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Does pre-exposure inhibit fear context conditioning? A Virtual Reality Study

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Abstract Several studies in animals and humans have indicated that familiarity toward cues reduces cue-conditioning effects. The influence of familiarity of a context on context conditioning has been confirmed in animal studies only. Thus, this study examined contextual fear conditioning in humans depending on pre-exposure to the to-be-conditioned context. To accomplish this, a virtual reality paradigm presented via a head mounted display was realized. During conditioning, participants were exposed to one of two office rooms (contexts), of which one became associated with aversive electric stimuli (UCS). 1 day before conditioning, participants were randomly exposed to either the later to-be-conditioned context ($n = 20$) or to an unrelated virtual environment ($n = 20$). Startle reflex, skin conductance response, heart rate, and ratings of valence, arousal, and anxiety were measured to assess context conditioning. Successful context conditioning was demonstrated for both ratings and physiological indicators. Pre-exposure did not prevent successful context conditioning. We conclude that in humans, contextual fear conditioning is not easily modified by pre-exposure to the context.

Keywords Fear conditioning · Context conditioning · Virtual reality · Anxiety · Psychophysiology

Introduction

Fear conditioning is believed to be important for the development and preservation of anxiety disorders (e.g., Mowrer 1953, Mineka and Zinbarg 2006). Based on classical conditioning (Pavlov 1927), a previously neutral stimulus is associated with an aversive unconditioned stimulus (UCS, e.g., painful stimulus), the neutral stimulus acquires the emotional properties of the UCS, and thus becomes a conditioned stimulus (CS) eliciting fear. In addition to classical conditioning, Mowrer's two factor theory (1947) proposed operant conditioning to be essential for the maintenance of anxiety, as avoidance behavior prevents the extinction of fear conditioning. These early conditioning models have been modified and extended over the years, and the conditioning theories of pathological anxiety are not without criticism (Rachman, 1991), but conditioning processes continue to play a central role in most theories explaining anxiety disorders. Evolutionarily prepared aversive associations explain the high prevalence of some specific phobias (e.g. spider phobia) (Öhman et al. 2001) and enhanced conditionability (Orr et al. 2000) may hint a reason why certain people are more prone to anxiety disorders than others. A meta-analysis by Lissek et al. (2005) confirmed that anxiety disorder patients are characterized by enhanced fear conditioning as reflected in speed of acquisition and strength of conditioned responses. Furthermore, animal models of fear conditioning have greatly advanced our understanding of neuronal processes underlying fear and anxiety (see e.g., Davis et al. 1997).

Classical conditioning provides a good model for the development of anxiety disorders characterized by fear triggered by specific stimuli (i.e., phobias), but it fails to explain more sustained anxiety responses (e.g., in post-traumatic stress disorder, see Grillon et al. 1998). Animal models suggest that these conditions are caused by context conditioning instead of cued fear conditioning, making the organism respond with sustained anxiety in the conditioned context (Davis 1998). This context conditioning occurs in

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particular whenever a clear cue to predict the UCS is absent (e.g., Baas et al. 2008; Iberico et al. 2008; Mol et al. 2007) and differs from cue conditioning. Animal studies have revealed that amygdala lesions impair any form of fear conditioning, whereas lesions of the bed nuclei of the stria terminalis or of the hippocampus impair only contextual fear conditioning (Phillips and LeDoux 1992; Sullivan et al. 2004; see also Wiltgen et al. 2006). For human participants, Marschner et al. (2008) observed a relatively faster decay of amygdala activity in cue conditioning, whereas context conditioning was characterized by a relatively faster decay of hippocampus activity. Similar findings were reported by Alvarez et al. (2008).

A well-known effect in cue conditioning is that familiarity with the cue prior to conditioning reduces the speed and extent of cue conditioning (Lubow and Moore 1959), an effect called latent inhibition (LI). LI has been demonstrated both in animal models (Batson and Best 1979; Zhang et al. 2004) and in humans (Lubow 1989; de la Casa 2005) and is thought to prevent the development of phobias (e.g., painless dental visits before a painful dental procedure should prevent the development of a dentist phobia). LI in cue conditioning is assumed to be caused by selective attention away from the CS (Lubow 1989) or by learning an association between the to-be-conditioned stimulus and the absence of a threatening UCS, which interferes with formation (Weiner 1990) or retrieval (Bouton 1993) of the new CS–UCS association. Furthermore, LI of cue conditioning has been found to be context specific in rats (e.g., Hall and Honey 1989; Gal et al. 2005) as well as in humans (e.g., Nelson and Sanjuan 2006).

The modulation of context conditioning by pre-exposure has been investigated in several animal studies. Richardson and Elsayed (1998) observed that only rats that were not pre-exposed to a to-be-conditioned context 24 h before conditioning showed a potentiated startle reflex after context conditioning to this context. Kiernan and Westbrook (1993) further clarified that in rats, only long lasting pre-exposure attenuates later context conditioned responses, whereas short pre-exposure can even enhance them. In addition, LI in context conditioning seems to depend on the time interval between pre-exposure and conditioning with LI being observed only for relatively long or short but not intermediate intervals (Westbrook et al. 1994). LI can also be abolished by exposing rats to a completely new context just after conditioning (Killcross et al. 1998), but only after massed and not distributed pre-exposure (Perez-Villalba et al. 2008).

Pre-exposure effects on context conditioning in humans have not been studied yet, although this may be important for understanding the development of sustained anxiety and related disorders. The problem is that in human research, a complex context is hard to manipulate without introducing many confounding and hardly controllable variables. In addition, exploring a context usually involves moving around, making reliable psychophysiological measurements of fear difficult. With the emergence of computers powerful enough to handle large three-dimensional data sets in real time, virtual reality (VR) simulations have proven to be a valid research tool for investigating context conditioning. Baas et al. (2004, 2008) used a virtual environment consisting of two rooms and a street on a computer screen, which participants explored on a prerecorded path. By pairing electric shocks with either one room or a cue inside the rooms, they successfully showed both cue and context conditioning in VR using the startle reflex and skin conductance response as dependent measures. Grillon et al. (2006) used a similar design with similar results, using different virtual environments and giving participants the opportunity to move around freely inside the virtual environment during a short familiarization phase.

The goal of our study was first to replicate context conditioning effects using virtual environments developed in our lab and second, to examine the influence of familiarity (pre-exposure to the environment) on context conditioning in humans. As in the study by Baas et al. (2008), we applied mildly painful electric stimuli in one of two virtual office rooms connected by a corridor; however, we did not present cues during conditioning. A greater level of immersion in the virtual environment was achieved by presenting the VR with a head mounted display (HMD), whereas Bass and colleagues used a computer screen. This change allowed participants to freely look around inside the simulation at all times by head movements while they were guided through the environment along a prerecorded path. We hypothesized that context conditioning would cause enhanced conditioned responses, that is, enhanced startle in the conditioned context (CTX+) compared to the safe context (CTX−), and familiarity with the to-be-conditioned context (pre-exposure) to reduce effects of context conditioning.

Method

Participants

Fifty-one participants were recruited through a classified advertisement on a local internet portal. Exclusion criteria were assessed by a self-report questionnaire and consisted of past or present psychological illnesses, use of psychoactive drugs, present alcohol or drug abuse, hearing impairment, and uncorrected sight problems. 11 participants had to be excluded from the analysis due to technical problems ($n = 8$) or simulator sickness ($n = 3$). The remaining 40 participants (10 male, 30 female) had a mean age of 24.5 years (SD = 4.8, range 19–39 years) and most were students (80%). They were randomly assigned to either a

Table 1 Demographic description and questionnaire scores of the participants

	Pre-exposure ($n = 20$)	No pre-exposure ($n = 20$)
Gender		
Female (*n*)	14	16
Age (years)	23.85 (4.60)	25.20 (4.96)
BFNE	35.10 (7.77)	38.45 (8.08)
STAI trait	45.10 (3.64)	45.15 (4.03)
STAI state		
Before	44.45 (3.13)	45.75 (3.26)
After	44.60 (2.39)	44.75 (2.84)
PANAS		
Positive affect before	26.63 (4.27)	28.55 (5.92)
Positive affect after	23.25 (6.58)	26.05 (7.47)
Negative affect before	12.47 (3.06)	14.75 (6.11)
Negative affect after	12.90 (4.66)	14.65 (7.02)

PANAS and STAI State scores are presented for measurement "before" and "after" the context conditioning VR-experiment. Given are numbers or means with SD in parenthesis

BFNE Brief Fear of Negative Evaluation Questionnaire, *STAI* State-Trait Anxiety Inventory, *PANAS* Positive And Negative Affect Schedule

pre-exposure ($n = 20$) or a no pre-exposure ($n = 20$) group. There was no significant difference between the groups in age, sex, education, or occupational status (all $P > 0.30$). Neither the fear of negative evaluation assessed by the Brief Fear of Negative Evaluation Questionnaire (BFNE) nor the state anxiety assessed by the state part of the State Trait Anxiety Inventory (STAI X2) revealed any significant differences between the groups, $t_{(38)} = 1.34$; $P = 0.19$; $t_{(38)} = 0.04$; $P = 0.97$, respectively (Table 1).

Participants were paid 16€ for their participation. All participants gave their written informed consent. The investigation was approved by the Ethics Committee of the University of Würzburg.

Stimuli and apparatus

VR environment

The VR environment was created with the Source Engine (Valve Corporation, Bellevue, WA, USA). The context-conditioning environment used for the pre-exposure and the conditioning consisted of two office rooms linked by a corridor (see Fig. 1). The office rooms had the same square footage but were apparently different in layout (wider than long vs. longer than wide), floor color (red vs. green), window view (city vs. village), and arrangement of the furniture. The corridor had a gray floor color and a door on each end leading to the office rooms. For the control group, instead of pre-exposure to the conditioning environment a conditioning-unrelated environment was presented. This environment was taken from an unpublished study on fear of heights consisting of a street view lined with houses (see Fig. 1). The VR environment was presented to the participants using a Z800 3D Visor head mounted display (800 × 600 pixels resolution, eMagin, Bellevue, Washington, USA). The head movements of the participants were assessed using the Patriot electromagnetic tracking device (Polhemus Corporation, Colchester, Vermont, USA). The participants were led through the environment on predefined paths with a constant speed while being able to look around freely by moving their heads. Instructions and questions during the VR simulation were presented visually over the HMD and simultaneously presented orally over headphones. The simulation was controlled by the virtual reality experimental control software CyberSession that was built in house.

Electric stimuli

The unconditioned stimulus was a mildly painful electric stimulus generated by a current stimulator (Digitimer DG2A, Digitimer Ltd, Hertfordshire, England) and delivered through an electrode at the dominant inner forearm. Electric stimuli were triggered automatically by CyberSession for 200 ms with a frequency of 50 Hz. They were sent by the simulator with a voltage of 230 V and duration of 2 ms. The intensity of the current could vary between 0 and 9.9 mA and was individually adjusted for each participant according to their pain threshold. In four alternately ascending and descending series of electric stimuli, the current was increased and decreased in steps of 0.5 mA, respectively, and participants rated the intensity of pain on a scale from 0 ("no sensation at all") to 10 ("very strong pain"), whereas 4 meant "a just noticeable pain." The first ascending series started at 0 mA and was stopped when the electric stimulus was rated 4 or more. The descending series started 0.5 mA higher than the stopping point of the preceding ascending series and stopped when the electric stimulus was rated below 4. The next ascending series started 0.5 mA below this stopping point. After this procedure, the individual current used as the US was determined by taking the lowest current of each series that was rated at least 4, calculating the mean and adding 0.25 mA. In cases in which this final US was rated below 4, the intensity was increased in steps of 0.25 mA until it was rated 4 or higher. In this sample, the electric stimuli had a mean current of 2.6 mA (SD = 1.6) and participants still rated its intensity with a mean of 4.1 (SD = 1.6) at the end of the experiment.

Recording of physiological data

All subjective and physiological measurements taken have been successfully used to asses conditioned responses, the

Fig. 1 Sample pictures of the VR environments. From *left* to *right*: first office room, second office room, corridor, and street view

startle reflex, the skin conductance response, heart rate, and subjective ratings of anxiety, valence, and arousal (Grillon and Baas 2003; Andreatta et al. 2010; Hermann et al. 2002). The startle reflex was measured by recording electromyographic activity (EMG) from the *M. orbicularis* oculi with two light 13/7 mm miniature Ag/AgCl electrodes placed below the left eye, one fixed centrally and the other one about 1 cm closer to the outer corner of the eye. The acoustic startle stimuli was a 103 dB(A) burst of white noise presented for 50 ms binaurally via headphones. The skin conductance was measured with two 13/7 mm miniature Ag/AgCl miniature electrodes fixed 10 mm apart on the ball of the thumb of the non-dominant hand. Heart rate was measured by recording an electrocardiogram with two adhesive Ag/AgCl electrodes, one fixed to the center of the breast right under the neck, the other one to the left of the middle of the stomach on the third rib. In addition, one 13/7 mm miniature electrode was fixed to the processus mastoideus behind the left ear as a reference electrode, and one was attached to the middle of the forehead right under the hairline as a ground electrode. Impedances were kept below 10 kΩ. All physiological data were amplified by a digital amplifier (V-Amp 16, Brain Products Inc., Munich, Germany) and recorded on a computer using Vision Recorder (Version 1.10, Brain Products Inc., Munich, Germany).

Psychometric measures

Participants were required to complete several questionnaires. Social anxiety was assessed using the BFNE (Brief Fear of Negative Evaluation Questionnaire, Leary 1983, German version, Vormbrock and Neuser 1983). State and trait anxiety was measured with the State-Trait Anxiety Inventory (STAI, Spielberger et al. 1970; German version, Laux et al. 1981), and positive and negative affect with the Positive And Negative Affect Schedule (PANAS, Watson and Clark 1988; German version, Krohne et al. 1996).

At several points during the experiment, participants had to orally rate the rooms while a picture of the room and the appropriate rating scale were shown on the head mounted display (HMD). Ratings of valence ("very negative" to "very positive"), arousal ("not arousing at all" to "very arousing"), anxiety ("no anxiety" to "extreme anxiety"), and contingency ("not likely at all" to "very likely") were collected, each on scales from 0 to 100. During and after acquisition, participants were additionally asked to rate whether the electric stimuli were predictable (possible answers being "yes," "no," and "I don't know") and to report ideas about at which points the stimuli occurred (open answer with the opportunity to answer "I don't know"). At the end of the experiment, there was an additional question asking participants to rate the probability of receiving an electric stimulus in each room using a scale from 0 (never) to 100 (always).

Procedure

Every participant took part in two sessions including experiences in virtual reality on two consecutive days. The first session included the familiarity manipulation, and the second session included the context conditioning (two acquisition phases) and the extinction test.

During all virtual reality experiences, the participants were guided along predefined and prerecorded paths. The paths started in the corridor in front of a door. After 14 s, the first office room was entered and the participants were led through the room once, which took about 85 s. Then the room was left, the corridor was entered again, and was crossed in about 35 s, after which the second office room was entered, and they were led through in about 85 s. Then the second office room was left and the corridor was entered again where the path ended after another 7 s. The doors opened and closed automatically 6 s before and after being passed, respectively. Two prerecorded paths existed, differing by which room was entered first. Startle tone or UCS were applied at the earliest 20 s after entering a room or 10 s after entering the corridor, and the interval between these events varied from 10 to 40 s. While in one room, no more than five events (startle tones and UCS) were presented. The movements created for the context conditioning were also used for the neutral virtual environment, resulting in exactly the same movements for both the experimental and control groups in both sessions. There were two combinations of movements and two rooms that could be paired with the UCS, so four different sequences

for the context conditioning simulation existed. Sequences, distribution of startle tones, UCS, and office rooms were balanced across participants.

At the first session, after giving informed written consent, participants filled out questionnaires for the assessment of sociodemographic data and exclusion criteria. ECG, SCR, startle electrodes, and simulator electrodes were adjusted to minimize differences in the general context between the first and the second setting. However, no recordings were taken and participants were explicitly told that the electric current stimulator was turned off and that no electric stimuli would be given. The HMD was adjusted and then participants were led six times either through the neutral street view environment (no pre-exposure group) or the context-conditioning environment (pre-exposure group). No startle tones occurred.

At the beginning of the second session, the participants filled out several questionnaires (BFNE, STAI-X1, STAI-X2, and PANAS). Then the electrodes and the HMD were affixed, and the pain threshold was assessed to determine the intensity of the electric stimuli. In order to get accustomed to the volume of the startle tone, participants were exposed to three startle probes before the start of the experiment. Then participants were informed that the experiment would consist of four phases, and the VR simulation began. After each phase (habituation, acquisition 1, acquisition 2, extinction), subjective ratings were given (see above). Before the habituation phase started, participants were told that no electric stimuli were to be expected during this phase. In the habituation, participants visited each office room once. Startle tones occurred three times in each room and twice in the corridor. After the habituation phase, they were instructed that from now on, electric stimuli would occur and could be predicted if the experiment was being followed attentively. From then on, only the start and the end of a phase were announced, and the instructions for the ratings after each phase were given. Then the participants completed the first and second acquisition phases. In both acquisition phases, participants were led through the context-conditioning environment three times, resulting in visiting each office room three times during each acquisition phase. During each visit to an office room, two to three startle tones were presented and one to two startle tones in the corridor when moving from one room to the other. In addition, the UCS was administered one to three times in one of the two office rooms, thus making the UCS paired room the CTX+. In the other office room, the UCS was never applied, thus making this room the CTX−. The corridor served as the inter-trial interval (ITI). Overall, during the acquisition phases, there were 15 startle tones in each room, 9 in the corridor, and 12 aversive electric stimuli in the CTX+. In the extinction phase, participants were again led through the same environment three times, thus visiting each office room three more times. As in the habituation phase, startle tones occurred three times in each room and twice in the corridor, but no more UCS was applied. After the end of the VR simulations, the participants filled out the STAI-X1 and PANAS again.

The duration of the familiarity manipulation (pre-exposure) at the first session was about 25 min, and the duration of the habituation, the context conditioning, and the extinction test in the second session was about 50 min.

Data analysis

Physiological variables were processed offline with the Vision Analyzer (Version 1.05, Brain Products Inc., Munich, Germany). Statistical tests were computed by SPSS (Version 16, SPSS Inc, Chicago, IL, USA).

Startle reflex

First, differences between outer and inner EMG electrodes were computed. Then, a 500 Hz high cutoff filter, a 30 Hz low cutoff filter, and a 50 Hz notch filter were administered, the data were rectified, and a moving average (50 ms) was calculated. For each startle tone, a baseline correction was conducted using the mean value of the 100 ms before each tone as the baseline. After that, peaks were marked automatically and manually controlled and corrected if necessary. Invalid segments containing artifacts were marked and excluded from further analysis. Finally, *T* values for the startle amplitudes were calculated and the mean T-values for each context (CTX+/CTX−/ITI) during each phase were used for analysis.

Skin conductance

The average skin conductance for the CTX+, the CTX−, and the ITI in each phase was calculated. For segments in which the UCS was applied, the data from onset to 10 s after the UCS were excluded before calculation of the average. The data were exported to SPSS and logarithmized (base 10).

Heart rate

Difference values between the heart rate electrodes were computed, R-spikes were automatically counted, and the averages for the CTX+, the CTX− and the ITI for each phase were calculated.

A 2 (familiarity) × 3 (context) × 4 (phase) repeated-measures ANOVA with familiarity as a between-subjects factor and context and phase as within-subject factors was conducted for startle reflex, skin conductance, and heart rate.

Questionnaires

Scales of the questionnaires were compared using t tests for independent samples. For the STAI-X1 and PANAS, which were administered twice, a 2 (familiarity) × 2 (time) repeated-measures ANOVA with familiarity as a between-subjects factor and time (before habituation and after extinction at the second session) as a within-subject factor was used for analysis.

Ratings

For the ratings of valence, arousal, and anxiety, a mixed ANOVA with the between-subjects factors familiarity (no pre-exposure, pre-exposure) and the within-subject factors context (CXT+, CXT−, ITI) and phase (habituation, acquisition 1, acquisition 2, extinction) was conducted.

Alpha was set at 0.05. Effect sizes are reported as partial η_P^2 scores. For all ANOVAs, when Mauchley's test for sphericity was significant, Greenhouse-Geisser corrections of the *P* values were applied. Significant interactions were followed by Bonferroni-corrected pairwise comparisons.

Results

Results for startle reflex, SCL, and ratings for group, phase, and context are depicted in Table 2.

Table 2 Means and standard deviations of startle, SCL, and ratings for group, phase, and context

	Pre-exposure						No pre-exposure					
	CTX+		CTX−		ITI		CTX+		CTX−		ITI	
	M	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD
Startle												
Habituation	55.9	6.5	55.9	5.4	54.0	9.2	53.1	6.0	54.6	4.2	58.0	9.5
Acquisition 1	57.1	5.7	56.2	6.3	51.5	4.6	55.1	5.0	53.9	4.2	51.3	4.4
Acquisition 2	50.0	3.8	47.1	2.4	47.9	5.3	50.2	3.9	48.8	2.7	46.5	3.4
Extinction	47.1	2.4	44.9	2.6	42.2	2.8	47.1	3.3	46.4	2.9	44.3	3.7
SCL												
Habituation	0.52	0.23	0.52	0.23	0.53	0.23	0.54	0.26	0.56	0.24	0.55	0.24
Acquisition 1	0.52	0.24	0.50	0.24	0.51	0.24	0.51	0.27	0.51	0.26	0.50	0.28
Acquisition 2	0.48	0.25	0.46	0.24	0.47	0.23	0.49	0.26	0.46	0.27	0.47	0.26
Extinction	0.44	0.22	0.42	0.22	0.41	0.23	0.46	0.26	0.45	0.26	0.45	0.27
Heart rate												
Habituation	77.8	12.2	75.8	9.9	77.1	9.3	76.7	8.8	75.0	9.9	76.8	8.8
Acquisition 1	77.2	9.3	76.9	9.9	77.5	9.5	76.8	8.5	75.6	9.4	76.6	9.1
Acquisition 2	77.2	10.1	77.7	9.5	77.8	9.3	75.3	8.1	74.7	8.6	75.7	8.9
Extinction	77.9	10.7	77.0	8.6	77.8	9.4	75.5	7.9	74.6	9.8	76.1	7.6
Valence												
Habituation	66.2	20.0	58.5	18.9	–	–	66.9	16.3	65.3	19.8	–	–
Acquisition 1	53.6	21.8	58.9	20.8	–	–	52.7	22.1	64.4	19.8	–	–
Acquisition 2	49.1	17.8	63.4	18.4	–	–	50.5	23.6	64.1	23.7	–	–
Extinction	60.1	13.8	61.1	18.8	–	–	57.3	20.5	60.7	24.2	–	–
Arousal												
Habituation	16.8	22.4	26.9	30.0	–	–	19.6	19.4	18.3	21.8	–	–
Acquisition 1	27.6	23.3	24.9	23.6	–	–	33.3	28.2	16.7	15.7	–	–
Acquisition 2	22.8	24.4	15.5	20.3	–	–	30.4	27.3	12.0	15.5	–	–
Extinction	19.3	23.8	19.5	23.6	–	–	20.0	21.4	11.6	10.8	–	–
Anxiety												
Habituation	9.4	19.2	14.3	23.2	–	–	9.2	18.9	8.5	14.9	–	–
Acquisition 1	15.5	23.0	13.3	21.8	–	–	18.6	23.8	9.7	13.1	–	–
Acquisition 2	12.5	22.2	7.7	17.7	–	–	20.7	25.4	7.6	10.0	–	–
Extinction	10.0	20.1	8.6	18.1	–	–	14.7	20.7	7.6	11.4	–	–

Startle in *T* values, SCL in log10, heart rate in beats per minute (bpm), ratings in raw values (0–100)

Startle reflex

The ANOVA returned significant main effects of phase ($F_{(3,114)} = 81.46$, $P < 0.001$, $\eta_P^2 = 0.68$) and context ($F_{(2,76)} = 9.23$, $P < 0.001$, $\eta_P^2 = 0.20$) and a significant interaction of Context × Phase ($F_{(6,228)} = 3.91$, $P < 0.01$, $\eta_P^2 = 0.09$). The main effect of familiarity was not significant ($F_{(1,38)} = 0.02$, $P = 0.90$, $\eta_P^2 < 0.001$), as were the two-way interactions Familiarity × Context ($F_{(2,76)} = 1.81$, $P = 0.17$, $\eta_P^2 = 0.05$) and Familiarity × Phase ($F_{(3,114)} = 1.16$, $P = 0.33$, $\eta_P^2 = 0.03$). Contrary to the hypothesis, the three-way interaction Familiarity × Context × Phase also failed to reach significance ($F_{(6,228)} = 1.86$, $P = 0.12$, $\eta_P^2 = 0.05$). The overall startle reflex amplitude decreased from acquisition 1 to acquisition 2 to extinction (habituation/acquisition 1: $P = 0.22$, acquisition 1/acquisition 2: $P < 0.001$, acquisition 2/extinction: $P < 0.001$). Pairwise comparisons between contexts showed no difference in startle reflex for the habituation phase (CTX+/CTX−: $P = 1.0$, CTX+/ITI: $P = 0.81$, CTX−/ITI: $P = 1.0$). During the first acquisition phase, the startle reflex in both office rooms (CTX+, CTX−) was higher than in the corridor (ITI, $P < 0.01$), but there was no difference between the office rooms ($P = 1.0$). During the second acquisition, the startle reflex in the CTX+ was higher than in the CTX− and the ITI ($P < 0.02$), but did not differ between CTX− and ITI ($P = 1.0$). For the extinction phase, the same differences as in the first acquisition were found (CTX+/CTX−: $P = 0.13$, CTX+/ITI: $P < 0.001$, CTX−/ITI: $P < 0.01$) (see Fig. 2).

Skin conductance

The ANOVA returned significant effects of phase ($F_{(3,114)} = 13.53$, $P < 0.001$, $\eta_P^2 = 0.26$), context ($F_{(2,76)} = 5.39$, $P < 0.01$, $\eta_P^2 = 0.12$), and Context × Phase ($F_{(6,228)} = 3.22$, $P < 0.01$, $\eta_P^2 = 0.08$). The effect of familiarity ($F_{(1,38)} = 0.03$, $P = 0.86$, $\eta_P^2 < 0.01$), the two-way interactions Familiarity × Context ($F_{(2,76)} = 1.25$, $P = 0.29$, $\eta_P^2 = 0.03$), Familiarity × Phase ($F_{(3,114)} = 0.53$, $P = 0.67$, $\eta_P^2 = 0.26$), and the three-way interaction Familiarity × Context × Phase ($F_{(6,228)} = 0.79$, $P = 0.58$, $\eta_P^2 = 0.02$) failed to reach significance. Skin conductance decreased over time (habituation/acquisition 1: $P = 0.01$, acquisition 1/acquisition 2: $P < 0.01$, acquisition 1/extinction: $P = 0.03$). In the habituation phase, there was no difference in skin conductance between contexts (CTX+/CTX−: $P = 0.84$, CTX+/ITI: $P = 0.23$, CTX−/ITI: $P = 1.0$). In the first acquisition phase, skin conductance in the CTX+ was higher than in the CTX− by trend ($P = 0.07$), but neither the CTX+ nor CTX− differed from the ITI ($P > 0.39$). In the second acquisition phase, the SCL in the CTX+ was higher than both in the CTX− and the ITI ($P < 0.01$), and in the CTX− marginally lower than during the ITI ($P = 0.055$). In the extinctions phase, the SCL in the CTX+ was higher than in the CTX− ($P = 0.05$); both were not significantly different from the ITI ($P > 0.30$) (see Fig. 3).

Heart rate

The ANOVA showed no effect of phase ($F_{(3,111)} = 0.23$, $P = 0.78$, $\eta_P^2 < 0.01$), context ($F_{(2,74)} = 1.66$, $P = 0.20$, $\eta_P^2 = 0.04$), or familiarity ($F_{(1,37)} = 0.25$, $P = 0.62$, $\eta_P^2 < 0.01$), and no significant interaction of Familiarity × Context ($F_{(2,74)} = 0.16$, $P = 0.86$, $\eta_P^2 < 0.01$), Familiarity × Phase ($F_{(3,111)} = 19.81$, $P = 0.21$, $\eta_P^2 = 0.04$), or Familiarity × Context × Phase ($F_{(6,222)} = 0.48$, $P = 0.70$, $\eta_P^2 = 0.01$).

Valence rating

For valence ratings, the ANOVA revealed a main effect of phase ($F_{(3,114)} = 5.25$, $P < 0.01$, $\eta_P^2 = 0.12$), but no effect

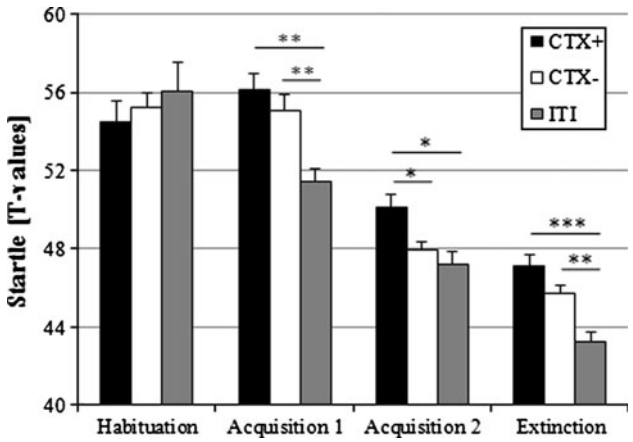

Fig. 2 Mean and standard errors of the startle amplitudes

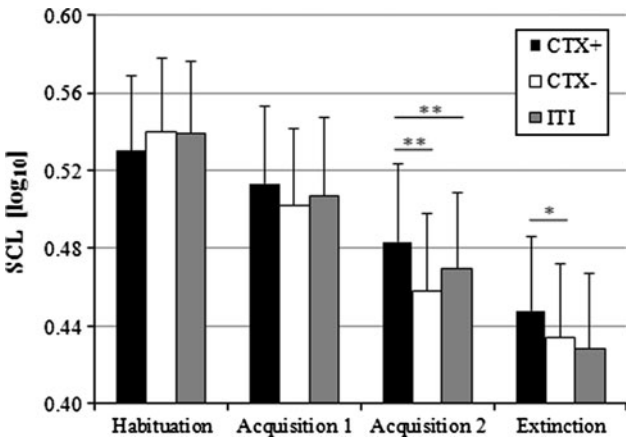

Fig. 3 Mean and standard errors of the skin conductance level

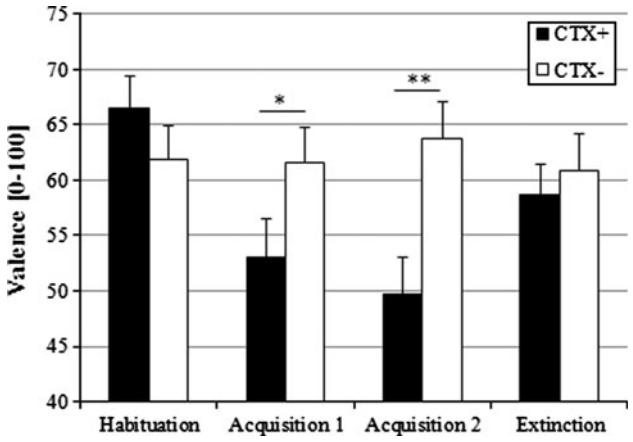

Fig. 4 Mean and standard errors of the valence ratings

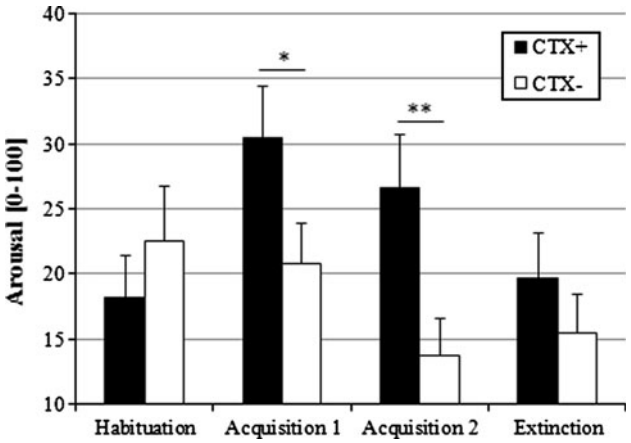

Fig. 5 Mean and standard errors of the arousal ratings

of context ($F_{(1,38)} = 1.77$, $P = 0.19$, $\eta_P^2 = 0.05$) or familiarity ($F_{(1,38)} = 0.12$, $P = 0.74$, $\eta_P^2 < 0.01$). As expected, the interaction of Context × Phase was significant ($F_{(3,114)} = 12.69$, $P < 0.001$, $\eta_P^2 = 0.25$). However, there was no interaction of Familiarity × Context ($F_{(1,38)} = 0.22$, $P = 0.64$, $\eta_P^2 < 0.01$), Familiarity × Phase ($F_{(3,114)} = 0.59$, $P = 0.62$, $\eta_P^2 = 0.02$), or Familiarity × Context × Phase ($F_{(3,114)} = 0.55$, $P = 0.59$, $\eta_P^2 = 0.01$). Pairwise comparisons showed no difference between contexts after the habituation phase ($P = 0.21$), but a more negative rating for the CTX+ than the CTX− after the first ($P = 0.01$) and the second acquisition phase ($P < 0.01$). This difference vanished after the extinction phase ($P = 0.46$) (see Fig. 4).

Arousal rating

As for the valence rating, the main effect of phase ($F_{(3,114)} = 3.82$, $P = 0.02$, $\eta_P^2 = 0.09$) and the interaction of Context × Phase ($F_{(3,114)} = 11.48$, $P < 0.001$, $\eta_P^2 = 0.23$) reached significance. The effect of context ($F_{(1,38)} = 3.89$, $P = 0.06$, $\eta_P^2 = 0.09$), familiarity ($F_{(1,38)} = 0.07$, $P = 0.79$, $\eta_P^2 < 0.01$), and the interaction of Familiarity × Context ($F_{(1,38)} = 3.98$, $P = 0.53$, $\eta_P^2 = 0.10$), Familiarity × Phase ($F_{(3,114)} = 0.53$, $P = 0.66$, $\eta_P^2 = 0.01$), or Familiarity × Context × Phase ($F_{(3,114)} = 0.23$, $P = 0.83$, $\eta_P^2 < 0.01$) were not significant. Pairwise comparisons showed no difference in arousal ratings between contexts after the habituation phase ($P = 0.20$) and after the extinction phase ($P = 0.15$), but higher arousal in the CTX+ than in the CTX− after the first ($P = 0.02$) and the second acquisition phases ($P < 0.01$) (see Fig. 5).

Anxiety rating

For the anxiety ratings, there were no significant main effects of context ($F_{(1,38)} = 3.86$, $P = 0.06$, $\eta_P^2 = 0.09$), phase ($F_{(3,114)} = 2.09$, $P = 0.13$, $\eta_P^2 = 0.05$), or familiarity ($F_{(1,18)} = 0.02$, $P = 0.90$, $\eta_P^2 < 0.001$), or the interactions Familiarity × Context ($F_{(1,38)} = 2.42$, $P = 0.13$, $\eta_P^2 = 0.06$), Familiarity × Phase ($F_{(3,114)} = 1.31$, $P = 0.27$, $\eta_P^2 = 0.03$), or Familiarity × Context × Phase ($F_{(3,114)} = 0.10$, $P = 0.93$, $\eta_P^2 < 0.01$). But again, the interaction of Context × Phase was significant ($F_{(3,114)} = 5.93$, $P < 0.01$, $\eta_P^2 = 0.14$). Pairwise comparisons showed no differences between contexts after the habituation phase ($P = 0.27$) or the first acquisition phase ($P = 0.09$), but did show higher anxiety ratings for the CXT+ than the CTX− after the second acquisition phase ($P = 0.01$) and after the extinction phase ($P = 0.03$) (see Fig. 6).

Questionnaires

The 2 (familiarity) × 2 (time) ANOVA for state anxiety (STAI-X1) and the negative affect scale of the PANAS revealed no main effects of familiarity ($F_{(1,38)} = 1.04$, $P = 0.33$, $\eta_P^2 = 0.03$, $F_{(1,37)} = 1.59$, $P = 0.22$, $\eta_P^2 = 0.04$,

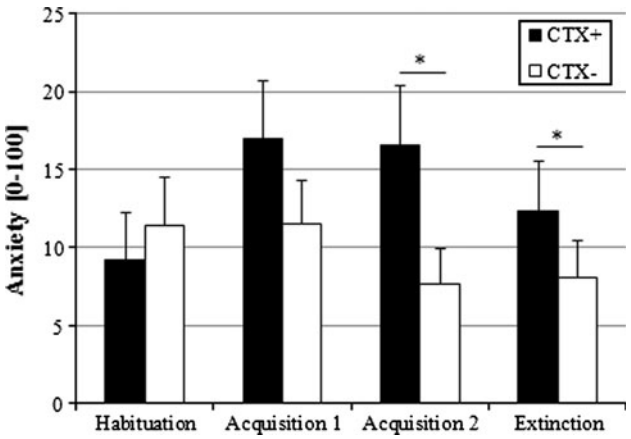

Fig. 6 Mean and standard errors of the anxiety ratings

respectively) or time ($F_{(1,38)} = 0.52$, $P = 0.48$, $\eta_P^2 = 0.01$, $F_{(1,37)} = 0.05$, $P = 0.83$, $\eta_P^2 < 0.01$, respectively) and no significant Familiarity × Time interaction ($F_{(1,38)} = 0.95$, $P = 0.34$, $\eta_P^2 = 0.02$, $F_{(1,37)} = 0.13$, $P = 0.72$, $\eta_P^2 < 0.01$, respectively). For the positive affect scale of the PANAS, there was a significant main effect of time ($F_{(1,37)} = 8.55$, $P < 0.01$, $\eta_P^2 = 0.19$), but no effect of familiarity ($F_{(1,37)} = 1.63$, $P = 0.21$, $\eta_P^2 = 0.04$) or Familiarity × Time ($F_{(1,37)} = 0.10$, $P = 0.75$, $\eta_P^2 < 0.01$). Positive affect decreased from the beginning to the end of the experimental session of the second day ($P < 0.01$). Overall, in the questionnaire data, there were no differences between groups.

Discussion

This study, in conformity with previous studies (Baas et al. 2004; Grillon et al. 2006; Baas et al. 2008), revealed that repeated application of an aversive stimulus in a VR context leads to context conditioning. On a subjective level, this was indicated by valence, arousal, and anxiety ratings. Before conditioning, there was no difference between contexts, but already after the first acquisition, the CTX+ was rated with a lower valence and a higher arousal than the CTX−. The differences remained stable after the second acquisition and vanished after the extinction phase. Interestingly, anxiety ratings were slower in conditioning and extinction because anxiety ratings differed significantly only after the second acquisition phase, but maintained this difference until after the extinction phase. This might be due to anxiety being a cognitively more complex construct than valence and arousal and thus being slower both to form by conditioning and to erase by extinction.

Physiological measures confirmed successful context conditioning. Startle responses changed from no difference between the contexts before conditioning to a distinct difference in the second acquisition phase where the startle response in the CTX+ was significantly larger than in the CTX− or ITI. In the extinction phase, this effect was diminished as startle responses were stronger in the CTX+ and the CTX− than in the ITI, and startle responses did not differ significantly between CTX+ and CTX−. However, the difference between CTX+ and CTX− might have reached significance with larger samples and increased power. We would like to mention that the interpretation of the results regarding the ITI should be taken cautiously. The time participants spent in the ITI (corridor) and other variables are not fully comparable to the CTX+ and CTX−. We decided to label the corridor as ITI because participants were in this "context" between being in the CTX+ and the CTX−. Beside methodical considerations the major difference between the ITI and the CTX− is that the ITI differs more from the CTX+ than the CTX− does as CTX+ and CTX− are both office rooms.

Successful context conditioning was also reflected in skin conductance where the same pattern as for the startle response could be seen. However, these findings, especially in the extinction phase, are less clear than in previous studies working with a context conditioning VR paradigm (Baas et al. 2004; Grillon et al. 2006; Baas et al. 2008). A reason might be that in our study, participants had a greater degree of freedom to move; in particular, to look around freely in the virtual environment to improve the ecological validity and realism. This leads to the effect that participants saw not exactly the same part of the context when experiencing the UCS. Thus, the UCS might be associated with different parts or objects in the CTX+ room that were seen at the time of UCS presentation. To differentiate such "cue conditioning" within the context conditioning paradigm is an interesting research question for further experiments. However, it is safe to assume that, if this happened, at least a generalization towards the whole context occurred as we saw context-conditioning effects in the startle reflex, which was measured at different positions in the room. An advantage of the present VR-paradigm is that participants could generate a spatial representation of the context, a feature that is unique for context conditioning. Another major difference to prior context conditioning studies (e.g., Baas et al. 2004) was a complete lack of cue conditioning in our experiment. The absence of relevant cues might have led to an active search for cues and thus made the participants less attentive to the context causing weaker UCS-context associations.

Importantly, we found no indication that a pre-exposure to the to-be-conditioned context prevents context conditioning in humans; thus, these findings are at variance with previous animal studies (e.g., Richardson and Elsayed 1998). Several factors might be responsible for this lack of effect. First, Escobar et al. (2005) reported that task-relevant stimulation between pre-exposure and context conditioning attenuated latent inhibition in cue conditioning in rats. Our participants had a full day of experience between pre-exposure and conditioning. However, Richardson and Elsayed (1998) observed latent inhibition in rats after roughly the same interval as realized in this study, and therefore we refute this explanation. Second, in most animal studies, pre-exposure was much longer compared to our experiment both absolutely and relatively to the context-conditioning phase. Therefore, we have to consider that our pre-exposure phase was too short to elicit latent inhibition. However, we have to assume that humans learn faster than rats, and previous studies suggest that in animal models, a too short pre-exposure does not neutralize but reverses the effect of latent inhibition (e.g. Kiernan and Westbrook 1993; Laurent and Westbrook 2011), which

was not the case in our study. Finally, it might be possible that latent inhibition as it occurs in cue conditioning does not exist in human context conditioning, or at least is not supported in the specific setting we realized.

If we consider selective attention to be the relevant factor, as Lubow (1989) does for cue conditioning, then it might be possible that this is irrelevant to context conditioning in humans since the context is too complex to be completely remembered due to pre-exposure and is always sufficiently "new." If we believe that latent inhibition in cue conditioning is caused by interference due to the learning of an association between the to-be-conditioned stimulus and the absence of a threatening UCS with learning (Weiner 1990) or retrieval (Bouton 1993) of the later CS-UCS association, we have to assume that the realized pre-exposure did not prevent the association between the context and the absence of a threatening UCS from developing. Such associations might develop during longer-lasting pre-exposures. Since the paradigm has now been established, future studies have to further elaborate the crucial factors that allow pre-exposure to affect context conditioning in humans. This will be important since in the long run, pre-exposure might be used to avoid the development of sustained anxiety and anxiety disorders.

Apart from the limitations noted above, the unbalanced gender distribution in our study may have biased our findings. Unfortunately, a comparison of gender was not possible because of too small sample sizes. Possible gender differences have to be investigated in further studies. Another limitation might be that the measurement of the startle reflex itself acts as UCS. However, the number of startle stimuli was balanced for CTX+ and CTX− and the method is well-established in conditioning paradigms. Thus, it is unlikely that the presentation of the startle stimuli has fundamentally changed the direction of our results. Furthermore, we chose to expose all groups to a VR-environment to exclude a novelty effect. Therefore we cannot make inferences how the familiarity with the VR simulation per se change context conditioning. It could be interesting to include VR-naive participants in a similar paradigm to investigate the effect of pre-exposure with VR itself. In sum, the VR paradigm used here proved to be a valid tool for realizing context conditioning. Interestingly, our study failed to show any influence of pre-exposure on context conditioning in humans in our specific experimental paradigm. This study might stimulate further research on this topic to evaluate under which specific circumstances pre-exposure might influence context conditioning.

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Conflict of interest Paul Pauli is stakeholder of a commercial company that sells virtual environment research systems, Andreas Mühlberger is stakeholder and executive officers of a commercial company that sells virtual environment research systems. No further potential competing financial interests exist.

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