Psychiatry Research: Neuroimaging 201 (2012) 214–217

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Resting cerebral glucose metabolism and perfusion patterns in women with posttraumatic stress disorder related to sexual assault

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ARTICLE INFO

Article history:
Received 21 March 2011
Received in revised form 28 July 2011
Accepted 18 August 2011

Keywords:
^{18}F-fluorodeoxyglucose
Positron emission tomography
Single photon emission computed tomography
Stress disorders
Post-traumatic

ABSTRACT

In the literature, numerous trials using neuroimaging techniques have investigated brain function in patients with post-traumatic stress disorder (PTSD). However, the contrasting results showed that improvements, including in the study design, were required to reach consistent and convincing conclusions. This study evaluated the functional neuroimaging pattern of resting cerebral blood flow and glucose metabolism in patients with PTSD related to sexual assault. Twelve patients were enrolled for both brain single photon emission computed tomography (SPECT) and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) investigations. All data were analyzed with statistical parametric mapping 2 (SPM2). The PTSD patients showed significant relative decreases in perfusion in the left hippocampus and in the basal ganglia compared with the control group. The PTSD group also had significantly lower cerebral glucosemetabolic activity in the left hippocampus and the superior temporal and precentral gyri than in the control group. These specific patterns of perfusion and glucose metabolism may be closely related to various neurophysiologic symptoms of PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a severe anxiety disorder that can develop after exposure to a terrifying event or ordeal in which significant physical harm occurred or was threatened. The diagnostic symptoms for PTSD include re-experiencing the original trauma through flashbacks or nightmares, avoidance of stimuli associated with the trauma, and increased arousal, such as difficulty falling or staying asleep, anger and hypervigilance (Brunet et al., 2007).

Brain function and activity, such as cerebral regional blood flow and metabolic consumption of either glucose or oxygen, can be evaluated with functional neuroimaging techniques, such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Therefore, using these techniques, researchers have attempted to uncover the neural network correlated with the pathophysiology of PTSD. Altered cerebral perfusion in various regions, such as the anterior and posterior cingulate cortices, right temporal and parietal lobes, right basal ganglia, left orbital cortex, hippocampus (Sachinvala et al., 2000), right precentral and superior temporal gyri, fusiform cortices (Bonne et al., 2003), and frontal and limbic regions (Chung et al., 2006) was found in several previous studies. Similarly, in PTSD patients, a few reports have investigated the metabolic changes in cerebral glucose using PET (Bremner et al., 1997; Molina et al., 2007; Shin et al., 2009).

Although numerous trials have investigated brain function in patients with PTSD using these neuroimaging techniques, results in the studies has been inconsistent. Therefore, finding consistent trends in results of functional imaging studies in PTSD patients is still difficult; consequently, the neurofunctional correlates of PTSD also remain unclear.

In each of the previous studies, only one functional neuroimaging dependent measure was used. Furthermore, most previous studies included participants with chronic PTSD. The current study included measures of both regional cerebral blood flow (rCBF) and glucose metabolism to study resting brain function in individuals with acute PTSD related to sexual assault.

2. Methods

2.1. Subjects

We enrolled 12 women (aged 19–51 years) suffering from PTSD as a result of experiencing sexual assault. The diagnosis of PTSD was made by a psychiatrist, according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DMS-IV) criteria (American Psychiatric Association, 1994). The mean duration of illness in patients with PTSD was 9.6 months. The patients were on a flexible dose of venlafaxine XR (75–225 mg/day) for a mean period of 5.2 months. All patients underwent both imaging tests (i.e. brain perfusion SPECT and ^{18}F-fluorodeoxyglucose PET) on the same day. None of the patients had a specific past history of cerebral disease. The

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doi:10.1016/j.pscychresns.2011.08.007

PTSD patients were compared with healthy control subjects matched for age; 10 women (aged 26–50 years) for the brain perfusion SPECT and 15 women (aged 32–53 years) for the ^{18}F-FDG PET investigation. Study groups (PTSD and controls for SPECT and PET) had similar mean ages (35.9 ± 13.8, 37.2 ± 10.4 and 38.4 ± 12.1 years, respectively) [$F(2, 36) = 0.38$. p = NS]. All patients and control subjects were right-handed. The clinical design of our trial was approved by the Ajou University Institutional Review Board, and informed consent was obtained from all subjects.

2.2. Brain perfusion SPECT data acquisition

Prior to tracer administration, subjects were advised to close their eyes and relax to avoid visual activation but not to sleep. While resting in the supine position, with their eyes open in a low-stimulation environment, they received 740 megabecquerel (MBq) of ^{99m}Tc-ethylcysteinate dimer (ECD) intravenously. The head of each subject was strapped down to restrain head movement. Brain SPECT was performed 5 min later, using a triple-headed gamma camera (MS3, Siemens, USA) equipped with a fan-beam collimator. A 128 × 128-pixel acquisition matrix was used with a 6-degree angular increment for 20 min. Images were reconstructed with the filtered back projection method, using the Butterworth filter (cut-off frequency: 0.35 cycle = pixel).

2.3. ^{18}F-FDG PET data acquisition

PET/computed tomography (CT) data were acquired on a Discovery ST scanner (General Electric Medical Systems, USA). After fasting for at least 4 h, patients received 300 MBq of ^{18}F-FDG intravenously. Serum glucose levels were checked in all subjects prior to the ^{18}F-FDG injection; subjects with glucose levels over 150 mg/dl were excluded from the study. All subjects were instructed to rest comfortably for 30 min with their eyes closed before starting image acquisition. We first performed the CT scan (tube-rotation time of 1 s per revolution, 120 kV, 70 mA, 5.0 mm per rotation, and an acquisition time of 11.8 s for a scan length of 150.42 mm). Then, 8 min per frame of emission PET data were acquired in the three-dimensional mode. PET images were obtained by iterative reconstruction (i.e. ordered subsets of expectation maximization, with one iteration and 32 subsets), using the CT images to correct the attenuation.

2.4. Data analysis

Brain images, including SPECT and PET data, were spatially normalized to a standard template provided by the statistical parametric mapping 2 (SPM2) method (Institute of Neurology, University of London, London, UK) included in the MATLAB software version 6.5 (Mathworks Inc., Natick, MA). Local optimization of the 12 parameters and affine transformation were applied to the spatial normalization. To minimize noise and to improve between-subject spatial alignments, the images were then smoothed with a Gaussian kernel (e.g. 16 mm full width at half maximum). The images included both SPECT and PET of patients with PTSD and were compared, in a voxel-by-voxel manner, with those taken from sex- and age-matched normal controls, using the SPM2 package software (i.e. two-sample t-test). An uncorrected p value of less than 0.005 and an extended threshold (Ke) > 100 was considered statistically significant. Anatomical labeling of significant clusters was performed using the Talairach Client 2.4 (Lancaster et al., 2000).

3. Results

There was no significant difference in age between the patients with PTSD and the control subjects. The SPM analysis showed that the patients with PTSD had significantly lower cerebral blood perfusion in the left hippocampus and the left basal ganglia (two-sample t-test, uncorrected p<0.005, as shown in Table 1 and Fig. 1A) compared with the control group. No brain region showed a relative increase of brain perfusion in the investigated patients. The PTSD group also had lower cerebral glucose metabolic activity than the control group in the left hippocampus, as well as the left superior temporal and precentral gyri (two-sample t-test, uncorrected p<0.005, as presented in Table 1 and Fig. 1B). In contrast, glucose metabolism was higher in subjects with PTSD than in control subjects in both hemispheres of the cerebellum (two-sample t-test, uncorrected p<0.005, Table 1 and Fig. 1B). When the comparing the brain SPECT and the ^{18}F-FDG PET studies were compared, the PTSD patients exhibited lower uptake of both radiotracers (i.e. ^{99m}Tc-ECD and ^{18}F-FDG) in the left hippocampal area compared with uptake in normal controls (Table 1 and Fig. 1).

4. Discussion

Neuroimaging studies using fMRI, SPECT, and PET have been performed to establish a correlation between brain function and several psychiatric disorders. Similarly, several neurofunctional studies have revealed brain activity alterations in patients suffering from PTSD (Francati et al., 2007). Despite these efforts, results from previous studies have been inconsistent, and little is known about specific patterns of neurofunctional activity in PTSD patients. The discrepancies in results in previous neuroimaging studies applied to PTSD could be due to the wide range of study designs, methodologies, and study paradigms used by different research groups. Our study investigated the patterns of both regional cerebral perfusion and glucose metabolism in PTSD patients. The investigated patients were all women and had experienced the same traumatic event (i.e. sexual assault), in an attempt to minimize variability between the studied subjects. To the best of our knowledge, no other studies of this type have been conducted.

The involvement of the hippocampus in PTSD was documented in several previous studies, but inconsistencies between findings have been an issue. Some functional neuroimaging studies used either cerebral perfusion SPECT (Bremner et al., 2003a, 2003b) or glucose metabolism PET (Bremner et al., 1997; Molina et al., 2007) and reported decreased brain activity in the hippocampi of patients suffering from PTSD. In contrast, others showed increased activity in the hippocampus (Shin et al., 2001, 2004). Structural abnormalities of the brain and a reduction in hippocampus volume have also been documented in patients with PTSD (Bremner, 2003).

Our study confirmed what we considered to be the typical pattern of brain activity in PTSD patients, i.e. decreased perfusion and glucose metabolism in the hippocampus, in a homogenous sample of patients. These changes might be linked to memory deficiencies and to facilitating fear extinction, one of the important functional roles of the hippocampus, as previously shown (Pitman et al., 2001; Francati et al., 2007).

Our PTSD patients showed significantly higher glucose metabolic activities in both hemispheres of the cerebellum than normal controls. In the literature, we also found a few studies reporting a significant relationship between cerebellar activity and PTSD. Two previous resting-state neuroimaging studies of PTSD showed increases of both blood perfusion and glucose metabolism bilaterally in the cerebellum (Bonne et al., 2003; Molina et al., 2007). The increased functional activity in the cerebellum may be linked to the hyperaroused state seen in PTSD patients and the expression of various symptoms,

Table 1
Brain areas showing significant differences in brain perfusion and glucose metabolism between patients with PTSD and normal subjects.

Talairach coordinate			Anatomic region	T value	Z score	Cluster size	Voxel-level
x	y	z					$P_{uncorrected}$
PTSD < normal controls (brain perfusion)							
−22	−6	−10	Left hippocampus	7.68	4.98	7413	<0.005
−18	15	7	Left caudate nucleus	4.37	3.52	344	<0.005
−30	10	−13	Left putamen	4.91	3.82	482	<0.005
PTSD > normal controls (brain perfusion)							
None							
PTSD < normal controls (glucose metabolism)							
−30	−9	−13	Left hippocampus	5.38	3.97	782	<0.005
−51	−13	7	Left superior temporal gyrus	5.11	4.41	6722	<0.005
−28	−23	48	Left precentral gyrus	4.99	4.34	5244	<0.005
PTSD > normal controls (glucose metabolism)							
31	−37	−40	Right cerebellum	4.82	4.22	1801	<0.005
−28	−39	−41	Left cerebellum	4.12	3.71	428	<0.005