Persistent attenuation of fear memories in humans: A registered replication of the reactivation-extinction effect

Anastasia Chalkia, Ann-Kathrin Zenses, Natalie Schroyens, Lukas Van Oudenhove, Tom Beckers

KU Leuven

Address for correspondence: Tom Beckers

Department of Psychology

KU Leuven

Tiensestraat 102, box 3712

3000 Leuven

Belgium

Tel +32 16 32 61 34

Fax +32 16 32 60 99

E-mail tom.beckers@kuleuven.be

This is a Registered Report manuscript that was Stage-1 accepted at Cortex on February 24, 2017 and modified on September 21, 2017 to incorporate changed participant exclusion criteria in light of information provided by the authors of the original report, in agreement with the editor.

Abstract

It has been proposed that memory retrieval can destabilize consolidated memories, after which they need to be reconsolidated in order to be retained. The presentation of relevant information during memory reconsolidation could then result in the modification of a destabilized memory trace, by allowing the memory trace to be updated before being reconsolidated. In line with this idea, Schiller et al. (2010) have demonstrated that memory retrieval shortly before extinction training can prevent the later recovery of conditioned fear responding that is observed after regular extinction training. Those findings have been the subject of considerable controversy, due in part to theoretical reasons but also due to a number of failures to obtain similar results in conceptual replication attempts. Here, we report the results of a direct, independent replication of the critical conditions of Schiller et al. (2010, Experiment 1).

Key words: fear learning; extinction; memory updating; reconsolidation; memory reactivation

1. Introduction

It has been known for almost 50 years that upon retrieval, memory traces can become sensitive to amnestic interventions that interfere with their later expression (Riccio, Millin, & Bogart, 2006; Sara, 2000). In contextual fear conditioning, when animals are first trained to be afraid of a context, e.g., by the administration of foot shock in that context, a brief re-exposure to that context the next day will retrieve the contextual fear memory. When retrieval is immediately followed by the administration of electroconvulsive shock to the brain, later expression of fear when the animals are brought into that same context will be prevented (Misanin, Miller, & Lewis, 1968). Similar effects can be obtained by the administration of amnestic drugs (e.g., anisomycin; Nader, Schafe, & Le Doux, 2000) or other interventions shortly after memory retrieval (for a review, see Beckers & Kindt, 2017). The standard account for such post-retrieval amnesia holds that memory retrieval can bring a firmly consolidated memory trace back into an active, unstable state, in which it critically depends on de-novo protein synthesis in dedicated brain areas in order to get reconsolidated and return to a stable state (Nader et al., 2000; Przybyslawski & Sara, 1997). Interventions that prevent protein synthesis during the time-limited reconsolidation period (such as the administration of electroconvulsive shock or pharmacological agents that impair protein synthesis) interfere with the restabilization of the memory trace, resulting in functional memory loss (for an alternative account of post-retrieval amnesia, see Riccio et al., 2006).

More recently, it has been proposed that the phenomenon of memory destabilization and reconsolidation upon retrieval allows for mnemonic outcomes other than the blunt induction of amnesia. More specifically, it has been argued that the reconsolidation process presents a window of opportunity to update the contents of the memory trace, by presenting novel

information after reactivation that is of relevance for the memory. One example in kind is the exploitation of reconsolidation to solidify the effects of extinction training after fear conditioning. In regular fear extinction training, a conditioned stimulus (CS) that was previously paired with an aversive unconditioned stimulus (US) is repeatedly presented on its own, resulting in a gradual decline of fear responding to the CS. An extensive body of research suggests that the decline in conditioned fear responding does not reflect a modification of the original fear memory trace but the creation of an additional, context-dependent extinction memory trace that competes with the fear memory for behavioral control (Bouton, 1993). As a consequence, fear tends to recover whenever the physical or temporal context of extinction training is abandoned (Bouton, 2002; Vervliet, Craske, & Hermans, 2013). Recent findings suggest that such recovery can be prevented by the execution of extinction training during a period of instability of the initial fear memory trace, that is, during the retrieval-induced reconsolidation window. More specifically, Monfils and colleagues demonstrated that if rats were given extinction training within a period of six hours after memory reactivation (reactivation being achieved by the presentation of a single CS, unreinforced), they did not exhibit any return of fear in later fear memory recovery tests (Monfils, Cowansage, Klann, & LeDoux, 2009). In contrast, rats that received extinction training outside of the reconsolidation window showed a recovery of fear when tested one month later (spontaneous recovery), when tested after the presentation of unsignalled shocks (reinstatement) or when tested in a novel context (renewal) after extinction training. The explanation offered by the authors is that the presentation of extinction training during memory reconsolidation allows for the extinction information to be incorporated in the original fear memory trace, rather than it resulting in the formation of a separate extinction

memory trace, thereby permanently modifying or updating the original fear memory and effectively preventing the possibility for the later recovery of fear.

Shortly thereafter, Schiller et al. (2010, Experiment 1) reported similar effects in humans. In a Pavlovian differential fear-conditioning procedure, participants first received acquisition using two fear-irrelevant stimuli (CS+ and CS-; pictures of a blue and a yellow square). The CS+ was paired with a mild 200-ms shock to the wrist (US), on 37.5% of the trials, while the CS- was never paired with the US. The following day, participants were allocated to one of three groups before receiving extinction training. The first group was presented with a single unreinforced CS+ trial to reactivate the fear memory ten minutes before the start of extinction training. The second group was presented with the reactivation trial six hours before receiving extinction training. In the third group, the fear memory was not reactivated prior to extinction training. Spontaneous recovery of conditioned fear was assessed 24 h later during a re-extinction test session, in which participants were again presented with unreinforced CS+ and CS- trials. In the group that received extinction training within the putative six-hour window of reconsolidation, spontaneous recovery was not observed, unlike in the other two groups. Likewise, in a subsample of the initial participants tested 12 months later, sensitivity to reinstatement was observed in participants from the latter two groups but not in those from the first group. According to the authors' interpretation, those results suggest that also in humans, conducting extinction training during a period of reconsolidation may permanently abolish conditioned fear, by inducing an update of the previously acquired fear memory.

The findings of Schiller et al. (2010), and the accompanying notion of persistent modification of emotional memory through a reactivation-extinction logic, have attracted tremendous attention, not in the least because of their clinical potential for the treatment of Post-

Traumatic Stress Disorder (PTSD) and other emotional memory disorders (Beckers & Kindt, 2017). However, they have also generated considerable controversy, in part due to theoretical reasons. The reactivation-extinction procedure essentially entails performing extinction training with a 10-min interval between the first and the second extinction trial, and the findings are not necessarily consistent with other observations regarding the spacing of extinction training (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013; Baker, McNally, & Richardson, 2013). As importantly, attempts at conceptual replication of these findings have yielded mixed results. In addition to two published successful replications from the same lab (Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Steinfurth et al., 2014), a few other groups have been able to demonstrate similar results in human aversive learning paradigms (Agren et al., 2012; Agren, Björkstrand, & Fredrikson, 2017; Asthana et al., 2016; Björkstrand et al., 2016; Johnson & Casey, 2015; Oyarzún et al., 2012). Of note, those studies were not exact replications of the original study by Schiller et al. (2010), as they exhibited variations in US selection procedures, US intensity used, reinforcement schedules and others. Other labs have failed to replicate the Schiller et al. (2010) findings (e.g., Fricchione et al., 2016; Golkar, Bellander, Olsson, & Ohman, 2012; Kindt & Soeter, 2013; Klucken et al., 2016; Meir Drexler et al., 2014; Soeter & Kindt, 2011; Warren et al., 2014). Those failed attempts deviated in important ways from the protocol of the original study as well, e.g., by the addition of fear-potentiated startle (FPS) measurements (necessitating the repeated presentation of loud noise bursts during acquisition, reactivation, extinction and testing), the trial-by-trial assessment of US expectancies, or the use of fear-relevant stimuli during conditioning. Independent replications of the related findings in rats by Monfils et al. (2009) have proven equally challenging, with some labs reporting successes (e.g., Clem & Huganir, 2011; Flavell, Barber, & Lee, 2011; Jones, Ringuet, & Monfils, 2013;

Olshavsky, Jones, Lee, & Monfils, 2013; Piñeyro, Ferrer Monti, Alfei, Bueno, & Urcelay, 2013; Rao-Ruiz et al., 2011) but others reporting failures (e.g., Chan, 2014; Chan, Leung, Westbrook, & McNally, 2010; Costanzi, Cannas, Saraulli, Rossi-Arnaud, & Cestari, 2011; Ishii et al., 2012; Luyten & Beckers, in prep; Pérez-Cuesta & Maldonado, 2009).

A recent meta-analysis of reactivation-extinction studies in humans and non-human animals suggests that there is no significant benefit of post-retrieval fear extinction over regular fear extinction training in animals, but that there is a small-to-moderate benefit in humans (Kredlow, Unger, & Otto, 2016). The opposite picture emerges for appetitive learning. Whereas the same meta-analysis yields a large and significant effect for preventing the return of appetitive memories in animals (Kredlow et al., 2016), results in humans are so far sparse and heterogeneous (e.g., Bakkour, Schonberg, Hover, & Poldrack, 2015; Xue et al., 2012).

While some have argued that the mixed findings discussed above cast doubts on the very possibility of fear memory updating through a reactivation-extinction procedure, others have suggested that the divergent results may be attributed to untested boundary conditions that may have been fulfilled in the original reports and the successful replications, but not in the failed attempts at conceptual replication (Auber et al., 2013; Kredlow et al., 2016; Schiller & Phelps, 2011). The divergence in procedures between the original reports and the subsequent replication attempts indeed allows for such an argument. For instance, the addition of noise probes or online US expectancy ratings or the use of fear-relevant CSs may lead to qualitative changes in fear learning that somehow present a challenge for the reactivation-extinction procedure (e.g., by making learning more explicit in nature). Of note, Kredlow and colleagues (2016) also conducted moderator analyses on the studies included in their meta-analysis, and indeed identified a number of potential moderators for the benefit of reactivation-extinction over regular

extinction (e.g., number of acquisition trials, shock duration, inclusion of expectancy ratings). Arguably, however, these potential moderators should be considered tentative, given the limited number and relatively small sample size of studies included in the meta-analysis, the fact that potential moderators identified there have not been systematically tested, and the possibility, as with any meta-analysis, of publication bias. Trim and fill analyses were conducted by Kredlow et al. (2016) to adjust reactivation-extinction effect sizes for publication bias, but no adjustment was deemed necessary. Nevertheless, they observed a tendency for larger effect sizes to be associated with smaller sample size. As such, the argument for boundary conditions as an explanation for the failed replication attempts may be considered premature in the absence of a direct, well-powered independent replication of the original findings. If the original findings would prove to be robust in a direct independent replication, a systematic assessment of critical boundary conditions would seem warranted and timely indeed. On the other hand, if the original findings would not be readily reproducible in a direct independent replication, an empirical search for theoretically inspired boundary conditions may be misguided. Therefore, the aim of the present replication report is to perform an exact replication of the critical conditions and manipulations reported by Schiller et al. in their seminal study (Schiller et al., 2010, Experiment 1).

2. Material and Methods

2.1 Participants

124 (n = 62 per group) participants within the age range of 18 to 48 years will be recruited through the KU Leuven experiment management system. All participants will be screened for the following medical exclusion criteria: Pregnancy, current or past heart or cardiovascular disease, lung disease or lung problems, neurological problems, any psychiatric diagnosis (in the past or

present), other severe medical problems, current use of anticholinergic or anti-adrenergic medication, benzodiazepines, or non-stable doses of psychotropic medication, request from the general practitioner to avoid stressful situations, any type of electronic implant, and pain or problems located at the hand or wrist. In line with Schiller et al. (2010), participants that do not show successful fear acquisition (first session) or extinction of fear (second session) in skin conductance responses (SCR) will also be excluded. Inspection of the original data and correspondence with the first and last author of Schiller et al. (2010) revealed that the exclusion criteria employed in their Experiment 1 deviated from the criteria as described in Schiller et al. (2010). We were presented with a new set of criteria by the authors, which they confirmed to be accurate to the editors of Cortex and us on September 21, 2017. It is that set of criteria that are applied here. In particular, with respect to acquisition, participants will be included if the differential CS+/CS- response is above an individually-standardized cut-off (0.1 microS divided by the participant's average square-rooted US response during acquisition) on either all of acquisition averaged; the first half of acquisition trials; the last half of acquisition trials; or the very last trial of acquisition, or if the increase in differentiation from the first trial of acquisition to the last trial of acquisition exceeds this cut-off value, or if the increase in differentiation from the first half to the last half of acquisition trials exceeds this cut-off value. With respect to extinction, participants will be included if the CS+/CS- difference is below this same cut-off for either all extinction trials averaged; the last half of extinction trials; or the last trial of extinction, or if the decline in differential responding from the first trial to the last trial of extinction exceeds this cut-off, or if the decline in differential responding from the first half to the last half of extinction exceeds this cut-off. Participants will be excluded if they fail to meet the stated criteria for either acquisition or extinction. Excluded participants will be replaced until the

predetermined sample size (N=124) is reached. The study has been granted full ethical approval by the Social and Societal Ethics Committee of KU Leuven. All participants will give informed consent before the start of the study, and will be reimbursed with 30 euros or partial course credit for their participation.

2.2 Stimuli and Behavioral Manipulation

A three-day Pavlovian cued fear conditioning paradigm will be employed. Sessions will be conducted on three consecutive days, about 24 hours apart. Two pictures of colored squares (yellow and blue) will serve as the CSs and a mild electric shock to the wrist will serve as the US. One CS, designated the CS+, will be paired with shock on 37.5% of the trials, while the other CS, the CS-, will never be paired with shock. Allocation of CSs will be counterbalanced across participants. CS pictures will be presented for 4 s, with a random 10-12 s inter-trial interval (ITI). Shocks will be delivered 3800 ms after CS onset, and will co-terminate with CS offset.

2.3 Psychophysiological Measures

2.3.1 Skin conductance response (SCR)

SCR will be measured continuously at 200 Hz using a pair of disposable, pre-gelled 8-mm Ag/AgCl electrodes (Biopac Systems, Goleta, California) attached to the index and middle fingers of the left hand, between the first and second phalanges. The electrodes are connected to an isolated skin conductance coupler (LabLinc v71-23, Coulbourn Instruments, Holliston, Massachusetts). The skin conductance module is further connected to a 16-bit AD-converter (National Instruments NI-6221, Austin, Texas), which digitizes the raw analogue SCR signal.

2.3.2 Electrical Stimulation

Mild electric shocks to the right inner wrist will be delivered through a stimulating bar electrode, composed of two 8-mm stainless steel electrodes with an inter-electrode distance of 30 mm (Digitimer, Hertfordshire, UK). All shocks will be given for 200 ms, at 50 pulses per second, and shock delivery will be controlled by a constant current stimulator (DS7A, Digitimer, Hertfordshire, UK). Using a shock work-up procedure, the shock intensity level will be determined for each participant individually. Specifically, each subject will be given a very low stimulus at first (1 mA), and the intensity will gradually increase in steps of 1 mA until a level is reached that is "uncomfortable, but not painful". Once selected, the intensity will remain the same for all three days of the experiment, and will not be re-calibrated again.

2.4 Subjective Assessments

In the original study by Schiller et al. (2010), no subjective assessments were reported. In order to obtain a baseline measure of anxiety, and to confirm that there are no significant differences between groups, the trait version of the State and Trait Anxiety Inventory (STAI-T; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1977) and the short version of the Fear of Pain Questionnaire (FPQ; McNeil & Rainwater, 1998) will be administered at the end of the experiment, as to not interfere with the original protocol.

2.5 Procedure

Following attachment of the electrodes, each day will begin with a 5-min SCR habituation phase for all groups, during which SCR will be recorded while no stimuli are presented (see Schiller, Raio, & Phelps, 2012). Two counterbalanced, pseudo-randomized orders of trial presentations will be pre-determined and used throughout the experiment, with the restriction that no trial type is presented more than two times in a row.

2.5.1 Acquisition

During the initial session, all participants will undergo fear acquisition. After electrode placement, the first session will begin with the shock work-up procedure. Afterwards, and upon completion of the habituation phase (see above), participants will be instructed to keep their eyes on the screen, breathe naturally, and refrain from any unnecessary movements. They will be informed that they will see some visual stimuli on the screen, and that they will receive occasional shocks. Their task will be to focus on the relationship between the images and the shock presentations. Conditioning will consist of 16 CS+ trials (6 reinforced, 10 unreinforced) and 10 CS- trials.

2.5.2 Reactivation and Extinction

Before the start of the second session, participants will be allocated randomly to one of two conditions: *1) Reactivation, or 2) NoReactivation*[1]. Participants in the reactivation group will be instructed as on day 1, and will receive a single, unreinforced CS+ trial, followed by a 10-min break. Participants in the no-reactivation group will not receive a reactivation trial, but will proceed directly to a 10-min break, during which all participants will watch a preselected Simpsons episode (see Schiller et al., 2012). All electrodes will remain attached (Schiller et al., 2012), but participants will be informed explicitly that no shock will be administered during the break.

After the break, both groups will proceed immediately to extinction training. For the reactivation group, extinction will consist of 10 unreinforced CS+ trials and 11 unreinforced CS- trials. For the no-reactivation group, extinction will consist of 11 CS+ and 11 CS- trials, thus equating the number of CS presentations across groups.

2.5.3 Spontaneous Recovery, Re-Extinction and Reinstatement

At the start of the third session, all participants will be instructed as on day 1 and presented with 10 unreinforced CS+ trials and 11 CS- trials in order to: 1) assess spontaneous recovery of fear, and 2) extinguish any remaining conditioned responding. As can be noticed above, during re-extinction one CS- trial more is presented than there are CS+ trials. The additional CS- trial will always be the very first trial; in line with Schiller et al. (2010), it will be discarded from analysis to remove the influence of orienting. After the first trial, the order of the stimuli will be counterbalanced between CS+/CS- across all participants. Following re-extinction, all participants will advance to a 10-min break, where they will be asked to sit quietly in the experimental room without doing anything. All electrodes will remain attached, but participants will be informed explicitly that no shocks will be administered during the break.

Schiller et al. (2010) re-invited participants to the lab one year later to test for reinstatement of fear. If the amnesia induced by their procedure is indeed invulnerable to reinstatement up to one year later, it should surely exhibit insensitivity to reinstatement on a shorter time scale. Therefore, we will test for reinstatement at the end of the third session, thereby avoiding the attrition observed by Schiller et al. (2010) and allowing to distinguish the presence of genuine reinstatement from the mere spontaneous recovery that may occur with the extended passage of time. This should provide an additional opportunity to observe differences between reactivation-extinction and regular extinction training in preventing recovery of fear should there not be any difference at the start of the spontaneous recovery test. Of note, this test of reinstatement does not aspire to directly replicate the methods of the reinstatement test of Schiller and colleagues (2010) and should be regarded as a supplementary test; the main measure of interest for the replication test is the degree of spontaneous recovery at the start of the test session. To test for reinstatement, following the 10-min break, four unsignalled shocks will be

delivered, with a random 10-12 s ITI. After another 10-min break where all participants will watch the same Simpsons episode (see Steinfurth et al., 2014), a test of reinstatement will be conducted, consisting of the presentation of 10 unreinforced CS+ trials and 10 unreinforced CS- trials. The session will conclude with the administration of the STAI-T and the FPQ-SF.

2.6 Analyses

2.6.1 Processing of psychophysiological data

Processing of SCR data will be completed offline, with two separate approaches, using MATLAB 8.4 (The Mathworks Inc., Natick, Massachusetts). First, and as the primary processing approach, raw SCR data will be processed according to the methods reported in Schiller et al. (2010). SCR to the CSs and USs will be determined separately, as the dependent variables for conditioned (CR) and unconditioned (UR) responding, respectively. SCR will be determined by taking the base to peak difference in the 0.5 to 4.5 s window following stimulus onset (CS and US onset separately). A minimum response criterion of 0.02 μs will be used. Raw SCR data will be square root transformed, and these values will further be range-corrected for each participant by dividing the value by that participant's mean square root transformed US response. Concurrently, a second processing method will be applied, for a second set of planned analyses. The mean baseline response in a 2 s period before CS onset will be subtracted from the highest skin conductance response obtained in the 0.5 to 4.5 s window following CS onset. To standardize the data, means and standard deviations from the first testing session will be used to calculate within-participant Z-scores. This is a method that is more typically applied in the processing of SCR data in our lab and elsewhere (Milad, Orr, Pitman, & Rauch, 2005; Pitman & Orr, 1986).

2.6.2 Statistical Analyses

The primary and critical set of statistical analyses will copy the analyses reported by Schiller et al. (2010). Only SCR responses during unreinforced trials will be included in the analysis, excluding the reinforced CS+ trials from the acquisition phase, to exclude an influence of unconditioned (shock-elicited) responding. A differential fear score will be calculated individually for each participant, by subtracting the values for CS- from those for CS+ for corresponding trials. These difference scores will then be averaged across the first and the second half (first 5 versus last 5 trials) of each phase and subjected to a repeated measures analysis of variance (rm-ANOVA) with group as a between-subjects factor and time (early versus late phase) as a within-subjects factor. To assess the decrease of fear responding from acquisition to extinction an rm-ANOVA will be used with group as a between-subjects factor and time (late acquisition, last trial of extinction) as a within-subjects factor. Follow up *t*-tests will be conducted for each group separately to assess successful acquisition and extinction. In line with Schiller et al. (2010), spontaneous recovery will be assessed by calculating the change in differential responding from the last trial of extinction to the first trial of re-extinction. Sensitivity to reinstatement will be assessed by calculating the change in differential responding from the last trial of re-extinction to the first trial of reinstatement testing. The critical test to evaluate a successful replication of Schiller et al. (2010) then involves an independent samples *t*-test that compares the changes in differential responding from the end of extinction to the start of re-extinction (for spontaneous recovery) between the groups. Additionally, and as a secondary outcome, reinstatement will be compared between the two groups through an independent samples *t*-test comparing the change in differential responding from the end of re-extinction to the start of reinstatement testing. Finally, one-sample *t*-tests will be conducted to evaluate the presence of spontaneous recovery and reinstatement within each group.

Furthermore, a second set of analyses will also be conducted. For these analyses, difference scores will not be calculated, but instead, responses for CS+ will be compared to those for CS-. So, using this method, and mimicking the set of analyses discussed above, cue (CS+ versus CS-) will be included as an additional within-subjects factor, to allow examination of the specific course of SCR responding throughout the three days of the study. Outliers will be defined for each day (Z-score > 3) and replaced by linear trend at point. Greenhouse–Geisser corrections will be applied in case of violation of sphericity. An alpha level of .05 will be set for all analyses.

2.6.3 Power Analysis

To determine the number of participants required to have sufficient power to replicate the effects reported by Schiller et al. (2010), an a priori power analysis was conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007). Based on the overall estimated effect size for the difference in spontaneous recovery between reactivation-extinction and regular extinction groups of g = 0.53 in human fear memory experiments included in the meta-analysis of Kredlow et al. (2016), and adopting an alpha level of .05 (one-tailed), a sample size of 62 participants per group yields a power of .9 to replicate the benefit of reactivation-extinction over regular extinction in preventing spontaneous recovery in the critical independent t-test described above (the effect size for the actual experiment replicated here (Schiller et al., 2010, Experiment 1) was g = .732). A sample size of 62 per group also clearly fulfills the suggestion that replication efforts include 2.5 times the original sample size, offered by Simonsohn (2015) on the basis of his "small telescopes" approach (which basically entails that if an effect is sufficiently large to have a minimal chance of being detected using a sample size of x, a sample of 3 times x should provide sufficient power to detect it in a replication irrespective of what the actual effect size is).

Footnote

1. The study of Schiller et al. (2010) included an additional group, in which memory reactivation was performed prior to extinction training, but the interval between retrieval and extinction training (6 h) was hypothesized to exceed the reconsolidation window. This condition has since been omitted from most replication studies, and will also not be included here, because no differences are expected between this group and the no reactivation group; the critical result to replicate is the significant difference in recovery of conditioned fear responding between the regular extinction group and the reactivation-extinction group included here.

Acknowledgement

Preparation of this manuscript and collection of the data was/will be supported by ERC Consolidator Grant 648176 awarded to Tom Beckers.

References

Agren, T., Björkstrand, J., & Fredrikson, M. (2017). Disruption of human fear reconsolidation using imaginal and in vivo extinction. *Behavioural Brain Research*, *319*, 9–15. http://doi.org/10.1016/j.bbr.2016.11.014

Agren, T., Engman, J., Frick, A., Björkstrand, J., Larsson, E.-M., Furmark, T., & Fredrikson, M. (2012). Disruption of reconsolidation erases a fear memory trace in the human amygdala. *Science (New York, N.Y.)*, *337*(6101), 1550–2. http://doi.org/10.1126/science.1223006

Asthana, M. K., Brunhuber, B., Mühlberger, A., Reif, A., Schneider, S., & Herrmann, M. J. (2016). Preventing the Return of Fear Using Reconsolidation Update Mechanisms Depends on the Met-Allele of the Brain Derived Neurotrophic Factor Val66Met Polymorphism. *International Journal of Neuropsychopharmacology*, *19*(6), 1–9. http://doi.org/10.1093/ijnp/pyv137

Auber, A., Tedesco, V., Jones, C. E., Monfils, M. H., & Chiamulera, C. (2013). Post-retrieval extinction as reconsolidation interference: Methodological issues or boundary conditions? *Psychopharmacology*, *226*(4), 631–647. http://doi.org/10.1007/s00213-013-3004-1

Baker, K. D., McNally, G. P., & Richardson, R. (2013). Memory retrieval before or after extinction reduces recovery of fear in adolescent rats. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *20*(9), 467–73. http://doi.org/10.1101/lm.031989.113

Bakkour, A., Schonberg, T., Hover, A., & Poldrack, R. (2015). Retrieval-extinction within the memory reconsolidation window does not influence appetitive choice. *bioRxiv*. http://doi.org/10.1101/014316

Beckers, T., & Kindt, M. (2017). Memory reconsolidation interference as an emerging treatment for emotional disorders: Strengths, limitations, challenges and opportunities. *Annu. Rev.*

Clin. Psychol, *13*.

Björkstrand, J., Agren, T., Hs, F. Å., Frick, A., Larsson, E.-M., Hjorth, O., … Fredrikson, M. (2016). Disrupting Reconsolidation Attenuates Long-Term Fear Memory in the Human Amygdala and Facilitates Approach Behavior. *Current Biology*, *26*, 1–6. http://doi.org/10.1016/j.cub.2016.08.022

Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry*, *52*(10), 976–986. http://doi.org/10.1016/S0006-3223(02)01546-9

Chan, W. Y. M. (2014). *The effects of retrieval - extinction training on the restoration of Pavlovian conditioned fear*.

Chan, W. Y. M., Leung, H. T., Westbrook, R. F., & McNally, G. P. (2010). Effects of recent exposure to a conditioned stimulus on extinction of Pavlovian fear conditioning. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *17*(10), 512–521. http://doi.org/10.1101/lm.1912510

Clem, R. L., & Huganir, R. L. (2010). Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science*, *330*(6007), 1108–1112. http://doi.org/10.1126/science.1195298.Calcium-Permeable

Costanzi, M., Cannas, S., Saraulli, D., Rossi-Arnaud, C., & Cestari, V. (2011). Extinction after retrieval: effects on the associative and nonassociative components of remote contextual fear memory. *Learning & Memory*, *18*, 508–518. http://doi.org/10.1101/lm.2175811

Faul, F., Erdfelder, E., Lang, A.-G. G., & Buchner, A. (2007). G * Power 3 : A flexible statistical power analysis program for the social , behavioral , and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. http://doi.org/10.3758/bf03193146

Flavell, C. R., Barber, D. J., & Lee, J. L. C. (2011). Behavioural memory reconsolidation of food and fear memories. *Nature Communications*, *2*, 504. http://doi.org/10.1038/ncomms1515

Fricchione, J., Greenberg, M. S., Spring, J., Wood, N., Mueller-Pfeiffer, C., Milad, M. R., … Orr, S. P. (2016). Delayed extinction fails to reduce skin conductance reactivity to fear-conditioned stimuli. *Psychophysiology*, *53*, 1343–1351. http://doi.org/10.1111/psyp.12687

Golkar, A., Bellander, M., Olsson, A., & Ohman, A. (2012). Are fear memories erasable?-reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. *Frontiers in Behavioral Neuroscience*, *6*(November), 80. http://doi.org/10.3389/fnbeh.2012.00080

Ishii, D., Matsuzawa, D., Matsuda, S., Tomizawa, H., Sutoh, C., & Shimizu, E. (2012). No erasure effect of retrieval – extinction trial on fear memory in the hippocampus-independent and dependent paradigms. *Neuroscience Letters*, *523*, 76–81. http://doi.org/10.1016/j.neulet.2012.06.048

Johnson, D. C., & Casey, B. J. (2015). reconsolidation blocks recovery of fear in adolescents. *Scientific Reports*, *5*(8863), 1–5. http://doi.org/10.1038/srep08863

Jones, C. E., Ringuet, S., & Monfils, M. (2013). Learned together, extinguished apart: reducing fear to complex stimuli. *Learning & Memory*, *20*(12), 674–685.

Kindt, M., & Soeter, M. (2013). Reconsolidation in a human fear conditioning study: A test of extinction as updating mechanism. *Biological Psychology*, *92*(1), 43–50. http://doi.org/10.1016/j.biopsycho.2011.09.016

Klucken, T., Kruse, O., Schweckendiek, J., Kuepper, Y., Mueller, E. M., Hennig, J., & Stark, R. (2016). ScienceDirect No evidence for blocking the return of fear by disrupting reconsolidation prior to extinction learning. *CORTEX*, *79*, 112–122. http://doi.org/10.1016/j.cortex.2016.03.015

Kredlow, M. A., Unger, L. D., & Otto, M. W. (2016). Harnessing reconsolidation to weaken fear and appetitive memories: a meta-analysis of post-retrieval extinction effects. *Psychological Bulletin, 142*(3), 314–336. http://doi.org/10.1037/bul0000034

Meir Drexler, S., Merz, C. J., Hamacher-Dang, T. C., Marquardt, V., Fritsch, N., Otto, T., & Wolf, O. T. (2014). Effects of postretrieval-extinction learning on return of contextually controlled cued fear. *Behavioral Neuroscience*, *128*(4), 474–481. http://doi.org/10.1037/a0036688

Milad, M. R., Orr, S. P., Pitman, R. K., & Rauch, S. L. (2005). Context modulation of memory for fear extinction in humans. *Psychophysiology*, *42*(4), 456–464. http://doi.org/10.1111/j.1469-8986.2005.00302.x

Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968). Retrograde Amnesia Produced by Electroconvulsive Shock after Reactivation of a Consolidated Memory Trace. *Science*, *160*, 554–555.

Monfils, M.-H., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science*, *324*(5929), 951–955. http://doi.org/10.1126/science.1167975

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, *406*(6797), 722–726. http://doi.org/10.1038/35021052

Olshavsky, M. E., Jones, C. E., Lee, H. J., & Monfils, M. (2013). Appetitive behavioral traits and stimulus intensity influence maintenance of conditioned fear. *Frontiers in Behavioral Neuroscience*, *7*, 1–7. http://doi.org/10.3389/fnbeh.2013.00179

Oyarzún, J. P., Lopez-Barroso, D., Fuentemilla, L., Cucurell, D., Pedraza, C., Rodriguez-

Fornells, A., & de Diego-Balaguer, R. (2012). Updating fearful memories with extinction training during reconsolidation: A human study using auditory aversive stimuli. *PLoS ONE*, *7*(6). http://doi.org/10.1371/journal.pone.0038849

Pérez-Cuesta, L. M., & Maldonado, H. (2009). Memory reconsolidation and extinction in the crab: mutual exclusion or coexistence? *Learning & Memory (Cold Spring Harbor, N.Y.)*, *16*(11), 714–721. http://doi.org/10.1101/lm.1544609

Piñeyro, M. E., Ferrer Monti, R. I., Alfei, J. M., Bueno, A. M., & Urcelay, G. P. (2013). Memory destabilization is critical for the success of the reactivation-extinction procedure. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *21*(1), 46–54. http://doi.org/10.1101/lm.032714.113

Pitman, R. K. & Orr, S. P. (1986). Test of the Conditioning Model of Neurosis: Differential Aversive Conditioning of Angry and Neutral Facial Expressions in Anxiety Disorder Patients. *Journal of Abnormal Psychology*, *95*(3), 208–213.

Przybyslawski, J., & Sara, S. J. (1997). Reconsolidation of memory after its reactivation. *Behavioural Brain Research*, *84*, 241–246. http://doi.org/10.1016/S0166-4328(96)00153-2

Rao-Ruiz, P., Rotaru, D. C., van der Loo, R. J., Mansvelder, H. D., Stiedl, O., Smit, A. B., & Spijker, S. (2011). Retrieval-specific endocytosis of GluA2-AMPARs underlies adaptive reconsolidation of contextual fear. *Nature Neuroscience*, *14*(10), 1302–1308. http://doi.org/10.1038/nn.2907

Riccio, D. C., Millin, P. M., & Bogart, A. R. (2006). Reconsolidation: a brief history, a retrieval view, and some recent issues. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *13*(5), 536–544. http://doi.org/10.1101/lm.290706

Sara, S. J. (2000). Retrieval and reconsolidation: Toward a neurobiology of remembering. *Learning & Memory*, *7*(2), 73–84. http://doi.org/10.1101/lm.7.2.73

Schiller, D., Kanen, J. W., LeDoux, J. E., Monfils, M.-H., & Phelps, E. A. (2013). Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(50), 20040–5. http://doi.org/10.1073/pnas.1320322110

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. http://doi.org/10.1038/nature08637

Schiller, D., & Phelps, E. A. (2011). Does reconsolidation occur in humans? *Frontiers in Behavioral Neuroscience*, *5*(24), 1–12. http://doi.org/10.3389/fnbeh.2011.00024

Schiller, D., Raio, C. M., & Phelps, E. A. (2012). Extinction training during the reconsolidation window prevents recovery of fear. *Journal of Visualized Experiments : JoVE*, (66), e3893. http://doi.org/10.3791/3893

Simonsohn, U. (2015). Small Telescopes : Detectability and the Evaluation of Replication Results. *Psychological Science*, *26*(5), 559–569. http://doi.org/10.1177/0956797614567341

Soeter, M., & Kindt, M. (2011). Disrupting reconsolidation: pharmacological and behavioral manipulations. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *18*(6), 357–66. http://doi.org/10.1101/lm.2148511

Spielberger, C. D., Gorsuch, R., Lushene, R., Vagg, P., & Jacobs, G. (1977). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press. http://doi.org/10.1037/t06496-000

Steinfurth, E. C. K., 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 (Cold Spring Harbor, N.Y.)*, *21*(7),

338–41. http://doi.org/10.1101/lm.033589.113

Vervliet, B., Craske, M. G., & Hermans, D. (2013). Fear Extinction and Relapse: State of the Art. *Annu. Rev. Clin. Psychol*, *9*, 215–48. http://doi.org/10.1146/annurev-clinpsy-050212-185542

Warren, V. T., Anderson, K. M., Kwon, C., Bosshardt, L., Jovanovic, T., Bradley, B., & Norrholm, S. D. (2014). Human fear extinction and return of fear using reconsolidation update mechanisms: The contribution of on-line expectancy ratings. *Neurobiology of Learning and Memory*, *113*, 165–173. http://doi.org/10.1016/j.nlm.2013.10.014

Xue, Y., Luo, Y., Wu, P., Shi, H., Xue, L., Chen, C., … Lu, L. (2012). A Memory Retrieval-Extinction Craving and Relapse. *Science*, *336*(6078), 241–245.