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Research Article

PTSD REMISSION AFTER PROLONGED EXPOSURE TREATMENT IS ASSOCIATED WITH ANTERIOR CINGULATE CORTEX THINNING AND VOLUME REDUCTION

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Background: ***Brain structures underlying posttraumatic stress disorder (PTSD) have been a focus of imaging studies, but associations between treatment outcome and alterations in brain structures remain largely unexamined. We longitudinally examined the relation of structural changes in the rostral anterior cingulate cortex (rACC), a previously identified key region in the PTSD fear network, to outcome of prolonged exposure (PE) treatment.*** **Method:** ***The sample included 78 adults (53 women): 41 patients with PTSD and 37 trauma-exposed healthy volunteers (TE-HCs). Patients underwent a 10-week course of PE treatment and completed pre- and posttreatment assessments and magnetic resonance imaging (MRI) structural scans. TE-HCs also underwent assessment and MRI at baseline and 10 weeks later. PE remitters (n = 11), nonremitters (n = 14), and TE-HCs, were compared at baseline on demographic and clinical characteristics and ACC structure. Remitters, nonremitters, and TE-HCs were compared for pre- to posttreatment clinical and structural ACC change, controlling for potential confounding variables.*** **Results:** ***There were no baseline differences in structure between PTSD and TE-HCs or remitters and nonremitters. Following treatment, PTSD remitters exhibited cortical thinning and volume decrease in the left rACC compared with PTSD nonremitters and TE-HCs.*** **Conclusions:** ***These results, while in need of replication, suggest that PE treatment for PTSD, by extinguishing maladaptive trauma associations, may promote synaptic plasticity and structure change in rACC. Future research should explore possible underlying mechanisms. Depression and Anxiety 33:384–391, 2016.***

Key words: ***trauma; treatment; structural imaging; posttraumatic stress disorder; ACC***

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PTSD REMISSION AFTER PROLONGED EXPOSURE TREATMENT IS ASSOCIATED WITH ROSTRAL ANTERIOR CINGULATE CORTEX THINNING AND VOLUME REDUCTION

Posttraumatic stress disorder (PTSD) is a debilitating disorder with widespread effects on physical health,[1] functioning,[2] and interpersonal relationships.[3] Among evidence-based treatments for PTSD,[4,5] prolonged exposure (PE) is considered the gold standard.[6] To reduce the excessive fear associated with trauma memories and reminders through habituation and eventual extinction,[7] PE patients repeatedly recount trauma memories and challenge trauma-related avoidances in graded fashion. Although PE shows moderate-to-high efficacy,[8] individual differences in response and remission are not fully understood, and neurobiological treatment mechanisms such as changes in the neural circuits implicated in fear processing remain unexplored.

Research on neural underpinnings of PTSD has previously described the role of the amygdala, hippocampus, and prefrontal cortex (PFC).[9] Yet, emerging evidence more specifically implicates the anterior cingulate cortex (ACC) as a key prefrontal region in posttraumatic symptoms and treatment response. Although ACC influences executive control of emotional responses,[10] its role in PTSD is not fully understood. Previous structural studies have found either no differences between patients and controls in ACC cortical thickness and volume[11,12] or a negative relationship between symptom severity, or diagnostic status, and thickness or volume of ACC.[13–16] Methodological differences may explain these contradictory findings: use of volume only in some studies,[16] both volume and cortical thickness in others,[11,12] and examination of different ACC regions (e.g., separate examination of caudal and rostral aspects vs.[14] examining entire ACC,[12,16]) and use of varied, homogeneous samples (veterans only,[11,14] female victims of sexual abuse,[12] victims of urban violence[13]). However, a recent meta-analysis associates a smaller ACC with PTSD.[15] Moreover, this region predicts treatment response in PTSD. Larger left rostral ACC volume pretreatment,[17] as well as greater left rACC gray matter density, predicted better treatment outcome in cognitive behavioral therapy.[18]

The left rACC was linked to emotional appraisal[19] and to resolving emotional conflict by inhibiting amygdala.[20] This is consistent with left lateralization of positive affect and approach motives.[21] If exposure therapy theoretically engages fear circuits and results in habituation, extinguishing maladaptive connections between innocuous but trauma-associated stimuli and fear circuitry, changes in this brain region may follow. Findings of thicker and denser pretreatment ACC in CBT responders[18] could indicate excess connectivity, representing the maladaptive connections requiring extinction in PE, perhaps due to futile attempts to inhibit amygdala in the face of continued activation, and might mark the best candidates for PE. This would lead us to hypothesize decreased thickness and volume following PE. The findings of thinner, or smaller, ACC in PTSD[15] may suggest an alternative mechanism wherein ACC is hypoactive, possibly due to avoidance; failing to inhibit amygdala; and having smaller volume due to diminished connectivity. A thicker, larger ACC might then be expected at the end of treatment. Supporting this hypothesis is the finding associating better response to exposure-based therapy for OCD with a thinner pretreatment left rACC.[22]

Only one published study has assessed posttreatment ACC structural changes, reporting null findings.[17] This study, however, examined pharmacotherapy, not exposure-based psychotherapy treatment, and examined changes only in the right subgenual ACC, which partly overlaps with ventral right rACC. It did not describe left ACC, and did not therefore gauge structural changes in left rACC previously associated with treatment outcomes.

Evidence associates ACC structure with PTSD symptoms and treatment, generally associating ACC reduction/thinning with PTSD. Thicker/larger left rACC,[18] as detailed above, may predict favorable treatment outcomes. However, structural changes associated with treatment have received little exploration, and the mechanism behind existing findings remains unclear. The current study therefore examined the association between changes in rACC thickness and volume and treatment remission, comparing patients with PTSD who remitted following treatment to nonremitters. Trauma-exposed healthy controls (TE-HCs) without PTSD, matched for age, ethnicity, and trauma, provided another comparison to allow examination of baseline differences and to control for nontreatment-related changes in left rACC structure followed over an identical interval. We expected the rACC to associate with treatment outcome, generating three a priori hypotheses:

H1: Pretreatment left rACC volume and thickness will be greater in the TEHC than in the PTSD group.
H2: Greater pretreatment left, but not right, rACC thickness and volume will be associated with remission after treatment in the PTSD group.
H3: At posttreatment follow up, remission status will be associated with left rACC thickness and volume changes. Specific direction is not hypothesized.

MATERIALS AND METHODS

SAMPLE AND PROCEDURE

PTSD patients and matched TE-HC subjects were recruited via advertisement and fliers. All participants met DSM-IV PTSD criterion A1 for adult traumatic events, including vehicular accidents, sexual or physical assaults, and witnessing serious injuries or deaths. Medical history, review of systems, physical examination, and laboratory tests determined participant health status. Two trained raters administered the Structured Clinical Interview for DSM-IV Axis I Disorders

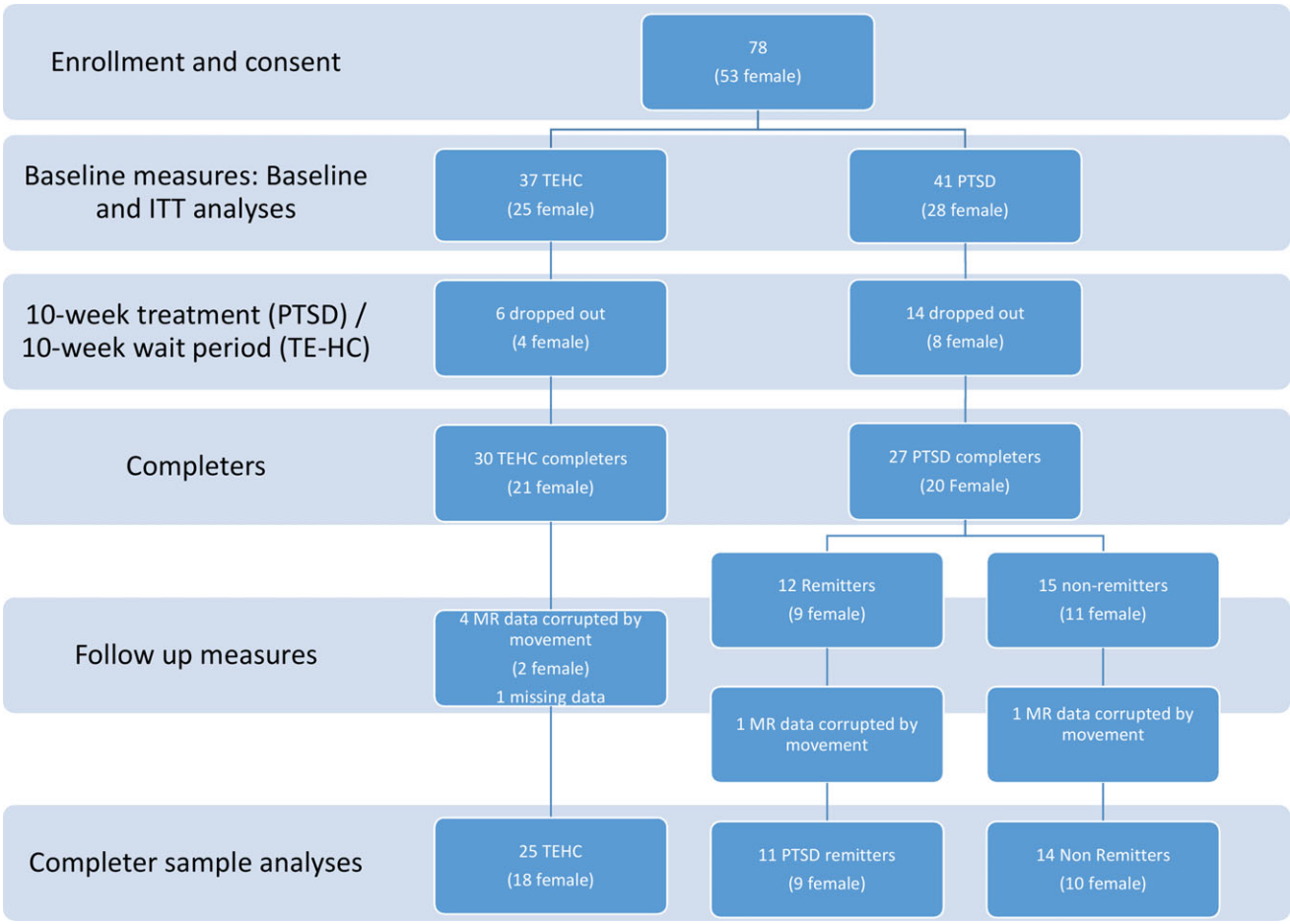

Figure 1. Enrollment flowchart. TEHC, trauma-exposed healthy controls; PTSD, posttraumatic stress disorder; ITT, intent to treat; MR, magnetic resonance

(SCID),[23] Hamilton Depression Rating Scale (HAM-D-17),[24] and the Clinician-Administered PTSD Scale (CAPS)[25] for DSM-IV to assess PTSD diagnosis and clinical severity. Training was received from a licensed senior clinician on conducting these prior to commencing evaluations, and their interrater reliability score ranged between .92 and .99.

For PTSD subjects, exclusion criteria included substance/alcohol dependence within the past 6 months or abuse within past 2 months, use of any psychotropic medication 4 weeks prior to participation (6 weeks for fluoxetine), HAM-D-17 score >24, or CAPS score <50. Exclusion criteria for TE-HC subjects were any current or past Axis I disorders, and CAPS scores >19 (considered symptomatic).[25] The New York State Psychiatric Institute Institutional Review Board approved all procedures, and all participants provided written informed consent for this clinicaltrials.gov-registered trial (identifier NCT01576510). While 78 participants consented and were included in intent-to-treat analyses, dropout, as well as data processing issues (e.g., movement in the MRI), yielded a completer sample of 51 subjects, including 26 TE-HCs and 25 PTSD patients (see Fig. 1).

All PTSD patients entered treatment with one of two trained therapists who adhered to the 10-week standard Foa et al. protocol.[8] Each therapist treated a minimum of two pilot cases to ensure expertise. Treatment sessions were audiotaped, monitored for adherence, and supervised by PE experts to ensure adherence and competence using the PE integrity measure developed by Foa et al.[26] Patients received independent evaluations and MRI scans pretreatment and posttreatment (week 10).

STRUCTURAL DATA

All T1-weighted structural images were acquired on a 1.5 T GE Twin Speed MR Scanner operating on the Excite 3 12.0 M4 HD platform with an eight-channel head coil. After inspection for motion artifacts and gross abnormalities, mean cortical thickness and volume values for anatomical regions were obtained by preprocessing the T1 images using Freesurfer 5.1.0 (http://surfer.nmr.mgh.harvard.edu) standard surface-based reconstruction pipeline. A complete description of the pipeline can be found in other studies;[27,28] technical details of the procedures are described in other studies.[27,29] No manual intervention was required. Both intensity and continuity information of the 3D T1 volume are used in Freesurfer's segmentation and deformation operations to produce estimate of cortical thickness, which is calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface.[28] These cortical thickness maps do not rely solely on absolute signal intensity, as they are created using spatial intensity gradients across tissue classes. As the cortical thickness maps produced are not restricted to the voxel resolution of the original data, they can identify submillimeter differences

TABLE 1. Baseline symptom and structure differences between groups

	TE-HC		PTSD			
	Mean	SD	Mean	SD	*F* (df)	*P*
TBV (mm^3)	217441.591	18506.455	215157.608	23004.117	0.228 (1,76)	.634
lrACC volume (mm^3)	2559.189	463.566	2602.200	673.247	0.105 (1,76)	.747
rrACC volume (mm^3)	2134.622	469.849	2266.100	576.646	1.191 (1,76)	.279
lrACC thickness (mm)	2.604	0.188	2.671	0.172	2.624 (1,76)	.109
rrACC thickness (mm)	2.615	0.206	2.651	0.262	0.430 (1,76)	.514
CAPS	4.438	5.962	80.6348	15.580	85.267 (1,72)	**<.001**
HAM-D	2.219	2.420	16.512	5.577	82.857 (1,72)	**<.001**

PTSD, posttraumatic stress disorder; TE-HC, trauma-exposed healthy controls; TBV, total brain volume; lrACC, left rostral anterior cingulate cortex; rrACC, right rostral anterior cingulate cortex; CAPS, clinician assessment of posttraumatic symptoms; HAM-D, Hamilton Depression Rating Scale

between groups. Procedures for measuring cortical thickness have been validated against histological analysis and manual measurements.[30–32] Freesurfer morphometric procedures show good test-retest reliability across scanner manufacturers and across field strengths.[33]

ANALYTIC STRATEGY

PTSD patients and TE-HCs were compared for pretreatment differences in lrACC, rrACC, and total brain volume (total brain volume [TBV], included to rule out non-ROI specific trends), as well as demographic differences (to gauge possible differences between remitters and nonremitters warranting control in further analyses), using ANOVA, to test H1. We expected thickness and volume to follow a TE-HC > PTSD pattern. To test H2, we conducted two MANOVAs, comparing baseline left rACC volume and thickness among remitters and nonremitters within the completer sample, controlling for sex, age, and TBV. We expected thickness and volume to follow a remitters > nonremitters pattern.

To test H3, we first conducted two general linear mixed models (GLMM) analyses on the intent-to-treat sample, maximizing power and reducing type I error probability.[34] Maximum likelihood (ML) method was used. lrACC thickness, then volume, were the dependent variables. Time, TBV, and age were entered as covariates. Remission status and sex were entered as between-subject factors. Time was defined as a repeated measure including pre- and posttreatment lrACC mean thickness or volume values, and remission status included effect coding for nonremitters (0), remitters (1), and TE-HCs (-1). TE-HCs were included in order to control the effects of time that are unrelated to treatment. Remission from PTSD was defined a priori as CAPS score posttreatment <20.[25] We examined main effects of time and remission status and added interaction of time by remission status in order to gauge effects for the relationship between structural changes and symptom reduction (time × CAPS percent reduction). Due to sample size, there would be insufficient power for analyses including additional interactions, but the entry of sex as a variable in the model served to control possible confounds related to sex differences.[35] Power analyses were conducted using G-Power software and provided an estimate of medium-to-high effect sizes ($f = .32$) required in order to reach acceptable (.80) power.

We additionally conducted two repeated-measures ANOVAs, one for mean volume and one for mean thickness, with a 2 × 3 design (time × remission status), using only the completer subsample. This aimed to further minimize probability of type II error.[34] Age, sex, and TBV covariates statistically controlled the variance attributable to these variables in these analyses. Power analyses were conducted using G-Power software and provided an estimate of high effect sizes ($f = .45$) required in order to reach acceptable (.80) power.

Several control analyses were conducted as follows: (1) Repeated measures analyses were conducted adding depression symptoms and years of education as covariates due to findings of between-group differences in these variables (see results), as well as time since trauma (chronicity) and age at first trauma (early exposure), due to purported structural change. (2) All analyses testing between-group differences were repeated using the remission variable created in accordance with the HAM-D clinical cutoff,[24] to test specificity of results to PTSD remission. (3) All analyses conducted with left ACC as the dependent variable were repeated for right ACC to test specificity of findings for this ROI. (4) Baseline analyses of differences between completers and dropouts were conducted to exclude confounds due to dropout. None of these analyses yielded significant results, supporting the specificity and validity of the findings reported below.

RESULTS

No baseline differences were found between PTSD patients and controls on any demographic variables except years of education (see Table 2). No hypothesized differences between groups in baseline rACC were observed (see Table 1): thus data did not support H1. Group differences were identified, as expected, in clinical symptoms of depression (HAM-D) and PTSD (CAPS) (Table 1). Similarly, results of the MANOVA did not support H2, showing no differences among remitters, nonremitters, and controls with regards to baseline left rACC thickness and volume when controlling for TBV, sex, and age (F [4,114] = 1.515, $P = .203$).

The results of the GLMM analysis supported H3, finding a significant interaction effect for remission status and time. A significant overall mean decrease in lrACC volume (*Estimate* = 30.930, $t = 2.194$, $P = .033$) and thickness (*Estimate* = −.019, $t = -2.792$, $P = .007$) over time was seen across the three remission status groups. Contrasts indicated lower lrACC mean thickness (*Estimate* = −.155, $t = -2.403$, $P = .019$) but comparable mean volume (*Estimate* = −15.333, $t = -.076$, $P = .940$) over both time points for TE-HCs when compared to remitters, and no differences in mean lrACC thickness (*Estimate* = −.082, $t = -1.091$, $P = .279$) or volume (*Estimate* = −29.107, $t = -.125$, $P = .901$) over both time points when comparing nonremitters to remitters. Contrasts for interaction effects

TABLE 2. Baseline demographics and differences between groups

		TE-HC		PTSD			
		Mean	SD	Mean	SD	F (df)	*P*
Age		34.595	10.708	35.895	9.442	0.286 (1,76)	.594
Years of education		15.290	1.935	14.244	1.972	14.285 (1,76)	**<.001**
		TE-HC		PTSD		χ^2	*P*
Ethnicity	White	29.7.3%		26.8%		3.056	.548
	Asian or Pacific Islander	2.7%		2.4			
	Hispanic	32.4%		41.5%			
	Black	35.1%		24.4%			
	Other	0%		4.9%			
Gender	Female	67.3%		68.6%		.005	.945

indicated a significantly less steep slope for lrACC thickness over time for TE-HCs (*Estimate* = .016, $t = 2.012$, $P = .049$) and for nonremitters (*Estimate* = .025, $t = 2.711$, $P = .009$) when compared to remitters. For volume, contrasts indicated a nonsignificantly steeper slope for remitters versus TE-HCs (*Estimate* = 26.489, $t = 1.590$, $P = .118$ for TE-HC vs. remitter contrast) and a significantly steeper slope for remitters versus non remitters (*Estimate* = 46.808, $t = 2.489$, $P = .016$ for nonremitters vs. remitters contrast). These results indicate overall thinning and volume reduction from pre- to posttreatment among remitters compared to nonremitters, specifically, despite similar overall thickness and volume. The effect for this contrast is robust: ICC .291 for volume, and ICC .371 for thickness (given this effect size, post hoc estimated power, even computed using a conservative *N* of completers only, was .958 and.998 for the two analyses, respectively), and likely drives the main effect seen for time, as this effect loses statistical significance when the interaction term is removed from the model.

The repeated measures analysis results also supported H3, finding a main effect for time (F [1,45] = 4.650, $P = .036$, $\eta^2_{\text{partial}} = .094$) driven by a significant interaction effect for time by remission (F [2,45] = 3.340, $P = .044$, $\eta^2_{\text{partial}} = .129$). Specifically examining differences in thickness between T1 and T2 revealed significant left rACC thinning from pre- to posttreatment in remitters (Fig. 2A). Volume analyses yielded a similar pattern (F [1,45] = 3.49, $P = .07$, $\eta^2_{\text{partial}} = .072$for time, F [2,45] = 3.46, $P = .04$, $\eta^2_{\text{partial}} = .133$for time by remission), with a nonsignificant trend toward reduced volume for remitters posttreatment (Fig. 2B). However, as the effect size was slightly lower than the estimate, the interaction effects for time and group failed to reach acceptable levels of power (the observed power was .603 for effect on thickness and .629 for effect on volume). Control analyses yielded no significant time by remission effect for right rACC (rrACC) volume (F[2,45] = .174, $P = .841$, $\eta^2_{\text{partial}} = .008$) or thickness ($F$ [2,45] = .546, $P = .583$, $\eta^2_{\text{partial}} = .024$), supporting the specificity of the association of left rACC cortical thinning and volume reduction with remission.

DISCUSSION

We found that remission from PTSD following prolonged exposure treatment was associated with volume reduction and thinning in the left rostral ACC (rACC). Thickness and volume of left or right rACC did not differ among the study groups before treatment, nor did associations appear between baseline ACC structure and baseline diagnostic status. While our findings are in line with previous studies finding no such differences in cortical thickness and volume among diverse groups such as veterans and female victims of sexual assault,[11,12] other studies, also in diverse groups including veterans and victims of violence, did uncover between-group differences.[13–16] This inconsistency may be attributed to methodological differences (e.g. sample and measurement) and heterogeneity of PTSD.[36,37] Our finding of thinning and volume reduction in this brain region in treatment remitters, but not nonremitters or controls, in a diverse sample, links the structural changes to treatment recovery specifically, rather than a general effect of completing PE treatment, or passage of time. This is the first evidence of neural structural change associated with efficacy of a psychotherapy based on processing and extinction of fear memories following PTSD-inducing traumatic experiences. Contrasting our findings with previous null findings regarding structural changes in this region over the course of pharmacotherapy[17] further emphasizes the possible role of this specific treatment mechanism in bringing about these changes, as opposed to reflecting mere symptom reduction.

These novel findings, showing structural change during the course of PE, do not directly gauge the mechanism of such change. However, previous literature provides a possible explanatory basis for how PE treatment may effect therapeutic benefit. Exposure treatment purportedly promotes extinction of maladaptive cognitive–emotional connections.[7,8] When translated to neural connectivity, as constant activation of specific

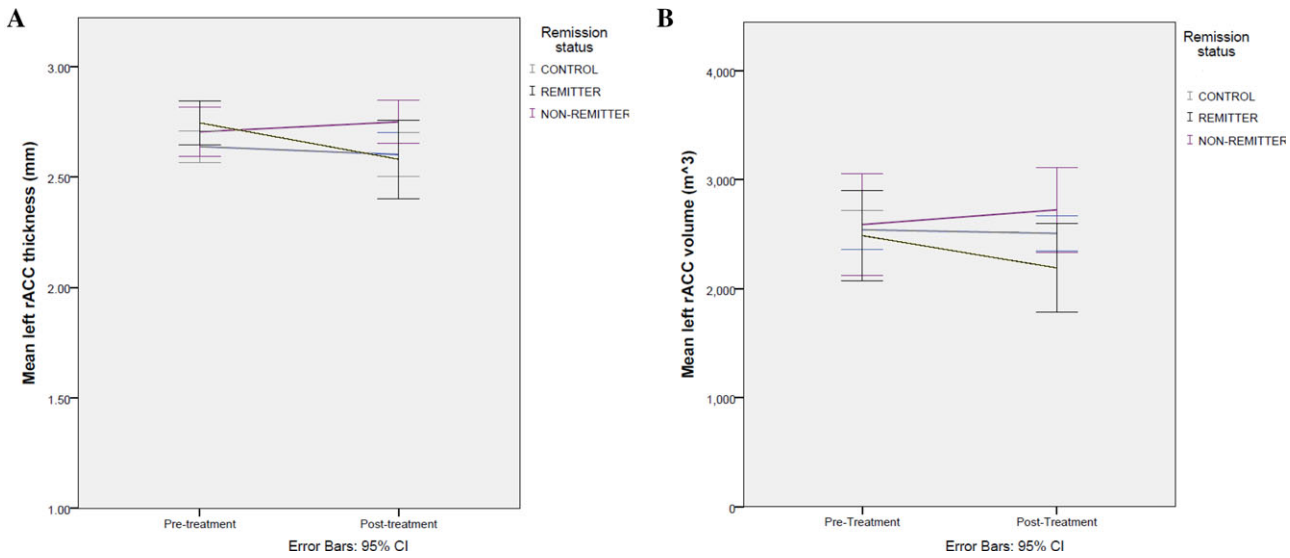

Figure 2. Changes in left rostral anterior cingulate cortex pre- to posttreatment. lrACC, left rostral anterior cingulate cortex.

pathways may reinforce existing connections and encourage the formation of new ones.[38] Extinction may suppress this activation and prune those connections. This process usually occurs into early adulthood,[39] but adult animal models have also shown recovery from cortical damage to occur later in life.[40–42] Therefore, thinning in the left rACC, a region involved in the control of emotional responses, may indicate changes in dendritic morphology.

Stress-induced changes have been demonstrated in prefrontal cortex synapse and dendritic spine morphology and density, with differential effects in different areas, including ACC.[42] Treatment may partially reverse such changes. Similar changes were previously shown to follow sex-specific, estrogen-dependent patterns, with stress-induced dendritic proliferation in females, and an opposite effect in males.[42] Thus our observation of ACC thinning following treatment remission may represent a pruning of overproliferated dendritic spines in a mostly female sample. The robust effect for thickness, but less so for volume, accords with this explanation, as differences in sulcination and gyration add to variance in cortical volume, but not thickness.[43,44] Hence changes in dendritic morphology would have greater impact on thickness. Sex-related variance may also explain the lack of baseline differences in PTSD symptoms between PTSD and TE-HC subjects as, consistent with stress-related proliferation, thinner baseline ACC thickness may be associated with PTSD symptoms for men but not women.[12] That pruning drives the efficacious treatment-related thinning would not only be congruent with PE theory—reducing dendritic spines while habituating to traumatic associations—but with the positive relationship previously found between pretreatment rACC thickness and gray matter density and PTSD treatment outcome,[18] as patients with greater baseline rACC connectivity may benefit most from exposure-based treatment. However, our sample showed no such difference in rACC thickness prior to treatment.

It is also important to note that findings may be seen in a larger context of fear circuitry abnormalities in PTSD. While this study particularly focused on the left rACC, structural abnormalities in additional parts of this circuitry, including hippocampus and amygdala, have also been implicated in PTSD.[9] Specifically, previous studies have showed hippocampal volume changes over the course of pharmacotherapeutical treatment,[45,46] but treatment-stable hippocampal differences between chronic and successfully treated PTSD patients have also been found.[47] Although amygdala has not shown treatment-related malleability,[46] it has evinced a specific pattern of connectivity to ACC among those with PTSD.[48] Our data, consistently with several previous studies, did not show change in these regions following treatment (all $P > .05$); however, future studies examining network connectivity would be advised to examine the interplay of these different regions.

Our findings, while significant, have limitations. Our sample included mostly women and lacked statistical power to test gender differences. Our repeated measures analyses could not include treatment dropouts ($N = 14$) who did not return for MRI follow-up assessments, and our GLMM analysis only statistically controlled for missingness; thus limitations inherent in a completer sample, or a sample with missing data, apply: despite lack of differences in baseline variables between completers and dropouts, the study cannot describe trajectories of structural changes among dropouts. Also, while evincing desirable effect size and power within the ITT analyses, these results require replication in larger samples in order to ascertain generalizability, especially in light of the post hoc loss of power in completer-only analyses due to

a lower effect size than expected. Finally, our interpretation of the mechanism behind left rACC thinning (i.e., pruning of maladaptive connectivity to amygdala) needs further testing using techniques gauging connectivity and dendritic arborization. Future studies should enroll larger, gender-balanced samples in order to further explore differences in structural correlates of treatment response. Functional analyses, exploring possible changes in connectivity pre- to posttreatment, may further elucidate the mechanisms driving symptom change. Nevertheless, our findings support the notion that exposure treatment may, indeed, effect relatively rapid changes in fear neurocircuitry, leading to clinical remission of PTSD.

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