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Opponent Effects of Hyperarousal and Re-experiencing on Affective Habituation in Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Aberrant emotion processing is a hallmark of posttraumatic stress disorder (PTSD), with neurobiological models suggesting both heightened neural reactivity and diminished habituation to aversive stimuli. However, empirical work suggests that these response patterns may be specific to subsets of those with PTSD. This study investigates the unique contributions of PTSD symptom clusters (re-experiencing, avoidance and numbing, and hyperarousal) to neural reactivity and habituation to negative stimuli in combat-exposed veterans.

METHODS: Ninety-five combat-exposed veterans (46 with PTSD) and 53 community volunteers underwent functional magnetic resonance imaging while viewing emotional images. This study examined the relationship between symptom cluster severity and hemodynamic responses to negative compared with neutral images (NEG>NEU).

RESULTS: Veterans exhibited comparable mean and habituation-related responses for NEG>NEU, relative to civilians. However, among veterans, habituation, but not mean response, was differentially related to PTSD symptom severity. Hyperarousal symptoms were related to decreased habituation for NEG>NEU in a network of regions, including superior and inferior frontal gyri, ventromedial prefrontal cortex, superior and middle temporal gyri, and anterior insula. In contrast, re-experiencing symptoms were associated with increased habituation in a similar network. Furthermore, re-experiencing severity was positively related to amygdalar functional connectivity with the left inferior frontal gyrus and dorsal anterior cingulate cortex for NEG>NEU.

CONCLUSIONS: These results indicate that hyperarousal symptoms in combat-related PTSD are associated with decreased neural habituation to aversive stimuli. These impairments are partially mitigated in the presence of re-experiencing symptoms, such that during exposure to negative stimuli, re-experiencing symptoms are positively associated with amygdalar connectivity to prefrontal regions implicated in affective suppression.

Keywords: Affective neuroscience, Emotion, fMRI, Habituation, Heterogeneity, PTSD

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Following traumatic events, individuals often experience acute stress responses, which are adaptive and usually dissipate over a period of days or weeks. However, in posttraumatic stress disorder (PTSD), trauma-related disturbances persist or intensify over time and include co-occurring symptoms of trauma re-experiencing, avoidance and numbing, and hyperarousal (1). Considerable work suggests that PTSD confers abnormalities in affective processing ranging from exaggerated emotional responses to trauma cues and emotion regulation deficits (2), to alexithymia (3). Furthermore, both heightened physiological reactivity to aversive stimuli (4–6) and diminished habituation of these reactions (4,7) have been implicated in PTSD-related difficulties. However, each of these response patterns characterizes only subsets of individuals with PTSD (8–10), suggesting that heterogeneity of symptom profiles may be associated with distinct aspects of emotion difficulties. In particular, evidence suggests that hyperarousal symptoms may be associated with increased neural responsiveness to negative stimuli (11) and difficulties down-regulating emotions (12). In contrast, findings indicate that re-experiencing symptoms may be associated with effortful suppression of intrusive emotions and thoughts (13,14). While the use of inhibitory control strategies may be associated with lower sympathetic arousal in the short term (15), over time, use has been linked to increased PTSD symptoms (2,15). Additionally, avoidance and numbing symptoms may manifest as a general disengagement from emotional processing with reduced neural responsiveness across stimuli (16–18). Here we seek to directly examine the relationships among symptom clusters and neural correlates of reactivity to negative stimuli and habituation over time.

Neurobiological models of emotional difficulties in PTSD implicate exaggerated amygdalar reactivity to aversive stimuli (19) coupled with inadequate modulation by ventromedial prefrontal cortical and hippocampal regions (20). Diminished habituation to negative stimuli has also been identified using

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both skin conductance and hemodynamic measures (4,12), providing preliminary evidence for PTSD-related habituation deficits in the amygdala (7,21) and subgenual cingulate cortex (21,22), in contrast to healthy individuals who exhibit habituation of neural responses in the amygdalae (23,24), as well as prefrontal (23,25,26) and parietal cortices (25).

Despite evidence linking PTSD to altered affective processing, inconsistencies in the presence and pattern of the underlying neural correlates exist (5,6,10,27). For example, meta-analytic evidence of PTSD-related hyperactive amygdalar responses to negative stimuli has been mixed, with one meta-analysis finding both hyperactivity and hypoactivity within the amygdala (5), one finding right amygdala hyperactivity (19), and two others finding PTSD-related hyperactive amygdalar responses under some but not all conditions (6,27). Discrepant findings may be explained, in part, by heterogeneity of symptom presentation. That is, although many individuals with PTSD exhibit heightened emotional responses to aversive stimuli and increased physiological responses, some experience a detached or dissociative emotional reaction coupled with stable or decreased physiological responses (8,9). Similar symptom-specific relationships have been identified in a variety of behavioral and neural correlates of PTSD, including measures of interpersonal functioning (28), treatment response (29), regional brain volumes (30), resting-state functional connectivity (31), and functional brain networks (32). However, research on the relationships between symptom clusters and biomarkers of affective responding in PTSD, a cardinal feature of the disorder, has thus far been limited [see (16,33,35)].

To test the possibility of systematic associations between heterogeneity of affective responding and PTSD symptom clusters, we examined the respective relationships of re-experiencing, avoidance and numbing, and hyperarousal symptom severity with neural responses to aversive (compared with neutral) images in a large cohort of combat-exposed veterans. Given prior work suggesting that neural habituation is a more reliable metric of affective responding than average neural activation (24), we primarily focused on the relationships between symptoms and neural habituation. Specifically, we hypothesized that greater severity of hyperarousal symptoms would be associated with diminished neural habituation to negative versus neutral images in limbic and salience network regions (12,36). Additionally, based on work showing greater re-experiencing severity with increased suppression of affective and physiological responses to aversive stimuli (13,15,37), we hypothesized that greater severity of re-experiencing symptoms would be associated with enhanced neural habituation to negative versus neutral images.

METHODS AND MATERIALS

All procedures were carried out in accordance with the Institutional Review Boards of Baylor College of Medicine and the Salem Veterans Affairs Medical Center. After receiving a description of the study's procedures and being given the opportunity to ask questions, all participants provided written informed consent.

Participants

Ninety-eight veterans who were deployed during post-9/11 conflicts (Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn) were recruited from the community as well as from Veterans Affairs medical centers. Data from 3 veterans were excluded for excessive head motion during functional magnetic resonance imaging (MRI), resulting in a final sample of 95 veterans (current PTSD: n = 46; no current PTSD: n = 49). Given our interest in dimensional effects of PTSD symptoms, we included veterans who did not meet full diagnostic criteria for PTSD but exhibited symptoms indicating subthreshold PTSD [as defined by Blanchard *et al.* (38); n = 16]. Of note, all veterans, regardless of PTSD status, reported experiencing one or more traumatic event(s) during deployment that met criterion A1 of the DSM-IV diagnostic criteria for PTSD (39). Additionally, 53 community volunteers were recruited to provide a civilian comparison group; our primary purpose for including this group was to illustrate normative brain responses to affective stimuli in a representative sample of the population (i.e., not restricted to age and gender demographic characteristics of our Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn veterans).

Exclusion criteria included MR contraindications; claustrophobia; pregnancy; substance use disorders, other than nicotine dependence, during the past month; and head injury with loss of consciousness >30 minutes. For the veteran group, additional psychiatric exclusion criteria were significant current suicidal or homicidal ideation, or history of schizophrenia, schizoaffective disorder, delusional disorder, or organic psychosis. For the civilian comparison group, use of psychotropic medication was an additional exclusion criterion.

Assessment of Psychiatric Disorders

In the veteran sample, the Clinician-Administered PTSD Scale for DSM-IV (CAPS) (40) and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (41) were used to assess PTSD diagnosis and severity of symptoms (42), and other Axis I disorders, respectively (Supplemental Methods and Materials). The past month's symptom cluster severity scores for re-experiencing, avoidance and numbing, and hyperarousal as measured by the CAPS were used as our primary covariates of interest.

Emotion Paradigm

During functional MRI, participants viewed images from the International Affective Picture System (43) (Figure 1A). Each image was presented for 4 seconds, and 8 to 10 images of the same valence (negative [NEG], positive, or neutral [NEU]) were presented in each block. Twenty-four blocks (8 of each type) were pseudo-randomly presented, separated by jittered fixation blocks of 4 to 12 seconds for a total task duration of approximately 18 minutes (Supplemental Methods and Materials).

Image Acquisition and Preprocessing

Magnetic resonance images were collected using 3T Siemens Trio MR scanners (Siemens, Erlangen, Germany). Whole-brain functional images were continuously acquired during a single run and a high-resolution T1-weighted structural scan was acquired. MR images were analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome

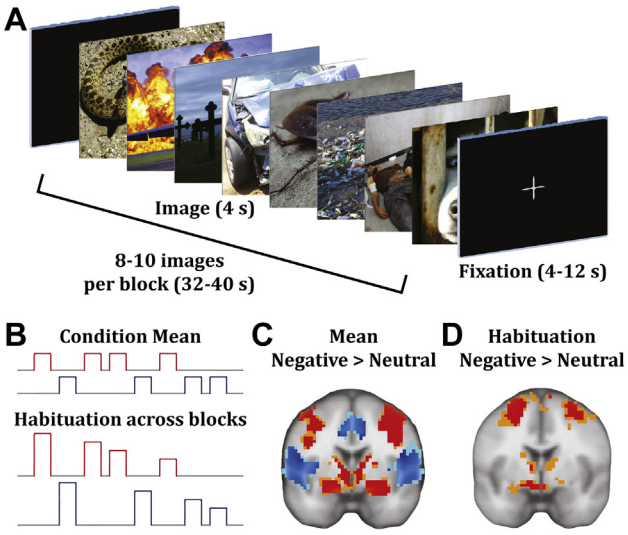

Figure 1. Experimental paradigm and neural response to negative and neutral images. **(A)** Blocks of 8 to 10 images of the same valence (negative, positive, or neutral) were presented, followed by a fixation screen of 4 to 12 seconds. **(B)** Block order was pseudo-randomized with ≤2 blocks of the same valence occurring consecutively. Eight blocks of each valence were displayed (24 blocks total) for a task duration of 17 minutes and 44 seconds. Regressors of interest for the imaging analyses modeled the overall effect of each valence (negative or neutral) and a parametric modulator used to capture the effect of habituation across blocks of each valence. For the contrast of negative>neutral, areas of significance for the overall mean **(C)** and for habituation **(D)** in the veteran group (n = 95) are shown ($p < .05$, familywise error–cluster-corrected, coronal slices displayed at y = −1 in Montreal Neurological Institute standard space). Red and orange indicate significant positive t values at cluster-defining primary thresholds of $p < .001$ and $p < .005$, respectively. Similarly, blue and light blue indicate significant negative t values at cluster-defining primary thresholds of $p < .001$ and $p < .005$, respectively. Comparable results for the civilian group (n = 53) can be found in Supplemental Figure S1. Owing to copyright restrictions associated with the International Affective Picture System, images in **(A)** are taken from the Open Affective Standardized Image Set (92).

Trust Centre for Neuroimaging, London, UK) and MATLAB R2010b (The MathWorks, Inc., Natick, MA). Standard preprocessing was performed. Additional details regarding scanning parameters and preprocessing methods are provided in the Supplemental Methods and Materials.

Whole-Brain Analyses

First-level general linear models included 2 regressors of interest (mean and habituation) for each valence (NEG, positive, and NEU) (Figure 1B). Specifically, valence-specific mean responses (hereafter, MEAN) were modeled as boxcar functions corresponding to each block's duration, and valence-specific patterns of habituation and/or sensitization of hemodynamic responses (hereafter, LIN) were modeled as a linear parametric modulation of each block corresponding to block order over time. For habituation analyses, positive β values reflect habituation and negative β values reflect sensitization. Regressors were convolved with a canonical hemodynamic response function. Six motion parameters were included as regressors, and a 180-second high-pass temporal filter was applied.

Analysis of effects related to positive image blocks is beyond the scope of this study. Here, we specifically focus on effects associated with NEG and NEU image blocks. Accordingly, β maps for contrasts of interest (i.e., NEG_MEAN>NEU_MEAN, NEG_LIN>NEU_LIN) were brought to the second-level for group analyses.

Whole-brain multivariate regressions were conducted on NEG_MEAN>NEU_MEAN and NEG_LIN>NEU_LIN contrasts, with simultaneous inclusion of 3 covariates of interest corresponding to current re-experiencing, avoidance and numbing, and hyperarousal symptom cluster severity. Depression severity, presence of probable mild traumatic brain injury (mTBI), combat exposure severity, and use of psychotropic medication were included as controlling covariates, as prior research indicates that these variables may be associated with distinct neural alterations (44–47) (Supplemental Methods and Materials). Given the expected correlation among PTSD symptom cluster severity scores (and to a lesser degree, controlling covariates), variance inflation factors were calculated for the covariates included in regression analyses; all covariates had variance inflation factors <5, indicating that multicollinearity was not a significant issue (48).

To facilitate comparison to prior work that focused on the overall impact of PTSD, we conducted secondary analyses to assess diagnostic and dimensional effects of PTSD. Specifically, for the contrasts of interest, 2-sample between-group Student's t tests were used to assess the effect of PTSD diagnosis within the veteran cohort (excluding veterans with subthreshold PTSD, n = 16). To examine dimensional effects of PTSD severity within the veteran cohort, whole-brain multivariate regressions were conducted on the contrasts of interest, with overall PTSD symptom severity included as a covariate of interest and depression, mTBI, combat exposure severity, and psychotropic medication usage included as controlling covariates.

Unless otherwise noted, all imaging results were assessed for significance using a cluster-level familywise error–corrected threshold of $p < .05$ with a cluster-defining primary threshold of $p < .001$. This thresholding approach has been shown to appropriately control for familywise error in cluster-level analyses employing similar methodology (49).

Exploratory Psychophysiological Interaction Analysis

The results of our primary analyses suggested a mitigating role of re-experiencing symptoms on hyperarousal-related impairments in affective habituation to aversive stimuli, which we hypothesized may be related to the use of suppression techniques. To examine this possibility, we assessed the impact of PTSD symptom clusters on valence-specific (NEG>NEU) functional connectivity of the amygdalae on cortical regions associated with suppression of thoughts and emotions. Specifically, we performed an exploratory generalized psychophysiological interaction analysis (PPI) using the gPPI toolbox (50). An amygdalar seed region was defined as all significant voxels within a bilateral anatomical amygdalar mask for the contrast, NEG_MEAN>NEU_MEAN, with a primary threshold of $p < .005$, for the veteran cohort. Additional gPPI analytic details are included in the Supplemental Methods and Materials. At the group level, the relationships between PTSD

symptom clusters and valence-specific, whole-brain amygdalar connectivity were analyzed, for the contrast of interest, NEG_PPI>NEU_PPI, using a multivariate regression with the same set of covariates as the main analyses.

RESULTS

Demographic and Clinical Characteristics of Participants

Demographic and clinical characteristics of participants are shown in Table 1 (40,41,51–54). The veteran sample included 82 male and 13 female participants, with a mean age of 32.2 years (range: 21–57, SD: 8.2). The civilian cohort included 26 male and 27 female participants, with a mean age of 27.2 years (range: 18–48, SD: 7.6).

Veterans with and without PTSD did not differ on age, gender, race, education, and household income; the diagnostic groups also did not differ on incidence of current anxiety disorders (other than PTSD) or incidence of past substance use disorders. As expected, veterans with PTSD reported more severe symptoms of depression, current PTSD, and lifetime PTSD; veterans with PTSD also had a significantly higher incidence of a current mood disorder diagnosis compared with veterans without PTSD. Veterans with PTSD also reported greater combat exposure, incidence of mTBI, and use of psychotropic medication, relative to veterans without PTSD. The Supplement provides additional information about psychotropic medication use, characteristics of the veteran cohort when separated into 3 diagnostic groups (current, subthreshold, no PTSD), and characteristics of the civilian cohort (Supplemental Methods and Materials; Supplemental Results; and Supplemental Tables S1–S3).

Neural Responses to Negative Images Compared With Neutral Images

Mean Effects. Veterans exhibited significant positive hemodynamic response for the contrast NEG_MEAN> NEU_MEAN in regions previously implicated in emotion processing including the amygdalae and thalamus as well as the

Table 1. Demographic and Clinical Characteristics of Civilians and Combat-Exposed Veterans With and Without Current PTSD

	Civilians	Combat-Exposed Veterans			Veterans With PTSD vs. No PTSD
Characteristic	All (n = 53)	All (n = 95)	PTSD[a] (n = 46)	No PTSD[a] (n = 49)	p Value[b]
Age, Years	27.2 (7.6)	32.2 (8.2)	32.4 (8.1)	32.0 (8.3)	.82
Education, Years	15.5 (2.0)	14.6 (1.5)	14.3 (1.3)	14.9 (1.7)	.08
Household Income, 1000s of Dollars[c]		45.1 (30.8)	41.3 (24.9)	48.6 (35.2)	.27
Combat Exposure[d]		19.1 (9.5)	21.2 (8.5)	17.0 (10.0)	.03
Depression Symptoms[e]	4.9 (5.9)	17.8 (12.5)	25.1 (11.7)	10.9 (8.9)	<.001
Current PTSD Symptoms[a]		44.7 (30.4)	69.1 (18.3)	21.8 (19.7)	<.001
Re-experiencing		10.2 (8.8)	16.7 (7.2)	4.1 (5.0)	<.001
Avoidance and numbing		18.0 (13.6)	28.9 (8.7)	7.7 (8.1)	<.001
Hyperarousal		16.5 (10.5)	23.5 (6.2)	10.0 (9.5)	<.001
Lifetime PTSD Symptoms[a]		70.9 (39.6)	100.5 (14.5)	43.1 (35.3)	<.001
Re-experiencing		19.5 (12.3)	28.8 (6.1)	10.7 (10.1)	<.001
Avoidance and numbing		27.5 (17.1)	40.0 (7.3)	15.7 (15.1)	<.001
Hyperarousal		23.9 (12.2)	31.7 (4.0)	16.7 (12.7)	<.001
Gender, Female, n (%)	27 (51)	13 (14)	7 (15)	6 (12)	.90
Race, Nonwhite[f], n (%)	23 (43)	37 (39)	20 (43)	17 (35)	.50
Current Mood Disorder[g], n (%)		32 (34)	28 (61)	4 (8)	<.001
Current Anxiety Disorder[g,h], n (%)		12 (13)	9 (20)	3 (6)	.10
Past Substance Abuse[g], n (%)		55 (58)	29 (63)	26 (53)	.44
Positive mTBI Screen[i], n (%)		29 (31)	22 (48)	7 (14)	<.001
Psychotropic Medication[j], n (%)		37 (39)	27 (59)	10 (20)	<.001

Unless otherwise indicated, data are reported as mean (SD) of group. See Supplemental Table S2 for demographic and clinical characteristics of the veteran cohort when separated into 3 groups (PTSD, subthreshold PTSD, and no PTSD).

mTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder.

[a]Past month's diagnosis and severity based on DSM-IV criteria as assessed by the Clinician-Administered PTSD Scale (40).

[b]The p values are based on 2-sample Student's t tests for continuous variables and χ^2 tests for dichotomous variables.

[c]Data not reported for 6 veterans (4 with current PTSD and 2 without current PTSD).

[d]Total raw score on Combat Exposure Scale (51). Data missing for 3 veterans (1 with current PTSD and 2 without current PTSD).

[e]Total score on Beck Depression Inventory-II (52).

[f]Based on participant's self-report.

[g]Diagnosis as assessed by the Structured Clinical Interview for DSM-IV (41); "current" defined as meeting criteria during the past month; "past" defined as meeting lifetime criteria prior to the past month.

[h]Anxiety disorders other than PTSD.

[i]Positive screen on the Brief Traumatic Brain Injury Screen (53).

[j]Psychotropic medication use was defined as self-reported current use of one or more medication(s) listed in the National Institute of Mental Health's publication on Mental Health Medications (54).

precentral gyrus, fusiform gyrus, and inferior frontal gyrus (IFG) (Figure 1C; Supplemental Table S4). Additionally, veterans exhibited significantly negative hemodynamic response bilaterally in the superior and inferior temporal gyri, angular gyri, inferior parietal lobules, posterior insular cortex, precuneus, and orbitofrontal cortex, as well as in the left anterior cingulate cortex (ACC), right posterior cingulate cortex, and right cerebellum. Similar response patterns were seen in the civilian group (Supplemental Figure S1A, Supplemental Table S5). A 2-sample Student's *t* test comparing veterans to civilians found no significant differences.

Habituation and Sensitization Effects. Consistent with prior findings of affective habituation, as a group, veterans exhibited greater habituation across negative blocks than across neutral blocks (NEG_LIN>NEU_LIN) bilaterally in middle temporal gyri, fusiform gyri, parahippocampal gyri, supplementary motor area, frontal eye fields, and precuneus (Figure 1D; Supplemental Table S6). For the contrast of interest, no regions showed significantly less habituation. Similar response patterns were seen in the civilian group (Supplemental Figure S1B, Supplemental Table S7). A 2-sample Student's *t* test comparing habituation patterns of veterans to civilians found no significant differences.

Effects of PTSD Symptom Cluster Severity

Mean Effects. Severity of re-experiencing, avoidance and numbing, and hyperarousal symptoms was not significantly related to the contrast of NEG_MEAN>NEU_MEAN; furthermore, none of the controlling covariates were significantly related to the NEG_MEAN>NEU_MEAN contrast.

Habituation and Sensitization Effects. When accounting for effects of controlling covariates and other symptom clusters, severity of re-experiencing symptoms was positively correlated with habituation to negative versus neutral images (i.e., greater habituation) in a widespread network including the superior and middle temporal gyri, superior and medial frontal gyri, ACC, supplementary motor area, precuneus, and IFG (Figure 2A, left; Supplemental Table S8). No significant relationship was found between severity of avoidance and numbing symptoms and neural response to NEG_LIN>NEU_LIN (Figure 2A, middle). Severity of hyperarousal symptoms was negatively related to neural responses to NEG_LIN>NEU_LIN (i.e., less habituation) in portions of the superior and middle temporal gyri, ACC, IFG, ventromedial prefrontal cortex, precuneus, and anterior insula (Figure 2A, right; Supplemental Table S8).

For NEG_LIN>NEU_LIN, no significant relationship was seen between hemodynamic responses and combat exposure severity or use of psychotropic medication; depression symptom severity was related to increased habituation in the right middle occipital gyrus, and presence of probable mTBI was related to increased habituation bilaterally in the precuneus as well as right midcingulate cortex (Supplemental Figure S2, Supplemental Table S9).

Opponent Effects of Re-experiencing and Hyperarousal. In an overlapping network of regions, re-experiencing and hyperarousal symptoms were related, in opposite directions, to widespread neural habituation to negative versus neutral images (i.e., for NEG_LIN>NEU_LIN, with increasing habituation related to re-experiencing severity and increasing sensitization with hyperarousal severity) (Figure 2B). Avoidance and numbing severity was not related to neural habituation in this network of regions.

Exploratory Analysis of Opponent Effects of Re-experiencing and Hyperarousal. Furthermore, in this same network of regions, we conducted an exploratory analysis of the additive effects of the re-experiencing and hyperarousal symptom clusters on habituation. Given the observed opponent effects of hyperarousal and re-experiencing symptom severity on neural habituation, we calculated each individual's severity discrepancy score (i.e., CAPS hyperarousal score − CAPS re-experiencing score) and entered the scores as independent variables in a linear regression analysis to predict neural habituation in the region of interest for NEG_LIN>NEU_LIN. As depicted in Figure 3, we found a significant negative relationship (adjusted $r^2 = .255$, $p = 1.1 \times 10^{-7}$), such that as the severity discrepancy between hyperarousal and re-experiencing symptoms increased, veterans exhibited diminishing neural habituation in the shared habituation network. These data suggest that combat-exposed veterans with prominent hyperarousal symptoms in the absence of significant re-experiencing symptoms are most likely to exhibit disrupted habituation to aversive stimuli. The Supplement provides additional details regarding the relationship between re-experiencing and hyperarousal symptom severity in this sample (Supplemental Figure S3) as well as analysis of the relationship of these symptoms with habituation and/or sensitization to neutral blocks only (Supplemental Results).

To confirm that these results were robust to individual differences in initial reactivity, secondary analyses were conducted in which absolute habituation, according to Montagu (55), was calculated to obtain habituation metrics that were independent of individuals' initial responses (Supplemental Methods and Materials). Similar opponent effects of re-experiencing and hyperarousal were seen when comparing absolute habituation across negative blocks to absolute habituation across neutral blocks (Supplemental Figure S4).

Exploratory PPI Analysis. For the contrast of interest, no significant effects were seen for avoidance and numbing symptom severity or hyperarousal symptom severity; however, greater severity of re-experiencing symptoms was significantly associated with increased amygdalar connectivity with the left IFG and dorsal ACC for the negative condition relative to the neutral condition (Figure 4).

Effects of Overall PTSD Severity

Overall PTSD symptom severity was not significantly related to hemodynamic responses for either the contrast of NEG_MEAN>NEU_MEAN or the contrast of NEG_LIN>NEU_LIN (see Supplemental Results for test of PTSD diagnostic group differences).

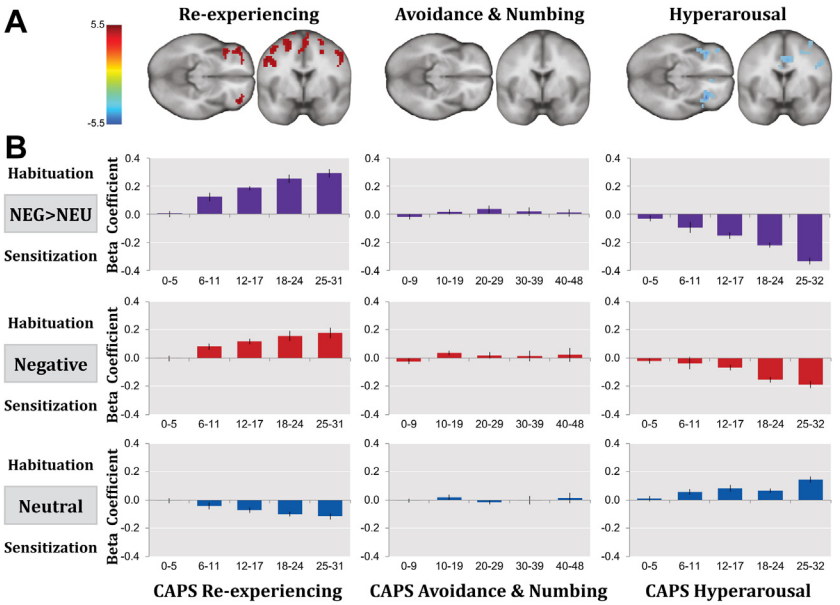

Figure 2. Habituation and sensitization of neural response across blocks of negative and neutral images related to posttraumatic stress disorder (PTSD) symptom clusters. **(A)** The images show the relations between neural habituation for the contrast of negative condition compared to neutral condition (NEG>NEU) and severity of each PTSD symptom cluster ($p < .05$, familywise error–cluster-corrected with cluster defining threshold of $p < .001$, axial and coronal slices shown at Montreal Neurological Institute coordinates z = −11 and y = −1, respectively). Increasing severity of re-experiencing symptoms is positively associated with neural habituation in NEG>NEU (left), while increasing severity of hyperarousal symptoms is positively associated with neural sensitization in NEG>NEU (right). No significant relation is found between avoidance and numbing symptoms and habituation or sensitization to NEG>NEU (middle). To visualize the separable effects of each symptom cluster on neural habituation, we defined a region of interest as the conjunction of re-experiencing and hyperarousal effects, seen in **(A)**, and within this region of interest, extracted the first eigenvariate from the habituation-related NEG>NEU contrast, as well as from habituation-related NEG and NEU contrasts separately. **(B)** The extracted values were used to calculate β estimates of the effect of each symptom cluster controlling for remaining PTSD clusters, depression, mild traumatic brain injury, combat exposure, and use of psychotropic medication. Bar plots illustrate mean β estimates by PTSD symptom cluster severity. Errors bars depict the standard error of the mean for each bin. Differences in habituation and sensitization for NEG>NEU contrast are depicted (top), as well as the separate effects across NEG (middle) and NEU (bottom) conditions. For the habituation-related NEG>NEU contrast, greater severity of re-experiencing is related to greater neural habituation and greater severity of hyperarousal is related to less neural habituation (for effects of controlling covariates, see Supplemental Figure S2). CAPS, Clinician-Administered PTSD Scale for DSM-IV.

DISCUSSION

Here, we sought to determine the associations between symptom clusters of PTSD and neural responsivity to negative emotional stimuli. We found that neural habituation to aversive stimuli relative to neutral stimuli is diminished among veterans with greater hyperarousal symptoms and enhanced among those with greater re-experiencing symptoms. Of note, the opponent associations of hyperarousal and re-experiencing symptoms with neural habituation were evident across a set of regions previously implicated in attention, cognitive control, and affective processing (56), suggesting that both symptom clusters are related to widespread modulation of habituation. Additionally, a significant negative relationship was found between the severity discrepancy of hyperarousal and re-experiencing symptoms and neural habituation in this set of regions, such that veterans who had more severe hyperarousal than re-experiencing symptoms showed the greatest impairment in habituation to negative versus neutral cues.

Hyperarousal's negative effect on neural habituation was seen in regions previously implicated in affective habituation in healthy individuals including the right spatial attention network, ventrolateral prefrontal cortex, dorsomedial prefrontal cortex (57), and anterior insula (58). Diminished habituation in the spatial attention network and other regions involved in attentional control, such as the right IFG (59), is consistent with hypervigilance, a symptom of hyperarousal that has been associated with increased visual scanning and autonomic arousal (60). Threat-related attentional biases have been repeatedly implicated in PTSD, lending support to the suggestion that hyperarousal symptoms may result, in part, from enhancement of these attentional biases (61). Taken together, these findings are in line with a conceptualization of hyperarousal symptoms resulting from a failure to habituate, oversensitization, or a combination of both processes (12).

PTSD-related attentional biases result not only from increased orientation toward threatening stimuli (62), but also from difficulty disengaging from threatening stimuli (63). Such attentional difficulties are associated with greater use of maladaptive coping strategies, such as thought suppression, which has been found to mediate the relationship between attentional interference and re-experiencing symptoms (13). Similarly, decreases in physiological arousal during attempts to reduce negative emotion have been associated with later increases in intrusive memories (37). Here, we found greater re-experiencing severity to be associated with stronger amygdalar connectivity to left IFG and dorsal ACC when viewing negative relative to neutral images, regions consistently implicated in suppression of thoughts and emotions (64–67). One possible interpretation of this finding is that when confronted with aversive cues, individuals with prominent re-experiencing symptoms may engage in coping behaviors such as thought suppression through attentional control, which in the short term may decrease physiological responses but in the long term may also lead to a rebound of intrusive thoughts. Thus, the finding that greater re-experiencing severity is associated with greater neural habituation for the contrast NEG_LIN>NEU_LIN may reflect a process by which individuals with severe re-experiencing symptoms engage in suppression in response to negative stimuli, leading to greater decreases in neural responses across the negative blocks, while potentially also resulting in subsequent rebound of intrusive thoughts.

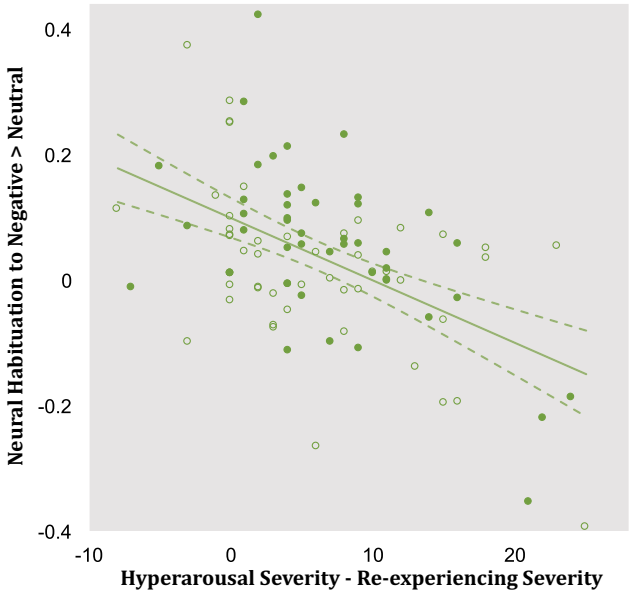

Figure 3. Relation between hyperarousal and re-experiencing severity discrepancy and neural habituation in veterans with and without posttraumatic stress disorder. Using each individual's severity discrepancy score (hyperarousal severity − re-experiencing severity) as a predictor variable, a linear regression analysis was conducted to predict neural habituation to negative>neutral for the network of regions in which habituation showed opponent relations with hyperarousal and re-experiencing severity (shown in Figure 2A). The scatter plot depicts the significant negative relation (adjusted r^2 = .255, $p < .001$) with data from veterans with and without posttraumatic stress disorder represented by filled (●) and open (○) points, respectively; the solid line represents the linear association and dashed lines show ±95% confidence intervals.

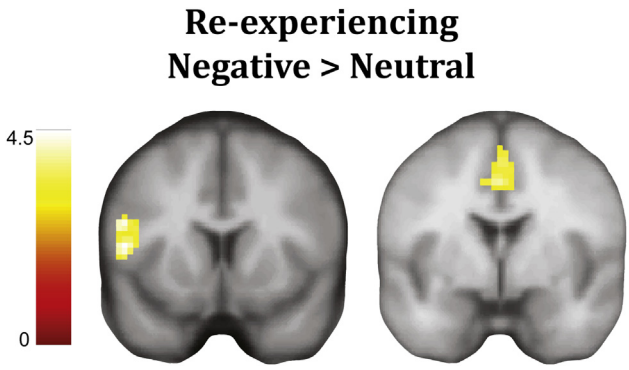

Figure 4. Relation of re-experiencing severity with context-modulated amygdalar connectivity for negative versus neutral conditions. Analysis of the effects of posttraumatic stress disorder symptom clusters on a psychophysiological interaction of amygdalar connectivity and valence (negative>neutral) found a positive relationship between re-experiencing severity and context-modulated amygdalar connectivity with the left inferior frontal gyrus (T_{peak} = 4.56; cluster size: 91 voxels) and dorsal anterior cingulate cortex (T_{peak} = 3.21; cluster size = 70 voxels) ($p < .05$, familywise error–cluster-corrected with cluster defining threshold of $p < .001$). Cluster peaks are located at Montreal Neurological Institute coordinates (−51, 11, 10) and (0, −1, 43) and shown above in coronal slices at y = 11 and y = −1.

No significant differences in neural activity or habituation to aversive images (compared with neutral images) were seen when veterans with PTSD were compared with veterans without PTSD; similarly, overall PTSD severity was not significantly associated with differences in neural activity or habituation to negative relative to neutral images. Given that prior work using similar affective paradigms have found significant diagnostic and dimensional effects of PTSD [e.g., (6,18,27,68–72)], these null results were somewhat surprising.

While the reasons for this inconsistency are unclear, differences in study design may be a potential factor. Prior studies of emotional reactivity in PTSD have sometimes selected for individuals based on heightened psychological or physiological responses to emotional stimuli (73,74). Thus, between-group comparisons may have be driven primarily by hyperarousal symptoms, associated here with diminished habituation. Significant differences in neural responses seen in previous studies may also be attributable to the use of trauma-specific and/or threat-specific stimuli, rather than to the more general negatively-valenced stimuli used in the present study (17,75). Finally, some previous studies have not accounted for potential confounding factors such as severity of trauma exposure [e.g., (69)] and comorbid disorders [e.g., (68,70)]; thus, between-group differences may be attributable to one or more confounding factor(s) rather than to PTSD diagnosis alone. A strength of this study was the accounting for potential confounds including combat exposure, comorbid depressive symptoms, probable exposure to mild traumatic brain injury, and use of psychotropic medications.

Another reason for the discrepant results between this study and previous studies may be related to statistical power. Notably, many previous neuroimaging studies of affective processing in PTSD have had substantially smaller sample sizes than that of the current study [e.g., (76–82)]. While sample size concerns are often focused on increased false-negative rates, low statistical power (as is seen in studies with small sample sizes) also makes false-positive rates more likely (83,84). Additionally, some past neuroimaging studies in this domain have employed statistical thresholds and/or corrections for multiple comparisons that have subsequently been associated with inflated false-positive rates (49).

Limitations

The current study focuses on combat-exposed veterans of post-9/11 conflicts, and almost all of our veteran participants (n = 90; 95%) reported experiencing one or more combat-related trauma(s). In addition, a relatively small number of women were included in our sample (n = 13; 14%). Thus, while our data have the advantage of sample homogeneity, generalizability across gender as well as across other types of trauma is unknown at this time. Additionally, we did not conduct toxicology screens on the day of scanning, so although individuals in our veteran sample were screened via clinical interview to assess criteria for current substance use disorders, we cannot exclude the possibility that one or more individual(s) used illicit substances. Also, as our study examined habituation to negative, relative to neutrally valenced images in general, we cannot draw conclusions about the impact of PTSD symptoms on neural habituation to trauma-specific images. Future research using trauma-specific

stimuli may further elucidate the effect of PTSD symptoms on neural habituation.

Conclusions

To our knowledge, the present data are among the first to show that re-experiencing and hyperarousal symptoms are differentially related to negative affective neural habituation. Moreover, negative affective neural habituation, compared with neutral habituation, is most adversely impacted not by the magnitude of hyperarousal symptoms alone, but rather by the relative severity of hyperarousal symptoms and re-experiencing symptoms. Re-experiencing and hyperarousal symptoms are generally highly correlated (85), and previous research on neural heterogeneity in PTSD has more often focused on differences between symptom clusters thought to reflect heightened responses (i.e., re-experiencing and hyperarousal) and those believed to represent diminished responses (i.e., avoidance and numbing) (8,34). However, the commonality of re-experiencing and hyperarousal clusters is cautioned by animal models of PTSD suggesting that hyperarousal and context-specific responses similar to re-experiencing may develop independently and may be differentially changed by treatment (86–88).

The positive association of re-experiencing symptoms with negative affective habituation suggests the intriguing possibility of a protective compensatory mechanism that offsets adverse effects of heightened arousal. Although re-experiencing is maladaptive in the long term (e.g., repeated intrusive memories result in increased distress), these symptoms have also been associated with coping behaviors [e.g., thought suppression (13,89)] that in the short term may prevent arousal overload (15). Additional research is needed to replicate this relationship and gain a clearer understanding of the impact of re-experiencing on negative affective habituation.

These results also suggest ways in which an individual's symptom presentation may be informative for treatment decisions. For instance, prior work has shown that individuals with severe hyperarousal symptoms are more likely to be treatment nonresponders (29). Moreover, individuals for whom hyperarousal is the most prominent initial symptom cluster show less symptom improvement over time (90). For individuals with prominent hyperarousal symptoms accompanied by minimal re-experiencing symptoms, treatments that facilitate the development of general habituation capacity to aversive relative to neutral stimuli may improve treatment outcomes (91).

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