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Deficient fear extinction memory in posttraumatic stress disorder

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD) might be maintained by deficient extinction memory. We used a cued fear conditioning design with extinction and a post-extinction phase to provoke the return of fear and examined the role of the interplay of amygdala, hippocampus and prefrontal regions.
Methods: We compared 18 PTSD patients with two healthy control groups: 18 trauma-exposed subjects without PTSD (nonPTSD) and 18 healthy controls (HC) without trauma experience. They underwent a three-day ABC-conditioning procedure in a functional magnetic resonance imaging scanner. Two geometric shapes that served as conditioned stimuli (CS) were presented in the context of virtual reality scenes. Electric painful stimuli were delivered after one of the two shapes (CS+) during acquisition (in context A), while the other (CS−) was never paired with pain. Extinction was performed in context B and extinction memory was tested in a novel context C.
Results: The PTSD patients showed significantly higher differential skin conductance responses than the non-PTSD and HC and higher differential amygdala and hippocampus activity than the HC in context C. In addition, elevated arousal to the CS+ during extinction and to the CS− throughout the experiment was present in the PTSD patients but self-reported differential valence or contingency were not different. During extinction recall, differential amygdala activity correlated positively with the intensity of numbing and ventromedial prefrontal cortex activity correlated positively with behavioral avoidance.
Conclusions: PTSD patients show heightened return of fear in neural and peripheral measures. In addition, self-reported arousal was high to both danger (CS+) and safety (CS−) cues. These results suggest that a deficient maintenance of extinction and a failure to identify safety signals might contribute to PTSD symptoms, whereas non-PTSD subjects seem to show normal responses.

1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by re-experiencing of the eliciting traumatic event, chronic hyperarousal, avoidance behaviors and negative alterations in cognition and mood (American Psychiatric Association, 2013). Prevalent theories about the disorder suggest that enhanced acquisition and delayed extinction of conditioned fear (Orr et al., 2000), disturbed trauma and extinction memories (Ehlers & Steil, 1995; Milad et al., 2008, 2009) and deficient processing of contextual information and safety cues play a role in the disorder (Acheson, Gresack, & Risbrough, 2012; Flor & Wessa, 2010; Jovanovic et al., 2010; Rougemont-Bucking et al., 2011; Wessa, Jatzko, & Flor, 2006). In pavlovian fear conditioning, an initially neutral or conditioned stimulus (CS) is repeatedly paired with an aversive unconditioned stimulus (US) until its presentation alone elicits a conditioned response (CR), which is often but not always similar to the unconditioned response (UR). In differential delay fear conditioning one CS acts as danger signal and predicts the occurrence of the US (CS+) whereas a second stimulus is never followed by a US and acts as safety signal (CS−) and the CS and the US overlap in time. The CR can be extinguished by presenting the CS repeatedly without subsequent delivery of the US. However, this procedure does not erase the originally acquired CS–US association, which can be reactivated and elicit the CR under certain circumstances (Bouton &

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Bolles, 1979; Lovibond, Davis, & O'Flaherty, 2000; Norrholm, Anderson, et al., 2011; Rescorla & Heth, 1975).

Several mechanisms can disturb extinction memory and can trigger the originally acquired CR after extinction. These include spontaneous recovery (the mere passage of time) (Pavlov, 1972; Rescorla, 2004), reinstatement (post-extinction confrontation with the US alone) (Rescorla & Heth, 1975) and renewal (context change after extinction) (Bouton & Ricker, 1994). In the case of renewal, it is important to note that the extinction of a fear response is context-specific (Bouton, 2002, 2004; Corcoran & Maren, 2001; Huff, Hernandez, Blanding, & LaBar, 2009) and a mere change of context can revoke the extinguished CR, whereas the acquisition of a fear response generalizes to different contexts. One explanation for this phenomenon is that after successful conditioning and extinction, two memory traces exist that compete against each other (Bouton, 1993): (1) the originally acquired CS–US association and (2) a newly formed CS–noUS association. Therefore the CS becomes ambiguous and external factors such as the context are thought to regulate the behavioral response (Bouton, 2002).

Brain imaging studies (Bremner, 2003; Liberzon & Sripada, 2008; Pitman et al., 2012; Shin, Rauch, & Pitman, 2006; Yehuda & LeDoux, 2007) have shown that (a) heightened amygdala activity results in exaggerated acquisition of fear and hyper-responsivity to threat-related stimuli (Bremner et al., 2005; Protopopescu et al., 2005; Rauch et al., 2000; Shin et al., 2004; Yang et al., 2008), (b) deficient frontal cortical function mediates a failure to maintain extinction and to suppress amygdala-driven responses to trauma-related stimuli (Bremner et al., 2005; Shin et al., 2005), and (c) deficient hippocampal function leads to deficits in explicit learning/memory (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003) and a failure to modulate cue-related memories by the context, i.e. to appreciate safe contexts (Acheson et al., 2012; Flor & Wessa, 2010; Steiger, Nees, Wicking, Lang, & Flor, 2015) in PTSD.

In line with this it was proposed (Acheson et al., 2012; Flor & Wessa, 2010) that in PTSD deficient hippocampal function at the time of trauma may lead to exaggerated associations between cues and the trauma and a deficient association of the context and the trauma. As a result, later exposure to a single element of the context can trigger a fear response and this is experienced out of the corrective context. Indeed, Milad et al. (2008, 2009) showed that recall of fear extinction is reduced in PTSD patients compared to trauma-exposed but unaffected controls in a context-dependent conditioning paradigm. During acquisition and extinction, the CSs (different colors of a lighted lampshade) where presented within two different contexts (stationary pictures of two different rooms). When subjects were again confronted with the CSs one day later in the extinction context (ABB), the PTSD patients showed elevated skin conductance responses. In accordance with the theoretical framework, this failure to retain extinction memory was accompanied by reduced activation in the hippocampus, as well as reduced activation in the ventromedial prefrontal cortex and enhanced activation in the dorsal anterior cingulate cortex (Milad et al., 2009).

Jovanovic, Kazama, Bachevalier, and Davis (2012) proposed that PTSD patients fail to inhibit fear responses to an acquired danger stimulus in the presence of a safety signal as a result of impaired safety learning and an inability to modulate fear responses with safety cues, which presumably requires a cognitive, cortical component (Bremner et al., 2005; Weike, Schupp, & Hamm, 2008). Indeed, several studies (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Grillon & Morgan, 1999; Peri, Ben-Shakhar, Orr, & Shalev, 2000) found evidence for a generalized (or sensitized) reaction to the unreinforced stimulus in PTSD.

Thus, in PTSD, the failure to maintain extinction could be enhanced since the contextual processing of stimuli may be compromised due to the hippocampal impairments found in PTSD patients and those vulnerable for PTSD (Acheson et al., 2012; Bremner et al., 2003a; Gilbertson et al., 2002; Steiger et al., 2015).

In our study, we presented two CSs in the context of virtual reality (VR) scenes and used an ABC conditioning procedure, where acquisition, extinction, and extinction memory were tested in three different contexts to increase the ecological validity of the experimental design. We further used a traumatized control group without PTSD and a never traumatized control group to differentiate the impact of and coping with trauma per se from the influence of PTSD symptomatology. We hypothesized that PTSD patients compared to traumatized persons without PTSD and healthy trauma-naïve controls show heightened return of fear in self-report, peripheral and central indicators of fear such as verbal ratings, differential SCR and amygdala activation.

2. Methods and materials

2.1. Participants

Eighteen persons with PTSD, 18 trauma-exposed subjects without PTSD (nonPTSD) and 18 healthy controls without trauma experience (HC) participated in the study. PTSD and nonPTSD were included if they had experienced a traumatic event meeting the A-criterion for PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association; American Psychiatric Association, 2013). The PTSD group additionally fulfilled criteria B through F verified by the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). All traumatic events were experienced in adulthood, i.e. after 18 years of age. The HC group was matched to the trauma-experienced samples but had never been confronted with a trauma. All participants underwent the Structured Clinical Interview for DSM-IV I and II (Fydrich, Renneberg, Schmitz, & Wittchen, 1997; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). Exclusion criteria were comorbid current or lifetime psychotic symptoms, borderline personality disorder and current alcohol/drug dependence or abuse, cardiovascular or neurological disorders, brain injury, acute pain, continuous pain or medication for attention deficit hyperactivity disorder, pregnancy and metal implants. All subjects completed a cognitive test battery in order to test memory and general cognitive function, including the Culture Fair Intelligence Test (CFT; Weiß, 1998), the Multiple Choice Word Fluency Test (MWT-B; Lehrl, 2005), and the "Kurztest für allgemeine Basisgrößen der Informati onsverarbeitung" [Short Test for General Factors of Information Processing] (KAI; Lehrl, Gallwitz, Blaha, & Fischer, 1991). There were no differences in cognitive and memory function as well as general intelligence (IQ) between the three groups. Subjects additionally answered questionnaires between sessions: PTSD patients scored higher in the Center for Epidemiological Studies Depression Scale (ADS; Hautzinger & Bailer, 1993), the Childhood Trauma Questionnaire (Bernstein & Fink, 1998) and the trait version of the State-Trait-Anxiety Inventory (Spielberger, 2010). The ethics committee of the Medical Faculty Mannheim, Heidelberg University approved the study. All participants gave written informed consent. The patients were offered treatment, controls were reimbursed (€80) for travel and other expenses. Table 1 presents the demographic and clinical characteristics of the participants (for patient flow see Supplemental Fig. S1). The study conformed to the Code of Ethics of the World Medical Association (World Medical Association, Declaration of Helsinki, seventh revision, 2013).

2.2. Stimuli and experimental procedure

We used a differential delay cued fear conditioning paradigm that was administered in three different VR environments (ABC