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Latent Inhibition Speeds up but Weakens the Extinction of Conditioned Fear in Humans

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Abstract

Prevention is better than cure, but little is known about effective prevention of anxiety disorders. Individuals vulnerable for trauma-exposure would benefit from effective techniques to prevent the development of post-traumatic stress. One reason for the apparent standstill in this literature may be the exclusive focus on the development of fear, while pre-clinical anxiety treatment research has turned to impaired extinction of fear as the main mechanism underlying abnormal anxiety. Conditioning theories propose latent inhibition as a technique to prevent the development of fears, but the effects on fear extinction have not been examined in detail. I conducted two experiments to evaluate the effects of latent inhibition on extinction in a standard human fear conditioning paradigm, which serves as a model for post-traumatic stress disorder. Skin conductance reactivity and online expectancy ratings revealed slower rates of fear acquisition in the latent inhibition groups, as well as a speeded extinction effect early in extinction. However, extinction of expectancy ratings was less complete in the latent inhibition groups. The beneficial effects of the latent inhibition technique may be in promoting early success of self-exposures or exposure treatment and motivating the patient to continue on the exposure path.

Keywords: Fear conditioning; Extinction; Latent inhibition; Skin conductance; Prevention; Anxiety disorders

Introduction

Post-traumatic stress disorder (PTSD) is a highly debilitating disorder that affects up to 40% of trauma victims [1]. Stress symptoms in the aftermath of a traumatic event are not abnormal, but can develop into full-blown PTSD when they take a chronic course. Hence, there are two windows of opportunity to intervene and prevent the development of PTSD: (1) resilience building before the traumatic experience (primary prevention), and (2) early intervention during the aftermath of the traumatic event (up to a few weeks) with the aim of preventing the transition from acute stress effects into chronic stress (secondary prevention). Research overall is scarce, but secondary prevention has received more attention than primary prevention [2-4]. Results have been modest at best, and some interventions are actually counter-indicated based on the available evidence [5]. Primary prevention has received much less attention [4], although there are identifiable groups vulnerable for trauma exposure (soldiers, rescue workers etc.) that may benefit from effective resilience building programs. The goal is to prevent the development of stress symptoms all together or to increase beneficial coping in the aftermath of the traumatic event. Typically, interventions that are being designed and tested in either window are relatively isolated from each other. The main aim of this study was to provide a laboratory test of an approach that combines the two windows of opportunity.

The development of anxiety is modeled in the laboratory through the use of Pavlovian conditioning procedures [6, 7]. Prototypically, presentations of a neutral stimulus (e.g., a green light), are followed by an aversive event (e.g., electrical stimulation). As a result, the green light presentations will start eliciting anticpatory fear reactions (e.g., freezing in rats; increased autonomic activity in humans). The analogy with PTSD is quite straightforward. Environmental stimuli that were present at the time of the trauma henceforth trigger strong fear reactions and re-experiences of the traumatic event in the PTSD patient [8]. Arguably, these stimuli have acquired an association with the memory of the traumatic event. This can lead to persistent avoidance of these stimuli, which further prevents the collection of new (safety) information and leaves these fear-associations intact. Cognitive-behavioral treatments are designed to adjust these associations: Repeated exposures to the fear-arousing stimuli in the presence of a supportive therapist produce a gradual reduction of fear [9]. This is again in line with the experimental case: presenting the conditioned green light in the absence of the shock gradually reduces the fear reaction to the light (extinction).

Conditioning theories have stimulated much research on designing novel extinction treatment approaches [10], but the impact on prevention is lagging behind. The only technique that has come out of this research tradition is latent inhibition (LI): pre exposing the green light often delays the development of fear reactions during later light-shock pairings [11]. This phenomenon has been demonstrated across different species and preparations, but it has proven to be quite fragile. The effect is not always easy to replicate in human learning and conditioning tasks [12-14], and the effect in animals is dependent on specific experimental parameters (e.g., the background context should not change between pre-exposure and conditioning [15, 16]. This limits the applicability of the LI technique to highly stable contexts like a dentist office for dentist phobia in children [17, 18]. As a result, clinical (anxiety) interest in this once promising approach has waned over time.

The current study builds on the assumption that not the development of fears, but the inability to extinguish fears is central to many anxiety problems [9,10]. In the aftermath of a traumatic event, confrontations with trauma-related stimuli are no longer followed by the traumatic event and should thus provide a sufficient basis for extinction. An inability to extinguish will maintain the fear and stress

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complaints over longer time, possibly culminating into chronic PTSD. There is an enormous research effort to optimize extinction protocols, both behaviorally and pharmacologically [10]. The current study takes a different approach and hypothesizes that the preventative technique of LI might also facilitate later extinction of acquired fears. This hypothesis is based on the fact that LI and extinction share similar procedures (CS-alone presentations) and possibly similar learning mechanisms as well (the development of a CS-noUS memory, [15]). This LI memory interferes with fear conditioning, as conditioning is based on the development of an opposite memory (CS-US). I hypothesize that the LI memory might enhance fear extinction, as the same type of CS-noUS memory is normally developed in extinction. In particular, the first CS-noUS trial in extinction may retrieve the CS-noUS memory formed during LI pre-exposure. This counteracts the CS-US memory formed during conditioning and speeds up the reduction of fear during subsequent extinction trials. There is some evidence in the human conditioning literature of weaker conditioned responding during extinction in a pre-exposure group than in a non-pre-exposure group [19, 20]. However, it is unclear in these studies whether these differences merely reflect differences in conditioning, or actual differences in the course of extinction itself.

The current study was set up to test the hypothesis in a laboratory fear conditioning procedure with healthy human subjects. Online shock-expectancy ratings tracked the trial-by-trial development of extinction and the potential differences between the groups. Skin conductance reactivity was measured and analyzed on a trial-by-trial level, for the same reason. Experiment 1 evaluated the effects of LI on the extinction of a CS that had been continuously reinforced (100%). Experiment 2 evaluated these effects on a 75% reinforced CS. It is well known that partial reinforcement delays extinction [21]. Experiment 2 examined the potential of LI to speed up delayed extinction as well.

Methods

Experiment 1

Participants: Thirty-eight first grade psychology students participated in Experiment 1 in exchange for course credits. The students were randomly assigned to group pre-exposure or group Control (N=19, mean age=18.52 years, 14 females, and N=19, age=17.90 years, 19 females, respectively). All participants gave informed consent before the start of the experiment and were told that they could decline further participation at any moment in the experiment. The experiment was approved by the Ethical Committee of the Psychology Department, KU Leuven.

Materials

Stimuli: Four geometrical figures served as experimental stimuli (square, circle, star and triangle) and were presented on a PC screen, located on eye-level in front of the participant at approximately 500 mm. The stimulus sequence, the presentation of the stimuli and the intertrial intervals were controlled by software designed in our lab, which can be downloaded freely [4]. A 2 ms electrocutaneous stimulus delivered to the upper forearm of the left hand served as the unconditional stimulus (US). It was administered by a Digitimer Ds7A constant current stimulator (Hertfordshire, UK) via a pair of 11-mm Fukuda Standard Ag/AgCl electrodes. The electrodes were filled with K-Y Jelly. Participants were seated in a regular chair in a sound attenuated experimental room, adjacent to the experimenter's room. Verbal communication was possible through an intercom system.

Measures: Electrodermal activity was recorded using a skin conductance coupler manufactured by Coulbourne instruments (model V71-23, Allentown, PA). During skin conductance measurement, the coupler applied a constant voltage of 0.5 V across a pair of sintered-pellet silver chloride electrodes (8 mm), applied to the hypothenar palm of the left hand. The inter-electrode distance was 7 mm. The electrodes were filled with K-Y Jelly. The resulting conductance signal was submitted through an analog-to-digital converter (National Instruments) and digitized at 10 Hz from 2 s prior to onset of each experimental stimulus until 6 s after offset. Participants used their right hand to record their subjective expectancy of the electrocutaneous stimulus on an 11-point rating scale that appeared at the bottom of the screen during each presentation of an experimental stimulus. The scale was from 0 "certainly no shock", over 5 "uncertain", to 10 "certainly shock". The scale appeared 1 s after stimulus onset. Participants used the mouse to select the appropriate value on the scale and clicked the left button to confirm. Five-hundred ms after confirmation, the scale disappeared (in the absence of confirmation, the scale disappeared at stimulus offset).

Questionnaires: Participants filled out the Trait component of the Dutch version of the State-Trait Anxiety inventory [22] and the Dutch version of the Penn-State Worry Questionnaire [23].

Procedure: Following completion of the informed consent and the questionnaires, participants were fitted with electrodes and were led through a work-up procedure to select a "definitely uncomfortable, but not painful" shock level. Next, participants were instructed that geometrical figures would be presented to them on the computer screen. They were also told that some of these figures would be followed by the shock and that it was their task to find out the relation between the figures and the shock. Next, the operation of the rating scale was explained.

The figures were always presented for 8s; the intertrial interval varied between 12s and 16s, with a mean of 14 s**.** There were no additional time intervals between the experimental phases in the experiment. The experiment started with the pre-exposure phase, in which two stimuli were presented 12 times without shock. For the pre-exposure group, these were the same stimuli that would later appear in the conditioning phase (circle and square); for the Control group, these were unrelated stimuli (triangle and star). In the conditioning phase, all participants received 6

Presentations of the circle and the square, one consistently followed by shock (the figure-shock relation was counterbalanced within groups). The other stimulus was never followed by the shock and served as comparison control. Next, both stimuli were presented 12 times, always without shock (extinction phase). During each experimental phase, the presentation sequence of the stimuli was randomized with the restriction that the same stimulus would not be presented more than two times in a row.

Experiment 2

Participants: Forty first grade psychology students participated in Experiment 2 in exchange for course credits. The students were randomly assigned to group pre-exposure or group Control (N=20, mean age=19.90, 15 females, and N=20, age=18.95, 16 females, respectively). All participants gave informed consent before the start of the experiment and were told that they could decline further participation at any moment in the experiment. The experiment was approved by the Ethical Committee of the Psychology Department, KU Leuven.

Materials: Exactly identical to Experiment 1

Procedure: Almost identical to Experiment 1. The only difference is the addition of two non-reinforced CS+ trials in the conditioning phase (randomly interspersed with the 6 reinforced CS+ trials). The number of CS- trials extended accordingly from 6 to 8. Experiment 2 was conducted by a different experimenter.

Results

Data reduction

Skin conductance response amplitudes were calculated by subtracting the baseline level (average value during the 2 s prior to stimulus presentation) from the maximal value during that stimulus presentation (0-8 s after CS onset). Negative responses were scored as zero and included in the analyses. Amplitudes were Z transformed prior to statistical analyses.

Experiment 1

Questionnaire data: The groups did not differ significantly on the trait anxiety questionnaire (STAI), group pre-exposure: M=35.39, group Control: M=35.16, t (35)=0.11, p=0.91, or on the worry questionnaire (PSWQ), group pre-exposure: M=44.67, group Control: M=46.89, t(35)=0.60, p=0.56. The two questionnaires correlated significantly, r=0.54, p=0.001.

Trial-by-trial shock-expectancy

Pre-exposure: The upper graph of Figure 1 suggests a continuous reduction of shock-expectancy over trials, for both stimuli in both groups. Accordingly, a 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant main effect of Trial, F(11,286)=31.45, p<0.001, *eta*=0.547, but no effect of Stimulus, F's<0.80, p's>0.64 for all effects including Stimulus. There was also no main effect of Group, F(1,26)=0.48, p=0.50. Unexpectedly, the Trial × Group interaction was marginally significant, F(11,286)=1.66, =0.08.

Conditioning. The upper graph of Figure 1 suggests gradual development of differential shock-expectancy in both groups, but more rapidly in the Control group. Accordingly, a 2 (Group) × 2 (Stimulus) × 6 (Trial) RM-ANOVA revealed a main effect of Stimulus, F(1,33)=462.59, p<0.001, *eta* =0.93, and a significant CS × Trial interaction, F (5,165)=96.161, p<0.001, *eta* =0.745, with a significant linear and quadratic trend, F (1,33)=234.78, p<0.001, *eta*=0.877, and F(1,33)=51.673, p<0.001, *eta*=0.61, respectively. Although the Stimulus × Group was not significant, F(1,33)=1.62, p=0.21, the Stimulus × Trial × Group interaction was marginally significant, F(5,165)=4.64, p =0.07, *eta* =0.06, indicative of different rates of conditioning in the two groups. Limiting the ANOVA to the first three trials of conditioning (where most learning takes place) did reveal the expected Stimulus × Group interaction, F(1,34)=5.13, p=0.03, *eta*=.13, but no Stimulus × Trial × Group interaction, F(2,68)=1.10, p=0.34. Limiting the ANOVA to the last acquisition trial confirmed that the end level of conditioning was comparable between the groups, F(1,35)=0.03, p=0.86.

Extinction: The upper graph of Figure 1 suggests different rates of extinction in the two groups. Accordingly, a 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant Stimulus × Trial × Group interaction, F(11,385)=2.78, p<0.01, *eta*=0.07. This interaction was further investigated by looking at the CS+ and CS- data in separate ANOVAs (Trial × Group). This revealed a significant Trial × Group interaction for the CS+ results, F(11,385)=4.89, p<0.001, *eta*=012, with a significant linear trend, F(1,35)=15.62, p<0.001, *eta*=0.31. The same analysis did not yield significant results for the CS-, F(11,396)=0.36, p=0.97. Figure 1 suggests that the difference emerges early in extinction. For that purpose, a separate ANOVA was conducted on the CS+ results on the first 2 extinction trials, which revealed a significant main effect of Group, F(1,36)=5.42, p=0.03, *eta*=0.13, but no significant Group × Trial interaction, F(1,36)=1.62, p=0.21. Figure 1 shows that the shock-expectancy on the first extinction trial differed somewhat between the groups, which may complicate the Group × Trial interaction. Therefore, the results on the last CS+ acquisition trial were entered as a co-variate into the ANOVA. This time, the interaction was significant, F(1,35)=4.62, p=0.04, *eta*=0.12, while the main effect of Group remained significant as well, F(1,35)=4.24, p=0.047, *eta*=0.11. This suggests a faster extinction rate in the Latent Inhibition group as compared to the Control group.

Figure 1 also suggests that extinction is less complete in the Latent Inhibition group. Accordingly, an ANOVA on the last 2 extinction trials did revealed a significant main effect of Group, F(1,36)=5.68, p=0.02, *eta*=0.14. In sum, the shock-expectancy ratings reveal that latent inhibition speeds up but weakens extinction in human fear conditioning

Skin conductance

Pre-exposure: The lower graph of Figure 1 suggests a progressive decline of skin conductance reactions to the two stimuli during pre-exposure. This was confirmed by a 2 (Group) × 2 (Stimulus) × 12 (Trial) repeated measures ANOVA, revealing a main effect of Trial, F(11,385)=2.38, p<0.01, *eta*=0.06, and no significant interactions with Group, all F's<1.38, p's>0.18.

Conditioning: The lower graph of Figure 1 suggests gradual development of differential skin conductance responding in the two groups, but more rapidly in the Control group. A 2 (Group) × 2 (Stimulus) × 6 (Trial) ANOVA revealed a main effect of Stimulus,

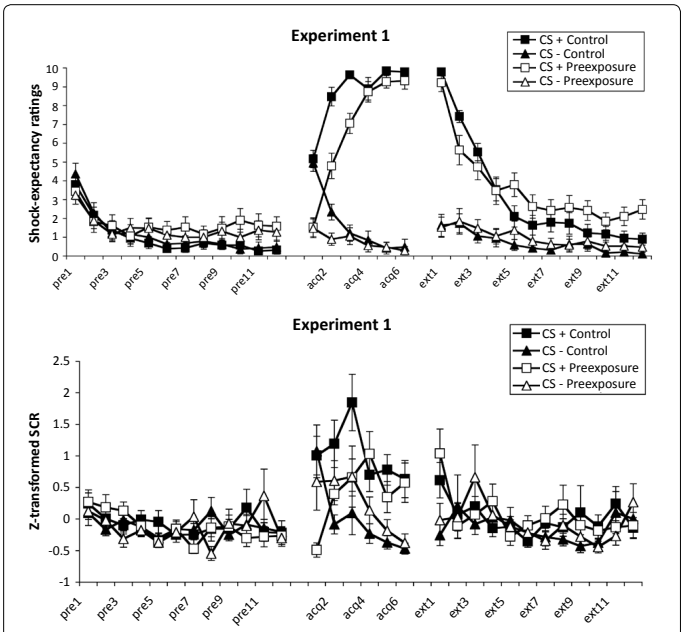

Figure 1: Online shock-expectancy ratings (upper graph) and Z-transformed skin conductance reactivity (lower graph) of Experiment 1. During the first phase, group Pre-exposure was exposed to the to-be-conditioned stimuli, whereas group Control was exposed to irrelevant stimuli (12 trials). The groups were identical in the remaining phases (conditioning, 6 trials, and extinction, 12 trials). CS+ was always followed by the US during conditioning, whereas CS- was never followed by the US.

$F(1,35)=11.01$, $p<0.01$, *eta*=0.23, and a significant Stimulus × Trial interaction, $F(5,175)=5.03$, $p<0.01$, *eta*=0.13, with a significant linear and quadratic trend, $F(1,35)=20.64$, $p<0.01$, *eta*=0.37, and $F(1,35)=4.23$, $p=0.047$, *eta*=0.11. The Group × Stimulus interaction was also significant, $F(1,35)=5.43$, $p=0.03$, *eta*=0.13, but the Group × Stimulus × Trial interaction was not, $F(5,175)=1.73$, $p=0.13$. A 2 (Group) × 2 (Stimulus) ANOVA on the last conditioning trial confirmed comparable levels of skin conductance by the end of conditioning: main effect of Stimulus, $F(1,35)=19.66$, $p<0.01$, *eta*=0.37, but no significant interaction with Group, $F(1,35)=0.11$, $p=0.75$.

Extinction: A 2 (Group) × 2 (Stimulus) × 12 (Trial) ANOVA revealed a marginally significant main effect of Stimulus, $F(1,35)=3.45$, $p=0.07$, *eta*=0.09, and a significant Stimulus × Trial interaction, $F(11,385)=2.34$, $p<0.01$, *eta*=0.06. Interactions with Group were not significant, all F's<0.91, p's>0.53. A separate 2 (Group) × 2 (CS) × 2 (Trial) ANOVA on the first 2 extinction trials revealed the same pattern of results: a main effect of Stimulus, $F(1,35)=4.62$, $p<0.04$, *eta*=0.12, and a significant Stimulus × Trial interaction, $F(2,70)=7.01$, $p=0.01$, *eta*=0.17, but no significant interactions with Group, all F's<1.58, p's>0.21. In analogy with the analyses of the trial-by-trial shock expectancy ratings, a 2 (Group) × 2 (Trial) ANOVA analyzed the decrease of the conditioned response over the two first extinction trials of the CS+. The mean difference between CS+ and CS- over the acquisition trials was added as a co-variate in the analysis, to take into account potential differences in conditioning. This ANOVA revealed the absence of a main effect of Trial, $F(1,34)=2.86$, $p=0.10$, but the expected Group x Trial interaction, $F(1,34)=5.44$, $p<0.03$, *eta*=0.14. Follow-up comparisons showed that the decrease was only significant in the pre-exposure group, $F(1,34)=17.35$, $p<0.01$, *eta*=0.34, not in the Control group, $F(1,34)=0.67$, $p=0.42$.

A separate 2 (Group) × 2 (Stimulus) × 2 (Trial) ANOVA on the last 2 extinction trials did not reveal a main effect of Stimulus, $F(1,35)=0.13$, $p=0.72$, or any effect of Group, all F's<2.38, p's>0.13.

Experiment 2

Questionnaire data

The groups did not differ significantly from each other on the trait anxiety questionnaire (STAI), group pre-exposure: $M=39.00$, group Control: $M=38.95$, $t(38)=0.02$, $p=0.99$, or on the worry questionnaire (PSWQ), group pre-exposure: $M=45.00$, group Control: $M=44.80$, $t(38)=0.06$, $p=0.95$. The two questionnaires correlated significantly, r=0.68, $p<0.001$.

Trial-by-trial shock-expectancy

Pre-exposure: A 2 (Group) × 2 (Stimulus) × 12 (Trial) ANOVA revealed a significant main effect of Trial, $F(11,231)=11.91$, $p<0.01$, *eta*=0.36, and surprisingly, a significant Group × Trial interaction, $F(11,231)=1.86$, $p=0.046$, *eta*=0.08, as well as a significant Group × Stimulus × Trial interaction, $F(11,231)=1.95$, $p=.04$, *eta*=0.09.

Conditioning: A 2 (Group) × 2 (Stimulus) × 8 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,37)=179.58$, $p<0.01$, *eta*=0.83, as well as a significant Group × Stimlus interaction, $F(1,37)=4.54$, $p=0.04$, *eta*=0.11. The Stimulus × Trial interaction was also significant, $F(7,259)=19.52$, $p<0.01$, *eta*=0.35. The Group × Stimulus × Trial interaction was not significant, $F(7,259)=1.76$, $p=0.89$. A separate 2 (Group) × 2 (Stimulus) ANOVA on the last conditioning trial confirmed that the level of shock-expectancy reached a comparable level in the two groups: a significant main effect of Stimulus, $F(1,38)=99.57$, $p<0.01$, *eta*=0.72, but no significant Group × Stimulus interaction, $F(1,38)=2.48$, $p=0.12$.

Extinction: A 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,36)=95.28$, $p<0.01$, *eta*=0.73, a significant Stimulus × Trial interaction, $F(11,396)=42.59$, $p<0.01$, *eta*=0.36, and a significant Group × Stimulus × Trial interaction, $F(11, 396)=2.37$, $p<0.01$, *eta*=0.06. This suggest different rates of extinction learning in the two groups. Separate Group × Trial RM-ANOVAs for the CS+ and the CS- did not reveal significant Group × Trial interactions, $F(11,407)=1.33$, $p=0.20$, $F(11,407)=1.19$, $p=0.29$, respectively. There seemed to be a difference in acquisition level at the start of the extinction phase (see upper graph of Figure 2), despite the absence of a significant Group difference on the last acquisition trial. For that reason, the acquisition level was added as co-variate to the 2 (Group) × 12 (Trial) ANOVAs (because of the partial reinforcement schedule, the average rating to the CS+ was taken rather than the last CS+ trial). This revealed a significant Group × Trial interaction on the CS+ results, $F(11, 396)=1.83$, $p=0.048$, *eta*=0.05, with a significant linear trend, $F(1,36)=5.19$, $p<0.03$, *eta*=0.13, but not on the CS- results, $F(11,396)=1.22$, $p=0.27$. This shows different extinction curves for the CS+ in the two groups. However, separate RM-ANOVAs over the first two or last two extinction trials failed to reveal significant group effects, $F(1,37)=0.03$, and $F(1,37)=0.08$, respectively. In sum, the overall analysis shows different extinction curves in the two groups, but detailed analyses could not replicate the speeded but weakened extinction results from Experiment 1.

Skin conductance

Pre-exposure: A 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant main effect of Trial, $F(11,385)=3.40$, $p<0.01$, *eta*=0.09, as well as an unexpected Stimulus × Trial interaction, $F(11,385)=1.83$, $p=0.048$, *eta*=0.05. No interactions with Group were significant, all F's<1.47, p's>0.14.

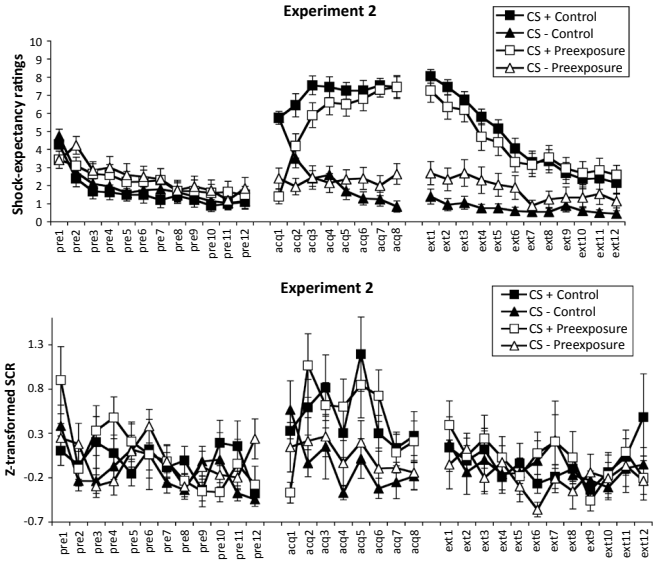

Figure 2: Online shock-expectancy ratings (upper graph) and Z-transformed skin conductance reactivity (lower graph) of Experiment 2. During the first phase, group Pre-exposure was exposed to the to-be-conditioned stimuli, whereas group Control was exposed to irrelevant stimuli (12 trials). The groups were identical in the remaining phases (conditioning, 8 trials, and extinction, 12 trials). CS+ was 6 times followed by the US during conditioning, whereas CS- was never followed by the US.

Conditioning: A 2 (Group) × 2(Stimulus) × 8 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,35)=14.43$, $p<0.01$, *eta*=0.29, and a significant Stimulus × Trial interaction, $F(7,245)=2.53$, $p<0.02$, *eta*=0.07, with a significant quadratic trend, $F(1,35)=2.27$, *eta*=0.06. No interactions with Group were significant, all *F*'s<1.49, *p*'s>0.17. A separate ANOVA on the last acquisition trial revealed a marginally significant main effect of Stimulus, $F(1,35)=3.01$, $p=0.09$, *eta*=0.08, and no significant interaction with Group, $F(1,35)=0.05$, $p=0.82$.

Extinction: A 2 (Group) × 2(Stimulus) × 12 (Trial) RM-ANOVA failed to reveal any significant main or interaction effects, all *F*'s<1.75, *p*'s>0.19. In analogy with the other analyses, a separate 2 (Group) × 2 (Trial) ANOVA was conducted on the first 2 CS+ extinction trials with the average differential conditioning effect as co-variate. Again, no effects were significant, all *F*'s<1.26, *p*'s>0.27.

Experiments 1 and 2 combined

The similarities between the two experiments allowed to analyze them together, in order to evaluate the effects of partial reinforcement and latent inhibition in a 2 × 2 factorial design. This provides a direct comparison of CS-noUS trials *before* versus *during* conditioning (pre-exposures versus partial reinforcement).

Trial-by-trial shock-expectancy

Pre-exposure: A 2 (Experiment) × 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant main effect of Trial, $F(11,517)=36.95$, $p<0.01$, *eta*=0.44, and an unexpected significant interaction with Group, $F(11,517)=2.77$, $p<0.01$, *eta*=0.03.

Conditioning. A 2 (Experiment) × 2 (Group) × 2 (Stimulus) × 6 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,70)=501.96$, $p<0.01$, *eta*=0.88, a significant Experiment × Stimulus interaction, $F(1,70)=48.62$, $p<0.01$, *eta*=0.41, and a significant Group × Stimulus interaction, $F(1,70)=4.84$, $p=0.03$, *eta*=0.07. In addition, the Stimulus × Trial interaction was significant, $F(5,350)=86.11$, $p<0.01$, *eta*=0.55, with significant linear and quadratic trend, $F(1,70)=212.13$, $p<0.01$, *eta*=0.75, and $F(1,70)=76.73$, $p<0.01$, *eta*=0.52, respectively. Finally, the Experiment × Stimulus × Trial interaction was significant, $F(5,350)=5.53$, $p<0.01$, *eta*=0.07, but the Group × Stimulus × Trial was not, $F(5,350)=1.15$, $p=0.34$. A separate 2 (Experiment) × 2 (Group) × 2 (Stimulus) ANOVA on the last conditioning trial revealed a significant main effect of Stimulus, $F(1,73)=67.58$, $p<0.01$, *eta*=0.48, but also significant interactions, Experiment × Stimulus: $F(1,73)=4.97$, $p<0.03$, *eta*=0.06, Group × Stimulus: $F(1,73)=58.40$, $p<0.01$, *eta*=0.44, Experiment × Group × Stimulus: $F(1,73)=3.32$, $p=0.07$, *eta*=0.04. The different manipulations influenced the end level of conditioning.

Extinction: A 2 (Experiment) × 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,71)=151.87$, $p<0.01$, *eta*=0.68, and a significant Stimulus × Trial interaction, $F(11,781)=58.64$, $p<0.01$, *eta*=0.45. In addition, the Experiment × Stimulus × Trial interaction was significant, $F(11,781)=4.41$, $p<0.01$, *eta*=0.06, as well as the Group × Stimulus × Trial interaction, $F(11,781)=4.31$, $p<0.01$, *eta*=0.06. These interactions were investigated further by first conducting a separate 2 (Experiment) × 2 (Group) × 12 (Trial) RM-ANOVA on the CS+ results. This analysis revealed a significant main effect of Trial, $F(11,792)=133.39$, $p<0.01$, *eta*=0.65, and significant interactions with Experiment, $F(11,792)=7.02$, $p<0.01$, *eta*=0.09, and with Group, $F(11,792)=4.47$, $p<0.01$, *eta*=0.06. The same analysis on the CS- results revealed no significant interactions with Experiment or Group, *F*'s <0.64, *p*'s>0.68. A separate ANOVA on the first 2 CS+ extinction trials revealed no significant Group × Trial interaction, $F(1,74)=1.55$, $p=0.22$. In analogy with the analyses of the separate experiments, the level of conditioning was added as co-variate to the ANOVA (because there were different numbers of acquisition trials and reinforcement schedules, the average rating to the CS+ was taken rather than the last CS+ trial). This resulted in a significant Group × Trial interaction, $F(1,73)=4.02$, $p<0.05$, *eta*=0.05, as well as a significant Experiment x Trial interaction, $F(1,73)=6.74$, $p=0.01$, *eta*=0.08. The Experiment × Group × Trial linteraction was not significant, $F(1,73)=0.88$, $p=0.35$. In order to investigate the Group × Trial interaction further, a separate 2 (Group) × 2 (Trial) RM-ANOVA was conducted (leaving out the Experiment factor), which again revealed a significant Group × Trial interaction, $F(1,75)=6.11$, $p<0.02$, *eta*=0.08. Follow-up comparisons revealed that the groups did not differ on the first extinction trial, $F(1,75)=0.14$, $p=0.71$, while CS+ expectancy was significantly lower on the second extinction trial in group pre-exposure, $F(1,75)=5.63$, $p=0.02$, *eta*=0.07. This confirms the extinction enhancing effect of the pre-exposure manipulation. Next, an analogous 2 (Experiment) × 2 (Trial) RM-ANOVA was conducted with conditioning level as co-variate, which revealed a significant Experiment × Trial interaction, $F(1,75)=9.43$, $p<0.01$, *eta*=0.11. Follow-up comparisons revealed that the expectancy ratings decreased significantly in the Experiment 1 groups (100% reinforcement), but only marginally so in the Experiment 2 groups (75% reinforcement), $F(1,75)=40.01$, $p<0.001$, *eta*=0.35, and $F(1,75)=3.74$, $p=0.057$, *eta*=0.05, respectively. These results show that pre-exposures produced speeded extinction, while partial reinforcement produced delayed extinction.

To evaluate the end level of extinction, a 2 (Experiment) × 2 (Group) × 2 (Trial) RM-ANOVA was conducted, with conditioning level as co-variate, over the last 2 extinction trials. This revealed a significant main effect of Group, $F(1,73)=4.50$, $p<0.04$, *eta*=0.06, and a significant main effect of Experiment, $F(1,73)=4.35$, $p=0.04$, *eta*=0.06, with no significant Experiment × Group interaction, $F(1,73)=1.05$, $p=0.31$. These results show that pre-exposures and partial reinforcement produced weakened extinction.

Skin conductance

Pre-exposure: A 2 (Experiment) × 2 (Group) × 2 (Stimulus) × 12 (Trial) RMANOVA revealed a significant main effect of Trial, $F(11,770)=4.61$, $p<0.01$, *eta*=0.06. No interaction effects with Experiment or Group were significant, all *F*'s<1.58, *p*'s>0.098.

Conditioning: A 2 (Experiment) × 2 (Group) × 2 (Stimulus) × 6 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,70)=24.05$, $p<0.01$, *eta*=0.26, and a significant Group × Stimulus interaction, $F(1,70)=4.42$, $p<0.04$, *eta*=0.06. The Group × Stimulus × Trial interaction was not significant, $F(5,350)=1.16$, $p=0.33$. A separate 2 (Experiment) × 2 (Group) × 2 (Stimulus) ANOVA on the last acquisition trial showed a significant main effect of Stimulus, $F(1,70)=28.90$, $p<0.01$, *eta*=0.29, and the absence of significant interactions with Group or Experiment, *F*'s<0.89, *p*'s>0.35. This suggests successful and non-different acquisition levels over the two Experiments and Groups.

Extinction. A 2 (Experiment) × 2 (Group) × 2 (Stimulus) × 12 (Trial) RM-ANOVA revealed a significant main effect of Stimulus, $F(1,70)=4.88$, $p=0.03$, *eta*=0.07, but no significant interactions with Group or Experiment, *F*'s<.77, *p*'s>0.38. When applying a conservative criterion of conditioning (higher average SCR to CS+ than to CS-), the Experiment × Stimulus × Trial interaction was significant, $F(11,550)=2.01$, $p=0.025$, *eta*=0.04, but Group × Stimulus × Trial interaction was again not significant, $F(11,550)=1.19$, $p=0.29$. Running

this RM-ANOVA (with the conditioning criterion) over the first 2 extinction trials, revealed a main effect of Stimulus, $F(1,50)=4.72$, $p=0.035$, $eta=0.09$, a Stimulus × Trial interaction, $F(1,50)=9.61$, $p=0.003$, $eta=0.16$, and an Experiment × Stimulus × Trial interaction, $F(1,50)=6.32$, $p=0.015$, $eta=0.11$, but no Group × Stimulus × Trial interaction, $F(1,50)=1.23$, $p=0.27$.

The comparable RM-ANOVA over the last two extinction trials revealed no significant main effect of Stimulus, $F(1,50)=0.35$, $p=0.56$, nor interactions with Group or Experiment, F's<2.64, p's>0.11.

Discussion

The present study was set up to investigate the effects of stimulus pre-exposures on the conditioning and extinction of fear responses in humans. Experiment 1 investigated this in a 100% reinforcement schedule during conditioning; Experiment 2 used a 75% reinforcement schedule. The results of the experiments are discussed separately, before turning to more general implications.

Experiment 1

pre-exposures of the to-be-conditioned stimulus (CS) slowed down fear conditioning, as measured through trial-by-trial expectancy ratings and skin conductance reactivity. This replicates the latent inhibition effect and confirms that prior non-fearful experiences can thwart the development of fears in humans [14]. Central to the purpose of this study, the CS pre-exposures also speeded up the extinction of conditioned fear, both in expectancy ratings and SCR. This is in line with the memory retrieval account developed in the Introduction: the first CS-noUS trial in extinction retrieves the CS-noUS memory of latent inhibition. Retrieval of this memory counteracts the CS-US conditioning memory and leads to a more rapid decline of conditioned fear reactions.

Surprisingly, extinction of the shock-expectancy ratings remained incomplete (compared to the control group). In particular, the upper graph of Figure 1 shows a cross-over of the extinction curves around trial 4. Before that trial, group pre-exposure showed lower levels of shock-expectancy ratings than group Control. After that trial, group pre-exposure showed higher levels of shock-expectancy ratings. These results suggest that CS pre-exposures speed up but weaken the extinction of conditioned fear in humans (although the data were not entirely paralleled in SCR).

Experiment 2

Experiment 2 was a replication of Experiment 1, but applied a partial reinforcement schedule during conditioning. The expectancy results again showed that the pre-exposure phase influenced the course of conditioning as well as extinction l earning, although there was no direct evidence of speeded extinction on the first trials. The skin conductance data showed significant conditioning effects, but no effects of the pre-exposure manipulation.

The absence of speeded extinction suggests that the pre-exposure technique is not as effective in a partial reinforcement schedule. My hypothesis was that the first CSnoUS trial in extinction would reactivate the CS-noUS memory from the pre-exposure phase and speed up the behavioral extinction effect. The current results may not be so lay-out deviant from this memory hypothesis. In partial reinforcement, the few CS-noUS trials that occur during conditioning are usually followed by one or more CS-US conditioning trials. Hence, the CS-noUS trials may become associated with the CS-US conditioning memory as well. Arguably, this will weaken the ability of CS-noUS trials to activate the CS-noUS memory during extinction.

Experiments 1 and 2 combined

The combined analysis of Experiments 1 and 2 revelead that both the pre-exposure and the partial reinforcement manipulation produced a delayed conditioning effect. This is in line with typical findings in the respective research literatures [11,24]. In addition, extinction of the shock-expectancy ratings was delayed in the partial reinforcement groups compared to the full reinforcement groups. This replicates the typical partial reinforcement extinction effect [21]. In contrast, the pre-exposure manipulation speeded up the extinction effect. This confirms the hypothesis that CSnoUS trials can have opposite effects on the speed of extinction, depending on the temporal relationship between the CS-noUS and the CS-US conditioning trials. Finally, the end levels of extinction remained incomplete in the Partial Reinforcement groups and the pre-exposure groups alike.

The skin conductance paralleled these results by showing effects of the pre-exposure manipulation on conditioning, and effects of the partial reinforcement manipulation on extinction. Interestingly, the SCR discrimination seems to break off much faster in extinction as compared to the shock-expectancy ratings that show a more gradual reduction over trials.

Theoretical implications

Experiment 1 showed speeded but incomplete extinction in the shock-expectancy ratings of group pre-exposure. The speeded extinction effect is in line with the memory retrieval account, but the incomplete extinction effect is not. The results are more in line with a trial sequence learning viewpoint [21]. This view was originally developed to account for the partial reinforcement extinction effect: why interspersed CS-noUS trials during conditioning would delay extinction. This view assumes that there is not only learning within trials (e.g., between a CS and a US), but also over trials (e.g., between successive CS-noUS trials). Experiences on previous trials may come to signal (non) reinforcements on later trials. In the partial reinforcement extinction effect, (numbers of) CS-noUS trials are repeatedly followed by CS-US trials, so that the former become a signal for the latter. During extinction, the CS-noUS trials continue to predict CS-US trials, thereby delaying extinction. The memory view on latent inhibition can also be approached from this perspective: during the pre-exposure phase, early CS-noUS trials precede a larger number of CS-noUS trials so that the first CS-noUS trial can become a signal for more CS-noUS trials. At the beginning of extinction, the early CS-noUS trials signal more CS-noUS trials, which speed up CR extinction. The incomplete extinction may reflect another learning experience during the previous experimental phases, namely, that the series of CS-noUS trials (pre-exposure) was eventually followed by CS-US trials (conditioning). Hence, replaying that series of trials in extinction may eventually signal a return of CS-US trials. This account can be tested in future research by manipulating the number of CS-noUS trials in the pre-exposure phase.

The combined analysis of the expectancy ratings in the two experiments also revealed the partial reinforcement extinction effect: slower extinction following partial reinforcement. This effect is fascinating, as the addition of nonreinforced CS+ trials produces more persistent conditioned responding [21]. The current study shows that the timing of the nonreinforced CS+ trials is crucial: when these trials occur prior to the reinforced CS-US trials, later extinction is accelerated; when they occur during conditioning, extinction

is delayed. Nonreinforced CS+ trials can have opposite effects on extinction depending on their timing relative to the reinforced CS+ trials. Surprisingly, the partial reinforcement extinction effect was not mirrored in the skin conductance reactivity. In all groups, the conditioning effect disappeared almost immediately after the first nonreinforced extinction trial. This stands in sharp contrast with the gradual extinction curves observed in the shock-expectancy ratings. It is not exactly clear why these measures dissociate in the extinction phases of the present experiments. One possibility is that CS-noUS experiences not only weaken the CS-US association (e.g., by forming an inhibitory CS-noUS association), but also devalue the representation of the US [25]. Expecting a less aversive shock US would produce less fear (c.q. less skin conductance reactivity). For instance, the very first exinction trial may produce relief, a positive emotion that can serve to devalue the aversive representation of the US. This would not influence the shock-expectancy ratings, as such ratings are valence-free. Another factor may be the use of fear irrelevant stimuli as conditional stimuli in the present study. It has been shown on various occasions that conditioned skin condutance responses to fear-relevant stimuli (e.g., snakes, spiders) show more resistance to extinction [26]. In any case, the dissociation between measures in extinction is an understudied topic in the human conditioning literature that is worthy of investigation.

Practical implications

Overall, the expectancy ratings and the skin conductance data showed delayed conditioning in the CS pre-exposure groups of both experiments, as compared to irrelevant pre-exposure control groups. This replicates the typical latent inhibition effect [11,14] and shows that it occurs irrespectively of the reinforcement schedule of conditioning. The current results support the applicability of pre-exposures to prevent the development of fear. In addition, the experiments provide evidence that prior non-fearful exposures to to-be-conditioned stimuli can accelerate subsequent extinction. Although the effect was less clear after partial reinforcement alone, the current results add to the potential of the latent inhibition technique as a preventative tool in individuals vulnerable for trauma-exposure.

Contemporary anxiety research focuses on disturbed fear extinction rather than enhanced fear acquisition as the responsible process for the development of anxiety disorders [10]. Latent inhibition may help to facilitate spontaneous fear extinction or exposure-based fear extinction treatments. However, this technique also produced less complete extinction in the present study. This suggests that the beneficial effects of pre-exposures may be limited to the production of early successes of self exposures or exposure treatments that can motivate patients to continue. The faster reduction of fear may promote a faster reduction of avoidance behaviors, which are often the strongest preventers of extinction learning [27]. In addition, early successes may motivate patients to continue the exposure treatment (or to continue self-exposures).

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