Cue-Selective Characteristics of the Reconsolidation Updating Mechanism in Remote Fear Memory Postprint

Authors: Hu Jingchu, Zhang Weixin, Chen Xiaoting, Wang Wenqing, Wang Zijie, Zhuang Chuqun, Feng Biao, Zheng Xifu

Date: 2018-12-04T00:00:00+00:00

Abstract

Both animal and human studies have demonstrated that the memory reconsolidation updating mechanism can effectively weaken newly formed conditioned fear memories (1 day) and exhibits cue-selective characteristics. However, post-traumatic stress disorder (PTSD) is often treated only after a considerable period following its formation, and in real life, people typically acquire fear to multiple cues simultaneously. Therefore, identifying effective therapeutic approaches for multi-cue traumatic memories is particularly crucial. Currently, no studies have investigated whether cue-selective characteristics exist in the reconsolidation updating mechanism of remote fear memories. To investigate whether the reconsolidation updating mechanism of remote fear memories (>7 days) similarly exhibits cue-selective characteristics, the present study employed a within-subjects experimental design, using skin conductance as an index of fear response, with multiple cues serving as conditioned stimuli for fear acquisition. Fourteen days after acquisition, a single cue was presented to subjects for fear memory retrieval, followed by extinction training 10 minutes later, and spontaneous recovery tests for different cues were conducted on day 15. Results showed that the spontaneous recovery level for non-retrieved cues was significantly higher than that for retrieved cues. This indicates that the reconsolidation updating mechanism of remote memories (14 days) also exhibits cue-selective characteristics, and confirms the effectiveness of retrieval-extinction as a behavioral approach for intervening in the reconsolidation of remote fear memories, which holds certain guiding significance for clinical intervention.

Full Text

Cue Specificity of Reconsolidation Update Mechanism in Remote Fear Memories

HU Jingchu[1],[2], ZHANG Weixin[1],[3], CHEN Xiaoting[1], WANG Wenqing[1], WANG Zijie[1], ZHUANG Chuqun[1], FENG Biao[1], ZHENG Xifu[1]

[1]School of Psychology, South China Normal University, Guangzhou 510631, China
[2]School of Life Sciences, South China Normal University, Guangzhou 510631, China
[3]Sun Yat-Sen Memorial Secondary School, Zhongshan 528400, China

Received: December 5, 2017
Supported by National Natural Science Foundation of China (31771218) and Guangdong Provincial Doctoral Startup Fund

HU Jingchu and ZHANG Weixin contributed equally to this work
Corresponding author: ZHENG Xifu, E-mail: zhengxf@scnu.edu.cn

Abstract

Recent studies of fear memories conducted in both humans and animals have suggested that new fear memories (less than 1-day old) can be attenuated using a reconsolidation update mechanism, which is selective to the reactivated cue. In real life, patients with post-traumatic stress disorder (PTSD) usually receive treatment much after the traumatic memories form, and a traumatic event can be associated with multiple cues. However, the cue specificity of reconsolidation update mechanism in remote fear memories (> 14 days) remains largely unknown.

To assess the cue specificity of remote fear memories (14 days) reconsolidation, we explored whether retrieval-extinction during the reconsolidation time window of remote fear memories is selective to the reactivated cue. We used a within-subject design, and skin-conductance response (SCR) served as the measurement. All subjects underwent fear conditioning by three coloured squares on day 1. Two squares (CSa+ and CSb+) were paired with the shock on 38% of the trials. The third square (CS−) was never paired with the shock. Fourteen days later, subjects received a single presentation of CSa+ (reactivated CS+) but not CSb+ (non-reactivated CS+). Ten minutes after the reminder trial, extinction training was conducted (within the reconsolidation window). Twenty-four hours later, all subjects returned to the experiment room and received spontaneous recovery test of the remote fear memories.

Results showed that there is no recovery for the reminded CS+, but significant recovery for non-reminded CS+ during spontaneous recovery testing. The recovery index (which was calculated as the first trial on day 16 minus the last

trial on day 15 by differential SCR) of non-reminded CS+ was found to be significantly higher than that of the reminded CS+ ($p < 0.05$). Thus, retrieval-extinction during reconsolidation window only attenuates the fear memory of the reactivated cue.

Our findings demonstrated that the reconsolidation update mechanism is effective for attenuating remote fear memories, and that this mechanism is selective to the reactivated cue of remote memories. We provide evidence to support the ongoing efforts in the development of novel strategies to combat remote pathogenic memories, which we think could lead to a more effective application of the reconsolidation update mechanism.

Keywords: remote memory reconsolidation; cue specificity; conditioned fear; retrieval-extinction
Classification Code: B845

Introduction

The formation of fear memory is typically based on the classical Pavlovian fear conditioning model, which posits that a neutral stimulus CS (Conditioned Stimulus, e.g., a tone) that originally does not elicit fear will, after being repeatedly paired with an aversive or frightening US (Unconditioned Stimulus, e.g., electric shock), gradually acquire the ability to evoke conditioned fear responses. When this neutral CS is presented alone, individuals will exhibit fear responses toward it (Mineka & Zinbarg, 2006). Conditioned fear can also be extinguished: when the CS continues to be presented without the aversive stimulus, the learned fear response gradually diminishes. In clinical practice, exposure therapy based on extinction training principles is commonly used to treat fear-related emotional disorders (Barlow, Allen, & Choate, 2016). However, fear often returns in various forms after extinction training, such as spontaneous recovery, renewal, and reinstatement, making the treatment effects suboptimal. This occurs because extinction training creates a new inhibitory memory that competes with the original CS-US fear memory, rather than weakening the original fear memory itself, resulting in a new CS-no US association (Bouton, 2002).

Traditional memory consolidation theory holds that once a memory is consolidated, it becomes permanent and unchangeable. This view has been challenged in recent years, as researchers have demonstrated that consolidated memories can be reactivated through retrieval, returning to a labile state before being restabilized through a process called reconsolidation (Alberini, 2005; Dudai, 2004; Nader, 2003). The reconsolidation update mechanism can effectively weaken fear memories and prevent their return. In animal studies, administering protein synthesis inhibitors (anisomycin) immediately after reactivating newly formed fear memories significantly reduced fear responses in subsequent tests (Nader, Schafe, & Le, 2000). Subsequently, Doyère, Debiec, Monfils, Schafe, and Ledoux (2007) found that reconsolidation of newly formed fear memories in rats exhibits cue specificity—meaning the reconsolidation update

mechanism can selectively attenuate fear memories for specific cues that have been retrieved, and this cue specificity is achieved by selectively altering synaptic plasticity in the amygdala through retrieval. Due to the side effects of drugs in humans, researchers later proposed a behavioral intervention paradigm called retrieval-extinction, which involves conducting extinction training within the reconsolidation time window after memory retrieval to weaken the original fear memory. Monfils, Cowansage, Klann, and Ledoux (2009) first validated the effectiveness of the retrieval-extinction paradigm, demonstrating that extinction training within the reconsolidation time window after memory retrieval effectively weakened newly formed fear memories in rats. Schiller et al. (2010) were the first to successfully intervene in human reconsolidation of newly formed fear memories using the retrieval-extinction paradigm and confirmed that human fear memory reconsolidation also exhibits cue specificity.

If the reconsolidation update mechanism can weaken fear memories, it would have significant implications for PTSD treatment. However, PTSD patients rarely receive immediate treatment after trauma memory formation, and most clinical interventions target remote memories. Remote fear memories have been shown to differ fundamentally from newly formed ones. Several rodent studies indicate that remote memories are less susceptible to retrieval interference compared to recent memories (Milekic & Alberini, 2002; Suzuki et al., 2004). Suzuki et al. (2004) found that administering anisomycin to interfere with memory reconsolidation 56 days after mice acquired conditioned fear responses did not produce the interference effect observed with recent memories. This is because remote and recent fear memories rely on different neural mechanisms: new fear memory encoding and storage depend more on the hippocampus, whereas remote memory storage depends more on the neocortex (Anagnostaras, Maren, & Fanselow, 1999; Eichenbaum, Otto, & Cohen, 1994; Frankland, O' Brien, Ohno, Kirkwood, & Silva, 2001; Kim & Fanselow, 1992; LeDoux, 1999; Mcclelland, Mcnaughton, & O' Reilly, 1995; McGaugh, 2000; Quevedo et al., 1999; Squire & Alvarez, 1995). Consequently, reactivating remote memories requires activating cortical regions rather than just the hippocampus, and because cortical areas are extensive, achieving such activation is more difficult (Bontempi, Laurentdemir, Destrade, & Jaffard, 1999; McClelland et al., 1995).

Currently, most human fear memory reconsolidation research has focused on newly formed (1-day-old) fear memories, with no studies examining fear memories older than 7 days. However, real-life traumatic memories are often remote and typically involve multiple learned cues. Therefore, whether reconsolidation of multi-cue remote fear memories can be successfully intervened and whether it exhibits cue specificity has become a critical question.

To investigate whether the reconsolidation update mechanism for remote fear memories exhibits cue specificity and whether this mechanism is effective for human remote fear memories, we employed Schiller et al.' s (2010) retrieval-extinction paradigm. Participants acquired fear memories on day 1, underwent retrieval on day 14, received extinction training within the reconsolidation time

window, and were tested for spontaneous recovery the following day. This design allowed us to examine whether 14-day-old conditioned fear memories could be intervened and whether the intervention exhibited cue specificity, thereby advancing the clinical application of memory reconsolidation update mechanisms in psychotherapy.

2. Method

2.1 Participants

Twenty-eight university students (15 male, 13 female) participated voluntarily, aged 18–23 years (M = 23.34, SD = 1.18). Participants were recruited through campus announcements. Potential subjects were first screened via telephone for history of mental disorders and recent use of psychiatric medication. Selected participants were right-handed, free from physical illness and mental disorders, had normal or corrected-to-normal vision, no color blindness or weakness, and no prior participation in similar experiments.

Before the formal experiment, participants were informed: "This is a fear emotion experiment. Electrodes will be attached to the distal pads of your left index and ring fingers to record skin conductance, and mild electric shocks will be administered to your right wrist. Since individual sensory thresholds vary, shock intensity will be assessed before the formal experiment. The shock equipment has been scientifically evaluated and will not cause any harm. You may terminate the experiment at any time if you feel uncomfortable, and you will be compensated after completing the three-day experiment." Participants then signed informed consent forms and completed the State-Trait Anxiety Inventory. Both state anxiety (M = 38.21, SD = 1.32) and trait anxiety (M = 38.90, SD = 2.29) were within normal ranges.

After equipment setup, we confirmed that participants could see the computer screen clearly and hear the experimenter' s instructions before proceeding with the formal experiment.

2.2 Experimental Stimuli

Conditioned Stimuli (CS): Visual images served as CSs—specifically, yellow, blue, and green squares. Two colors were paired with the US (CSa+ and CSb+), while the third color was never paired with the US (CS−) [Figure 1: see original paper]. To avoid color preferences and order effects, stimulus colors and presentation sequences were counterbalanced. All three images were standard colors of equal size and brightness, presented for 4 s against a standard white background. To balance potential effects across participants, each color had equal probability of serving as CS+.

Unconditioned Stimulus (US): Following Schiller et al. (2010), we used wrist shock as the US to evoke fear. Shock duration was 200 ms. Considering individual differences in sensory thresholds, participants self-determined the shock

intensity that felt "extremely uncomfortable but tolerable" before the formal experiment.

2.3 Experimental Procedure

Shock Intensity Assessment: Before the formal experiment, each participant' s tolerable shock intensity was determined—the level that felt extremely uncomfortable but bearable. Assessment began at a mild 10 V and increased in 10 V increments, with participants reporting their feelings after each increase until they indicated reaching the target level (maximum 50 V). Each shock lasted 200 ms at 50 pulses per second. This intensity remained constant throughout all subsequent experimental phases.

The experiment spanned three days: day 1 (acquisition phase), day 15 (retrieval-extinction phase), and day 16 (spontaneous recovery test phase) [Figure 2: see original paper]. Before the formal experiment, participants received detailed instructions to ensure comprehension.

Day 1—Acquisition Phase: CSa+ and CSb+ were each presented 13 times (no more than two consecutive presentations of the same CS), each lasting 4 s with an inter-trial interval (ITI) of 12–18 s. Thirty-eight percent (5 trials) of CSa+ and 38% (5 trials) of CSb+ were paired with shock. CS− was presented 8 times without shock.

Day 15—Retrieval-Extinction Phase: Participants received a single 4-s presentation of CSa+ to reactivate the learned fear memory. After a 10-min rest, extinction training commenced. During extinction, CSa+, CSb+, and CS− were each randomly presented 11 times (33 trials total), each lasting 4 s with ITI of 12–18 s, all without shock.

Day 16—Spontaneous Recovery Test Phase: CSa+, CSb+, and CS− were each randomly presented 11 times (33 trials total), each lasting 4 s without shock, with ITI of 12–18 s.

All stimuli were presented using E-prime 2.0. Each trial began with a red fixation cross "+" (1000 ms), followed by the CS (4 s), and then either the US or a white screen (200 ms) [Figure 3: see original paper]. Participants made no button responses during the experiment.

2.4 Measurement Indices

Skin conductance response (SCR) served as the fear index. A Biopac MP150 polygraph recorded SCR via electrodes connected to the EDA100C module at a sampling rate of 2000 samples/second. Biopac' s AcqKnowledge software processed the data offline: the maximum and minimum values within a 0.5–4.5 s window after CS onset were extracted, and their difference (in microsiemens) served as the CS-evoked SCR. Responses below 0.02 microsiemens were considered noise and scored as zero. All SCR values were range-corrected: square-root

transformed to normalize distribution and reduce skewness, then divided by each participant' s average US-evoked SCR.

All data were analyzed using SPSS 17.0. Repeated measures ANOVA with Stimulus Type (CSa+, CSb+, CS−) × Phase (Early, Late) was conducted for each experimental phase (acquisition, extinction, spontaneous recovery), with Bonferroni post-hoc tests or paired-sample t-tests for specific comparisons.

3. Results

3.1 Acquisition Phase

A repeated measures ANOVA with Stimulus Type (CSa+, CSb+, CS−) and Experimental Phase (Early Acquisition: first 4 trials; Late Acquisition: last 4 trials) revealed significant main effects of Stimulus Type, $F(2, 56) = 9.79$, $p < 0.001$, $^2p = 0.26$, and Experimental Phase, $F(1, 28) = 18.70$, $p < 0.001$, $^2p = 0.40$, as well as a significant interaction, $F(2, 56) = 3.89$, $p < 0.05$, $^2p = 0.12$.

Bonferroni post-hoc tests showed no significant differences among CSa+, CSb+, and CS− during early acquisition ($p = 1.00$, $p = 0.45$, $p = 0.37$). However, during late acquisition, significant differences emerged between CSa+ and CS− and between CSb+ and CS− ($p < 0.001$, $p < 0.01$), while CSa+ and CSb+ remained nonsignificant ($p = 0.30$).

Paired-sample t-tests on late acquisition SCR means comparing CSa+ vs. CS− and CSb+ vs. CS− revealed significantly higher SCRs to CSa+ and CSb+ than to CS− [CSa+: $t(28) = 6.07$, $p < 0.001$, Cohen' s d = 1.25; CSb+: $t(28) = 3.95$, $p < 0.001$, Cohen' s d = 0.83], with no significant difference between CSa+ and CSb+, $t(28) = 1.70$, $p = 0.10$, Cohen' s d = 0.32.

Overall, participants showed comparable fear levels to all three stimulus types during early acquisition. As the phase progressed to late acquisition, SCRs to CSa+ and CSb+ became significantly higher than to CS−, while remaining comparable between CSa+ and CSb+, indicating successful fear conditioning [FIGURE:4, FIGURE:5].

3.2 Extinction Phase

A repeated measures ANOVA with Stimulus Type (CSa+, CSb+, CS−) and Experimental Phase (Early Extinction: first 4 trials; Late Extinction: last 4 trials) showed significant main effects of Stimulus Type, $F(2, 56) = 6.50$, $p < 0.01$, $^2p = 0.19$, and Experimental Phase, $F(1, 28) = 25.56$, $p < 0.001$, $^2p = 0.48$, and a significant interaction, $F(2, 56) = 4.16$, $p < 0.05$, $^2p = 0.13$.

To assess extinction efficacy, we compared SCR means for the first three and last three trials of each stimulus type. Paired t-tests revealed significantly higher SCRs to CSa+ and CSb+ than to CS− during early extinction [CSa+: $t(28) = 2.94$, $p < 0.01$, Cohen' s d = -0.05; CSb+: $t(28) = 3.48$, $p < 0.01$, Cohen' s d = 0.78]. By late extinction, no significant differences remained between

CSa+/CSb+ and CS− [CSa+: t(28) = -0.69, p = 0.50, Cohen' s d = -0.13; CSb+: t(28) = 1.63, p = 0.12, Cohen' s d = 0.31].

Paired t-tests on the final extinction trial confirmed comparable SCRs among CSa+, CSb+, and CS− [CSa+: t(28) = 0.17, p = 0.87, Cohen's d = 0.03; CSb+: t(28) = 0.99, p = 0.33, Cohen' s d = 0.19], indicating successful extinction. No significant difference between CSa+ and CSb+ in the final trial, t(28) = -0.89, p = 0.38, Cohen' s d = 0.17, suggested equivalent extinction across cues [FIGURE:4, FIGURE:5].

3.3 Spontaneous Recovery Test Phase

A repeated measures ANOVA with Stimulus Type (CSa+, CSb+, CS−) and Experimental Phase (Early Recovery: first 4 trials; Late Recovery: last 4 trials) revealed significant main effects of Stimulus Type, $F(2, 56) = 3.17$, $p < 0.05$, $^2p = 0.10$, and Experimental Phase, $F(1, 28) = 26.43$, $p < 0.001$, $^2p = 0.49$, and a significant interaction, $F(2, 56) = 4.69$, $p < 0.05$, $^2p = 0.14$.

Bonferroni post-hoc tests showed that during early recovery, SCRs to CSb+ were significantly greater than to both CSa+ ($p < 0.05$) and CS− ($p < 0.01$), while CSa+ and CS− did not differ ($p = 1.00$). By late recovery, all differences among CSa+, CSb+, and CS− became nonsignificant (ps = 1.00). This pattern indicates that during early spontaneous recovery, participants showed significant recovery to the non-reactivated CSb+ but not to the retrieval-extinction trained CSa+. As the phase progressed without US presentation, initial recovery to CSb+ gradually extinguished, and responses to all stimuli converged [Figure 4: see original paper].

To further examine changes from extinction to recovery, we conducted a two-way repeated measures ANOVA on differential SCRs (CSa+ minus CS−; CSb+ minus CS−) with Stimulus Type (CSa+, CSb+) and Experimental Phase (final extinction trial; first recovery trial). Results showed a significant main effect of Stimulus Type, $F(1, 28) = 10.15$, $p < 0.01$, $^2p = 0.27$, no main effect of Phase, $F(1, 28) = 0.52$, $p = 0.48$, and a significant interaction, $F(1, 28) = 5.63$, $p < 0.05$, $^2p = 0.17$.

Paired t-tests comparing differential SCRs between the final extinction trial and first recovery trial revealed that the CSb+ vs. CS− difference was significantly larger during early recovery than at the end of extinction, $t(28) = -2.07$, $p < 0.05$, Cohen' s d = 0.15, whereas the CSa+ vs. CS− difference remained unchanged, $t(28) = 0.78$, $p = 0.44$, Cohen' s d = -0.39 [Figure 6: see original paper]. This confirms that the retrieved CSa+ showed no spontaneous recovery, while the non-retrieved CSb+ exhibited significant recovery.

Discussion

This study investigated whether retrieval-extinction training can intervene in human remote fear memory reconsolidation and whether cue specificity exists.

Participants acquired fear on day 1, underwent fear memory retrieval and extinction training on day 15, and completed spontaneous recovery testing on day 16. Results demonstrated that retrieval-extinction successfully intervened in remote fear memory reconsolidation, prevented spontaneous recovery of remote fear, and exhibited cue specificity.

The cue specificity observed in remote memory reconsolidation update mechanisms may occur because retrieving a single cue selectively reactivates only the specific remote fear memory trace for that cue in the cerebral cortex, rendering only that memory labile and susceptible to intervention. This suggests that fear memories for different cues may be encoded and stored via distinct pathways in specific cortical regions, highlighting the complexity of human memory encoding and storage.

Our findings align with some animal studies using pharmacological interventions on remote fear memory reconsolidation (Debiec, Ledoux, & Nader, 2002; Nader et al., 2000) and with Steinfurth et al.' s (2014) human study, which used retrieval-extinction to intervene in 7-day-old fear memory reconsolidation and successfully prevented remote fear return. Our results confirm memory lability: both newly formed and remote memories can be readily modified when new safety information enters the reconsolidation window.

Notably, our results diverge from some animal studies using retrieval-extinction for remote fear memories. For example, Clem and Huganir (2010) found that retrieval-extinction could not prevent return of 7-day-old remote memories in mice, possibly due to stronger fear memories in laboratory animals. Ethical considerations prevent creating excessively strong fear memories in human participants, making laboratory-conditioned fear memories potentially more malleable. Additionally, although molecular mechanisms of memory consolidation are similar across species, memory time scales may differ due to lifespan variations. With human lifespan around 70 years and mouse lifespan about 2 years, 14 days for a mouse may correspond to approximately 490 days of human memory (Dutta & Sengupta, 2016; Quinn, 2005).

This study is the first to use retrieval-extinction to intervene in 14-day-old remote memory reconsolidation in humans and confirms cue specificity in remote fear memory reconsolidation update mechanisms. For humans, even 14-day-old remote memories can be modified through retrieval-induced reactivation. These findings advance our understanding of human fear memory characteristics and facilitate translation of basic research to clinical applications, enabling targeted interventions based on differences between recent and remote traumatic memories. The study also illuminates human-animal differences: humans can rapidly retrieve specific fear memories through brief cue exposure, with remote fear memories following the same principles. Our findings provide guidance for using retrieval-extinction to treat traumatic memories, offering clinical value since real-life traumatic memories rarely receive immediate intervention, unlike typical laboratory-conditioned fear memories.

Several limitations should be noted. First, because fear acquisition and extinction were prerequisites, we excluded participants who failed to acquire or extinguish fear, preventing measurement of spontaneous recovery in these individuals (Kindt, Soeter, & Vervliet, 2009; Sotres-Bayon, Diaz-Mataix, Bush, & Ledoux, 2009; Yang, Chao, & Lu, 2006). Second, we used SCR, an autonomic nervous system index, to measure conditioned fear. However, SCR is sensitive to room temperature and weather, which differed substantially between day 1 (acquisition) and day 15 (retrieval-extinction), explaining why day 1 SCR ranges were much lower than day 15. Third, we used only SCR without cognitive explicit measures (e.g., US expectancy ratings, which estimate shock probability on each trial and represent explicit learning of CS-US associations). However, research indicates that cognitive measures can strengthen learning, making CS-US associations more explicit and potentially resistant to extinction (Warren et al., 2014), while also interacting with SCR measures. For these reasons, we preferred a non-invasive, autonomic index, though this limited data acquisition.

In conclusion, this study confirms cue specificity in remote fear memory reconsolidation update mechanisms and demonstrates that 14-day-old remote fear memories can be successfully weakened through extinction training within the reconsolidation window following retrieval, reaffirming retrieval-extinction as an effective behavioral intervention for memory reconsolidation.

References

Alberini, C. M. (2005). Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes?. *Trends in Neurosciences*, 28(1), 51–56.

Anagnostaras, S. G., Maren, S., & Fanselow, M. S. (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: within-subjects examination. *Journal of Neuroscience*, 19(3), Bontempi, B., Laurent-demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature*, 400(6745), 671–675.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biological Psychiatry*, 52(10), 976–986.

Barlow, D. H., Allen, L. B., & Choate, M. L. (2016). Toward a unified treatment for emotional disorders. *Behav Ther*, 35(2), 838–853.

Clem, R. L., & Huganir, R. L. (2010). Calcium-permeable ampa receptor dynamics mediate fear memory erasure. *Science*, 330(6007), 1108–1112.

Debiec, J., Ledoux, J. E., & Nader, K. (2002). Cellular and systems reconsolidation in the hippocampus. *Neuron*, 36(3), 527–538.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram?. *Annual Review of Psychology*, 55(1), 51–86.

Doyère, V., Debiec, J., Monfils, M. H., Schafe, G. E., & Ledoux, J. E. (2007). Synapse-specific reconsolidation of distinct fear memories in the lateral amygdala. *Nature Neuroscience*, 10(4), 414–416.

Dutta, S., & Sengupta, P. (2016). Men and mice: relating their ages. *Life Sciences*, 152, 244–248.

Eichenbaum, H., Otto, T., & Cohen, N. J. (1994). Two functional components of the hippocampal memory system. *Behavioral & Brain Sciences*, 17(3), 449–472.

Frankland, P. W., O' Brien, C., Ohno, M., Kirkwood, A., & Silva, A. J. (2001). Alpha-camkii-dependent plasticity in the cortex is required for permanent memory. *Nature*, 411(6835), 309–313.

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science*, 256(5057), 675–677.

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: erasing human fear responses and preventing the return of fear. *Nature Neuroscience*, 12(3), 256–258.

Ledoux, J. E. (1999). Emotion circuits in the brain. *Annual Review of Neuroscience*, 23(23), 155–184.

Mcclelland, J. L., Mcnaughton, B. L., & O' Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, 102(3), 419–457.

Mcgaugh, J. L. (2000). Memory–a century of consolidation. *Science*, 287(5451), 248–251.

Milekic, M. H., & Alberini, C. M. (2002). Temporally graded requirement for protein synthesis following memory reactivation. *Neuron*, 36(3), 521–525.

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. *American Psychologist*, 61(1), 10–26.

Monfils, M., Cowansage, K. K., Klann, E., & Ledoux, J. E. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science*, 324(5929), 951–955.

Nader, K. (2003). Memory traces unbound. *Trends in Neuroscience*, 26, 65–72.

Nader, K., Schafe, G. E., & Le, D. J. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, 406(6797), 722–726.

Quevedo, J., Vianna, M. R., Roesler, R., De-Paris, F., Izquierdo, I., & Rose, S. P. (1999). Two time windows of anisomycin-induced amnesia for inhibitory

avoidance training in rats: protection from amnesia by pretraining but not preexposure to the task apparatus. *Learning & Memory*, 6(6), 600–607.

Quinn, R. (2005). Comparing rat' s to human' s age: how old is my rat in people years?. *Nutrition*, 21(6), 775–777.

Rie, I., Hotaka, F., Frankland, P. W., & Satoshi, K. (2016). Hippocampal neurogenesis enhancers promote forgetting of remote fear memory after hippocampal reactivation by retrieval:. *Elife*, 5.

Schiller, D., Monfils, M. H., Raio, C. M., Johnson, D. C., Ledoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, 463(7277), 49–53.

Sotres-Bayon, F., Diaz-Mataix, L., Bush, D. E., & Ledoux, J. E. (2009). Dissociable roles for the ventromedial prefrontal cortex and amygdala in fear extinction: nr2b contribution. *Cerebral Cortex*, 19(2), 474–482.

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology*, 5(2), 169–177.

Steinfurth, E. C., Kanen, J. W., Raio, C. M., Clem, R. L., Huganir, R. L., & Phelps, E. A. (2014). Young and old pavlovian fear memories can be modified with extinction training during reconsolidation in humans. *Learning & Memory*, 21(7), 338–341.

Suzuki, A., Josselyn, S. A., Frankland, P. W., Masushige, S., Silva, A. J., & Kida, S. (2004). Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *Journal of Neuroscience the Official Journal of the Society for Neuroscience*, 24(20), 4787–4795.

Warren, V. T., Anderson, K. M., Kwon, C., Bosshardt, L., Jovanovic, T., & Bradley, B., et al. (2014). Human fear extinction and return of fear using reconsolidation update mechanisms: the contribution of on-line expectancy ratings. *Neurobiology of Learning & Memory*, 113(3), 165–173.

Yang, Y. L., Chao, P. K., & Lu, K. T. (2006). Systemic and intra-amygdala administration of glucocorticoid agonist and antagonist modulate extinction of conditioned fear. *Neuropsychopharmacology*, 31(5), 912–924.

Note: Figure translations are in progress. See original paper for figures.