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Impact of Posttraumatic Stress Symptom Dimensions on Amygdala Reactivity to Emotional Faces

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Abstract

Posttraumatic stress disorder (PTSD) is highly prevalent and associated with impairment, even at the subthreshold level. It is therefore important to identify biological processes that contribute to the pathophysiology of posttraumatic stress symptoms (PTSS). Although neuroimaging research has highlighted the importance of heightened amygdala reactivity to aversive stimuli in PTSS, not all studies have yielded evidence of this relationship. Given that PTSS is comprised of four, factor analytically distinct dimensions of symptoms – re-experiencing, avoidance, hyperarousal, and negative cognitions and mood – it is possible that heightened amygdala reactivity to aversive stimuli is specific to certain PTSS clusters. In a sample of 45 trauma-exposed individuals, the present study therefore examined how specific PTSS clusters relate to amygdala responding during functional magnetic resonance imaging (fMRI) to both negative and positive emotional faces during a well-validated social-emotional task, the Emotional Face Assessment Task (EFAT). Results indicated that hyperarousal symptoms were positively associated with left amygdala reactivity across all emotional face conditions. There was no interaction of hyperarousal by condition (i.e., fearful, sad, angry, or happy faces), and other PTSS clusters were not associated with amygdala reactivity. These results indicate that the hyperarousal cluster of PTSS may have a

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Ethical Statement

All participants provided written informed consent as approved by the local Institutional Review Board at the University of Illinois at Chicago and all procedures complied with the Helsinki Declaration. Our manuscript meets the guidelines for ethical conduct and report of research.

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unique relationship with amygdala reactivity to socioemotional information. The results also corroborate a growing literature suggesting that trauma-exposed individuals characterized by high PTSS hyperarousal symptoms may display exaggerated psychophysiological reactivity to appetitive and aversive stimuli.

Keywords

posttraumatic stress symptoms; amygdala; emotional faces

1. Introduction

Trauma exposure and posttraumatic stress disorder (PTSD) are highly prevalent, and PTSD is disabling (Gadermann et al., 2012). Even at the sub-syndromal level (i.e., when an individual exhibits some, but not all of the required symptoms for a diagnosis), posttraumatic stress symptoms (PTSS) are associated with significant impairment and economic cost (Zlotnick, Franklin & Zimmerman, 2002). Although effective treatments with empirical support are available for PTSS, a significant proportion of individuals fail to respond and experience persistent symptoms over time (Bradley, et al., 2005). It is therefore critical to identify novel, mechanistic treatment targets for which effective interventions can be designed around.

In line with this goal, neuroimaging studies have begun to elucidate the neural processes that contribute to the development and maintenance of PTSS. One neural region that has been researched extensively with respect to PTSD is the amygdala, a limbic structure which mediates fear and anxiety (Davis, 2006; Davis et al., 2010) and the processing of social-emotional stimuli (Fitzgerald & Palmieri, 2005; Morris et al., 1996). For instance, relative to trauma-exposed controls, individuals with PTSD have been found to exhibit greater reactivity of the amygdala during the presentation of trauma-related stimuli (Liberzon et al., 1998). There is also an extensive literature implicating impaired fear extinction, a process of inhibitory learning that involves the amygdala (Barad & Lutz, 2006), in the pathophysiology of PTSD (Milad et al., 2009; Norrholm et al., 2011). Furthermore, amygdala dysfunction has been directly associated with aberrant fear extinction in PTSD, such that exaggerated amygdala reactivity during extinction learning predicts impaired extinction recall (Milad et al., 2009). Individuals with PTSD have also been found to display hyperactivity of the amygdala during the presentation of aversive social-emotional information, such as fearful faces (e.g., Armony et al., 2005; Stevens et al., 2013; Williams et al., 2006), which has shown to be normalized with successful reduction in PTSD symptom severity (Felmingham et al., 2007). Taken together, several studies indicate that PTSD is characterized by exaggerated amygdala reactivity to aversive stimuli, and this neural abnormality has been suggested as a novel PTSD treatment target.

Although amygdala reactivity to aversive stimuli has been emphasized as playing a key role in PTSD, meta-analyses indicate that not all studies have found evidence for this association (Etkin & Wager, 2007; Hayes et al., 2010). For example, several studies have found individuals with PTSD to display blunted amygdala reactivity to aversive stimuli, such as

unpleasant images and trauma-related cues, relative to trauma-exposed controls (Britton et al., 2005; Phan, Britton, Taylor, 2006). Grupe and colleagues (2016) reported no association between PTSS and amygdala reactivity during the anticipation of unpredictable threat. Moreover, results from a recent meta-analysis suggest that amygdala reactivity is more commonly associated with other internalizing conditions, such as social anxiety and specific phobia, than PTSD (Etkin & Wager, 2007).

One factor that may contribute to mixed findings on the relation between PTSD and amygdala reactivity to negative information is the highly heterogeneous nature of posttraumatic stress symptomology, as is evidence by the fact that there are over 600,000 combinations of PTSS that could make up a PTSD diagnosis (Galatzer-Levy & Bryant, 2013). Moreover, multiple factor analytic studies have concluded that PTSS consists of four qualitatively different factors of symptoms: (1) re-experiencing, (2) avoidance, (3) negative cognitions and mood, and (4) hyperarousal symptoms (clusters B, C, D, and E, respectively). Given this heterogeneity, there are likely multiple phenotypes of posttraumatic stress symptomology that may be characterized by distinct neural correlates and thus have separate treatment targets.

Hyperactivity of the amygdala during the processing of negative information may be specific to certain profiles of PTSS. It is therefore necessary to assess how specific PTSS clusters relate to amygdala responding during the presentation of aversive stimuli; however, few studies have addressed this important empirical question. As examples of this approach, Grupe et al. (2016) found a negative association between hyperarousal symptoms only and ventromedial prefrontal cortex reactivity to threat, whereas Hopper et al. (2007) assessed reactivity to trauma-related imagery and found that re-experiencing symptoms were associated with greater right anterior insula and reduced rostral anterior cingulate cortex (rACC) reactivity, and avoidance symptoms were negatively associated with rACC reactivity. Most relevant to the current study, Stevens and colleagues (2013) found a positive association between hyperarousal symptom severity and amygdala reactivity to fearful faces among individuals with PTSD, and this relation was specific to hyperarousal symptoms relative to other DSM-IV clusters (i.e., avoidance and re-experiencing). An association between hyperarousal symptoms and amygdala reactivity is consistent with the broader literature, which implicates the amygdala in the modulation of physiological arousal responses to aversive stimuli (e.g., skin conductance responding; Critchley et al., 2000; Williams et al., 2001). Lastly, with regard to positive affective information, Felmingham et al. (2014) found a negative association between amygdala reactivity to happy faces and emotional numbing (DSM-IV PTSS that were subsumed under Cluster D [negative alterations in cognition/mood], in DSM-5).

These studies provide important initial evidence to suggest that distinct PTSS clusters are associated with aberrant neural affective responding, and hyperarousal symptoms in particular may be characterized by heightened amygdala reactivity to certain negative stimuli. However, several important questions remain. First, only one of the abovementioned studies specifically examined how the amygdala relates to PTSS clusters. This study was limited to examining amygdala reactivity to fearful and neutral faces (Stevens et al., 2013). It is therefore unknown whether the relation between hyperarousal symptoms and amygdala

responding is specific to fearful faces, or generalizes to stimuli of other valences (e.g., happy faces). Moreover, Stevens et al. (2013) included only female, African American participants. It is therefore important to examine amygdala reactivity to fearful faces among individuals with PTSS in a more diverse, generalizable sample. Second, the abovementioned studies used DSM-IV defined PTSS, which were significantly revised for DSM-5 and restructured from three, to four clusters (a change based on numerous factor-analyses of the PTSD symptom structure; Elklit & Shevlin, 2007; Yufik & Simms, 2010). Therefore, it is presently unknown how the four, DSM-5 PTSS clusters relate to amygdala responding to affective stimuli. This is important given that the DSM-5 PTSS clusters are currently referred to in clinical settings and have better psychometric properties than the prior versions. Third, the majority of the abovementioned neuroimaging studies have focused on full-syndromal PTSD, therefore ignoring individuals who are subthreshold – a group that is known to display functional impairment (Gadermann et al., 2012; Zlotnick et al., 2002).

The present study therefore examined how the four, DSM-5 clusters of PTSS – re-experiencing, avoidance, negative cognitions and mood, and hyperarousal – relate to amygdala reactivity to negative and positive affective stimuli. In particular, all participants completed a well-validated social-emotional task designed to elicit amygdala activity, the Emotional Face Assessment Task (EFAT; Hariri et al. 2002; Kirsch et al. 2005), during which participants were presented with positive emotional faces (i.e. happy) and negative emotional faces (i.e., angry, sad, fearful). PTSS was defined dimensionally rather than categorically, to include the full PTSS spectrum. Based on prior findings from Stevens et al., 2013, and the broader literature on the relation between physiological arousal and amygdala reactivity, we hypothesized that hyperarousal symptoms would relate to greater amygdala reactivity, particularly to negative faces (Critchley, 2000; Stevens et al., 2013; Williams et al., 2001). As for happy faces, we posited a potential specific negative association between amygdala reactivity and cluster D (negative cognition/mood), which include the emotional numbing symptoms that were previously found to be negatively associated with amygdala reactivity to happy faces Felmingham et al. (2014).

2. Methods

2.1. Participants

Participants were recruited from the community as a part of a larger investigation on affective and physiological abnormalities across internalizing psychopathology. A variety of advertisements were used to recruit a clinically representative patient population with a range of internalizing disorders and symptoms. In line with the aims of the larger study, participants were included if they either 1) seeking treatment with pharmacotherapy (selective serotonin reuptake inhibitors/SSRIs) or cognitive behavioral therapy (CBT) for anxiety or depressive symptoms (i.e., patients), or 2) had no lifetime history of psychopathology (i.e., healthy controls). Participants were required to be between the ages of 18 and 65 years. Exclusion criteria included an inability to provide consent and read and write in English, a major active medical or neurological problem that could impact psychophysiological and brain function, lifetime history of mania or psychosis, any contraindication to receiving SSRIs, being already engaged in psychiatric treatment,

psychoactive medication use within the past four months, history of traumatic brain injury, and being pregnant.

The study took place at the University of Illinois-Chicago and was approved by the university Institutional Review Board. All participants provided written informed consent after review of the protocol. Participants completed a set of laboratory tasks and battery of questionnaires, which were administered in a counterbalance order to eliminate potential order effects. Participants received cash as payment for participation.

Of the 190 individuals who met inclusionary criteria for the larger study, 51 endorsed a trauma that met Criterion A for PTSD, as defined by DSM-5. Of those 51, 6 were excluded due to poor quality fMRI data (i.e., excessive motion artifact; greater than 2mm displacement in any one direction). The final sample included 45 participants (6 controls, 39 patients). See Table 1 for demographic and clinical characteristics of this sample. All data used in the current study was assessed prior to treatment, participants tested negative on a urine drug screen before fMRI assessment, and none of the participants were taking psychoactive medications at the time of study entry.

2.2. Measure of Posttraumatic Stress Symptoms

Current and lifetime Axis-I psychopathology was assessed using a Structured Clinical Interview for DSM-5 Disorders (SCID-5; American Psychiatric Association [APA], 2013). Of note is that the SCID-5 is a well-validated instrument that allows for the assessment of whether specific symptoms of DSM-defined disorders are absent, subthreshold, or threshold across a range of populations (i.e., individuals with and without a known history of psychopathology; First et al., 2014; Spitzer et al., 1992). The SCID-5 used in the present study was also modified (Shankman et al., *Invited Revision*) such that interview skip-outs were ignored and each and every symptom was given a dimensional rating (1 = not present, 2 = subthreshold, or 3 = present). Because no items were omitted, an assessment of both categorical diagnoses (e.g., PTSD yes/no) and individual symptom severity is allowed. All research staff were trained to criterion on the SCID. After the evaluation, a consensus panel of at least 3 study staff/trained clinicians determined subjects' eligibility and if there were co-occurring disorders, which was the principal disorder warranting treatment. Clinician-determined principal diagnosis was determined by the most severe and impairing symptoms from clinical interviews and self-reports.

With this SCID modification, the entire PTSD module, including each symptom, was administered to each participant. PTSS symptom cluster scores were therefore calculated by summing all the symptom items within each cluster. Based on the DSM-5, the clusters included re-experiencing (e.g., recurrent and intrusive distressing recollections of the event, Cluster B), avoidance (e.g., efforts to avoid reminders of the event, Cluster C), negative cognitions and mood (e.g., persistent negative emotional state, Cluster D), and hyperarousal (e.g., persistent symptoms of increased arousal, Cluster E). Given differences in total number of items between the different clusters, each of the four cluster dimensions were standardized using a Z-transformation prior to analyses. The overall PTSS dimension yielded from this modified SCID was found to exhibit significant retest reliability (current symptoms $r = .87$, $p < .05$; lifetime symptoms $r = .85$, $p < .05$) and acceptable Cronbach's

alpha values (.89 and .94 for current and lifetime symptoms, respectively [Nunnally, 1978; Shankman et al., *Invited Revision*]). In the present sample, clusters B, C, D, and E exhibited acceptable internal consistencies (Cronbach's alphas ranging from .80 to .86).

2.3. Emotional Face Assessment Task (EFAT)

The EFAT task has previously been described in detail (see Phan et al. 2008). The EFAT and variants of the task have been shown to reliably and robustly engage the amygdala (Hariri et al. 2002; Kirsch et al. 2005). In brief, participants viewed three faces (one on the top of the screen and two on the bottom) and were asked to select one of the two faces on the bottom of the screen that expressed the same emotion as the target face on the top of the screen. Participants made responses by pressing the left or right response buttons with their dominant hand. The identity of all three faces was always different and an equal number of male and female faces were presented. The target face and the congruent probe face always displayed one of four expressions - angry, fearful, sad, or happy- and the other (i.e., incongruent) probe face always displayed a neutral expression. The face photographs were selected from the validated stimulus set from Gur et al. (2002). The angry, fearful, sad and happy target faces were presented in separate blocks and a total of six blocks of each target expression were presented. In addition to faces, there were also blocks in which participants similarly matched simple geometric shapes (i.e., circles, rectangles, or triangles). This 'control' task was included to maintain attention and allow limbic brain responses to return to baseline. The paradigm consisted of 48, 20-seconds blocks: 24 blocks of matching emotional faces, interleaved with 24 blocks of matching shapes (blocks occurred back-to-back without intervening fixation), counterbalanced across two runs for a total task time of 16-minutes.

2.4. fMRI Data Collection and Processing

Functional MRI was performed on a 3.0 Tesla GE MR 750 scanner (General Electric Healthcare, Waukesha, WI) using an 8-channel phased-array radio frequency head coil. A standard T2-sensitive gradient-echo echoplanar imaging sequence was used (2 s TR; 22.2 ms TE; 90° flip; 64 × 64 matrix; 22 cm FOV; 44 axial slices; 3.44 × 3.44 × 3.0 mm voxels). All fMRI data met criteria for high quality and scan stability with minimum motion correction (i.e., < 2 mm displacement in any direction). Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuro-Science, London, UK) was used to perform conventional preprocessing steps. In brief, images were spatially realigned to correct for head motion, warped to standardized Montreal Neurological Institute (MNI) space using the participants' mean functional image, resampled to 2 mm³ voxels, and smoothed with an 8 mm³ kernel to minimize noise and residual differences in gyral anatomy. The general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Condition effects (fearful, angry, sad, happy faces, and shapes) were separately estimated at each voxel for each subject. Individual contrast maps for angry faces > shapes, fearful faces > shapes, sad faces > shapes, and happy faces > shapes were created for each subject.

2.4.1. Data Analytic Plan—As a manipulation check, we first examined whether our fMRI task successfully elicited amygdala reactivity by conducting a second-level one-

sample t -test for all faces > shapes across all subjects. We considered activations that survived whole-brain, family-wise error (FWE) correction at $p < 0.05$ as significant. As is presented below, the bilateral amygdala was robustly activated by the EFAT task, as expected. To test our primary hypotheses, we then extracted BOLD parameter estimates (arbitrary units [a.u.]) from bilateral amygdala anatomical masks, defined via the AAL atlas and created using MARINA (<http://www.bion.de/Marina.htm>; Walter et al., 2003), for each subject, for each emotion type (fearful, angry, sad, and happy). We conducted two repeated measures general linear models, one for right amygdala and one for left amygdala. Task condition (angry, sad, fearful, happy) was included as within-subjects factor. Consistent with prior studies of specific PTSS dimensions (e.g., Grupe et al., 2016), in order to evaluate the unique variance associated with each PTSS cluster, all four scales were entered simultaneously as between-subjects factors. Of note, entering the PTSS clusters into the model simultaneously is useful in preventing mutual suppressor effects in which two correlated predictor variables (see Table 2) have the opposite effect on the criterion/outcome variable, causing the associations to be obscured when each subscale is examined separately (see Watson et al., 2013). To assess whether the observed effects of PTSS clusters were above and beyond that of broad anxiety and depressive symptoms, HAM-A (Hamilton, 1959) and HAM-D (Hamilton, 1959) total scores were included as covariates, respectively. Biological sex was also included as a covariate.

The above region-of-interest (ROI) approach is focused on amygdala reactivity given our strong a priori hypotheses. However, there are several other frontolimbic regions that have been implicated in PTSD specifically, and the processing of affective stimuli more broadly (e.g., insula; anterior cingulate cortex [ACC]; Bruce et al., 2013; Etkin et al., 2007). We therefore conducted supplementary whole-brain analyses to explore whether PTSS symptom clusters were associated with reactivity in regions other than the amygdala. To do so, we conducted a whole-brain, repeated measures general linear model in SPM. Analogous to the above analyses, PTSS clusters were entered simultaneously as between-subjects factors, and task condition as a within-subjects factor. Biological sex, HAM-A, and HAM-D were included as covariates. Given the exploratory nature of these analyses, we used a conservative threshold by considering activations that survived whole-brain, FWE correction at $p < .05$ as significant.

3. Results

3.1. Manipulation Check

Examination of the fMRI task conditions indicated that across all participants, emotional faces (i.e., happy, angry, fearful, sad faces > shapes) significantly activated left (MNI peak $[-28, -6, -18]$, $Z = 5.57$, $k = 4,168\text{mm}^3$, $p < .05_{\text{corrected}}$) and right amygdala (MNI peak $[20, -8, 18]$, $Z = 5.98$, $k = 107,520\text{mm}^3$, $p < .05_{\text{corrected}}$ [see Figure 1]). Emotional faces also significantly activated a large contiguous cluster that included the bilateral fusiform gyrus, a region implicated in face processing (MNI peak $[-40, -44, -26]$, $Z = 7.56$, $k = 221,544\text{mm}^3$, $p < .05_{\text{corrected}}$).

3.2. Posttraumatic Stress Symptom Associations with Amygdala Reactivity

There was a main effect of hyperarousal symptoms (Cluster E) on left, $F(1, 37) = 5.67$, $p < .05$, but not right, $F(1, 37) = 1.12$, ns , amygdala reactivity during emotional faces (see Figure 1). There was no significant main effect of re-experiencing, avoidance, or negative cognition/mood symptoms (clusters B, C, and D, respectively) on amygdala reactivity, p 's $> .32$. There were also no two-way cluster B, C, D, or E x condition interactions for left or right amygdala, p 's $> .20$. Of note, replacing the individual PTSS symptom clusters with the broad total PTSS score indicates no PTSS main effect (i.e., overall PTSS symptoms, collapsed across clusters) or condition by PTSS interaction (p 's $> .12$) on left or right amygdala reactivity. There were also no main effects or two-way effects of HAM-A or HAM-D total scores, although there was a trending main effect of HAM-A on right amygdala reactivity, $p = .08$. Thus, there was no effect of broad anxiety or depression symptoms on amygdala reactivity.¹

3.3. Whole-Brain Associations with Posttraumatic Stress Symptoms

There was no significant main effect of PTSS Clusters B, C, D, or E at the whole-brain level, nor were there significant two-way cluster B, C, D, or E x condition interactions.

3.4 Post-hoc Analysis

The hypothesized association between amygdala reactivity and negative cognition/mood symptoms (cluster D) was based on a previous investigation that found a negative association between amygdala reactivity to happy faces and emotional numbing symptoms (Felmingham et al., 2014), which were moved from the Cluster C (avoidance) to the new cluster D in DSM-5. It is therefore possible that emotional numbing symptoms are associated with blunted amygdala responding to positive social-emotional stimuli, but that the broader range of Cluster D PTSS is not. To test this exploratory hypothesis, *post-hoc* we conducted two repeated measures general linear models with the extracted amygdala reactivity estimates, one for right amygdala and one for left amygdala. Task condition (angry, sad, fearful, happy) was included as within-subjects factor. As the between-subjects factors, PTSS cluster D was replaced with the Z-transformed sum of emotional numbing symptoms (i.e., inability to recall important aspects of the trauma; diminished interest or participation in significant activities; feeling detached from others; inability to experience positive emotions [Felmingham et al., 2014]). Clusters B, C, and E were also included as between-subjects factors. Gender, and HAM-A and HAM-D remained as covariates. There was no main effect of emotional numbing symptoms on left or right amygdala reactivity during emotional faces, p 's $> .85$. There was also no two-way emotional numbing x condition interaction for left or right amygdala, p 's $> .48$.

¹Pattern of results remained the same when HAM-A and HAM-D were removed from the models. Specifically, there was a main effect of hyperarousal symptoms of left, $F(1, 39) = 6.24$, $p < .05$, but not right, $F(1, 39) = 1.53$, ns , amygdala. There were no main effects of clusters B, C, or D on left or right amygdala reactivity, p 's $> .31$, and no two-way cluster x condition interactions for left or right amygdala reactivity, p 's $> .19$.

4. Discussion

Parsing the heterogeneity within PTSD and mapping individual PTSS symptom clusters to specific neural abnormalities is critical for advancing prevention and treatment efforts. Aberrant amygdala responding to affective stimuli has been emphasized as playing an important role in the pathophysiology of PTSS (e.g., Felmingham et al. 2014; Liberzon et al., 1998; Milad et al., 2009). However, the literature on amygdala reactivity to affective stimuli in PTSS is inconsistent (Britton et al., 2005; Phan et al., 2006), which is likely related to the fact that different PTSS symptoms are related to amygdala reactivity in different ways. The present study therefore examined the association between specific PTSS clusters and amygdala reactivity to negative and positive emotional faces among trauma-exposed individuals with a range of PTSS severity. Results indicated that greater hyperarousal symptoms (Cluster E) were associated with greater left amygdala reactivity across all emotional faces (i.e., happy, fearful, sad, angry). These results were also relatively specific to the amygdala as our supplementary whole-brain analyses indicated no association between PTSS symptom clusters and regions beyond the amygdala.

The current results suggest that, among trauma-exposed individuals, hyperarousal symptoms are associated with heightened responding to social-emotional stimuli, irrespective of valence (i.e., positive or negative emotional faces). As indicated above, given the broader internalizing literature on amygdala reactivity, we hypothesized that hyperarousal symptoms would be associated with heightened amygdala responding to negative, but not positive faces. These findings are notably consistent with Stevens et al. (2013), which found a positive association between hyperarousal symptom severity and amygdala reactivity to fearful faces. The findings are also in line with a prior study by our group which found that greater levels of hyperarousal PTSS (only) are associated with greater reactivity to monetary reward *and* the commission of errors, as indexed by separate event-related potential components called the reward-related positivity (RewP) and error-related negativity (ERN), respectively (Lieberman et al., *In Press*). Errors are inherently aversive events as they signal the potential for harm and require corrective action (Hajcak & Foti, 2008; Hajcak, Moser, Yeung, & Simons, 2005), whereas monetary reward is a known robust elicitor of appetitive motivation (Thut et al., 1997; Shankman et al., 2007). Across two distinct neural measures (i.e., fMRI and ERPs), there is now evidence to suggest that hyperarousal PTSS are uniquely associated with heightened reactivity to positive and negative stimuli. Therefore, individuals characterized by high PTSS hyperarousal symptoms likely display heightened physiological reactivity across numerous contexts.

There are several mechanisms that may explain why individuals with greater levels of hyperarousal symptoms display exaggerated amygdala reactivity to affective facial expressions. For instance, hyperactivity of the amygdala to emotional faces could represent aberrant salience processing, as it has been suggested that the amygdala plays a critical role in determining the relevance of affective stimuli (Phelps & LeDoux, 2005; Adolphs, 2010). That is, amygdala reactivity may be indicative of a broader tendency to overestimate the value of social-emotional cues. Given that the amygdala is also involved in the allocation of attentional resources (Phelps & LeDoux, 2005), greater valuation of positive and negative affective facial expressions could also result in enhanced attentiveness to social-emotional

cues in the environment. It is therefore possible that heightened amygdala reactivity to affective faces contributes to chronic hypervigilance and anticipatory anxiety, a core feature of the hyperarousal PTSS cluster.

The amygdala has also been implicated in the modulation of peripheral physiological responses, such as skin conductance responding and the startle reflex (Critchley et al., 2000; Campeau & Davis, 1995). Heightened amygdala reactivity to positive and negative affective facial expressions may therefore contribute to heightened physiological responses to a range of social-emotional stimuli, which could ultimately result in sustained physiological arousal across different social contexts. Relatedly, heightened amygdala reactivity to affective facial expressions may represent a failure to inhibit defensive responding across different social contexts. That is, individuals high in hyperarousal PTSS may display fear responding to social-emotional stimuli, irrespective of whether danger is actually present. Consistent with this hypothesis, Jovanovic and colleagues (2010) found that individuals high in hyperarousal symptoms fail to inhibit conditioned fear-potentiated startle in the presence of safety signals. Moreover, heightened defensive reactivity (e.g., exaggerated startle response) across contexts is a core feature of hyperarousal symptomology. This literature together implies that exaggerated reactivity to affective stimuli likely drives anxious responding and could therefore be a valuable treatment target for individuals characterized by high levels of PTSS hyperarousal symptoms.

It is important to note that we found an effect of hyperarousal symptoms for the left, but not the right, amygdala. This is consistent with many other studies which have found localized hemispheric differences in amygdala reactivity (Fitzgerald et al., 2006; Zald, 2003). Interestingly, it has been suggested that the right amygdala habituates more rapidly to social-emotional stimuli than the left amygdala (Breiter et al. 1996; Wright et al., 2001). Rapid habituation of right amygdala reactivity may have diminished amygdala responding to faces over time, making it difficult to detect an association between hyperarousal symptoms and right amygdala reactivity.

The hypothesized negative relation between amygdala reactivity to positive faces and negative cognition/mood symptoms (cluster D) was not found in the present study. As mentioned above, this hypothesis was based on a prior investigation that found blunted amygdala reactivity to happy faces among individuals high in DSM-IV emotional numbing symptoms (Felmingham et al, 2014), which were moved to cluster D from cluster C (avoidance) for DSM-5. We therefore explored whether there was an association between emotional numbing symptoms of cluster D and amygdala reactivity, and found no association. Although inconsistent with the findings of Felmingham and colleagues (2014), the lack of association found in the present study could be due to the changes made to the emotional numbing symptoms themselves. For example, “sense of foreshortened future” is no longer included as a PTSS, and “restricted range of affect” was revised to be “persistent inability to experience positive emotions”. Future studies should therefore compare the association between amygdala reactivity and emotional numbing PTSS using DSM-IV and DSM-5.

The present study adds to the field's understanding of the pathophysiology of PTSS, and has several notable strengths, including the dimensional assessment of posttraumatic stress, and a sample with a range of PTSS severity. However, there are several important limitations of the present study that should be considered. First, participants had co-occurring psychopathologies which may have impacted the relation between PTSS and amygdala reactivity. Second, because PTSS were assessed using just one diagnostic tool (the SCID-5), converging evidence from other dimensional PTSS measures was not available. Future studies should therefore examine whether these results are replicated using additional PTSS measures, such as the Clinician Administered PTSD Scale (CAPS; Weathers et al., 2013). Third, given that the present study's sample size was moderate, a greater sample size may have revealed additional associations between PTSS clusters and amygdala reactivity. Fourth, the Emotional Face Assessment Task used in the present study does not include a neutral face baseline condition. This makes it difficult to distinguish whether the amygdala reactivity reflects the processing of social facial cues specifically, versus the processing of emotional cues more broadly. Lastly, the EFAT task is a well-known, effective amygdala probe but is limited in capturing activation in broader frontolimbic neural circuits. Future studies on PTSS should therefore use additional tasks that activate a broader network of regions to explore associations with regions outside of the amygdala to fully elucidate the pathophysiology of distinct PTSS symptom clusters.

4.1. Conclusion

Taken together, results from the present study suggest that the broader dimension of PTSS is not associated with heightened amygdala responding to social-emotional stimuli. Rather, individuals high in hyperarousal PTSS may be characterized by heightened amygdala responding social-emotional information. This pattern of results highlights the possibility that specific profiles of posttraumatic stress symptomology may be characterized by distinct neural abnormalities. Given that participants were not required to have full syndromal PTSD, these results also suggest that the presence of hyperarousal PTSS may be associated with hyperactivity of the amygdala to affective cues regardless of whether full-syndromal PTSD is also present. This aberrant response of the amygdala may therefore represent a treatment target for individuals experiencing high level of hyperarousal PTSS, even if those individuals do not meet DSM criteria for PTSD.

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Highlights

- Studied impact of specific PTSD clusters on amygdala reactivity to emotional faces
- Amygdala reactivity assessed during well-validated Emotional Faces Assessment Task
- Hyperarousal symptoms positively associated with reactivity to emotional faces
- No other PTSD clusters associated with amygdala reactivity to emotional faces
- Heightened amygdala reactivity to emotional stimuli may contribute to hyperarousal

Figure 1. Bilateral amygdala activation to emotional faces > shapes across all participants (on left). Association between left amygdala reactivity to emotional faces > shapes and Z-transformed hyperarousal symptoms, controlling for covariates and PTSS clusters B, C, and D (on right).

Table 1

Demographics and clinical characteristics

Demographics	
Age (years)	27.72 (9.44)
Sex (% female)	80%
Race/Ethnicity (%)	
Caucasian	66.7%
African American	15.6%
Asian	13.3%
Other	4.4%
Principal Diagnosis	
Generalized anxiety disorder	37.8%
Social anxiety disorder	8.9%
Panic disorder	6.7%
Posttraumatic stress disorder	8.9%
Dysthymia	2.2%
Major depressive disorder	22.2%
Current Diagnoses (Including Primary)	
Posttraumatic stress disorder	35.3%
Generalized anxiety disorder	70.6%
Social anxiety disorder	45.1%
Panic disorder	21.6%
Specific Phobia	13.7%
Dysthymia	2.0%
Major depressive disorder	45.1%
Lifetime posttraumatic stress disorder	51.1%
Mean PTSS Cluster Score	
Re-experiencing (Cluster B)	7.98 (2.85)
Avoidance (Cluster C)	3.44 (1.57)
Negative cognitions/mood (Cluster D)	10.33 (3.48)
Hyperarousal (Cluster E)	7.87 (2.53)

Note. There are five symptoms in cluster B, two in cluster C, 7 in Cluster D, and 6 in Cluster E.

Table 2

Bivariate correlations of Internalizing Symptoms

	Re-experiencing PTSS	Avoidance PTSS	Negative Cog/Mood PTSS	Hyperarousal PTSS	HAM-A	HAM-D
Re-experiencing PTSS	—					
Avoidance PTSS	.55*	—				
Negative Cog/Mood PTSS	.57*	.60*	—			
Hyperarousal PTSS	.52*	.48*	.55*	—		
HAM-A	.39*	.34*	.41*	.32*	—	
HAM-D	.32*	.34*	.52*	.44*	.70*	—

* $p < .05$