Review

# Neurocircuitry models of posttraumatic stress disorder and beyond: A meta-analysis of functional neuroimaging studies

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## ABSTRACT

Over the past two decades a relatively large number of studies have investigated the functional neuroanatomy of posttraumatic stress disorder (PTSD). However, findings are often inconsistent, thus challenging traditional neurocircuitry models of PTSD. As evidence mounts that cognition and behavior is an emergent property of interacting brain networks, the question arises whether PTSD can be understood by examining dysfunction in large-scale, spatially distributed neural networks. We used the activation likelihood estimation quantitative meta-analytic technique to synthesize findings across functional neuroimaging studies of PTSD that either used a non-trauma ($N = 20$) or trauma-exposed ($N = 19$) comparison control group. In line with neurocircuitry models, our findings support hyperactive amygdala and hypoactive medial prefrontal regions, but suggest hyperactive hippocampi. Characterization of additional regions under a triple network model showed functional alterations that largely overlapped with the salience network, central executive network, and default network. However, heterogeneity was observed within and across the neurocircuitry and triple network models, and between results based on comparisons to non-trauma and trauma-exposed control groups. Nonetheless, these results warrant further exploration of the neurocircuitry and large-scale network models in PTSD using connectivity analyses.

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Posttraumatic stress disorder (PTSD) is characterized by a constellation of symptoms related to the experience of a traumatic event, resulting in significant distress and impaired daily functioning (Hoge et al., 2006; Van Ameringen et al., 2008). Advancing our understanding of neurobiological dysfunction in PTSD will be a critical step toward improving clinical management of this disorder (Garfinkel and Liberzon, 2009). Toward this goal, identifying reliable biomarkers through neuroimaging techniques may yield important targets for therapeutic intervention. For example, using functional magnetic resonance imaging (fMRI), Bryant et al. (2008) showed that PTSD-related hyperactivation of the amygdala was a significant predictor of poor response to cognitive-behavioral therapy. A broad range of experimental paradigms including those related to symptom provocation, emotional processing, and cognitive activation have been used to assess the neural underpinnings of PTSD. In recent years there has been a growing body of narrative reviews providing qualitative syntheses of neuroimaging findings in the PTSD literature (Bremner, 2004; Francati et al., 2007; Garfinkel and Liberzon, 2009; Lanius et al., 2006; Rauch et al., 2006; Villarreal and King, 2004). In the current study, we present a systematic and quantitative meta-analytic approach to identify reliable patterns of brain activity in PTSD. This synthesis reveals a common set of brain regions that can be targeted or leveraged for further investigation as well as informing the development of therapeutic interventions.

## 1. The traditional neurocircuitry model of PTSD

Abnormal patterns of brain activity have been characterized as showing greater activation (hyperactivation) or less activation (hypoactivation) in PTSD relative to a comparison control group. Alterations in regional activation are thought to underlie behavioral, cognitive, or emotional symptomatology. For instance, the widely adopted neurocircuitry model of PTSD first proposed by Rauch et al. (1998) suggests hypoactivation of the medial prefrontal cortex (encompassing the anterior cingulate cortex (ACC), ventromedial prefrontal cortex, subcallosal cortex, and oribitofrontal cortex) results in an inability to effectively control attention and response to trauma-related stimuli. Combined with this loss of top-down inhibitory control, amygdalar hyperresponsivity promotes the vivid nature of trauma recollections and symptoms of hyperarousal (Rauch et al., 2006). The model further proposes that abnormal functioning of the hippocampus underlies PTSD-related deficits in learning and memory (e.g., the inability to extinguish a fear response).

Although the neurocircuitry model has proven useful in the understanding of PTSD, it has been challenged by inconsistent findings in the literature. For instance, whereas a number of studies report lower hippocampal activation in PTSD relative to controls (e.g., Bremner et al., 2003; Hayes et al., 2011), others report greater hippocampal activation in response to both threat-related (Shin et al., 2001; Thomaes et al., 2009) and non-threat-related stimuli (Werner et al., 2009). Likewise, some studies report less activation (e.g., Britton et al., 2005; Shin et al., 2001) while others report greater activation in the rostral ACC (e.g., Bryant et al., 2005; Felmingham et al., 2009). Inconsistent findings also extend beyond the traditional model to other areas implicated in PTSD such as the insular cortex (e.g., Chen et al., 2009; Fonzo et al., 2010).

Numerous factors including differential levels in baseline activity (Shin et al., 2004), the nature of the experimental task (e.g., symptom provocation vs. cognitive activation paradigms), the type of trauma experienced (e.g., childhood sexual abuse vs. combat-war exposure), and the salience of probing stimuli (e.g., emotionally arousing vs. non-arousing stimuli) have all been raised as potential moderators or sources of method variance contributing to the heterogeneous findings. Another factor that is often overlooked in the literature is the use of different control or comparison groups. That is, neuroimaging findings in PTSD are often compared to either non-PTSD individuals without a history of trauma exposure or non-PTSD individuals with a history of trauma exposure. In the current meta-analysis, we present separate syntheses of the PTSD neuroimaging data relative to each comparison group. To our knowledge, this is the first review to systematically address this distinction in assessing the neural correlates of PTSD.

## 2. Beyond the neurocircuitry model

Others have suggested the traditional neurocircuitry model might be constrained by its focus on threat. That is, while some PTSD symptoms may stem from deficits in threat-related processing, other symptoms (e.g., emotional numbing, avoidance behaviors) are unexplained by this model (Liberzon and Garfkinkel, 2009). In their model, Liberzon and Garfkinkel (2009) emphasize the role of medial prefrontal cortex in contexualization, the process by which stimuli in varying situational contexts are interpreted, represented, and used to guide behavioral action. Since a number of processes that rely on contexualization, including extinction, emotion regulation, social cognition, and self-referential processing, all implicate the medial prefrontal cortex, the authors propose that altered functioning of this region could explain a number of disparate problems that are characteristic of PTSD (e.g., re-experiencing phenomena, emotional numbing). Moreover, it is important to consider the complex roles of the medial prefrontal cortex afforded by its high connectivity with other areas, such as the anterior insula. Paulus and Stein (2006) propose that individuals who are likely to experience an interoceptive state as dangerous have an augmented signal between their observed and expected body state. This signal is thought to be mediated by heightened activity in the anterior insula. Cognitive (e.g., worrying) and behavioral (e.g., avoidance) symptoms might arise from neural resources attempting to attenuate the discrepancy between these two states (Paulus and Stein, 2006).

The models reviewed thus far have implicated the insula, medial-temporal (amygdala, hippocampus) and medial prefrontal regions in the pathophysiology of PTSD. However, brain imaging studies typically implicate additional regions of altered activation in PTSD. Thus, a main objective of the current meta-analysis was to shed more light on the degree of consistency of these regions across studies. Moreover, in order to facilitate the characterization and interpretation of reliable brain regions, we adopted a unifying triple-network framework of psychopathology recently put forth by Menon (2011). Increasing evidence supports human behavior and cognition as an emergent property of interacting, large-scale brain networks (Bressler and McIntosh, 2007; Dosenbach et al., 2007; Postle, 2006). Menon (2011) has proposed that a broad range of neurological and psychiatric disorders can be understood

by evaluating dysfunction in three core neurocognitive networks: the default network (Buckner et al., 2008), the frontoparietal central executive network, and the salience network (Menon, 2011). The default network comprises a set of interconnected brain regions, including the medial prefrontal cortex, posterior cingulate cortex, lateral and medial temporal lobes, and posterior inferior parietal lobule, that are suppressed during externally oriented, attention-demanding tasks relative to when participants are at rest (Buckner et al., 2008; Gusnard and Raichle, 2001). In contrast, activation of the default network has been linked to various processes of internal mentation, such as autobiographical memory, self-referential thinking and social cognition (Andrews-Hanna, 2012; Spreng et al., 2009). The central executive network is anchored in the dorsolateral prefrontal cortex and anterior inferior parietal lobule, and subserves processes related to working memory and attentional control (Menon, 2011). Third, the salience network is anchored in the frontoinsular cortex and dorsal ACC, with extensive connectivity to subcortical regions including the amygdala, thalamus, ventral striatopallidum, and substantia nigra/ventral tegmental area (Menon and Uddin, 2010; Seeley et al., 2007). Together, these regions subserve processes related to autonomic and emotion regulation, conflict monitoring, and reward-processing.

These three networks normally interact in a dynamic and complementary manner. Regions of the central executive and salience networks become engaged (i.e., show greater activation) during stimulus-oriented cognitive and affective information processing, whereas the default network disengages when demands for external attention are high and internally focused processes are minimized. Aberrant organization or dysfunction in any part of these networks can lead to dysfunction in the remaining networks and a unique constellation of clinical symptoms (Menon, 2011). Given its comprehensive scope, we apply the triple-network approach in addition to harnessing the traditional neurocircuitry model of PTSD as a guiding framework in this quantitative synthesis.

## 3. Study aims

There is a growing corpus of studies examining brain (dys)function in PTSD in relation to many behavioral domains. Yet, to our knowledge, no studies have examined the possibility that PTSD is associated with common or domain-general patterns of altered brain function. Evidence of reliable, domain-general aberrations in PTSD would set the stage for future investigations to elucidate how these global effects interact with more differentiated, domain-specific functional differences.

In this vein, we surveyed whole-brain functional neuroimaging investigations of PTSD, irrespective of experimental paradigm. We used the activation likelihood estimation (ALE) approach for quantitative meta-analysis (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) to synthesize the findings from these studies. To address the relevance of comparison groups noted earlier, we analyzed the neural correlates associated with PTSD separately relative to non-trauma exposed and trauma-exposed comparison groups. To aid interpretation, we applied a framework comprising the traditional neurocircuitry model of PTSD and the triple network model of psychopathology. By advancing understanding of neurobiological dysfunction in PTSD, we hope to identify important neural markers for rehabilitation.

## 4. Methods and materials

### 4.1. Study selection

A systematic literature search was conducted to identify neuroimaging studies of PTSD. Peer-reviewed articles published in English up to January 2011 were selected from the search results of two separate databases: MEDLINE and PsycINFO via Scholar's Portal. The literature search was conducted using the following search words: (1) keywords "post-traumatic stress disorder" <OR> "PTSD" <OR> "acute stress disorder" <OR> "trauma" AND (2) keywords "fMRI" <OR> "PET" <OR> "functional MRI" <OR> "functional magnetic resonance" <OR> "neuroimaging". The search yielded 343 unique peer-reviewed papers.

A total of 36 papers met the following inclusion requirements: (1) group of individuals given a formal diagnosis of PTSD; (2) matched-control group without a diagnosis of PTSD; and (3) reported a voxel-wise whole-brain analysis. Theoretical papers and reviews were excluded ($n = 29$) as well as those articles that reported region-of-interest analyses in the absence of whole-brain analyses ($n = 11$; e.g., Frewen et al., 2008; Protopopescu et al., 2005; Rauch et al., 2000; Thomaes et al., 2009) to avoid bias toward specific regions. A secondary search using reference lists from review-based articles yielded an additional set of papers that met our inclusion criteria ($n = 15$). In total, 51 papers were identified as meeting initial inclusion criteria. Of these studies, those comparing PTSD with other psychiatric illnesses (e.g., borderline personality disorder) without a healthy control group ($n = 1$; Driessen et al., 2004) and/or using adolescent samples ($n = 2$; Carrion et al., 2008; Yang et al., 2004) were excluded. Studies failing to report activation foci as 3D coordinates in stereotaxic space ($n = 1$; Bremner et al., 1997) were also excluded because these studies could not be meaningfully analyzed with ALE. For studies that reported results for multiple tasks using the same group of patients (e.g., Hou et al., 2007; Felmingham et al., 2009), the contrast with the greatest number of foci for only one task was selected in order to limit the contribution of any one set of participants to the pool of foci. In cases where multiple studies were performed by the same group, we contacted first authors to determine if there was any sample overlap between studies. When the presence of overlapping samples was confirmed (e.g., Geuze et al., 2007, 2008), we limited selection to those studies that included non-overlapping, independent samples ($n = 5$ studies excluded). Papers that reported results for PTSD and control groups separately and/or without a between-subjects analysis were also omitted ($n = 6$; e.g., Lanius et al., 2004; Liberzon et al., 1999; Shin et al., 1997). In total, 36 appropriate papers were identified for ALE analysis. These papers were then split into two samples based upon the control group: *non-trauma* controls (NTC; $n = 20$; Appendix A) and *trauma-exposed* controls (TEC; $n = 19$; Appendix B) (see Tables 1a and 1b for study details). Three papers employing a three-group design (e.g., New et al., 2009) contributed separate sets of foci to the NTC and TEC analyses. Within each study set, data were analyzed across experimental paradigms in order to assess domain-general changes in neural activation for PTSD (see Tables 2a and 2b).

### 4.2. ALE Method

ALE was performed using BrainMap GingerALE v. 2.0.4 (Eickhoff et al., 2009), a coordinate-based random-effects meta-analysis for functional neuroimaging data. The ALE method uses a series of permutations to differentiate statistically significant patterns of brain activity from random clustering (i.e., noise) of foci, across multiple independent experiments (Eickhoff et al., 2009). ALE maps are derived based on foci of interest, which comprise statistically significant peak activation locations from multiple studies (Laird et al., 2005; Turkeltaub et al., 2002). We conducted four separate ALE analyses, each yielding an ALE map and corresponding cluster report: (A) greater brain activity in PTSD relative to the NTC group; (B) greater brain activity in PTSD relative to TEC group; (C) less brain activity in PTSD relative to the NTC group, and (D) less brain activity in PTSD relative to TEC group. All study coordinates were entered

**Table 1a**
Details of included studies for PTSD versus non-trauma controls analyses. For complete reference, see Appendix A.

| Study | First author | Year | Imaging | PTSD N | Age (SD/range) | Control N | Age (SD/range) | Foci PTSD > HC | Foci PTSD < HC |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Astur | 2006 | fMRI | 12 | n/a | 12 | n/a | 0 | 9 |
| 2 | Bonne | 2003 | PET | 11 | 34 (9) | 11 | 33 (12) | 10 | 0 |
| 3 | Bremner | 2003 | PET | 10 | 40 (6) | 11 | 38 (8) | 15 | 14 |
| 4 | Bremner | 2005 | PET | 8 | 38 (10) | 11 | 36 (11) | 20 | 16 |
| 5 | Bryant | 2005 | fMRI | 14 | n/a | 14 | n/a | 10 | 7 |
| 6 | Chung | 2006 | SPECT | 23 | 43 (21–63) | 64 | 43 (23–63) | 8 | 4 |
| 7 | Elman | 2009 | fMRI | 20 | 33.0 (10.5) | 26 | 28.0 (8.2) | 0 | 2 |
| 8 | Felmingham | 2009 | fMRI | 9 | n/a | 11 | n/a | 11 | 0 |
| 9 | Fonzo | 2010 | fMRI | 12 | 35.4 (8.6) | 12 | 37 (6.49) | 11 | 1 |
| 10 | Jatzko | 2006 | fMRI | 10 | 50 (13) | 10 | 51 (11) | 3 | 3 |
| 11 | Kim | 2008 | fMRI | 12 | 33.3 (9.1) | 12 | 29.0 (6.2) | 7 | 6 |
| 12 | Liberzon | 2007 | PET | 16 | 53.8 (4.2) | 14 | 47.7 (7.3) | 2 | 9 |
| 13 | Moores | 2008 | fMRI | 13 | 44.23 (9.18) | 12 | 40.41 (10.93) | 0 | 49 |
| 14 | New | 2009 | fMRI | 14 | 38.7 (11.2) | 14 | 31.7 (10.3) | 4 | 9 |
| 15 | Phan | 2006 | PET | 16 | 53.8 (4.2) | 15 | 48.7 (8.0) | 0 | 2 |
| 16 | Sailer | 2008 | fMRI | 13 | 16.4 (2.8) | 13 | 28.9 (7.1) | 0 | 4 |
| 17 | Sakamoto | 2005 | fMRI | 16 | 42.3 (13.6) | 16 | 40.1 (11.4) | 1 | 4 |
| 18 | Strigo | 2010 | fMRI | 23 | 35.9 (8.5) | 15 | 35.2 (12.7) | 10 | 1 |
| 19 | Werner | 2009 | fMRI | 12 | 33.08 (7.89) | 12 | 36.17 (5.57) | 23 | 13 |
| 20 | Williams | 2006 | fMRI | 13 | 36.5 (9.7) | 13 | 34.8 (8.5) | 9 | 5 |

HC, healthy control; fMRI, functional magnetic resonance imaging; n/a, data not available; PET, positron emission tomography SPECT, single-photon emission computed tomography.

**Table 1b**
Details of included studies for PTSD versus trauma-exposed controls analyses. For complete reference, see Appendix B.

| Study | First author | Year | Imaging | PTSD N | Age (SD/range) | Control N | Age (SD/range) | Foci PTSD > HC | Foci PTSD < HC |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Bonne | 2003 | PET | 11 | 34 (9) | 11 | 35 (8) | 8 | 0 |
| 2 | Bremner | 1999a | PET | 10 | 47 (3) | 10 | 50 (3) | 7 | 7 |
| 3 | Bremner | 1999b | PET | 10 | 35 (6) | 12 | 32 (8) | 9 | 19 |
| 4 | Bremner | 2004 | PET | 12 | 37 (11) | 9 | 35 (9) | 2 | 6 |
| 5 | Chen | 2009 | fMRI | 12 | 34.56 (4.91) | 12 | 33.25 (5.27) | 0 | 11 |
| 6 | Geuze | 2008 | fMRI | 12 | 34.82 (5.78) | 12 | 34.69 (3.70) | 7 | 6 |
| 7 | Hou | 2007 | fMRI | 10 | 34.30 (4.55) | 7 | 40.57 (5.26) | 1 | 9 |
| 8 | Lanius | 2002 | fMRI | 7 | 36 (10.0) | 10 | 35 (12.3) | 9 | 3 |
| 9 | Lanius | 2005 | fMRI | 10 | 37.7 (11.1) | 10 | 35.2 (12.3) | 3 | 2 |
| 10 | Lanius | 2003 | fMRI | 10 | 35 (12.3) | 10 | 39 (11.03) | 0 | 11 |
| 11 | Liberzon | 2007 | PET | 16 | 53.8 (4.2) | 15 | 56.5 (4.9) | 4 | 2 |
| 12 | Lindauer | 2004 | PET | 15 | 36.2 (11.3) | 15 | 37.2 (9.9) | 3 | 2 |
| 13 | New | 2009 | fMRI | 14 | 38.7 (11.2) | 14 | 38.5 (10.8) | 2 | 3 |
| 14 | Shin | 1999 | PET | 8 | 37.1 (13.5) | 8 | 37.5 (8.3) | 4 | 14 |
| 15 | Shin | 2004a | PET | 10 | 51.8 (1.9) | 10 | 51.6 (1.6) | 0 | 3 |
| 16 | Shin | 2009 | PET | 14 | 57.8 (2.8) | 19 | 57.1 (2.2) | 2 | 0 |
| 17 | Shin | 2001 | fMRI | 8 | 50.6 (4.6) | 8 | 54.1 (3.2) | 21 | 12 |
| 18 | Shin | 2004b | PET | 8 | 50.3 (10.3) | 8 | 43.5 (8.8) | 3 | 3 |
| 19 | Whalley | 2009 | fMRI | 16 | 36.8 (7.6) | 16 | 32.5 (7.8) | 10 | 0 |

HC, healthy control; fMRI, functional magnetic resonance imagine; PET, positron emission tomography.

in GingerALE in the stereotaxic space of the Montreal Neurologic Institute (MNI) atlas. Studies that reported coordinates in Talairach space derived within SPM (http://www.fil.ion.ucl.ac.uk/spm/) were back-transformed into MNI space using tal2mni, as implemented in GingerALE 2.0.4. Studies that originally reported coordinates in Talairach space were converted to MNI space using the Lancaster transformation (Laird et al., 2010). Across all studies, ALE statistics were computed for each voxel in the brain, reflecting the likelihood that a given voxel was activated across studies in each respective analysis. For all analyses, the false discovery rate method was used to correct for multiple comparisons at $p < .05$. This method provides increased sensitivity over methods that control for family-wise error regarding chance of any false positives across all analyses (e.g., Bonferroni; Genovese et al., 2002). Next, we set a cluster-level threshold such that only clusters of contiguous voxels exceeding a volume of 200 mm$^3$ were considered statistically significant and reliable (Eickhoff et al., 2009). All ALE maps were transformed from

a volume image to a surface map using Caret software (Van Essen, 2005) for presentation.

We also used a recently released GingerALE 2.1 beta version to perform subtraction analyses in order to detect statistically significant differences in activity between the two control groups. Four subtraction analyses were performed, two reflecting greater activation in PTSD relative to controls (i.e., analysis A minus B and B minus A, as described above) and two reflecting less activation in PTSD relative to controls (i.e., C minus D; D minus C). Regions that survived these subtraction analyses indicate significant regional differences in the reported activity between the control groups and are denoted in Tables 3a, 3b and 4a, 4b. For example, the results for analysis of A (PTSD > NTC) minus B (PTSD > TEC) reflect regions for which PTSD-related hyperactivation is significantly greater relative to NTC than TEC groups.

Finally, to aid synthesis of the resultant clusters, we characterized each region with respect to the traditional neurocircuitry

**Table 2a**

Experimental details for each study included in the PTSD vs. non-trauma control analyses.

| Study | Paradigm | Contrast or condition |
|---|---|---|
| 1 | Virtual water maze task | Hidden vs. visible platform |
| 2 | Cerebral perfusion | Resting state condition |
| 3 | Word list recall | Retrieval of deeply encoded emotional vs. neutral words |
| 4 | Fear acquisition and extinction | Fear conditioning vs. random shock condition |
| 5 | Auditory oddball task | Target vs. standard auditory tones |
| 6 | Cerebral perfusion | Resting state condition |
| 7 | Wheel of fortune-type game | Gains vs. losses in outcome phase |
| 8 | Auditory oddball task | Target vs. standard auditory tones |
| 9 | Emotional face-matching task | Angry vs. happy target face |
| 10 | Positive mood induction | Positive emotion-eliciting film clip vs. baseline |
| 11 | Emotion perception task | Fearful vs. neutral face contrast |
| 12 | μ-Opioid receptor availability | Resting state condition |
| 13 | Working memory task | Variable vs. fixed target in updating comparison |
| 14 | Emotion regulation task | Diminish vs. maintain contrast |
| 15 | Emotional processing of pictures | Aversive vs. nonaversive contrast |
| 16 | Decision making task | Gains vs. losses in late experimental phase |
| 17 | Implicit affective processing task | Traumatic vs. control stimulation |
| 18 | Temperature stimulation paradigm | Run 2 vs. run 1 across all temperatures |
| 19 | Associative learning task | Encoding condition |
| 20 | Fear perception task | Fear vs. neutral contrast |

**Table 2b**

Experimental details for each study included in the PTSD versus trauma-exposed control analyses.

| Study | Paradigm | Contrast or condition |
|---|---|---|
| 1 | Cerebral perfusion | Resting state condition |
| 2 | Symptom provocation | Combat vs. neutral slides and sounds |
| 3 | Script-driven reading task | Traumatic vs. neutral script |
| 4 | Stroop task | Emotional vs. neutral Stroop |
| 5 | Word recognition task | Encoding of target words |
| 6 | Associative learning | Encoding of word pairs vs. baseline |
| 7 | Stimulus provocation task | Trauma-related vs. neutral scenes |
| 8 | Symptom provocation | Memory recall vs. implicit baseline |
| 9 | Script-driven imagery task | Neutral memory recall |
| 10 | Script-driven imagery task | Sad memory recall vs. implicit baseline |
| 11 | μ-Opioid receptor availability | Resting state condition |
| 12 | Script-driven imagery task | Neutral-script condition |
| 13 | Emotion regulation task | Enhance vs. maintain contrast |
| 14 | Script-driven imagery task | Traumatic vs. neutral event script |
| 15 | Script-driven imagery task | Traumatic vs. neutral script |
| 16 | Cerebral metabolic rate for glucose | Resting state condition |
| 17 | Emotional counting Stroop task | Combat vs. general negative condition |
| 18 | Explicit word-stem memory task | High vs. low memory recall |
| 19 | Episodic memory retrieval | Positive vs. neutral hits |

model of PTSD (Rauch et al., 2006) and the triple neurocognitive networks (see Tables 3a, 3b and 4a, 4b). Assignments to the default, salience, and central executive networks were performed using close anatomic inspection of the network characterizations reported by Buckner et al. (2008), Seeley et al. (2007), and Menon (2011).

## 5. Results

### 5.1. PTSD > NTC

Reliable clusters of activity were observed in the PTSD group relative to the NTC group in a number of brain regions (Table 3a). Of relevance to the neurocircuitry model, both the left amygdala and right hippocampus demonstrated greater activation in PTSD; these structures also contribute to the salience and default networks, respectively. Additional clusters of reliable activation in the salience networks were found in the bilateral anterior insula and left putamen (Fig. 1A and B). In the central executive network, reliable clusters of increased activation were found in the left precuneus and right middle frontal gyrus. The PTSD group also showed greater activity in right fusiform gyrus and right postcentral gyrus.

### 5.2. PTSD > TEC

Table 3b lists brain regions with reliably greater activity the PTSD group relative to the TEC group. In the salience network, a reliable cluster of activity was found in the dorsal ACC, while in the central executive network, a reliable cluster of activation was found in the right precuneus. In the default network, reliable clusters of activity were also detected in the lateral areas of the medial temporal lobe (Fig. 1A). Other regions that showed reliably greater activation included the right thalamus and the left fusiform gyrus.

### 5.3. PTSD < NTC

The PTSD group showed less activation relative to the NTC group in a number of regions (see Table 4a). In the default network, reliable clusters were found in the left angular gyrus, right posterior cingulate cortex, and right medial prefrontal cortex; the latter is also consistent with the neurocircuitry model. In the central executive network, reliable clusters of lower activation were found in the left supramarginal gyrus and left middle frontal gyrus (Fig. 2). Other regions that showed reliably less activation included the bilateral precentral gyrus and right caudate nucleus.

### 5.4. PTSD < TEC

Relative to the neurocircuitry model and the default work, reliable clusters of less activation in PTSD were found in the right medial prefrontal cortex and left parahippocampal gyrus, respectively. In the central executive network, clusters were found in lateral prefrontal cortex, including bilateral inferior frontal gyrus, bilateral middle frontal gyrus, and left frontal pole. In the salience network, a reliable cluster of less activation was found in the dorsal ACC. Consistent with the neurocircuitry model, less activation was found in the right orbitofrontal cortex. Additional clusters of less activation were in the right precentral gyrus and left thalamus (see Table 4b).

### 5.5. Comparison of control groups

Four subtraction analyses were conducted to directly compare the results obtained between the two control groups. The first subtraction analysis [PTSD > NTC minus PTSD > TEC] revealed significantly higher activation in PTSD relative to TEC than NTC in the left precuneus, right postcentral gyrus, and right middle frontal gyrus (Table 3a). The reverse subtraction [PTSD > TEC minus PTSD > NTC] failed to reveal any effects. Our next subtraction analysis [PTSD < NTC minus PTSD < TEC], revealed significantly lower activation in PTSD relative to NTC than TEC groups in the right inferior frontal gyrus and right middle frontal gyrus (Table 4b). The reverse subtraction [PTSD < TEC minus PTSD < NTC] failed to

**Table 3a**
Brain regions showing reliably greater activity in PTSD vs. non-trauma controls ($p < 0.05$, FDR-corrected).

| Lat | Region | BA | Vol (mm³) | ALE ($10^{-2}$) | x | y | z | Contributing studies[a,b] | PTSD model | Network |
|---|---|---|---|---|---|---|---|---|---|---|
| R | Fusiform gyrus | 37 | 832 | 1.77 | 54 | −38 | −16 | 11 | | |
| R | Insula | 13 | 456 | 1.36 | 46 | 6 | 8 | 9 | | SN[c] |
| R | Hippocampus | 36 | 440 | 1.27 | 28 | −12 | −24 | 8, 6 | X | DMN |
| | | | | | 28 | −20 | −30 | | X | |
| L | Precuneus[d] | 7 | 352 | 1.20 | −10 | −50 | 48 | 3, 9 | | CEN |
| L | Amygdala | | 344 | 1.40 | −20 | −8 | −16 | 4, 6 | X | SN |
| L | Putamen | | 344 | 1.19 | −32 | −20 | −8 | 8, 19 | | SN |
| R | Postcentral gyrus[d] | 2 | 344 | 1.30 | 50 | −20 | 48 | 5, 20 | | |
| L | Anterior insula | 13 | 312 | 1.27 | −46 | 12 | −10 | 9 | | SN |
| R | Middle frontal gyrus[d] | 9 | 232 | 1.06 | 40 | 24 | 22 | 4, 19 | | CEN |

SN: salience network; DMN: default mode network; CEN: central executive network.
[a] Ginger ALE reports only those studies that fall directly within a cluster's boundary, even though studies with foci that lie outside the boundary may still contribute to the ALE cluster.
[b] Refer to Appendix A for studies.
[c] Cluster of activation on the border of the anterior insula.
[d] Region survived substraction analysis.

**Table 3b**
Brain regions showing reliably greater activity in PTSD vs. trauma-exposed controls ($p < 0.05$, FDR-corrected).

| Lat | Region | BA | Vol (mm³) | ALE ($10^{-2}$) | x | y | z | Contributing studies[a] | PTSD model | Network |
|---|---|---|---|---|---|---|---|---|---|---|
| R | Dorsal anterior cingulate | 24 | 808 | 0.97 | 4 | −6 | 34 | 2, 8, 16, 19 | | SN |
| | | | | 0.92 | 14 | −6 | 40 | | | |
| | | | | 0.88 | 16 | −4 | 44 | | | |
| L | Insula | 13 | 792 | 1.16 | −38 | −18 | 18 | 17, 19 | | |
| R | Precuneus | 7 | 536 | 1.01 | 12 | −48 | 52 | 3, 4, 17 | | CEN |
| L | Superior temporal gyms | | 320 | 1.00 | −54 | 0 | −2 | 6, 17 | | DMN |
| L | Inferior temporal gyrus | 20 | 288 | 0.94 | −52 | −12 | −24 | 4, 15 | | DMN |
| L | Fusiform gyrus | 37 | 280 | 0.89 | −46 | −42 | −12 | 1, 12 | | |
| R | Thalamus | | 256 | 0.92 | 4 | −6 | 0 | 9, 17 | | SN;CEN |

SN: salience network; DMN: default mode network; CEN: central executive network.
[a] Refer to Appendix B for studies.

**Table 4a**
Brain regions showing reliably less activity in PTSD vs. non-trauma controls ($p > 0.05$. FDR-corrected).

| Lat | Region | BA | Vol (mm³) | ALE ($10^{-2}$) | x | y | z | Contributing studies[a] | PTSD Model | Network |
|---|---|---|---|---|---|---|---|---|---|---|
| L | Angular gyrus | 39 | 752 | 1.55 | −42 | −60 | 38 | 4, 6, 14 | | DMN |
| L | Rostral anterior cingulate | 32 | 736 | 1.30 | −10 | 42 | 4 | 5, 11 | | |
| L | Precentral gyrus | 6 | 608 | 1.30 | −38 | −4 | 38 | 13,14 | | |
| R | Posterior cingulate | 31 | 472 | 1.24 | 14 | −44 | 38 | 4,14 | | DMN |
| R | Medial frontal gyrus | 10 | 440 | 1.80 | 12 | 52 | 4 | 4, 11 | X | DMN |
| L | Rostral anterior cingulate | 24 | 416 | 1.04 | 2 | 26 | 22 | 13, 19,20 | X | |
| R | Precentral gyrus | 4 | 360 | 1.31 | 28 | −22 | 60 | 4, 17 | | |
| R | Caudate | | 344 | 1.14 | 4 | 10 | −4 | 16 | | CEN |
| L | Supramarginal gyrus | 40 | 240 | 1.09 | −62 | −28 | 26 | 13, 19 | | CEN |
| L | Middle frontal gyrus | 8 | 200 | 0.10 | −26 | 20 | 42 | 1, 19 | | CEN |

SN: salience network; DMN: default mode network; CEN: central executive network.
[a] Refer to Appendix A for studies.

**Table 4b**
Brain regions showing reliably less activity in PTSD vs. trauma-exposed controls ($p < 0.05$, FDR-corrected).

| Lat | Region | BA | Vol (mm³) | ALE ($10^{-2}$) | x | y | z | Contributing studies[a] | PTSD Model | Network |
|---|---|---|---|---|---|---|---|---|---|---|
| R | Dorsal anterior cingulate | 24 | 992 | 1.01 | 10 | 6 | 36 | 9, 10, 17 | | SN |
| | | 32 | | 0.78 | 10 | 22 | 32 | | | |
| R | Orbitofrontal cortex | 47 | 624 | 0.97 | 24 | 16 | −20 | 3, 11, 17 | X | |
| R | Inferior frontal gyrus[b] | 46 | 616 | 1.40 | 54 | 38 | 2 | 5, 6 | | CEN |
| R | Medial frontal gyrus | 10 | 576 | 0.96 | 8 | 58 | −20 | 3, 15, 18 | X | DMN |
| L | Frontal pole | 10 | 456 | 1.11 | −26 | 58 | 2 | 14, 17 | | CEN |
| R | Precentral gyrus | | 456 | 1.12 | 44 | 14 | 38 | 8, 13 | | |
| R | Middle frontal gyrus[b] | 46 | 432 | 1.05 | 46 | 52 | 0 | 14, 17 | | CEN |
| L | Parahippocampal gyrus | 27 | 416 | 1.06 | −20 | −32 | −6 | 5, 8 | | DMN |
| L | Thalamus | | 352 | 0.89 | −10 | −20 | 12 | 2, 9 | | SN:CEN |
| L | Inferior frontal gyrus | 9 | 272 | 0.89 | −54 | 18 | 26 | 5, 7 | | CEN |
| L | Insula | 13 | 208 | 0.79 | −40 | −22 | 4 | 4, 8 | | |
| L | Middle frontal gyrus | 6 | 208 | 0.80 | −34 | 6 | 54 | 4, 6 | | CEN |

SN: salience network; DMN: default mode network; CEN: central executive network.
[a] Refer to Appendix B for studies.
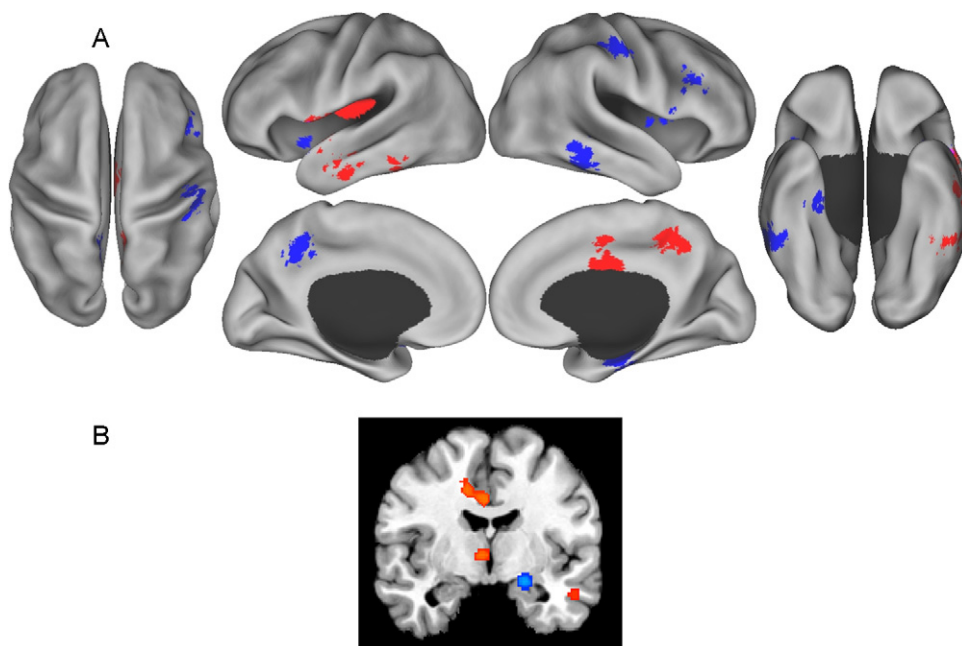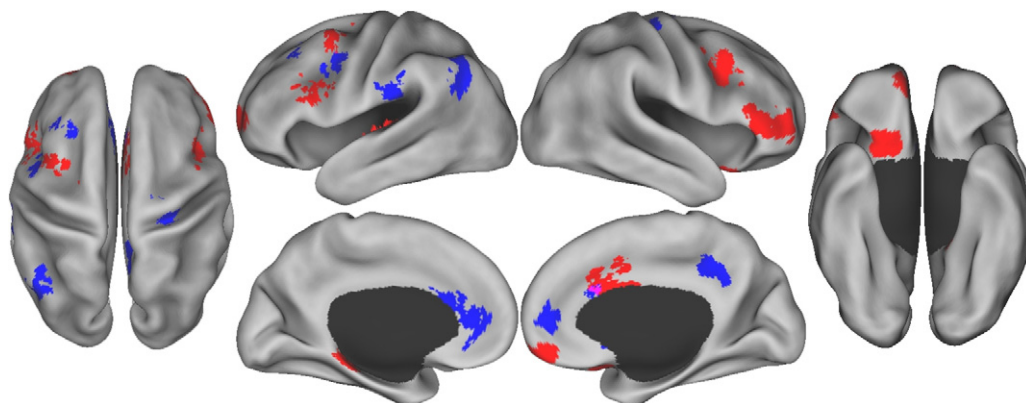[b] Region survived substraction analysis.

**Fig. 1.** (A). Brain regions showing greater activation in PTSD relative to the non-trauma control group (blue clusters) and trauma-exposed control group (red clusters). (B). Coronal view of brain regions showing greater activity in PTSD relative to the non-trauma control group (blue clusters) and trauma-exposed control group (red clusters). *Note.* Left hemisphere is represented on the right side of the image. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)



**Fig. 2.** Brain regions showing less activation in PTSD relative to the non-trauma control group (blue clusters) and trauma-exposed control group (red clusters). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

reveal any regions where PTSD-related hypoactivation was greater relative to TEC.

## 6. Discussion

We used quantitative ALE meta-analytic methods to synthesize findings from 36 functional neuroimaging studies of PTSD. Results revealed reliable clusters of abnormal activation in PTSD within the regions comprising the traditional neurocircuitry model (e.g. Rauch et al., 2006), as well as several additional clusters reflecting PTSD-related perturbations across the three large-scale brain networks implicated in the triple network model of psychopathology (Menon, 2011). Nonetheless, the patterns of regional brain activation revealed inconsistencies in directionality within these models as well as differences that depended upon the nature of the comparison group.

### 6.1. Evidence for the traditional neurocircuitry model of PTSD

The amygdala was confirmed as a consistent site of greater activation among PTSD groups. Interestingly, however, this was only true of the left amygdala and only in comparison to the NTC group (discussed further below). The neurocircuitry model also predicts hypoactivation of the medial prefrontal cortex, which contributes to a loss of top-down regulation of emotional systems (i.e., amygdala). Our findings provide more robust support for this component of the model in that relative to both control groups, groups with PTSD exhibited less activation in the medial prefrontal cortex. Moreover, this finding extended to other areas encompassing the medial prefrontal cortex including the rostral ACC (NTC group) and orbitofrontal cortex (TEC group). Collectively, our results support the notion of diminished medial prefrontal function as a reliable neural marker of PTSD, whereas amygdalar hyperactivation may relate more generally to trauma exposure.

The model also posits that deficits in identifying safe contexts and difficulties in learning and memory are mediated by dysfunctional hippocampi (Rauch et al., 1998, 2006). A left parahippocampal cluster was less active in PTSD relative to the TEC group. In contrast, we found greater hippocampal activation in PTSD as compared to the NTC group. Of note, however, the main studies contributing to the hippocampal hyperactivity used an oddball paradigm and resting state condition, as opposed to mnemonic tasks per se. Our finding of PTSD-related hyperactivation in the hippocampus is consistent with prior research demonstrating individuals with PTSD have elevated baseline levels of hippocampal activity (Shin et al., 2004). These findings are also consistent with the notion that exaggerated activity in this region may serve to promote fear conditioning in non-threatening contexts while interfering with normal extinction processes (Rauch et al., 2006). Individuals with PTSD also showed greater activation in surrounding areas of the lateral temporal lobe as compared to the TEC group. Taken together, our results suggest that medial-temporal and temporal cortical regions are reliably over-engaged in PTSD. The amygdala and hippocampus are both known to play critical roles in the consolidation of emotionally laden memories in healthy adults (Kensinger and Corkin, 2004; Hamann et al., 1999). Interactions between these two hyperresponsive regions may contribute to the intrusive nature of trauma recollections in PTSD.

## 6.2. Evidence for the triple network model of psychopathology

The triple network model of psychopathology proposes that cognitive and affective disturbances in psychiatric conditions may arise from dysfunction in large-scale brain networks. Specifically, the model proposes that aberrant functioning in three core networks, the central executive, salience, and default networks, may underlie clinical manifestations for a broad range of psychopathologies, including PTSD (Menon, 2011). Thus, we applied this emerging and unifying framework to facilitate characterization of the several brain regions determined by the meta-analyses.

As compared to both control groups, PTSD groups exhibited less activation in areas overlapping with the central executive network including the dorsolateral prefrontal cortex (BA 8, 9, 46) and lateral areas of the parietal cortex (BA 40; NTC group). These areas are known to play a key role in working memory and attentional control processes, which are often found to be impaired in PTSD (e.g., Falconer et al., 2008; Weber et al., 2005). Noteworthy is that one area of the central executive network, the precuneus, was reliably associated with greater activation in PTSD. Located on the medial aspect of the parietal lobe, the precuneus has been implicated in the fronto-parietal central executive network (see Margulies et al., 2009). Critically, only studies that used tasks related to affective processing directly contributed to the clusters of precuneal activity in our meta-analysis. This finding is consistent with previous meta-analytic results that reveal negative emotional processing in PTSD is associated with reliable engagement of the precuneus (Etkin and Wager, 2007). Taken together, these findings suggest that in PTSD, medial-based nodes of the central executive network may be differentially affected than lateral nodes, although future work is needed to thoroughly investigate this possibility.

In contrast to areas of the central executive network, individuals with PTSD showed greater activation in areas of the salience network including its two central nodes, the anterior insula (relative to NTC) and the dorsal ACC (relative to TEC). A slightly more anterior section of the ACC was hypoactive, hindering clear interpretation regarding this region based on the meta-analysis. Previous findings have revealed that pre-scan ratings of anxiety significantly correlate with activity in the dorsal ACC node of the salience network (Seeley et al., 2007). Dorsal ACC hyperactivity in PTSD relative to TEC also parallels recent findings in combat veterans showing greater dorsal ACC activity among those with PTSD than without in response to a cognitive interference task (Shin et al., 2011). The level of dorsal ACC activity in the PTSD veteran group was further correlated with their level of symptom severity. In addition, individuals with PTSD exhibited greater activation than controls in other key regions of the salience network including the putamen, amygdala, and thalamus. Taken together, these findings suggest hyperactivation across key nodes of the salience network in PTSD may underlie disruptions in conflict monitoring, autonomic regulation, and reward-processing.

PTSD was associated with less activation in the default network, including in the medial prefrontal cortex relative to both control groups, the posterior cingulate cortex and posterior inferior parietal lobule relative to the NTC group, and the left parahippocampal gyrus relative to the TEC group. Increased suppression of these default areas may therefore serve as a reliable neural marker of reduced cognitive flexibility in PTSD. However, our meta-analysis also showed clusters of hyperactivity in the right hippocampus and left temporal cortices. Overall, these findings suggest a functional dissociation within the default network. Indeed, recent studies have revealed altered functional connectivity between areas of the default network in PTSD (Bluhm et al., 2009; Daniels et al., 2010).

While the results of the current meta-analysis provide some evidence toward aberrant functioning within each of the core networks of the triple network model, we caution that there was inconsistency in the direction (hyper- and hypo-activation) of findings within each network relative to controls and that several nodes across these models did not emerge from the meta-analysis. In addition, reliable clusters of activity were found in regions that do not conform to the triple network or neurocircuitry models proper (see Tables 3a, 3b and 4a, 4b). For example, PTSD showed lower activation in premotor and motor regions and greater activation in sensory processing areas including the fusiform gyrus (both control groups) and the postcentral gyrus (relative to NTC). The latter findings are consistent with the proposal that heightened salience of emotional, motivational, and threat information detected by limbic and salience network regions feeds back to enhance processing in primary and associative sensory areas (Morey et al., 2009). Indeed, a 'sensorimotor' subnetwork consisting of primary motor and sensory regions may also interact with large-scale brain networks (Menon, 2011).

## 6.3. Integrating models of PTSD

We note that models of PTSD are not mutually exclusive. Neurocircuitry models have consistently emphasized diminished activation of the medial prefrontal cortex and exaggerated activity in limbic regions such as the amygdala as hallmark features of PTSD. A loss of top-down inhibition is thought to be one of the main components underlying impaired extinction (Rauch et al., 2006) or under-modulation of affect (e.g., symptoms of trauma re-experiencing, hyperarousal, anger; Lanius et al., 2011). However, the precise mechanism by which prefrontal systems lose their control over limbic areas is still unclear. Under the triple network model, a loss of prefrontal inhibition might result from aberrant functioning of the anterior insula. An increasing number of models have implicated exaggerated activity in the anterior insula as the neural locus for heightened interoceptive and emotional awareness (Lanius et al., 2011; Paulus and Stein, 2006; Shin and Liberzon, 2010), a view that fits well with the notion of an over-active salience network in PTSD. Indeed, Paulus and Stein (2006) propose that enhanced activity in the anterior insula may be in part due to enhanced salience signaling from the amygdala. In addition to subserving functions related to salience detection and interoceptive processing, the triple network model posits that the anterior insula acts as critical hub that facilitates access to other large-scale,

neurocognitive networks. Aberrant functioning of the anterior insula in PTSD may therefore disrupt control signals that facilitate proper engagement of networks mediating higher-order cognitive functions that are dependent on the prefrontal cortex and that are involved in normal fear extinction and emotion regulation. Our finding that PTSD was reliably associated with hyperresponsivity in the anterior insula across multiple studies lends some support to this view.

Important to mention is that areas of the traditional neurocircuitry model are also key nodes of networks implicated in the triple-network model. For instance, our finding of hyperactivation of the amygdala in PTSD (vs. NTC group) is also consistent with a hyperresponsive salience network. In contrast, heightened activity in the temporal cortex (NTC and TEC groups) interacting with less activity in the medial prefrontal cortex (NTC and TEC groups) might reflect functional dissociations within the default network. Recent models have highlighted that symptoms of PTSD related to deficits in self-referential processing (e.g., symptoms of depersonalization) may be linked to aberrant connectivity between regions of the default network (Lanius et al., 2011). Dysfunction within and between networks could lead to a unique constellation of PTSD symptoms. For example, interactions between an overactive salience network and increased suppression of default regions could form a basis for intrusive trauma recollections and impaired autobiographical recall. Altered functioning of areas implicated in neurocircuitry models might also have downstream effects within the context of their respective neurocognitive network thus impacting a range of cognitive and affective functions in PTSD. Further investigation of regions implicated in these existing models within the context of large-scale neurocognitive networks may therefore reveal novel markers of neural dysfunction in PTSD. Consideration of such network-based markers may more closely reflect the complex clinical presentations that typically accompany chronic forms of PTSD, as compared to exploring relations between brain regions and symptoms in isolation.

### 6.4. Control-group related differences in brain activation

The nature of the control group moderated the neural signature associated with PTSD. For instance, in contrast to the NTC group, the TEC group showed greater activity in prefrontal regions. One possible interpretation of this finding is that prefrontal systems may act as a neural marker of resilience. In a direct three-group comparison, Falconer et al. (2008) found that both NTC and TEC control groups showed greater activity in prefrontal areas including the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and medial prefrontal cortex, than PTSD during an inhibitory control task. There were no significant differences between the two control groups, indicating the TEC group showed a similar profile of prefrontal activation as the NTC group. These findings further implicate the involvement of the prefrontal cortex as a neural locus for trauma-related resilience factors.

We also found increased amygdala activation in PTSD only when compared to the NTC group, though this finding did not survive the formal subtraction analysis. Nonetheless, this result is striking given that exaggerated amygdala activity is often cited as a critical neural marker of PTSD (e.g., Armony et al., 2005; Hendler et al., 2003; Liberzon et al., 1999; Rauch et al., 2000). Although speculative, it may be the case that exposure to trauma results in a general increase in amygdala responsivity, and that when directly compared, amygdala hyperactivity in PTSD was not sufficiently greater than the TEC groups across included studies. This interpretation is consistent with recent findings reported by Simmons et al. (2011). Their findings revealed that while the PTSD group exhibited greater amygdala activation to fearful versus happy faces than both TEC and NTC groups, combined PTSD and TEC groups showed greater

amygdala activation during a face versus shape matching task than the NTC group. These findings lend further support for the notion that trauma exposure may lead to a general increase in amygdala hyperresponsivity.

These findings suggest that exposure to trauma in the absence of PTSD may be associated with distinct brain changes compared to individuals who have not experienced any traumatic event. Alternatively, the different neural signature associated with trauma exposure without PTSD might reflect differences in resilience to trauma. Further longitudinal work would be valuable in addressing these potential interpretations as they hold important implications for advancing intervention. For instance, the finding that TEC group is associated with significantly greater prefrontal activity suggests strengthening of prefrontal systems may prove to be more effective in reducing PTSD symptoms than targeting amygdala/arousal-based systems. Indeed, a recent longitudinal study showed PTSD symptom improvement across time was associated with increasing activity in the subgenual ACC, and unrelated to activity in the amygdala (Dickie et al., 2010).

### 6.5. Limitations and future directions

In addressing our goal of identifying domain-general alterations in functional brain response in PTSD, our findings reveal regions that are reliable across a heterogeneous set of tasks. In this regard, it is possible that our separate analyses by NTC vs. TEC control groups may be differentially biased by the composition of studies contributing to each of these analyses. However, assessment of the contributing studies fails to reveal a systematic difference in the distribution of task domain (e.g., cognitive, emotional, resting state) across analyses (see Tables 2a, 2b, 3a, 3b and 4a, 4b). Domain-general differences in PTSD-related activation might also serve as the basis for smaller-scale, task-specific changes in neural activity. At present, the relatively small body of studies within each of our analyses (PTSD vs. NTC and PTSD vs. TEC) precludes meaningful evaluation of this possibility from a meta-analytic perspective. Future studies are needed to determine the relative contributions of domain-general changes, as characterized here, and domain-specific alterations within task specific networks to PTSD symptomatology.

Our meta-analysis also pooled across studies that used fMRI or PET/SPECT in order to identify domain-general markers of brain dysfunction in PTSD. For three of our analyses (PTSD > NTC; PTSD < NTC; and PTSD < TEC), 50% of those clusters that had two or more contributing studies were made up of studies containing both fMRI and PET/SPECT (30% for the PTSD > TEC analysis). Taken together, these data suggest our overall results were not strongly influenced by one neuroimaging method over the other. However, as investigations of functional neuroimaging in PTSD continue to grow, future work should aim to evaluate the potential relevance of differences in regional sensitivity between these neuroimaging methods.

Our coordinate-based meta-analysis used peak locations ($x$, $y$, $z$) in order to identify reliable estimates of spatial convergence across studies. While this reflects the current gold standard for conducting neuroimaging meta-analyses, recent evidence shows image-based meta-analyses are likely to derive even more spatially precise estimates of spatial convergence (Salimi-Khorshidi et al., 2009). However, image-based meta-analysis requires access to whole brain statistical parametric images, which are currently not readily available to the research community. Finally, in order to minimize bias toward a select group of regions, our meta-analysis drew upon neuroimaging investigations of PTSD that surveyed the whole brain. However, studies that use region-of interest analyses provide greater sensitivity (at the cost of specificity) for characterizing patterns of functional brain response in smaller

structures such as the amygdala. Thus, the findings reported here might reflect a conservative view of neural dysfunction in PTSD[1].

The current findings may offer some unique insights into current psychosocial theories of PTSD (for review, see Brewin and Holmes, 2003). For instance, in their cognitive model of PTSD, Ehlers and Clark (2000) propose that inefficient encoding leads to distortions in trauma memory whereby proper contextualization of the memory trace in time, place, and relative to other autobiographical memories, is disrupted. Results from our meta-analysis suggest functional dissociations within the default network may act as the neural substrate for poor contextualization of autobiographical trauma-based memory. The model also suggests that retrieval of trauma memory is often cue-driven and unintentional (i.e., implicit), which could reflect altered signaling of an overactive salience network. Nodes of the salience network may inappropriately respond to semantically-related and -unrelated trauma cues, leading them to be experienced as strong sensory impressions or visual images. Other aspects of the model, including negative appraisals involving perceived danger to the self and others, may be related to a loss of top-down signaling from central executive network. Further investigation of these hypotheses may serve to better integrate how psychosocial theories are informed by the neurobiological frameworks discussed in this paper.

## 7. Conclusion

In this meta-analysis, we aimed to characterize domain-general markers of neural activity reliably associated with PTSD. To this end, we used the ALE method to identify regions that reliably show altered activation in PTSD relative to two non-PTSD control groups: NTC and TEC groups. Our results generally supported the traditional neurocircuitry model of PTSD in terms of lower activation in medial prefrontal regions and hyperactivation of the amygdala, as well as abnormal activation in the hippocampus which was characterized by hyperactivation. Our meta-analysis also implicated several other brain regions that were largely captured within the triple-network model. Overall, our results suggest individuals with PTSD may over-engage the salience network, while failing to properly recruit the central executive network, and show differential changes in the activation of the default network. While this pattern of results suggests that these models warrant further consideration, we also caution against their strict application and interpretation due to the observed heterogeneity in findings. Future studies using functional and effective connectivity analyses will be needed to directly investigate how these generalized brain changes may serve as the basis for smaller-scale, task-specific alterations within and between networks. Future work is also needed to determine how the findings reported here are moderated by key factors such as symptom severity in PTSD and trauma exposure (type of trauma, severity, neuroimaging method). Last, we propose that improved characterization of alterations among spatially distributed functional networks may define reliable neural markers to predict unique constellations of symptoms in PTSD and consequently, act as effective targets for rehabilitation.

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[1] Upon the acceptance of this article, we learned of a concurrent ALE meta-analysis by Hayes et al. (in press) that collapses different control groups, but examines task-specific neural changes in PTSD and presents findings with and without ROI-based studies. Overall, their findings of PTSD-related hyperactivity in the dorsal ACC and amygdala and hypoactivity in areas of the medial prefrontal cortex, show good convergence with the domain-general findings presented here.

## Appendix A.

Meta-analysis studies for PTSD and non-trauma exposed controls.

1. Astur, R.S., St. Germain, S.A., Tolin, D., Ford, J., Russell, D., Stevens, M., 2006. Hippocampus function predicts severity of post-traumatic stress disorder. Cyberpsychology Behav. 9, 234–240.
2. Bonne, O., Gilboa, A., Louzoun, Y., Brandes, D., Yona. I., Lester, H., et al., 2003. Resting regional cerebral perfusion in recent posttraumatic stress disorder. Biol Psychiatry 54, 1077–1086.
3. Bremner, J.D., Vythilingam, M., Vermetten, E., Southwick, S.M., McGlashan, T., Staib L.H., et al., 2003. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biol Psychiatry 53, 879–889.
4. Bremner, J.D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N. et al., 2005. Positron emission tomographic imaging of neural correlates of a fear and acquisition and extinction paradigm in women with childhood sexual-abuse-related post traumatic stress disorder. Psychol Med. 35, 791–806.
5. Bryant, R.A., Felmingham, K.L., Kemp, A.H, Barton, M., Peduto, A.S., Rennie, C., et al., 2005. Neural networks of information processing in post traumatic stress disorder: a functional magnetic resonance imaging study. Biol Psychiatry 58, 111–118.
6. Chung, Y.A., Kim, S.H., Chung, S.K., Chae, J.H., Yang, D.W., Sohn, J.S., et al., 2006. Alterations in cerebral perfusion in posttraumatic stress disorder patients without re-exposure to accident-related stimuli. Clin Neurophysiol. 117, 637–642.
7. Elman, I, Lowen, S., Frederick, B.B., Chi W, Becerra L, Pitman, R.K., 2009. Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. Biol Psychiatry 66, 1083–1090.
8. Felmingham, K.L., Williams, L.M., Kemp, A.H,, Rennie, C., Gordon, E., Bryant, R.A., 2009. Anterior cingulate activity to salient activity is modulated by autonomic arousal in posttraumatic stress disorder. Psychiatry Res. 173, 59–62.
9. Fonzo, G.A., Simmons, A.N., Thorp, S.R., Norman, S.B, Paulus, M.P., Stein, M.B., 2010. Exaggerated and disconnected insular-amygdala blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. Biol Psychiatry 68, 433–441.
10. Jatzko, A., Schmitt, A., Demirakca, T., Weimer, E., Braus, D.F., 2006. Disturbance in the neural circuitry underlying positive emotional processing in post-traumatic stress disorder (PTSD) an fMRI study. Eur Arch Psychiatry Clin Neurosci. 256, 112–114.
11. Kim, M.J., Chey, J., Chung, A., Bae, S., Khang, H., Ham, B., et al., 2008. Diminished rostral anterior cingulate activity in response to threat-related events in posttraumatic stress disorder. J Psychiatr Res. 42, 268–277.
12. Liberzon, I, Taylor, S.F., Phan, K.L., Britton, J.C., Fig, L.M., Bueller, J.A., et al., 2007. Altered central μ-opioid receptor binding after psychological trauma. Biol Psychiatry 61, 1030–1038.
13. Moores, K.A., Clark, C.R., McFarlane, A.C., Brown, G.C., Puce, A., Taylor, D.J., 2008. Abnormal recruitment of working memory updating networks during maintenance of trauma-neutral

information in post-traumatic stress disorder. Psychiatry Res. 163, 156–170.

14. New, A.S., Fan, J., Murrough, J.W., Liu, X., Leibman, R.E., Guise, K.G., et al., 2009. A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and post-traumatic stress disorder. Biol Psychiatry 66, 656–664.

15. Phan, K.L., Britton, J.C., Taylor, S.F., Fig, L.M, Liberzon, I., 2006. Corticolimbic blood flow during nontraumatic emotional processing in posttraumatic stress disorder. Arch Gen Psychiatry 63, 184–192.

16. Sailer, U., Robinson, S., Fischmeister, F.P.S, Konig, D., Oppenauer, C., Lueger-Schuster, et al., 2008. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. Neuropsychologia 46, 2836–2844.

17. Sakamoto, H., Fukuda, R., Okuaki, T., Rogers, M., Kasai, K., Machida, T., et al., 2005. Parahippocampal activation evoked by masked traumatic images in posttraumatic stress disorder: A functional MRI study. NeuroImage 26, 813–821.

18. Strigo, I.A., Simmons, A.N., Matthews, S.C., Grimes, E.M. Allard, C.B., Reinhardt, L.E., et al., 2010. Neural correlates of altered pain response in women with posttraumatic stress disorder from intimate partner violence. Biol Psychiatry 68, 442–450.

19. Werner, N.S., Meindl, T., Engel, R.R., Rosner, R., Riedel, M., Reiser, M., et al., 2009. Hippocampal function during associative learning in patients with posttraumatic stress disorder. J Psychiatr Res. 43, 309–318.

20. Williams, L.M., Kemp, A.H., Felmingham, K., Barton, M., Olivieri, G., Peduto, A., et al., 2006. Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. NeuroImage 29, 347–357.

## Appendix B.

Meta-analysis studies for PTSD and trauma-exposed controls.

1. Bonne, O., Gilboa, A., Louzoun, Y., Brandes, D., Yona, I., Lester, H., et al., 2003. Resting regional cerebral perfusion in recent posttraumatic stress disorder. Biol Psychiatry 54, 1077–1086.

2. Bremner, J.D., Staib, L.H., Kaloupek, D., Southwick, S.M., Soufer, R., Charney, D.S., 1999a. Neural correlates of exposure to traumatic pictures and sound in vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. Biol Psychiatry 45, 806–816.

3. Bremner, J.D., Narayan, M., Staib, L.H., Southwick, S.M., McGlashan, T., Charney, D.S., 1999b. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry 156, 1787–1795.

4. Bremner, J.D., Vermetten, E., Vythilingam, M., Afzal, N., Schmahl, C., Elzinga, B., et al., 2004. Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. Biol Psychiatry 55, 612–620.

5. Chen, S., Li, L., Xu, B., Liu, J., 2009. Insular cortex involvement in declarative memory deficits in patients with post traumatic stress disorder. BMC Psychiatry 9, 1–9.

6. Geuze, E., Vermetten, E., Ruf, M., de Kloet, C.S., Westenberg, H.G.M., 2008. Neural correlates of associative learning and memory in veterans with posttraumatic stress disorder. J Psychiatr Res. 42, 659–669.

7. Hou, C., Liu, J., Wang, K., Li, L., Liang, M., He, Z., et al., 2007. Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. Brain Res. 1144, 165–174.

8. Lanius, R.A., Williamson, P.C., Boksman, K., Densmore, M., Gupta, M., Neufeld, R.W.J., et al., 2002. Brain activation during

script-driven imagery induced dissociative responses in PTSD: A functional magnetic resonance imaging investigation. Biol Psychiatry 52, 305–311.

9. Lanius, R.A., Williamson, P.C., Bluhm, R.L., Densmore, M., Boksman, K., Neufeld, R.W.J. et al., 2005. Functional connectivity of dissociative responses in posttraumatic stress disorder: a functional magnetic resonance imaging investigation. Biol Psychiatry 57, 873–884.

10. Lanius, R.A., Williamson, P.C., Hopper, J., Densmore, M., Boksman, K., Gupta, M.A., et al., 2003b. Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. Biol Psychiatry 53, 204–210.

11. Liberzon, I., Taylor, S.F., Phan, K.L., Britton, J.C., Fig, L.M., Bueller, J.A., et al., 2007. Altered central μ-opioid receptor binding after psychological trauma. Biol Psychiatry 61, 1030–1038.

12. Lindauer, R.J.L., Booij, J., Habraken, J.B.A., Uylings, H.B.M., Olff, M., Carlier, I.V.E., et al., 2004. Cerebral blood flow changes during script-driven imagery in police officers with posttraumatic stress disorder. Biol Psychiatry 56, 853–861.

13. New, A.S., Fan, J., Murrough, J.W., Liu, X., Liebman, R.E., Guise, K.G., 2009. A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and posttraumatic stress disorder. Biol Psychiatry 66, 656–664.

14. Shin, L.M., McNally, R.J., Kossyln, S.M., Thompson, W.L., Rauch, S.L., Alpert, N.L., et al., 1999. Regional cerebral blood flow during script driven imagery in childhood sexual abuse-related PTSD: A PET investigation. Am J Psychiatry 156, 575–584.

15. Shin, L.M., Orr, S.P., Carson, M.A., Rauch, S.L., Macklin, M.L., Lasko, N.B., et al., 2004. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female vietnam veterans with PTSD. Arch Gen Psychiatry 61, 168–176.

16. Shin, L.M., Lasko, N.B., Macklin, M.L., Karpf, R.D., Milad, M.R., Orr, S.P., et al., 2009. Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. Arch Gen Psychiatry 66, 1099–1107.

17. Shin, L.M., Whalen, P.J., Pitman, R.K., Bush, G., Macklin, M.L., Lasko, N.B., et al., 2001. An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biol Psychiatry 50, 932–942.

18. Shin, L.M., Shin, P.S., Heckers, S., Krangel, T.S., Macklin, M.L., Orr, S.P., et al., 2004. Hippocampal function in posttraumatic stress disorder. Hippocampus 14, 292–300.

19. Whalley, M.G., Rugg, M.D., Smith, A.P.R, Dolan, R.J., Brewin, C.R., 2009. Incidental retrieval of emotional contexts in post-traumatic stress disorder and depression: an fMRI study. Brain and Cogn. 69, 98–107.

## References

Andrews-Hanna, J.R., 2012. The adaptive role of the default network in internal mentation. The Neuroscientist 18, 251–270.

Armony, J.L., Corbo, V., Clement, M.H., Brunet, A., 2005. Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. American Journal of Psychiatry 162, 1961–1963.

Bluhm, R.L., Williamson, P.C., Osuch, E.A., Frewen, P.A., Stevens, T.K., Boksman, K., et al., 2009. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. Journal of Psychiatry and Neuroscience 34, 187–194.

Bremner, J.D., Vythilingam, M., Vermetten, E., Southwick, S.M., McGlashan, T., Staib, L.H., et al., 2003. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biological Psychiatry 53, 879–889.

Bremner, J.D., 2004. Brain imaging in anxiety disorders. Expert Review of Neurotherapeutics 4, 275–284.

Bremner, J.D., Innis, R.B., Ng, C.K., Staib, L.H., Salomon, R.M., Bronen, R.A., et al., 1997. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. Archives of General Psychiatry 54, 246–254.

Brewin, C.R., Holmes, E.A., 2003. Psychological theories of posttraumatic stress disorder. Clinical Psychology Review 23, 339–376.

Bressler, S.L., McIntosh, A.R., 2007. The role of neural context in large-scale neurocognitive network operations. In: Jirsa, V.K., McIntosh, A.R. (Eds.), Springer Handbook on Brain Connectivity. Springer, New York, pp. 403–419.

Britton, J.C., Phan, K.L., Taylor, S.F., Fig, L.M., Liberzon, I., 2005. Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. Biological Psychiatry 15, 832–840.

Bryant, R.A., Felmingham, K., Kemp, A., Das, P., Hughes, G., Peduto, A., et al., 2008. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behavior therapy for post-traumatic stress disorder. Psychological Medicine 38, 555–561.

Bryant, R.A., Felmingham, K.L., Kemp, A.H., Barton, M., Peduto, A.S., Rennie, C., et al., 2005. Neural networks of information processing in posttraumatic stress disorder: a functional magnetic resonance imaging study. Biological Psychiatry 58, 111–118.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Annals of the New York Academy of Sciences 1124, 1–38.

Carrion, V.G., Garrett, A., Menon, V., Weems, C.F., Reiss, A.L., 2008. Posttraumatic stress symptoms and brain function during a response-inhibition task: an fMRI study in youth. Depression and Anxiety 25, 514–526.

Chen, S., Li, L., Xu, B., Liu, J., 2009. Insular cortex involvement in declarative memory deficits in patients with post-traumatic stress disorder. BMC Psychiatry 9, 39.

Daniels, J.K., McFarlane, A.C., Bluhm, R.L., Moores, K.A., Clark, C.R., Shaw, M.E., et al., 2010. Switching between executive and default mode networks in PTSD – alterations in functional connectivity. Journal of Psychiatry and Neuroscience 35, 1258–1266.

Dickie, E.W., Brunet, A., Akerib, V., Armony, J.L., 2010. Neural correlates of recovery from post-traumatic stress disorder: a longitudinal fMRI investigation of memory encoding. Neuropsychologia 49, 1771–1778.

Dosenbach, N.U.F., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A.T., et al., 2007. Distinct brain networks for adaptive and stable task control in humans. Proceedings of the National Academy of Sciences of the United States of America 104, 11073–11078.

Driessen, M., Beblo, T., Mertens, M., Piefke, M., Rullkoetter, N., Silva-Saavedra, A., 2004. Posttraumatic stress disorder and fMRI activation patterns of traumatic memory in patients with borderline personality disorder. Biological Psychiatry 15, 603–611.

Ehlers, A., Clark, D.M., 2000. A cognitive model of posttraumatic stress disorder. Behaviour Research and Therapy 38, 319–345.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Human Brain Mapping 30, 2907–2926.

Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. American Journal of Psychiatry 164, 1476–1488.

Falconer, E., Bryant, R., Felmingham, K.L., Kemp, A.H., Gordon, E., Peduto, A., et al., 2008. The neural networks of inhibitory control in posttraumatic stress disorder. Journal of Psychiatry and Neuroscience 33, 413–422.

Felmingham, K.L., Williams, L.M., Kemp, A.H., Rennie, C., Gordon, E., Bryant, R.A., 2009. Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in posttraumatic stress disorder. Psychiatry Research 173, 59–62.

Fonzo, G.A., Simmons, A.N., Thorp, S.R., Norman, S.B., Paulus, M.P., Stein, M.B., 2010. Exaggerated and disconnected insular-amygdala blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. Biological Psychiatry 68, 433–441.

Francati, V., Vermetten, E., Bremner, J.D., 2007. Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. Depression and Anxiety 24, 202–218.

Frewen, P., Lane, R.D., Neufeld, R.W., Densmore, M., Stevens, T., Lanius, R., 2008. Neural correlates of levels of emotional awareness during trauma script-imagery in posttraumatic stress disorder. Psychosomatic Medicine 70, 27–31.

Garfinkel, S.N., Liberzon, I., 2009. Neurobiology of PTSD: a review of neuroimaging findings. Psychiatric Annals 39, 370–381.

Genovese, C.R., Lazar, N., Nichols, T.E., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15, 870–878.

Geuze, E., Westenberg, H.G., Jochims, A., de Kloet, C.S., Bohus, M., Vermetten, E., et al., 2007. Altered pain processing in veterans with posttraumatic stress disorder. Archives of General Psychiatry 64, 76–85.

Geuze, E., Vermetten, E., Ruf, M., de Kloet, C.S., Westenberg, H.G., 2008. Neural correlates of associative learning and memory in veterans with posttraumatic stress disorder. Journal of Psychiatric Research 42, 659–669.

Gusnard, D.A., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. Nature Reviews Neuroscience 2, 685–694.

Hamann, S.B., Ely, T.D., Grafton, S.T., Kilts, C.D., 1999. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nature Neuroscience 2, 289–293.

Hayes, J.P., Hayes, S.M., Mikedis, A.M., in press. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. Biology of Mood & Anxiety Disorders 2: 9. http://dx.doi.org/10.1186/2045-5380-2-9.

Hayes, J.P., LaBar, K.S., McCarthy, G., Selgrade, E., Nasser, J., Dolcos, F., et al., 2011. Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. Journal of Psychiatric Research 45, 660–669.

Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben-Bashat, D., et al., 2003. Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. NeuroImage 19, 587–600.

Hoge, C.W., Auchterlonie, J.L., Milliken, C.S., 2006. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. JAMA 295, 1023–1032.

Hou, C., Liu, J., Wang, K., Li, L., Liang, M., He, Z., et al., 2007. Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. Brain Research 1144, 165–174.

Kensinger, E.A., Corkin, S., 2004. Two routes to emotional memory: distinct neural processes for valence and arousal. Proceedings of the National Academy of Sciences of the United States of America 101, 3310–3315.

Laird, A.R., Fox, P.M., Price, C.J., Glahn, D.C., Uecker, A.M., Lancaster, J.L., et al., 2005. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Human Brain Mapping 25, 155–164.

Laird, A.R., Robinson, J.L., McMillan, K.M., Tordesillas-Gutiérrez, D., Moran, S.T., Gonzales, S.M., et al., 2010. Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. NeuroImage 51, 677–683.

Lanius, R.A., Bluhm, R., Lanius, U., Pain, C., 2006. A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. Journal of Psychiatric Research 40, 709–729.

Lanius, R.A., Williamson, P.C., Densmore, M., Boksman, K., Neufeld, R.W., Gati, J.S., et al., 2004. The nature of traumatic memories: a 4-T FMRI functional connectivity analysis. American Journal of Psychiatry 161, 36–44.

Lanius, R.A., Bluhm, R.L., Frewen, P.A., 2011. How understanding the neurobiology of complex post-traumatic stress disorder can inform clinical practice: a social cognitive and affective neuroscience approach. Acta Psychiatrica Scandinavica 124, 331–348.

Liberzon, I., Taylor, S.F., Amdur, R., Jung, T.D., Chamberlain, K.R., Minoshima, S., Koeppe, R.A., et al., 1999. Brain activation in PTSD in response to trauma-related stimuli. Biological Psychiatry 45, 817–826.

Liberzon, I., Garfinkel, S.N., 2009. Functional neuroimaging in post-traumatic stress disorder. In: Shiromani, P.J., et al. (Eds.), Post-Traumatic Stress Disorder: Basic Science and Clinical Practice. Humana Press, New York, pp. 297–317.

Margulies, D.S., Vincent, J.L., Kelly, C., Lohmann, G., Uddin, L.Q., Biswal, B.B., et al., 2009. Precuneus shares intrinsic functional architecture in humans and monkeys. Proceedings of the National Academy of Sciences of the United States of America 106, 20069–20074.

Menon, V., 2011. Large-scale brain networks and psychopathology: A unifying triple network model. Trends in Cognitive Sciences 15, 483–506.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Structure & Function 214, 655–667.

Morey, R.A., Dolcos, F., Petty, C.M., Cooper, D.A., Hayes, J.P., LaBar, K.S., et al., 2009. The role of trauma-related distractors on neural systems for working memory and emotion processing in posttraumatic stress disorder. Journal of Psychiatric Research 43, 809–817.

New, A.S., Fan, J., Murrough, J.W., Liu, X., Liebman, R.E., Guise, K.G., 2009. A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and posttraumatic stress disorder. Biological Psychiatry 66, 656–664.

Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. Biological Psychiatry 60, 383–387.

Postle, B.R., 2006. Working memory is an emergent property of the mind and brain. Neuroscience 139, 23–38.

Protopopescu, X., Pan, H., Tuescher, O., Cloitre, M., Goldstein, M., Engelien, W., et al., 2005. Differential time courses and specificity of amygdala activity in posttraumatic stress disorder subjects and normal control subjects. Biological Psychiatry 57, 464–473.

Rauch, S.L., Shin, L.M., Whalen, P.J., Pitman, R.K., 1998. Neuroimaging and the neuroanatomy of PTSD. CNS Spectrums 3 (Suppl. 2), 30–41.

Rauch, S.L., Shin, L.M., Phelps, E.A., 2006. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. Biological Psychiatry 60, 376–382.

Rauch, S.L., Whalen, P.J., Shin, L.M., McInerney, S.C., Macklin, M.L., Lasko, N.B., et al., 2000. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biological Psychiatry 47, 769–776.

Salimi-Khorshidi, G., Smith, S.M., Keltner, J.R., Wager, T.D., Nichols, T.E., 2009. Meta-analysis of neuroimaging data: a comparison of image-based and coordinate-based pooling of studies. NeuroImage 45, 810–823.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., et al., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. Journal of Neuroscience 27, 2349–2356.

Shin, L.M., Whalen, P.J., Pitman, R.K., Bush, G., Macklin, M.L., Lasko, N.B., et al., 2001. An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biological Psychiatry 50, 932–942.

Shin, L.M., Shin, P.S., Heckers, S., Krangel, T.S., Macklin, M.L., Orr, S.P., et al., 2004. Hippocampal function in posttraumatic stress disorder. Hippocampus 14, 292–300.

Shin, L.M., Kosslyn, S.M., McNally, R.J., Alpert, N.M., Thompson, W.L., Rauch, S.L., et al., 1997. Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. Archives of General Psychiatry 54, 233–241.

Shin, L.M., Liberzon, I., 2010. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 35, 169–191.

Shin, L.M., Bush, G., Milad, M.R., Lasko, N.B., Brohawn, K.H., Hughes, K.C., et al., 2011. Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. American Journal of Psychiatry 168, 979–985.

Simmons, A.N., Matthews, S.C., Strigo, I.A., Baker, D.G., Donovan, H.K., Motezadi, A., et al., 2011. Altered amygdala activation during face processing in Iraqi and Afghanistan war veterans. Biology of Mood & Anxiety Disorders 1, 1–12.

Spreng, R.N., Mar, R.A., Kim, A.S.N., 2009. The common neural basis of autobiographical memory, prospection, navigation, theory of mind and the default mode: a quantitative meta-analysis. Journal of Cognitive Neuroscience 21, 489–510.

Thomaes, K., Dorrepaal, E., Draijer, N.P., de Ruiter, M.B., Elzinga, B.M., van Balkom, A.J., et al., 2009. Increased activation of the left hippocampus region in complex PTSD during encoding and recognition of emotional words: a pilot study. Psychiatry Research 171, 44–53.

Turkeltaub, P.E., Eden, G.F., Jones, K.M., Zeffiro, T.A., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. NeuroImage 16, 765–780.

Van Ameringen, M., Mancini, C., Patterson, B., Boyle, M.H., 2008. Posttraumatic stress disorder in Canada. CNS Neuroscience & Therapeutics 14, 171–181.

Van Essen, D.C., 2005. A population-average. Landmark- and surface-based (PALS) atlas of human cerebral cortex. NeuroImage 28, 635–662.

Villarreal, G., King, C.Y., 2004. Neuroimaging studies reveal brain changes in posttraumatic stress disorder. Psychiatric Annals 34, 845–856.

Weber, D.L., Clark, C.R., McFarlane, A.C., Moores, K.A., Morris, P., Egan, G.F., 2005. Abnormal frontal and parietal activity during working memory updating in posttraumatic stress disorder. Psychiatry Research 140, 27–44.

Werner, N.S., Meindl, T., Engel, R.R., Rosner, R., Riedel, M., Reiser, M., et al., 2009. Hippocampal function during associative learning in patients with posttraumatic stress disorder. Journal of Psychiatric Research 43, 309–318.

Yang, P., Wu, M.T., Hsu, C.C., Ker, J.H., 2004. Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: a functional MRI study. Neuroscience Letters 370, 13–18.