Journal of Psychiatric Research 45 (2011) 660–669

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD

Jasmeet Pannu Hayes [a,b,c,d,e], Kevin S. LaBar [c,g], Gregory McCarthy [c,e,f], Elizabeth Selgrade [c,e], Jessica Nasser [c,e], Florin Dolcos [h], VISN 6 Mid-Atlantic MIRECC workgroup, Rajendra A. Morey [c,d,e,*]

[a] National Center for PTSD, VA Boston Healthcare System, Boston, MA, USA
[b] Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA
[c] Duke-UNC Brain Imaging and Analysis Center, Duke University, Durham, NC 27710, USA
[d] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA
[e] Mental Illness Research Education and Clinical Center, Durham VA Medical Center, Durham, NC, USA
[f] Department of Psychology, Yale University, New Haven, CT, USA
[g] Center for Cognitive Neuroscience, Duke University, Durham, NC, USA
[h] Department of Psychology and the Beckman Institute, University of Illinois at Urbana-Champaign, IL, USA

ARTICLE INFO

Article history:
Received 30 July 2010
Received in revised form
24 September 2010
Accepted 5 October 2010

Keywords:
fMRI
Gist
Contextual memory
Military
Subsequent memory paradigm
Precuneus

ABSTRACT

Neurobiological models of posttraumatic stress disorder (PTSD) suggest that altered activity in the medial temporal lobes (MTL) during encoding of traumatic memories contribute to the development and maintenance of the disorder. However, there is little direct evidence in the PTSD literature to support these models. The goal of the present study was to examine MTL activity during trauma encoding in combat veterans using the subsequent memory paradigm. Fifteen combat veterans diagnosed with PTSD and 14 trauma-exposed control participants viewed trauma-related and neutral pictures while undergoing event-related fMRI. Participants returned one week after scanning for a recognition memory test. Region-of-interest (ROI) and voxel-wise whole brain analyses were conducted to examine the neural correlates of successful memory encoding. Patients with PTSD showed greater false alarm rates for novel lures than the trauma-exposed control group, suggesting reliance on gist-based representations in lieu of encoding contextual details. Imaging analyses revealed reduced activity in the amygdala and hippocampus in PTSD patients during successful encoding of trauma-related stimuli. Reduction in left hippocampal activity was associated with high arousal symptoms on the Clinician-Administered PTSD Scale (CAPS). The behavioral false alarm rate for traumatic stimuli co-varied with activity in the bilateral precuneus. These results support neurobiological theories positing reduced hippocampal activity under conditions of high stress and arousal. Reduction in MTL activity for successfully encoded stimuli and increased precuneus activity may underlie reduced stimulus-specific encoding and greater gist memory in patients with PTSD, leading to maintenance of the disorder.

Published by Elsevier Ltd.

1. Introduction

Posttraumatic stress disorder (PTSD) has been characterized as a disorder of memory, with key features including intrusive memories of the traumatic event, flashbacks, and nightmares. While the re-experiencing symptoms of traumatic events are often difficult to inhibit, PTSD is paradoxically related to abnormal access to trauma memories and difficulty remembering certain aspects of the trauma (Amir et al., 1998; Foa et al., 1995; Koss et al., 1996). The nature of memory for traumatic events may represent the single most controversial topic in the field of traumatic stress (McNally, 2003) and has garnered great attention due to implications for recovered memories and eyewitness testimony. However, of the few published studies that have examined the neurobiology of negative memory encoding in PTSD (Dickie et al., 2008; Thomaes et al., 2009), none have directly examined memory encoding of *trauma-specific* information, despite indications that traumatic memories in particular are subject to distortions. In the present study, we provide evidence that altered neural activity for encoding of trauma reminders may have implications for understanding how the disorder is maintained.

A prominent hypothesis of PTSD etiology suggests that inefficient encoding may result in distortions in traumatic memory (Ehlers and Clark, 2000). According to this model, traumatic memories are characterized by confusing sensory impressions that

* Corresponding author. Duke-UNC Brain Imaging and Analysis Center, Duke University Medical Center, Box 3918, Durham, NC 27710, USA. Fax: +1 919 416 5912.
E-mail address: Rajendra.morey@duke.edu (R.A. Morey).

0022-3956/$ – see front matter Published by Elsevier Ltd.
doi:10.1016/j.jpsychires.2010.10.007

are temporally related to the trauma, but are disconnected from the context in which they were formed. These altered memory traces impede the individual's ability to discriminate between stimuli that represent real danger and those that serve as relatively harmless reminders of the trauma (e.g., a patient with combat-related PTSD has a flashback at a Fourth of July fireworks display). The clinical implication is maintenance of the disorder through persistent re-experiencing, heightened arousal, and further avoidance of the trauma. There is some evidence that PTSD patients' memories for emotional events are overly general, or gist-based, rather than detailed (Harvey et al., 1998; Kaspi et al., 1995; McNally et al., 1994). Given that gist-based representations are often subject to misinformation and false alarms (Roediger and McDermott, 1995; Wright and Loftus, 1998), it is possible that encoding of trauma memories that are gist-based and without specific, contextual details is one mechanism associated with memory distortions in PTSD.

Although several researchers have advanced ideas suggesting that encoding abnormalities during the trauma event underlie memory difficulties observed in PTSD (Ehlers and Clark, 2000; Layton and Krikorian, 2002; Nadel and Jacobs, 1998), there is no direct evidence to support these hypotheses. One obvious ethical and practical problem in humans is that it is impossible to study the neurobiology of trauma memory while it is occurring. However, it is possible to examine the maintenance of memory distortions in PTSD by studying memory encoding of *trauma reminders*. A salient feature of PTSD is that re-experiencing symptoms of the trauma occurs within a safe context, suggesting that patients have difficulty updating their contextual representations of the trauma event. It is possible that maintenance of the disorder may in part be mediated by encoding of trauma reminders that are gist-based and devoid of contextual and specific episodic information.

Drawing from the well-supported animal literature on trauma and stress, involvement of medial temporal lobe (MTL) structures including the hippocampus and amygdala are vital for successful encoding of negative information (McGaugh, 2004). According to the *modulation hypothesis*, emotional events are generally remembered better than neutral events due to the modulatory effect of the amygdala on other MTL structures including the hippocampus (McGaugh et al., 1996). The hippocampus in particular is necessary to the formation of specific, contextual memories. However, hippocampal function in response to stress may be an inverted U-shape (Nadel and Jacobs, 1998). That is, the hippocampus functions optimally at moderate levels of stress, but suboptimally at very low and very high levels of stress. There is ample evidence that high levels of stress impair hippocampal activity (de Quervain et al., 1998; Foy et al., 1987; Kim and Diamond, 2002) and that, in humans, negative valence increases the likelihood of false memories (Brainerd and Reyna, 2002). Chronic hyperarousal and stress results in elevated secretion of glucocorticoids, catecholamines, and other neuromodulators which affect the hippocampus (Kim and Diamond, 2002). These studies point to a neurotoxic role for corticosteroids that cause atrophy and cell death in hippocampal neurons. Several structural MRI studies have reported smaller hippocampal volume in chronic unremitting PTSD (Bremner et al., 2003a; Gurvits et al., 1996; Stein et al., 1997; Villarreal et al., 2002; Wignall et al., 2004). Magnetic Resonance Spectroscopy (MRS) studies of PTSD have documented decreased N-acetyl aspartate (NAA) in the hippocampus that is suggestive of impaired neuronal integrity (Brown et al., 2003; Schuff et al., 2001; Winter and Irle, 2004). Finally, examination of trauma memory or encoding of trauma-related information provides evidence of diminished hippocampal activation in PTSD (Bremner et al., 1999, 2003a, 2003b; Geuze et al., 2008b; Shin et al., 1999). Therefore, suboptimal hippocampal activity during presentation of highly stressful trauma reminders may lead to decontextualized memory traces for these stimuli in patients with PTSD. This hypothesis is consistent with the aforementioned cognitive model of PTSD, which posits that trauma memory traces are characterized by distortion and confused sensory impressions rather than an elaborated memory that can be readily integrated into one's autobiographical knowledge base.

In order to study the neural underpinnings of encoding of trauma reminders, we employed the subsequent memory paradigm which provides a powerful translational approach in understanding the neural basis of successful memory encoding and retrieval in humans (Paller and Wagner, 2002). In this paradigm, BOLD activity is measured during encoding of stimuli that are probed for memory success after a delay. Differences in encoding activity for successfully remembered or forgotten material is evaluated on a participant-by-participant basis to identify brain regions that mediate the interaction between emotional arousal and successful memory operations. The difference between remembered and forgotten activation is referred to as the 'difference due to memory effect,' or Dm effect (Dolcos et al., 2004). As a measure of gist memory and lack of contextual details, novel lures were introduced to the subsequent memory test to examine false alarm rates. Accurate recognition of previously studied items depends on gist and item-specific information, whereas false recognition of related lures depends on remembering gist but not on item-specific information (Budson et al., 2000; Payne et al., 1996; Reyna and Brainerd, 1995b; Schacter et al., 1996; Verfaellie et al., 2002). Due to our strong *a priori* interest in MTL regions, we used a region-of-interest (ROI) analysis to interrogate activity in the amygdala, hippocampus, and parahippocampul gyrus in response to subsequently remembered and forgotten material. We hypothesized that patients with PTSD would show greater amygdala activity and reduced hippocampal activity during successful encoding of trauma reminders compared with trauma-exposed control participants, and greater false alarms indicating gist-based, rather than specific detailed memory representations. To examine the relationship between arousal and hippocampal function, we conducted a correlation analysis between CAPS cluster scores and hippocampal activity with the hypothesis that PTSD hyperarousal symptoms would be negatively correlated with hippocampal activation, in support of the notion that hippocampal activity is disrupted under conditions of high arousal and stress. Finally, as a secondary analysis, we examined the relationship between emotional encoding and memory regions along the longitudinal axis of the MTL. Previous work suggests that MTL memory regions are differentially sensitive to the effects of emotion on successful encoding, such that anterior regions of the MTL are more responsive for emotional material while posterior regions of the MTL respond to neutral material (Dolcos et al., 2004). These data support the notion that the amygdala has a modulatory effect on anterior MTL regions. We predicted that trauma-exposed controls would show a shift in neural response for emotional and neutral stimuli along the longitudinal axis of the MTL similar to healthy normal subjects, but this MTL relationship might be disrupted in PTSD as a response to the neurotoxic effects of stress on the hippocampus (Kim and Diamond, 2002).

2. Materials and methods

2.1. Participants

Demographic information of study participants is displayed in Table 1. Twenty-nine veterans who had returned from their deployment in support of recent war operations (e.g., veterans who served in Iraq or Afghanistan) completed the fMRI procedures (average time since return from deployment = 3 years, 9 months).