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Reinstatement of contextual anxiety in humans: Effects of state anxiety

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ABSTRACT

After successful extinction of conditioned fear, the presentation of an unsignaled unconditioned stimulus (US) leads to return of fear, thus, the previously extinguished conditioned stimulus (CS) triggers fear responses again. Human studies on such reinstatement processes are still inconclusive. Some revealed a general increase of fear reactions, both to the fear (CS+) and the safety stimulus (CS−), whereas other studies discovered a differential return of fear with enhanced fear responses to the CS+ only. Moreover, we know little about reinstatement of contextual anxiety, a state of general anxious apprehension and chronic worry. Therefore, the present study investigated reinstatement of contextual anxiety with an ecological valid virtual reality (VR) design. Additionally, we examined whether the current state anxiety might modulate the reinstatement of contextual anxiety. To this end, two groups underwent context conditioning on Day 1, i.e., one context (CXT+) became paired with unpredictable USs, but not the other context (CXT−), and an extinction training on Day 2. On Day 3 a reinstatement test was conducted, i.e., one group (reinstatement group, $n = 21$) received one unsignaled US before testing, whereas the control group ($n = 21$) did not. Only the reinstatement group showed a differential return of contextual anxiety as measured by fear-potentiated startle and anxiety ratings. Interestingly, the reinstatement of fear-potentiated startle was additionally influenced by state anxiety. Conclusively, an anxious state before an unsignaled aversive event might favor a return of contextual anxiety.

1. Introduction

The survival of an organism crucially depends on the prediction of danger, the basic learning mechanism underlying fear conditioning. During cued fear conditioning a neutral stimulus is paired with an aversive unconditioned stimulus (US). After several pairings the neutral stimulus becomes a conditioned stimulus (CS) which then elicits fear responses (conditioned response, CR) on itself. During extinction fear responses to the CS will decrease, if the CS is presented without any US (Pavlov, 1927). However, extinction training does not erase the original fear memory but establishes an extinction memory which inhibits the fear memory. This fear memory inhibition is not permanent but can be weakened by several mechanisms leading to a re-emergence of the fear response even after successful extinction training (Bouton, 2002).

One of these mechanisms is called *reinstatement* which is defined as the return of fear (CR) to an extinguished fear cue (CS) after the presentation of an unsignaled US without any CS (Bouton, 2002; Rescorla and Heth, 1975). In an animal study, rodents were conditioned in context A, extinction took place in context B, and afterwards only the US was again presented either in context A or B. Importantly, the CS was presented again without any US in context B to test for the reinstatement of the CR. Interestingly, reinstatement could only be observed, if the CS was presented in the same context where the unsignaled US was presented previously (context B), but not if the US was presented in a different context (context A) (Bouton and Bolles, 1979). Similarly, reinstatement of fear responses in humans was only observed, if the CS was presented in the same context where the unsignaled US was presented previously, but not if the US was presented in a different context (LaBar and Phelps, 2005). Additionally, patients with hippocampal damage did not show reinstatement of fear, and hippocampal lesions before conditioning in rats led to an impaired reinstatement of fear, but did not affect the initial acquisition and extinction of fear (Frohardt et al., 2000). Thus, the hippocampus and the context seem to play a critical role in the reinstatement of fear (LaBar and Phelps, 2005). Therefore, context conditioning is discussed to be the underlying mechanism for reinstatement of cued fear after extinction (Bouton, 2002). Context conditioning is established by presenting unpredictable USs not associated with specific cues. Then, the context becomes associated with the US and the conditioned context later elicits anxiety and a sustained state of apprehension (Grillon, 2002). In the case of reinstatement, it is assumed that an unsignaled US presentation after extinction leads to contextual fear conditioning to this context, which in turn influences the responses to the CS presented later in this context, possibly due to the expectation of an US in this context (Bouton, 2002).

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However, humans studies on reinstatement of cued fear reported inconsistent results even if the unsignaled US was presented in the same physical context as the CS afterwards. Some studies found a differential return of fear, i.e. higher fear responses to the fear cue which was paired with the US (CS+) compared to the safety cue which was never paired with the US (CS−). This differential return of fear has been demonstrated in various fear measures like ratings, skin conductance response (SCR) and fear-potentiated startle (FPS) (Dirikx et al., 2004; Golkar et al., 2012, 2013; Hermans et al., 2005; LaBar and Phelps, 2005; Norrholm et al., 2006). In contrast, other studies reported only a non-differential return of fear, i.e. increased fear responses (ratings, SCR) to both CS+ and CS− which did not differ from each other (Dirikx et al., 2009; Kull et al., 2012).

Surprisingly, reinstatement of contextual anxiety has been rarely studied until now, although contextual anxiety, in contrast to cued fear, is discussed to better mirror chronic states of apprehension and pathological anxiety states as seen in panic disorder or posttraumatic stress disorder patients (Davis et al., 2010). Some rodent studies found reinstatement of contextual anxiety by either presenting the US in the conditioned context or in a different context. In both cases reinstatement was tested one day later in the originally conditioned context (Bertotto et al., 2006; Stern et al., 2012; Yamada et al., 2009). However, these procedures might not only account for reinstatement of anxiety, but may also entail different processes. Presenting the US again in the previous conditioned context can result in rapid re-acquisition of the original anxiety memory by means of only one learning-trial (Bouton, 2004; Kindt and Soeter, 2013). Moreover, presenting the US in a different context can establish new contextual conditioning and may lead to a fast generalization process from the new context to the formerly conditioned context.

Recently, a human study combined cued and contextual fear conditioning and tested for reinstatement of fear and anxiety. Three different contexts were shown with either cue-signaled predictable USs (cue conditioning), unpredictable USs (context conditioning), or no US (safe condition). After extinction, unsignaled USs were presented while participants saw a neutral gray screen. Reinstatement was tested afterwards for conditioned cues and contexts (Haaker et al., 2013). Interestingly, participants showed a non-differential return of anxiety in FPS, skin conductance level (SCL), and fear ratings to all conditioned contexts, whereas a return of fear to the CS was absent.

The divergent results for reinstatement of cued fear and contextual anxiety raise the question whether additional cognitive mechanisms than pure contextual fear conditioning to the physical context are involved in the differential return of fear. According to Bouton (2002), the internal context of the individual, which is comprised of the internal drug and hormonal state, deprivation state, expectation of events, passage of time, or mood state, plays a critical role in the return of fear. Supportively, a recent cue fear conditioning study reported differential reinstatement of conditioned SCR in a group of participants who were exposed to stress after extinction training, but the non-stressed control group did not (Hamacher-Dang et al., 2015). However, the effect of state anxiety on the return of fear has not been investigated so far.

To unequivocally demonstrate reinstatement of differential contextual anxiety in humans and to further elucidate underlying mechanisms of state anxiety, we realized an ecologically valid research design using virtual reality (VR) (Glotzbach-Schoon et al., 2013a; Tröger et al., 2012). To this end, a three-day differential contextual fear conditioning, extinction and reinstatement protocol was established. During fear conditioning on Day 1, one virtual office was paired with unpredictable electrical stimuli (US), thus becoming the anxiety context (CXT+). A second virtual office was never paired with any US, thus becoming the safety context (CXT−). Twenty-four hours later, on Day 2 extinction training was conducted without any US in any context. Another 24 h later, on Day 3 one group (reinstatement group) underwent a reinstatement procedure by presenting one unsignaled US followed by a re-extinction training, i.e., additional exposures to the conditioned contexts (CXT+ and CXT−) without US presentations. The control group did not receive any US on Day 3 and underwent the re-extinction training immediately. Reinstatement of contextual anxiety was tested during the first trial of re-extinction. Additionally, we examined whether the internal emotional state modulated the reinstatement of anxiety (Bouton, 2002) by assessing the state anxiety on Day 3. We hypothesized that (1) the US-only presentation 24 h after extinction would result in a return of differential anxiety as reflected in elevated FPS, SCL, and anxiety and US-expectancy ratings in CXT+ compared to CXT−. This effect should be obvious in the first re-extinction trial, but is not expected in the later trials, because of fast re-extinction effects (Golkar et al., 2012; Haaker et al., 2013, 2014). During the first re-extinction trial participants did not know whether they would receive the US or not, but after the omission of the shock, re-extinction should be initiated fast during the following trials (Menz et al., 2013). The control group should display no return of contextual anxiety, meaning that they show no difference in anxiety responses to CXT+ and CXT− on Day 3. (2) State anxiety should influence the reinstatement of contextual anxiety; we expected that the higher the state anxiety on Day 3, the higher the return of differential contextual anxiety.

2. Materials and methods

2.1. Participants

The final sample consisted of 42 participants with 21 participants in the reinstatement group and 21 participants in the control group. Demographic and psychometric information of participants is provided in Table 1. All participants gave their written informed consent. Participants gained 30 € for their participation. The study was approved by the Ethics Committee of the Medical Faculty of the University of Würzburg and was in accordance with the Declaration of Helsinki. Due to the assessment on three days and a considerable loss of participants mostly

Table 1
Demographic and psychometric data of both groups.
Data are shown separately for the control vs. reinstatement group. Frequencies and means (SD) are displayed.

	Control group $n = 21$	Reinstatement group $n = 21$	χ^2, t	p
Gender	10 females	12 females	0.38	.537
Age [years]	24.05 (2.85)	23.62 (2.97)	0.48	.636
US valence	34.05 (15.13)	37.14 (13.47)	0.70	.448
US arousal	37.62 (27.23)	64.05 (16.93)	3.77	.001
US current intensity [mA]	2.21(0.91)	2.12 (1.05)	0.28	.778
US pain rating Day 1	5.17 (1.09)	5.19 (1.25)	0.07	.984
STAI Trait	38.05 (9.27)	37.76 (8.10)	0.11	.916
ASI	16.57 (8.72)	16.24 (6.63)	0.14	.890
BIS	2.76 (0.60)	2.89 (0.55)	0.73	.470
BAS	3.24 (0.32)	3.24 (0.29)	0.25	.980
PSQI	5.33 (2.35)	5.86 (3.24)	0.60	.553
STAI State Day 1	34.62 (8.66)	35.30 (6.12)	0.29	.774
STAI State Day 2	34.95 (7.34)	36.30 (5.06)	0.51	.613
STAI State Day 3	34.00 (8.37)	36.20 (10.14)	0.73	.471
NA Day 1	12.29 (3.27)	12.25 (2.57)	0.04	.969
NA Day 2	11.67 (2.52)	13.05 (3.44)	1.34	.189
NA Day 3	11.24 (1.87)	12.90 (3.77)	1.68	.102
PA Day 1	28.76 (5.94)	29.45 (5.61)	0.38	.705
PA Day 2	27.90 (6.50)	27.25 (5.66)	0.23	.821
PA Day 3	27.90 (7.62)	27.15 (5.73)	0.18	.857
Sleep quality Day 1	0.76 (0.70)	0.80 (0.52)	0.20	.845
Sleep quality Day 2	0.86 (0.85)	0.90 (0.64)	0.21	.838
Sleep quality Day 3	0.95 (0.67)	0.70 (0.73)	1.11	.273
IPQ Day 1	5.00 (11.18)	0.14 (16.25)	1.23	.266
IPQ Day 2	−0.81 (10.75)	−4.52 (17.87)	0.82	.419
IPQ Day 3	−0.57 (12.77)	−7.43 (18.64)	1.39	.172

Note: STAI = State-Trait-Anxiety-Inventory; ASI = Anxiety Sensitivity Index; BIS = Behavioral Inhibition System; BAS = Behavioral Activation System; MEQ = Morningness-Eveningness-Questionnaire; PSQI = Pittsburgh Sleep Quality Index; PA = positive affect; NA = negative affect; IPQ = Igroup Presence Questionnaire.