



## Behavioral and central correlates of contextual fear learning and contextual modulation of cued fear in posttraumatic stress disorder



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### ABSTRACT

Patients with posttraumatic stress disorder (PTSD) show persistent fear responses to trauma cues in contexts in which these cues no longer predict danger. This might be related to deficient context and enhanced cue conditioning. To test this hypothesis, we examined context conditioning directly followed by a cue conditioning phase against the background of the previously conditioned context in 12 patients with PTSD, 14 traumatized control subjects without PTSD and 11 matched never-traumatized controls. We used differential context and cue conditioning paradigms, with rooms as contexts and geometric figures as cues, and assessed valence, arousal and contingency ratings as well as brain responses using functional magnetic resonance imaging. The PTSD patients showed more hippocampal activation and differentiated the threat and safe contexts less in their contingency ratings than the healthy controls during context acquisition. In the subsequent cue acquisition against the background of the conditioned context, they displayed similar threat versus safe cue differentiation in contingency ratings as the two control groups. Moreover, PTSD patients failed to extinguish the differential conditioned context and cued fear responses and showed increased fear to both the dangerous and the safe conditioned contexts and cues in some ratings. This study provides evidence for a dissociation of brain responses and contingency awareness in PTSD which represents impaired context learning and a deficient contextual modulation of cue-related associations. In addition, extinction and extinction recall were impaired in PTSD. These changes were related to PTSD symptoms and suggest that contextual learning deficits may contribute to PTSD.

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### 1. Introduction

Posttraumatic stress disorder (PTSD) is a trauma- and stress-related disorder (American Psychiatric Association, 2013) that develops after exposure to life-threatening or violent events. However, not everyone who experiences severe traumatic events develops PTSD, suggesting that individual vulnerabilities and characteristics of the trauma exposure may influence the onset of the disorder. Jovanovic and Ressler (2010) highlighted the interaction of genetic, neurobiological, environmental and associative learning processes that contribute to the risk of developing PTSD.

Pavlovian fear conditioning is a commonly used experimental paradigm to study learning mechanisms and fear circuitry and has a long tradition in the study of PTSD (Grillon and Morgan, 1999; Holmes and Singewald, 2013; Lissek and van Meurs, in press; Milad et al., 2009; Orr et al., 2000; Pitman and Orr, 1986; Vervliet et al., 2013).

Context conditioning refers to the pairing of an external or internal context (CON) such as a certain environment or a mood state with an unconditioned stimulus (US), whereas cue conditioning refers to the pairing of a discrete cue (CS) such as a tone with the US. It has been suggested that PTSD may result from enhanced fear conditioning processes and reduced fear extinction. As a consequence, PTSD symptoms such as reexperiencing, avoidance and hyperarousal are viewed as manifestations or re-occurrences of the conditioned fear response. This is related to trauma-related cues and may also involve second order conditioning where originally neutral stimuli that are associated with trauma reminders, which then function as unconditioned stimuli, become danger signals (e.g., Wessa and Flor, 2007). Failure to extinguish may also be supported by deficient context conditioning and a subsequent deficient association of contexts with the conditioned stimuli, which may lead to a failure to learn about safe contexts and is also a prerequisite in the process of extinction (cf. Bouton, 2004; Acheson et al., 2012; Flor and Wessa, 2010; Maren et al., 2013). Moreover, similar to the blocking effect in cue conditioning, where conditioned responses to a stimulus are blocked if this stimulus is reinforced in a compound with a previously reinforced stimulus, conditioned responding to a context may similarly partially block new (cue) fear conditioning and vice versa

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(contextual blocking, cf. [Tomie, 1976](#)). Impaired context conditioning in PTSD may result in better learning (less “blocking”) of later aversive encounters (new cue fear conditioning) compared to controls.

In a review on human fear conditioning, [Sehlmeyer et al. \(2009\)](#) identified the amygdala, insula and the medial prefrontal cortex (mPFC) including the anterior cingulate cortex (ACC) as key regions involved in fear learning. Substantial evidence from neurobiological studies points to the role of various neural systems in cue fear versus context conditioning ([Bouton, 1993](#); [Bouton and Nelson, 1994](#); [Maren et al., 2013](#)). While the amygdala is pivotal in cue conditioning and also involved in context conditioning in both animals and humans ([Phelps and LeDoux, 2005](#); [LaBar et al., 1998](#); [LaBar and LeDoux, 1996](#)), the hippocampus plays a key role in context conditioning (e.g., [Marschner et al., 2008](#); [Lang et al., 2009](#); [Pohlack et al., 2012](#)), specifically when configural associations have to be discriminated ([Sutherland and McDonald, 1990](#); [Rudy and Sutherland, 1995](#); [Shin et al., 2006](#); [Alvarez et al., 2008](#); [Lang et al., 2009](#); [Marschner et al., 2008](#); [Hasler et al., 2007](#)). Finally, we assumed deficient context conditioning to be related to PTSD symptoms. This is supported by animal studies where configural memory is disrupted and learning strategies tend towards discrete cue associations when the hippocampus is impaired ([Iordanova et al., 2009](#)). The hippocampus is also important in extinction learning and extinction retrieval where contextual associations may be more important compared to cue acquisition ([Corcoran and Maren, 2001](#); [Kalisch et al., 2006](#)), and in contingency awareness (e.g., [Cacciaglia et al., 2014](#)). Moreover, activation in the ventral striatum commonly observed during reward processing, was also found to be associated with the learning of CS-US contingencies ([Klucken et al., 2009](#)). Significant progress has been made in the analysis of the neural correlates of PTSD. Functional magnetic resonance imaging (fMRI) findings have shown that brain circuits such as the amygdala, hippocampus and prefrontal cortex are altered in PTSD ([Etkin and Wager, 2007](#); [Milad et al., 2007](#)). PTSD patients show a hyperactivity of the amygdala as well as a reduced activation of the ventromedial PFC and the hippocampus, associated with a diminished extinction of the fear response ([Etkin and Wager, 2007](#)). In addition, smaller hippocampal volumes are a core finding in studies on structural brain changes in PTSD ([Bremner et al., 1995](#); [Karl et al., 2006](#); [Woon et al., 2010](#)) and may be a predisposing factor for the disorder ([Gilbertson et al., 2002, 2007](#)).

The maintenance of PTSD symptoms might be related to deficient context conditioning favoring cue conditioning. This might prevent the integration of the trauma into the proper context and at the same time lead to intrusions, flashbacks and nightmares ([Pitman and Orr, 1986](#); [Flor and Nees, 2014](#)). In the present study, we examined whether context conditioning is impaired in PTSD ([Flor and Nees, 2014](#); [Garfinkel et al., 2014](#); [Rougemont-Bucking et al., 2011](#)) and subsequently leads to enhanced conditioning of cues against the background of the conditioned contexts compared to the control groups where intact contextual learning was expected. This may be viewed as similar to a context blocking effect. We employed a human fear conditioning procedure using a differential context acquisition where one context (danger context) was combined with a slightly painful stimulation as US whereas the other context (safe context) was never paired with the US. This learning phase was followed by cued acquisition where geometrical figures served as CSs that was presented in the previously conditioned contexts displayed as a background on the computer screen (cf., [Fonteyne et al., 2009](#)). In this phase a danger cue (that signaled painful stimulation) was presented in the danger context and the safe cue (that signaled the absence of the painful stimulation) was presented in the safe context. Moreover, we tested the extinction of the previously conditioned contexts and the cues against the background of the contexts immediately after the cued acquisition and one day later (extinction recall). We examined behavioral (ratings of arousal, valence and contingency) and central physiological responses using subjective ratings and fMRI data and expected contingency ratings and hippocampal activation to be most affected in the PTSD group. For both extinction

and extinction recall of the contexts and cues we expected – an impaired response in the PTSD compared to both control groups.

## 2. Methods

### 2.1. Participants

We examined 12 PTSD patients (8 female), 14 trauma-exposed healthy subjects (trauma control group) (5 female), and 11 matched healthy subjects (HC; 6 female). The PTSD patients were recruited via the outpatient clinic of the Central Institute of Mental Health, Mannheim and press coverage. All participants were right-handed and non-medicated. The PTSD patients met the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text rev.; [American Psychiatric Association, 2000](#)) criteria for chronic PTSD. Exclusion criteria for PTSD patients were comorbid borderline personality disorder, history of schizophrenia-spectrum psychosis, bipolar type I affective disorder, and current substance abuse. Exclusion criteria for healthy controls comprised any personality disorder or Axis I disorder assessed by the German Version of the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SKID-II and SKID-I; [Fydrich et al., 1997](#); [Wittchen et al., 1997](#)), or any history or current psychiatric treatment, and history of trauma. Further exclusion criteria for all participants were neurological disorders, head traumata, mental retardation, lack of German language skills, and magnetic metals in the body. Participants of the trauma control group were only included when they had a history of a criterion A trauma at least 3 months before participation in the study (see [Table 1](#) for demographic and clinical data). The participants received a reimbursement of 80 Euro plus travel costs. Written informed consent was obtained after a complete description of the study. The study was approved by the Ethics Committee of the Medical Faculty Mannheim of the Heidelberg University and adhered to the Declaration of Helsinki.

### 2.2. Clinical assessment

The Structured Clinical Interview for DSM-IV Axis I Disorders (SKID-I; [Wittchen et al., 1997](#)) was used to assess mental disorders including PTSD. Additionally, the German version of the Clinician-Administered PTSD Scale (CAPS; [Schnyder and Moergeli, 2002](#)) was used to examine the current diagnosis of PTSD and the German version of the Childhood Trauma Questionnaire (CTQ; [Gast et al., 2001](#)) was employed to assess childhood traumata. Axis II diagnoses were determined using the Structured Clinical Interview for DSM-IV Axis II disorders (SKID-II; [Fydrich et al., 1997](#)). The German version of the Center for Epidemiological Studies Depression Scale (Allgemeine Depressionsskala, ADS-L; [Hautzinger and Bailer, 1991](#)) was used to assess comorbid depressive symptoms.

The PTSD patients, trauma control group, and HC subjects did not significantly differ in age, handedness, or education. PTSD patients scored significantly higher in depressive symptoms than the other groups. Five PTSD patients met criteria for current major depressive disorder and 11 PTSD patients met criteria for panic disorder.

### 2.3. Experimental design

We used a differential Pavlovian conditioning procedure consisting of habituation, two different acquisition phases (context and cued acquisition on the background of the previously learned context), and two extinction phases that were separated by one day to assess immediate extinction and extinction recall (see [Fig. 1](#)). Throughout the experiment the participants looked through a mirror mounted on the head coil where they viewed the screen, presented by a projector. The participants were not informed about the contingency of the CON or CS and US and were told to passively view all stimuli.

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