INTRODUCTION

Post-traumatic stress disorder (PTSD) is characterized by various altered emotional responses as a result of trauma exposure (e.g., combat, assault, and disasters). Patients with PTSD not only experience intense negative emotional reactions when reminded of their trauma but also report exaggerated arousal (poor sleep, restlessness, hypervigilance), anhedonia, social withdrawal, and decreased emotional expressivity, referred to as “emotional numbing.” Characterizing the neural basis of these diverse, distorted emotional responses poses a major challenge to contemporary psychiatric research. Functional neuroimaging techniques have focused primarily on the study of brain function related to fear perception and response, and have consistently implicated aberrant amygdala reactivity to fear-relevant probes and other abnormalities in a broad aberrant amygdala-linked circuitry involving the medial prefrontal cortex (mPFC), insula, anterior cingulate cortex (ACC), and hippocampus (Rauch and Shin, 1997; Pitman et al., 2001; Nemeroff et al., 2006; Rauch et al., 2006; Etkin and Wager, 2007; Liberzon and Sripada, 2008; Shin, 2009; Shin and Liberzon, 2010). Together these interconnected regions form a disrupted functional network thought to be responsible for impaired regulation of fear responses, enhanced attention to threat-related stimuli, and biased memory for adverse events (Shin, 2009). Anxiety disorders, such as PTSD, are believed to manifest from dysfunction in a complex integrated functional network, largely, between cortical and limbic regions (Gilboa et al., 2004; Ianius et al., 2005; Simmons et al., 2008; Bluhm et al., 2009; Shaw et al., 2009; Daniels et al., 2010). Some studies have begun to examine these brain circuits and region-to-region interactions, by measuring the extent to which activity in one region is correlated with activity in another during a particular task. Although these dysfunctional networks have been implicated in mediating several characteristics of PTSD, such as, hyperarousal, abnormal reactivity to emotional stimuli, and avoidance of emotionally distressing memories (Nemeroff et al., 2006; Shin and Liberzon, 2010), little is known about how these regions may interact dynamically within individual subjects.

Keywords: amygdala, resting-state, functional magnetic resonance imaging, post-traumatic stress disorder
Dysfunctions within discrete areas that form an amygdala–paralimbic/frontal network have been implicated in mediating several characteristics of PTSD, such as, hyperarousal, abnormal reactivity to emotional stimuli, and avoidance of emotionally distressing memories (Nemeroff et al., 2006; Shin and Liberonz, 2010). In particular, many studies have shown aberrant amygdala hyperactivity in PTSD in response to trauma-related imagery (Shin et al., 1997, 2004a), combat-related sounds or smells (Liberonz et al., 1999; Pissiota et al., 2002; Vermetten et al., 2007), trauma-related photographs or words (Hendler et al., 2003; Driessen et al., 2004; Protopopescu et al., 2005; Morey et al., 2009), and fearful facial expressions (Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006; Bryant et al., 2008). Exaggerated amygdala reactivity observed in PTSD has been posited to be a result of insufficient top-down regulation from the mPFC and ACC, consequently leading to hyperarousal and deficits in extinction as well as the inability to suppress enhanced fear perception or exaggerated fear responses to trauma-related stimuli (Rauch and Shin, 1997; Rauch et al., 1998; Pitman et al., 2001; Liberonz and Phan, 2003); for example, Shin et al. (2004a, 2005) have observed that exaggerated amygdala reactivity is negatively correlated with responses in the dorsal and ventral mPFC across individuals with PTSD. However, Gilboa et al. (2004) found little evidence for failure of inhibition of ACC over the amygdala in individuals with PTSD related to civilian trauma during symptom provocation and in fact found that amygdala activity significantly influenced ACC activity. Insula hyperactivity has been observed in PTSD patients and given its role in the experience (e.g., somatic sensation) of negative emotions and structural connectivity to amygdala (Augustine, 1996; Aggleton and Saunders, 2000; Freee and Amaral, 2009), the insula may be working in concert with aberrant amygdala responses (Bremner et al., 2003, 2005; Lanius et al., 2007; Vermetten et al., 2007; Lindauer et al., 2008; Simmons et al., 2008; Werner et al., 2009; Whalley et al., 2009). Although less commonly implicated, abnormal hippocampal function, and diminished hippocampal volumes in PTSD patients have been associated with deficits in contextual processing, as well as memory impairments, and neuroendocrine dysregulation (Bremner et al., 1999, 2003; Bonne et al., 2001; Shin et al., 2004a,b, 2006; Werner et al., 2009).

Recently these functional connectivity techniques have been applied to the study of corticolimbic circuitry abnormalities at baseline or “at rest” (resting-state functional connectivity). Studies of functional interconnectivity of brain regions derived from “resting-state” scans provides insight into the relationship of spontaneous brain activity between brain regions without being confounded by task influences on activation and has even been shown to reflect structural connectivity between brain regions (Grecius et al., 2009; van den Heuvel et al., 2009). In healthy humans resting-state functional connectivity of the amygdala has revealed patterns of connectivity consistent with task-based connectivity patterns (Stein et al., 2007a; Roy et al., 2009). Moreover, resting-state functional connectivity has been a useful tool for identifying abnormalities in the functional organization of brain systems in several anxiety and mood disorders (Grecius, 2008). However, little is known about what abnormalities, if any, in amygdala connectivity exist at rest in PTSD. Therefore the primary aim of the present experiment was to investigate aberrant amygdala functional connectivity patterns in returning Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans with combat-related PTSD (PTSD group) and combat-exposed OEF/OIF veterans without PTSD [combat-exposed control (CEC) group] during resting-state. We hypothesized that amygdala connectivity to the ACC, mPFC, insula, and hippocampus would differentiate the PTSD group from the CEC group. If observed, such findings would extend our understanding of the pathophysiology of PTSD by identifying a disturbed network that exists.
Table 1 | Group demographic and clinical characteristics.

| Group mean (±SD) | t Value | p Value |
|------------------|---------|---------|
|                   | PTSD    | CEC     |
| Age              | 30.12 (7.70) | 33.71 (9.12) | -1.24 | 0.22 |
| CAPS             | 67.35 (12.41) | 5.24 (5.75) | 18.72 | <0.001 |
| PCL-M            | 54.59 (9.78) | 25.06 (7.34) | 9.96 | <0.001 |
| BDI-II           | 22.76 (7.46) | 5.53 (6.25) | 7.30 | <0.001 |
| HAM-D            | 10.18 (3.75) | 2.18 (2.38) | 7.44 | <0.001 |
| CES              | 23.88 (5.98) | 21.47 (5.50) | 1.22 | 0.23 |

PTSD, post-traumatic stress disorder; CEC, combat-exposed controls; CAPS, Clinician Administered PTSD Scale; PCL-M, PTSD Checklist: Military; BDI-II, Beck Depression Inventory; HAM-D, Hamilton Depression Inventory; CES, Combat Exposure Scale.

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Materials and Methods

Participants

Thirty-four, right-handed, male veterans returning from OEF/OIF with documented exposure to combat-related trauma participated in this study. Based on the DSM-IV (APA, 1994), 17 participants met criteria for current PTSD (PTSD group; age: 30.12 ± 7.70 years; Caucasian = 16; Hispanic or Latino = 1) and the other 17 participants were combat-exposed matched controls without PTSD (CEC group; age: 33.71 ± 9.12; Caucasian = 16; Asian = 1). Psychiatric diagnoses were established via the Structured Clinical Interview for DSM-IV (First et al., 1996). Additional standardized clinical instruments including the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995), the PTSD Checklist: Military (PCL-M; Blanchard et al., 1996), the Combat Exposure Scale (CES; Keane et al., 1989), the Hamilton Depression Inventory (HAM-D; Williams, 1988), and the Beck Depression Inventory (BDI-II; Beck et al., 1996) were administered to quantitatively characterize PTSD symptoms, severity of trauma exposure, and depression.

Table 1 shows the participant’s demographic and clinical characteristics. Relative to the CEC group, the PTSD group had significantly higher scores on the CAPS, PCL-M, and HAM-D and BDI-II. Of note, the groups did not differ in severity of trauma exposure. Some of the PTSD patients had current psychiatric co-morbidity ($n = 2$ with current major depressive disorder; $n = 2$ with current alcohol abuse) or had a past co-morbidity more than 6 months ago ($n = 1$ had major depressive disorder; $n = 4$ had alcohol abuse, one of whom also had past opioid abuse; $n = 1$ had alcohol dependence in full sustained remission) at the time of scanning. In addition, some PTSD patients had a history of psychotropic medication usage ($n = 8$ had taken a selective serotonin reuptake inhibitor, one of whom had also taken a norepinephrine–dopamine reuptake inhibitor; $n = 1$ had taken a tri-cyclic antidepressant; $n = 2$ had taken a serotonin antagonist-reuptake inhibitor), but none of the PTSD patients were currently taking any psychotropic medications at the time of scanning. All participants were free of any clinically significant medical or neurologic condition that would affect brain blood flow/metabolism or function and/or task performance. None of the subjects had a positive urine toxicology screen at the time of scanning. All participants gave written informed consent after explanation of the experimental protocol, as approved by the VA Ann Arbor Healthcare System and University of Michigan Institutional Review Boards.

Functional Imaging Acquisition

All participants underwent an 8-min resting-state fMRI scan in which they were instructed to fixate on a white crosshair that was centrally projected against a black background and let their mind wander without falling asleep. fMRI scanning was performed on a 3T GE Signa System (General Electric; Milwaukee, WI, USA) using a standard radiofrequency coil at the University of Michigan Functional MRI Laboratory. Whole-brain functional images (i.e., blood oxygenated level-dependent, BOLD) were collected from 43 axial, 3-mm-thick slices using a $T_2^*$-sensitive gradient echo reverse spiral acquisition sequence (repetition time, 2000 ms; echo time, 30 ms; $64 \times 64$ matrix; $220 \text{mm field of view}$; flip angle, 90°), optimized to minimize susceptibility artifacts (signal loss) at the medial temporal lobe (including the amygdala; Stenger et al., 2000). Cardiac and respiratory cycles were recorded with MRI vendor supplied pulse-oximeter and respiratory belt for physiological corrections on resting-state data. A $T_1$-weighted anatomical image was collected in the same planes as the functional data, but with higher in-plane resolution (1 mm², $T_1$-overlay) to aid in later co-registration. A high resolution, $T_1$-weighted volumetric anatomical scan ($T_1$-SPGR; three-dimensional spoiled gradient echo) was also acquired for precise anatomical localization and normalization.

Functional Imaging Analysis

Data from 32 participants (CEC = 17; PTSD = 15) met criteria for high quality and scan stability with minimum motion correction and were subsequently included in fMRI analyses (<3 mm displacement in any one direction; two PTSD patients were excluded for poor data quality due to excessive head movement). The first four volumes were discarded to allow for $T_1$ equilibration effects. Functional data were processed and analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London) using similar methods previously published from our lab (Jelsone-Swain et al., 2010). Images were corrected for physiological signal fluctuations using a custom code written in MATLAB (MathWorks, Natick, MA, USA; Noll et al., 1991). Slice timing and motion correction was done to the time-series data using SPM8. Each participant’s $T_1$-overlay was co-registered to the time-series data and the $T_1$-SPGR was then co-registered to the co-registered $T_1$-overlay image. The co-registered $T_1$-SPGR was then segmented into gray matter, white matter, and cerebrospinal fluid (CSF) and normalized to Montreal Neurological Institute (MNI) space using VBM8 toolbox of SPM8 and the resulting normalization matrix was applied to the time-series data. These normalized time-series data were subsequently re-sampled.

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to 2 mm³ voxels and smoothed with an 8-mm Gaussian kernel to minimize noise and effects due to residual differences in functional and gyral anatomy during inter-subject averaging. Then the resulting white matter and CSF segments were further defined using a custom algorithm previously described (Welsh et al., 2007). Each voxel's time-series was detrended to correct for linear drift over time. Nine nuisance covariates (time-series predictors for global signal, white matter, CSF, and the six movement parameters, including the first derivative, obtained during realignment to account for motion-related effects in BOLD) were sequentially regressed from the time-series. The resulting time-series were then band-passed filtered between the frequencies of 0.01 and 0.10-Hz to limit the analysis to resting-state frequencies of interest.

To determine amygdala connectivity during resting-state, seed regions in the left and right amygdala were defined by an anatomically based amygdala mask in each hemisphere (from MAsk of region of interest analysis software, MARINA; Tzourio-Mazoyer et al., 2002; Walter et al., 2003). We then extracted the averaged time course from these seed regions in each participant's data and calculated correlation coefficients between these average time courses and all other voxels of the brain resulting in an r-image for amygdala connectivity. The resulting correlation coefficients were then transformed into Z-scores using a Fisher r-to-Z transformation and the resulting Z images were analyzed at the second level in a random-effects statistical model. Two-tailed independent samples t tests were used to identify areas of the brain that exhibited activity that covaried with the amygdala differentially during resting-state between the two groups (PTSD > CEC; CEC > PTSD). Significant activations were identified with a whole-brain voxel-wise threshold of p < 0.005 with a minimum cluster extent of >387 contiguous voxels (3096 mm³), to correct for multiple comparisons. Of note, we did not conduct statistical tests on these measures, as they were defined from significant activations resulting from whole-brain maps of group differences in connectivity.

RESULTS

Across the entire brain, we observed a discretely localized difference in amygdala connectivity pattern between groups. From the right amygdala anatomical “seed” region, we observed that PTSD patients exhibited stronger connectivity with the insula than CEC subjects (MNI peak: [38, −18, −2], Z-score = 4.29, volume = 440 voxels; Figure 1); this pattern was not detected from the left amygdala seed. Follow-up ROI analyses on the extracted Z-scores of the strength of connectivity from the insula revealed that both groups exhibited positive amygdala–insula coupling, however, the extent of connectivity between the amygdala and insula was greater in the PTSD group than the CEC group (Figure 1). To explore the clinical relevance of the observed amygdala–insula connectivity abnormalities, we performed correlational analyses between the extracted values of the strength of connectivity and PTSD symptom severity measures (CAPS, BDI-II, PCL-M, and HAM-D) but did not observe any significant correlations (all ps > 0.05, corrected for multiple comparisons). Of note, we did not observe group differences in any other a priori areas that we predicted, such as the ACC, mPFC, and hippocampus in relation to amygdala connectivity at rest.

DISCUSSION

This is the first study to our knowledge that examines intrinsic amygdala functional connectivity patterns during rest in returning OEF/OIF veterans with combat-related PTSD compared to a

![Figure 1](http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html)
group of OEF/OIF veterans with combat exposure, but without PTSD. We found stronger amygdala–insula resting-state functional connectivity in the PTSD group compared to the CEC group. Of note, this connectivity pattern was from the right amygdala “seed” and was not shown from the left amygdala. Although we did not make an a priori prediction about lateralization of amygdala resting-state connectivity several findings of amygdala hyperactivity in PTSD and correlations between PTSD symptom severity and amygdala activity have been right-sided (Rauch et al., 1996, 2000; Pissioti et al., 2002; Fredrikson and Furmark, 2003; Driessen et al., 2004; Shin et al., 2004a). Contrary to our original hypothesis we did not observe any significant differences in amygdala connectivity to any other a priori regions (mPFC, ACC, hippocampus) in the PTSD group compared to the CEC group at rest. This is a notable negative finding and requires replication; however, we acknowledge that the absence of differences in amygdala–frontal or amygdala–hippocampal connectivity between groups could have resulted from: (1) Our stringent, whole-brain correction for multiple comparisons to detect significance coupled with a small sample size may have led to false negatives and/or more subtle connectivity abnormalities; and/or (2) The resting-state task may be insensitive to detecting amygdala–prefrontal and amygdala–hippocampal connectivity abnormalities, which may require engagement by an overt task.

Both the amygdala and insula have been separately implicated in the pathophysiology of anxiety and PTSD (Rauch et al., 2000; Osuch et al., 2001; Pissioti et al., 2002; Shin et al., 2004a; Protopopescu et al., 2005; Nemeroff et al., 2006; Hopper et al., 2007; Carrion et al., 2008; Shin and Liberzon, 2010). The amygdala plays an important role in the subjective and attentional-vigilance aspects of threat processing, and thus abnormalities in amygdala activity may be associated with hyperarousal and hypervigilance to threat in PTSD (Etkin, 2009). Moreover, several studies have shown that the amygdala is hyperresponsive to both trauma-related (Rauch et al., 1996; Shin et al., 1997, 2004a; Liberzon et al., 1999; Pissioti et al., 2002; Hendler et al., 2003; Driessen et al., 2004; Protopopescu et al., 2005; Verm et al., 2007) and unrelated stimuli in PTSD (Rauch et al., 2000; Armony et al., 2005; Shin et al., 2005; Williams et al., 2006), amygdala activation is positively correlated with PTSD symptom severity (Rauch et al., 1996; Shin et al., 2004a; Armony et al., 2003; Protopopescu et al., 2005) and self-reported anxiety (Pissioti et al., 2002; Fredrikson and Furmark, 2003), and symptom reduction after treatment is associated with decreased amygdala activation (Felmingham et al., 2007). Likewise, PTSD patients display exaggerated insula activation during script-driven imagery (Lan ius et al., 2007; Lindauer et al., 2008), fear conditioning and extinction (Bremner et al., 2005), the anticipation of negative images (Simmons et al., 2006), the retrieval of emotional or neutral stimuli (Bremner et al., 2003; Werner et al., 2009; Whalley et al., 2009), and aversive smells and painful stimuli (V ermetten et al., 2007) and is also positively correlated with PTSD symptom severity (Osuch et al., 2001; Hopper et al., 2007; Carrion et al., 2008). The insula controls evaluative, experiential, and expressive aspects of internal emotional states via visceral and somatic changes (e.g., autonomic “flight-or-fight” responses) evoked during presentations of aversive stimuli (Phan et al., 2002; Anderson et al., 2003; Dupont et al., 2003; Critchley et al., 2004; Simmons et al., 2004; Paulus and Stein, 2006) and it has been posited that the insula relays interoceptive information to the amygdala to help guide behavioral responses (Augustine, 1996; Craig, 2002; Simmons et al., 2004; Paulus and Stein, 2006). In fact, the insula provides some of the strongest cortical connections to the major output division of the amygdala responsible for generating fear responses to symptom-provoking stimuli (Augustine, 1996; Aggleton and Saunders, 2000; Freese and Amaral, 2009) and abnormalities in these structures has been suggested to underlie exaggerated fear responses and the persistence of traumatic memories (Shin and Liberzon, 2010), as well as anxiety prone-ness (Paulus and Stein, 2006; Simmons et al., 2006; Stein et al., 2007b). Furthermore, evidence from a recent study suggests that a functional network between the amygdala and insula mediates anxious anticipation of negative events and anxious individuals display exaggerated activity within this network during anticipation of aversive stimuli (Carlson et al., 2010). Individuals with PTSD display excess anticipation of negative events and because of this are preoccupied with studying their environment for possible threats (i.e., hypervigilance) and increased amygdala–insula functional coupling may be a mechanism supporting hypervigilance in patients with PTSD.

Besides the present study, others have investigated baseline connectivity patterns in patients with PTSD and observed abnormalities in functional connectivity within the default-mode network when compared to healthy controls (although sometimes inconsistent) (Bluhm et al., 2009; Daniels et al., 2010; Lanius et al., 2010), not directly related to amygdala connectivity. Our study extends these findings to resting-state amygdala coupling within a corticolimbic network known to be dysfunctional during trauma-related anxiety provocati on, emotionally based tasks, and evocative stimuli in PTSD patients. However, our study has some important limitations. First, our study only included males and therefore cannot be generalized to females. Second, the resting-state analysis of changes in amygdala–insula connectivity do not allow for inferences about directionality or causality, which await task-based path or dynamic causal analyses. In addition, we have interpreted our resting-state findings based on previous functional and structural imaging studies, however, research with converging methods (i.e., task-dependent and -independent fMRI, diffusion tensor imaging) are much needed to link connectivity at rest with brain structure and function. Lastly, the cross-sectional nature of our measurement does not allow us to ascertain whether enhanced amygdala–insula resting-state connectivity was present before the traumatic experience and if so, makes it a potential vulnerability maker for PTSD.

Despite these limitations, our findings demonstrate that alterations in these connectivity patterns in a network involved in emotional processing and regulation may be relevant to a brain model of PTSD that involves baseline abnormalities in amygdala–insula functional connectivity that exist even without task induction. These findings suggest that the aberrant amygdala and insula activation to fear-evocative probes previously characterized in PTSD may be driven by an underlying enhanced connectivity between amygdala, a region known for perceiving threat and generating fear responses, and the insula, a region known for processing the meaning and prediction of aversive bodily states. This enhanced
“at rest” extends our understanding of the pathophysiology of PTSD, and the current findings prompt further investigation in this emerging area of neuroimaging research.

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