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Fear conditioning in posttraumatic stress disorder: Evidence for delayed extinction of autonomic, experiential, and behavioural responses

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Abstract

Aversive conditioning has been proposed as an important factor involved in the etiology of posttraumatic stress disorder (PTSD). However, it is not yet fully understood exactly which learning mechanisms are characteristic for PTSD.

PTSD patients ($n = 36$), and healthy individuals with and without trauma exposure (TE group, $n = 21$; nTE group, $n = 34$), underwent a differential fear conditioning experiment consisting of habituation, acquisition, and extinction phases. An electrical stimulus served as the unconditioned stimulus (US), and two neutral pictures as conditioned stimuli (CS+, paired; CS−, unpaired). Conditioned responses were quantified by skin conductance responses (SCRs), subjective ratings of CS valence and US-expectancy, and a behavioural test.

In contrast to the nTE group, PTSD patients showed delayed extinction of SCRs to the CS+. Online ratings of valence and US-expectancy as well as the behavioural test confirmed this pattern. These findings point to a deficit in extinction learning and highlight the role of affective valence appraisals and cognitive biases in PTSD. In addition, there was some evidence that a subgroup of PTSD patients had difficulties in learning the CS–US contingency, thereby providing preliminary evidence of reduced discrimination learning.

Keywords: Posttraumatic stress disorder; Pavlovian differential fear conditioning; Skin conductance; Evaluative conditioning; US-expectancy bias; Contingency awareness

Introduction

Posttraumatic stress disorder (PTSD) is a pervasive psychiatric condition characterised, inter alia, by symptoms of persistent re-experiencing of the traumatic event (DSM-IV, American Psychiatric Association, 1994). Contemporary theories of PTSD concur in assuming that memory and learning processes like perceptual priming and fear conditioning underlie these re-experiencing symptoms (Michael et al., 2005; Pitman, 1989; Rothbaum & Davis, 2003). According to the fear conditioning approach, the traumatic event

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(unconditioned stimulus, US) triggers an unconditioned response (UR) which is characterised by strong arousal and intense fear. This UR becomes associated with cues, such as smells, voices, or sights (conditioned stimuli, CSs) which were present during the traumatic event. As a result of this pairing, these cues can trigger similar responses (conditioned responses, CRs) even in the absence of the US. Thus, re-experiencing symptoms can be understood as CRs, which remain persistent, even a long time after the trauma.

As such, the fear conditioning account cannot explain why these symptoms disappear in the aftermath of a traumatic event in most individuals, but persist in those who develop PTSD. Within the conditioning framework, three accounts have been put forward to answer this question: enhanced conditionability, reduced conditioned inhibition, and reduced discrimination learning.

The concept of *enhanced conditionability* refers to a hypothetical trait predisposing to the development of stronger CRs to a traumatic event, and/or to a reduced ability to extinguish these CRs (Orr et al., 2000). Experimentally, conditionability is typically assessed in a differential fear conditioning paradigm in which one CS is paired with the US during the acquisition phase (the CS+) and another CS is not (the CS−). During a subsequent extinction phase, both CSs are presented without the US. The difference between reactions to the CS+ and the CS− (also called differential or discriminative learning) during acquisition and/or extinction indexes conditionability. An individual high on conditionability is thought to be at risk for the development of PTSD subsequent to trauma exposure since particularly strong CRs develop and persist.

However, conditionability, as assessed by differential fear conditioning, actually confounds two processes: excitatory conditioning and inhibitory conditioning (assessed by responses to the CS+ and the CS−, respectively) which each may be informative in its own right (Lissek et al., 2005). In fact, it has been suggested that the inability to inhibit fear in the presence of safety cues (i.e. the CS−) causes excessive fear responses in PTSD patients (Davis, Falls, & Gewirtz, 2000; Grillon & Morgan, 1999; Rothbaum & Davis, 2003). Thus, it is proposed that PTSD patients should differ from controls mainly because of poor inhibitory processes, i.e. they should show heightened responding to the CS−. In the following we will refer to this account as *conditioned inhibition account*.[1]

In line with the enhanced conditionability account, Orr and coworkers found stronger differential responding during acquisition and extinction in PTSD in comparison to trauma exposed controls (Orr et al., 2000). Similarly, Peri and colleagues found enhanced differential responses during the extinction phase in PTSD patients in contrast to healthy and traumatised controls (Peri, Ben-Shakhar, Orr, & Shalev, 2000). However, Peri and colleagues also found heightened reactions in PTSD with respect to the CS− during acquisition and extinction. Although these two studies interpreted their findings to support enhanced conditionability in PTSD, they are also partially consistent with the conditioned inhibition account.

In addition to these two accounts, a third conceptualisation of *reduced discrimination learning* has received support in the clinical conditioning literature. Investigating eye blink conditioning[2] in combat veterans with and without PTSD and control participants, Ayers, White, and Powell (2003) found differential responding to the CSs only in control participants. They attributed this to impaired discriminative learning in combat veterans, possibly due to general memory deficits. Grillon and Morgan (1999) measured the fear potentiated startle reactions in a differential fear conditioning paradigm in two separate sessions separated by one week. In contrast to trauma exposed controls, PTSD patients failed to acquire differential conditioning during the first session. Only during the second conditioning session did they show differential startle responses similar to controls. In opposition to the enhanced conditionability account, the reduced discriminative learning account conceptualises this type of learning as a highly functional process by which participants learn to distinguish between threat and safety cues (Grillon, 2002a).

At this stage, research has yielded partial support for the enhanced conditionability account of PTSD. While some studies were supportive of this view (Orr et al., 2000; Peri et al., 2000) at least two others found

[1]Although it is more of a suggestion rather than a formal theory, the conditioned inhibition account is an interesting complementary approach to the heightened conditionability account (S. Lissek, personal communication). In addition, a differential fear conditioning paradigm cannot be expected to produce equally strong inhibitory effects as obtained in studies using A + /AB− procedures (Rescorla, 1969). In the latter, one stimulus is followed by the US (A+ trials), except when accompanied by a second stimulus B (AB− trials, e.g. Chan & Lovibond, 1996).

[2]While eye blink conditioning is also a form of Pavlovian discriminative learning it might differ on a number of aspects from the present design, i.e. it is less dependent on contingency awareness (Clark & Squire, 1998).

equal (Orr et al., 2006; Vythilingam et al., 2006) or impaired discrimination learning (Ayers et al., 2003; Grillon & Morgan, 1999) in PTSD patients. This heterogeneity of findings clearly warrants further investigation. In addition, the conditioned inhibition account, predicting enhanced responding in PTSD patients to the CS−, has not been explicitly addressed in previous fear conditioning studies of PTSD.

Previous conditioning studies in PTSD have focused primarily on implicit indicators of conditioning, such as skin conductance responses (SCRs) or the fear potentiated startle. However, this focus on implicit measurements unnecessarily confines the window of scientific inquiry and disregards the domains of verbal-cognitive and behavioural responses. Contemporary conditioning models highlight the role of cognitive processes (Davey, 1997; Lovibond, 2006). According to the expectancy model of fear conditioning (Lovibond, 2006; Reiss, 1991) individuals continuously and explicitly adjust their expectancies regarding the likelihood of the US when the CS+ and the CS− are repeatedly presented. A growing number of studies have successfully included continuous "online" measures of US-expectancy (e.g., Lovibond, Davis, & O'Flaherty, 2000; Neumann, Lipp, & Cory, 2007). Another important process involved in human conditioning relates to conditioned changes in affective valence appraisals of the CSs, a process called evaluative conditioning (for review, see De Houwer, Thomas, & Baeyens, 2001). According to this theory, affective valence is transferred from the US to the CS as a result of paired presentations during conditioning.

In this study we examined differential fear conditioning in PTSD patients using a more comprehensive set of dependent measure which assessed autonomic (SCRs), affective (valence ratings), and cognitive (US-expectancy ratings) responses. As a subsidiary aim we explored if conditioned responding also generalises to the behavioural domain using a behavioural forced choice test (Michael, Blechert, & Vriends, unpublished data). In order to maximise the conclusiveness of between-group comparisons, we included two healthy control groups, one group with trauma exposure (TE group) and one group with no-trauma exposure (nTE group). Statistical analyses assessed differential conditioning (differences in responses to both CSs) but also included single CS analyses to evaluate the accounts of heightened conditionability, conditioned inhibition, and reduced discrimination learning. The enhanced conditionability account would predict *larger* differential reactions in the PTSD group compared to the other two groups while the account of reduced discrimination learning would predict *smaller* differential responses. The latter account would also predict impaired explicit learning of the CS–US contingency in the PTSD group. The conditioned inhibition account would predict enhanced responding to the CS− in the PTSD group.

Method

Participants

We recruited three study groups: the PTSD group consisted of 36 adults qualifying for a primary diagnosis of current chronic PTSD according to the DSM-IV (American Psychiatric Association, 1994), the TE group consisted of individuals who had been exposed to a traumatic event without developing PTSD ($n = 21$), and the nTE group consisted of healthy individuals, who had never been exposed a traumatic event ($n = 34$). Participants were included into the TE group if they fulfilled the A-criterion of the DSM-IV diagnosis of PTSD but reported no current mental disorder. However, past disorders other than an anxiety disorders were accepted. Healthy participants did not report any current or past mental disorder. Further exclusion criteria for all participants were: lifetime history of psychosis, bipolar disorder, mental disability, drug/alcohol abuse or dependence, a medical history of conditions that might affect the physiological systems under examination (e.g. angina, myocardial infarction), use of medication with strong autonomic effects. Trauma types in the PTSD and the TE group were accidents (traffic and work-related; $n = 11$ in the PTSD group, $n = 7$ in the TE group), physical or sexual violence (11, 6), natural disasters (2, 2), war-related traumata (e.g. imprisonment, torture; 3, 0), life threatening illness (2, 1) and other traumata (7, 5). Trauma type were equally distributed across both groups, $\chi^2(5) = 4.48$, $p = 0.48$. There were equal percentages of female participants in the PTSD, the TE group and the nTE group (72.2%, 47.6%, 73.5%, $\chi^2(2) = 4.67$, $p = 0.097$).

The diagnosis was assessed using the F-DIPS ("Diagnostic Interview for Mental Disorders—Research Revision"; Margraf, Schneider, Soeder, Neumer, & Becker, 1996), a well-validated structured interview for

diagnosing DSM-IV disorders. The F-DIPS is a modified German version of the Anxiety Disorder Interview Schedule for DSM-IV—Lifetime version (ADIS-IV-L; DiNardo, Brown, & Barlow, 1994), which is widely used for the assessment of anxiety disorders and shows excellent psychometric properties (Brown, DiNardo, & Lehman, 2001). The F-DIPS further contains diagnostic modules for mood and substance-related disorders, as well as a screening for schizophrenia and other psychotic disorders.

Participants were either referred to us by collaborating mental health institutions or responded to advertisements in the local press. If patients were taking psychoactive drugs, inclusion required that they had been on a constant regimen for at least two weeks before testing, in order to avoid possible side effects or withdrawal symptoms due to dose alternations. Six patients reported occasional use and two patients regular use of benzodiazepines. Patients who used benzodiazepines occasionally were asked not to do so on study days. Nine patients took selective serotonin or noradrenaline reuptake inhibitors and two patients took tricyclic antidepressants. Participants were told to abstain from alcohol for 24 h before testing. The following secondary disorders were diagnosed in the PTSD group: major depression ($n = 11$), panic disorder with or without agoraphobia ($n = 9$), social phobia ($n = 4$), pain disorder ($n = 4$), generalised anxiety disorder ($n = 3$), and dysthymic disorder ($n = 2$).

Anxiety and depressive symptoms were assessed with the German versions of the State-Trait Anxiety Inventory (STAI, Laux, Glanzmann, Schaffner, & Spielberger, 1981) and the Beck Depression Inventory (BDI, Hautzinger, Bailer, Worall, & Keller, 1994). In the PTSD and the TE group, PTSD symptoms and dissociative symptoms were assessed with the Posttraumatic Diagnostic Scale (PDS, Ehlers, Steil, Winter, & Foa, 1996) and the Dissociative Experiences Scale (DES, Freyberger et al., 1998).

The study was approved by the local ethics committee and participants gave written consent before participating. Each participant received a payment of 90 CHF (approximately 70 USD).

Procedure

Following the diagnostic assessment, eligible participants took part in an implicit evaluative conditioning task, the results of which will be presented elsewhere (Michael, Vriends, Blechert, & Margraf, in preparation). One week thereafter, the current experiment was conducted. On arrival, electrodes were attached and participants watched a short film instructing them about the stepwise adjustment of the electrical stimulation. The film depicted a participant and the experimenter adjusting the level of electric current. Together with the experimenter, participants then adjusted the intensity of the stimulation to a level which they described as being "unpleasant and demanding some effort to tolerate". For 5 min thereafter participants sat quietly and given time to adapt to the laboratory environment and the electrodes. The experimenter then introduced the rating procedure, consisting of a rating dial (a linear slider on which a vertical visual analogue scale was affixed with the lower label "−100" and the upper label "+100" and a corresponding scale on the computer screen, indicating the respective verbal anchors). After these instructions participants gave a retrospective rating of the US aversiveness (anchor labels: "−100 = very slightly unpleasant" to "+100 = extremely unpleasant/painful").

The conditioning task commenced with written instructions that two pictures would be shown on the screen in random order and that only one of the pictures would occasionally be accompanied by the electrical stimulation. The experimenter verbally repeated these instructions and assured that participants understood them. Two pictures of coloured symmetrical pictures (Rorschach inkblots) served as CS+ and CS− (counterbalanced across participants). The conditioning task consisted of a habituation, an acquisition, and an extinction phase. In each phase, the CS+ and CS− were each presented six times. CS duration was 8 s and the intertrial interval (ITI) was 18 +/−2 s (determined at random). During acquisition, each CS+ was immediately followed by a 500 ms US.

During the conditioning procedure, ratings of US-expectancy and CS valence were repeatedly obtained. Six valence ratings were obtained for each CS in the middle and the end of each conditioning phase (every third CS was rated, yielding a total of 12 ratings). During these rating trials a visual analogue scale appeared on the screen 4 s after CS offset prompting participants to give retrospective valence ratings ("How did you like the last picture?" anchors "pleasant", −100; to "unpleasant", 100). Completion of the rating commenced the ITI. US-expectancy ratings were obtained on the first and last presentation of each CS during

extinction.[3] A baseline US-expectancy rating was obtained at the end of habituation. On these trials a visual analogue scale appeared on the screen immediately after CS offset (''Do you believe that this stimulus will be paired with an electric stimulation?'' anchors ''No'', −100; ''Yes'', 100). Previous research established that these ratings do not influence the psychophysiological outcome variables in a differential aversive conditioning paradigm (Blechert, Michael, Williams, Purkis, & Wilhelm, in press; Lipp, Oughton, & LeLievre, 2003). Following extinction, contingency awareness was assessed by a screen presenting the CS+, the CS−, and a control stimulus and asking which of the three pictures had previously been paired with the US. This recognition measure of contingency awareness is considered more sensitive than post-experimental questionnaires which require recall of contingency knowledge (Lovibond & Shanks, 2002). The experimenter then entered the room with a bowl containing 20 chocolate bars (50% depicting the CS− picture and 50% depicting the CS+ picture) and asked them to pick one chocolate bar ''as a small token for your participation''. Selection of the chocolate bar depicting CS− was interpreted as avoidance of the CS+. Finally, the experimenter removed all electrodes, debriefed participants verbally and gave patients information regarding treatment opportunities in the surrounding area.

Apparatus and physiological recordings

The experiment took place in a temperature-controlled, fully lit, and sound-attenuated room, connected to an adjoining control room in which the experimental apparatus was located. Participants were seated in a comfortable armchair placed 1 m in front of a 19-in monitor with a refresh rate of 100 Hz. An electrical stimulator (constant current unit, Biopac Systems, Inc., Goleta, CA, USA) was used to deliver the US via Ag/AgCl electrodes on the right lower arm. Stimulus delivery and physiological data acquisition were controlled by two PCs running E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and Acqknowlege software (Biopac Systems, Inc., Goleta, CA, USA). Physiological channels and rating dial information were recorded at a rate of 1000 Hz in continuous mode using the Biopac MP150 system. Skin conductance was obtained using 11-mm inner diameter Ag/AgCl electrodes filled with isotonic electrode paste (Fowles et al., 1981). Electrodes were placed on the middle phalanx of the index and middle finger of the left hand. Two channels were obtained as control measures: body movement was assessed using an accelerometer attached to the left shoulder, since movement may trigger spurious SCRs; respiration pattern was recorded using two pneumagraphic bellows, one at the rib cage and one at the abdomen.

Data reduction and statistical analysis

An SCR was calculated by subtracting the average skin conductance level (SCL) for the 2 s immediately before CS onset (baseline) from the maximum SCL recorded during the first 4 s (first interval response, FIR)[4] of the 8 s CS presentation time. The UR to the electric stimulation was computed by subtracting the average SCL during the last 2 s of the CS presentation from the maximum SCL recorded during the 8 s following the US. SCRs below 0.025 μS were scored as zero and square root transformation was applied to normalise the distribution of SCRs. Artefact correction for the SCRs consisted of a careful visual inspection of respiration and accelerometer channels and the manual exclusion of SCRs which appeared to be influenced by movement,

[3]Due to the presentation of the US it was not possible to obtain US-expectancy ratings during the acquisition phase. Therefore US-expectancies for the CS+ and the CS− were collected during the first extinction trial for each CS. Since participants did not know until after the rating that the US would be withheld their ratings functionally reflected acquisition expectancies. On trials containing both US-expectancy and valence ratings, US-expectancy was obtained immediately after CS offset, followed by the valence rating (after 4 s) and the ITI.

[4]Analyses of second interval responses (time window 4–8 s of the 8 s CS presentation time) were also done, but did not reveal significant between group effects. For ease of reading, all FIR-SCR effects are referred to a SCR effects. The FIR has higher internal consistency and temporal stability compared to the SIR and might therefore better suited for the examination of a potential trait variable like conditionability (Fredrikson, Annas, Georgiades, Hursti, & Tersman, 1993). Following Orr et al. (2000), we also measured and analysed heart rate responses and musculus corrugator electromyographic responses (corrugator-EMG). Heart rate level was higher in the PTSD group compared to both control groups, but contrary to Orr et al., heart rate responses to the CSs and the US were generally lower in PTSD. However, no meaningful conditioning effects (i.e. CS-type-effects) were observed for heart rate or corrugator-EMG, hence these data are not reported. Results are available from the authors on request.

deep breaths, coughs or sighs (5.0%/5.4% of CS − /CS+ trials were excluded). Due to technical failure, no SCR data were available for four cases. SCR responses to each CS− type (CS+, CS−) on three consecutive presentations were averaged, resulting in two blocks per conditioning phase (e.g. first and second half of habituation). Two indices of electrodermal responding during habituation were computed to be used as covariates in the subsequent analyses: mean SCL during habituation (SCL_{hab}) was estimated by averaging the 2-s baselines preceding the 12 habituation CS presentations. Likewise, SCRs to the first CS+ and the first CS− during habituation were averaged as an index of orienting responses (OR, see also Orr et al., 2000).

Statistical analyses: Separate analyses were conducted for each outcome measure and each conditioning phase. Repeated measures ANOVAs were calculated for the between subjects factor Group (three levels for the omnibus test and two levels for the group contrasts) and the within subject factors CS-type (CS+, CS−) and Time (first vs. second half of phases) using the SPSS 12 (SPSS Inc., Chicago, IL) General Linear Modelling procedure. Analyses of US-expectancy ratings did not involve the Time factor because only one measurement was taken per conditioning phase. To specifically assess the differences between the three groups, significant between group effects in the omnibus analyses were followed by three planned comparisons (PTSD vs. nTE group, PTSD vs. TE group, and TE group vs. nTE group) using Time × CS-type × Group ANOVAs. The accounts of enhanced and reduced discriminative learning would predict interaction effects of the factors Group with CS−type and/or Time in these comparisons. When the Group effect reached significance these pairwise ANOVAs were broken down per stimulus to evaluate the conditioned inhibition account which would predict heightened responding of the PTSD group to the CS− in comparison with the control groups. This was done by calculating Group × Time ANOVAs separately for the CS+ and the CS−. If the sphericity assumption was not met, a Greenhouse–Geisser correction was computed, with nominal degrees of freedom values being reported. Due to missing values, degrees of freedom varied across analyses. An alpha level of 0.05 determined statistical significance.

Results

Demographics, psychometrics and control variables

Table 1 shows demographic, psychometric, and control measures for the three groups. Groups did not differ in age and years of education. In accordance with the diagnostic categorisation, the PTSD group scored higher than the control groups on the PDS, DES, STAI, and the BDI. PTSD patients tended to select a lower US

Table 1
Demographic, psychometric and control measures for the study groups

	PTSD group, *M* (SD)	TE group, *M* (SD)	nTE group, *M* (SD)	Inferential statistics
Age (years)	41.0 (11.1)	42.5 (13.)	42.2 (8.58)	$F(2, 89) = 0.15$, $p = 0.86$
Education (years)	10.6 (2.18)	10.10 (1.71)	11.1 (2.06)	$F(2, 89) = 1.52$, $p = 0.23$
PDS	32.5 (10.1)[a]	8.90 (5.75)[b]	–	$t(1, 46) = 9.04$, $p < 0.01$
DES	18.3 (18.4)[a]	5.84 (5.34)[b]	–	$t(1, 35) = 2.10$, $p < 0.04$
STAI-State	52.5 (10.1)[a]	37.1 (10.8)[b]	36.5 (8.38)[b]	$F(2, 88) = 27.8$, $p < 0.001$
STAI-Trait	57.4 (9.33)[a]	37.1 (9.31)[b]	32.7 (8.81)[b]	$F(2, 89) = 69.4$, $p < 0.001$
BDI	26.5 (9.51)[a]	5.86 (4.99)[b]	4.53 (4.57)[b]	$F(2, 89) = 100$ $p < 0.001$
US level (mA)	2.26 (1.85)	3.09 (2.81)	3.74 (2.90)	$F(2, 89) = 3.04$, $p = 0.053$
US rating (−100 to 100)	22.2 (57.9)	22.9 (58.4)	29.8 (55.6)	$F(2, 89) = 0.17$, $p = 0.840$
SCL_{hab} (μS)	8.38 (2.73)[a]	9.93 (6.79)	7.13 (2.51)[b]	$F(2, 85) = 3.24$, $p = 0.044$
OR_{hab} (μS)	0.26 (0.22)	0.25 (0.22)	0.18 (0.21)	$F(2, 85) = 1.15$, $p = 0.320$
UR: SCR (μS)	1.04 (0.49)	0.99 (0.45)	0.80 (0.38)	$F(2, 85) = 2.64$, $p = 0.077$

Note: PTSD, posttraumatic stress disorder group; TE, trauma exposed group; nTE, non-trauma exposed group; PDS, Posttraumatic Diagnostic Scale; DES, Dissociative Experience Scale; STAI-State/Trait, Spielberger State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; US, unconditioned stimulus; UR, unconditioned response; SCL_{hab}, mean skin conductance level during habituation; OR_{hab}, orienting response; a, b, c, different superscripts indicate that groups differed from each other at $p < 0.05$ in post hoc tests.

level than both control groups, but subjective ratings of US intensity did not differ between groups. PTSD patients also showed higher SCL during habituation and a trend to higher URs compared to the nTE group.

Contingency awareness: The results of the recognition test of contingency awareness indicated that 19 out of the 91 participants were unable to correctly identify the CS+ after extinction (i.e. were unaware of stimulus contingencies). There were more unaware participants in the PTSD group compared to both the TE group ($n = 12$ vs. 2, $\chi^2(1) = 4.06$, $p = 0.044$) and (as a trend) the nTE group ($n = 5$, $\chi^2(1) = 3.30$, $p = 0.069$) while the TE and the nTE group did not differ from each other. Since contingency awareness is frequently correlated with differential conditioning (Lovibond & Shanks, 2002) unaware participants were excluded from the analyses of SCRs and ratings of valence and US-expectancy.

Conditioning procedure

Omnibus analyses (PTSD group vs. TE group vs. nTE group)

Fig. 1 displays means for all three study groups for the CS+ and the CS− during first and second halves of habituation, acquisition, and extinction. Omnibus ANOVAs *across all three groups* yielded significant between group effects for SCRs during acquisition, $F(2, 66) = 3.45$, $p = 0.038$, and extinction, $F(2, 66) = 4.07$, $p = 0.022$. Likewise, Group effects were significant for valence ratings during extinction, $F(2, 69) = 3.68$, $p = 0.030$, as well as for US-expectancy during extinction, $F(2, 69) = 3.64$, $p = 0.031$. Thus, follow-up analyses involving pairwise group comparisons (i.e. PTSD vs. TE, PTSD vs. nTE, and TE vs. nTE) were computed for all measures.

Table 2 lists the results of the ANOVAs of the three pairwise comparisons of the three groups. The columns of Table 2 display the effects of the factors Group (between group effects, df = 1), CS-type (CS-type effects indicate differential conditioning, i.e. higher responses to the CS+ than to the CS−), and Group × CS-type interactions. Significant effects of the factor Group were followed by separate ANOVAs for the CS+ and the CS−, (column "Post hoc" in Table 2). For the sake of brevity, significant effects of the factor Time are reported in the text only when it interacted with the group variable.

As can be seen from column "CS-type" of Table 2, differential conditioning effects were present in all groups and for all measures during acquisition and extinction. Thus, successful discrimination learning occurred in aware participants across all study groups.

Comparison of the PTSD group and the nTE group

SCR: No significant effects involving the factor Group were found during habituation. During acquisition, significant Group and CS-type effects emerged which were modulated by a Group × CS-type × Time interaction $F(1, 49) = 4.66$, $p = 0.036$ (not shown in Table 2). This interaction pointed to stronger differential reactions during the second half of acquisition in the PTSD group than in the nTE group. Post hoc ANOVAs for the CS+ and the CS− indicated heightened reactions both to the CS+ and the CS− in the PTSD group. During extinction, significant Group and CS-type effects were modulated by a Group × CS-type interaction which reflected higher SCRs to the CS+ in the PTSD group than in the nTE group. This was confirmed by the post hoc ANOVAs which yielded a significant Group effect for the CS+ but not for the CS−.

Valence ratings: During habituation, a significant Group effect was found. Post hoc ANOVAs for each CS did not yield significant group effects. No significant Group effects emerged during acquisition. During extinction, a significant Group effect was present. Post hoc analyses showed that this Group effect could be attributed primarily to more negative ratings for the CS+ in the PTSD group compared to the nTE group.

US-expectancy: No significant Group effects were found during habituation or acquisition. During extinction, the Group effect was significant, which was mainly due to higher US-expectancy ratings for the CS+ in the PTSD group compared to the nTE group.

Comparison of the PTSD group and the TE group

SCR: No between group main effects were significant during habituation, acquisition or extinction. During extinction, a significant Time × Group interaction emerged, $F(1, 38) = 6.13$, $p = 0.018$. This interaction pointed to higher SCRs in the PTSD group to both CSs during the second half of the extinction phase.

Valence ratings: No significant Group effects emerged during habituation, acquisition or extinction.

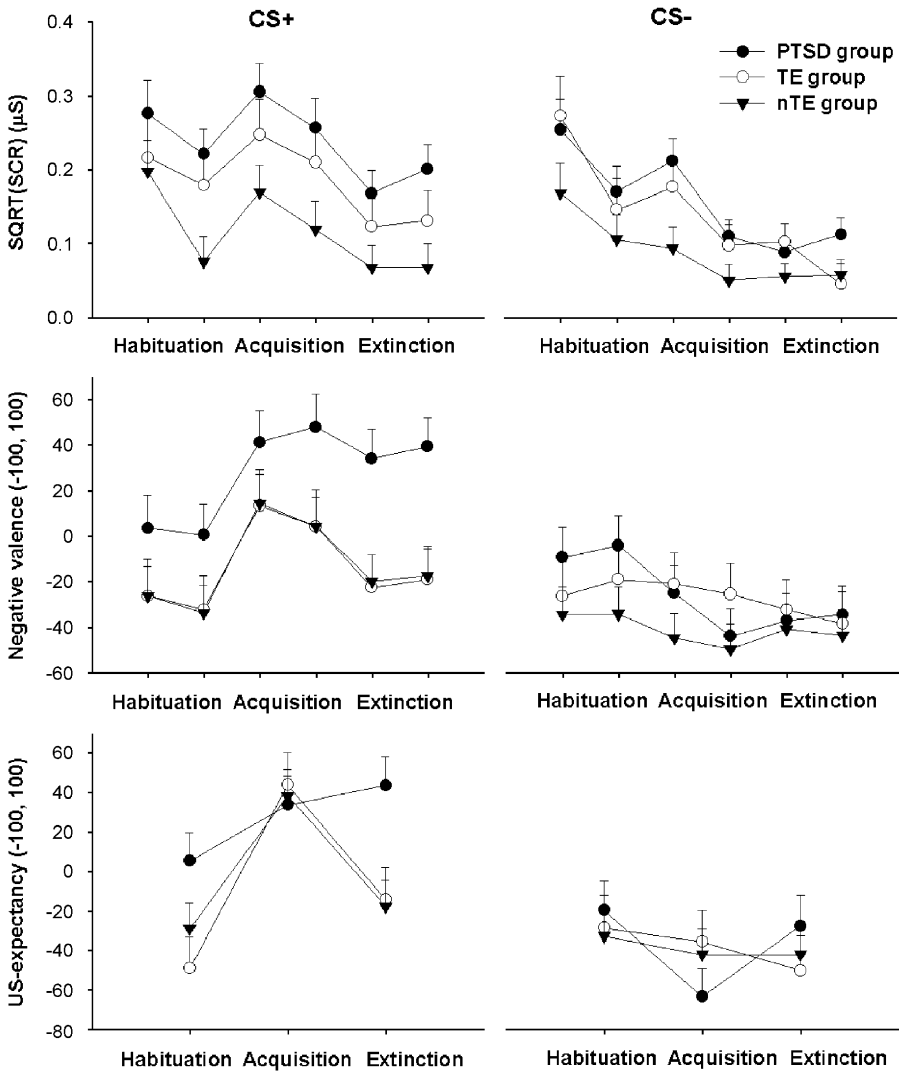

Fig. 1. Skin conductance responses (SCR), valence ratings, and US-expectancy ratings for the CS+ and the CS− during habituation, acquisition and extinction across study groups. *Note*: PTSD, posttraumatic stress disorder; TE, trauma exposed; nTE, non-trauma exposed; SCR, skin conductance reaction; US, unconditioned stimulus.

US-expectancy ratings: Interestingly, the Group factor was significant during habituation and extinction. During both phases this was mainly due to higher US-expectancy ratings for the CS+ in the PTSD group in contrast to the TE group (the CS-type × Group interaction was not significant during any phase).

Comparison of the nTE group and the TE group

No significant between group effects were found on SCR, valence or US-expectancy ratings.

Adjustment for pre-acquisition differences: Analysis of covariance (ANCOVA)

It has been shown that electrodermal responsivity during habituation is positively correlated with differential conditioning effects (Ohman & Bohlin, 1973a, 1973b; Orr et al., 2000). To examine if the slightly elevated electrodermal responsivity found in the PTSD group during habituation (OR, SCL_{hab}) explains the between group effects observed in the PTSD vs. nTE comparison, they were entered separately as covariates in two Group × CS-type × Time ANCOVAs for acquisition and extinction. The covariate SCL_{hab} was

Table 2
Selected ANOVA effects for group comparisons on SCRs, and ratings of stimulus valence and US-expectancy

	ANOVA				
	Group, *F*, *p*	CS-type, *F*, *p*	Group × CS-type, *F*, *p*	Post hoc[a]	
				CS−, *F*, *p*	CS+, *F*, *p*
PTSD vs. nTE					
SCR[b]					
Habituation	ns	ns	ns	–	–
Acquisition	8.14, 0.006	25.7, 0.000	ns	5.99, 0.018	7.30, 0.009
Extinction	7.93, 0.007	12.6, 0.001	8.39, 0.006	ns	10.6, 0.002
Valence[c]					
Habituation	4.42, 0.042	ns	ns	ns	ns
Acquisition	ns	48.4, 0.000	ns	–	–
Extinction	4.85, 0.032	31.8, 0.000	ns	ns	10.5, 0.002
US-expectancy[c]					
Habituation	ns	ns	ns	–	–
Acquisition	ns	43.0, 0.000	ns	–	–
Extinction	5.71, 0.021	13.8, 0.001	ns	ns	9.95, 0.003
PTSD vs. TE					
SCR[d]					
Habituation	ns	ns	ns	–	–
Acquisition	ns	22.6, 0.000	ns	–	–
Extinction	ns	11.5, 0.001	ns	–	–
Valence[e]					
Habituation	ns	ns		–	–
Acquisition	ns	22.2, 0.000	ns	–	–
Extinction	ns	18.6, 0.000	ns	–	–
US-expectancy[e]					
Habituation	5.32, 0.026	ns	ns	ns	6.12, 0.015
Acquisition	ns	28.8, 0.000	ns	–	–
Extinction	4.07, 0.050	15.6, 0.000	ns	ns	6.49, 0.015
nTE vs. TE					
SCR[f]					
Habituation	ns	ns	ns	–	–
Acquisition	ns	29.7, 0.000	ns	–	–
Extinction	ns	5.75, 0.021	ns	–	–
Valence[g]					
Habituation	ns	ns	ns	–	–
Acquisition	ns	18.8, 0.000	ns	–	–
Extinction	ns	6.04, 0.018	ns	–	–
US-expectancy[g]					
Habituation	ns	ns	ns	–	–
Acquisition	ns	30.3, 0.000	ns	–	–
Extinction	ns	4.92, 0.031	ns	–	–

Note: PTSD, posttraumatic stress disorder group; TE, trauma exposed group; nTE, non-trauma exposed group; SCR, skin conductance reaction.

[a]Post hoc tests were Group (df = 1) × Time (df = 1) ANOVAs.
[b]$F(1, 49)$.
[c]$F(1, 51)$.
[d]$F(1, 38)$.
[e]$F(1, 41)$.
[f]$F(1, 45)$.
[g]$F(1, 46)$.

significant, $F(1,48) = 5.343$, $p = 0.025$, but PTSD still showed significantly heightened responding during acquisition, $F(1,48) = 4.69$, $p = 0.036$. A similar pattern was observed for extinction, effects of SCL_{hab}: $F(1,48) = 3.25$, $p = 0.078$, Group effect: $F(1,48) = 4.32$, $p = 0.043$, CS-type × Group interaction: $F(1,48) = 5.46$, $p = 0.024$. The covariate OR was significant during acquisition, $F(1,48) = 12.6$, $p = 0.001$, but not during extinction, $F(1,48) = 2.54$, $p = 0.12$, Group effects remained significant in the ANCOVAs for acquisition, $F(1,48) = 7.29$, $p = 0.010$, and extinction, $F(1,48) = 6.85$, $p = 0.012$, CS-type × Group interaction: $F(1,48) = 7.45$, $p = 0.009$.

Similarly, significant group differences were present on valence ratings during habituation in the PTSD vs. the nTE group. Parallel to SCRs, the two habituation ratings were averaged separately for the CS+ and the CS− and entered as covariates into the analyses of acquisition and extinction of this group comparison. The Group effects during acquisition and extinction were not significant after adjusting for these covariates. However, the post hoc ANCOVA for the CS+ during extinction remained significant even after adjustment for its habituation valence ratings, $F(1,50) = 7.05$, $p = 0.011$.

Inclusion of unaware participants

A considerable number of participants failed to acquire contingency awareness in the present study with the largest proportion belonging to the PTSD group. We excluded these participants, based on the understanding of differential electrodermal conditioning to be dependent on contingency awareness (Lovibond & Shanks, 2002). To determine whether this exclusion affected the pattern of results, analyses were redone including all participants, regardless of contingency awareness. All between group effects remained intact, or were even more pronounced when all participants were included. The same was true for the group contrasts and the post hoc analyses.[5] Thus, the exclusion of unaware participants did not affect the pattern of results.

Behavioural forced choice test

Fig. 2 displays the number of participants in each group choosing the chocolate bar depicting the CS− vs. the CS+. While the nTE group selected almost equal numbers of both types of chocolate bars, the PTSD and the TE group chose the CS+ less frequently than could be expected by chance, $\chi^2(1) = 5.12$, $p = 0.024$, and $\chi^2 = 3.86$, $p = 0.050$, respectively. Hence, the PTSD and the TE group, but not the nTE group were inclined to show behavioural avoidance with respect to the CS+.

Discussion

Test of theoretical accounts: Consistent with the enhanced conditionability account, we found stronger electrodermal differential conditioning during late acquisition and slowed extinction of responding to the CS+ in the PTSD group compared to the nTE group. This corresponds well with findings of Orr et al. (2000) and Peri et al. (2000) who both found delayed extinction of SCRs to the CS+. In the PTSD vs. nTE group comparison, however, group differences were less convincing: only during the second half of extinction did the PTSD group respond stronger to both CSs.

We found only partial support for the conditioned inhibition account postulating an inability of PTSD patients to inhibit fear in the presence of safety cues: heightened SCRs to the CS− were present during acquisition but not during extinction. During acquisition group effects for single CS analyses (in contrast to Group × CS-type effects) might also be due to sensitisation, a non-associative effect of increased responding to any stimulus when the experimental context becomes more aversive after the introduction of the US (Ohman, Fredrikson, Hugdahl, & Rimmo, 1976). Assuming that PTSD patients suffer from an enhanced sensitivity to aversive and threatening contexts (Grillon, 2002b; Grillon & Morgan, 1999; Morgan, Grillon, Southwick,

[5] In addition to the effects reported in Table 2, the following between group effects reached significance after inclusion of unaware participants: higher SCRs in the PTSD compared to the nTE group during habituation, $F(1,65) = 4.42$, $p = 0.042$, attributable mainly to the CS+, $F(1,65) = 5.31$, $p = 0.024$ as well as more negative valence ratings in the PTSD vs. the TE group during extinction, $F(1,55) = 5.86$, $p = 0.019$, attributable mainly to the CS+, $F(1,55) = 7.64$, $p = 0.008$.

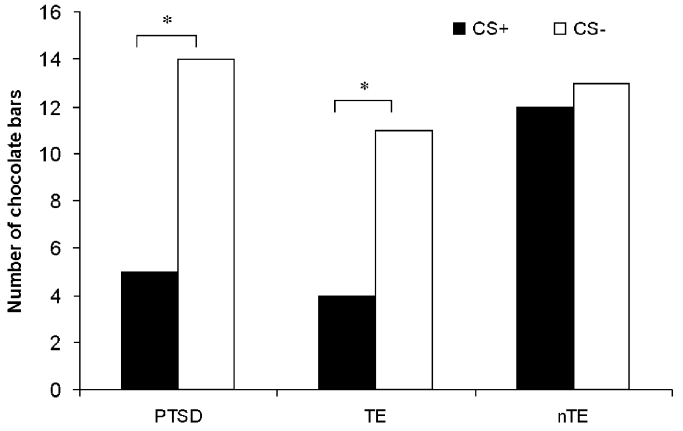

Fig. 2. Number of participants choosing the chocolate bar depicting the CS− vs. the CS+ across groups. *Note*: (*), significantly different from equal distribution by χ^2-test, $\alpha < 0.05$; PTSD, posttraumatic stress disorder; TE, trauma exposed; nTE, non-trauma exposed.

Davis, & Charney, 1995), their elevated reactions to the CS− could reflect enhanced sensitisation rather than a deficit in inhibitory conditioning.

Partial support was found for the account of reduced discriminative learning assuming a deficit in PTSD patients to discriminate between threat and safety cues: although reliable differential conditioning of SCRs and ratings (i.e. CS-type effects) was observed in all study groups, a sizable proportion of the PTSD group did not verbally report the CS–US contingency. It is conceivable that this subgroup of patients expressed a deficit in verbal discrimination learning.

The percentage of unaware participants in the present study (20.2% overall, 33.3% among PTSD participants) appears high in comparison to other clinical fear conditioning studies (7.4% unaware participants overall, none among PTSD in Orr et al., 2000; 8.3% overall, 8.3% among PTSD in Grillon & Morgan, 1999; 25.9% overall in Orr et al., 2006). Differences in the instructions might have played a role here. For example, Orr and co-workers instructed their participants about the nature of the different phases beforehand (habituation, acquisition, extinction were termed phase I, II, and III) and announced these phases during conditioning. By contrast, neither did our participants know that there were different conditioning phases nor were these phases announced. This might have slowed or prevented contingency learning in some of our participants. But why was lack of contingency awareness so prevalent in the PTSD group? The PTSD patients, reporting more anxious, depressive and dissociative symptoms, could have had particular difficulties attending to the contingency information. Alternatively, they could have recognised the contingency but failed to retain it through the course of extinction. In fact, mounting evidence suggests general memory impairments in PTSD (see Buckley, Blanchard, & Neill, 2000 for review). Until replication of this finding, complemented by standardised assessments of memory, intelligence and attention these explanations must remain speculative.

Expectancy bias: To our knowledge, this is the first study explicitly assessing US-expectancy ratings during aversive conditioning in PTSD, thereby providing an interesting link to cognitive research relating to information processing biases in this disorder (see Coles & Heimberg, 2002 for review). We found an overestimation of the probability of the US following CS+ presentations during extinction in PTSD, in contrast to both control groups. Thus, US-expectancy ratings were more sensitive to group differences than SCRs which only differentiated between the PTSD and the nTE group. Interestingly, US-expectancy ratings were already heightened during habituation in the PTSD group in contrast to the TE group but no group differences were observed during acquisition. This suggests that PTSD patients displayed a US-expectancy bias only under conditions of ambiguity about the contingency (i.e. habituation and extinction) but not when the contingency information was obvious (i.e. at the end of acquisition)[6]. Alternatively, it has been proposed that covariation assessments are determined by both the individual's prior beliefs about the contingency and

[6]Absence of any group differences at the end of the acquisition phase could also be a result of ceiling/floor effects for the CS+/CS−: 43.2% of participants gave ratings between 95 and 100 for the CS+ and 50.0% gave ratings of less than −95 for the CS−.

the current situational information regarding the objective contingency between events (Alloy & Tabachnik, 1984). Accordingly, our PTSD patients could have expressed a general expectancy bias during habituation, which then interacted with conditioning in a confirming manner.

Evaluative conditioning and behavioural avoidance: PTSD patients rated the valence of both CSs more negatively throughout all conditioning phases and no differential effects (i.e. CS-type × Group interactions) were found. This could be the result of a general bias to rate stimuli negatively. However, negative valence of the CS+ was most pronounced during extinction in the PTSD group compared to the nTE group, an effect which remained significant even when group differences during habituation were statistically controlled. Thus, similar to their SCRs, PTSD patients demonstrated reduced extinction of negative valence, particularly for the CS+. This is consistent with Michael, Blechert, Vriends, Margraf, and Wilhelm (in press), who found delayed extinction of valence ratings of the CS+ in panic disorder compared to healthy controls. Our behavioural avoidance measure underscores these findings: the PTSD group which gave the most negative valence ratings for the CS+ showed higher behavioural avoidance of the CS+ compared to the nTE group. Yet, it is not clear why also the TE group showed this avoidance, since their valence ratings were very similar to those of the nTE group.

Clinical implications: Delayed extinction in PTSD patients was the most robust finding in our study (see also Orr et al., 2000; Peri et al., 2000; Pitman & Orr, 1986). Extinction of conditioned fear can be viewed as a laboratory analogue for exposure therapy (Bouton, Mineka, & Barlow, 2001; Davey, 1997; Rothbaum & Davis, 2003). The phenomenon of reduced extinction of differential fear reactions indicates that PTSD patients need more time and repetitions to extinguish fear reactions. This is consistent with studies showing that prolonged exposure therapy is effective in PTSD (e.g. Foa et al., 2005).

Not only did PTSD patients demonstrate delayed extinction of psychophysiological responding, they were also slower to extinguish conditioned negative valence in comparison to control participants. These persistent negative evaluations might be relevant for psychotherapy since they have been linked with reinstatement, a laboratory analogue for the return of fear after successful exposure therapy (Rachman, 1989). Reinstatement refers to the re-emergence of conditioned responding after extinction due to unpaired presentations of the US (e.g. Bouton, 1988). Preliminary experimental evidence indicates that the negative valence of the CS+ is correlated with the magnitude of reinstatement (Hermans et al., 2005).

Moreover, stimulus valence has been linked to avoidance behaviour. Subtle valence differences (preferences) are thought to guide behaviour especially in situations with low differential response costs (Baeyens, Eelen, & Crombez, 1995; De Houwer et al., 2001). Our behavioural forced choice test represented a situation with low differential response cost, and the results showed that conditioning affected the preferences of the PTSD and the TE group. To illustrate the potential clinical relevance of this point, imagine a PTSD patient who has to choose between two different ways to drive to work, with one of them passing by the street where the traumatic event happened. Exposure therapy (extinction) might have reduced this patient's fear reactions and negative expectancies with respect to this street. Yet, if subtle conditioned negative valence outlived exposure therapy it might facilitate the avoidance of this street; thereby possibly increasing the chance of relapse. These negative evaluations of CSs might be treated with reappraisal procedures or counter-conditioning (Baeyens, Eelen, Van den Bergh, & Crombez, 1989; Hermans, 2002; but see also de Jong, Vorage, & van den Hout, 2000).

Limitations: Several limitations have to be considered when interpreting the current findings. First, the usage of several psychoactive medications was reported by the PTSD patients in our study. While some of these agents might depress electrodermal reactions, other might increase them. However, the consistency of our results with findings in non-medicated samples (Orr et al., 2000) makes us confident of the robustness of our findings. More so, it appears unlikely that explicit measures of conditioning (e.g. valence, US-expectancy) were influenced by these medications.

Second, most of the significant group differences were found when comparing PTSD patients with the nTE group while the TE group was not well distinguished from PTSD patients. Thus, trauma exposure represents an alternative explanation for the differences between the PTSD and the nTE group. In addition, we did not include a measure of trauma severity. Future studies should strive to recruit a trauma exposed control group which is comparable in size and trauma severity to the PTSD group.

Third, a conceptual limitation of the present study is the use of a cross-sectional design to investigate etiological issues. Conditioning studies assume to measure a *trait-like* predisposition to respond stronger to

conditioning episodes. Hence, the responses to conditioning protocols obtained in PTSD patients *after* trauma exposure are assumed to reflect their trait-conditionability *before* trauma exposure. Support for this assumption comes from studies showing that conditionability demonstrates considerable heritability (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003), is highly stable over repeated testing (Fredrikson et al., 1993), and that conditioning is already altered in anxious children (Liberman, Lipp, Spence, & March, 2006). A first longitudinal study provided preliminary evidence that delayed extinction during fear conditioning before trauma exposure was predictive of PTSD symptoms after trauma exposure (Guthrie & Bryant, 2006). While these findings are generally supportive of the *trait-account* of conditionability, other conceptualisations are possible. Stressful experiences can enhance fear conditioning, possibly by sensitising subjects to subsequent learning (*state-account*). Unsignalled footshocks enhanced subsequent fear conditioning in rats (Rau, DeCola, & Fanselow, 2005). In humans, a social stressor was found to enhance subsequent differential fear conditioning in male participants (Jackson, Payne, Nadel, & Jacobs, 2006). Interestingly, our TE group evidenced an intermediate electrodermal responsivity, differing from both the PTSD and the nTE group on a descriptive level. One could speculate that trauma exposure sensitised these individuals to respond stronger to the conditioning paradigm. More longitudinal research is clearly needed to evaluate state and trait accounts of fear conditioning in PTSD.

Conclusions: Delayed extinction of conditioned responding to the CS+, as postulated by the enhanced conditionability account, was the most consistent finding of the present study. It seems to mirror the course of PTSD, in which the reactions to cues associated with traumatic experiences do not decay over time. Particularly the persistent re-experiencing symptoms seen in PTSD could be explained by this mechanism. The overestimation of aversive outcomes indexed by US-expectancy ratings and the inability to distinguish between safe and unsafe situations could be related to the sense of current threat and hypervigilance frequently found in PTSD (Ehlers & Clark, 2000). Likewise, persistent negative evaluations and behavioural avoidance of the CSs could threaten the maintenance of social functioning and behavioural flexibility established by successful exposure therapy.

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