Neural function during emotion processing and modulation associated with treatment response in a randomized clinical trial for posttraumatic stress disorder

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Abstract
Background: Posttraumatic stress disorder (PTSD) has been associated with exaggerated threat processing and deficits in emotion modulation circuitry. It remains unknown how neural circuits are associated with response to evidence-based treatments for PTSD.
Method: We examined associations between PTSD symptoms and indicators of neural response in key emotion processing and modulation regions. Fifty-six military Veterans with PTSD were randomly assigned to one of three evidence-based treatments (prolonged exposure, sertraline, and PE plus sertraline) in a randomized clinical trial (“PROGrESS”; 2018, Contemp Clin Trials, 64, 128–138). Twenty-seven combat-exposed controls (CCs) served as a comparison group at pretreatment.
Exposure (PE) therapy (Rauch, Eftekhari, & Ruzek, 2017a, 2017b; Whalen et al., 2003) has also been associated with PTSD (Stevens et al., 2012). Prior findings document both overactivity of emotion processing (anterior cingulate cortex, amygdala) and underactivity of emotion modulation (prefrontal cortex) brain regions in PTSD to various emotion paradigms (Bremner, 2006; Etkin & Wager, 2007; Hayes, Hayes, & Mikkelsen, 2012; Liberzon & Phan, 2003; S. L. Rauch, Shin, & Phelps, 2006). However, some evidence also suggests that people with PTSD demonstrate less activation in the amygdala (Phan, Britton, Taylor, & Liberzon, 2006) and greater activation in the prefrontal cortex (PFC) (Bryant et al., 2008; Felmingham et al., 2010; Fonzo et al., 2010; Garrett et al., 2012). Thus, individual differences, PTSD subtypes, and other factors likely impact relationships between neural function and PTSD symptom presentations.

Altered connectivity between emotion processing and modulation regions has also been associated with PTSD (Stevens et al., 2013). Attention control is one strategy often used to modulate emotion, and individuals with PTSD have been shown to perform worse on attention control tasks, with poorer performance associated with reduced activation of brain regions involved in emotion regulation (e.g., superior parietal cortex, prefrontal cortex; Aupperle et al., 2012; Blair et al., 2013) and reduced connectivity between these regions (Russman Block et al., 2016).

Evidence-based treatments for PTSD include prolonged exposure (PE) therapy (Rauch, Eftekhari, & Ruzek, 2012) and selective serotonin reuptake inhibitors (SSRIs; Baldwin et al., 2005; Zohar & Westenberg, 2000). SSRIs can modulate PFC and amygdala activation, which has been associated with symptom improvement in people with generalized anxiety and depression (Saxena et al., 2003; Whalen et al., 2009). Trauma-focused psychotherapy for PTSD has been associated with reductions in amygdala activation and increases in PFC activation (Roy et al., 2010; Zantvoord, Diehle, & Lindauer, 2013). People with less amygdala activation and greater dorsal PFC activation during an emotion reactivity task, and greater PFC activation during an emotion conflict task at pretreatment had greater symptom reductions after PE for PTSD (Fonzo et al., 2017a, 2017b). Increased activation and greater connectivity within frontal brain regions were associated with greater symptom improvements following PE, but amygdala activation was not observed to vary as a function of treatment (Fonzo et al., 2017a, 2017b). In addition, some evidence suggests that greater reactivity to trauma-related threat at the beginning of PE was predictive of reduced distress following treatment (Tuerk et al., 2018) and that low levels of trauma-related reactivity during PE was associated with poorer outcomes (Wangelin & Tuerk, 2015). These findings suggest that both emotion processing and regulation regions are involved in PTSD and change with treatment, but in slightly different ways depending on treatment type, patterns of pretreatment symptoms and underlying brain activation, and methods used to probe specific neural functions.

Overall, the majority of existing evidence suggests that effective treatment (both PE and sertraline [SERT]) might be associated with reduced threat processing and improved emotion modulation, via decreased amygdala activation and increased PFC activation, accordingly. However, no studies have directly compared these treatment modalities in Veterans; thus it is unknown whether they impact neural function and treatment outcome differentially. The specific neurocognitive mechanisms underlying symptom improvements in PTSD remain largely unexplored and additional studies are needed to further understand ways to optimize and tailor treatments.

The Shifted Attention Emotion Appraisal Task (SEAT; Duval, Joshi, Block, Abelson, & Liberzon, 2018; Liberzon et al., 2015; Sripada et al., 2013; Wang et al., 2016) was developed to probe neural function associated with naturalistic emotion regulation processes:
implicit emotional processing, attention modulation of emotion, and emotion modulation by appraisal. This task activates key regions of emotion processing (amygdala, anterior insula) and emotion modulation (vmPFC, dIPFC; Duval et al., 2018; Liberzon et al., 2015; Rauch et al., 2018). The SEAT has been used to demonstrate changes in anterior insula and mPFC activation associated with acute PTSD symptoms following traumatic motor vehicle collision (Wang et al., 2016). It is unknown, however, whether the above-mentioned findings predict response to treatment.

We aimed to identify differences between participants with PTSD and combat-exposed controls (CC) in neural response during emotion processing and modulation, and to establish brain-based predictors of treatment response. On the basis of prior research (Bremner, 2006; Etkin & Wager, 2007; Hayes et al., 2012; Liberzon & Phan, 2003; Rauch et al., 2006), we expected that participants with PTSD would have greater activation in threat processing regions and less activation in emotion modulation regions, compared with CC. We expected that less activation in threat processing regions and greater activation in, and connectivity between, emotion modulation regions would be associated with greater reductions in PTSD symptoms from pretreatment to posttreatment.

2 | METHOD

2.1 | Participants

Sixty-six participants with PTSD and 29 CCs completed functional magnetic resonance imaging (fMRI) scanning in the context of the larger randomized trial investigating the effects of evidence-based treatment on PTSD symptoms (“PROGrESS”; Rauch et al., 2018). In the PTSD group, ten participants’ data were excluded from this analysis due to technical or poor performance issues. Thus, 56 participants with PTSD completed a baseline scan during SEAT and were randomized to treatment. Of the 29 participants comprising the CC comparison group, two were excluded due to technical issues and scan discontinuation, resulting in a total of 27 CC participants. Forty-three of the original 56 participants randomized to treatment completed the posttreatment MRI scan. The 13 lost participants were mainly lost to follow-up or time incompatibility. Technical issues resulted in an additional seven participants’ posttreatment MRI data being excluded. This resulted in a final sample of 36 participants with PTSD with both pretreatment and posttreatment data (See Supporting Information CONSORT diagram and Section 2.3 for more details on these exclusions). However, while only 36 participants had complete pretreatment and posttreatment MRI and symptom data, 49 of the 56 randomized participants had a pretreatment MRI scan and both pretreatment and posttreatment symptom data. Thus, 49 participants were included in analyses examining pretreatment brain function as a predictor of symptom change from pretreatment to posttreatment.

As described previously (Rauch et al., 2018, 2019), key inclusion criteria for the PTSD group were: combat Veterans from Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), Operation New Dawn (OND), and/or active duty; combat-related PTSD; and significant symptom severity (Clinician-Administered PTSD Scale for DSM-IV [CAPS-IV; Blake & Terence, 1995] ≥50) of at least 3 months duration. Exclusion criteria included: imminent risk of suicide; active psychosis; alcohol or substance dependence in the past 8 weeks; inability to attend regular appointments; prior failure of an adequate trial of PE or SERT; medical illness likely to result in hospitalization or for which treatments were contraindicated; serious cognitive impairment; concurrent antidepressants or antipsychotics. Participants could have been on antidepressants before the start of the study but had discontinued their medication at least 2 weeks before randomization. Benzodiazepines, prazosin, and sleep agents (e.g., Zolpidem) were allowed if the dose was stable for at least 2 weeks. Approximately half of our participants screened positive for mild traumatic brain injury on the brief traumatic brain injury screen (BTBIS).

Participants in the CC group met the same inclusion/exclusion criteria as the PTSD group, including exposure to a criterion A combat-related trauma, based on Combat Exposure Scale (CES) score ≥17 (e.g., at least moderate exposure) during OEF/OIF/OND, except they had no history of PTSD symptoms (i.e., CAPS-IV < 20) related to any trauma.

2.2 | Procedures

All procedures were approved by Institutional Review Boards at the VA Ann Arbor Healthcare System, the University of Michigan, Ralph H Johnson VA Medical Center, VA San Diego Healthcare System, and Massachusetts General Hospital. Written informed consent was obtained from all participants. Detailed methodology for the larger study is reported elsewhere (Rauch et al., 2018). In brief, participants underwent initial structured clinical assessment by a certified independent evaluator. The primary outcome measure was CAPS-IV (Blake & Terence, 1995) which assessed severity of total PTSD symptoms and symptom clusters (re-experiencing, avoidance, and hyperarousal) before and after treatment. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to screen for other mental health conditions.

2.2.1 | fMRI task

Participants completed the SEAT (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Klumpp et al., 2011) during fMRI scanning. Participants viewed compound images of neutral and threat (fearful and angry) faces superimposed on indoor and outdoor scenes. Before each image, one of three cues appeared: “Male/Female” (identify the gender of the face), to probe implicit emotional processing; “Indoor/Outdoor” (is the scene indoor or outdoor), to probe emotion modulation by attention shifting; or “Like/Dislike” (do you like or dislike the face), to probe emotion modulation by appraisal. Neutral faces
alone and places alone trials were also presented throughout the task to control for brain activation associated with simply viewing faces and scenes. Trials were randomly presented in an event-related design. Additional tasks to assess emotion processing and regulation (Joshi et al., 2020), and a resting-state scan were also completed (Sheynin et al., 2018).

### 2.2.2 | MRI data collection

MRI assessment was conducted in a single Philips 3-T Achieva X-series MRI scanner (Philips Medical Systems, Andover, MA), with an 8-channel SENSE Head coil. T1-weighted anatomic images were acquired with a 3D fast field echo-turbo field echo sequence (field of view (FOV) = 256 × 256 mm, slice thickness = 1 mm, 0 mm gap). Axial slices aligned with the anterior commissure posterior commissure plane were used for slice localization, transformation, and co-registration. Functional images were acquired with gradient-echo blood oxygen level-dependent scans. Echo planar imaging (EPI) single-shot sequence was used (EPI factor = 43, repetition time/echo time (TR/TE) = 2,000/25 ms, flip angle = 90°, FOV = 220 × 220 mm, slice thickness = 2.8 mm, 0 mm gap, 42 data points, 150 dynamic scan).

### 2.2.3 | Treatment trial

While both psychotherapy and medication have been shown to be effective in reducing PTSD symptoms and altering underlying neurocircuitry (Baldwin et al., 2005; Fonzo et al., 2017a, 2017b; Rauch et al., 2012; Roy et al., 2010; Saxena et al., 2003; Whalen et al., 2009; Zantvoord et al., 2013; Zohar & Westenberg, 2000), very few investigations have directly compared the efficacy of evidence-based psychotherapy and medications. Given that most Veterans with PTSD receive a combination of psychotherapy and medication treatments, a primary goal of the larger PROGrESS trial was to examine effects of PE therapy, SERT, and their combination. Participants with PTSD were randomly assigned to one of three treatment arms [Prolonged Exposure plus pill placebo (PE + PLB), Sertraline plus Enhanced Medication Management (SERT + EMM), or the combination (PE + SERT)]. All participants received both an active psychotherapeutic intervention and a blinded medication. To balance the groups for differences in time spent with the therapist/psychiatrist and nonspecific therapy effects, the SERT condition participants received 30 min of EMM during the initial 12 weeks. Details about the treatment protocols are reported elsewhere (Rauch et al., 2018). At Week 24 (posttreatment), participants with PTSD completed another fMRI scanning and blinded clinical interview with CAPS-IV. These assessments were completed at 24 weeks to allow for maximum therapeutic effect of SERT in PTSD (Rauch et al., 2018; Stein, Ipser, & Seedat, 2006). PE was delivered as typical with up to 13 sessions aimed to be delivered weekly, but with flexibility to make up missed sessions in the follow-up period and to continue skills learned in follow-up. The 24-week endpoint was thus designed to measure outcomes for both treatments at a time when all gains should have been reached. CC participants were not followed beyond the initial assessment and MRI scan.

### 2.3 | Data scoring and analysis

MRI data processing and analysis were performed using statistical parametric mapping (SPM8;Welcome Centre for Human Neuroimaging, London, UK) for MATLAB. Functional images were slice-time corrected with sinc interpolation, realigned and co-registered to the structural images, normalized to the Montreal Neurological Institute (MNI) standard brain, and smoothed with a 5 mm kernel. Runs with more than 3 mm of motion in any plane (x, y, z, pitch, roll, yaw) were excluded from further analysis. Excessive motion resulted in the exclusion of 16 total runs across 11 participants (four runs across three CC participants and four runs across two participants with PTSD at pretreatment; eight runs from six participants with PTSD at posttreatment). These exclusions resulted in the loss of one participant with PTSD, producing the final sample of 56 participants with PTSD. All motion parameters and their derivatives were nuisance regressors in the subject-level analysis.

Consistent with prior studies using the SEAT (Duval et al., 2018; Liberzon et al., 2015; Wang et al., 2016), regions of interest (ROIs) were defined based on task-related activation across all participants, orthogonal to group membership, treatment type, or change over time. We identified a priori regions that were previously reported to be involved in the SEAT (anterior insula, amygdala, dACC, dPFC, mPFC; Duval et al., 2018; Liberzon et al., 2015; Wang et al., 2016). ROIs were defined as 3 mm-radii spheres centered at the activation peaks in the a priori regions (p < .050 family-wise error (FWE) corrected, after initial thresholding at p < .001 uncorrected; see Figure 1). This method allowed us to ensure independence of our ROIs from any group effects, while identifying the ROIs that are most specific to our overall cohort task effects for each contrast of interest (male/female > face/place, in/out > male/female, like/dislike > male/female). We then extracted beta-weights from significant ROIs and submitted them to a series of analyses in SPSS (IBM, version 24) to examine (a) differences between PTSD and CC at pretreatment, (b) changes over time (pretreatment to posttreatment), and (c) relationships between neural response and treatment outcomes. Three linear regression models (one for each construct of implicit emotional processing, emotion modulation by attention shifting, emotion modulation by appraisal) were conducted. We included all a priori regions of interest in each model to examine brain function at pretreatment, and change in brain function over time, as predictors of the change in PTSD symptoms over time.

To examine patterns of brain connectivity during SEAT associated with change in PTSD symptoms, we conducted generalized psychophysiological interaction analyses (gPPI; Sripada et al., 2014) to examine task by functional connectivity interactions. The ROIs from the task-based analyses described above were used as seeds for the gPPI analyses. We examined differences in connectivity between the ROI seed and all other voxels of
the brain that differed in PTSD versus CC groups, and that was predictive of CAPS change. All analyses were FWE corrected at \( p < .050 \) at the whole-brain level (after thresholding at \( p < .001 \) uncorrected). Analyses were run for each of the SEAT contrasts (implicit emotional processing, emotion modulation by attention shifting, and emotion modulation by appraisal) separately, as they probe separate constructs.

3 | RESULTS

3.1 | Demographics and symptoms

Participants with PTSD (\( M = 74.02 \), standard deviation [SD] = 14.08) and CC participants (\( M = 1.96 \), SD = 3.61) had significantly different pretreatment total CAPS scores, \( t(83) = 26.12, p < .001 \). There were no statistically significant differences in gender distribution between PTSD (90% male) and CC (100% male, \( \chi^2(1) = 3.01, p = .083 \) groups, no statistically significant difference in age between PTSD (\( M = 32.13, SD = 8.33 \)) and CC (\( M = 35.48, SD = 8.86; t(83) = -1.69, p = .095 \) groups, and no statistically significant difference in motion during fMRI scanning between PTSD (\( M = 0.630, SD = 1.00 \)) and CC (\( M = 0.687, SD = 1.09; t(82) = -0.232, p = .814 \) groups. For participants with PTSD, there were no statistically significant differences in clinical or demographic variables, including TBI, between treatment arms for those assigned to treatment or the subset of participants who completed posttreatment assessment (Table 1). Within our sample of participants in the MRI study, those with PTSD who completed treatment were more likely to be married (\( p = .039 \)), were less likely to have comorbid panic disorder (\( p = .022 \)), and were marginally more likely to be taking antidepressant medications before the start of the study (\( p = .058 \)), compared with non-completers. No other demographic variables, including TBI, differed between completers and non-completers (Table 2). TBI was not associated with symptom change from pretreatment to posttreatment (\( p = .253 \)).

Mixed analysis of variance (ANOVA) examining the time by treatment-arm interaction on total CAPS scores in the PTSD group revealed a significant effect of time, \( F(1,34) = 89.74, p < .001, \eta_p^2 = .725 \), with symptoms reducing from pretreatment (\( M = 73.86, SD = 14.71 \)) to posttreatment (\( M = 37.27, SD = 26.79 \)) across all participants with PTSD. There was no main effect of treatment arm and no time by treatment arm interaction for symptom outcomes. Given the lack of difference in symptom outcomes between treatment arms in the larger clinical trial (Rauch et al., 2019) and the current MRI study, and low power due to small sample size at posttreatment, we did not examine the effect of treatment arm in our analyses. We did, however, examine treatment arm as a covariate in our regression analyses to determine whether treatment type accounted for significant variance in our models. Primary analyses focus on relationships between brain function measures and PTSD symptom change.

FIGURE 1 | Task-based activation on the SEAT across all participants. Coordinates represent the center of each ROI sphere extracted for analyses, along with corresponding cluster size (k), t value, and family-wise error (FWE) corrected p value. ROI, regions of interest; SEAT, Shifted Attention Emotion Appraisal Task.
3.2 | Pretreatment neural activation

3.2.1 | Task-based neural activation on SEAT

We examined task-based activation across all participants at pretreatment, independent of group. During implicit emotional processing (male/female > face/place contrast), there were predicted activations in regions associated with emotion processing (dACC and bilateral anterior insula) and predicted deactivation in regions associated with emotion modulation (bilateral dlPFC; Figure 1a) at pretreatment.

During emotion modulation by attention shifting (in/out > male/female contrast), we observed predicted activation in regions associated with attention modulation (bilateral dlPFC) and predicted deactivation in regions associated with emotion processing (bilateral amygdala and bilateral anterior insula; Figure 1b) at pretreatment.

During emotion modulation by appraisal (like/dislike > male/female contrast), there were predicted activations in emotion processing and regulatory regions (left dlPFC, bilateral amygdala, bilateral anterior insula/IFG, and mPFC; Figure 1c) at pretreatment.

3.2.2 | Differences between PTSD and CC groups

There were no differences in activation in any of the ROIs examined (amygdala, anterior insula, dACC, mPFC, dlPFC) between participants with PTSD and CCs at pretreatment ($p > .05$).

3.3 | Pretreatment to posttreatment change in neural activation

During implicit emotional processing, there was a decrease ($M(SD)_{\text{pre}} = 0.748(0.438); M(SD)_{\text{post}} = 0.544(0.477)$) in activation in
right anterior insula, \( t(35) = 2.08, p = .045 \) from preposttreatment to posttreatment, but this change was not associated with change in CAPS scores from preposttreatment to posttreatment, and did not survive correction for multiple comparisons. No effect of time was observed during emotion modulation by attention shifting \((p > .05)\). In concert with our findings for implicit emotional processing, during attention modulation by appraisal, there was a decrease from pretreatment to posttreatment in the left anterior insula/IFG, \( t(35) = 2.94, p = .006 \) \( M(SD)_{pre} = 0.840(0.561); \) \( M(SD)_{post} = 0.512(0.513) \), which survives Bonferroni’s correction for multiple ROI comparisons (0.05/7 = 0.007). Activation in left anterior insula/IFG was not associated with change in CAPS scores from pretreatment to posttreatment.

### 3.4 Relationships between pretreatment neural function and symptom change

The regression model examining activation in ROIs at pretreatment as predictors of change in CAPS scores from pretreatment to posttreatment was not significant for implicit emotional processing \((p > .05)\) or emotion modulation by attention shifting \((p > .05)\). During emotion modulation by appraisal, the combined patterns of activation in all seven ROIs (bilateral dlPFC, bilateral amygdala, bilateral anterior insula, and mPFC) at pretreatment accounted for 29.7% of the variance in change in total CAPS scores from pretreatment to posttreatment, \( R^2 = 0.279, F(8,41) = 2.17, p = .051 \). Left dlPFC \( \beta = -0.432, p = .009 \), right anterior insula \( \beta = .287, p = .039 \), and mPFC \( \beta = .365, p = .026 \) each significantly contributed to the model (Figure 2). Secondary analyses examining CAPS symptom subscales found that this model was significant for avoidance subscale symptoms, such that activation in ROIs at pretreatment accounted for 32.3% of the variance in change in avoidance scores from pretreatment to posttreatment, \( R^2 = 0.323, F(7,44) = 2.45, p = .029 \). This model was not significant for re-experiencing or hyperarousal symptoms.

### 3.5 Functional connectivity

#### 3.5.1 Differences between PTSD and CC groups

There were no differences in connectivity for any of the seeds examined between participants with PTSD and CCs at pretreatment \((p > .05)\).

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**TABLE 2** Mean (SD) and number (%) for participants with PTSD who completed treatment, compared with those who did not complete treatment

<table>
<thead>
<tr>
<th></th>
<th>Completers</th>
<th>Non-Completers</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>36</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>32.9 (8.26)</td>
<td>30.87 (8.49)</td>
<td>.372</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>32 (89%)</td>
<td>20 (91%)</td>
<td>.806</td>
</tr>
<tr>
<td>Marital status (married)</td>
<td>20 (56%)</td>
<td>6 (27%)</td>
<td>.039*</td>
</tr>
<tr>
<td>Race (White)</td>
<td>22 (61%)</td>
<td>15 (68%)</td>
<td>.811</td>
</tr>
<tr>
<td>Pretreatment CAPS</td>
<td>74.44 (14.48)</td>
<td>73.32 (14.67)</td>
<td>.770</td>
</tr>
<tr>
<td>Pretreatment motion</td>
<td>0.702 (1.26)</td>
<td>0.515 (0.327)</td>
<td>.500</td>
</tr>
<tr>
<td>Negative TBI</td>
<td>21 (58%)</td>
<td>12 (55%)</td>
<td>.777</td>
</tr>
<tr>
<td>Current Psych Meds</td>
<td>10 (28%)</td>
<td>2 (9%)</td>
<td>.116</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>9 (25%)</td>
<td>1 (5%)</td>
<td>.058**</td>
</tr>
<tr>
<td>Sedatives/Hypnotics</td>
<td>6 (17%)</td>
<td>1 (5%)</td>
<td>.269</td>
</tr>
<tr>
<td>Comorbid MDD</td>
<td>27 (75%)</td>
<td>15 (68%)</td>
<td>.573</td>
</tr>
<tr>
<td>Comorbid Panic</td>
<td>3 (8%)</td>
<td>7 (32%)</td>
<td>.022*</td>
</tr>
<tr>
<td>Comorbid Alcohol Use</td>
<td>6 (17%)</td>
<td>3 (14%)</td>
<td>.757</td>
</tr>
<tr>
<td>Comorbid GAD</td>
<td>12 (46%)</td>
<td>6 (27%)</td>
<td>.628</td>
</tr>
</tbody>
</table>

Bold text indicates significant differences. Abbreviation: MDD, major depressive disorder; GAD, generalized anxiety disorder.

*Significance < .05.

**Significance < .10.

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3.5.2 | Relationship between neural connectivity and symptom change

During implicit emotional processing, there were no significant relationships between connectivity patterns at pretreatment and change in CAPS scores from pretreatment to posttreatment ($p > .05$).

During emotion modulation by attention shifting, greater connectivity between the right dIPFC seed and superior parietal cortex at pretreatment had a trend-level association with reductions in CAPS scores from pretreatment to posttreatment ($p = .052$ FWE corrected; Figure 3a). Furthermore, increase in connectivity between dIPFC and superior parietal cortex from pretreatment to posttreatment was associated with an improvement in symptoms from pretreatment to posttreatment ($p < .05$ FWE corrected; Figure 3b).

During emotion modulation by appraisal, greater connectivity between left amygdala seed and superior parietal cortex at pretreatment predicted greater decrease in CAPS scores from pretreatment to posttreatment ($p < .05$ FWE corrected; Figure 4a). On the contrary, less connectivity between left amygdala and dIPFC from pretreatment to posttreatment was associated with an improvement in symptoms from pretreatment to posttreatment ($p < .05$ FWE corrected; Figure 4b).

4 | DISCUSSION

This study examined whether patterns of pretreatment brain function (both activation and connectivity) associated with emotion processing and modulation differ in PTSD compared with CC, and whether patterns of brain function were associated with symptom response to PTSD treatment. The SEAT was used to probe emotion processing and modulation, and patterns of activation on SEAT replicated prior findings in other samples (Duval et al., 2018; Liberzon et al., 2015; Wang et al., 2016). Our results document changes in brain activation during SEAT from pretreatment to posttreatment, and identify relationships between brain function (both activation and connectivity) and treatment response.

Activation in the anterior insula decreased from pretreatment to posttreatment during implicit emotional processing and emotion modulation by appraisal. This suggests diminished response or “habituation” of emotions/salience processing regions, and is consistent with previous observation that PTSD patients, responsive to PE, demonstrated reduction in anterior insula activation during anticipation of negative images, as compared with treatment nonresponders (Simmons, Norman, Spadoni, & Strigo, 2013). Prior findings also demonstrate that SSRIs reduce activation in emotion processing regions from pretreatment to posttreatment in anxiety and depression (Saxena et al., 2003; Whalen et al., 2009). However, in our study, reductions in anterior insula activation were not associated with symptom change, suggesting that change in anterior insula activation may not be indicative of a treatment mechanism, and may be representative of habituation or practice effects.

Importantly, we observed relationships between brain activation at pretreatment and symptom change from pretreatment to posttreatment, during emotion modulation by appraisal. Participants with...
PTSD who displayed greater activation, in both emotion processing (anterior insula) and modulation (mPFC) regions, and less activation in an attentional control (dlPFC) region, had greater improvements in symptoms. This is in contrast to previous reports of reduced activation in emotion processing regions being associated with symptom improvements following psychotherapy, fear extinction, and treatment with SSRIs (Fonzo et al., 2017a, 2017b; Rauch et al., 2000; Rougemont-Bücking et al., 2011; Saxena et al., 2003; Whalen et al., 2009). This study's findings can be viewed as consistent, however, with previous research suggesting that greater trauma engagement during PE is associated with better outcomes (Tuerk et al., 2018; Wangelin & Tuerk, 2015). The differences in tasks might also contribute to inconsistent findings in the literature, and in the case of more "naturalistic" tasks like appraisal during SEAT, greater general task engagement may be associated with symptom improvements.

Our findings further demonstrate that pretreatment levels of connectivity between superior parietal cortex and dlPFC (associated with attentional control), and amygdala (associated with emotion processing) were associated with symptom improvement. Better treatment outcomes were associated with stronger connectivity between attention control regions during attention modulation of emotion. During emotion modulation by appraisal, stronger connectivity between amygdala and superior parietal cortex, and less connectivity between amygdala and dlPFC, were associated with symptom improvements. The finding that enhanced connectivity within attention control regions was associated with symptom improvements is consistent with the finding that participants with PTSD demonstrate deficits in attention control (Russman Block et al., 2016) and is also consistent with recent findings that greater connectivity between emotion modulation regions was associated with symptom improvements following PE (Fonzo et al., 2017a, 2017b). Our findings suggest that patients who begin treatment with greater connectivity within executive control networks and between executive control and emotional processing networks are better able to benefit from treatment. Thus, neural activation and connectivity during emotion modulation (both by attention shifting and appraisal) seem to be important constructs associated with PTSD treatment response.

Somewhat surprisingly, we did not find pretreatment differences in brain activation or connectivity between PTSD and CC groups. This "baseline" lack of group difference could be the result of several factors, including relatively low power due to the smaller CC group. The SEAT, involving affective faces and indoor/outdoor scenes may not probe specific PTSD-related differences as robustly as trauma-related tasks. There is evidence that exposure to adversity and trauma itself may alter brain function associated with emotion processing and regulation (Bremner, 2006; Evans et al., 2016; Liberzon et al., 2015). Our procedure to match control participants to the PTSD participants based on trauma exposure could have obscured our ability to detect group differences, as all participants reported significant trauma. The fact that we did observe correlations between brain activation during SEAT and PTSD symptom change, suggests that there may be modifiable factors that do not reach group-level significance, but change at an individual level. Such individual factors, associated with executive control and emotion processing, may allow people to more effectively make use of treatment.

**FIGURE 4** Symptom improvement was predicted by (a) connectivity between left amygdala ROI seed and superior parietal cortex (−36, −19, 52) at pretreatment and (b) change in connectivity over time between left amygdala ROI seed and dlPFC (36, 20, 43) during modulation by appraisal (Like/Dislike > Male/Female). Scatter plots are provided for illustration purposes only. ROI, regions of interest.
Due to treatment drop-out, and logistical challenges associated with all participants being scanned in one location, our final sample was underpowered to detect differences in neural function between the three treatment groups. While treatment arm was not a significant predictor of symptom change, collapsing across treatment types obscured our ability to examine differences in neural mechanisms associated with different treatment modalities. Future studies should continue to investigate whether patterns of neural activation can predict response to different types of treatments with larger samples. In addition, participants without posttreatment assessments were not included in our pretreatment to posttreatment analyses, preventing any conclusions regarding changes in brain function that may occur in those who do not complete treatment. Participants in this study were primarily young male Veterans with combat trauma, or earlier eras of combat. About half our sample of female participants, participants with PTSD resulting from non-combat trauma, or earlier eras of combat. About half our sample screened positive for having experienced a mild TBI. While presence of TBI did not differ between groups and was not associated with symptom change, it is impossible to rule out impacts of TBI on brain function, PTSD symptoms, and treatment response. Finally, we did not include a nontreatment control group to examine changes in symptoms and brain function over time, in the absence of treatment. The addition of a nontreatment control would help further distinguish between treatment-specific and nonspecific changes over time in future studies.

Our findings suggest that treatment outcomes in combat-related PTSD are associated with brain function in circuits underlying emotion processing and modulation. Emotion appraisal appears to be a particularly important process to examine, as activation in emotion processing and modulation regions during emotion appraisal at pretreatment were associated with PTSD symptom change. This study is one of the first to examine task-based functional connectivity in a real-world PTSD treatment study, with evidence to suggest that connectivity between regions involved in emotion processing and modulation as well as attentional control, are important predictors of treatment response.

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CONFlict OF INTERESTS
The authors declare that there are no conflict of interests.

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

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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