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Reinstatement of Conditioned Fear in Humans Is Context Dependent and Impaired in Amnesia

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A contextual reinstatement procedure was developed to assess the contributions of environmental cues and hippocampal function in the recovery of conditioned fear following extinction in humans. Experiment 1 showed context specificity in the recovery of extinguished skin conductance responses after presentations of an auditory unconditioned stimulus. Experiment 2 demonstrated that fear recovery did not generalize to an explicitly unpaired conditioned stimulus. Experiment 3 replicated the context dependency of fear recovery with a shock as an unconditioned stimulus. Two amnesic patients failed to recover fear responses following reinstatement in the same context, despite showing initial fear acquisition. These results extend the known functions of the human hippocampus and highlight the importance of environmental contexts in regulating the expression of latent fear associations.

Keywords: amygdala, associative learning, emotion, implicit memory, anxiety

Spatial and temporal contexts play an important role in regulating the expression of acquired fears. Researchers have accumulated much evidence to demonstrate that conditioned fear is not erased following extinction training, beginning with Pavlov's (1927) original description of spontaneous recovery. In humans, fear recovery following exposure therapy complicates the treatment of anxiety disorders and is hypothesized to involve reinstatement by contextual cues (Bouton & Swartzentruber, 1991; Rodriguez, Craske, Mineka, & Hladek, 1999). However, the mechanisms underlying contextual mediation of fear behavior in humans remain largely unknown.

Recent studies conducted in nonhuman animals have begun to provide clues regarding the factors that contribute to the recovery of conditioned fear associations. Bouton has shown that contextual cues play a key role in determining when conditioned responses reappear following extinction (Bouton, 1993). One experimental paradigm that has established this relationship is called *reinstatement* (Rescorla & Heth, 1975). In a fear reinstatement task, rats undergo acquisition and extinction of a simple conditioned stimulus (CS)–unconditioned stimulus (US) association in a given environmental context. Following extinction, the fearfulness of the context is reestablished by several presentations of the aversive US alone. Recovery of fear to the CS is then tested. If the reinstatement and recovery test phases occur in the same context, conditioned fear to the CS transiently recovers and then reextinguishes. Recovery is not observed if reinstatement takes place in a novel (irrelevant) context (Bouton, 1984; Bouton & Bolles, 1979; Bouton & King, 1983).

Bouton (1988, 1993) has theorized that the reinstatement effect is related to a contextual conditioning mechanism that disambiguates the meaning of the extinguished CS. During the reinstatement phase, the association between the US and the background contextual cues is strengthened. When the subject subsequently encounters the extinguished CS in this fearful context, the fear response to the CS reemerges because the contextual cues promote retrieval of the CS–US association. If the reinstatement context is different than the recovery test context, the contextual fear does not transfer.

Lesion studies have shown that the hippocampus is critical for mediating the contextual associations that give rise to fear recovery following reinstatement. Rats with fornix transection (Wilson, Brooks, & Bouton, 1995) or excitotoxic hippocampal lesions (Frohardt, Guarraci, & Bouton, 2000) can acquire and extinguish the initial CS–US association but fail to show the context-dependent recovery of fear following reinstatement. This effect may be selective for aversive training protocols, as reinstatement of appetitive behaviors is not impaired in rats with hippocampal lesions (Fox & Holland, 1998), although other differences in the experimental procedure may also account for these discrepant results. Other procedures that promote extinguished fear recovery by contextual cues, such as *renewal* (Bouton & Bolles, 1979), depend on hippocampal processing only in some circumstances (Corcoran & Maren, 2004; Frohardt et al., 2000; Wilson et al., 1995). Thus, the hippocampus may play a special role in the contextual reinstatement of conditioned fear following extinction, consistent with other evidence regarding its selective involvement in forming conjunctive representations between the US and environmental cues during contextual fear acquisition (reviewed in Fanselow, 2000; Maren & Holt, 2000; Rudy & O'Reilly, 2001).

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Although animal studies of fear reinstatement have theoretical relevance for understanding relapse following extinction therapy in anxiety disorders, direct laboratory demonstrations of reinstatement or other context-dependent recovery phenomena have been lacking in the human literature. Successful demonstration of fear reinstatement and its modulation by spatial contextual cues would provide a direct link between animal models of associative learning and potential applications in clinical settings. A recent study of fear reinstatement in humans found that valence ratings and reaction times to extinguished fear stimuli change following presentation of the unconditioned stimulus after extinction (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004). However, the context specificity, psychophysiological correlates, and neural mechanisms underlying these behavioral effects have not been established. In the present study, a human analog of a reinstatement task was developed to investigate the dependency of conditioned fear recovery on contextual cues and hippocampal function. In Experiment 1, healthy participants underwent acquisition and extinction of conditioned fear to an aversive, white noise US using a single-cue delay procedure. Following extinction, fear reinstatement took place either in the same environmental context or a novel (irrelevant) context. Recovery and reextinction of conditioned fear was then tested in the original context. Experiment 2 tested whether conditioned fear recovery generalized to nonpredictive cues using a delay discrimination procedure in healthy participants. Experiment 3 replicated the single-cue delay procedure with wrist shock as the US, and the performance of healthy participants was compared with the performance of two amnesic patients with hypoxic insults. We made the following three predictions. First, healthy participants would show context-dependent recovery of conditioned fear in Experiments 1 and 3. Second, fear recovery would be specific to the predictive CS (the CS+) in Experiment 2. Third, amnesic patients in Experiment 3 would acquire and extinguish fear responses to the CS, but they would not show fear recovery following reinstatement.

Experiment 1

Method

Participants. Forty-three healthy Yale University undergraduates (15 male, 28 female; age range = 18–22 years) provided informed consent and were paid $10 per hour to participate in the study. Ten additional participants took part in the study but were removed from the data analysis because their skin conductance responses (SCRs) were more than two *SD* below the group mean in at least one phase of the experiment (*nonresponders*; Björkstrand, 1990; Olsson & Phelps, 2004; Schell, Dawson, & Marinkovic, 1991). Participants were recruited by posted advertisements. None of the participants had a history of neurologic or psychiatric disorder as assessed by self-report questionnaires. The study was approved for the ethical treatment of human participants in accordance with local Institutional Review Board guidelines.

Stimuli and apparatus. The CS was a blue square subtending 7.67° of visual angle, which was presented for a 4-s duration on a color computer monitor. The US was a 100-dB binaural white noise burst (1-s total duration consisting of four consecutive on–off bursts of 125-ms duration coterminating with the CS). The US was delivered by headphones after amplification and bandpass filtering from 1 Hz–20 kHz. The US intensity was maintained within ± 2 dB for each participant by a sound level meter.

SCRs were recorded as the dependent measure of fear conditioning, as described previously (LaBar, LeDoux, Spencer, & Phelps, 1995). Briefly, SCRs were recorded by silver–silver chloride electrodes attached by Velcro straps to the middle phalanges of the second and third digits of the nondominant hand (BIOPAC Systems, Goleta, CA). Lafayette Instruments electrode gel (Lafayette, IN) was used as an electrolyte. The skin conductance module was triggered to start recording by Superlab software (Cedrus Corporation, San Pedro, CA) interfaced with a National Instruments DIO-24 card (Austin, TX). Data sampling took place at 250 Hz and was analyzed offline through the use of AcqKnowledge software (BIOPAC Systems). Skin conductance was low-pass filtered with a Blackman window (cutoff frequency = 31 Hz) and smoothed over three consecutive data points prior to scoring.

Procedure. Participants were told that the purpose of the experiment was to examine their sweat gland activity in reaction to sensory events, both auditory and visual, and that different portions of the experiment may be conducted in different rooms. They were also told that the task was passive; that is, no overt response was required. Participants washed their hands prior to electrode placement and were instructed to keep their hands still on their lap during the study to reduce motion artifacts in the SCR recordings.

The participants were randomly assigned to one of two experimental conditions. For the same-context group, all phases of the experiment took place in the same environmental context. For the different-context group, all phases except the reinstatement phase took place in the same environmental context. Two testing rooms were used as experimental contexts, with the starting context counterbalanced across individuals (see Figure 1). Context A was a typical laboratory setting in a windowless sound-attenuating 5.10 m × 3.00 m × 2.70 m room containing two computers separated by a table and chairs, a blackboard, a bookcase, hardwood floors, overhead fluorescent lighting, and a green soundproof chamber. Context B was designed as a more domestic sound-attenuating 3.00 m × 3.15 m × 3.00 m room containing a desk, contemporary paintings, large windows, a reclining leather chair, a floor rug, several plants, potpourri, and dried flower arrangements, with ambient instrumental music playing in the background. In Context A, the CS was presented against a solid beige background, whereas in Context B, the CS was presented against a red and green plaid background. The same monitor, computer processor, and SCR recording equipment were used in both rooms and were transported between the rooms on a wheeled table. This was done to ensure that any differences in responding across contexts were not due to differences in calibration of SCR equipment or differential sensitivity of SCR electrodes from two different setups. Of the 43 participants who were included in the study, 23 were randomly assigned to the same-context group (11 in Context A, 12 in Context B), and 20 were assigned to the different-context group (10 started in Context A, 10 started in Context B).

All participants received four habituation trials in which the CS was presented alone, four acquisition trials in which the CS coterminated with the US, and eight extinction trials in which the CS was again presented alone (see Figure 2). The habituation, acquisition, and extinction trials took place continuously (intertrial interval = 16 ± 2 s). Following the last extinction trial, the headphones and SCR electrodes were removed from the participant, who was led to a waiting room for a 5-min interval before the reinstatement phase began. This period of time was required to move

Figure 1. Illustration of the experimental contexts. a and b: Contexts used in Experiments 1 and 3. c: Context used for Experiment 2.

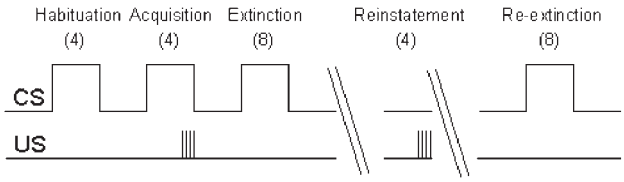

Figure 2. Timeline of the four experimental phases in the single-cue delay paradigm (Experiments 1 and 3). Number of trials in each phase is given by numbers in parentheses. Diagonal lines indicate interposed 5-min periods in which participants were moved to an adjacent waiting room. CS = conditioned stimulus; US = unconditioned stimulus.

the computer equipment into the alternative context for participants in the different-context condition. Following the 5-min waiting period, participants in the same-context group were taken back into the original context, whereas those in the different-context group were taken into the other (novel) context. The headphones and SCR electrodes were reattached, and participants were reminded to attend to the auditory and visual stimuli and to keep their nondominant hand still during the session. During the reinstatement phase, four presentations of the US alone were given (intertrial interval = 50 ± 1 s). The appropriate computer screen background was left on as part of the context throughout the reinstatement phase, although no CSs were presented. Following reinstatement, the headphones and SCR electrodes were removed again, and participants were placed back in the waiting room for another 5-min interval. This time period was needed to return the computer equipment to the original context for the different-context group. Note that we refer to this as the *reinstatement phase* only to distinguish it from the subsequent *recovery test* phase, even though the consequences of US presentation in this phase on fear reinstatement are not measured until the CS is presented in the recovery phase. Following the 5-min waiting interval, recovery of fear to the CS was tested in the original learning context for both groups. The headphones and SCR electrodes were reattached, and the instructions were repeated. Eight CS-alone trials (intertrial interval = 16 ± 2 s) were given during this phase. The first trial of this phase served as the recovery test trial, and the subsequent trials served to reextinguish the fear response.

Statistical analysis. SCR amplitudes to the CS and US were the dependent measures of conditioned and unconditioned responsivity, respectively. Only those deflections initiated between 1.0 and 4.0 s after stimulus onset and lasting between 0.5–5.0 s in duration were included in the analysis. A minimum response criterion of 0.02 microSiemens (μS) was established, and all other responses were scored as zero. Responses to the CS were square-root transformed prior to statistical analysis to reduce skewness. These scoring parameters have been described previously (e.g., LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). Trials were averaged into blocks representing the first half and second half of each experimental phase prior to statistical analysis (e.g., early habituation, late habituation). The number of trials included in these averages was doubled for the extinction and reextinction phases of the study, as the total number of trials in these phases was doubled to ensure adequate opportunity for extinction to take place. For the recovery test, data from the first reextinction trial (recovery test trial) was compared with that of the last extinction trial (pre- vs. postreinstatement comparison; Rescorla & Heth, 1975). An alpha level of .05 was set for all statistical comparisons.

Results and Discussion

Preliminary analyses of variance (ANOVAs) were conducted to assess whether the specific environmental context in which learning occurred (Context A or B) had any overall impact on conditioned responding. No significant main effects of specific learning context were found for any phase of the experiment, so SCR data were combined across all participants in each of the two experimental groups irrespective of which particular context served as the learning context.

Unconditioned responses. A three-way (Phase × Group × Trial Block) mixed ANOVA was computed for unconditioned responses elicited during acquisition and reinstatement (see Table 1). The analysis revealed significant main effects of phase, $F(1, 41) = 10.43$, $p < .002$, trial block, $F(1, 41) = 33.73$, $p < .01$, and a Phase × Trial Block interaction, $F(1, 52) = 4.67$, $p < .04$. Post hoc dependent t tests showed significant habituation of the unconditioned response across trial blocks during both acquisition, $t(42) = 6.08$, $p < .01$, and reinstatement, $t(42) = 2.87$, $p < .006$, although the impact of trial block was greater in the acquisition phase. There were no significant main effects or interactions with the group factor. These results show that the experimental groups had equivalent unconditioned response magnitude and habituation during the acquisition and reinstatement phases.

Table 1
Mean (± SEM) Unconditioned Skin Conductance Responses (in μS) as a Function of Group and Phase for All Three Experiments

Group	*n*	Early acq	Late acq	Early reinst	Late reinst
			Experiment 1		
Diff ctxt	20	2.28 (.35)	1.28 (.26)	1.30 (.24)	0.90 (.39)
Same ctxt	23	1.68 (.25)	1.09 (.18)	1.24 (.19)	0.82 (.16)
			Experiment 2		
Same ctxt	27	1.73 (.30)	1.11 (.16)	1.22 (.17)	0.79 (.12)
			Experiment 3		
Diff ctxt	8	1.78 (.63)	1.62 (.57)	1.65 (.58)	1.58 (.56)
Same ctxt	8	0.93 (.15)	0.78 (.11)	1.11 (.18)	1.00 (.14)
Amnesic	2	0.89 (.14)	0.67 (.05)	0.97 (.03)	1.00 (.07)

Note. Acq = acquisition, Reinst = reinstatement, Diff ctxt = different context, Same ctxt = same context.

Habituation, acquisition, and extinction. A three-way (Group × Phase × Trial Block) mixed ANOVA was computed on conditioned SCRs observed during the habituation, acquisition, and extinction phases (see Figure 3). The results showed a main effect of phase, $F(2, 82) = 10.44$, $p < .0001$, and a Phase × Trial Block interaction, $F(2, 82) = 8.65$, $p < .0004$. Post hoc dependent t tests showed that conditioned SCRs decreased during the habituation phase, $t(42) = -3.01$, $p < .004$, and increased during the acquisition phase, $t(42) = 2.90$, $p < .006$. The lack of a significant trial block effect during extinction was due to the fairly rapid rate of extinction, which occurred between the last acquisition block and the first extinction block, $F(1, 41) = 24.86$, $p < .00001$. It is important to note that there were no main effects or interactions with group, showing equivalent responding of the two experimental groups across all three phases of the experiment prior to the reinstatement manipulation.

Recovery test and reextinction. The recovery of conditioned fear following reinstatement was analyzed by a two-way (Group × Trial) mixed ANOVA comparing the last extinction trial (immediately prior to the reinstatement phase) with the first recovery test trial (immediately following the reinstatement phase). This analysis yielded a Group × Trial interaction, $F(1, 41) = 5.87$, $p < .02$ (see Figure 3). Post hoc dependent t tests showed that conditioned responses in the same-context group significantly increased from extinction to the recovery test, $t(22) = 2.39$, $p < .03$, whereas conditioned responses in the different-context group remained constant, $t(19) = 1.20$, $p = .24$.

A two-way (Group × Trial Block) mixed ANOVA computed on data from all reextinction trials showed a main effect of group, $F(1, 41) = 4.71$, $p < .04$, and a main effect of trial block, $F(1, 41) = 4.73$, $p < .04$. Overall, the same-context group had greater SCRs during the reextinction phase, but the responses extinguished over trial blocks in both groups. These results confirm the primary hypothesis that conditioned fear recovery following reinstatement is context specific.

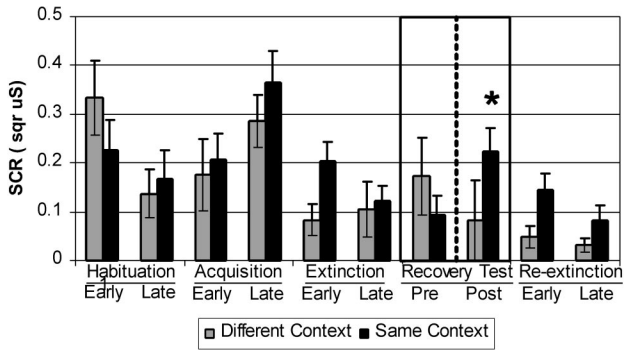

Figure 3. Mean (±*SEM*) conditioned responses by group and experimental phase for Experiment 1. The reinstatement phase occurred at the time point indicated by the vertical dashed line. Recovery of extinguished fear (between vertical solid lines) occurred only for participants who underwent the reinstatement phase in the same environmental context. SCR = skin conductance response; sqr = square-root transformed; μS = microsiemens; Pre = last prereinstatement trial; Post = first postreinstatement trial. *$p < .05$.

Experiment 2

Method

Participants. Twenty-seven healthy Duke University undergraduates (11 male, 16 female; age range = 18–22 years) provided informed consent and were paid $10 per hour to participate in the study. Sixteen additional participants took part in the study but were removed from the data analysis because their SCRs were more than 2 *SD* below the group mean during at least one experimental phase (nonresponders). This number of nonresponders is larger than that seen in Experiments 1 and 3. We believe this is likely because the experiment was run over the summer months, when overall SCR levels decrease after participants come to the laboratory from the outdoors. Alternatively, it could reflect a sampling issue, as autonomic responses during fear conditioning tasks vary widely across individuals according to personality, genetics, and stress hormone levels (Eysenck, 1983; Hettema, Annas, Neale, Kendler, & Fredrikson, 2003; Zorawski, Cook, Kuhn, & LaBar, 2005). Participants were recruited by posted advertisements. None of the participants had a history of neurologic or psychiatric disorder as assessed by self-report questionnaires. The study was approved for the ethical treatment of human participants in accordance with local Institutional Review Board guidelines.

Procedure and statistical analysis. A discrimination version of the procedure was developed in which participants were given one visual CS, designated the CS+, that predicted the occurrence of the white noise US during the acquisition phase, and another CS, designated the CS−, that was unreinforced. Colored squares (red and green) served as the conditioned stimuli, and color assignment was counterbalanced across participants. Two presentation sequences were constructed and counterbalanced across participants such that the CS+ and CS− were pseudorandomly presented within each phase subject to the constraint that no more than two trials of each CS occurred consecutively. The total number of conditioning trials was doubled in each phase relative to that shown in Figure 2 (e.g., eight habituation trials; half CS+, half CS−). The US was identical to that in Experiment 1, and the same number of reinstatement trials were given as in Experiment 1. Because the main objective of this study was to examine the specificity of fear recovery to the CS+, all participants were run in the same-context group in which reinstatement trials occurred in the same experimental context as all other phases of the study. All participants were run in one experimental context (typical windowless 4.20 m × 2.24 m × 2.34 m laboratory setting containing a computer, desk, chair, and psychophysiological recording equipment) shown in Figure 1c. All other aspects of the design and statistical analysis were identical to that in Experiment 1.

Results and Discussion

Unconditioned responses. Unconditioned responses during acquisition and reinstatement were analyzed by a two-way (Phase × Trial Block) repeated measures ANOVA (see Table 1). A main effect of phase, $F(1, 26) = 5.37$, $p < .03$, indicated greater unconditioned responses during acquisition than during reinstatement. In addition, a main effect of trial block, $F(1, 26) = 13.52$, $p < .001$, indicated habituation of the unconditioned response over time across both experimental phases.

Habituation, acquisition, and extinction. A three-way (Phase × Trial Block × CS Type) repeated measures ANOVA was computed on conditioned SCRs observed during the habituation, acquisition, and extinction phases (see Figure 4). The results showed a significant main effect of trial block, $F(1, 26) = 10.05$, $p < .004$, and CS type, $F(1, 26) = 4.56$, $p < .04$. The interaction between phase and trial block was also significant, $F(2, 52) = 5.06$, $p < .01$. Additional trends were found in the two-way interaction between phase and CS type, $F(2, 52) = 2.52$, $p = .09$,

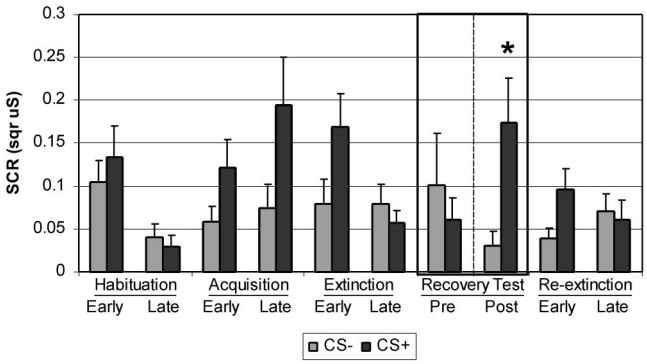

Figure 4. Mean (±*SEM*) conditioned responses by stimulus type and experimental phase for Experiment 2. All participants were run in the same experimental context throughout all experimental phases. The reinstatement phase took place at the time point indicated by the vertical dashed line. Fear acquisition and recovery (between vertical solid lines) occurred only for the conditioned stimulus paired with the reinforcer (CS+) and did not generalize to the unpaired cue (CS−). SCR = skin conductance response; sqr = square-root transformed; μS = microsiemens; Pre = last prereinstatement trial; Post = first postreinstatement trial; CS = conditioned stimulus. *$p < .05$.

and the three-way interaction between phase, trial block, and CS type, $F(2, 52) = 3.01$, $p = .06$. Post hoc two-way ANOVAs conducted on each experimental phase separately showed a significant effect of trial block in both the habituation phase, $F(1, 26) = 13.33$, $p < .001$, and the extinction phase, $F(1, 26) = 4.83$, $p < .04$, indicating response decrements over time in both phases. However, in the extinction phase, the trial block effect also interacted with CS type, $F(1, 26) = 8.05$, $p < .009$, indicating greater extinction to the CS+ than the CS−. The acquisition phase was characterized by a significant simple main effect of CS type, $F(1, 26) = 5.56$, $p < .03$, with greater conditioned responses to the CS+ than the CS− throughout the acquisition phase. Collectively, these results show that the CS+ and CS− initially elicited equivalent SCRs, which habituated prior to the onset of conditioning, and that conditioned fear was selectively acquired and extinguished to the CS+.

Recovery test and reextinction. The recovery of conditioned fear following reinstatement was analyzed by a two-way (CS Type × Trial) repeated measures ANOVA comparing the last extinction trial (immediately prior to the reinstatement phase) with the first recovery test trial (immediately following the reinstatement phase). This analysis yielded an interaction between CS type and trial, $F(1, 26) = 7.39$, $p < .01$ (see Figure 4). Post hoc dependent t tests showed that conditioned responses to the CS+ significantly increased from extinction to the recovery test, $t(26) = 2.12$, $p < .04$, whereas those to the CS− remained constant, $t(26) = 1.20$, $p = .24$. A two-way (CS Type × Trial Block) repeated measures ANOVA computed on data from all reextinction trials also revealed a significant interaction between these two factors, $F(1, 26) = 4.22$, $p < .05$. Post hoc dependent t tests showed greater responses to the CS+ than the CS− early in the reextinction phase, $t(26) = 2.53$, $p < .02$, but not on later trials, $t(26) = 1.43$, $p = .16$. These results confirm the primary hypothesis that conditioned fear recovery was specific to the predictive CS+ and did not generalize to the unpaired CS−. The findings rule out the possibility that the recovery of fear in this paradigm is due to general arousability, such as elevated baseline skin conductance levels, which would not differentiate these two trial types.

Experiment 3

Method

Participants. Two amnesic patients, F.S. (female, age 61, 18 years education) and W.S. (male, age 43, 14 years education), participated. Both patients suffered an ischemic episode several years prior to testing with no other significant neurologic history. Both patients have above average IQ scores (Wechsler Adult Intelligence Scale full-scale scores 113 and 109, respectively) and show normal performance on the Wisconsin Card Sorting Test (six categories each), but both patients are severely impaired on tests of long-term memory (Wechsler Memory Scale delay scores <50). Patient F.S. has been described in more detail previously (Hirst, Phelps, Johnson, & Volpe, 1988). Bilateral ischemic damage to the hippocampus proper was confirmed by structural magnetic resonance imaging (MRI) in patient W.S., with sparing of adjacent medial temporal lobe structures (see Figure 5). Although the extent of brain injury in patient F.S. could not be confirmed by MRI because of claustrophobia, the etiology is consistent with that of patient W.S. and other amnesics with hypoxic insults described in the literature (Verfaille, Koseff, & Alexander, 2000; Zola-Morgan, Squire, & Amaral, 1986).

Two healthy control groups matched for age and level of education also participated. For one control group ($N = 8$; mean age = 45 ± 5.76 years, mean education = 15 ± 2.14 years), the experimental protocol was identical to that conducted in the amnesics (same context). This group is the primary comparison group for the amnesic patients. The second control group ($N = 8$; mean age = 49 ± 7.70 years, mean education = 16 ± 3.67 years) underwent reinstatement in a novel (irrelevant) environmental context to demonstrate the context specificity of fear recovery in the paradigm (different context). Five additional participants took part in the study but were removed from the data analysis because their SCRs were more than 2 *SD* below the group mean during at least one experimental phase (nonresponders). All participants provided informed consent for their participation. Control participants were paid $10 per hour and amnesic patients were paid $20 per hour to participate. Controls were recruited by posted advertisements at Yale University and the surrounding community. None of the controls had a history of neurologic or psychiatric disorder as assessed by self-report questionnaires. The study was approved for the ethical treatment of human participants in accordance with local Institutional Review Board guidelines.

Procedure and statistical analysis. Participants underwent the single-cue delay protocol described for Experiment 1 (see Figure 2). The only difference was that the US was an electric shock (stimulus duration = 200 ms, coterminating with CS) delivered transcutaneously to the participants' median nerve (Nicolet stimulating bar electrode model #019–722400 [Madison, WI] with 30 mm electrode spacing). Electrode leads were

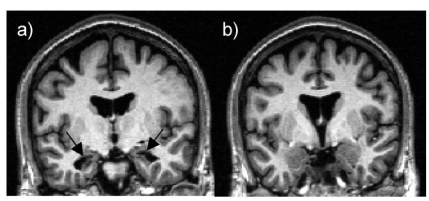

Figure 5. MRI of patient W.S. Two coronal sections of a T1-weighted structural scan obtained at the level of the anterior hippocampus (a) and amygdala (b). Arrows in Panel a indicate selective bilateral atrophy of the hippocampus proper.

secured by a Velcro strap to the wrist of the participant's dominant hand and attached to a Grass Instruments SD-9 stimulator (Quincy, MA) via coaxial cables. Shock intensity was adjusted to be mildly aversive but not painful according to each participant's tolerance (LaBar et al., 1998). Performance of each amnesic patient was compared with the same-context control group by *z*-score transformations of the SCR data. Mean *z* scores lower than 1.5 *SD* from controls were taken as evidence for impairment in the patients.

Awareness of the reinforcement contingencies was assessed immediately following the extinction phase in a verbal semistructured interview (LaBar, Cook, Torpey, & Welsh-Bohmer, 2004). Participants were asked general questions about the US ("Did you find the shock to be aversive?") that increased in specificity to probe knowledge about the CS–US contingency ("Did you try to anticipate when the shock would occur?" to "Did you think there was any relationship between the presentation of the square and the shock?"). Participants were only classified as aware if they could verbally state that the shock followed the presentation of the CS.

Results and Discussion

Preliminary ANOVAs were conducted to assess whether the specific environmental context in which learning occurred (Context A or B) had any overall impact on conditioned responding. No significant main effects of learning context were found for any phase of the experiment, so SCR data were combined across all participants in each of the two control groups irrespective of which particular context served as the learning context.

Unconditioned responses. Unconditioned responses during acquisition and reinstatement were analyzed by a three-way (Group × Phase × Trial Block) mixed ANOVA in controls (see Table 1). A main effect of trial block was found, $F(1, 14) = 9.51$, $p < .008$, indicating habituation to the US over time in both acquisition and reinstatement phases. A main effect of group was also found, $F(1, 14) = 5.68$, $p < .03$, indicating greater US responsivity in the different-context group relative to the same-context group. Amnesic patients F.S. and W.S. were within 1 *SD* of their same-context controls with regard to US responsivity across both phases. The group effect in controls is likely attributable to the subjective thresholding of shock intensity that was adjusted to each person's tolerance level. Because of this group difference in unconditioned responsivity, SCR normalization procedures were conducted prior to statistical analysis of the conditioned response data according to standard methods described by Lykken (1972). This range-correction procedure expresses responses to the CS relative to each participant's largest unconditioned response. In this way, conditioned responses can be directly compared across groups without confounding baseline differences in overall arousability, including a general increase in skin conductance levels (LaBar et al., 2004).

Habituation, acquisition, and extinction. A three-way (Group × Phase × Trial Block) mixed ANOVA was computed on conditioned SCRs observed during the habituation, acquisition, and extinction phases to compare performance across the two control groups (see Figure 6). The results showed a main effect of phase, $F(2, 28) = 4.72$, $p < .02$. Follow-up dependent *t* tests showed that responses in acquisition were greater than those in habituation, $t(15) = 3.15$, $p < .007$, and there was a similar trend for increased responses in extinction compared with habituation, $t(15) = 2.00$, $p = .07$. These results suggest that fear was acquired and persisted into the extinction phase. To confirm that responses were extinguished prior to reinstatement, we conducted a dependent *t* test on the last half of the acquisition and extinction phases only. This analysis yielded a significant main effect of phase, $t(15) = 2.26$, $p < .04$, indicating greater responses at the end of acquisition than at the end of extinction. It is important to note that there were no significant group effects. The two control groups thus had similar levels of habituation, acquisition, and extinction prior to the reinstatement manipulation.

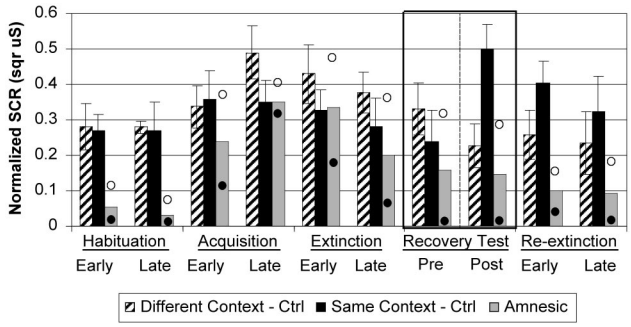

Figure 6. Mean (±*SEM*) conditioned responses by group and experimental phase for Experiment 3. The reinstatement phase took place at the time point indicated by the vertical dashed line. Recovery of extinguished fear (between vertical solid lines) occurred only for control participants who underwent reinstatement in the same environmental context. Data from each amnesic patient are indicated by circles (open circle = W.S.; closed circle = F.S.), and their mean is indicated by the gray bar. Amnesics showed intact acquisition and extinction of fear during the initial training session, but they did not show fear recovery following reinstatement in the same environmental context. SCR = skin conductance response; sqr = square-root transformed; μS = microsiemens; Pre = last prereinstatement trial; Post = first postreinstatement trial; Ctrl = control. *$p < .05$.

Relative to their same-context control group, amnesic patients F.S. and W.S. achieved the same level of fear acquisition and extinction during the initial training session (see Figure 6). Each of the patients exhibited greater conditioned responses during acquisition than during habituation or extinction. Their performance was within 1 *SD* of controls on all phases of the initial training session except the first habituation trial block ($z = -1.64$). This latter result suggests a deficit in initial orienting responses to novel stimuli in amnesia.

Awareness of the reinforcement contingencies was assessed by probing each participant's declarative knowledge of the stimulus relationships after the last extinction trial in a semistructured interview (see *Method*). Neither amnesic patient was able to verbalize the predictive relationship between the CS and US. All control participants were able to report the correct stimulus contingency.

Recovery test and reextinction. Recovery of conditioned fear following reinstatement was analyzed by a two-way (Group × Trial) mixed ANOVA comparing the last extinction trial (immediately prior to the reinstatement phase) with the first recovery test trial (immediately following the reinstatement phase) in control subjects. This analysis yielded a Group × Trial interaction, $F(1, 14) = 14.98$, $p < .002$ (see Figure 6). Post hoc dependent *t* tests showed that conditioned responses in the same-context group significantly increased from extinction to the recovery test, $t(7) = 3.17$, $p < .02$, whereas conditioned responses in the different-context group showed a decreasing trend, $t(7) = -2.25$, $p = .06$.

When responses across the two groups were directly compared on the recovery test trial, the same-context group showed larger responses than the different-context group, $t(14) = 2.90$, $p < .01$. These results confirm the primary hypothesis that conditioned fear recovery following reinstatement is context specific. A two-way (Group × Trial Block) mixed ANOVA computed on data from all reextinction trials did not show any significant effects, although recovery in the same-context group was numerically greater throughout the phase. The lack of statistically significant effects throughout the reextinction phase may be partly due to the lower sample size relative to those in Experiments 1 and 2.

Despite intact acquisition and extinction of fear, amnesic patients F.S. and W.S. did not exhibit fear recovery following reinstatement in the same context (see Figure 6). Neither patient increased their conditioned responses from the last extinction trial to the first recovery test trial. Relative to their same-context control group, the amnesics showed impairments on the first recovery test trial ($z = -1.75$), which extended into the early trial block of reextinction ($z = -1.71$). These results support the primary hypothesis that fear recovery following reinstatement is hippocampus-dependent.

General Discussion

The present series of experiments showed that recovery of extinguished fears can be experimentally manipulated in humans through the use of a reinstatement procedure. The reinstatement effect was found to be context dependent in healthy participants, as conditioned fear recovery was found only for participants who underwent reinstatement in the same environmental context and not for those who underwent reinstatement in a novel (irrelevant) environmental context (Experiments 1 and 3). The findings were not related to group differences in habituation, acquisition, or extinction (Experiments 1–3), nor were they related to differences in global autonomic responsivity, as unconditioned responses were the same across the groups in Experiment 1, and group differences in unconditioned responding were controlled in Experiment 3 through SCR normalization procedures (LaBar et al., 2004; Lykken, 1972). The reinstatement effect was consistent across two different USs (white noise in Experiments 1 and 2; wrist shock in Experiment 3) and two different conditioning procedures (single-cue delay in Experiments 1 and 3; discrimination in Experiment 2). Experiment 2 established that conditioned fear acquisition and recovery was specific to the CS+ paired with the US and did not generalize to an explicitly unpaired CS−, underscoring the role of associative learning in the paradigm and the cue specificity of the reinstatement effect. Experiment 2 also ruled out the possibility that the recovery of fear was due to general elevation of baseline skin conductance levels, which would have affected the CS+ and CS− trials indiscriminately. Fear recovery following reinstatement was transient and reextinguished after several CS-alone trials. The context dependence, cue specificity, and extinction of fear recovery are consistent with behavioral studies of the reinstatement phenomenon in nonhuman animals (Bouton, 1984; Bouton & Bolles, 1979; Bouton & King, 1983; Rescorla & Cunningham, 1978; Rescorla & Heth, 1975).

Two amnesic patients with hypoxic insults did not exhibit recovery of fear responses following reinstatement in the same context, despite showing intact conditioned fear acquisition and extinction during the initial training session (Experiment 3). Because group differences in overall arousability were controlled through SCR normalization procedures, the lack of fear recovery cannot be attributed to lower baseline skin conductance levels during the recovery test. The acquisition of conditioned fear in the amnesics occurred despite having impaired declarative knowledge about the reinforcement contingency. These patients were also deficient in generating initial orienting responses to the CS during the habituation phase, although they had normal unconditioned responses. Their performance is consistent with lesion studies of the hippocampus in animal models of fear reinstatement (Frohardt et al., 2000; Wilson et al., 1995). Collectively, these findings highlight the importance of contextual cues in modulating the expression of latent conditioned associations in humans and suggest that behavioral and neural mechanisms of fear reinstatement are conserved across species.

Modulatory Influence of Environmental Contextual Cues on Memory Retrieval

On a theoretical level, the results of the present study are important in demonstrating contextual influences on human memory performance. Despite the predominant role of spatiotemporal binding in theories of memory function, environmental contextual manipulations on memory have produced inconsistent results in the laboratory (Fernandez & Glenberg, 1985). There have been several successful reports of context-facilitated memory when items are studied and tested in the same environmental setting (Balch, Bowman, & Mohler, 1992; Godden & Baddeley, 1975; Parker & Gellatly, 1997; Schab, 1990; Smith, 1985, 1988). These studies have involved direct memory assessments, such as recall and recognition, which tap into explicit or declarative memory processes (Schacter, 1987; Squire, 1992).

Fewer studies have found contextual influences using indirect memory assessments, such as incidental learning, transfer-of-learning paradigms, or tests of implicit (nondeclarative) memory (Chun & Jiang, 1998; Jacoby & Witherspoon, 1982; Smith, Heath, & Vela, 1990). Proponents of the multiple memory system viewpoint hypothesize a more restricted effect of contextual manipulations on implicit forms of memory, given that contextual binding is a distinguishing characteristic of episodic memory formation (Tulving, 1983). These theories typically classify simple forms of Pavlovian conditioning as examples of implicit memory, especially for single-cue delay procedures in which learning can occur in the absence of explicit knowledge (Clark, Manns, & Squire, 2002; LaBar & Disterhoft, 1998; but see Lovibond & Shanks, 2002). The results of Experiments 1 and 3, then, implicate the contextual modulation of an implicitly derived behavioral response. This interpretation is bolstered by the results from the amnesic patients (Experiment 3) and animal studies (see below). Because explicit knowledge influences conditioned fear acquisition on discrimination procedures (see LaBar et al., 2004), the results from Experiment 2 cannot be interpreted similarly.

In comparison with previous environmental context manipulations in humans, the present study is also noteworthy in two respects. The first is that the original learning and test contexts were identical within subjects. The experimental groups differed only with respect to the context in which an interposed experimental phase (reinstatement) took place. This contrasts typical

context studies in which the spatial configurations are varied between the study and test environments. Another feature that distinguishes our experiment is that it does not rely on list learning (see also Chun & Jiang, 1998; Smith & Vela, 1992). One criticism concerning the inconsistency of environmental context manipulations is that most studies involve learning of word lists whose items have been previously established in semantic memory and whose encounters span multiple context instantiations. In the present study, the introduction of an aversive US and its affiliation with distinct sensory cues provide a more unique and salient environmental linkage.

Human Amnesia and Hippocampal Contributions to Contextual Fear Memory

Previous studies of human fear conditioning have revealed a double dissociation between the role of the amygdala and hippocampus with respect to conscious awareness and physiological indices of learning (reviewed in LaBar & Disterhoft, 1998). Bechara et al. (1995) described an amnesic patient with spared amygdala function who acquired simple conditioned fear associations but who failed to explicitly recall the stimulus contingencies. Patients with amygdala damage who are not amnesic exhibit the opposite dissociation—they do not acquire conditioned fear physiologically but they do have intact declarative memory for the conditioning episode (Bechara et al., 1995; LaBar et al., 1995; Phelps et al., 1998). The two patients in the present report provide further evidence for a dissociation between impaired explicit memory but intact physiological acquisition of cued fear on single-cue delay tasks in amnesia. In addition, our findings go beyond prior research by revealing that simple conditioned associations that are acquired in amnesia are not appropriately bound to contextual features of the environment. In particular, the amnesics performed as through they underwent reinstatement in an irrelevant context (see Figure 6). This result provides a novel demonstration of a deficit in contextual fear memory in amnesia.

Bouton (1988, 1993) has hypothesized that the mechanism underlying fear recovery in this paradigm is related to the US–context associations that are reestablished in the reinstatement phase of the experiment. Such US–context pairings signal the extinguished CS–US association and promote fear recovery, provided that the reinstatement and recovery phases occur in the same environmental context. Two lines of evidence support this interpretation. First, direct tests show that contextual fear occurs during the reinstatement phase (Bouton, 1984; Bouton & King, 1983). Second, fear recovery is reduced by mere exposure to the context between reinstatement and recovery testing (Bouton & Bolles, 1979). This indicates that recovery is dependent on the fearfulness of the contextual cues presented in the test phase. It is thought that the hippocampus forms associations between the US and features of the environmental context in which reinstatement occurs, which serves to recover the latent association of the CS with the aversive reinforcer and disambiguate the meaning of the extinguished CS (Frohardt et al., 2000; Wilson et al., 1995). Findings from reinstatement procedures support other evidence for a role of the hippocampus in forming fear associations with environmental contexts (Fanselow, 2000; Maren & Holt, 2000; Rudy & O'Reilly, 2001).

The results of the present study show that this selective role of the hippocampus in mediating contextual aspects of conditioned fear extends to the human brain. Structural MRI confirmed that in patient W.S., ischemic damage was limited to the hippocampus proper, with sparing of adjacent medial temporal lobe regions. In patient F.S., MRI information was not available, but the etiology, neuropsychological profile, and task performance were similar to W.S. and other patients reported in the literature (Bechara et al., 1995; Verfaille, Koseff, & Alexander, 2000; Zola-Morgan, Squire, & Amaral, 1986). The hippocampus is especially susceptible to hypoxic insults, but we cannot rule out the contribution of other brain regions to task performance in this patient. It must be noted that other organic syndromes that affect medial temporal lobe function often include both the amygdala and the hippocampus, including temporal lobe epilepsy, viral encephalitis, and Urbach-Wiethe syndrome in some cases. Consequently, in many amnesic patients, contextual fear recovery cannot be assessed because the concomitant amygdala damage precludes initial acquisition of the conditioned fear response.

An incidental finding in these patients was a reduction in autonomic orienting responses to the initial CS presentation in the habituation phase. This result is consistent with previous reports of decreased orienting and novelty detection in patients with medial temporal lobe damage, including Alzheimer's disease (Daffner, Scinto, Weintraub, Guinessey, & Mesulam, 1992). Because the patients had normal responses to the US, it appears that orienting deficits can be overcome by increasing the emotional salience of the stimulus (see also LaBar, Mesulam, Gitelman, & Weintraub, 2000).

Clinical Implications

The findings of the present study may help to elucidate the psychological and neural mechanisms by which conditioned behaviors recover in affective disorders following extinction therapy (Bouton & Swartzentruber, 1991; Rodriguez et al., 1999). Many anxiety disorders, including phobias and posttraumatic stress disorder, are characterized by hippocampal dysfunction and inappropriate contextual control over the expression of acquired fear responses (Charney, Deutsch, Krystal, Southwick, & Davis, 1993; Mineka & Zinbarg, 1996). The present results indicate that the hippocampus plays a critical role in fear recovery when latent conditioned fear associations are reinstated by encountering a US and subsequent extinguished CSs in the same environment. It is important to note that fear recovery is transient in healthy adults and reextinguishes following several CS encounters in the absence of reinforcement. It is unknown whether patients with affective disorders would show normal extinction of the recovered fear response, generalization of the reinstatement effect to different contexts or different sensory cues (e.g., the CS−), or reinstatement by internal rather than external contexts. If anxiety patients experience reinstatement after extinction and engage in avoidance responses that preclude reextinction of the fear response, maladaptive emotional responses may persist. The present study provides an experimental framework to test these ideas, thereby linking contemporary associative learning theory and clinical applications of animal conditioning models.

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