Basal ganglia functional connectivity in combat-related PTSD

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Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder that can develop following traumatic experience. PTSD symptoms are characterized by re-experiencing of traumatic memory, hyper-arousal, avoidance and emotional numbing [1]. Blood oxygenation level dependent functional MRI (BOLD-fMRI), is helpful in revealing PTSD associated neuropathology [2]; however, previous studies have been focused on the responsivity patterns of a few regions such as the amygdala and hippocampus, not much attention has been paid to other important regions and the functional connectivity in the brain. The present study aims to investigate the functional connectivity with the basal ganglia. Basal ganglia are a group of nuclei suited at the base of the forebrain with intensive connections with the cerebral cortex. They are involved in many functions such as voluntary motor control, action selection [3], procedural learning, as well as related cognitive and emotional processing. This important structure has not been paid much attention in the PTSD literature; however, potentially the basal ganglia may play important roles in the intrusive traumatic memory recollection and emotion dysregulation in PTSD patients.

Methods

Volunteers were recruited from community as well as VA mental health clinic. General inclusion criteria include being a US veteran of OIF/OEF, between the age of 20 and 60 years, and being able to understand the protocol and willing to provide written informed consent, and exclusion criteria include substance dependence, life time history of psychiatric disorder, history of close-head injury with loss of consciousness over 30 minutes, or with any metal in body including a pacemaker. Based on clinical interview, criteria for PTSD+ were war-zone exposure related PTSD symptoms of at least 3 month duration as indexed by the Clinician Administered PTSD Scale (CAPS) [4]. The criteria for PTSD- were warzone exposure and no history of PTSD symptoms over lifetime that was no less than 20 on the CAPS. One hundred and one male veterans, with forty nine PTSD+ and fifty two PTSD-, were included in this cohort of study, with the two groups matched on age gender and ethnicity. Images were acquired on a SIEMENS 3T Trio whole-body scanner (Siemens AG, Erlangen Germany) using a 12 channel array coil. Anatomical images were acquired with T1-weighted Magnetization Prepared RApid Gradient Echo (MP-RAGE) sequence (iPAT factor = 2) with phase-encoding in the sagittal plane, with TE/TI/TR=2.98/900/2300 ms, 256×240 matrix, 256×240 mm^2 field-of-view (FOV), flip angle=9; 192 slices 1 mm thick 3D-MRI were obtained from each subject. Rs-fMRI was obtained using an EPI sequence (TR/TE = 2000/29 ms, flip angle = 90◦), 64×64 matrix, pixel size 3.125×3.125mm^2. A total of 200 volumes with each volume containing 32 contiguous axial slices at 3.5 mm thickness (without gaps) covering the whole cortex, were acquired from each subject. Throughout the scanning, subjects were instructed to lay in the scanner supine, relaxed, stay awake, remain still and keep their eyes open. After preprocessing, the average signal from each of the following seeds: left caudate, right caudate, left putamen, right putamen, NAcc, substantia nigra, left globus pallidus, and the right globus pallidus as provided in the Talairach template, was obtained from the normalized data of each subject to be used as a reference for FC analysis on that subject. For each of the seeds, Pearson correlation was used to measure temporal synchronization between the reference signal and the signal in every voxel in the preprocessed data in each subject, generating an R-map for each subject. The fisher r-z transformation was conducted to transform the *r* scores of each voxel into z scores, generating a Z-map for each subject. An independent two-sample t-test was conducted on the Z maps of the two groups with 3dttest++ command in AFNI. Age, education level, ethnicity and BDI scores were used as covariates. Clusters showing significant group differences were identified with a threshold of $p < 0.05$ (FDR corrected) and a minimum cluster size of 810 mm^3. Pearson correlations were conducted between regional Z values (from the significant clusters) and clinical scales.

Results & Discussion

Compared to the PTSD- group, the PTSD+ group had decreased functional connectivity between the caudate and the precuneus as well as the prefrontal cortex, as well as decreased functional connectivity between seeds globus pallidus and NAcc and the prefrontal cortex, the precuneus/posterior cingulate cortex, the anterior cingulate cortex, the insula, and the precentral cortex. In contrast the PTSD+ group had increased functional connectivity between the putamen and the precuneus/posterior cingulate cortex cluster, the prefrontal cortex as well as the primary sensory areas. With the substantia nigra as a seed, the PTSD+ group showed increased functional connectivity with the posterior cingulate cortex and the parahippocampal gyrus but decreased FC with the precentral cortex. These functional connectivity also showed significant correlations with the amount of clinical symptoms. The functional connectivity between the left caudate and the middle frontal cortex showed significant correlation with the amount of peritraumatic dissociative symptoms ($p < 0.05$, corrected). The functional connectivity between the right globus pallidus and the insula and the precuneus showed significant negative correlation with the amount of re-experiencing symptoms ($p < 0.05$, corrected). The functional connectivity between the NAcc and the insula showed significant positive correlation with scores in the early trauma inventory ($p < 0.05$, corrected). The functional connectivity between the substantia nigra and the posterior cingulate cortex showed significant correlation with the amount of depression symptoms ($p < 0.05$, corrected).

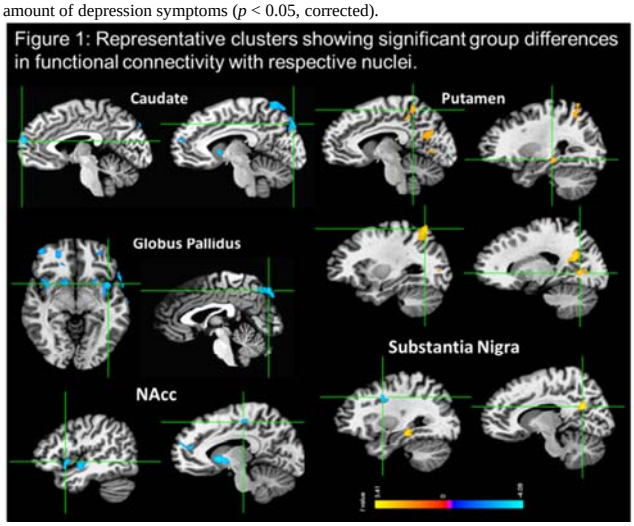

Figure 1: Representative clusters showing significant group differences in functional connectivity with respective nuclei.

A few previous PTSD studies reported volumetric or activation abnormality in basal ganglia nuclei, e.g., two studies reported larger caudate volume in PTSD patients compared to controls [140, 141], while another two studies reported volume decrease [142, 143]. One study reported that the PTSD patients had increased activation at the globus pallidus in response to direct gazes as a form of interpersonal trauma [145]. The NAcc has been known to play an important role in reward, pleasure, addiction, aggression, and fear, but it has rarely been specifically investigated in the PTSD literature. A study with single photon emission computerized tomography (SPECT) using a trauma provocation experimental paradigm revealed activation in the NAcc cluster extended from the amgydala only in PTSD subjects but not in controls [154]. Another study revealed that PTSD patients had lower activation in the NAcc during a decision-making task [155]. The putamen is known to play an important role in motor skills, reinforcement learning as well as negative emotions. A PTSD study revealed a positive correlation between the intensity of flashback memories and the rCBF of the putamen [160]. A meta-analysis reported hypoactivation of the putamen in response to negative emotional stimuli in PTSD [37]. The substantia nigra also plays an important role in reward, addiction, and movement. In the PTSD literature, there has not been much consideration about this structure. The present study revealed decreased functional connectivity between the caudate, globus pallidus and NAcc with the default mode network, insula and thalamus, and increased functional connectivity between the putamen and the substantia nigra with the precuneus and the parahippocampal gyrus. Such pattern suggests decreased association between the reward circuitry and the default mode network but with enhanced association with the fear circuitry, with the former could contribute to reduced emotion regulation and the later could contribute to reinforcement fear conditioning in PTSD.

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