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An fMRI investigation of memory encoding in PTSD: Influence of symptom severity

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Abstract

Previous studies have shown memory deficits in Post-Traumatic Stress Disorder (PTSD) patients, as well as abnormal patterns of brain activity, especially when retrieving trauma-related information. This study extended previous findings by investigating the neural correlates of successful memory encoding of trauma-unrelated stimuli and their relationship with PTSD symptom severity. We used the subsequent memory paradigm, in the context of event-related functional magnetic resonance imaging, in 27 PTSD patients to identify the brain regions involved in the encoding of fearful and neutral faces. Symptom severity was assessed by the Clinically Administered PTSD Scale (CAPS) scores. It was found that memory performance was negatively correlated with CAPS scores. Furthermore, a negative correlation was observed between CAPS scores and ventral medial prefrontal cortex (vmPFC) activity elicited by the subsequently forgotten faces. Finally, symptom severity predicted the contribution of the amygdala to the successful encoding of fearful faces. These results confirm the roles of the vmPFC and the amygdala in PTSD and highlight the importance of taking into account individual differences when assessing the behavioural and neural correlates of the disorder.

Keywords: Post-Traumatic Stress Disorder; Magnetic resonance imaging; Memory; Encoding; Medial frontal cortex; Amygdala

1. Introduction

Several of the clinical symptoms associated with Post-Traumatic Stress Disorder (PTSD) – including intrusive memories, flashbacks and psychogenic amnesia (American Psychiatric Association, 2000) – suggest the existence of disturbances in memory function in this disorder. Numerous functional neuroimaging studies have examined brain activity associated with the recall of the traumatic event, mostly using symptom-provocation paradigms through personalized scripts, images or sounds (for reviews see Francati, Vermetten, & Bremner, 2007; Rauch, Shin, & Phelps, 2006). Most of these studies have shown that PTSD patients, when compared to healthy controls or trauma-exposed individuals without PTSD, exhibit decreases in activity within regions of the medial prefrontal cortex, including the anterior cingulate and orbital frontal cortices (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Britton, Phan, Taylor, Fig, & Liberzon, 2005; Lanius et al., 2001; Rauch et al., 1996; Shin, Orr, et al., 2004), and, although less consistently, increased amygdala activation (e.g., Liberzon et al., 1999; Shin, Orr, et al., 2004; but see Britton et al., 2005; Lanius et al., 2001).

Importantly, a growing body of literature suggests that memory dysfunction in PTSD may not be limited to material related to the traumatic event, but it may extend to trauma-unrelated, including emotionally neutral, information (for reviews see Brewin, Kleiner, Vasterling, & Field, 2007; Isaac, Cushway, & Jones, 2006). However, unlike the case of traumatic memories, the neural correlates of memory deficits for trauma-unrelated stimuli in PTSD have not been greatly explored. To date, only a handful of studies have examined this issue. Bremner et al. (2003) scanned survivors of early sexual abuse with PTSD and healthy controls using PET while they recalled previously learned emotionally charged and neutral word pairs. Although no differences in memory performance were observed between groups, PTSD participants showed decreased activity in the

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medial prefrontal and orbital frontal cortices while recalling the emotional word pairs. In another PET study of memory retrieval (Shin, Shin, et al., 2004), firefighters with and without PTSD were scanned while they were cued to retrieve neutral words that had been previously encoded. Again, no behavioural differences were found between the PTSD patients and controls. However, the PTSD group showed decreased hippocampal and enhanced prefrontal activity, relative to controls, when comparing the recall of deeply vs. shallowly encoded words. Finally, in a recent fMRI study, Geuze, Vermetten, Ruf, de Kloet, and Westenberg (2007) scanned PTSD patients and matched controls during both encoding and retrieval of neutral verbal paired associates. Behaviourally, a trend towards a deficit in performance was observed for PTSD patients. In addition, the PTSD group exhibited reduced activity, relative to controls, in regions of the frontal lobe together with larger activation in the temporal lobe during the encoding phase. At retrieval, they showed decreased activity in areas of the frontal lobe and the posterior hippocampus.

Taken together, these findings provide further support for a dysfunction of the fronto-temporal circuit in individuals with PTSD. In addition, they suggest that a common neural substrate may underlie the abnormal memory patterns for both traumatic and neutral information observed in these individuals. However, because all of these studies employed a block design, in which the activity associated with both remembered and forgotten stimuli was grouped together in the analysis, the relation between the observed differences in brain activation and the behavioural memory deficits present in PTSD patients remains unclear.

Furthermore, PTSD is a complex disorder, characterized by the simultaneous presence of a number of symptoms. The specific combination of symptoms, as well as the intensity of each of them can vary among patients, spanning a considerable range (Weathers, Keane, & Davidson, 2001). In addition to the obvious influence on an individual's quality of life and emotional well-being (Johansen, Wahl, Eilertsen, Weisaeth, & Hanestad, 2007), overall PTSD symptom severity has been shown to be an important predictor of the magnitude of the cognitive impairments and their neural correlates, associated with the disorder. For instance, several PTSD studies have reported that increased symptom severity is associated with larger memory deficits (Bremner et al., 1993; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Kivling-Boden & Sundbom, 2003; Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006). In addition, PTSD symptom severity has been shown to be negatively correlated with activity in the mPFC (Bryant et al., 2007; Kim et al., 2007; Shin et al., 2005; Williams et al., 2006) and positively correlated with amygdala responses to emotional stimuli (Armony, Corbo, Clement, & Brunet, 2005; Rauch et al., 2000) or during traumatic memory retrieval (Shin, Orr, et al., 2004).

Thus, in addition to studying the differences in brain activity between PTSD patients and control groups in episodic memory, it seems important to investigate the influence of symptom severity in this process. Indeed, studying individual differences within a PTSD group, by taking into account not only the presence of PTSD symptoms but also their intensity, may reveal effects that would be "washed-out" in a between-groups comparison.

We therefore conducted a study to investigate the relation between memory for faces (fearful and neutral) and PTSD symptom severity, as measured by the Clinically Administered PTSD Scale (CAPS) score. We specifically focused on memory encoding, as it has been suggested that the memory deficits shown in PTSD may in part be due to attention and working memory difficulties at the time of encoding (Brandes et al., 2002; Isaac et al., 2006; Jenkins, Langlais, Delis, & Cohen, 2000; Koso & Hansen, 2006; Vasterling, Brailey, Constans, & Sutker, 1998). In order to directly isolate the neural regions involved in successful memory formation, we used the subsequent memory paradigm (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998) in the context of an event-related analysis. This procedure allowed us to categorize each stimulus as remembered or forgotten based on each subjects' behavioural response in a subsequent memory test administered outside the scanner. Recent investigations from our laboratory have shown that the amygdala is critically involved in the successful encoding of fearful, relative to neutral faces (Sergerie, Lepage, & Armony, 2006). Therefore, fearful and neutral faces were chosen as stimuli in order to explore the potential interactions between PTSD symptoms and this emotion-specific, amygdala-mediated modulation of memory encoding. We hypothesized that PTSD symptom severity should predict overall memory performance (Bremner et al., 1993; Gilbertson et al., 2001; Kivling-Boden & Sundbom, 2003; Lindauer et al., 2006) with concomitant changes in activity in medial prefrontal and temporal regions as a function of memory success. Furthermore, we predicted that CAPS scores would correlate with the amygdala responses to subsequently remembered fearful faces.

2. Methods

2.1. Participants

Thirty-two individuals (range: 20–60 years) suffering from PTSD were recruited from two Montreal clinics (the Traumatys Clinic and the Charles LeMoyne Hospital). All recruitment and testing procedures were approved by the ethical review boards of the Douglas Mental Health University Institute, the Montreal Neurological Institute and the McGill University Health Centre. PTSD diagnosis was verified in all participants using the Clinically Administered PTSD Scale (CAPS; Blake et al., 1995), which was administered and scored by a clinical psychologist (V.A.). Inclusion criteria required participants to have a CAPS score greater than 45 and no history of neurological, learning or psychotic disorders. Five subjects were excluded from the final analysis for the following reasons: excessive movement during the scan ($n = 2$), below-chance performance during the memory test ($n = 1$) and no responses for one of the stimulus categories ($n = 2$; see *fMRI data acquisition and analysis* below). Thus, the final sample consisted of 27 individuals (19 female, 8 male; age $M = 36$ years, S.D. = 11 years), all with CAPS scores greater than 50 ($M = 83$, S.D. = 16, median: 87). The nature of the trauma for these participants included motor vehicle accidents ($n = 13$), physical assault and/or death threats ($n = 7$), sexual assault ($n = 1$), witnessing a violent physical assault or death ($n = 5$), and combat exposure during the Rwanda Genocide ($n = 1$). The time elapsed between their trauma and MRI scanning ranged from 5 to 62 weeks ($M = 16$, S.D. = 12), with the exception of the latter participant, who was exposed to trauma 11 years prior to the experiment. Post hoc analyses showed that removal of this subject from the analysis did not significantly change the pattern of results reported here (data not shown).

The severity of participants' subjective traumatic experiences was assessed further using the Peritraumatic Distress Inventory (Brunet et al., 2001; $M = 31.6$, S.D. = 11.7) and the Peritraumatic Dissociative Experience Questionnaire (Birmes et al., 2005; $M = 29.7$, S.D. = 10.0). Psychiatric comorbidity was