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Hippocampal function during associative learning in patients with posttraumatic stress disorder

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Abstract

In the last decade several studies have shown memory deficits in patients with posttraumatic stress disorder (PTSD) which have been associated with a reduced hippocampus volume. However, until now we do not know how or whether these structural abnormalities turn into functional abnormalities. Thus, the primary purpose of the present study was the investigation of the hippocampal function using functional magnet resonance imaging (fMRI).

We compared PTSD patients and healthy control participants using an associative learning paradigm consisting of two encoding and one retrieval condition. During fMRI scanning participants had to learn face-profession pairs. Afterwards only faces were presented as cue stimuli for associating the category of the prior learned target profession and the participants had to decide whether this face belonged to a scientific or an artistic profession. Additionally, cognitive functioning, i.e. memory and attention, was examined using neuropsychological standard tests.

During encoding PTSD patients showed stronger hippocampal and weaker prefrontal activation compared to healthy control participants. During retrieval the two groups did not differ neither in hippocampus activation nor in accuracy of retrieval. PTSD patients however showed a reduced activation in the left parahippocampal gyrus and other memory-related brain regions. We did not find any significant memory differences between PTSD patients and healthy control participants.

The results suggest that PTSD has an effect on memory-related brain function despite intact memory functioning. In particular the hippocampal/parahippocampal regions and the prefrontal cortex show functional alterations during associative learning and memory.

Keywords: Posttraumatic stress disorder; Associative learning; Memory; Hippocampus; Parahippocampus; fMRI

1. Introduction

Patients with posttraumatic stress disorder (PTSD) frequently report difficulties in remembering aspects of their traumatic event (Tromp et al., 1995), so that this subjective symptom has been included in the diagnostic criteria for PTSD in the diagnostic and statistical manual of mental disorders (DSM-IV, American Psychiatric Association, 1994). Hence, many attempts have been made to obtain objective quantifications of memory impairments associated with PTSD. Over the last decade, numerous studies have revealed memory deficits in adults with PTSD related to combat exposure or childhood physical or sexual abuse using neuropsychological standard tests of verbal and figural memory (Barrett et al., 1996; Bremner et al., 1995a,b; Gilbertson et al., 2001, 2006; Vasterling et al., 1998, 2002). These deficits were often associated with

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hippocampus damage, since the hippocampus has been shown to be essential for learning and memory (Squire and Zola-Morgan, 1991) and in particular for encoding of relational representations and configural associations, respectively (Rudy and Sutherland, 1994). As a matter of fact multiple magnet resonance imaging (MRI) studies have revealed reduced hippocampal volume in patients with chronic PTSD compared to healthy participants (Bremner, 1999; Bremner et al., 1999a,b; Bremner et al., 1995a,b, 2003a,b; Gurvits et al., 1996; Sapolsky, 1996).

Research in non-human primates has suggested that chronic stress and prolonged exposure to glucocorticoids which are released during stressful events may damage the hippocampus (e.g. Sapolsky et al., 1990). Various studies have demonstrated that prolonged glucocorticoid exposure results in neuron loss, reduced efficiency and impaired integrity of inhibitory interneurons within the hippocampus (e.g. Magarinos et al., 1997; Sapolsky et al., 1990). These findings have suggested that extreme stress may also result in a reduced hippocampus volume in humans with PTSD (Bremner, 1999; Sapolsky, 1996). Recent data however also propose that the hippocampus may be smaller already prior to trauma. Thus, the hippocampus dysfunction may indicate a preexisting genetic vulnerability factor for PTSD development (Gilbertson et al., 2006; Bremner et al., 2003b).

Despite numerous structural studies on hippocampus volume, it is still unclear how or whether these structural abnormalities turn into functional abnormalities. To understand the underlying neural basis of learning and memory focusing onto the hippocampus function, neuroimaging investigation may be helpful but only few findings of functional studies have been published until now. Astur et al. (2006) used a spatial memory task during functional magnet resonance imaging (fMRI) to assess hippocampal function in patients with PTSD. This study yielded reduced hippocampal activation for PTSD patients compared to healthy controls, though the authors did not find any behavioral differences in this memory task. A very recent fMRI study of Geuze et al. (2008) investigated associative memory processing in PTSD. This study compared neural activation during encoding and retrieval of word-pair associates in veterans with and without PTSD. During encoding veterans with PTSD showed underactivation of the frontal cortex and overactivation of the temporal cortex, whereas during retrieval frontal areas as well as the left posterior hippocampus/parahippocampal gyrus were less activated. Beyond, Shin et al. (2004) demonstrated a reduced regional cerebral blood flow measured with positron emissions tomography (PET) during recall of an explicit memory paradigm within the left hippocampus in firemen with PTSD compared to firemen without PTSD, but they did not find any significant differences in the accuracy of recall as Astur and his colleagues. Two other PET studies investigated memory and hippocampus function and showed a reduced hippocampal activity during recall (Bremner et al., 2003a,b). However, hippocampal activity was only reduced for negative but not for neutral word pairs in PTSD (Bremner et al., 2003b). The most widely used paradigm to evaluate changes in neural activations in PTSD has been symptom provocation. Various stimuli, including emotional stimuli, pictures and biographical scripts have been used to generate neural responses. These studies (cf. Francati et al., 2006) have revealed increased cerebral activation in the amygdala and decreased activation in the medial prefrontal cortex. Some also showed decreased neural response in the hippocampus and an increased parahippocampal activity.

The purpose of the present study was primarily to investigate the functional role of the hippocampus in PTSD and to analyze the relationship between hippocampus function and memory deficits using fMRI. To investigate the functional role of the hippocampus, we relied on an associative learning paradigm of Henke et al. (2003) since this paradigm has already been shown to be a sensitive method for producing hippocampal activation in healthy participants. In this paradigm, participants had to learn face-profession associations and to remember the professional category of each face. We hypothesized that patients with PTSD show (1) reduced hippocampal activation during encoding and retrieval of the associative learning paradigm and (2) worse memory performance relative to healthy non-traumatized control participants. Since memory deficits may be due to attention deterioration which has also been found in PTSD patients (Vasterling et al., 1998, 2002), we examined attention performance to avoid confounding causes for possible memory deficits.

2. Methods and materials

2.1. Participants

Twelve patients with current PTSD were recruited through the Trauma Health Care Center of the Ludwig-Maximilians-University (LMU) in Munich (Germany) and the Health Care Center of the Clinic of Psychiatry and Psychotherapy of the LMU in Munich. All patients met the DSM-IV criteria for chronic PTSD on the basis of an interview with the Clinician-Administered PTSD Scale (CAPS, Blake et al., 1995) and the Structured Clinical Interview for DSM-IV (SCID, Wittchen et al., 1997). Severity of PTSD was assessed by the CAPS. According to Weathers et al. (2004), the average CAPS total score corresponded to a moderate PTSD ($M = 57.75$, $SD = 22.06$). PTSD patients experienced different traumata. Six out of 12 patients (50%) experienced a sexual abuse in childhood, three patients (25%) experienced a physical threat, one patient (8%) had a severe car accident, one (8%) experienced death of a close person and another (8%) suffered a severe organic disease. Comorbid disorders were assessed by the SCID. Four out of 12 patients (33%) fulfilled criteria for a comorbid disorder: One patient (8%) met criteria for a major depression, one (8%) for alcohol abuse, one (8%) for a panic disorder and one (8%) for a depressive personality