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Neural correlates of recovery from post-traumatic stress disorder: A longitudinal fMRI investigation of memory encoding

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ABSTRACT

Post-traumatic stress disorder (PTSD) is characterized by a failure of psychological recovery from a traumatic experience. At a neural level, it is associated with abnormalities of the areas of the neural system that process threatening information, including the amygdala and medial-prefrontal cortex, as well as of that involved in episodic memory, including the hippocampus. However, little is known about how the function of these regions may change as one recovers from the disorder. In this investigation, PTSD patients underwent two functional magnetic resonance imaging (fMRI) scans, 6–9 months apart, while viewing fearful and neutral faces in preparation for a memory test (administered outside the scanner). At Time 2, 65% of patients were in remission. Current symptom levels correlated positively with memory-related fMRI activity in the amygdala and ventral-medial prefrontal cortex (vmPFC). In addition, the change in activity within the hippocampus and the subgenual anterior cingulate cortex (sgACC) was associated with the degree of symptom improvement ($n = 18$). These results suggest differential involvement of structures within the fear network in symptom manifestation and in recovery from PTSD: whereas activity within the amygdala and vmPFC appeared to be a marker of current symptom severity, functional changes in the hippocampus and sgACC reflected recovery. These results underscore the importance of longitudinal investigations for the identification of the differential neural structures associated with the expression and remission of anxiety disorders.

1. Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder arising as a result of exposure to a traumatic event (Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR), 2000). It is associated with a variety of symptoms, including intrusions (e.g., nightmares and flashbacks of the trauma), avoidance of trauma reminders and hyperarousal. Neuroimaging studies have shown decreased activity in the medial prefrontal cortex (mPFC) and, less frequently, increased activity of the amygdala in PTSD individuals exposed to trauma reminders, compared to controls (Francati, Vermetten, & Bremner, 2007; Rauch, Shin, & Phelps, 2006). Importantly, similar patterns of activity, particularly an exaggerated amygdala response, have been observed with trauma unrelated threat-relevant stimuli (e.g., fearful faces) (Armony, Corbo, Clement, & Brunet, 2005; Rauch et al., 2000; Shin et al., 2005), suggesting that PTSD is associated with a general dysfunction of the brain's networks involved in the detection of threatening information (Armony & LeDoux, 1997; Rauch et al., 2006). In addition, PTSD is also thought to involve a dysfunction of the memory system, as some of its symptoms are directly associated with the traumatic memory itself (Ehlers, Hackmann, & Michael, 2004), and as patients consistently perform more poorly than controls on memory tests (Brewin, Kleiner, Vasterling, & Field, 2007; Isaac, Cushway, & Jones, 2006).

Notably, only a fraction of trauma-exposed individuals develop PTSD and, of these, a large proportion recover with time (Breslau, 2001; Breslau et al., 1998; North, Smith, & Spitznagel, 1997). It has therefore been proposed that chronic PTSD be considered the result of two types of pathogenic processes, the first characterized by exaggerated responses to a stressful event, and the second by inadequate mechanisms of recovery (Yehuda & LeDoux, 2007).

While most previous studies have focused, directly or indirectly, on the first question, by exploring the neural correlates of current PTSD, little is known about the brain processes involved in the successful recovery from the disorder. As a first step in addressing this issue, we conducted a longitudinal fMRI study on a group of individuals suffering from PTSD using an emotional face memory

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paradigm. We chose this paradigm (adapted from Sergerie, Lepage, & Armony, 2005) as it can be considered a point of convergence of the two main processes thought to be affected in PTSD, namely threat-detection and memory. We tested subjects twice, once when they were highly symptomatic and again 6–9 months later, when most, but not all, of the participants had seen their symptoms diminish substantially. Results from data obtained at Time 1 were previously reported (Dickie, Brunet, Akerib, & Armony, 2008) and showed that PTSD symptom severity correlated with overall memory encoding-related activity in the ventral medial prefrontal cortex and with the successful encoding of fearful, but not neutral, faces in the amygdala. Here, we directly compared activity between the two sessions and therefore were able to directly identify (1) the neural correlates of current PTSD symptom severity (i.e., those regions showing a significant correlation with current PTSD symptom severity at both time points), and (2) the brain regions associated with the recovery process, that is, areas where change in neural activity between testing times correlated with the improvement of PTSD symptom severity.

2. Methods

2.1. Participants

Thirty-two individuals (age range: 20–60 years) with a primary diagnosis of PTSD were recruited from two clinics in Montreal (Traumatys Clinic and Charles LeMoyne Hospital). PTSD diagnosis was verified in all participants using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). All participants had a CAPS score greater than 45 at initial assessment and no history of neurological, learning or psychotic disorders. Psychiatric comorbidity and depressive symptoms were assessed with the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) and Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), respectively. Most patients underwent psychotherapy between first (Time 1) and second (Time 2) testing sessions (confirmed by all but two participants contacted at follow-up). As we were not able to fully characterize the precise nature of this treatment (beyond prescribed medications), we did not include it in the analysis as an independent variable of interest. Participants provided written informed consent and received financial compensation for their time and travel expenses. All procedures were approved by the ethical review boards of the Douglas Mental Health University Institute, the Faculty of Medicine of McGill University and the Charles Lemoyne University Hospital.

Of the 32 participants recruited, complete data was available for 27 participants at Time 1 (Dickie et al., 2008). For 18 of these participants, complete data was also available at Time 2, 6–9 months following the first scan [exclusions: dropouts ($N = 6$), excessive movement during the scan ($N = 2$), technical malfunction ($N = 1$)]. Their demographic and clinical information is listed in Table 1. Two additional subjects were included in the Time 2 analysis (cf. Section 3.3.1) even though their data at Time 1 was incomplete due to no responses for one of the stimulus categories (see Section 2.3 below).

2.2. Experimental design

The stimuli and experimental procedure used have been previously described (Dickie et al., 2008) and are depicted in Fig. 1. Briefly, 224 face stimuli (112 fearful, 112 neutral; half female) were selected from several validated databases, modified to remove gender-typical features and pseudo-randomly divided into four equivalent sets of 56 faces. Faces from each set were used as either encoding stimuli or lures at either Time 1 or Time 2 (counterbalanced across subjects). Consequently, the procedures for Time 1 and Time 2 testing were identical and no face was repeated between testing sessions. Fifty-six indoor and outdoor scenes were also presented, intermixed with the faces during the fMRI scanning (data not reported here). During the fMRI scans (encoding session), one set of faces was presented twice and 56 scenes were presented once for 1500 ms each, preceded by a 1000 ms cue instructing subjects to indicate, by pressing one of two buttons, whether the face presented was male or female, or whether the scene corresponded to an interior or an exterior location. In addition, subjects were told to memorize all images in preparation for a memory test (the longitudinal aspect of the study precluded the use of a surprise recognition test). The inter-stimulus interval was 2000 ms on average; longer intervals (so-called null events) were also included in order to obtain an adequate estimate of baseline activity (Josephs, Turner, & Friston, 1997).

Following the scanning session, participants completed a face recognition memory test. The encoding set and a new one (lures) were presented on a PC laptop screen while participants performed an old/new task. Faces were presented for 1500 ms each with a 2000 ms inter-stimulus interval.

Table 1
Demographic and clinical data ($n = 18$).

Mean years of age (SD)	36.8	(11.8)
Years of education (SD)	12.9	(1.9)
Number right handed (%)	15	(83%)
Number female (%)	13	(72%)
Trauma type		
Motor vehicle accident	9	(50%)
Physical assault or death threat	2	(11%)
Sexual assault	1	(6%)
Witness to physical assault or death threat	6	(33%)
Peri-traumatic distress inventory (Brunet et al., 2001)	30.1	(12.1)
Peri-traumatic dissociative experience questionnaire (Birmes et al., 2005)	28.2	(9.61)
Mean weeks since trauma (SD)	17.8	(13.0)
Mean time 1 to time 2 weeks (SD)	31.0	(4.4)
Number recovered at *T2* (%)	11	(61%)

Repeated measures	Time 1		Time 2	
Clinical measure means (SD)				
Clinician administered PTSD scale (CAPS)	80.6	(15.9)	44.7	(29.9)
Beck depression inventory (BDI)[a]	9.9	(5.45)	7.7	(6.3)[a]
Number with comorbid disorder (%)	14	(78%)	7	(39%)
Major depression	9	(50%)	4	(22%)
Other anxiety disorder	10	(56%)	6	(33%)
Bulimia	1	(6%)	1	(6%)
Number taking medication (%)[a]	8	(44%)	7	(39%)
Anti-depressants	7	(39%)	7	(39%)
Benzodiazepines	5	(28%)	1	(6%)
Anti-psychotic	1	(6%)	2	(11%)

[a] Missing data from one participant.

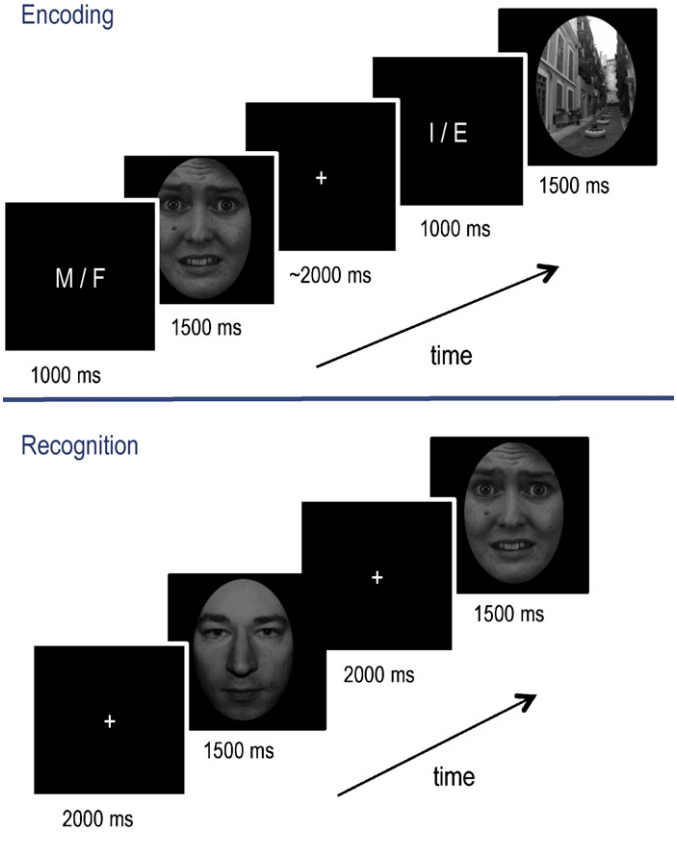

Fig. 1. Schematic of the memory encoding task. During the scan, 28 fearful and 28 neutral faces were presented, as well as 56 scenes, in a pseudo-random order. Depending on the preceding cue, participants were instructed to indicate whether the face presented was male or female (M/F), or whether the scene corresponded to an interior or an exterior location (I/E). Immediately following the encoding scanning session, the encoding set and an equal set of new faces (lures) were presented in pseudo-random order on a PC laptop. Participants indicated whether the face was seen during the preceding scan (*old*) or never seen before (*new*).