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Brain activation and heart rate during script-driven traumatic imagery in PTSD: Preliminary findings

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ABSTRACT

Patients with posttraumatic stress disorder (PTSD) experience psychological and physiological distress. However, imaging research has mostly focused on the psychological aspects of the disorder. Considered an expression of distress, heart rate (HR) in PTSD is often elevated. In the current study, we sought to identify brain regions associated with increased HR in PTSD. Nine patients with PTSD and six healthy trauma survivors were scanned while resting, clenching teeth, and listening to neutral and traumatic scripts. Brain function was evaluated using H_2O^{15} positron emission tomography (PET). HR was monitored by electrocardiogram. Data were analyzed using statistical parametric mapping (SPM). Subjects with PTSD exhibited a significant increase in HR upon exposure to traumatic scripts, while trauma survivors did not. Correlations between regional cerebral blood flow and HR were found only in patients with PTSD, in orbitofrontal, precentral and occipital regions. Neither group showed correlation between rCBF and HR in the amygdala or hippocampus. These preliminary results indicate that "top down" central nervous system regulation of autonomic stress response in PTSD may involve associative, sensory and motor areas in addition to regions commonly implicated in fear conditioning.

1. Introduction

Posttraumatic stress disorder (PTSD) is a stress-related psychiatric condition, with prevalence rates of 7–12% in the general population (Kessler et al., 2005). It is associated with significant psychiatric comorbidity, functional impairment, compromised health status, and substantial economic costs to society. One in two individuals in the general population will experience a traumatic incident at some point in their lives, and 10–25% of traumatized subjects subsequently develop PTSD. Patients with PTSD suffer from intrusive memories of the trauma, emotional and physiological arousal responses to cues resembling their traumatic experience, and avoidance of such cues. Signs of increased arousal and vigilance, expressed by an exaggerated startle response, elevated blood pressure, sleep disturbance and increased skin conductance accompany the disorder (Pitman et al., 1987). Elevated basal heart rate (HR) and stimulus-triggered HR (Orr et al., 2002) as well as non-extinction of HR elevation on repeated stimuli (Peri et al., 2000, Wessa and Flor, 2007), are perhaps the most common physiological findings in PTSD. HR is regulated by the autonomic nervous system. Increased heart rate in PTSD is considered a measure of increased sympathetic and decreased parasympathetic activity (Orr et al., 2002; Cohen and Benjamin, 2006).

The autonomic nervous system is regulated by a network of cortical and subcortical structures, including the insula, frontoparietal cortex, cerebellum, anterior cingulate, orbitofrontal cortex, amygdala and diverse thalamic and hypothalamic nuclei, referred to in animals as the 'central autonomic network' (Janig and McLachlan, 1992). In humans, changes in blood pressure and heart rate can be elicited by stimulating the insula, medial prefrontal cortex, anterior cingulate gyrus and medial temporal lobe (Fish et al., 1993).

Imaging research in PTSD traditionally sought brain correlates of behavioral, emotional and cognitive symptoms. Abnormalities were primarily found in prefrontal cortex (PFC), amygdala and hippocampus (Shin et al., 2006). The amygdala regulates fear conditioning in both animals and humans (Phelps and LeDoux, 2005). Along with visual processing regions, both primary and higher order, the amygdala shows increased response to threat-

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related stimuli, in subjects without PTSD (van Marle et al., 2009). Increased amygdala response to stressful stimuli has also been found in PTSD (Rauch et al., 2000), in association with decreased response in the medial prefrontal cortex (mPFC) (Shin et al., 2004, 2005; Etkin and Wager, 2007) and hippocampus (Etkin and Wager, 2007). The amygdala projects to most sensory-related association cortices, and is involved in sensory modulation from the early stages in the cortical hierarchy (Amaral et al., 1992). In particular, a close working relationship has been demonstrated between the amygdale and the occipital cortex (Hendler et al., 2001). Furthermore, it has been repeatedly shown that the occipital lobe, in particular on the right (Daniels et al., 2012), is involved in memory of emotional events. The hippocampus is involved in declarative memory generation as well as in stimuli contextualization, both of which are impaired in PTSD. Hippocampal dysfunction is one of the most consistent findings in functional and anatomical imaging studies in PTSD (Acheson et al., 2012). The mPFC is considered to play a key role in the extinction of fear conditioning, which is thought to be impaired in PTSD. Several functional neuroimaging studies of PTSD have shown decreased or complete lack of mPFC activation during traumatic script driven imagery (e.g. Lanius et al., 2001). Alterations in the insula, orbitofrontal cortex, posterior cingulate and parietal somatosensory regions have also been described (Bremner et al., 2008; Liberzon and Sripada, 2008). In addition to regionalized brain dysfunction in PTSD, cortical excitability changes in PTSD have been demonstrated by the application of single-pulse transcranial magnetic stimulation (TMS) to the motor cortex of drug naïve patients (Rossi et al., 2009). The authors contend that prolonged illness could be associated with lasting (GABAa related) functional or structural changes even in brain regions such as the motor cortex that are outside, although functionally connected with, regions usually found dysfunctional in PTSD, such as the anterior cingulate cortex, amygdala, limbic and paralimbuc regions.

In the current study we set out to determine which brain regions are involved in differential HR response, as an indicator of the exaggerated autonomic response to trauma-related stimuli in PTSD. Central autonomic regulation of cardiovascular response may be similar in PTSD and healthy controls, yet brain regions whose activity correlates with PTSD-specific autonomic activation may be involved in modulation of autonomic response in PTSD. The orbitofrontal cortex, the amygdala, and the hippocampus are involved in processing and integrating stress-related input and in triggering autonomic arousal response to both psychological and physiological stressors (for review, see Ulrich-Lai and Herman, 2009). We assumed that differential autonomic response to repeated trauma-related cues, in PTSD and non-PTSD subjects would be associated with differential activation in these regions. Specifically, we assumed that increased activation would be seen in the hippocampus and amygdala while decreased activation would be seen in the mPFC. We further expected to note differences in regional brain activation in regions functionally related to constituents of the "central autonomic network".

2. Materials and methods

2.1. Subjects

Twenty-one individuals with a history of civilian trauma (road and work accidents), nine with and 12 without PTSD, took part in the study. PTSD subjects ($n=9$) were outpatients treated in our PTSD clinic. Matched control subjects ($n=12$) were recruited from a research-designated pool of trauma-exposed healthy control individuals. Groups were similar in age, gender and education. Two subjects in each group smoked. All were physically healthy, free of medication (with the exception of psychotropic medication), with no history of head trauma, major neurological illness or substance abuse. Three PTSD patients were currently on clonazepam (0.5–1.5 mg/day), and two had previously been treated with benzodiazpines. Three PTSD patients were treated in the past with selective serotonin reuptake inhibitors (SSRIs).

Prior to the imaging session, all subjects attended an evaluation session, during which the study was explained and written informed consent obtained. This was followed by a physical examination (including blood pressure measurement, blood chemistry, complete blood count and thyroid function), clinical interview and psychometric assessment. The Clinician-Administered PTSD Scale (CAPS) conferred diagnosis of current and lifetime PTSD. The Structured Clinical Interview for DSM-IV (SCID) was used to exclude Axis I disorders other than PTSD. Additionally, the Impact of Events Scale-Revised (IES), State/Trait Anxiety Inventory (STAI; TRAI) and Beck Depression Inventory (BDI) were administered (clinical and demographic data for scanned subjects are presented in Table 1). The institutional review board at Hadassah University Hospital in Jerusalem approved all procedures.

Data are presented for 15 subjects, six with and nine without PTSD. Among trauma controls one did not show up for PET scanning, in another subject two scan conditions were not performed and another had technically uninterpretable data; among subjects with PTSD two could not tolerate the four repeated traumatic script presentations and one had technically uninterpretable data. Demographic and clinical characteristics of subjects actually scanned are similar to those of the larger, recruited cohort.

2.2. Scripts and experimental paradigm

Personal-neutral and trauma-related scripts, 45–60 seconds long, were devised according to established procedure (Pitman et al., 1987), written in the second person, singular, present tense. Scripts were tape-recorded by the same neutral male voice for playback in the PET scanner. Participants were instructed to listen to each script and try to form a vivid mental image of the script as soon as playback has ended. Participants were scanned seven times, in all but the first scan after script presentation. Scripts were presented in the same order. Before the first

Table 1
Clinical and demographic features of patient and control cohorts.

	PTSD ($n=6$) mean ($\pm$ S.D.)	Controls ($n=9$) mean ($\pm$ S.D.)	Significance (p)
Gender (male/female)	3/3	4/5	NS
Age (years)	37 (6.8)	34 (6.2)	NS
Time since trauma (years)	7 (8.2)	6 (7.7)	NS
Education (years)	13.6 (7.2)	13.8 (3.5)	NS
CAPS B	21.3 (9.4)	1.1 (1.6)	$p<0.0001$
CAPS C	35.3 (12.7)	1.3 (2.3)	$p<0.0001$
CAPS D	24.7 (8.1)	0.8 (1.3)	$p<0.0001$
CAPS Total	84.3 (24.20)	3.2 (3.7)	$p<0.0001$
IES	61.5 (16.5)	5.2 (3.7)	$p<0.0001$
STAI	59.3 (10.6)	31.1 (12.8)	$p<0.002$
TRAI	57.3 (8.0)	29.0 (14.3)	$p<0.002$
BDI	25.2 (11.1)	3.3 (4.5)	$p<0.0001$

CAPS: Clinician-Administered PTSD Scale; CAPS-B: CAPS re-experiencing symptoms; CAPS-C: CAPS avoidance/numbing symptoms; CAPS-D, CAPS hyperarousal symptoms; IES, Impact of Events Scale; STAI, Spielberger State Anxiety Inventory; TRAI, Spielberger Trait Anxiety Inventory; and BDI, Beck Depression Inventory.