

RESULTS

Demographic and trauma-related characteristics of the final sample are reported in Table 1. Female participants had significantly higher PTSD symptom severity than male participants 1 month post-trauma (t(85) = 2.28, $p = 0.03$). There was no significant difference in PSS scores between females and males at 6 months (t(60) = 1.13, $p = 0.26$). There was no significant sex difference in change in PSS scores between timepoints (t(45) = 1.59, $p = 0.12$).

Table 2. Regional brain volume and thickness by sex.

Regional volume/ thickness (μL for hippocampus and amygdala, mm for dACC and rACC	Female *M(SD)*	Male *M(SD)*
Total intracranial volume	1,308,609.00 (140,029.10)	1,557,524.00 (173,987.30)
Right amygdala	1,496.76 (206.76)	1,665.86 (246.55)
Left amygdala	1,463.81 (196.16)	1,668.59 (219.88)
Right hippocampus	3,791.43 (404.58)	4,163.26 (581.15)
Left hippocampus	3,742.74 (405.42)	4,069.49 (482.03)
Right dACC	2.55 (0.29)	2.45 (0.22)
Left dACC	2.71 (0.34)	2.57 (0.26)
Right rACC	2.79 (0.24)	2.69 (0.23)
Left rACC	2.91 (0.26)	2.76 (0.22)

dACC dorsal anterior cingulate cortex, *rACC* rostral anterior cingulate cortex.

There was a significant sex interaction effect with right rACC thickness in predicting 6-month PTSD symptom severity (Fig. 1, Supplementary Table S1; ß = 33.96, $\Delta R^2 = 0.16$, $t = 3.41$, $p = 0.001$; Model: F(7,67) = 2.61, $p = 0.01$). This interaction effect persisted when 1-month PSS was included in the model (Supplementary Table S2, ß = 18.98, $\Delta R^2 = 0.05$, $t = 2.59$, $p = 0.01$; Model: F(8,66) = 12.88, $p < 0.001$). Follow-up analyses showed a significant positive correlation between right rACC and 6-month PTSD symptoms in female participants (r(27) = 0.42, $p = 0.02$), but not male participants (r(44) = −0.22, $p = 0.15$). There was no main effect or interaction for the left or right amygdala, hippocampus, or dACC. Furthermore, exploratory analyses of regions outside our ROIs showed no significant interactions with sex at a corrected significance threshold, for either regional thickness (Supplementary Table S3), or surface area (Supplementary Table S4). These findings suggest that greater early post-trauma rACC thickness is related to PTSD risk in female participants only.

To evaluate whether this sex-dependent effect may be driven by specific PTSD symptom subcategories or depression symptoms, we conducted regression models investigating the sex*right rACC effect on 6-month intrusive symptoms, avoidance, symptoms, numbing symptoms, hyperarousal symptoms, and depression symptoms from the BDI (Fig. 1C, D). Regression models showed that right rACC thickness interacted with sex to predict 6-month

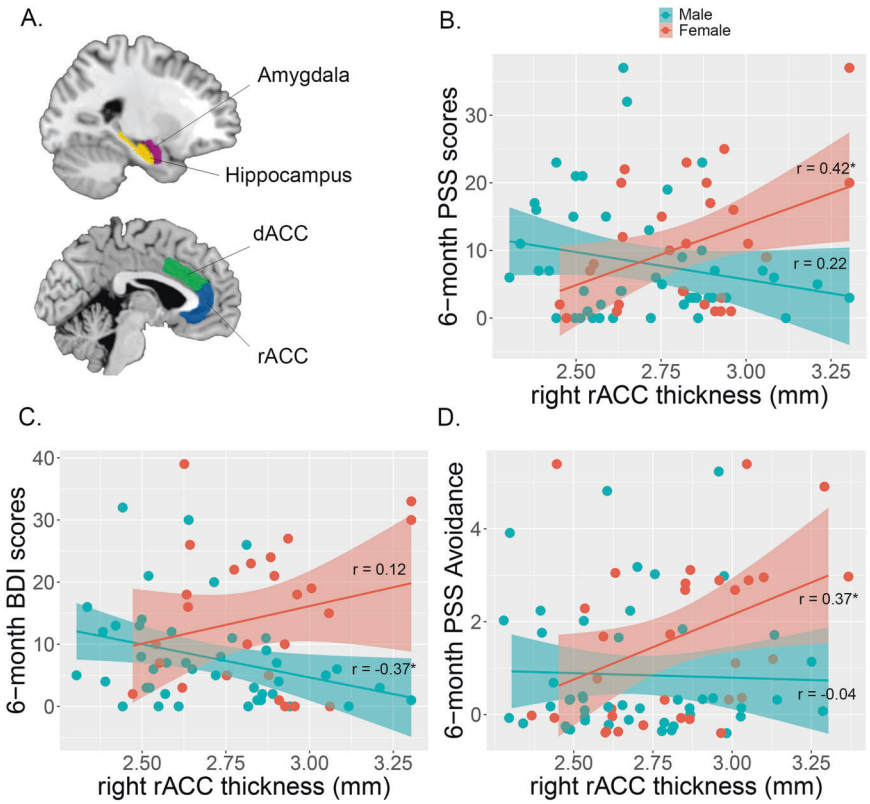

Fig. 1 Regions of interest and sex-by-region interaction effects predicting subsequent PTSD symptoms. Amygdala, hippocampus, rACC, and dACC regions segmented (**A**). There was a significant sex interaction effect (**B**) for right rostral ACC thickness and 6-month PSS total scores when accounting for scanner site, trauma type, age, and race ($t = 3.41$, $p = 0.001$). Female participants showed a significant positive correlation between right rACC thickness and 6-month PSS total scores (r(27) = 0.42, $p = 0.02$), while male participants did not show a significant correlation (r(44) = −0.22, $p = 0.15$). To further understand the relationship between right rACC thickness and 6-month PSS, PSS subcategories and depression symptoms were analyzed. Male participants showed a significant negative correlation (**C**) between right rACC and 6-month depression symptoms (r(42) = −0.37, $p = 0.01$). Female participants showed a significant positive correlation (**D**) between right rACC and 6-month avoidance symptoms (r(27) = 0.37, $p = 0.04$). *$p < 0.05$.

avoidance symptoms (ß = 3.61, $\Delta R^2 = 0.12$, $t = 2.13$, $p = 0.04$), numbing symptoms (ß = 8.15, $\Delta R^2 = 0.11$, $t = 2.69$, $p = 0.01$), hyperarousal symptoms (ß = 12.27, $\Delta R^2 = 0.13$, $t = 2.67$, $p = 0.01$), and intrusive symptoms (ß = 6.99, $\Delta R^2 = 0.08$, $t = 2.39$, $p = 0.02$). Follow-up analyses showed that right rACC thickness was positively correlated with avoidance symptoms in females ($r(27) = 0.37$, $p = 0.04$), but not males ($r(44) = -0.04$, $p = 0.79$). There were no significant correlations for numbing, hyperarousal, or intrusive symptoms for either sex ($ps > 0.05$). For 6-month depression symptoms, there was a sex*right rACC interaction effect (ß = 34.85, $\Delta R^2 = 0.24$, $t = 3.19$, $p = 0.002$). Here, interestingly, right rACC thickness correlated negatively with 6-month BDI in male participants ($r(42) = -0.37$, $p = 0.01$), but not female participants ($r(25) = 0.12$, $p = 0.56$). There were no sex differences between avoidance symptoms, numbing symptoms, hyperarousal symptoms, or intrusive symptoms at 6 months ($p > 0.05$). There was a significant difference for depression symptoms, with female participants having significantly higher depression symptoms ($t(41.57) = 2.56$, $p = 0.01$).

To see if prior trauma had an impact on results, we further analyzed two self-report measures, the CTQ and a self-report number of prior traumatic events, as covariates. Female and male participants did not significantly differ in their CTQ scores nor their amount of prior reported trauma ($p > 0.05$; Table 1). When CTQ was included in our regression model as a covariate, the interaction between sex and right rACC was attenuated, but still significant (CTQ: ß = 0.20, $\Delta R^2 = 0.08$, $t = 2.41$, $p = 0.003$; sex*right rACC: ß = 12.00, $\Delta R^2 = 0.08$, $t = 2.41$, $p = 0.02$). A second model including number of prior traumatic events as a covariate showed a strong remaining sex * rACC effect (traumatic events: ß = 1.28, $\Delta R^2 = 0.15$, $t = 2.39$, $p = 0.01$; sex*right rACC: ß = 30.57, $\Delta R^2 = 0.15$, $t = 2.93$, $p = 0.005$). This suggests that the observed sex-dependent rACC effect predicts PTSD symptoms above and beyond lifetime or childhood trauma history.

DISCUSSION

The results of the current study provide evidence for sex-related differences in how early-post-trauma brain cortical thickness predicts longitudinal PTSD severity. In female participants, greater right rACC thickness 1 month post-trauma predicted PTSD severity at 6 months post-trauma, as well as avoidance symptoms, while smaller rACC thickness in male participants predicted greater subsequent depression symptom severity. Amygdala volume, hippocampal volume, dACC, and left rACC thickness 1-month post-trauma did not predict 6-month PTSD severity. These findings support the rACC as a vital neural region regarding mood and PTSD. This study fills a gap in the literature by investigating the influence of sex on how brain structure predicts PTSD longitudinally, which has not been examined previously.

For females, these results differ from prior rACC findings with respect to PTSD. Previous longitudinal studies showed reduced rACC thickness and surface area predict later probable PTSD diagnosis 3 months [26] and 6 months [26, 27]. However, within these studies, individuals were either only exposed to motor vehicle accidents [27] or also experienced mild traumatic brain injury during a traumatic event [26]. These studies also did not differentiate by sex nor examine PTSD symptom subtypes, making it difficult to draw direct comparisons.

Interestingly, a similar phenotype has been identified in neuroimaging studies of the dissociative subtype of PTSD. Those studies suggest that greater PFC activation relates to emotional overmodulation and dissociation symptoms. There is evidence for a dissociative subtype of PTSD, with findings suggesting that, within this subtype, overmodulation of prefrontal areas over the amygdala leads to diminished fear response. This is in contrast to traditional PTSD models, in which under-modulation of prefrontal areas over the amygdala leads to hyperactive fear response [66, 67]. Our findings may be consistent with this differentiation, with larger right rACC correlating with avoidance symptoms. While we did not collect information about dissociative symptoms in the current study, avoidance and numbing symptoms are known to reflect hypoarousal, and to share some overlap with dissociation symptoms [68]. Notably, much of the neuroimaging work on trauma-related dissociation or the dissociative subtype of PTSD has been conducted in females [69–71]. It may be the case that the neural features associated with PTSD in females have been undercharacterized to date, and that a more male-typical pattern drives the models of PTSD neurocircuitry in the existing literature. There are no structural or fMRI studies that have focused on PTSD subtypes and differences across sex longitudinally. However, one study looking specifically at the influence of interpersonal violence in women with PTSD compared to non-trauma controls found PTSD subtypes did predict differences in cortical thickness and gray matter volume throughout the brain [72], consistent with our findings.

For males, smaller right rACC thickness correlated with greater depression symptoms. This supports prior findings, which suggest that this region is thinner in those with depression, and thickens in those who show clinical improvement following transcranial magnetic stimulation treatment [73–75]. Interestingly, one prior study found the rACC to be thinner only in boys with depressive symptoms, but not girls [74]. The results of the current study build upon these findings and suggest the rACC plays a role in vulnerability to post-trauma depression in males following trauma, but not in females.

These contrasting findings point to the importance of considering sex differences in assessing biological risk factors for PTSD. As mentioned, differences in PTSD symptom presentation between females and males may influence these results, with a dissociative/overmodulatory phenotype correlating with rACC thickness in female participants in this study, and with depression symptoms correlating with lower rACC thickness in male participants in this study. It would be of interest to examine populations of male and female individuals post-trauma who develop emotional overmodulation vs. undermodulation symptoms as well as depression symptoms, to examine more closely the relationship between sex, brain volume, and PTSD subtypes. It is worth noting that, when 1-month PSS symptoms were included in models as a baseline collected at the time of the scan, this removed significant sex interaction effects when correcting for multiple comparisons. 1-month PSS scores were correlated with 6-month PSS scores ($r = 0.74$, $p < 0.001$), with this high collinearity likely obscuring the association with rACC. Other studies also suggest predisposing factors pre-index trauma, such as childhood trauma, may influence rACC volume and PTSD symptomology [76–81]. However, when childhood trauma and number of prior traumas were added to regression models as covariates, the interaction between sex and right rACC was still significant, meaning sex-dependent rACC predicts PTSD symptoms regardless of earlier trauma. Hormonal differences between males and females may also explain differences in rACC thickness. Estradiol is known to mediate dendritic growth in the mPFC and its projections to the amygdala in response to stress in female rodents [32, 33]. Regarding humans, hormone fluctuations have been shown to play a role in fear learning in females, and may also play a role in PTSD severity [82–84] and sex differences through influence on the rACC and the vmPFC [33, 85]. However, this is outside the scope of the current study. Differences in trauma type experienced between male and female individuals may also influence rACC thickness results [1]. Trauma type is shown to impact hippocampal volume [37], although there is no current evidence for how trauma type influences rACC thickness.

Weaknesses of the current study include sample size and generalizability. Only 93 of the 504 participants recruited for this study had MRI scans collected, when it is becoming clearer that

larger sample sizes are needed for observational studies [86]. While findings suggest that rACC may be causally involved in PTSD development, these are observational findings done in a small sample size. Due to the nature of trauma research, in which participants are usually only able to be recruited for longitudinal studies after a traumatic event has occurred, it is difficult to assess the exact influence of traumatic events on the brain from pre-trauma to post-trauma, thus making it more difficult to determine a causal influence of the rACC in PTSD neuroimaging studies. Participants were also only recruited from the ED at Grady Hospital in Atlanta, GA, meaning that findings may be specific to this population. Biological sex was indicated by participants via survey, and there was no data collected regarding gender identity. Thus, this paper is limited to the analysis of sex. Additionally, only 6-month follow-up data were used for this analysis. While this is a strong indicator of which participants will go on to develop chronic symptoms [87], we did not evaluate the influence of chronic vs. acute PTSD symptoms post-trauma within this analysis. Individuals with chronic PTSD may wait years before pursuing treatment, and we did not collect PSS scores at timepoints past one year. We also utilized the PSS as a self-report measure to evaluate PTSD symptom severity rather than relying on a clinical diagnostic interview. Further longitudinal research is necessary to understand brain volume differences and what they might mean for individuals with PTSD long-term.

In summary, findings support incorporating both PTSD symptom subtypes and sex differences into models of predicting PTSD from rACC thickness. In female participants, greater right rACC thickness predicted later overall PTSD and avoidance symptoms, suggesting a relation with emotional overmodulation. While in male participants, smaller right rACC thickness predicted later depression severity, in line with prior findings. In utilizing our understanding of how brain volume differentially predicts symptoms across sex, we may continue to improve upon efforts to find neurobiological predictors of PTSD following traumatic events. This may lead to more accurate identification of individuals at risk of PTSD immediately following trauma, refining patient-specific targets for preventative care.

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AUTHOR CONTRIBUTIONS

Design and conceptualization of the study: ARR, SS, VM, BOR, TJ, KJR, JSS. Data collection and recruitment: VM, RH, SJHVR, JSS. Data processing and statistical analyses: ARR, SS, VM, JSS. Initial drafting of the paper: ARR, SS, JSS. All authors revised the paper critically for important intellectual context and agree to be accountable for all aspects of the work, and ensure the accuracy and integrity of the findings.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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