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Neural affective mechanisms associated with treatment responsiveness in veterans with PTSD and comorbid alcohol use disorder

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Abstract

Post-traumatic stress disorder (PTSD) is associated with neuro-physiological abnormalities reflecting increased anticipatory anxiety and reactivity to traumatic cues. It remains unclear whether neural mechanisms associated with PTSD treatment responsiveness, i.e. hyperactivation of the affective salience network in the brain, extend to a comorbid PTSD and substance use disorder population.

Thirty-one Veterans with PTSD and co-occurring alcohol use disorder (AUD) were randomly assigned to either prolonged exposure or a non-exposure based treatment. They completed an affective anticipation task while undergoing fMRI, immediately prior and after completing treatment.

After controlling for type and length of treatment, larger reduction of PTSD symptoms was associated with decreased anticipatory activation to negative trauma-related cues in the right pre-Supplementary Motor Area (pre-SMA), a region associated with emotion regulation. Smaller reduction in PTSD severity was associated with enhanced anticipatory activation to those cues within the right para-hippocampal region, an affective processing region.

Our findings suggest that post-treatment reductions in anticipatory reactivity to trauma-related cues in the pre-SMA and para-hippocampal area are associated with larger PTSD symptom reduction in individuals with co-occurring PTSD and AUD. These results may offer neurofeedback training targets as an alternative to or enhancement of other PTSD treatment modalities in this population.

Keywords

PTSD; Negative anticipation; Stimex; Fmri; Prolonged exposure; Seeking safety

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1. Introduction

Disruptions in the anticipation and processing of traumatic cues or "triggers" is a hallmark of Posttraumatic-Stress Disorder (PTSD) and is intricately related to each of the four clusters of PTSD symptoms, i.e., re-experiencing, avoidance, negative cognitions, and physiological arousal. Dysregulation of the neuro-endocrine stress response system is associated with enhanced physiological arousal and threat monitoring. Such hyperarousal is likely to play a critical role in perpetuating the cycle of anticipatory anxiety (negative thoughts and arousal) and re-experiencing symptoms (e.g., flashbacks, nightmares) by activating and generalizing traumatic memories to trauma-unrelated contexts (Hayes et al., 2012; Sherin and Nemeroff, 2011), which may in turn increase hypervigilance and avoidance of those trauma-related cues (Foa, 2006). Understanding how the neurophysiological substrates of such anticipatory anxiety relates to PTSD severity and treatment responsiveness may help identify new treatment targets for individuals with PTSD, including those with clinical comorbidities such as alcohol and substance use disorders who may have particularly high traumatic cue reactivity and anticipatory anxiety (Brady et al., 2000; Coffey et al., 2002).

At the neural level, evidence points to a dysregulation of the fear appraisal and regulation system in PTSD. Neuroimaging studies suggest that individuals with PTSD have greater activation of the emotional salience network, including the amygdala, anterior insular cortex, and the dorsal anterior cingulate cortex (ACC)/pre-supplementary motor areas (SMA). The amygdala has been robustly involved in processing affective salience, while the insula is implicated in interoceptive awareness (Paulus and Stein, 2006) including prediction error and expectancy violation monitoring (Preuschoff et al., 2008). The dorsal ACC/pre-SMA region has been associated with monitoring of emotional conflict and emotional awareness (Etkin and Wager, 2007; Lazarov et al., 2017), and the pre-SMA has been proposed as an extension of the dorsal ACC emotional salience hub (Jilka et al., 2014; Nachev et al., 2008). Finally, the hippocampus and parahippocampal area, regions associated with encoding and activating of episodic memories (Van Strien et al., 2009), are recruited during the anticipation of pain and other emotionally salient stimuli (Brooks et al., 2013; Brown and Jones, 2008; Simmons et al., 2004). Importantly, this region is more activated, along with salience network regions, in individuals with PTSD both with and without affective or substance use comorbidities (Falconer et al., 2008; Linnman et al., 2011; Sakamoto et al., 2005; Semple et al., 2000). Such pattern of increased emotional salience processing is coupled with reduced activation of ventrolateral prefrontal cortex (PFC), regions associated with reflective regulation of negative emotion and associated decrease in emotional salience network recruitment (Etkin and Wager, 2007; Shin and Liberzon, 2010). Overall, this points to a pattern of increased processing and monitoring of emotionally salient stimuli as well as ineffective regulation of this network in PTSD, leading to a failure to downregulate psychophysiological response to traumatic cues.

While most evidenced-based treatments for PTSD aim to reduce anticipatory negative emotion associated with trauma, exposure-based treatments appear particularly effective at decreasing traumatic cue reactivity, particularly in individuals with co-occurring PTSD and substance use disorders (Coffey et al., 2006; Nosen et al., 2014; Rauch et al., 2004). Prolonged exposure (PE), a first-line manualized treatment for PTSD (Department of

Veterans Affairs, 2017), is grounded in classical conditioning principles and the premise that trauma-related cues become conditioned to elicit a heightened stress response (Foa et al., 2007; Foa, 2006). Both imaginal and in-vivo exposure to those cues are thought to facilitate regulation of the distress they evoke, so that cue-related anticipatory anxiety can be extinguished (Foa, 2006). In contrast, other types of empirically based PTSD treatments typically involve cognitive behavioral strategies focused on coping better in the present, and do not include a focus on exposure to memories of past traumatic events, e.g., Seeking Safety (SS) (Najavits, 2002). However, such modalities may still facilitate some degree of exposure to traumatic memories, as trauma is discussed and processed with regard to how trauma is affecting patients in the present. Present-focused treatments may also successfully decrease anticipatory dysregulation symptoms in other ways, e.g., through practice of cognitive reframing and relaxation techniques.

Consistent with the above neural findings, several cognitive-behavioral treatment studies have linked a decrease in PTSD symptoms with post-treatment reduced activation of the salience network during anticipation of negative stimuli, particularly the amygdala and insula (Aupperle et al., 2013; Felmingham et al., 2007; Simmons et al., 2013b). A study of combat Veterans undergoing 6–8 months of trauma-focused therapy found that, relative to PTSD persistence, PTSD remission was associated with lower pre-treatment activation of dorsal ACC, amygdala, and insula to negative pictures, similar to healthy Veteran controls' activation patterns (Van Rooij et al., 2015). Although some of these changes could relate to treatment-specific effects (e.g., exposure-based vs not), they were observed regardless of treatment structure, which may more primarily relate to mechanisms of change associated with resolution of PTSD symptoms. For instance, the above study (Van Rooij et al., 2015) identified affective neural markers of PTSD treatment responsiveness across a range of trauma-focused treatments with distinct modalities (e.g., cognitive processing therapy, eye-movement desensitization and reprocessing/EMDR, etc). Moreover, these studies did not specifically control for the level of alcohol and substance use (e.g., as these may relate to avoidance symptoms and neurophysiological changes). Thus, it remains unclear whether the above findings may extend to a comorbid PTSD and alcohol use disorder (AUD) population. In particular, some of the neural systems associated with PTSD severity decrease in a non-comorbid PTSD population may be more complexly affected by heavy alcohol use and hinder responsiveness of these neural regions to treatment regardless of modality. A more limited or distinct set of neurophysiological markers may also be identified as more responsive to PTSD symptom change and/or treatment modality in individuals with comorbid PTSD and AUD.

To assess affective anticipation in this study, we used the Stimulus Expectancy Task (STIMEX) which has been used extensively in both clinical and healthy populations, and shown to reliably activate salience network areas (e.g., insula, amygdala) (Aupperle et al., 2013; Aupperle et al., 2011; Simmons et al., 2004; Simmons et al., 2006; Simmons et al., 2013b) as well as psychophysiological markers of hyperarousal (e.g., startle response) (Acheson et al., 2012) in anticipation negative affective stimuli. Importantly, affective anticipation activation patterns associated with this paradigm can differentiate individuals with anxiety (Simmons et al., 2006; Simmons et al., 2011) and PTSD (Aupperle et al., 2012; Simmons et al., 2013a; Simmons et al., 2013b) from healthy controls. The goals

of this study were to: 1) extend previous neural studies of negative anticipation in PTSD and identify treatment-related changes in affective anticipation among individuals with co-occurring PTSD and AUD, the most prevalent substance use comorbidity in Veterans with PTSD (Pietrzak et al., 2011); and 2) assess the distinct relationship of treatment type vs treatment responsiveness (operationalized as PTSD symptom deduction) with neural processing changes supporting affective anticipation. An additional exploratory goal was to assess the relationship between alcohol use change (assessed by proportion of heavy drinking days) and neural activation associated with negative anticipation. Based on the above research, we hypothesized that both PTSD symptom reduction and PE (relative to a non exposure-based treatment) would have independent effects on decreasing anticipatory anxiety to trauma cues, reflected by pre-to-post decreases in activation of emotional salience and processing areas, including subcortical regions (e.g., amygdala, hippocampal area), insula, and dorsomedial prefrontal/pre-SMA areas.

2. Methods

2.1. Participants

This study protocol was approved by the VA San Diego Human Subjects Review Board and all participants gave written informed consent. A total of 51 Veterans recently diagnosed with PTSD and comorbid AUD with heavy drinking (i.e., >20 days of heavy drinking within the last 90 days not in a restricted environment) were recruited for the fMRI study. Participants from the parent study (clinical trial.gov number: NCT01601067; (Norman et al., 2019) were randomly assigned to one of two evidence-based behavioral treatments, PE or SS. SS is an integrated protocol focusing on coping skills for both PTSD and comorbid substance use disorders (Najavits, 2002). This treatment addresses four components, including cognitive skills, behavioral skills, interpersonal skills, and case management. In contrast, PE focuses on both imaginal exposure to the traumatic event and in-vivo exposure to avoided activities/ locations associated with the trauma (Foa et al., 2007; Foa, 2006). This treatment encourages processing of trauma related emotions and cognitions during exposure. Both therapies were 12 sessions with the option to extend to up to 16 sessions if therapy goals were not yet met. Attendance in the current study ranged from 5 to 16 sessions (see below). Treatment was administered by trained therapists supervised by licensed clinicians in an individual therapy format at the San Diego VA Substance Abuse/Mental Illness (SAMI) clinic.

Participants in the parent study were offered the opportunity to be screened for the neuroimaging portion of the study during their parent study consent appointment. Exclusion criteria included: being at acute suicidal risk, lifetime diagnosis of bipolar disorder or schizophrenia, and fMRI-related criteria (i.e., irremovable ferromagnetic material, pregnancy, claustrophobia). Any participant who received less than 4 face-to-face 90-minute sessions of therapy were excluded from the study, as such minimum treatment dose has been shown to be effective in reducing PTSD symptoms with both cognitive behavioral therapy (Sijbrandij et al., 2007) and PE (Cigrang et al., 2017; Rauch et al., 2017) modalities. This approach allowed us to maximize inclusion of treatment responders while controlling for dosage effects in the subsequent analyses. Overall, 5 participants dropped out of the study before completing treatment, and 14 participants dropped out of the study later but were

unable to complete Post-treatment assessment. In total, 31 participants (about 61% of the baseline sample) with both Pre- and Post-treatment assessments were included in the present analyses.

Participants completed a clinical interview and a functional magnetic resonance imaging (fMRI) session during which they performed the Stimulus Expectancy Task at two timepoints: within 1–2 weeks before (pre-treatment) and after completing treatment (post-treatment). Lifetime DSM-IV Axes I and II diagnoses were assessed with the Structured Clinical Interview for DSM-IV (SCID)(First et al., 1995) and the Clinician-administered PTSD scale for DSM-5 (CAPS-5)(Weathers et al., 2018), which has a high inter-rater reliability (i.e., Cohen Kappa coefficients > .75 for PTSD diagnosis (Aker et al., 1999). Level of alcohol use, including days of heavy drinking (defined as >4 drinks per day in women and >5 drinks per day in men), was assessed with the timeline followback for a 90 days retrospective period (Sobell et al., 1988).

2.2. Stimulus expectancy task (STIMEX)

To measure potential changes in negative affective anticipation in relation to treatment responsiveness and/or treatment type, participants completed the STIMEX while undergoing fMRI, both prior to and immediately after completing treatment. The STIMEX is designed to assess the perturbation from anticipating affective stimuli on neural processes supporting performance on a continuous performance task (CPT), which measures one's ability to maintain selective attention on a repetitive task, e.g., cue-matched button presses (Simmons et al., 2006). In the task, participants had to press a 'Left' or 'Right' mouse button whenever they saw a blue circle or blue square, respectively, accompanied by a medium 500 Hz tone (CPT). Each individual CPT trial were 2s long. Participants were instructed that if the squares or circles turned green, accompanied by 250Hz tone, a relaxing nature image would appear (n=86), whereas if they appeared in red and accompanied by 1000Hz tone, a negative combat-related image would appear (n=86). Positive, affective control images were selected from the International Affective Picture System (Bradley and Lang, 2007). Negative images were selected from a picture database, and included military combat related images from Iraq. Image presentation started 6 seconds after stimulus onset (anticipation phase) and lasted 2 seconds (see Fig. 1). There are a total of 290 trials (total duration 580 s), including 154 task control trials with no anticipation. Trial condition (CPT, positive-anticipation, negative-anticipation) was pseudo-randomized. Behavioral data were collected and scored for accuracy and latency of response during the CPT.

2.3. Image acquisition and preprocessing

Participants completed each of their scanning sessions (baseline and post-treatment) on a 3T Siemens scanner with a twelve-channel head array coil. For each participant, T2*-weighted echo planar imaging run sensitive to blood oxygenation level-dependent (BOLD) contrast was collected while they completed the task (TR=2000msec, TE=40msec, 64×64 matrix, 20 4-mm axial slices, 290 scans). The fMRI acquisitions were time-locked to the onset of each trial. The task was projected on a screen visible to participants through a mirror in the head coil and participants used standard 4-key button press device to respond to stimuli. During the same experimental session, a high resolution T1-weighted image was

collected for each participant (MPRAGE, TR=11.4msec, TE=4.4msec, flip angle=10°, field-of-view=256 × 256, 1 mm³ voxels).

2.4. fMRI analyses

2.4.1. Individual-level analyses—Structural and functional image processing and analysis were completed using analysis of functional neuroimages (AFNI) software (Cox, 1996) and R statistical packages (Pinheiro et al., 2011). Echo planar images were slice-time (AFNI:3dTshift) and motion-corrected and aligned to high-resolution anatomic images in ANTsR (antsRegistration:"SynBold"). Preprocessing steps also included temporal whitening and a CompCor component-based noise correction. Volumes with >2% voxels marked as outliers were censored and dropped from the analysis (AFNI: 3dToutcount). Outlier voxels in the time series were interpolated (AFNI:3dDespike). Due to signal noise, a band pass (-lowpass 0.08; -highpass 0.009) was applied to functional data. Time course of the BOLD response during positive (affective control) and negative image anticipation relative to the active CPT control was modeled with a General Linear Model (GLM) using 3dDeconvolve/3dREMLfit (modeled with the linear interpolation TENT function) for the epoch starting at stimulus onset over the following 18 seconds (modeled by 9 time GLM regressors). This approach allowed us to estimate the hemodynamic response in the affective condition of interest (negative-anticipation) relative the affective control (positive-anticipation).

2.4.2. Group-level analyses—Three types of effects on the negative anticipation phase were investigated: treatment type (PE vs SS), pre-to-post change in PTSD symptom severity, pre-to-post change in heavy alcohol use. In order to estimate the specific independent effect of PTSD symptom change vs treatment, and given the constraints of our sample size and data points, we conducted separate analyses, each controlling of the effect of the other. For each analysis, a voxel-wise linear mixed-effects (LME) model was applied to the regressor t statistics of our first-level 3dREMLfit using the R statistical software lme4 package (Pinheiro et al., 2011). In a first LME analysis, a treatment type (PE vs SS) × Visit (Pre- vs Post-Treatment) × Time (i.e., 9 TENT regressor) interaction was included, with baseline/pre-treatment CAPS score, Pre- to Post- change in CAPS score, baseline level of heavy drinking (i.e., percentage of heavy drinking days assessed over retrospective assessment TLFB period), and number of therapy sessions received (to account for treatment dosage) as covariates. A second LME tested a CAPS score × Visit (pre- vs post-treatment) × Time interaction was included, with baseline CAPS score, treatment type (PE vs SS), baseline level of heavy drinking, and number of therapy sessions received as covariates. A third LME included percentage of heavy drinking days × Visit (pre- vs post-treatment) × Time interaction, with baseline CAPS score, treatment type (PE vs SS), baseline level of heavy drinking, and number of therapy sessions received as covariates. In these LMEs, subject was treated as a random factor and all independent variables were centered. Variance inflation factors (VIFs) were estimated for each model to gage any potential collinearity and over-specification problems (e.g., VIF>5; R:usdm). We note that Pre-to-Post change in heavy drinking was not included in the first two models as a covariate because: a) treatment groups did not differ on this measure (see below) and b) inclusion of such covariate resulted in model convergence failures due excessive collinearity (i.e., VIFs>5; see Supplemental Material for group-level baseline analyses).

Voxelwise t-statistics for each interaction contrast of interest were extracted and submitted to a multiple comparisons correction to determine a threshold cluster size based on Monte Carlo simulations (AFNI: 3dFWHMx, 3dClustSim). Based on a voxel-wise a priori probability of $p<.001$, a minimum of 6 contiguous voxels was found to result in a corrected cluster-wise activation probability (i.e., familywise error/FWE) of $p<.05$. Finally, for visualization and descriptive purposes, average percent signal difference for each time point regressor was extracted from regions of activation that were found to survive this cluster thresholding correction.

3. Results

3.1. Participants characteristics and clinical profile

Participants were mostly male (83.8%) with a mean age of 38.5 (SD=10.8). The sample included 54.8% non-Hispanic Caucasian, 19.4% Hispanic, 6.5% African American, 6.5% Asian American, 3.2% American Indian, and 9.7 % mixed race participants. Most participants had completed some college (61.3%), while others graduated from college (29.0%), or had completed high-school/GED (9.7%). Treatment groups (PE vs SS) did not differ on these demographics or in the average number of therapy sessions completed during treatment, M=12.2 (SD=2.8; $ps>.05$; Table 1).

As expected, PTSD symptom severity significantly decreased between Pre-treatment (M=43.5, SD=9.0) and Post-treatment (M=24.5, SD=14.0) assessments, average Pre- to Post-treatment change=−22.3, t (30)=7.8,$p<.001$. Average percentage decrease in CAPS from baseline was −44.7% (SD=32%), which was significantly greater in the PE (−67.0%) relative to the SS condition (−26.5%; t(30)=3.9,$p<.001$). Based on a median split on Pre-Post CAPS difference scores (Median=−24), individuals with low CAPS decrease had CAPS difference scores ranging from −2 to −19 (M=−7.8), while those with high CAPS decrease had CAPS difference scores ranging from −24 to −36 (M=−27.9). This grouping was used to summarize behavioral and neural differences pertaining to individuals' CAPS decrease (i.e., PTSD symptom decrease) in subsequent tables and figures (while actual Pre-, Post-treatment, and Pre-Post Change CAPS scores were used in the data analyses; see Methods). The average Pre- to Post-treatment difference in percentage of heavy drinking days was −36.0% (SD=27.7%), which represented an average percentage change from individual baseline of −74.9% (SD=28.3%). Treatment did not significantly differ in such patterns of heavy drinking change ($p>.05$; see Table 1).

3.2. Behavioral performance

3.2.1. Response latencies—Overall, response times were similar across task conditions Continuous Task/No Anticipation: Mean=905ms, Positive/Affective Control Anticipation: Mean=905ms, Negative Anticipation: Mean=911ms; $\chi^2(2)=.2,p>.05$). Visit (Pre- vs Post-treatment) was not predictive of response time (Pre-Treatment=912ms; Post-Treatment=901ms) and did not interact with condition to predict response time ($\chi^2(2)=4.5,p>.05$). There were no main effect of treatment (PE vs SS) on response latencies ($\chi^2(1)=1.4,p>.05$) or any interaction with visit and task condition ($\chi^2(5)=4.8,p>.05$). Similarly, CAPS score was not a significant predictor of response time ($\chi^2(1)=.8,p>.05$)

and did not interact with visit and task condition ($\chi^2(5) =2.1, p>.05$) to predict response time (see Table 2).

3.2.2. Performance accuracy—As expected, participants' accuracy on the continuous performance task was high (Mean=96.5%), which did not differ across conditions (Continuous Task/No Anticipation: Mean=96.8%, Positive/Affective Control Anticipation: Mean=96.8%, Negative Anticipation: Mean=95.8%; $\chi^2(2)=.9, p>.05$). Accuracy rates were also similar between Pre- and Post-treatment assessments ($\chi^2(1)=1.6, p>.05$). Treatment group (PE vs SS) was not significantly predictive of accuracy overall ($\chi^2(1)=2.4, p>.05$) and did not significantly interact with visit or task condition to predict accuracy ($\chi^2(5)=1.3, p>.05$). Similarly, CAPS score was not a significant predictor of accuracy ($\chi^2(1) =3.1, p>.05$), and did not interact with visit or task condition ($\chi^2(5) =1.9, p>.05$; see Table 2).

3.3. fMRI analyses

3.3.1. Treatment-related neural modulation of negative anticipation—
Controlling for baseline symptom severity, change in PTSD symptoms, baseline and change in heavy drinking level, and number of therapy sessions, we found no cluster of activation consistent with a Treatment × Visit × Time interaction on negative anticipation.

3.3.2. PTSD symptom change-related neural modulation of negative anticipation—Two clusters were identified consistent with a CAPS × Visit × Time interaction on BOLD signal during negative anticipation. One region was located in the right pre-Supplementary Motor Area (SMA)/Brodmann Area 6 (volume=10 voxels/640mm^3; Peak-voxel (x, y, z): 11, 35, 57; F=25.1, p<.001; Fig. 2A). In this region, individuals with greater pre-to-post CAPS decrease (described for ease of understanding by grouping individuals into low and high CAPS-decreasers based on a median split of CAPS Pre-Post difference scores) exhibited a greater deactivation in response negative anticipation after treatment relative to their baseline assessment (Fig. 2B, top-left graph). In contrast, individuals with lower CAPS decrease, i.e., those with smaller reduction of PTSD symptoms, exhibited a positive activation to negative anticipation both before and following treatment, with an earlier peak post-treatment (Fig. 2B, bottom left graph). Moreover, at baseline, high and low-CAPS decreasers had a similar pattern of activation to negative anticipation (Fig. 2B top-right graph), whereas high-CAPS decreasers exhibited less activation to negative anticipation post-treatment (Fig. 2B bottom-right graph).

Another cluster of activation consistent with a significant CAPS × Visit × Time interaction during negative anticipation was identified within the right para-hippocampal gyrus/Brodmann Area 19 (volume=8 voxels/512mm^3; Peak-voxel (x, y, z): 19, −44, −4; F=20.1, p<.001; Fig. 3A). In this region, high CAPS-decreasers showed a similar deactivation before and after treatment (Fig. 3B top-left graph), whereas low CAPS-decreasers' neural pattern changed from a deactivation to positive activation (Fig. 3B bottom left graph). Before treatment, individuals with both low and high CAPS decrease exhibited deactivations in anticipation of negative images (Fig. 3B top-right graph). After treatment, a positive activation to negative anticipation was observed among low CAPS-decreasers,

whereas high CAPS-decreasers exhibited a deactivation to such negative anticipation (Fig. 3B bottom-right graph).

3.3.3. Heavy drinking change-related neural modulation of negative anticipation—Controlling for baseline PTSD symptom severity, baseline heavy drinking level, treatment type (PE vs SS), and number of therapy sessions, we found no cluster of activation consistent with a percentage of heavy drinking days × Visit × Time interaction on negative anticipation.

4. Discussion

The goal of this study was to identify neural mechanisms of negative affective anticipation associated with PTSD treatment responsiveness in a comorbid PTSD and AUD population. While both Prolonged Exposure (PE) and Seeking Safety (SS) were associated with a significant pre-to-post decrease in PTSD symptoms, PE resulted in a significantly larger decrease in PTSD symptoms relative to SS. Pre-to-post decrease in PTSD symptoms, independently of treatment type, was associated with pre- to-post neural changes in two areas associated with emotional processing, including the pre-SMA and para-hippocampal regions. Individuals with larger decreases in PTSD symptoms (i.e., better treatment responsiveness) exhibited a reduced anticipatory activation to negative cues, whereas those with lower reductions in PTSD symptoms showed an enhanced activation during negative anticipation in those regions after treatment. After controlling for pre-to-post change in PTSD symptoms, no additional activation change pattern related to treatment type (PE vs SS) was identified.

Negative anticipation neural activity was associated with the degree of PTSD symptom change in the right pre-SMA, a prefrontal region adjacent to the dorsal ACC. In this cluster, high vs low treatment responders, as defined by the degree of pre-to-post treatment CAPS score change, did not differ at baseline with minimal anticipatory activation to negative cues. Post-treatment, the high responder group (those with higher CAPS decrease) exhibited a significant de-activation compared to baseline, whereas low responders exhibited a similar but earlier activation peak when anticipating negative cues. The dorsal ACC/pre-SMA region has been associated with emotional processing and regulation (Etkin and Wager, 2007; Lazarov et al., 2017), particularly more explicit type of regulation such as re-appraisal (Etkin et al., 2015). The significant pre-to-post deactivation in this region among high CAPS decreasers suggests that individuals who reduced PTSD symptoms to a larger extent may be more likely to modulate such type of affective processing, with a reduced need to engage this region after treatment. In contrast, those with a lower CAPS decrease may still be relying on such explicit regulation strategy following treatment. Relatedly, among Veterans with combat-related PTSD performing an affective re-appraisal task, lower pre-treatment activation of the dorsomedial PFC, an emotion regulation region adjacent to the dorsal ACC, was associated with greater PTSD symptom reduction (Joshi et al., 2020). Overall, these findings support the notion that reduced neural affective regulatory needs may be a key indicator of better treatment responsiveness and clinical improvement. While explicit regulation strategies were neither instructed nor assessed in the present study, future research should incorporate such assessment to help elucidate individual differences in affective

anticipation processes among PTSD patients with comorbid AUD. Individuals with alcohol dependence show greater pre-SMA activation in anticipation of conflict, which has been linked to compensatory mechanism for cognitive control (Hu et al., 2015). It may be useful to gage the efficacy of such affective regulation strategies in individuals with more complex affective reactivity profiles, such as those with comorbid PTSD and AUD, for whom bottom up emotional processing systems (e.g., limbic regions) may be more severely dysregulated upon entering treatment (Semple et al., 2000).

Change in PTSD severity following treatment was also related to activation change in the right para-hippocampal region. Specifically, those who responded better to treatment (with larger symptom decrease) exhibited a similar deactivation pattern during negative anticipation before and after treatment, whereas those with lower PTSD severity decrease showed a significant increase in activation following treatment in this region. The parahippocampus region activates in anticipation of aversive images in a similar task as used in the present study (Simmons et al., 2004) and, like the insular cortex, has been robustly involved in affective anticipation, including negative (Brown and Jones, 2008) and rewarding stimuli (Brooks et al., 2013, food). Notably, parahippocampal activation has been observed in response to both explicit and implicit presentation of aversive/trauma related cues in individuals with PTSD (Linnman et al., 2011; Sakamoto et al., 2005; Thomaes et al., 2009). Hyper-activation has also been observed in individuals with comorbid PTSD-AUD (Semple et al., 2000) and heavy alcohol use has been linked to lower para-hippocampal gray matter volumes and impaired memory (Meda et al., 2018). This points to a more reactive affective processing role of this region, along with other salience processing regions such as the amygdala, in the context of negative anticipation. One possible explanation for the present results is that reduced ability to respond to a behavioral intervention and reduce PTSD symptoms may relate to a paradoxical enhanced reactivity of this region to trauma-related cues. This could reflect a failure to habituate to or re-frame the context of traumatic cues despite being exposed to them in therapy.

In this study, we did not find any symptom-related or treatment-related effects in activation of the amygdala or the insula, two salience network regions implicated in aversive anticipation. Decreased activations in those regions have been observed following behavioral treatment in individuals with PTSD (Aupperle et al., 2013; Duval et al., 2020; Felmingham et al., 2007; Simmons et al., 2013b; Van Rooij et al., 2015) . However, in a recent clinical trial examining treatment-related neural change in affective processing, reduced pre-to-post treatment insula activation was not related to PTSD symptom changes based on CAPS measures (Duval et al., 2020). Thus, such treatment-related reduction in insular activation to affective processing may not necessarily have a systematic relationship with the magnitude of symptoms change. While it is difficult to speculate on a null finding, one possible interpretation is that heavy alcohol use in this dual diagnosis PTSD sample may impact the neurobiology of these regions to limit change in response to treatment. Alcohol dependence has been linked to lower amygdala volume (Wrase et al., 2008; Zhang et al., 2013), while individuals with PTSD and comorbid alcohol abuse show abnormal activation of the amygdala in a continuous performance task (Semple et al., 2000). Similarly, AUD is associated with reduced insular volume and activation (Droutman et al., 2015; Makris et al., 2008; Senatorov et al., 2014). Given the high rate of heavy drinking at baseline in

this sample, amygdala and insula neural reactivity to the anticipation of traumatic cue may be less detectable or more resistant to change after a behavioral intervention, relative to other more plastic areas (e.g., hippocampus/para-hippocampal region) or regions involved in explicit regulation (e.g., pre-SMA). The present results suggest that the pre-SMA and para-hippocampal regions may be more promising markers of aversive anticipation modulation in individuals with co-occurring PTSD and AUD.

This study has several limitations, including the absence of no-treatment and PTSD-only control groups, and a relatively small sample size (albeit with a typical attrition rate). Treatment length was also variable, although we controlled for treatment length in the analyses. The results of this study are also specific and only generalizable to a population of Veterans with co-occurring PTSD and AUD, which is a frequent comorbidity in the general population (Smith and Cottler, 2018) and particularly common in trauma-exposed Veterans (Norman et al., 2018; Norman et al., 2019). However, the absence of results specific to heavy drinking or AUD symptoms, perhaps related to the limited range of severe alcohol use at baseline in the present sample, is a limitation. Future investigations should assess the neural signature of negative anticipation in a comorbid PTSD-AUD population with a wider range of alcohol use pattern and severity. Finally, the present study focused on assessing neural affective mechanisms of change associated with treatment responsiveness in individuals with comorbid PTSD and AUD. A distinct and equally important question for future research will be to identify baseline affective predictors of treatment responsiveness in this population, which will be critical in order to develop robust predictive models of treatment response.

In conclusion, among individuals with PTSD and comorbid AUD, greater PTSD symptom reduction after a cognitive behavioral treatment is associated with reduced engagement of a medial prefrontal region linked to emotional regulation during anticipation of traumatic cues. In addition, low PTSD symptom reduction was associated with enhanced neural reactivity of the parahippocampal region, a more reactive affective processing area, during such negative anticipation. These effects extend above and beyond treatment-specific factors, such as the degree of exposure therapy and amount of treatment sessions. Given that PE has been associated with larger decreases in PTSD symptoms relative to non trauma-focused comparison treatments (Watts et al., 2013), our findings are congruent with recent studies highlighting the effectiveness of PE in reducing anticipatory cue reactivity at the neural level (Aupperle et al., 2013; Simmons et al., 2013b). Our results are also consistent with the notion that PE's effectiveness in reducing PTSD symptoms may be mediated by a reduced neurophysiological reactivity to traumatic cues. The regions identified in this study may thus be promising neural targets for Veterans with comorbid PTSD and AUD in order to help assess aversive anticipation reactivity and predict Veterans' ability to successfully reduce such reactivity with a cognitive behavioral intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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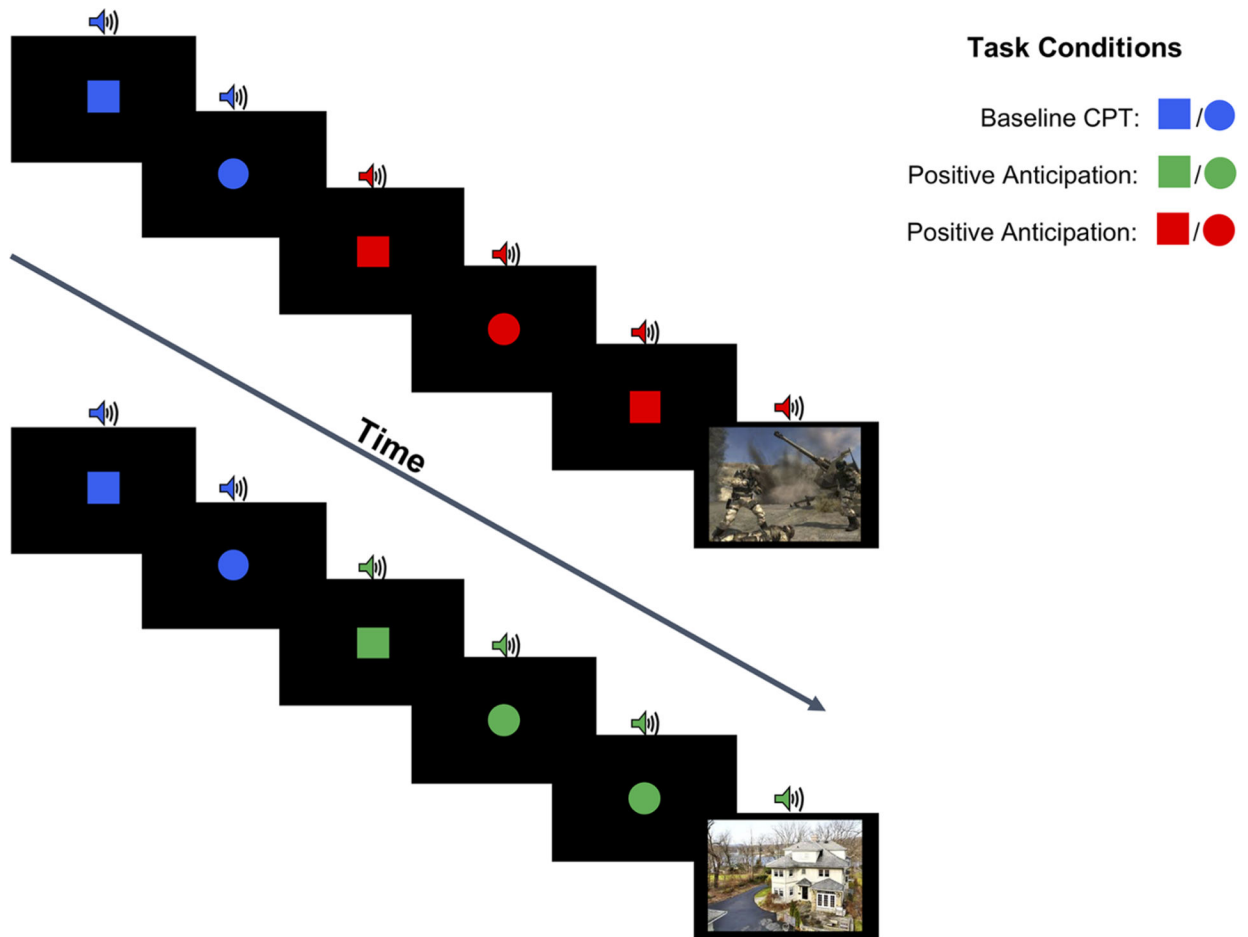
Fig. 1.
Stimulus Expectancy Task (STIMEX) Timeline. In the task, participants had to press a 'Left' or 'Right' mouse button whenever they saw a blue circle or blue square, a medium 500 Hz tone (CPT condition). If the squares or circles turned green, accompanied by a 250 Hz tone, a relaxing nature image would appear (Positive Anticipation). If they appeared in red and accompanied by a 1000 Hz tone, a negative combat trauma-related image would appear (Negative Anticipation). Each individual CPT trial and image presentation were 2s long. Anticipation phase (red or green trials) lasted 6s.
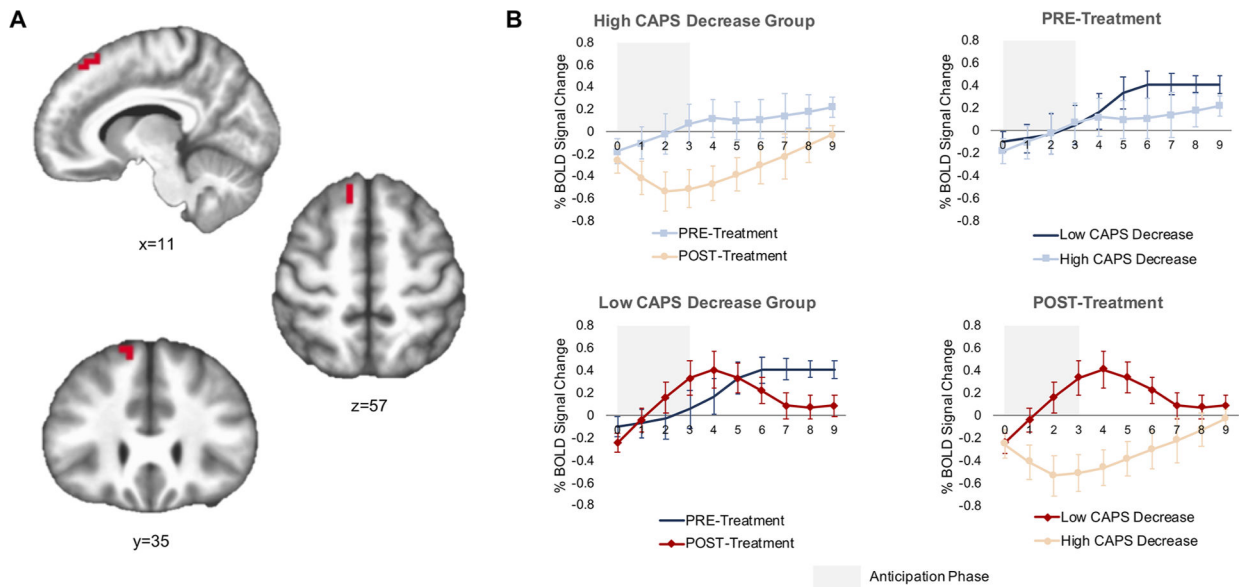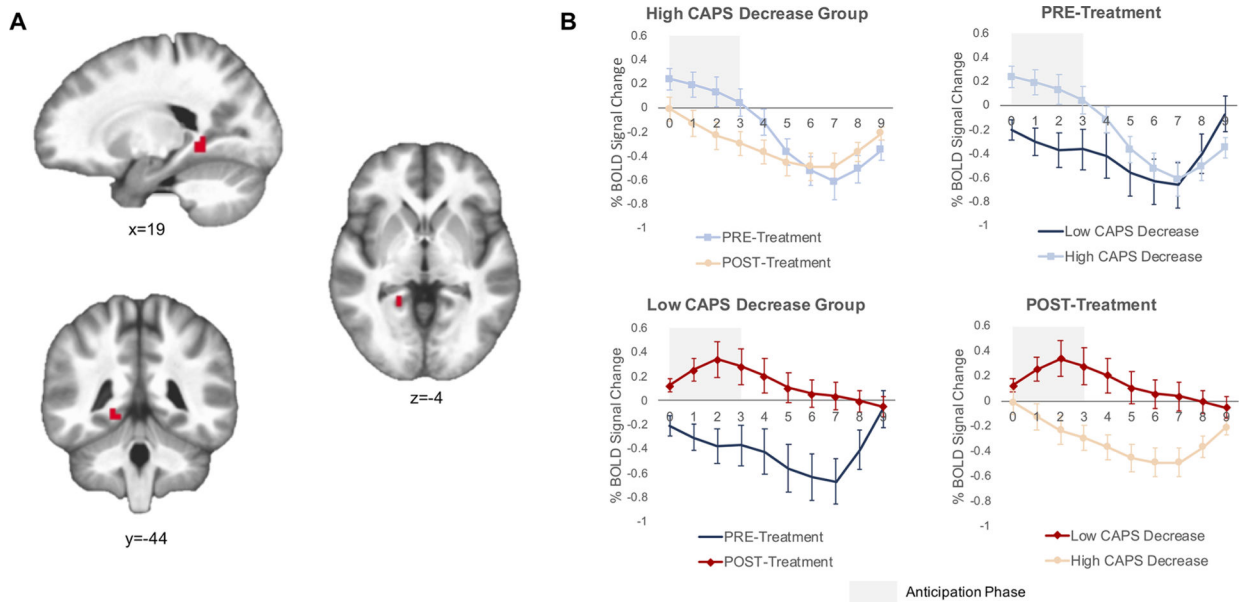
Fig. 2.
A. Cluster of activation reflecting a significant Time × CAPS × Visit (Pre vs Post-Treatment) during anticipation of negative images in the right pre-SMA (supplementary motor area/ Brodmann Area 6; cluster size= 11 voxels/704 mm^3). **B.** Descriptive activation time course by visit (pre/post) and extent of CAPS decrease (represented here as low vs high CAPS decrease based on a median split for ease of presentation; i.e., Low CAPS Decrease: Pre-Post CAPS Difference >−.24; High CAPS Decrease: Pre-Post CAPS Difference <−.24; CAPS decrease was entered as a continuous variable in the present analyses). *Left Side:* Individuals with greater CAPS decrease (Pre- to Post-Treatment), i.e., those with greater reduction of PTSD symptoms, exhibited a deactivation during negative anticipation at Post-Treatment (top graph); in contrast, individuals with lower CAPS decrease, i.e., those with smaller reduction of PTSD symptoms, exhibited a positive earlier peak of activation of similar amplitude to negative anticipation following treatment between pre- and post-treatment assessments (bottom graph). *Right Side:* Before treatment, groups with a low vs high CAPS decrease had minimal and similar anticipatory activation to negative images (top graph); following treatment, individuals with a low CAPS decrease exhibited a positive activation during negative anticipation, whereas those with a high reduction in PTSD symptoms exhibited a deactivation to such negative anticipation (bottom graph). All graphs (x axis): task trial time period in units of Repetition Time (TR) = 2s; Error bars=SEM.

Fig 3.
A. Cluster of activation reflecting a significant Time × CAPS × Visit (Pre vs Post-Treatment) during anticipation of negative images in the right para-hippocampal gyrus/Brodmann Area19; cluster size= 8 voxels/512 mm^3). **B.** Descriptive activation time course by (pre/post) and extent of CAPS decrease (represented here as low vs high CAPS decrease based on a median split for ease of presentation, i.e., Low CAPS Decrease: Pre-Post CAPS Difference >−.24; High CAPS Decrease: Pre-Post CAPS Difference <−.24; CAPS decrease was entered as a continuous variable in the present analyses). *Left Side:* Individuals with greater CAPS decrease (pre- to post-treatment), exhibited similar deactivations during negative anticipation before and after treatment (top graph); relative to baseline, individuals with lower CAPS decrease exhibited a significantly higher activation to negative anticipation following treatment (bottom graph). *Right Side:* Before treatment, both groups of individuals with a low and high CAPS decrease exhibited similar deactivations in anticipation of negative images (top graph); at Post-Treatment, individuals with a low CAPS decrease exhibited a positive activation during negative anticipation, whereas those with a high reduction in PTSD symptoms exhibited a deactivation to such negative anticipation (bottom graph). All graphs (x axis): task trial time period in units of Repetition Time (TR) = 2s; Error bars=SEM.

Table 1

Participant demographic and clinical profile

	Aggregate (n=31)		SS Group (n=17)		PE Group (n=14)		Group Diff. (p val)
	Mean / %	SD	Mean / %	SD	Mean / %	SD	
Demographics							
Age	38.5	10.8	36.6	9.5	40.9	11.8	n.s.
Education [a]	61.3% Some College		64.7% Some College		57.2% Some College		n.s.
Gender [a]	83.8% Male		88.2% Male		78.6% Male		n.s.
Ethnicity [a]	54.8% non-Hispanic White		52.9% non-Hispanic White		57.2% non-Hispanic White		n.s.
Clinical Severity							
CAPS: Pre-Treatment	43.5	9.0	43.3	9.7	43.8	8.2	n.s
CAPS: Post-Treatment	24.5	14.0	31.9	11.4	15.3	11.4	$p<.01$
CAPS: Pre - Post Change	−44.7%	32.0%	−26.5%	26.5%	−67.0%	23.2%	$p<.001$
Childhood Family Environment (DRRI [b] Section B Total)	47.6	16.1	50.3	15.0	44.3	17.3	n.s.
Percentage of Heavy Drinking Days: Pre-Post Difference	−36.0%	27.7%	−35.2%	28.9%	−37.1%	26.0%	n.s.
Treatment Intensity							
Number of therapy sessions	12.2	2.8	12.0	3.1	12.4	2.4	n.s.

[a] Mode; SS=Seeking Safety; PE=Prolonged Exposure; SD=Standard Deviation; CAPS=Clinician-Administered PTSD Scale; n.s. = group difference (PE vs SS) not statistically significant ($p>.05$)

[b] DRRI=Deployment Risk and Resiliency Inventory, possible range for DRRI Section B (Childhood Family Environment) is 15 to 75; higher scores are indicative of greater cohesion, accord, and closeness among family members (in Veteran samples, mean score ranges from 52 to 58 (SD:10–25)(King et al., 2006).

Table 2

Participant's reaction times and accuracy on the stimulus expectancy task (STIMEX)

	Aggregate (n=31)		Low CAPS Decrease (n=16)		High CAPS Decrease (n=15)		Group Diff. (p value)
	Mean/%	SD	Mean/%	SD	Mean/%	SD	
REACTION TIMES [a]							
Pre-Treatment							
Positive Anticipation	906.8	124.7	907.3	157.4	906.3	93.2	n.s.
Negative Anticipation	906.1	112.2	919.6	132.6	893.4	95.0	n.s.
No Anticipation/CPT	925.1	109.6	915.1	133.5	935.2	86.7	n.s.
Post-Treatment							
Positive Anticipation	902.1	112.1	906.1	125.3	899.2	110.9	n.s.
Negative Anticipation	913.9	110.0	922.1	123.5	907.5	106.9	n.s.
No Anticipation/CPT	883.8	114.2	887.7	125.3	880.9	114.0	n.s.
ACCURACY							
Pre-Treatment							
Positive Anticipation	96.9%		98.2%		95.5%		n.s.
Negative Anticipation	95.0%		95.9%		94.2%		n.s.
No Anticipation/CPT	97.1%		97.9%		96.3%		n.s.
Post-Treatment							
Positive Anticipation	96.8%		97.4%		96.2%		n.s.
Negative Anticipation	96.6%		96.7%		96.6%		n.s.
No Anticipation/CPT	96.4%		96.5%		96.4%		n.s.

[a] Reaction times in ms; CAPS=Clinician-Administered PTSD Scale; Low CAPS Decrease: Pre-Post CAPS Difference >−.24; High CAPS Decrease: Pre-Post CAPS Difference <−.24; CPT=Continuous Performance Task; n.s.: p>.05 (not statistically significant).