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Spontaneous brain activity in combat related PTSD

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HIGHLIGHTS

- PTSD shows increased spontaneous activity at amygdala and insula.
- PTSD shows decreased spontaneous activity at precuneus and thalamus.
- Precuneal and thalamic activity negatively correlates with re-experiencing symptoms.

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a prevalent psychiatric disorder, especially in combat veterans. Existing functional neuroimaging studies have provided important insights into the neural mechanisms of PTSD using various experimental paradigms involving trauma recollection or other forms of emotion provocation. However it is not clear whether the abnormal brain activity is specific to the mental processes related to the experimental tasks or reflects general patterns across different brain states. Thus, studying intrinsic spontaneous brain activity without the influence of external tasks may provide valuable alternative perspectives to further understand the neural characteristics of PTSD. The present study evaluated the magnitudes of spontaneous brain activity of male US veterans with or without PTSD, with the two groups matched on age, gender, and ethnicity. Amplitudes of low frequency fluctuation (ALFF), a data driven analysis method, were calculated on each voxel of the resting state fMRI data to measure the magnitudes of spontaneous brain activity. Results revealed that PTSD subjects showed increased spontaneous activity in the amygdala, ventral anterior cingulate cortex, insula, and orbital frontal cortex, as well as decreased spontaneous activity in the precuneus, dorsal lateral prefrontal cortex and thalamus. Within the PTSD group, larger magnitudes of spontaneous activity in the thalamus, precuneus and dorsal lateral prefrontal cortex were associated with lower re-experiencing symptoms. Comparing our results with previous functional neuroimaging findings, increased activity of the amygdala and anterior insula and decreased activity of the thalamus are consistent patterns across emotion provocation states and the resting state.

1. Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder that may emerge following a traumatic event. It is characterized by a group of symptoms including re-experiencing of traumatic memories, hyperarousal, avoidance and emotional numbing [49]. PTSD is particularly prevalent among combat veterans [5], for example, approximately 18% of the army had PTSD after deployment to Iraq, which is much higher than the pre-deployment rate of 9.4% [20]. Functional neuroimaging studies, with positron emission tomography or blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI), have identified several brain structures associated with PTSD [27], such as the amygdala, medial prefrontal cortex, insula [39,40], thalamus, and the anterior

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cingulate cortex [32]. These studies have used various experimental tasks involving trauma recollection or other forms of emotional processes; however, it is not clear whether the observed abnormal neural responses are specific to the mental processes targeted by the experimental tasks or reflect general functionality across different brain states. Therefore, studying the intrinsic spontaneous brain activity using resting state fMRI, which is conducted without prescribed external tasks, may provide valuable alternative insights into the pathogenesis of PTSD.

Although the neural activity in "resting state" is still a burgeoning area of research, it has been postulated that "*rest activity patterns may reflect neural functions that consolidate the past, stabilize brain ensembles, and prepare us for the future*" [9]. A large number of studies have confirmed that resting state fMRI is an informative and reliable research approach [37], which can provide valuable insights for understanding neurological and psychiatric disorders [8], including PTSD [7,26,42]. Existing resting state fMRI studies of PTSD are focused on *functional connectivity* [7,26,42], which reflects the *temporal synchronization* in pre-defined brain circuitries, rather than magnitudes of spontaneous brain *activity*. In order to evaluate the spontaneous brain *activity* in resting state to compare with the patterns of brain *activity* in task-based neuroimaging studies, the present study used an established protocol to calculate the amplitudes of low frequency fluctuation (ALFF) on each voxel [51], followed by voxelwise group statistics to identify brain areas with significantly higher or lower magnitudes of spontaneous activity. This protocol was previously used in two PTSD cohorts studied soon after exposure to single incident traumatic events [4,50], but it is not clear whether the findings also apply to other types of trauma. The present study focuses on combat veterans, who have experienced prolonged repeated trauma during their deployment to Iraq and Afghanistan. Considering the heterogeneity of PTSD neuroimaging findings with respect to types of trauma [22,27], the present study may reveal different patterns compared to previous studies. It is also worth noting that the present study has a much larger sample compared to the majority of the above mentioned studies [4,7,26,42].

Based on existing findings from functional neuroimaging studies of PTSD, we were interested to see the patterns of spontaneous activity in the amygdala, insula, anterior cingulate cortex and the thalamus. Among these, increased activation at the amygdala and insula and decreased activation in the thalamus seem to be relatively consistent findings in previous studies, thus we predicted that in resting state, PTSD compared controls would also demonstrate increased spontaneous activity in the amygdala and insula and decreased thalamic spontaneous activity. The data-driven whole brain voxelwise analysis approach also allowed us to identify other brain regions demonstrating significant group differences.

2. Method and materials

2.1. Participants

Participants were recruited from New York City Veteran Affairs medical centers at Manhattan and Bronx, as well as other veteran service organizations. Participants gave written informed consent after receiving a complete description of the study. All procedures were approved by the Institute Review Boards of NYU School of Medicine and Mount Sinai School of Medicine. General inclusion criteria include being a US veteran who served in Operation Enduring Freedom in Afghanistan and/or Operation Iraqi Freedom, between the age of 20 and 60 years, being able to understand the protocol and willing to provide written informed consent. Exclusion criteria include head injury, neurological disorders, alcohol and substance abuse, suicidality, lifetime history of any psychiatric disorder with psychotic features, bipolar disorder or obsessive-compulsive disorder, as well as MRI exclusion criteria [7,26].

Doctoral level clinical psychologists conducted structured diagnostic interviews. Criteria for the PTSD group include warzone exposure and related PTSD symptoms of at least three months duration as indexed by the clinician administered PTSD scale (CAPS) [6]. The criteria for control group include warzone exposure and not meeting CAPS criteria for lifetime or current combat or civilian PTSD. The Structured Clinical Interview for DSM-IV Diagnosis [46] was used to diagnose comorbid disorders and to assess for exclusion criteria. The military version of the PTSD Checklist (PCL-M) [47], and the Beck depression index (BDI) [2] were also used as self-report questionnaires to assess symptom severity. After clinical screening, Fifty-two male subjects who met the diagnosis criteria for PTSD with CAPS score above forty were included in the PTSD group and another fifty-two male combat veterans with CAPS score below twenty were included in the control group. Because of the nature of warzone trauma and the recruitment feasibility of combat veterans, PTSD subjects in the present study were chronic cases, and both groups had undergone prolonged warzone exposure.

2.2. Data acquisition

Images were acquired on a Siemens 3 T Trio scanner (Siemens AG, Erlangen Germany). Anatomical images were acquired with magnetization prepared rapid gradient echo sequence with TE/TI/TR = 2.98/900/2300 ms, 256 × 240 matrix, 256 mm × 240 mm field-of-view, flip angle = 9°, slice thickness = 1 mm and total slice number = 191; resting state fMRI was obtained using an echo-planar imaging sequence (TR/TE = 2000/29 ms, flip angle = 90°), 64 × 64 matrix, pixel size 3.125 mm × 3.125 mm, total slice number = 32, slice thickness = 3.5 mm (without gaps), total volume number = 200. Throughout the scanning, subjects were instructed to lay in the scanner supine, relaxed, stay awake, remain still and keep their eyes open. Foams were inserted to restrict head motion. Earplugs and blankets were provided for comfort.

2.3. Data processing

The following pre-processing steps of the resting state fMRI data were conducted using Analysis of Functional NeuroImages software (http://afni.nimh.nih.gov) for each subject: slice timing, motion correction, removal of linear drift, bandpass (0.01–0.08 Hz) filtering with fast Fourier transform, and smoothing with a Gaussian filter of 6 mm full width at half maximum. A six dimensional (three for translation and three for rotation) head motion profile was estimated for each subject, and the data of two PTSD subjects and one control subject were excluded according to the criteria described in the supplementary material [51]. A regression analysis was conducted to remove identifiable variance in the BOLD signal with the following regressors: the estimated profiles of head motion, and the average time series from white matter and cerebrospinal fluid [16]. Residuals from the regression were used for further analysis. The anatomical data was aligned with the functional data and transformed to the Talairach and Tournoux standard space [44]. The ALFF maps of each subject, calculated according to the ALFF protocol [51], were normalized to the Talairach and Tournoux space with reference to their anatomical data. An independent two-sample *t*-test was conducted on the ALFF maps of the two groups, with age, education level, ethnicity and BDI scores as covariates. Clusters showing significant group differences were identified with a threshold of $p < 0.05$ (corrected) and a minimum cluster size of 810 mm^3 (Fig. 1 and Table S2). Within the PTSD group, Pearson correlations were conducted between regional ALFF values from the significant clusters and clinical scale scores. Bonferroni

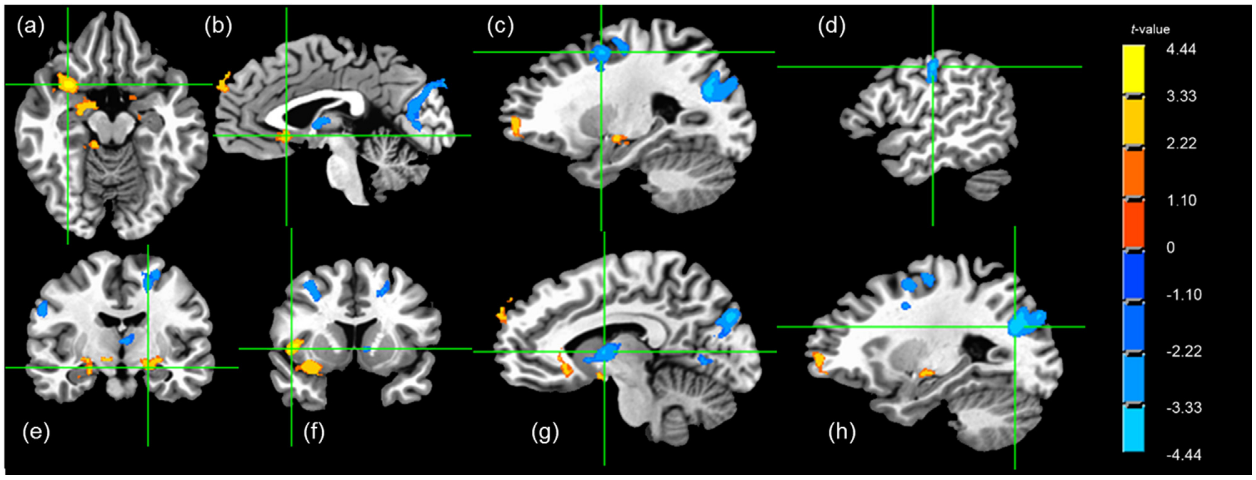

Fig. 1. Brain regions showing significant group differences between PTSD and controls in terms of magnitudes of spontaneous activity. The crosshairs are focused at the following brain regions: (a) orbital frontal gyrus, (b) anterior cingulate cortex, (c) superior frontal gyrus, (d) dorsal lateral prefrontal cortex, (e) amygdala, (f) insula, (g) thalamus and (h) precuneus. Warm colors (red and yellow) represent increased spontaneous activity in the PTSD group compared to the control group, whereas cold color (blue) represents decreased spontaneous activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

correction was applied to address the issue of multiple comparisons when determining significance.

3. Results

The two groups were matched on age, gender, and ethnicity. The PTSD group had a mean age of 33.18 (standard deviation, SD = 7.60, range 23–52) and the control group had a mean age of 33.57 (SD = 8.98, range 20–57). The average CAPS score for the PTSD group was 66.75 with a standard error (SE) of 2.69, which was significantly higher ($p < 0.001$) than that of the control group (mean ± SE = 4 ± 0.93). In the PTSD group, the average scores of BDI, PCL-M, and the re-experiencing, avoidance and hyperarousal subscale of PCL-M were (mean ± SE): 23.20 ± 1.73, 58.13 ± 1.75, 16.15 ± 0.62, 23.07 ± 0.84 and 18.9 ± 0.58, which were significantly higher ($p < 0.001$) compared to those of the control group (5.54 ± 0.99, 26.73 ± 1.50, 6.73 ± 0.49, 10.33 ± 0.61, and 9.68 ± 0.67) (Table S1).

Compared to the control group, the PTSD group had significantly higher ALFF values, which reflect increased spontaneous activity, in the amygdala, insula, ventral anterior cingulate cortex, orbitofrontal cortex and superior frontal cortex, and decreased spontaneous activity in the precuneus, dorsal lateral prefrontal cortex, and thalamus. There were negative correlations between the scores of the PCL-M re-experiencing subscale and the ALFF values in the thalamus ($r = -0.57$, $p < 0.001$), precuneus ($r = -0.51$, $p < 0.001$) and the dorsal lateral prefrontal cortex ($r = -0.58$, $p < 0.001$).

4. Discussion

The present study examined magnitudes of spontaneous brain activity in US veterans who served in Iraq and Afghanistan. Compared to warzone exposed controls, veterans with PTSD showed increased spontaneous activity in the left amygdala, right anterior insula, ventral anterior cingulate cortex, and orbital frontal cortex, and decreased spontaneous activity in the precuneus, dorsal lateral prefrontal cortex, and thalamus. The following discussion will compare the *spontaneous* brain activity in the present study with the *evoked* brain activity in previous task-based functional neuroimaging studies, in search of consistent patterns across different brain states.

Increased activation of the amygdala, a key structure in the "fear circuitry", has been reported in multiple task-based functional neuroimaging studies of PTSD [21,38]. As shown in the present study, such increased activity also exists in spontaneous brain activity in the absences of a trauma provocation task. This finding suggests that the amygdala of PTSD patients not only has increased response to threatening stimuli, but also has increased activity even in resting state. Similarly, the present study also revealed increased magnitudes of spontaneous brain activity in the anterior insula, which has been known to be involved in interoception [12] and in processing negative emotions [10,36]. The insula has also shown greater activation in PTSD subjects during trauma provocation experiments [28,35,41], which seems to be another consistent pattern across different brain states.

The anterior cingulate gyrus, also a component of the "fear circuitry" [38], showed increased spontaneous activity in the PTSD group. The ventral anterior cingulate cortex serves as an interface between cognition and emotion and modulates the allocation of attention between cognitive and emotional processes [34]. Thus, its increased spontaneous activity in PTSD could reflect increased attempts to modulate the intensified conflicts between the two systems. However, previous task-based neuroimaging studies primarily revealed lower activation of the ventral anterior cingulate cortex in PTSD compared to control subjects [21,38,48]. The different patterns in different states are not necessarily mutually exclusive, but rather may reflect an imbalance in the anterior cingulate cortex. The increased spontaneous activity might work toward depletion of the neuronal resources at the anterior cingulate cortex, which impairs its functionality and consequently leads to decreased responsivity in specified tasks.

There are different cross-state activity patterns in the anterior cingulate cortex, the insula and the amygdala. The complexity may be attributed to the heterogeneity of hemodynamic physiology in different brain regions [33]. In addition, a recent study revealed that the amygdala of PTSD subjects had stronger functional connectivity with the insula, but weaker functional connectivity with the anterior cingulate cortex [42], which also suggests a possibly dissociated pattern of abnormality between the amygdala and insula with that of the anterior cingulate cortex.

Furthermore, the present study revealed decreased thalamic spontaneous activity in the PTSD group compared to the control group. In previous studies using trauma recollection tasks [3,24,29,30], the thalamus has also shown decreased

responsivity. There is also a case report about new onset of PTSD after thalamic infarct in a Korean war veteran [14]. Thus decreased thalamic activity across different brain states may be another neural characteristic of PTSD. The present study revealed a negative correlation between magnitudes of thalamic spontaneous activity and severity of re-experiencing symptoms within the PTSD group. It has been previously postulated that thalamic abnormality in PTSD reflects a deficiency in thalamic-mediated integration of sensory information, which leads to impaired memory processing [31] and eventually contributes to the re-experiencing or flashback symptoms of PTSD [45].

In addition, the present study revealed decreased precuneal spontaneous activity among veterans with PTSD compared to controls, and the magnitudes of precuneal spontaneous activity were negatively correlated with the severity of re-experiencing symptoms. The precuneus is a key region for the well-known "default mode network" in resting state brain [17], and it has important functions for self-related mental representations [11,15] and integration of past and present information [17]. A previous fMRI study with a memory formation task also revealed reduced precuneal activation in PTSD, as well as a negative correlation between precuneal activity and PTSD severity [18]. Such correlations may be related to PTSD patients' memory impairments [19] and their difficulties in relating memories to the present context [21]. A previous study revealed decreased temporal coherence within the default mode network in subjects with early life trauma [7], which highlights the non-negligible relevance of the precuneus and related default mode network brain regions to PTSD pathogenesis. Besides, the present study also revealed that PTSD subjects had decreased spontaneous activity in the dorsal lateral prefrontal cortex, with higher activity accompanied by less re-experiencing symptoms, which might be related to its function for inhibition of unwanted memories [1].

Previous neuroimaging studies have suggested complicated heterogeneity in the neurobiology of PTSD with respect to different types of trauma [23,27], e.g., a meta-analysis revealed different degrees of hippocampal volume reduction related to different types of trauma [23]; a review on functional neuroimaging studies of PTSD [27] pointed out that "*Differences between study samples, including chronicity of illness, comorbidity, or* ***type of trauma****, may play a role in different activation patterns*..." (p. 720). Existing studies using ALFF were conducted on PTSD cases after a single traumatic event, such as earthquake survivors [50], or motor vehicle accidents survivors [4], whereas the combat veterans in the present study went through prolonged repeated trauma. In the existing studies, earthquake survivors diagnosed with PTSD compared to survivors without PTSD showed increased spontaneous activity in the right medial frontal cortex but decreased spontaneous activity in the right lingual gyrus and occipital cortex [50]; survivors of motor vehicle accidents showed increased spontaneous activity in the medial prefrontal cortex, anterior cingulate cortex and the cerebellum [4]. But neither of these studies had significant findings in the precuneus or dorsal lateral prefrontal cortex, which have shown decreased spontaneous activity in the present study. Types of trauma may be related to the differences [27]. Besides, gender could be another possible factor [23] because the present study only included males whereas previous studies used mixed-gender samples [4,50].

Finally, it is important to note the complexity of the neural and psychological underpinnings of PTSD neuroimaging findings. For example, some neural characteristics could be *pre-existing* vulnerability factors rather than *sequelae* of the disease [25]. Some functional neuroimaging characteristics could be related to complex integration between mental state and trait, and can be observed in multiple disorders, e.g., increased amygdala and insula activation has also been observed in phobia [13] and anxiety-prone subjects who do not necessarily have a psychiatric disorder [43]. Such complexity should be kept in mind for properly understanding psychiatric neuroimaging findings.

In summary, the present study investigated the magnitudes of spontaneous brain activity of PTSD. Comparing the results with existing findings, increased activity of the amygdala and anterior insula, and decreased activity of the thalamus seem to be consistent patterns across different brain states. Furthermore, our study also revealed decreased spontaneous activity in the precuneus, a structure that deserves more attention in future studies. The male-only sample and chronic PTSD focus may constitute limitations of the present study. Nonetheless, these findings have expanded our understanding about the neural characteristics of PTSD, and future studies will examine whether the identified neural characteristics may usefully and reliably predict the development of PTSD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2013.04.032.

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