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Harnessing Reconsolidation to Weaken Fear and Appetitive Memories: A Meta-Analysis of Post-Retrieval Extinction Effects

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Abstract

A new understanding of the mechanisms of memory retrieval and reconsolidation holds the potential for improving exposure-based treatments. Basic research indicates that following fear extinction, safety and fear memories may compete, raising the possibility of return of fear. One possible solution is to modify original fear memories through reconsolidation interference, reducing the likelihood of return of fear. Post-retrieval extinction is a behavioral method of reconsolidation interference that has been explored in the context of conditioned fear and appetitive memory paradigms. This meta-analysis examines the magnitude of post-retrieval extinction effects and potential moderators of these effects. A PubMed and PsycINFO search was conducted through June 2014. Sixty-three comparisons examining post-retrieval extinction for preventing the return of fear or appetitive responses in animals or humans met inclusion criteria. Post-retrieval extinction demonstrated a significant, small-to-moderate effect (g = .40) for further reducing the return of fear in humans and a significant, large effect (g = 0.89) for preventing the return of appetitive responses in animals relative to standard extinction. For fear outcomes in animals, effects were small (g = 0.21) and non-significant, but moderated by the number of animals housed together and the duration of time between post-retrieval extinction/extinction and test. Across paradigms, these findings support the efficacy of this pre-clinical strategy for preventing the return of conditioned fear and appetitive responses. Overall, findings to date support the continued translation of post-retrieval extinction research to human and clinical applications, with particular application to the treatment of anxiety, traumatic stress, and substance use disorders.

Keywords

post-retrieval extinction; reconsolidation; fear conditioning; appetitive memory; cognitive-behavior therapy; exposure therapy

Exposure procedures are a core component of cognitive behavioral treatments for anxiety disorders (McHugh, Smits, & Otto, 2009; Hofmann & Smits, 2008). These procedures rely on the repeated presentation of fear cues in the presence of relative safety, designed to

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weaken the ability of these cues to evoke anxiety. Yet, despite the relative efficacy of exposure-based interventions for anxiety (Hofmann & Smits, 2008; Olatunji, Cisler, & Deacon, 2010) and trauma-related disorders (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010), there remains a large percentage of individuals who do not respond to, relapse after, or drop out of treatment (Bystritsky, 2006; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008), motivating the search for ways to augment treatment effects (Pollack et al., 2008). Exposure procedures have also been applied to substance use disorders, but have met with limited success (Conklin & Tiffany, 2002), again motivating the search for strategies to augment these procedures.

Over the last decade, translational research has played an important role in identifying potential strategies to enhance exposure-based interventions. For example, advances in the understanding of the neural circuits underlying fear acquisition and extinction led to investigations of ways to pharmacologically enhance extinction learning (Davis, Myers, Ressler, & Rothbaum, 2005; Richardson, Ledgerwood, & Cranney, 2004), with a number of promising clinical trials following (for review se Rodrigues et al., 2014). Overall, these pharmacologic strategies are aimed at enhancing the learning of safety in relation to fear cues so that in the competition between fear and safety memories (Bouton, 2002), safety learning can be more likely to dominate. One problem with extinction-based approaches, however, is that fear can return at a later time or when the feared stimulus is encountered in a new context (Bouton, 2002), a phenomenon thought to be parallel to clinical relapse after exposure therapy. Enhancing extinction does not necessarily address this problem because of the continued competition between the original fear learning and subsequent safety memories.

At present, the field is now poised to consider the clinical benefit of another important translational-research finding, which may address this issue: the finding that memories may be rapidly changed by interference with the memory reconsolidation process. New learning leads to a cascade of changes at both the cellular synaptic level and brain systems level (Dudai, 2012; Eichenbaum, 2000), whereby newly-learned information is stored. This process is referred to as *memory consolidation*, and is further defined by a time window in which the newly-formed memory becomes less labile - less susceptible to interference. Once the memory is consolidated, for example, amnestic agents no longer have an effect on the memory, unless the memory is reactivated. That is, upon memory retrieval the neural systems involved in the memory are again activated and go through another period of re-stabilization called *reconsolidation*. As with consolidation, during reconsolidation, memories are labile and susceptible to interference and this window of susceptibility is time limited (thought to be within 6 hours of retrieval). Like consolidation, reconsolidation involves integrating new information into existing memory structures (McKenzie & Eichenbaum, 2011), thereby updating/changing the memory. Interfering with the reconsolidation of a fear memory thus acts on the original fear memory; this contrasts with extinction, which is thought to leave the original memory intact but offset the original memory through introducing new memories of relative safety (Bouton, 2002; Myers & Davis, 2002). In line with this idea, reconsolidation and extinction have been shown to be

distinct processes with unique biochemical signatures (Lee, Milton, & Everitt, 2006; Suzuki et al., 2004).

The clinical research agenda of interfering with memory reconsolidation was set into action by Nader and colleagues (Nader, Schafe, & Le Doux, 2000) who found that during the time period following memory retrieval—a window of time during which the memory was being reconsolidated (i.e. reconsolidation window)—the memory was sensitive to disruption. Specifically, using a de novo fear conditioning paradigm, Nader et al. (2000) showed that administration of a protein-synthesis inhibitor, following presentation of a memory retrieval cue of the conditioned stimulus (i.e. a tone), could block the return of fear. This important finding has been replicated and extended to appetitive memories, using a variety of pharmacologic memory interfering strategies, including the administration of B-Adrenergic and NMDAergic antagonists during the reconsolidation window. Two meta-analyses of these studies (Das, Freeman, & Kamboj, 2013; Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013), indicate reductions in the return of fear or the return of appetitive responses on the order of moderate effect sizes.

In 2009, another innovation was introduced for modifying fear memories. Rather than using pharmacologic strategies to interfere with memory reconsolidation, Monfils and colleagues (Monfils, Cowansage, Klann, & LeDoux, 2009) examined the role of extinction learning during the reconsolidation window. Specifically, they showed that extinction following a memory retrieval cue was more effective than extinction that was not conducted during the reconsolidation window. Their paradigm, termed "*post-retrieval extinction*," mirrored that of Nader and colleagues (2000), except that memory retrieval was followed by the administration of extinction trials rather than a protein synthesis inhibitor. This design was predicated on the theory that reconsolidation is not only a mechanism for re-solidifying a memory, but it can also be instrumental in "updating" a memory with new information (McKenzie & Eichenbaum, 2011;Sara, 2000). In this case, the fear memory is updated with information about safety provided through extinction learning.

Subsequently, Schiller and colleagues (2010) tested this protocol in humans in a de novo fear conditioning paradigm. Healthy participants underwent fear acquisition during which one of two colored shapes (conditioned stimulus, CS+) was associated with a shock (unconditioned stimulus, US). One day later, participants were randomized to extinction training in one of three conditions: (1) extinction without a memory retrieval cue, (2) extinction training 10 minutes after a memory retrieval cue (a single presentation of the CS +), or (3) extinction training 6 hours after a memory retrieval cue (i.e., extinction outside the presumed reconsolidation window). Participants who had received extinction during the reconsolidation window (condition 2) demonstrated significantly less return of fear when tested one day later, with some evidence of maintenance of this effect one year later (Schiller et al., 2010). In contrast, fear returned in the groups that received traditional extinction (condition 1) and extinction outside of the reconsolidation window (condition 3), which is the typical pattern largely observed across extinction studies (Bouton, 2002). Consistent with findings from other studies of reconsolidation (Nader et al., 2000; Monfils et al., 2009), this study also confirmed the notion that the reconsolidation window is time-limited and closes within 6 hours of memory retrieval.

Since this initial research, there have been dozens of studies examining post-retrieval extinction as a means to interfere with the reconsolidation of conditioned fear memories. In addition, researchers have begun to apply the paradigm to appetitive memories, with early promising results (Xue et al., 2012). Yet findings have been mixed, with some studies replicating the positive results of early studies (e.g., Agren, Engman, et al., 2012) and others reporting null results (e.g., Soeter & Kindt, 2011). This has spurred much debate as to whether there are “boundary conditions” which limit the efficacy of the post-retrieval extinction paradigm and reconsolidation interference in general (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013; Lee, 2009; Nader & Hardt, 2009). Although excellent review articles have been written on this topic (Agren, 2014; Auber et al., 2013) and two meta-analyses have been published on pharmacologic strategies to interfere with memory reconsolidation (Lonergan et al., 2013; Das et al., 2013), a meta-analytic review of the post-retrieval extinction literature has not been published, to our knowledge.

In this article, we provide a meta-analysis of the magnitude of post-retrieval extinction effects. Our goal was to examine the reliability of these effects, and, if appropriate, encourage clinical application of these novel strategies which have been largely confined to the research lab in conditioning paradigms. In addition to providing a literature-wide estimate of the overall magnitude of post-retrieval extinction effects, we employed moderator analyses to try to identify potential “boundary conditions” around these effects. Accordingly, one goal for this meta-analysis was to account for some of the substantial variation in results of post-retrieval extinction in order to hone the application of these strategies. In line with the translational nature of this research, we evaluated both animal and human paradigms (cf., Norberg, Krystal, & Tolin, 2008). Further, to address the potential application of findings to both fear-based and addiction-based disorders, we evaluated the magnitude of post-retrieval extinction effects for both fear and appetitive memories, respectively.

Method

Search Strategy

A search of PubMed and PsycINFO was conducted on articles published through June 18, 2014. The Boolean search term *((((reconsolid*) OR reconsolidation) OR "post retrieval extinction") OR "post-retrieval extinction") OR (post AND retrieval AND extinction)* was utilized to encompass any articles including the following search terms: “reconsolid*”, “reconsolidation”, "post retrieval extinction", "post-retrieval extinction", and “post AND retrieval AND extinction.” The reference lists of relevant reviews (Agren, 2014; Auber et al., 2013; Besnard, Caboche, & Laroche, 2012; Bossert, Marchant, Calu, & Shaham, 2013; Cammarota, Bevilaqua, Vianna, Medina, & Izquierdo, 2007; Curran & Robbins, 2013; Debiec, 2012; Dudai, 2012; Flavell, Lambert, Winters, & Bredy, 2013; Gisquet-Verrier & Riccio, 2012; Hartley & Phelps, 2010; Hong et al., 2011; Hunter, 2011; Izquierdo, Cammarota, Vianna, & Bevilaqua, 2004; Lee, 2009; Milton & Everitt, 2010; Nader & Einarsson, 2010; Nader, Hardt, & Lanius, 2013; Robertson, 2012; Schiller & Phelps, 2011; Sorg, 2012; Taylor, Olausson, Quinn, & Torregrossa, 2009; Torregrossa & Taylor, 2013; Wang & Morris, 2010) were also searched manually to identify additional studies. In

addition, email inquiries were sent out to listservs of psychology organizations to solicit unpublished data. Two of the authors independently screened titles, abstracts, and manuscripts of potentially eligible studies.

Selection

Animal or human studies utilizing post-retrieval extinction to interfere with the reconsolidation of fear or appetitive memories were included. Post-retrieval extinction was defined as retrieval of an existing memory through presentation of a conditioned stimulus (CS), followed by extinction conducted during the reconsolidation window (Monfils et al., 2009). Based on existing research (for review, Auber et al., 2013), the reconsolidation window was defined as within 6 hours of retrieval of a memory. Studies of post-retrieval extinction that met the following criteria were included in analyses: 1) conducted in mammals; 2) examined fear or appetitive memories; 3) compared a post-retrieval extinction group/condition to a control group/condition; 4) assessed return of fear/appetitive response through a test of reinstatement, renewal, spontaneous recovery, or reacquisition which took place at least 24 hours after initiation of post-retrieval extinction or extinction; and 5) for human fear studies, outcome was assessed using skin conductance response (SCR). Studies that met any of the following exclusion criteria were eliminated: 1) no full text version in English available; 2) did not include experiments (e.g. reviews); 3) tested aspects of memory other than reconsolidation (e.g. consolidation); 4) used methods other than post-retrieval extinction to interfere with memory reconsolidation (e.g. pharmacological methods); 5) reactivated only part of a compound conditioned stimulus during post-retrieval extinction; 6) involved lesions to the brains of animal subjects; 7) involved human subjects with high likelihood of cognitive impairment (i.e. Xue et al., 2012 human study); 8) in order to increase the homogeneity of the sample, studies of memories which were greater than 7 days old (only one study, Costanzi, Cannas, Saraulli, Rossi-Arnaud, & Cestari, 2011, was excluded for this reason) and 9) to increase consistency with other studies, studies administering different levels of US intensity at acquisition and test; this resulted in the exclusion of such studies from two manuscripts (Chan, 2014; Pineyro, Ferrer Monti, Alfei, Bueno, & Urcelay, 2014). Data from pharmacological studies comparing a post-retrieval extinction and extinction group that were both administered saline were included (Flavell, Barber, & Lee, 2011).

Data Abstraction

Articles meeting the selection criteria were collected and data were abstracted for analysis by the second author and independently checked for accuracy by the first author. Errors were reconciled through discussion amongst the authors.

Study designs—Studies utilized standard experimental methods for appetitive and fear conditioning (for review see Bouton, 2007), thus only unique aspects will be described in detail in this manuscript. All studies involved three sequential procedures: 1) acquisition of conditioned fear or appetitive responses, 2) completion of subsequent extinction or post-retrieval extinction, and 3) a test of return of conditioned behavior. For between-subject designs, subjects were randomized to receive extinction with or without a retrieval cue. For within-subject designs, subjects were presented with two CSs (i.e. CSa+ and CSb+), one of

which was retrieved prior to extinction (CSa+) and one of which was not (CSb+). Within the group of studies that utilized between-subject designs, some studies utilized cued conditioning whereas other studies utilized contextual conditioning.

In appetitive studies, acquisition also consisted of cued or contextual conditioning. In cued conditioning subjects self-administered food or a drug (US) through the active nosepoke operandum, which was associated with a light or light-tone pairing (CS). Extinction involved free access to the nosepoke operandum with presentation of the CS, but without reinforcement (US). Studies achieved retrieval with 1) an unreinforced presentation of the CS without the nosepoke operandum (Olshavsky, Song, et al., 2013) or 2) a brief exposure to the nosepoke operandum with nosepoke responses associated with the CS but not the US (Flavell et al., 2011; Xue et al., 2012). Appetitive studies of contextual conditioning utilized the conditioned place preference (CPP) paradigm. In CPP studies, drug injections were administered while the subject was in one compartment of a multi-compartment apparatus, and saline injections (serving as placebo) were administered while the subject was in another compartment. CPP was established when the subject showed an increase in preference towards the drug-paired compartment. Extinction of CPP was reached either by alternate confined exposure to each compartment until no preference for either compartment was reached (Ma, Zhang, & Yu, 2012) or by sessions of free access to both compartments of the apparatus until preference for the drug-paired compartment was considered extinguished (Sartor & Aston-Jones, 2014). CPP studies achieved post-retrieval extinction by either of two methods: 1) brief confinement to the drug-paired compartment before free access to both compartments was granted, or 2) brief access to both compartments of the apparatus without consequence (e.g., delivery of the US) followed by confinement to the drug- and saline-paired compartments alternatively.

Within studies that met our inclusion criteria, it was often possible for multiple comparisons to be made. In cases when two post-retrieval groups were present within one study, both groups were included in the analyses with statistical procedures accounting for clustering of the data. Some studies also contained more than one group which could be considered a control group, in which case the extinction-only group was favored as the comparison condition. Early articles of post-retrieval extinction often included an additional group receiving retrieval followed by extinction outside of the reconsolidation window (e.g. 6 hours after retrieval) in order to establish that retrieval alone was not driving the effect and that reconsolidation was in fact a time-limited process (e.g. Monfils et al., 2009). In these studies, return of fear in this group mirrored that of the extinction-only group. Given this consistent finding regarding the reconsolidation window, subsequent studies exploring post-retrieval extinction effects focused on the critical comparison between the post-retrieval extinction group and extinction-only group (e.g., Soeter & Kindt, 2011). Thus, for the purposes of this meta-analysis, the group with retrieval and extinction outside of the reconsolidation window was typically not used in the analyses. In the rare case that an extinction-only group was not present, a group with retrieval and extinction outside of the reconsolidation window was considered to be a control group (e.g. Agren et al., 2012). If data were not available for solely the extinction-only control group but rather for the extinction-only group and a group with retrieval outside the reconsolidation window

combined (e.g. Schiller et al., 2010), the combined data was used as the comparison condition.

Study outcomes—In the current meta-analysis, the following tests were examined to evaluate the return of conditioned fear/appetitive learning after extinction (for review, see Bouton, 2002): the unexpected presentation of the US (reinstatement), re-exposure to the acquisition context (renewal), presentation of CS after the passage of time (spontaneous recovery), and presentation of the CS with the US (reacquisition). When studies presented a progression of findings (e.g. a test of reinstatement then reacquisition) from the same group of subjects, all outcomes were included in the analysis and statistical procedures were used to account for clustering of the data.

Effect size data—Methods of data analysis varied considerably across studies, thus we deferred to the authors of each study and, if possible, utilized the data as analyzed in the publication to calculate effect sizes. Data analysis strategies included: 1) examining change in fear or appetitive responses from end of extinction to beginning of test; 2) demonstrating no significant difference in fear or appetitive responses between conditions at the end of extinction, then examining responses during test. In cases where both types of analyses were presented, the first type of data analysis method was favored over the second. For between-subject studies, responses were compared between the post-retrieval extinction and extinction-only group. For within-subject studies, responses to the CSa+ versus the CSb+ were compared within each subject. Studies varied in the number/duration of extinction and test trials examined in their analyses; once again, we deferred to the authors and utilized the data as analyzed in the publication. For the calculation of effect sizes, means and standard deviations, *F* statistics, *p*-values, and *t*-values were utilized.

In instances when insufficient data were presented to calculate an effect size, two or more attempts were made to contact the authors of the study. For studies that did not report whether *t*-tests were one- or two-sided, it was assumed that tests were two-sided. For studies that failed to report an exact *p*-value but reported a less-than statement (e.g., $p < .05$), a conservative assumption was made equating the *p*-value to the stated amount (e.g., $p = .05$). For studies that did not report an exact sample size but a sample size range (Xue et al., 2012), the average of the range, or lower value if the range was equal to one, was utilized in analyses. To calculate effect sizes for between-subject designs with pre- and post- data (e.g. end of extinction and test data), pre-post measure correlations or change score standard deviations were needed. In cases when this information was not provided in published reports, a pre-post correlation of $r = 0.6$ was imputed. This value was chosen because it falls between published recommendations for imputation of pre-post correlations which vary between $r = 0.5$ (Follmann, Elliott, Suh, & Cutler, 1992) and $r = 0.7$ (Rosenthal, 1991). Sensitivity analyses were conducted as recommended by the Cochrane Collaboration (2011), using values of 0.5 and 0.7. This did not significantly alter the main outcomes.

Moderator variables—Data regarding study design, subject, and conditioning characteristics were abstracted to be used in moderator analyses.

Study design

Between/within-subject designs: We examined whether effects varied for between-subject and within-subject experimental designs. Although within-subject designs are more statistically powerful than between-subject designs, a level of complexity is introduced (as three conditioned stimuli need to be utilized) which may impact outcomes.

Participant characteristics

Demographics (human only): The mean age of subjects, as well as the percentage of female subjects was abstracted. All animal studies were conducted with male rats/mice and insufficient information was provided regarding animal age, thus these moderators were only examined for human studies.

Housing conditions (animal only): Because social buffering can affect fear conditioning outcomes when applied to the conditioning environment (Kiyokawa, Takeuchi, Nishihara, & Mori, 2009) or home cage (Kiyokawa, Honda, Takeuchi, & Mori, 2014), housing conditions were examined as a moderator. Animal housing conditions have also been suggested as a possible explanation for discrepant results in the literature (Auber et al., 2013). For animal studies, the number of subjects housed together during the study was abstracted. If a range was provided, the median of that range was utilized in analyses.

Conditioning procedures: Various aspects of conditioning procedures were abstracted, including characteristics of the stimuli, timing of procedures, and use of expectancy ratings.

Stimuli: Information about the CSs, including the exact type of CS, was abstracted. In addition, CSs were coded as conditioned learning-irrelevant (e.g. geometric shapes) or conditioned learning-relevant (e.g. pictures of spiders in the case of fear conditioning). Learning-relevant stimuli have been shown to be more resistant to extinction (Mineka & Ohman, 2002) and thus the learning-relevance of the CS may serve as a proxy for memory strength. While cued conditioning involves the pairing of a cue (i.e. the CS) with an inherently negative/positive stimulus (i.e. the US), contextual conditioning involves the pairing of a context, rather than a cue, with an inherently negative/positive stimulus. Thus, for studies that utilized contextual conditioning, the context was considered to be the CS. Of note, research indicates that contextual conditioning is more hippocampal-dependent than cued conditioning (Phillips & LeDoux, 1992). This is of interest given questions raised about whether post-retrieval extinction is effective for hippocampal-dependent memories (Ishii et al., 2012). The type of US was also abstracted. In cases when electric shock was utilized as the US, the shock duration (in msec) and intensity (in mA) were abstracted.

Timing of procedures: Characteristics of conditioning procedures were abstracted. For cued conditioning, the number of acquisition trials was operationalized as the number of CS+ trials for between-subject designs and the number of CSa+ trials for within-subject designs. For contextual conditioning, the time in the acquisition context was abstracted. The reinforcement schedule (i.e. percent of CS+s or CSa+s paired with the US) was also abstracted. The number of reinforced acquisition trials was calculated by multiplying the number of acquisition trials by the reinforcement schedule. The number of acquisition trials

and reinforcement schedule may both be related to the strength of the acquired memory (Gallistel & Gibbon, 2000).

The number of extinction trials was abstracted. For between-subject designs, in all cases one additional CS+ presentation was administered to the extinction-only group to account for the additional CS+ presentation during the retrieval trial that is administered to the post-retrieval extinction group. Thus, for consistency, we operationalized extinction trials as the total number of CS+ presentations received by the extinction-only group. Similarly, in the case of within-subject designs, one additional CSb+ trial than CSa+ trial was consistently administered to account for the CSa+ reactivation trial. Thus, we operationalized extinction trials as the number of CSb+ trials. In a few cases, subjects underwent two rounds of extinction trials (Clem & Huganir, 2010; Ishii et al., 2012), in which case the total number of trials administered during the reconsolidation window (within 6 hours of retrieval) was utilized in the analyses. For contextual conditioning, the duration of time in the extinction context was abstracted. This was dictated by the extinction-only group as the time spent in the extinction context was again balanced in this group for the additional time the post-retrieval extinction group received due to the reactivation exposure. As research suggests that massed extinction attenuates renewal (Denniston, Chang, & Miller, 2003), massed extinction after reactivation has been explored as a potential method to enhance the effects of post-retrieval extinction (Ishii et al., 2012). This raises the question of whether the number of extinction trials could moderate post-retrieval extinction effects.

The relative timing of acquisition, post-retrieval extinction/extinction, and test procedures was also abstracted. Specifically, the hours between acquisition and post-retrieval extinction/extinction were abstracted, allowing us to quantify memory age. The hours between post-retrieval extinction/extinction and test were abstracted to examine the potential maintenance of post-retrieval effects over time. For two studies (Chan, Leung, Westbrook, & McNally, 2010, experiments 4a and 4b), reinstatement shocks were administered 24 hours before test trials, in which case the time between extinction and the test trials was utilized in analyses. The duration of the retrieval trial and the time between the end of the retrieval trial and start of extinction within the post-retrieval extinction group were also abstracted and examined as moderators. Some have questioned whether longer retrieval trials lead to extinction rather than interference with reconsolidation (Pineyro et al., 2014), thus this could potentially explain some discrepant results. In addition, although the reconsolidation window has been consistently established as within 6 hours of retrieval (Monfils et al., 2009; Schiller et al., 2010), it is possible that the time gap between retrieval and extinction may influence the magnitude of post-retrieval extinction effects.

Expectancy ratings (human only): We recorded whether participants rated US expectancy (i.e. whether they expect the US to occur after seeing a CS), and if so, whether ratings took place during or after acquisition procedures. Rating expectancy may result in more declarative awareness of the CS-US contingency (Warren et al., 2014), and declarative awareness of CS-US contingency has been shown to engage the hippocampus (Bechara et al., 1995). Thus, this is one potential method to examine whether hippocampal-engagement impacts the efficacy of post-retrieval extinction.

Details of Analyses

Effect size analyses—Individual effect sizes were calculated using the Comprehensive Meta-Analysis software program (Version 2; Borenstein, Hedges, Higgins, & Rothstein, 2005). Hedges's *g* (Rosenthal, 1991) was used as an indicator of effect size, as it corrects for small sample sizes. These controlled effect sizes may be conservatively interpreted using Cohen's standards (Cohen, 1977): small (0.2), moderate (0.5), and large (0.8). Aggregate effect size calculations and moderator analyses were conducted in the statistical package *R* utilizing the *metaSEM* package (Cheung, 2014). As some studies contained multiple post-retrieval extinction groups or assessed multiple outcomes, they contributed more than one effect size to the analysis. As such, a three-level meta-analysis was conducted to address the dependence among effect sizes derived from the same study (Cheung, 2014). Aggregate effect sizes were calculated separately for animal fear studies, animal appetitive studies, and human fear studies. Aggregate effect sizes were calculated for all test types (i.e. reinstatement, renewal, spontaneous recovery, reacquisition) combined and separately by test type. Additionally, aggregate effect sizes were compared across test type to determine if the efficacy of post-retrieval extinction varied across test type. Results of this comparison were considered in conducting and interpreting moderator analyses.

Moderator analyses—We examined the influence of the moderators outlined above on our main effects. Moderator analyses were conducted across all studies in a grouping utilizing metaSEM. For categorical moderators, separate effect sizes were calculated for each group and the significance was evaluated between groups. For continuous moderators, unstandardized regression coefficients were computed and *z*-tests were applied to evaluate significance. To reduce the likelihood of Type I errors, moderator analyses were conducted only when a total of 8 or more comparisons and at least 3 comparisons across at least two studies for any particular categorical moderator grouping were available to contribute to the analyses.

Publication bias—In addition to our comprehensive search strategy, we utilized funnel plots and the Trim and Fill method (Duval & Tweedie, 2000) to explore the potential impact of publication bias on our results. In order to examine the full pattern of effects, a multi-level approach was not used and these analyses were conducted in Comprehensive Meta-Analysis with each effect treated as independent. Funnel plots for each significant outcome were visually inspected to assess symmetry relative to the mean effect size. The Trim and Fill method (Duval & Tweedie, 2000) is a conservative strategy which assumes that funnel plot asymmetry characterized by more positive than negative small study effects is due to publication bias. Trim and Fill analysis imputes artificial negative studies to the left of the mean effect size to balance out asymmetric funnel plots.

Results

Trial Flow

Using the search strategy described above, 791 unique articles were identified. Titles and abstracts were examined, resulting in the exclusion of 731 articles. Full text articles were obtained for the 60 remaining articles. Of the articles initially identified and reviewed in full

text by both authors (n = 53), the agreement rate for inclusion/exclusion was 91% with authors disagreeing on 5 articles. There were 7 articles which were identified and reviewed in full text by one author, but not identified by the second author; upon subsequent review by the second author, the agreement rate was 86% for these articles. Disagreement was reconciled through discussion with the final author. Ultimately, 36 articles were excluded for various reasons (see Figure 1) and 24 articles were included in this meta-analysis. Within these articles, 79 studies were examined, of which 32 were not included in the analyses for reasons presented in Figure 1, and 47 studies were included in the analyses. Within these 47 studies, 65 comparisons of post-retrieval extinction to a control group were identified. In one case, the data for one test was compromised, according to the authors (Agren, Furmark, Eriksson, & Fredrikson, 2012), thus it was not included in our analyses. In another case, three tests were conducted, however, we were only able to obtain the necessary data to include two of them in our analyses (Kindt & Soeter, 2013). Ultimately, 63 comparisons were included in the analyses.

Study Characteristics

Of the 63 comparisons included in the analysis, 50 were comparisons of conditioned fear (34 animal comparisons, 16 human comparisons) and 13 were comparisons of conditioned appetitive responses (13 animal comparisons, 0 human comparisons). The analyses comprise data from 1,061 subjects; 553 animals (84% rats, 16% mice) and 310 humans (*M(SD) age* = 24.1(1.9), 58% female) were examined in studies of fear memories and 198 animals (100% rats) were examined in studies of appetitive memories. Details on study characteristics are outlined in Tables 1, 2, and 3. The sample sizes reported from here after reflect number of comparisons unless stated otherwise.

Quantitative Data Synthesis

Animal – Fear—The accuracy rate for abstraction of fear memory-related effect size data in animals was high; with 98% accuracy between abstractors for the memory outcomes, and 97% accuracy for the moderator variables.

Main effects: When examining all test outcomes combined, post-retrieval extinction did not have a significant effect on preventing the return of fear in animals relative to standard extinction procedures (g = 0.21, 95% CI [−0.19, 0.60], p = .30; n = 34). Individual and aggregate study effect sizes are presented in Figure 2. When examining specific tests of return of fear separately, a moderate effect was observed for spontaneous recovery at a trend level (g = 0.45, 95% CI [−0.06, 0.96], p = .08; n = 10). No significant effects were found for tests of reinstatement (g = −0.47, 95% CI [−1.45, 0.51], p = .35; n = 4), renewal (g = 0.34, 95% CI [−0.18, 0.87], p = .20; n = 13), or reacquisition (g = 0.17, 95% CI [−0.57, 0.91], p = .65; n = 7). The overall non-significant effect of post-retrieval extinction for fear memories in animals and inconsistent results across test type prompted the search for potential moderators. The type of test for return of fear did not significantly moderate overall outcomes (χ^2 = 2.30, df = 3, p = .51). As such, outcomes for all tests were grouped together for the moderator analyses.

Moderators

Study design

Between/within-subject designs: All but one study utilized between-subject designs, thus study design was not examined as a moderator.

Subject characteristics

Animal housing conditions: The number of animals housed together significantly moderated effects in that larger effects were observed when a smaller number of animals were housed together ($B = -0.19$, $SE = 0.05$, $p < .001$, $n = 29$; Figure 3). Furthermore, mean positive effects were seen for animals housed alone ($g = 0.78$, $p < .05$, $n = 11$) and mean negative effects were seen for animals housed together ($g = -0.20$, $p = .40$, $n = 18$; $B = 0.81$, $SE = 0.41$, $p = .05$). Thus the advantage of post-retrieval extinction over standard extinction was more evident for animals housed alone. Animal housing was found to explain 30.8% of the variance in effect sizes (Figure 3).

Conditioning procedures

Stimuli: Four comparisons utilized context as the CS (i.e. contextual conditioning) and 30 utilized a cue as the CS (i.e. cued conditioning). No significant differences were found in effect sizes between comparisons utilizing context ($g = 0.64$, $p = .22$, $n = 4$) and comparisons utilizing cues ($g = 0.14$, $p = .53$, $n = 30$; $B = 0.51$, $SE = 0.57$, $p = .37$). Of the studies utilizing cues as the CS, the majority of studies used an auditory stimulus (i.e. tone, white noise) or a combination of visual and auditory stimuli (i.e. light and tone). Only one study used a solely visual CS (i.e. light). Thus we were unable to examine CS type further in our moderator analyses.

All studies utilized electric shock as the US, thus type of US was not examined as a moderator. US duration was examined as a moderator and was not found to significantly moderate overall outcomes ($B = 0.45$, $SE = 0.31$, $p = .15$, $n = 34$). A trend, however, was observed indicating that US intensity (i.e. shock intensity), which ranged from 0.3 mA to 1.5 mA, moderated overall outcomes ($B = 1.50$, $SE = 0.83$, $p = .07$, $n = 34$), with larger effects for studies utilizing higher US intensity. After controlling for number of animals housed together, however, the moderating effect of US intensity was no longer at a trend level ($p = 0.53$).

Timing of procedures: Amongst studies utilizing cued conditioning, main effects were not moderated by number of acquisition trials ($B = -0.02$, $SE = 0.18$, $p = .90$, $n = 30$) or number of extinction trials ($B = -0.00$, $SE = 0.01$, $p = .99$, $n = 30$). Main effects were also not moderated by the duration of the retrieval trial ($B = -0.00$, $SE = 0.00$, $p = .76$, $n = 34$) or the time between retrieval and extinction in the post-retrieval extinction group ($B = -0.00$, $SE = 0.00$, $p = .38$, $n = 34$). All studies utilized a 100% reinforcement schedule, so reinforcement schedule and number of acquisition trials reinforced were not examined as moderators. Thus, variation in acquisition or post-retrieval extinction/extinction procedures cannot explain the inconsistent post-retrieval extinction findings in animals.

With regard to the relative timing of procedures, our analyses were limited by the lack of variation in study designs. The time between acquisition and post-retrieval extinction/extinction (representing memory age) was most often 24 hours (n = 29), with a few comparisons utilizing 48 hours (n = 5). In comparing aggregate effect sizes for comparisons that utilized a 24-hour-old memory (g = 0.32, p = .14) to comparisons that utilized a 48-hour-old memory (g = −0.29, p = .53), no significant differences were found (B = −0.61, SE = 0.51, p = .24). This indicates that at least across a short time frame, memory age did not influence post-retrieval extinction effects for fear memories in animals.

With regard to time between post-retrieval extinction/extinction and test, about half of comparisons tested for return of fear 24 hours after extinction (n = 14). Some tested after a slightly longer delay (24 – 48 hours, n = 4; 48 hours, n = 9; 72 hours, n = 1) and six tested after a much longer delay (6 – 30 days). Effect sizes for the 24-hour and 48-hour groups did not significantly differ (B = −0.65, SE = 0.41, p = .12). In comparing studies that tested return of fear after a short-delay (24 – 72 hours after post-retrieval extinction/extinction) to studies that tested return of fear after a long-delay (6 – 30 days), mean effect sizes were small and non-significant for short-delay studies (g = 0.12, p = .53, n = 28) but large and significant for long-delay studies (g = 0.78, p < .05, n = 6; B = 0.66, SE = 0.31, p < .05). After controlling for number of animals housed together, the difference between long-delay and short-delay studies remained significant (B = 1.67, SE = 0.63, p < .01). This may indicate that the advantage of post-retrieval extinction over standard extinction is more likely to be observed after a longer period of time has passed.

Summary: Overall, the effect of post-retrieval extinction for preventing the return of fear in animals relative to standard extinction was small and non-significant. This effect, however, was substantially moderated by animal housing conditions, with large and significant effects observed for studies that housed animals alone. This indicates that either solo housing facilitates or group housing interferes with post-retrieval extinction. The effect of post-retrieval extinction for preventing the return of fear in animals was also moderated by the duration of time between post-retrieval extinction/extinction and test in that large and significant effects were observed for comparisons involving a test that took place at least 6 days after post-retrieval extinction/extinction. This indicates that post-retrieval extinction effects may be better observed across a longer time window. There was also some indication that US intensity may influence effects, however this effect was not maintained after controlling for animal housing. Effects were not found to be moderated by test type, CS type (context or cued), US duration, number of acquisition or extinction trials, or time between acquisition and post-retrieval extinction/extinction (24 vs. 48 hrs). A summary of results is presented in Table 4.

Animal – Appetitive—The accuracy rate for abstraction of appetitive memory-related effect size data was high; with 100% accuracy between abstractors for the memory outcomes, and 95% accuracy for the moderator variables.

Main effects: When examining all outcomes combined, post-retrieval extinction had a large significant effect on preventing the return of appetitive responses in animals relative to standard extinction procedures (g = 0.89, 95% CI [0.36, 1.41], p < .001, n = 13). Individual

and aggregate study effect sizes are presented in Figure 4. When examining specific tests of return of appetitive responses separately, post-retrieval extinction had a large significant effect on preventing reinstatement (g = 0.96, 95% CI [0.47, 1.45], p < .001; n = 6) and spontaneous recovery (g = 1.00, 95% CI [0.38, 1.63], p < .01; n = 5). Only one study assessed renewal so mean effect sizes are not reported; however this individual study reported a large significant effect (g = 1.22, 95% CI [0.21, 2.24], p < .05; n = 1). Similarly, only one study assessed reacquisition so mean effect sizes are not reported; interestingly, this study reported a large significant negative effect (g = −1.02, 95% CI [−2.02, −0.03], p < .05; n = 1). Test type significantly moderated the effects of post-retrieval extinction over extinction in preventing the return of appetitive responses (χ^2 = 7.85, df = 3, p < .05). As outlined above, all tests resulted in large positive significant outcomes except for reacquisition, which resulted in a large negative significant outcome. Given the small number of comparisons within each test type, outcomes for all tests were grouped together for the moderator analyses despite the significant moderation of test type. Removing the one reacquisition study from moderator analyses did not change results.

Moderators

Study design

Between/within-subject designs: All studies utilized between-subject designs, thus study design was not examined as a moderator.

Subject characteristics

Animal housing conditions: The number of animals housed together did not significantly moderate effects (B = −0.09, SE = 0.12, p = .46, n = 13). This finding is inconsistent with our results for studies of fear memories in animals and may indicate that housing conditions uniquely impact the efficacy of post-retrieval extinction for fear memories.

Conditioning procedures

Stimuli: Six comparisons utilized context as the CS and seven comparisons utilized cues as the CS. The mean effect size for the comparisons that utilized context (g = 0.46, p = .18, n = 6) did not significantly differ from the mean effect size for the comparisons that utilized cues (g = 1.20, p < .001, n = 7; B = −0.75, SE = 0.47, p = .11). Of note, when removing the one study that utilized a test of reacquisition as the outcome, the mean effect size for studies utilizing context as the CS was large and significant (g = 0.79, p < .05, n = 5). There was insufficient variation to examine CS type further. With regard to the US, studies either utilized food pellets or drug injections. The mean effect sizes for both types of unconditioned stimuli were large (food: g = 0.95, p = .06; drug: g = 0.86, p < .01) and they did not significantly differ from each other (B = 0.09, SE = 0.59, p = .87). Of note, when removing the one study that utilized a test of reacquisition as the outcome, the mean effect size for studies utilizing drug as the US was large and significant (g = 1.08, p < .001, n = 4).

Timing of procedures: There was inconsistency of methods and insufficient variation within method for adequate examination of acquisition and extinction characteristics. With regard to the relative timing of procedures, there was also insufficient variability in the time

between acquisition and post-retrieval extinction/extinction to examine this variable as a moderator. Consistent with animal fear studies, main effects were not moderated by the duration of the retrieval trial ($B = 0.02$, $SE = 0.05$, $p = .72$, $n = 13$) or the time between retrieval and extinction in the post-retrieval extinction group (10 minutes: $g = 1.08$, $p < .01$; 60–70 minutes: $g = 0.74$, $p < .05$; $B = -0.34$, $SE = 0.54$, $p = .53$). Thus, these variations in post-retrieval extinction procedures did not significantly influence effects.

With regard to time between post-retrieval extinction/extinction and test, about half of comparisons tested for return of fear after a short-delay (24 – 72 hours after post-retrieval extinction/extinction, $n = 5$) and half tested return of fear after a long-delay (7 – 28 days, $n = 5$). One comparison tested for return of fear across a range of days (1–20 days) and two others did not report the delay between post-retrieval extinction/extinction and test; thus, these comparisons were not included in this moderator analysis. Mean effect sizes were large and significant for both and did not differ between ($B = 0.00$, $SE = 0.30$, $p = .99$) short-delay ($g = 0.93$, $p < .01$, $n = 5$) and long-delay comparisons ($g = 0.94$, $p < .01$, $n = 5$). In contrast to results from animal fear studies, this suggests that post-retrieval extinction effects in animal appetitive studies were observed when tested in the short- and long-term.

Summary: Overall, the effect of post-retrieval extinction for preventing the return of appetitive responses in animals relative to standard extinction was large and significant. Effects were not found to be moderated by number of animals housed together, US type (food or drug), CS type (context or cued), duration of retrieval in the post-retrieval extinction group, time between retrieval and extinction in the post-retrieval extinction group, or duration of time between post-retrieval extinction/extinction and test. There was an inconsistency of methods and insufficient variation within methods for adequate examination of other moderators. A summary of results is presented in Table 4.

Human – Fear—The accuracy rate for abstraction of fear memory-related effect size data in humans was high; with 97% accuracy between abstractors for the memory outcomes, and 98% accuracy for the moderator variables.

Main effects: When examining all outcomes combined, post-retrieval extinction demonstrated a significant, small-to-moderate effect for preventing the return of fear in humans relative to standard extinction procedures ($g = 0.40$, 95% CI [0.11, 0.68], $p < .01$; $n = 16$). Individual and aggregate study effect sizes are presented in Figure 5. Upon examination of specific tests of return of fear, post-retrieval extinction had a small-to-moderate and significant effect on preventing reinstatement ($g = 0.42$, 95% CI [0.01, 0.74], $p < .01$; $n = 9$). Aggregate effect sizes for tests of spontaneous recovery, reacquisition, and renewal alone were limited by small sample sizes ($n \leq 3$ comparisons). From the data available, post-retrieval extinction appeared to have a moderate positive and significant effect on spontaneous recovery ($g = 0.53$, 95% CI [0.03, 1.03], $p < .05$; $n = 3$), a small positive effect on reacquisition ($g = 0.36$, 95% CI [−0.13, 0.85], $p = .15$, $n = 3$), and a small negative effect on renewal ($g = -0.19$, 95% CI [−1.00, 0.63], $p = .65$, $n = 1$). Test type did not significantly moderate the effects of post-retrieval extinction over extinction in preventing the return of fear ($\chi^2 = 3.17$, df = 3, $p = .37$). As such, outcomes for all tests were grouped together for the moderator analyses.

Moderators

Study design

Between/within-subject designs: Eight comparisons were calculated from between-subject designs and eight comparisons were calculated from within-subject designs. Study design did not significantly moderate overall outcomes ($B = 0.06$, $SE = 0.28$, $p = 0.84$). Both designs resulted in small-moderate effects, however, the aggregate effect for between-subject designs was significant ($g = 0.43$, $p < .05$, $n = 8$), while that for within-subject designs fell just below significance ($g = 0.37$, $p = .057$, $n = 8$).

Participant characteristics

Demographics: The effect of post-retrieval extinction on return of fear in humans was not significantly moderated by age ($B = 0.04$, $SE = 0.08$, $p = 0.61$) or gender ($B = -0.01$, $SE = 0.02$, $p = .53$).

Conditioning procedures

Stimuli: The type of conditioned stimuli utilized varied considerably across studies, with eight comparisons from studies utilizing fear-relevant stimuli (e.g. pictures of spiders) and eight comparisons from studies utilizing fear-irrelevant stimuli (e.g. colored shapes). The fear relevance of the CS significantly moderated overall outcomes with moderate-to-large significant effects found for fear-irrelevant stimuli ($g = 0.66$, $p < .001$; $n = 8$) and non-significant near zero effects found for fear-relevant stimuli ($g = 0.02$, $p = .86$, $n = 8$; $B = -0.64$, $SE = 0.18$, $p < .001$). No studies examined context as the CS, thus contextual and cued conditioning could not be compared.

All but one study utilized electric shock as the US, thus type of US was not examined as a moderator. Within the studies utilizing electric shock, shock duration ranged from 2 msec (Kindt & Soeter, 2013; Soeter & Kindt, 2011) to 500 msec (Agren, Engman, et al., 2012; Agren, Furmark, et al., 2012). Shock duration was found to significantly moderate overall outcomes ($B = 2.31$, $SE = 0.58$, $p < .001$, $n = 15$). Larger effects were observed for studies utilizing longer shock durations; specifically, a 100 msec increase in shock duration was associated with an increase in effect size of post-retrieval extinction over extinction of 0.23 standard deviation units. For example, based on the regression slope and intercept, the estimated effect size of post-retrieval extinction over extinction for individuals who undergo acquisition with a 100 msec shock duration is 0.23, whereas the estimated effect size for individuals who undergo acquisition with a 400 msec shock duration is 0.92. While US duration was selected by investigators, shock intensity was self-selected by participants based on their comfort level, as is typical for human subject research of de novo conditioning. The majority of studies did not report the average selected shock intensity, thus it could not be examined as a moderator.

Timing of procedures: The effect of post-retrieval extinction on overall outcomes was significantly moderated by number of acquisition trials ($B = 0.08$, $SE = 0.03$, $p < .01$, $n = 16$); an additional acquisition trial was associated with an increase in effect size of post-retrieval extinction over standard extinction of 0.08 standard deviation units. For example, the estimated effect size of post-retrieval extinction over extinction for individuals who

undergo 10 acquisition trials is 0.10, whereas the estimated effect size for individuals who undergo 14 acquisition trials is 0.38. This result was not explained by the number or the percentage of reinforced acquisition trials; both of these effects were not significant (number of reinforced acquisition trials: $B = 0.03$, $SE = 0.03$, $p = .31$, $n = 16$; percent of reinforced acquisition trials: $B = -0.005$, $SE = 0.006$, $p = .43$, $n = 16$). Hence, the relevant moderator appears to be experience with the CS in the acquisition environment rather than the degree of the CS-US contingency; perhaps reflecting the ease by which the retrieval cue can activate the conditioning memory. The effect of post-retrieval extinction on return of fear in humans was not moderated by number of extinction trials ($B = -0.12$, $SE = 0.08$, $p = .19$, $n = 16$).

With regard to the relative timing procedures, all studies conducted post-retrieval extinction/extinction 24-hours after acquisition and all studies used a 10 minute delay between retrieval and extinction in the post-retrieval extinction group. There was also little variation in the time between post-retrieval extinction/extinction and test, with the majority of comparisons conducting the test 24-hours after post-retrieval extinction/extinction ($n = 13$). Thus, these factors could not be examined as moderators. The duration of retrieval in the post-retrieval extinction group varied from 4 seconds to 2 minutes and did not moderate the effect of post-retrieval extinction on return of fear in humans ($B = 0.004$, $SE = 0.003$, $p = .22$, $n = 16$).

Expectancy ratings: Three out of the 11 studies included expectancy ratings, two of which had participants rate expectancy during procedures and one at the end of procedures. Effect sizes for comparisons from studies with expectancy ratings were nearly zero and non-significant ($g = .001$, $p = .99$, $n = 7$) and significantly differed from effect sizes for comparisons from studies without expectancy ratings, which were moderate-large and significant ($g = .59$, $p < .001$, $n = 9$; $B = -0.59$, $SE = 0.19$, $p < .01$). This may indicate that contingency awareness and possibly the hippocampal-dependence of the acquired fear memory influences post-retrieval extinction effects.

Summary: Overall, the effect of post-retrieval extinction for preventing the return of fear in humans relative to standard extinction was approaching moderate and significant. This effect was substantially moderated by CS type (fear-relevant vs. fear-irrelevant), US duration, number of acquisition trials, and the use of expectancy ratings. These results indicate that procedural differences in how the conditioned association is acquired may explain some of the variation seen in effect sizes for post-retrieval extinction. The magnitude of effects was not found to be moderated by study design (between- vs. within-subject), age of participants, gender of participants, number of reinforced acquisition trials, reinforcement schedule, number of extinction trials, or duration of the retrieval trial. There was insufficient variation to examine memory age, the time between retrieval and extinction in the post-retrieval extinction group, or the time between post-retrieval extinction/extinction and test as moderators. A summary of results is presented in Table 4.

Publication Bias

Funnel plots for the effects of post-retrieval extinction in preventing the return of appetitive responses in animals and fear responses in humans across all outcomes (Figures 6–7) were

inspected and observed to be slightly asymmetrical displaying more positive small-study effects than negative small-study effects. Conservative Trim and Fill analyses (Duval & Tweedie, 2000) resulted in imputed effect sizes for the effect of post-retrieval extinction over extinction on the return of appetitive response in animals (Figure 8). This suggests that the aggregate effect size for appetitive studies in animals may be influenced by publication bias, however, even with adjustment the effect size is still estimated to be moderate-to-large. No adjustment to the effect of post-retrieval extinction over extinction on the return of fear in humans was suggested by the Trim and Fill analyses. This suggests that the aggregate effect size for fear studies in humans is likely not influenced by publication bias. It is important to consider that funnel plot asymmetry may be due to factors other than publication bias and because of this, the Trim and Fill method may lead to overcorrection (Vevea & Woods, 2005).

Discussion

Main Effects of Post-Retrieval Extinction

Although two meta-analyses have been published examining pharmacological methods to interfere with memory reconsolidation, the current meta-analysis is, to our knowledge, the first to examine post-retrieval extinction, a behavioral method to interfere with memory reconsolidation. Forty-seven studies provided a total of 63 comparisons between post-retrieval extinction and standard extinction outcomes. Overall, post-retrieval extinction, compared to standard extinction, has a large significant effect in preventing the return of appetitive responses in animals ($g = 0.89$, $p < .001$, $n = 13$), and approached a moderate effect in preventing the return of fear in humans ($g = 0.40$, $p < .01$; $n = 16$). These effect sizes compare well to the pharmacologic reconsolidation blockade literature, with pharmacologic effect sizes (i.e. advantage of study drug over placebo) in the moderate range for both appetitive responses in animals ($d = 0.47$, Das et al., 2013) and fear response in humans ($g = 0.56$, Lonergan et al., 2013). In contrast to these strong effects, the overall effect size for post-retrieval fear extinction in animals, the paradigm that initiated research in this area (Monfils et al., 2009), was small and non-significant ($g = 0.21$, $p = .30$; $n = 34$).

We were not able to identify moderators that were significant across paradigms (animal fear, human fear, and animal appetitive). Different moderators were identified for post-retrieval extinction findings in animal and human fear studies, and no moderators were identified for appetitive conditioning models in animals. Nonetheless, as is discussed below, there are theoretical reasons why moderators may have different effects across these paradigms. These paradigm-specific moderators have the potential to clarify some of the boundary conditions for post-retrieval extinction effects and to suggest new directions in research.

Moderators of Post-Retrieval Extinction Effects in Animals

The wide variability in effect-size estimates for post-retrieval extinction effects on conditioned fear in animals (ranging from $g = 3.4$ to -2.3) motivates the search for moderators to explain these variable results. Although we were unable to explain discrepant results in terms of test type, type of CS (context vs. cued), US duration, number of acquisition or extinction trials, duration of retrieval, time between retrieval and extinction, or

time between acquisition and post-retrieval extinction/extinction; two variables emerged as significant moderators: (1) number of animals housed together, and (2) time between post-retrieval extinction/extinction and test. Shock intensity also emerged as a trend level moderator.

Consideration of the number of animals housed together explained over 30% of the variance in effect sizes for preventing the return of fear in animals. Specifically, for animals housed alone the mean effect size for the advantage of post-retrieval extinction over standard extinction was large and positive, whereas for animals housed in groups, the mean effect size was small and negative. Research on "social buffering" effects, which occur when animals undergo fear conditioning or extinction in the presence of conspecifics (Guzman et al., 2009; Hunter, 2014; Kiyokawa, Takeuchi, & Mori, 2007; Nowak, Werka, & Knapska, 2013), provides a potential explanation for this moderation. Specifically, fear conditioning of animals in pairs and paired-housing of animals following conditioning have been shown to attenuate conditioned fear expression and result in the lack of neural responses (Fos expression) in certain areas of the amygdala (i.e. lateral amygdala for paired conditioning and basal amygdala for paired-housing), potentially resulting in interference with consolidation or leading to extinction processes (Kiyokawa et al., 2007). Likewise, strategies targeting interference with reconsolidation in animals aim to block protein synthesis in the basolateral amygdala (Nader et al., 2000) and a recent neuroimaging study in humans suggests that post-retrieval extinction results in decreased activation in the basolateral amygdala (Agren, Engman, et al., 2012). It is unclear whether these two processes (i.e. social buffering and post-retrieval extinction) are redundant or conflicting, however, this research indicates that group housing of animals may not only influence fear conditioning processes, but may also modulate areas of the brain that are key to reconsolidation interference strategies.

There is also some evidence that the impact of group housing may depend on the behavior of the conspecifics; a recent study demonstrated that housing with a fearful cage mate is associated with robust renewal of freezing after previous successful extinction (Nowak et al., 2013). Thus, it is also possible that group housing facilitated return of fear in both post-retrieval extinction and extinction-only groups. In addition, paired housing in particular has also been shown to dampen the HPA-axis stress response to threat (Hostinar, Sullivan, & Gunnar, 2014; Kiyokawa et al., 2007), which could influence extinction and/or post-retrieval extinction processes. Likewise, individual housing of rats has also been associated with increased reactivity to stress (Bartolomucci et al., 2003) and changes in fear conditioning processes (Voikar, Polus, Vasar, & Rauvala, 2005). Although the specific mechanism is unclear at this time, our meta-analytic results introduce housing conditions as an important moderator of post-retrieval extinction effects in animals, and suggest that this variable should be carefully evaluated in future study designs.

The effect of post-retrieval extinction on preventing the return of fear in animals was also significantly moderated by the duration of time between post-retrieval extinction/extinction and test. Studies testing return of fear after a long delay (6–30 days) demonstrated large and significant effects whereas studies testing return of fear after a short delay (1–3 days) demonstrated small and non-significant effects. This may indicate that the advantage of

post-retrieval extinction over extinction is better observed over a longer time frame. Yet, this was not observed in animal appetitive studies. Additional research is needed as few studies manipulated the time between post-retrieval extinction and test.

Moderators of Post-Retrieval Extinction Effects in Humans

Concerning findings for human fear studies, our moderator analyses also provide insight into potential boundary conditions of post-retrieval extinction effects. Our results are in line with the general hypothesis that variables influencing presumed memory strength will moderate the efficacy of post-retrieval extinction (Auber et al., 2013; Schwabe & Wolf, 2009). For example, a greater number of acquisition trials and longer duration of shocks were both associated with a greater advantage of post-retrieval extinction over standard extinction in human fear studies. It is especially noteworthy that two of the four human studies that displayed negative or null results (Kindt & Soeter, 2013; Soeter & Kindt, 2011) utilized a shock duration of 2 msec, which is 1% of the duration which was used by Schiller et al. (2010), who used 200 msec, to initiate exploration of post-retrieval extinction in humans. Although these findings are contrary to the hypothesis that post-retrieval extinction would prove to be less effective for stronger memories (Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009), it is consistent with the notion that these conditions represent greater challenges for standard extinction. We did not find, however, that the reinforcement schedule during acquisition, another factor which could presumably impact memory strength, moderated post-retrieval extinction effects.

These moderation effects may also be related to the nature of the fear learning that occurs. According to a dual-model theory of de novo conditioning, some fear learning is implicit and relies on lower-order mechanisms (i.e. amygdala-based) that are rapid and automatic whereas other fear learning is explicit and relies on higher-order mechanisms (i.e. hippocampus-based) that are slow and deliberate (Grillon, 2009). It is possible that longer shock duration improves the likelihood of lower-order conditioning processes and a more amygdala-based fear. This is consistent with research suggesting that the use of more intense US leads to implicit fear learning (Bridger & Mandel, 1964). Thus, it could be that more potent acquisition results in a more amygdala-dependent fear providing a greater opportunity for benefit from amygdala-based, post-retrieval extinction effects. This may imply that post-retrieval extinction would be beneficial for more automatic amygdala-based clinical fears rather than ones formed through more conscious processes.

Consistent with this hypothesis, we found some support for moderation of post-retrieval extinction by the degree of hippocampal-dependence of a memory (Ishii et al., 2012). One marker of some degree of hippocampal-dependence is declarative awareness of the contingency between the CS and US (Bechara et al., 1995; Weike, Schupp, & Hamm, 2007). Few studies in our meta-analysis utilized expectancy ratings, preventing direct analysis of this variable. However, some have hypothesized that the act of completing expectancy ratings during acquisition trials encourages participants to identify the contingency between the CS and US (Warren et al., 2014). Here we found that the use of expectancy ratings significantly moderated the effects of post-retrieval extinction on return of fear in humans,

with more favorable outcomes for studies that did not involve expectancy ratings, suggestive of greater benefit for non-hippocampal dependent memories.

In contrast to human studies, fear conditioning in rodents is thought to be dominated by lower-order subcortical automatic processes and has been suggested to lead to stronger fears compared to fear conditioning in humans (Grillon, 2009), perhaps attenuating the effects of variations in fear acquisition characteristics for rodents. Accordingly, we found no evidence for number of acquisition trials and shock duration and only trend level evidence for shock intensity moderating post-retrieval extinction effects in animal fear studies, with this trend no longer being evident when variation due to animal housing conditions was controlled. Also, we found that no significant differences in effects were observed for cued and contextual conditioning in animal studies of fear or appetitive memories; comparison of cued and contextual conditioning is another method of examining whether the hippocampal-dependence of a memory moderates post-retrieval extinction effects (Phillips & LeDoux, 1992). Nonetheless, only a few studies of contextual conditioning in animals were conducted, and no studies of post-retrieval extinction for contextual fear memories have been published in humans. Accordingly, a fuller perspective on the role of hippocampal dependence in humans awaits further research.

We also found that the effect of post-retrieval extinction on return of fear in humans was significantly moderated by the fear-relevance of the CS in that significant post-retrieval extinction advantages were observed for fear-irrelevant stimuli, but not fear-relevant stimuli. It is not clear whether this is an effect of stronger conditioning with fear-relevant stimuli (Mineka & Ohman, 2002), or whether pre-existing associations with fear-relevant stimuli changes the nature of reconsolidation effects. Humans are more likely to develop fear towards objects that pose a threat to survival (i.e. preparedness, Mineka & Ohman, 2002). Research suggests that the fear network can be automatically activated (without conscious awareness) by fear-relevant stimuli (Mineka & Ohman, 2002), suggesting that fear-relevant stimuli hold pre-existing negative associations. Thus, it is possible that fear-relevant stimuli may present a more diffuse target for post-retrieval extinction and that previous associations with these real-world stimuli may insulate the fear memory from erasure. Regardless of mechanism, this finding does raise questions about the applicability of post-retrieval extinction to anxiety disorders where fear-relevant (e.g. spiders) rather than fear-irrelevant stimuli (e.g. shapes) may be feared. Yet, it is important to consider that only four studies using fear-relevant stimuli were conducted and further confirmation of these findings is needed. More generally, additional research is needed to examine how different aspects of memory strength and relevance of the stimulus materials may influence post-retrieval extinction effects.

Through our moderator analyses, we also observed that some variables did not impact post-retrieval extinction effects in humans. Notably, age and gender did not moderate post-retrieval extinction effects. This is interesting given that differences in fear extinction have been observed between men and women and research suggests that sex hormones may influence extinction processes (Milad et al., 2010). We were unable, however, to examine sex across the animal studies because all studies utilized male animals. This is a limitation of the animal literature at large (Beery & Zucker, 2011), although researchers are beginning to

examine fear extinction specifically in female rats across stages of the menstrual cycle (Milad, Igoe, Lebron-Milad, & Novales, 2009). Similar examination in post-retrieval paradigms is warranted. With regard to age as a moderator of post-retrieval extinction effects, our analyses were limited by the small age range of subjects in the present studies. As research has suggested that extinction processes may vary across development, particularly in adolescence (Pattwell et al., 2012), future research on the impact of age and developmental phase on post-retrieval extinction effects is needed.

Variability in effect sizes was also not explained by variations in extinction or post-retrieval extinction procedures across studies (i.e. number of extinction trials, duration of retrieval, time between retrieval and extinction). Given that number of extinction trials did not moderate outcomes, it is unlikely that null post-retrieval extinction effects are due to the extinction only group catching up with the post-retrieval extinction group, a phenomenon that has disguised the effects of other translational research paradigms (Siegmund et al., 2011). Evidence of return of fear in both the extinction and post-retrieval extinction conditions in null studies (e.g. Golkar, Bellander, Olsson, & Ohman, 2012; Kindt & Soeter, 2013) is also inconsistent with the notion of a floor effect due to strong fear elimination in both groups. All studies conducted extinction within the presumed reconsolidation window, thus it is not surprising that we did not see an effect of time between retrieval and extinction. Lastly, the boundary between extinction and reconsolidation is thought to depend on the duration of retrieval, with long retrieval leading to extinction processes and short retrieval leading to reconsolidation processes (Suzuki et al., 2004). This, however, was not seen to be a moderator of effects here, potentially due to all studies utilizing relatively short retrieval trials. More research is needed to explore neurobiological distinctions between extinction and post-retrieval extinction and the boundary between these two processes.

Limitations

One limitation of this meta-analysis is that we were unable to examine thoroughly the proposed potential boundary condition of memory age (Inda, Muravieva, & Alberini, 2011). The time between acquisition and post-retrieval extinction/extinction procedures was rarely manipulated. Thus, we were only able to compare 24-hour- and 48-hour-old memories for animal fear studies, for which no differences in post-retrieval extinction effects were observed. In addition, in order to increase the homogeneity of the sample, the one study examining 30-day-old memories (Costanzi et al., 2011) was excluded and the range of memory age represented in our studies was limited to within 7 days. Future studies should aim to manipulate the time between acquisition and post-retrieval extinction in order to examine the efficacy of post-retrieval extinction for older memories. Exploration of memory age is especially important given that the majority of PTSD patients come into treatment many years after experiencing a trauma (Wang et al., 2005). In addition, we were unable to examine the effects of post-retrieval extinction on return of appetitive responses in humans as only one such study (which failed to meet our inclusion/exclusion criteria) was conducted (Xue et al., 2012). Furthermore, we did not observe moderation effects for any of the variables we examined (test type, animal housing, CS type, US type, duration of retrieval, time between retrieval and extinction in the post-retrieval extinction group, and time between post-retrieval extinction/extinction and test) for the effects of post-retrieval

extinction on appetitive memories in animals. Given strong overall effects for animal studies of appetitive memories, further application of post-retrieval extinction to appetitive memories—for example, to interfere with the reconsolidation of drug-associations in the treatment of substance dependence—is encouraged. Lastly, although we were able to examine features of acquisition and extinction design, due to a lack of information, we were unable to examine whether mean levels or variability in acquisition or extinction (i.e. actual levels of freezing or SCR response during acquisition/extinction) influenced the effect of post-retrieval extinction over extinction. Future research in this area should report this information.

Clinical Research Applications

Overall, this meta-analysis provides strong support for the efficacy of post-retrieval extinction in preventing the return of appetitive memories in animals and fear memories in humans. Given these findings, continued translation from the animal conditioning laboratory to human conditioning laboratory is warranted. In addition, in humans, careful translation of this work to controlled experiments with clinical populations should be explored. As noted, the size of effects across studies compares well to the pharmacologic reconsolidation blockade literature. There has already been translation of pharmacologic reconsolidation blockade strategies to the clinic. Specifically, a placebo controlled trial of post-retrieval administration of the B-adrenergic blocker, propranolol, in patients with chronic posttraumatic stress disorder indicated significantly less physiologic reactivity in the propranolol group upon exposure to mental imagery of their traumatic event one week later (Brunet et al., 2008). This study was followed by three open trials combining propranolol and six brief trauma reactivation sessions for patients with posttraumatic stress disorder, with results reflecting large symptom improvements over time (Brunet et al., 2011). These effects await replication, but suggest promise for the application of pharmacologic reconsolidation strategies to anxiety and traumatic stress-related disorders. Likewise, given the effect size estimates from the present analysis, similar translation of behavioral post-retrieval extinction strategies to the clinic is encouraged.

In the case of substance use disorders/appetitive memories, translation of post-retrieval extinction strategies to the clinic has already started. Xue and colleagues (2010) applied the post-retrieval extinction paradigm in heroin addicts by using a 5 minute video of scenes of heroin smoking and injection as the retrieval cue. They randomized patients to watch a neutral video or the heroin-cue video followed by 60 minutes of exposure therapy (exposure to pictures, videos, and handling of drug-use material) ten minutes later. Consistent with effect sizes for appetitive conditioning in animals, cue-induced heroin craving was significantly lower in the post-retrieval extinction group 1, 30, and 180 days after completion of exposure therapy. This result is especially noteworthy given limitations in standard exposure-based approaches to substance abuse (Conklin & Tiffany, 2002). Although this initial study is promising, additional work with substance-using populations is needed that further translates post-retrieval extinction to the clinic and examines outcomes such as relapse rates.

In summary, results of this meta-analysis provide strong encouragement for the evaluation of the potential clinical benefits of providing retrieval cues as a prelude to exposure interventions for anxiety, traumatic stress, and substance use disorders. Preclinical studies suggest that provisions of these cues may offer an advantage in terms of attenuating the return of fear and appetitive responses targeted by exposure procedures. Accordingly, there is the potential for post-retrieval extinction to improve outcomes for one of the stronger empirically-supported treatments in the field - exposure-based cognitive behavioral therapy (Hofmann et al., 2008; McHugh et al., 2009; Olatunji et al., 2010).

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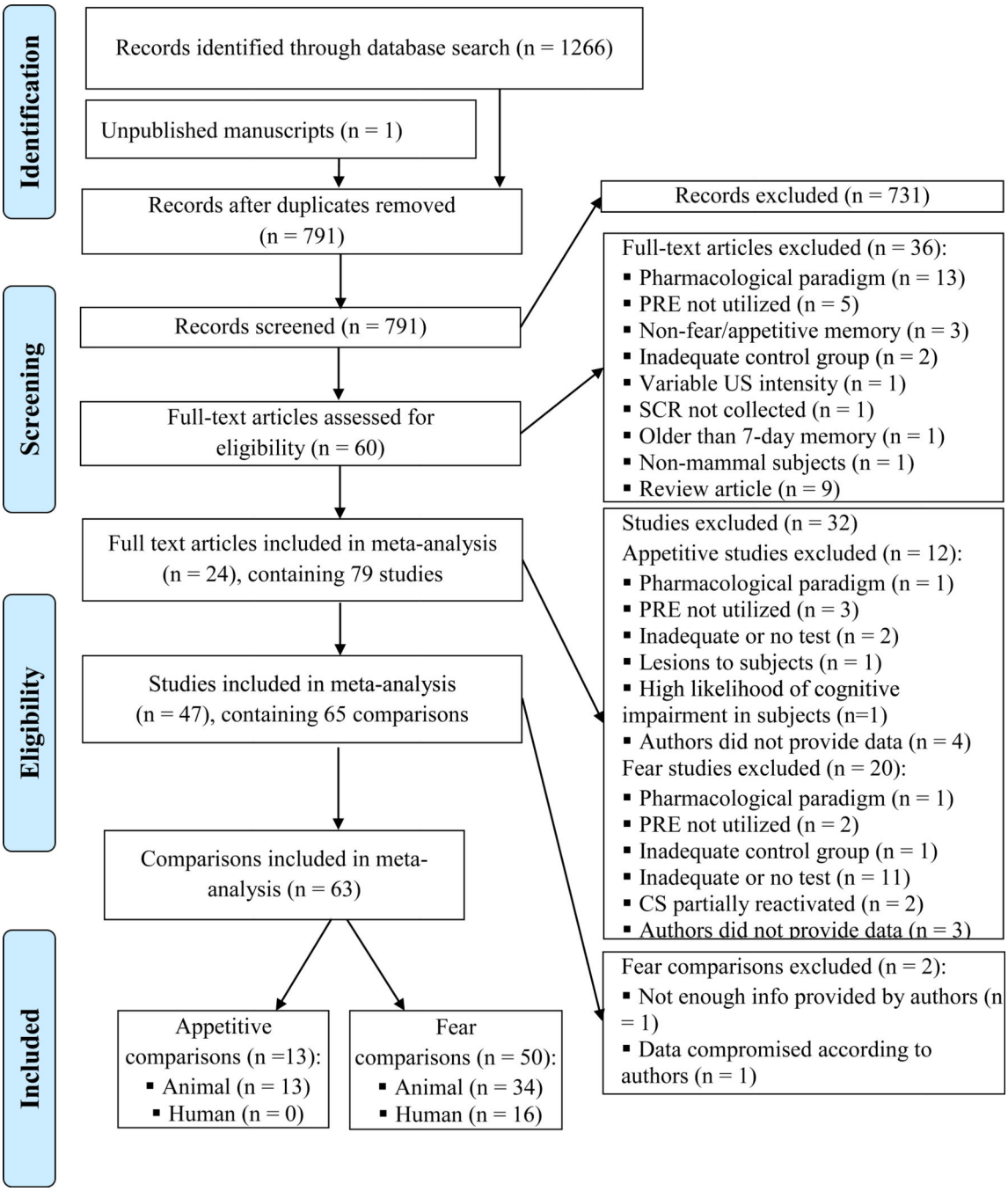

Figure 1.
CONSORT diagram of the articles searched and selection process.

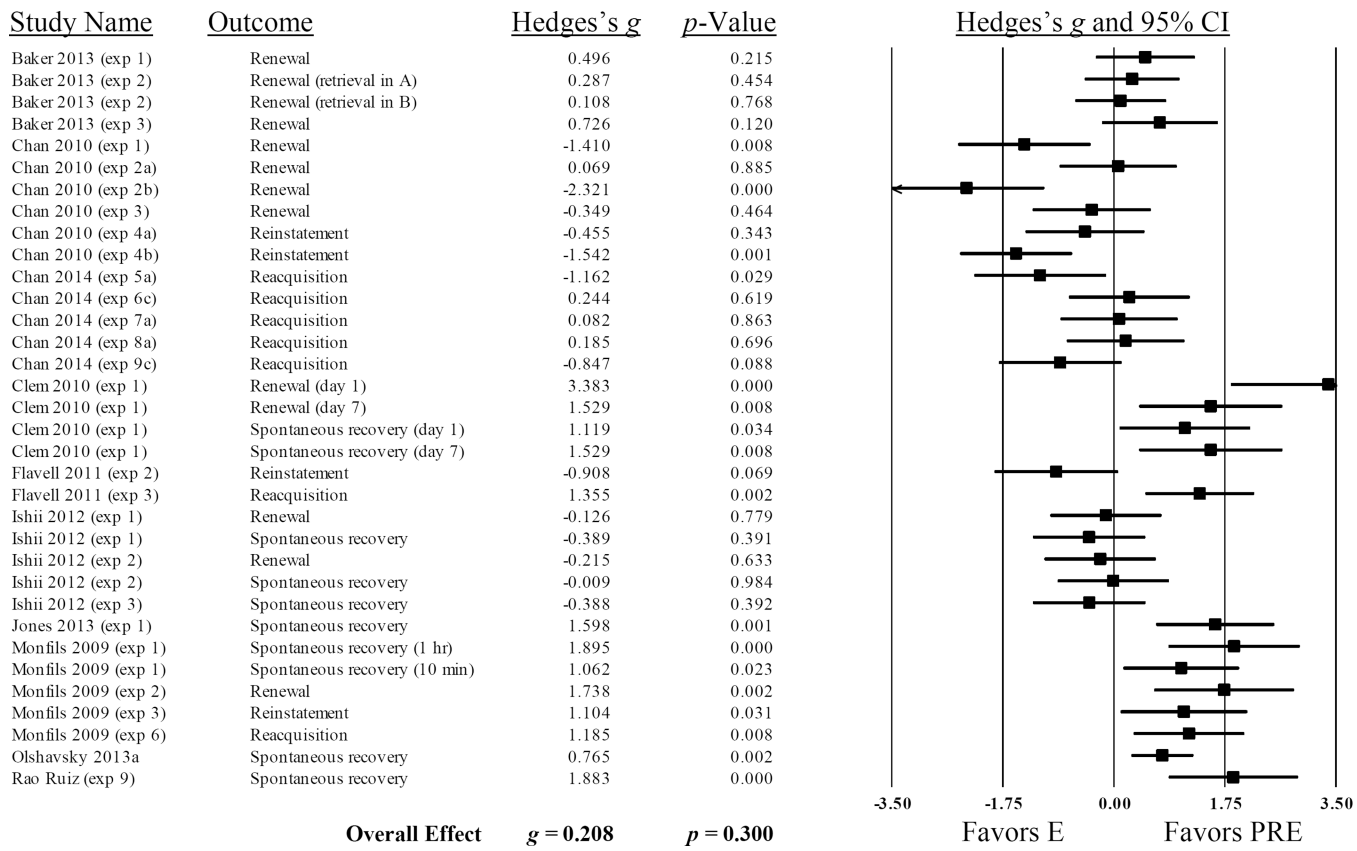

Figure 2.

Forest plot of individual study effects of post-retrieval extinction (PRE) over extinction (E) on return of fear in animals.

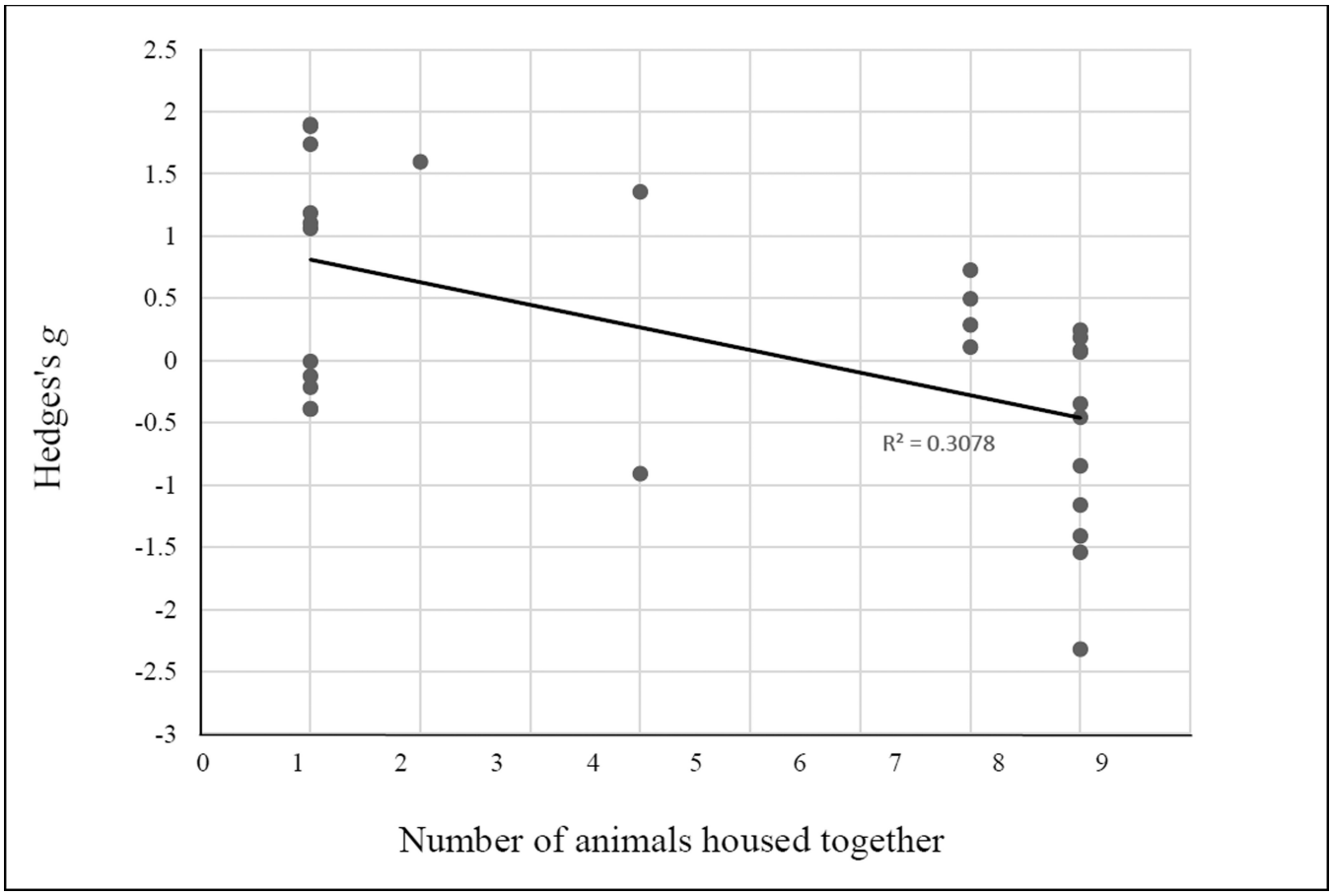

Figure 3.
Regression plot of return of fear effect sizes in relation to the number of animals housed together.

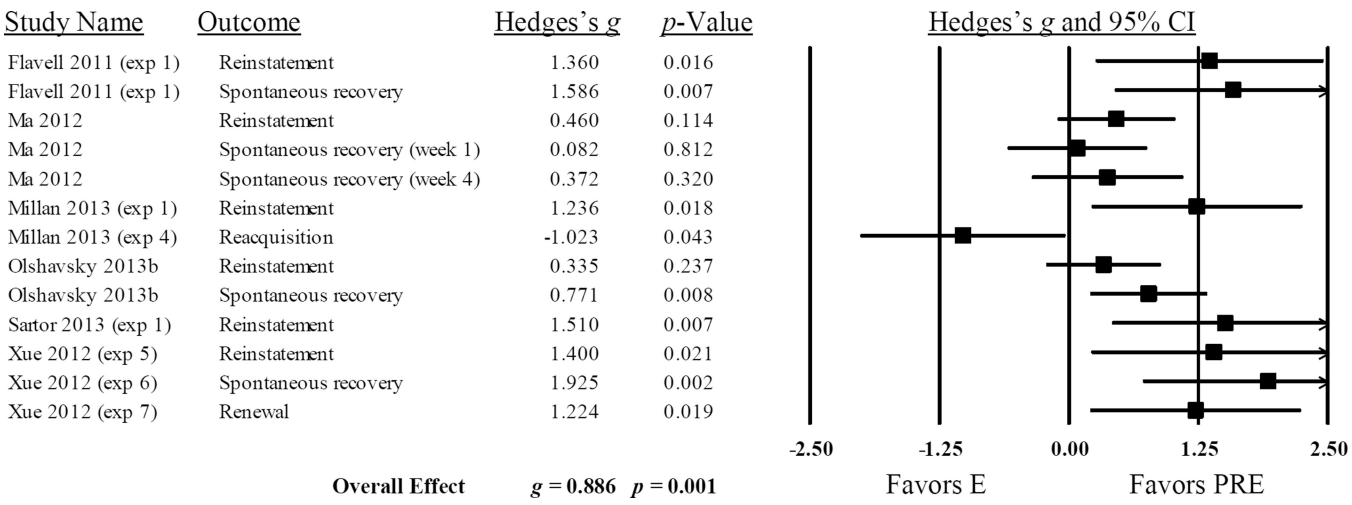

Figure 4.

Forest plot of individual study effects of post-retrieval extinction (PRE) over extinction (E) on return of appetitive memories in animals.

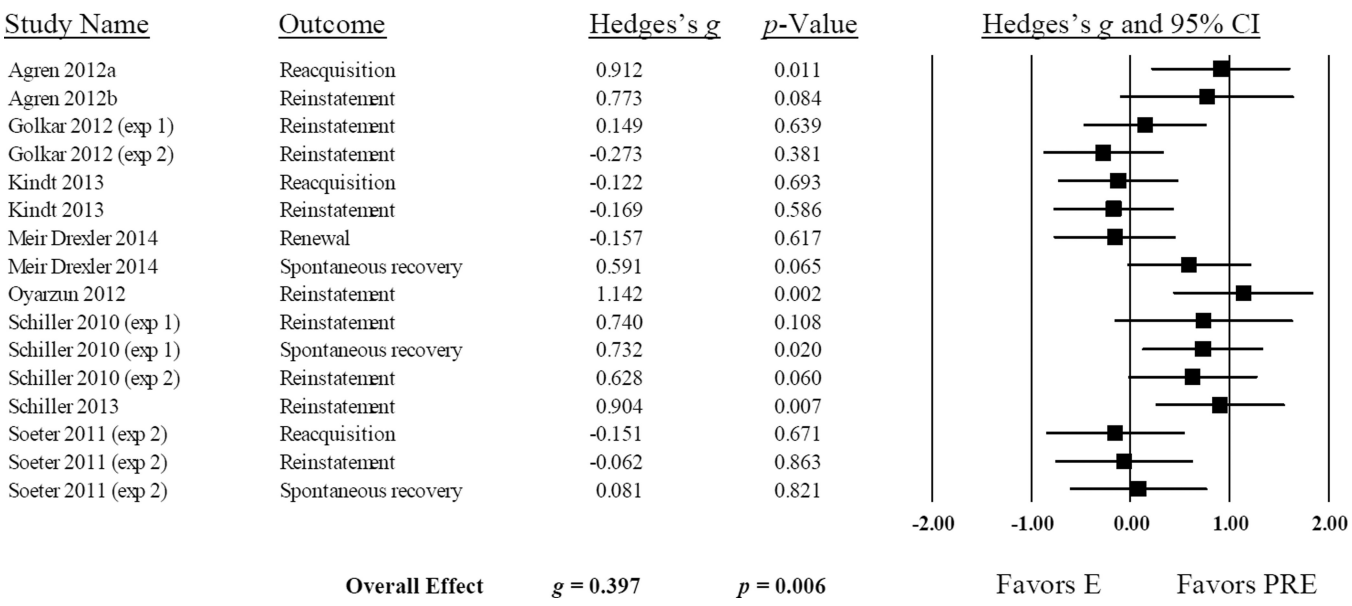

Figure 5.

Forest plot of individual study effects of post-retrieval extinction (PRE) over extinction (E) on return of fear in humans.

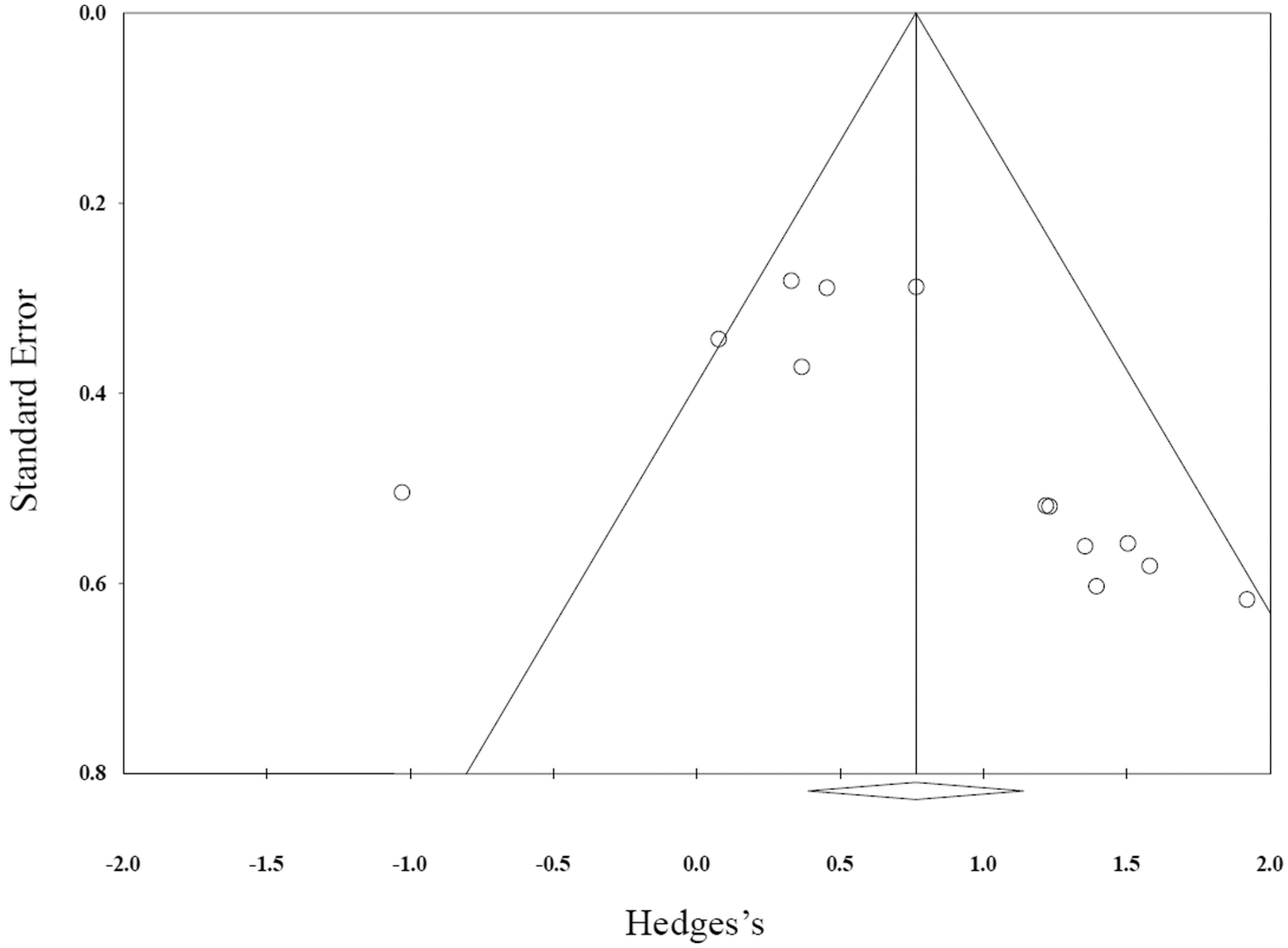

Figure 6.

This funnel plot presents individual study effects of post-retrieval extinction (PRE) over extinction (E) on return of appetitive memories in animals across all test types.

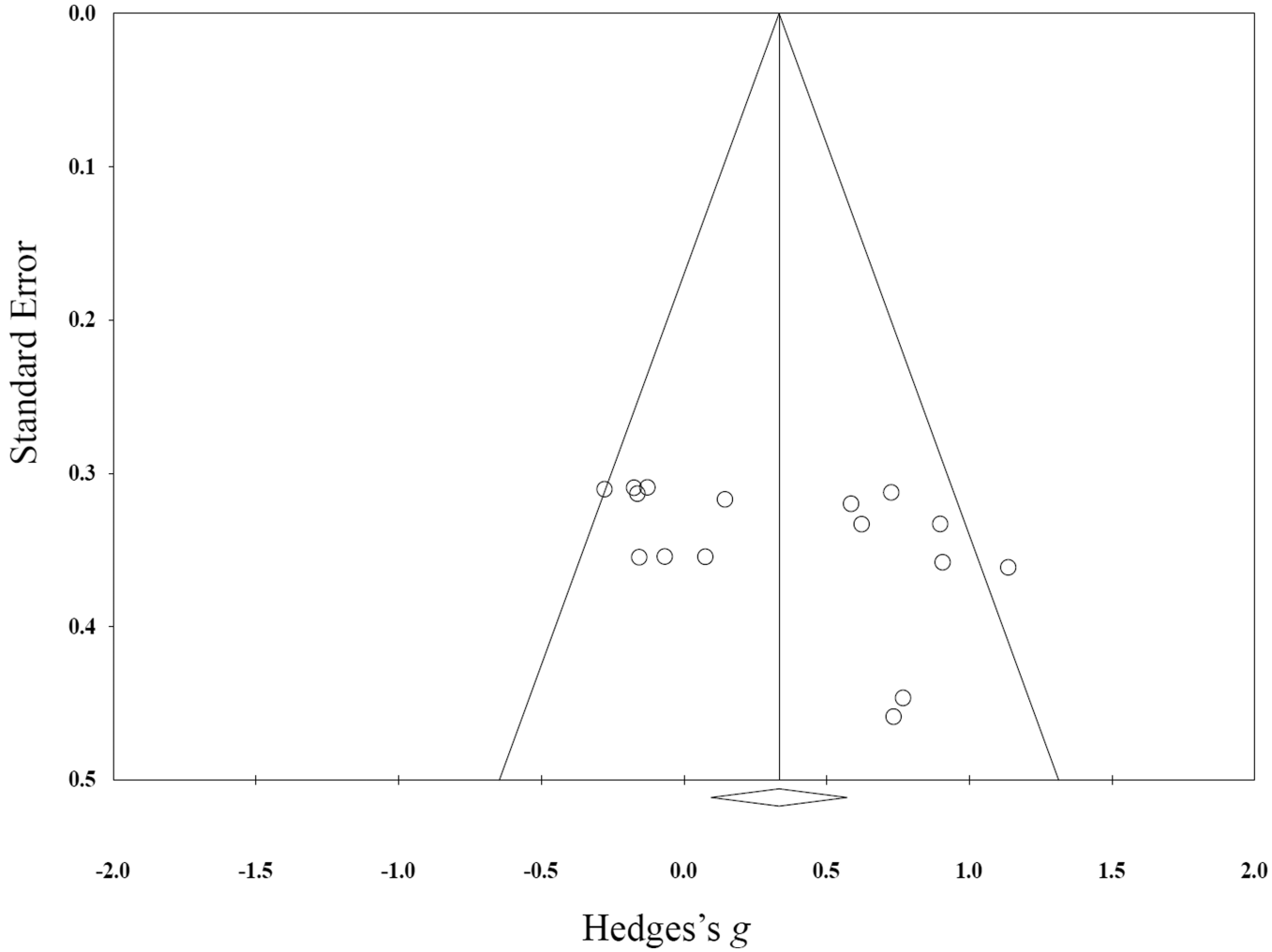

Figure 7.

This funnel plot presents individual study effects of post-retrieval extinction (PRE) over extinction (E) on return of fear memories in humans across all test types.

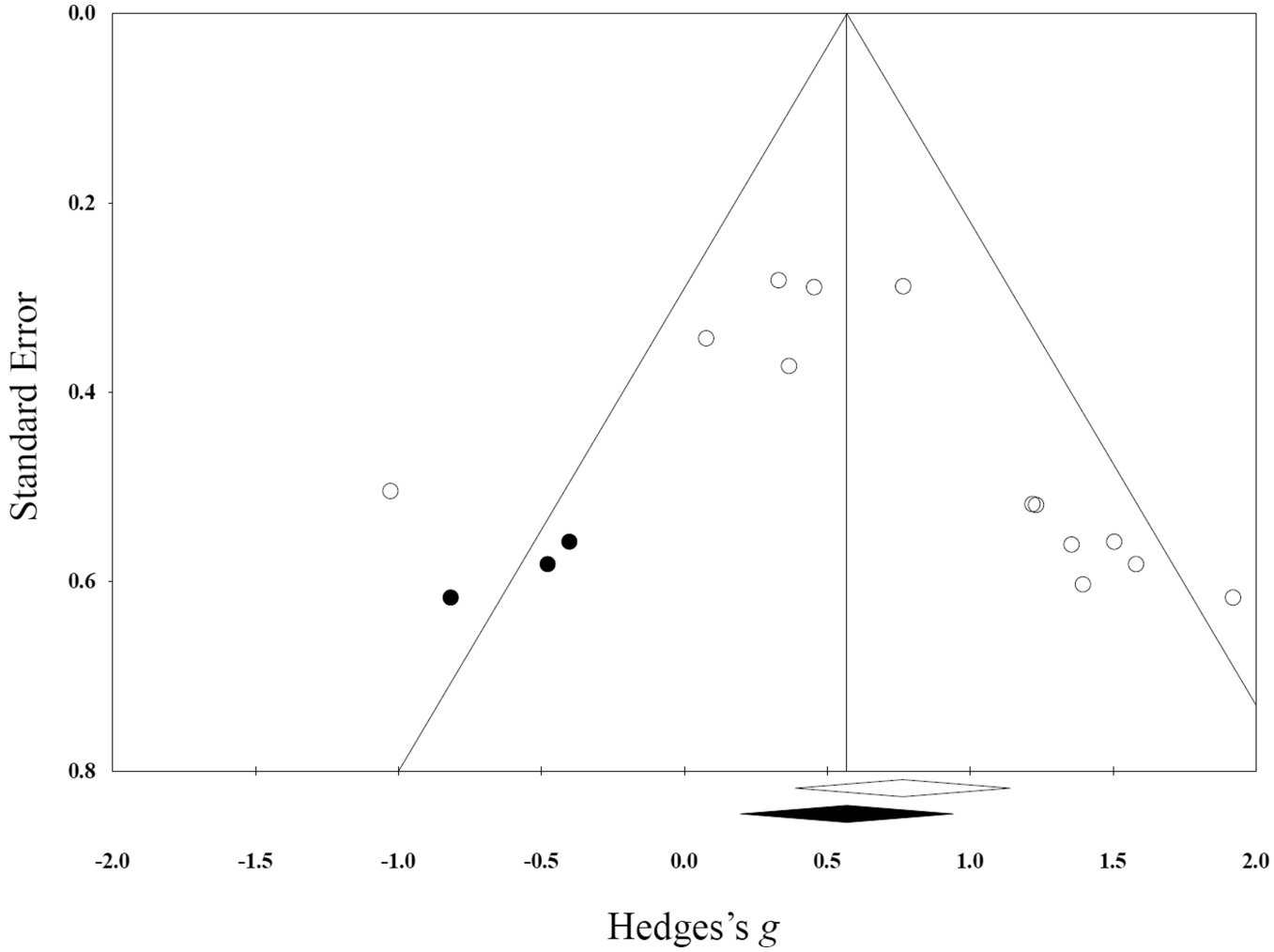

Figure 8.

This funnel plot presents individual study effects of post-retrieval extinction (PRE) over extinction (E) on return of appetitive memories in animals across all test types (open circles) and imputed effects from Trim and Fill analyses (filled circles).

Table 1

A *Animal - Fear Study Characteristics*

Study Information					Study Design		Subject Characteristics				Conditioning Procedures			
First Author(s)	**Year**	**Exp #**	**Effect Size, Direction**	**n**	**Test Type**	**Between- or Within-Subjects Design**	**Animal type**	**% Female**	**Age**	**# Housed Together**	**CS**	**US**	**US Duration (msec)**	**US Intensity (mA)**
Baker	2013	1	Moderate/+	24	Renewal	Between	Rats	0%	34–37 days	6–8	White Noise	Shock	1000	0.6
Baker	2013	2a	Small/+	28	Renewal (Retrieval in B)	Between	Rats	0%	34–37 days	6–8	White Noise	Shock	1000	0.6
Baker	2013	2b	Small/+	26	Renewal (Retrieval in A)	Between	Rats	0%	34–37 days	6–8	White Noise	Shock	1000	0.6
Baker	2013	3	Moderate to large/+	18	Renewal	Between	Rats	0%	34–37 days	6–8	White Noise	Shock	1000	0.6
Chan	2010	1	Large/−**	16	Renewal	Between	Rats	0%	Adult	8	Tone	Shock	500	0.7
Chan	2010	2a	Moderate/+	16	Renewal	Between	Rats	0%	Adult	8	Tone	Shock	500	0.7
Chan	2010	2b	Large/−***	16	Renewal	Between	Rats	0%	Adult	8	Tone	Shock	500	0.7
Chan	2010	3	Small/−	16	Renewal	Between	Rats	0%	Adult	8	Tone	Shock	500	0.7
Chan	2010	4a	Moderate/−	16	Reinstatement	Between	Rats	0%	Adult	8	Flashing light + Tone	Shock	500	0.7
Chan	2010	4b	Large/−**	12	Reinstatement	Within	Rats	0%	Adult	8	Flashing light + Tone	Shock	500	0.5
Chan	2014	5a	Large/−*	15	Reacquisition	Between	Rats	0%	Adult	8	Tone	Shock	500	0.3
Chan	2014	6c	Small/+	15	Reacquisition	Between	Rats	0%	Adult	8	Tone	Shock	500	0.8
Chan	2014	7a	Small/+	16	Reacquisition	Between	Rats	0%	Adult	8	Tone	Shock	500	0.3
Chan	2014	8a	Small/+	16	Reacquisition	Between	Rats	0%	Adult	8	Context	Shock	500	0.3
Chan	2014	9c	Large/−	16	Reacquisition	Between	Rats	0%	Adult	8	Context	Shock	500	0.8
Clem	2010	1a	Large/+*	15	Spontaneous Recovery (Day 1)	Between	Mice	0%	30–50 days	No info	Tone	Shock	2000	1.5
Clem	2010	1b	Large/+***	15	Renewal (Day 1)	Between	Mice	0%	30–50 days	No info	Tone	Shock	2000	1.5
Clem	2010	1c	Large/+**	15	Spontaneous Recovery (Day 7)	Between	Mice	0%	30–50 days	No info	Tone	Shock	2000	1.5

A *Animal - Fear Study Characteristics*

Study Information					Study Design		Subject Characteristics				Conditioning Procedures			
First Author(s)	**Year**	**Exp #**	**Effect Size, Direction**	**n**	**Test Type**	**Between- or Within-Subjects Design**	**Animal type**	**% Female**	**Age**	**# Housed Together**	**CS**	**US**	**US Duration (msec)**	**US Intensity (mA)**
Clem	2010	1d	Large/+**	15	Renewal (Day 7)	Between	Mice	0%	30–50 days	No info	Tone	Shock	2000	1.5
Flavell	2011	2	Large/−	16	Reinstatement	Between	Rats	0%	Adult	4	Auditory Clicker	Shock	500	0.5
Flavell	2011	3	Large/+**	24	Reacquisition	Between	Rats	0%	Adult	4	Context	Shock	2000	0.5
Ishii	2012	1a	Small/−	18	Renewal	Between	Mice	0%	56 days	1	Tone	Shock	2000	0.75
Ishii	2012	1b	Small/−	18	Spontaneous Recovery	Between	Mice	0%	56 days	1	Tone	Shock	2000	0.75
Ishii	2012	2a	Small/−	18	Renewal	Between	Mice	0%	56 days	1	Tone	Shock	2000	0.75
Ishii	2012	2b	Small/−	18	Spontaneous Recovery	Between	Mice	0%	56 days	1	Tone	Shock	2000	0.75
Ishii	2012	3	Small/−	18	Spontaneous Recovery	Between	Mice	0%	56 days	1	Tone	Shock	2000	0.75
Jones	2013	1	Large/+**	22	Spontaneous Recovery	Between	Rats	0%	Not specified	2	Light	Shock	500	0.7
Monfils	2009	1a	Large/+*	20	Spontaneous Recovery (10 min)	Between	Rats	0%	Not specified	1	Tone	Shock	500	0.7
Monfils	2009	1b	Large/+***	20	Spontaneous Recovery (1 hr)	Between	Rats	0%	Not specified	1	Tone	Shock	500	0.7
Monfils	2009	2	Large/+**	16	Renewal	Between	Rats	0%	Not specified	1	Tone	Shock	500	0.7
Monfils	2009	3	Large/+*	16	Reinstatement	Between	Rats	0%	Not specified	1	Tone	Shock	500	0.7
Monfils	2009	6	Large/+**	23	Reacquisition	Between	Rats	0%	Not specified	1	Tone	Shock	500	0.7
Olshavsky, Jones	2013	1	Large/+**	67	Spontaneous Recovery	Between	Rats	0%	Not specified	No info	Tone	Shock	500	0.85
Rao-Ruiz	2011	9	Large/+***	20	Spontaneous Recovery	Between	Mice	0%	56–70 days	1	Context	Shock	2000	0.7

B ***Animal - Fear Study Characteristics cont.***

Study Information				Conditioning Procedures cont.									
First Author(s)	**Year**	**Exp #**	**Effect Size/ Direction**	**Duration of Acquisition, # US Administrations (Context Conditioning)**	**# of Acquisition Trials (Cued Conditioning)**	**Reinforcement Schedule**	**# of Reinforced Acquisition Trials**	**Duration of memory retrieval (seconds)**	**Time between Retrieval and Extinction (min)**	**Duration of Extinction (Context Conditioning)**	**# of Extinction Trials (Cued Conditioning)**	**Time between Acquisition and Extinction (Memory Age)**	**Time between Extinction and Test**
Baker	2013	1	Moderate/+	N/A	3	100%	3	10	10	N/A	31	24h	24–48h
Baker	2013	2a	Small/+	N/A	3	100%	3	10	10	N/A	31	24h	24–48h
Baker	2013	2b	Small/+	N/A	3	100%	3	10	10	N/A	31	24h	24–48h
Baker	2013	3	Moderate to large/+	N/A	3	100%	3	10	10	N/A	31	24h	24–48h
Chan	2010	1	Large/−**	N/A	3	100%	3	20	90	N/A	19	24h	48h
Chan	2010	2a	Moderate/+	N/A	3	100%	3	20	90	N/A	19	24h	48h
Chan	2010	2b	Large/−***	N/A	3	100%	3	20	90	N/A	19	24h	48h
Chan	2010	3	Small/−	N/A	3	100%	3	20	10	N/A	19	24h	48h
Chan	2010	4a	Moderate/−	N/A	3	100%	3	30	10	N/A	19	24h	48h
Chan	2010	4b	Large/−**	N/A	4	100%	4	30	10	N/A	21	24h	72h
Chan	2014	5a	Large/−*	N/A	3	100%	3	120	10	N/A	12	48h	24h
Chan	2014	6c	Small/+	N/A	3	100%	3	120	10	N/A	12	48h	24h
Chan	2014	7a	Small/+	N/A	3	100%	3	120	10	N/A	12	48h	24h
Chan	2014	8a	Small/+	180s, 1 US	N/A	N/A	N/A	300	10	30 min	N/A	48h	48h
Chan	2014	9c	Large/−	180s, 1 US	N/A	N/A	N/A	300	10	30 min	N/A	48h	48h
Clem	2010	1a	Large/+*	N/A	6	100%	6	20	30	N/A	38	24h	24h
Clem	2010	1b	Large/+***	N/A	6	100%	6	20	30	N/A	38	24h	24h
Clem	2010	1c	Large/+**	N/A	6	100%	6	20	30	N/A	38	24h	6 days
Clem	2010	1d	Large/+**	N/A	6	100%	6	20	30	N/A	38	24h	6 days
Flavell	2011	2	Large/−	N/A	2	100%	2	60	60	N/A	11	24h	24h

B *Animal - Fear Study Characteristics cont.*

Study Information				Conditioning Procedures cont.									
First Author(s)	**Year**	**Exp #**	**Effect Size/ Direction**	**Duration of Acquisition, # US Administrations (Context Conditioning)**	**# of Acquisition Trials (Cued Conditioning)**	**Reinforcement Schedule**	**# of Reinforced Acquisition Trials**	**Duration of memory retrieval (seconds)**	**Time between Retrieval and Extinction (min)**	**Duration of Extinction (Context Conditioning)**	**# of Extinction Trials (Cued Conditioning)**	**Time between Acquisition and Extinction (Memory Age)**	**Time between Extinction and Test**
Flavell	2011	3	Large/+**	180s, 1 US	N/A	N/A	N/A	120	60	30 min	N/A	24h	24h
Ishii	2012	1a	Small/−	N/A	6	100%	6	20	30	N/A	40	24h	24h
Ishii	2012	1b	Small/−	N/A	6	100%	6	20	30	N/A	40	24h	24h
Ishii	2012	2a	Small/−	N/A	6	100%	6	20	30	N/A	80	24h	24h
Ishii	2012	2b	Small/−	N/A	6	100%	6	20	30	N/A	80	24h	24h
Ishii	2012	3	Small/−	N/A	6	100%	6	20	30	N/A	80	24h	24h
Jones	2013	1	Large/+**	N/A	3	100%	3	20	10	N/A	19	24h	24h
Monfils	2009	1a	Large/+*	N/A	3	100%	3	20	10	N/A	19	24h	30 days
Monfils	2009	1b	Large/+***	N/A	3	100%	3	20	60	N/A	19	24h	30 days
Monfils	2009	2	Large/+**	N/A	3	100%	3	20	60	N/A	19	24h	48h
Monfils	2009	3	Large/+*	N/A	3	100%	3	20	60	N/A	19	24h	48h
Monfils	2009	6	Large/+**	N/A	3	100%	3	20	60	N/A	19	24h	24h
Olshavsky, Jones	2013	1	Large/+**	N/A	3	100%	3	20	10	N/A	19	24h	22 days
Rao-Ruiz	2011	9	Large/+***	180s, 1 US	N/A	N/A	N/A	180	120	30 min	N/A	24h	14 days

Note.

* $p<0.05$

** $p<0.01$

*** $p<0.001$

Table 2

A *Animal – Appetitive Study Characteristics*

Study Information					Study Design		Subject Characteristics				Conditioning Procedures					
First Author(s)	Year	Exp #	Effect Size/ Direction	n	Test Type	Between- or Within-Subjects Design	Animal Type	% Female	Age	# Housed Together	CS	US	US intensity	Duration of Acquisition Trial	# of Acquisition Trials/Day	# of Acquisition Days
Flavell	2011	1a	Large/+**	14	Spontaneous Recovery	Between	Rats	0%	Adult	4	Light	Food	45 mg	20 min	1	9
Flavell	2011	1b	Large/+*	14	Reinstatement	Between	Rats	0%	Adult	4	Light	Food	45 mg	20 min	1	9
Ma	2012	1a	Moderate/+	47	Reinstatement	Between	Rats	0%	Not specified	4	Context	Drug (morphine)	5 mg/kg	45 min	1	10
Ma	2012	1b	Small/+	28	Spontaneous Recovery (Week 1)	Between	Rats	0%	Not specified	4	Context	Drug (morphine)	5 mg/kg	45 min	1	10
Ma	2012	1c	Small/+	32	Spontaneous Recovery (Week 4)	Between	Rats	0%	Not specified	4	Context	Drug (morphine)	5 mg/kg	45 min	1	10
Millan	2013	1	Large/+*	16	Reinstatement	Between	Rats	0%	Not specified	8	Context	Drug (beer)	4% v/v, 0.6 ml	60 min	1	7
Millan	2013	4	Large/−*	16	Reacquisition	Between	Rats	0%	Not specified	8	Context	Drug (beer)	4% v/v, 0.6 ml	60 min	1	7
Olshavsky, Song	2013	1[a]	Small/+	48	Reinstatement	Between	Rats	0%	Adult	1	Light	Food	no info	N/A	8 on day 1, 16 on day 2–4	4
Olshavsky, Song	2013	1b [a]	Large/+**	48	Spontaneous Recovery	Between	Rats	0%	Adult	1	Light	Food	no info	N/A	8 on day 1, 16 on day 2–4	4
Sartor	2013	1	Large/+**	15	Reinstatement	Between	Rats	0%	Adult	2	Context	Drug (cocaine)	10 mg/kg	60 min	2	3
Xue	2012	5	Large/+*	12	Reinstatement	Between	Rats	0%	Not specified	5	Tone-light	Drug (heroin)	0.05 mg/kg	60 min	3	10
Xue	2012	6	Large/+**	14	Spontaneous Recovery	Between	Rats	0%	Not specified	5	Tone-light	Drug (cocaine)	0.75 mg/kg	60 min	3	10
Xue	2012	7	Large/+*	16	Renewal	Between	Rats	0%	Not specified	5	Tone-light	Drug (cocaine)	0.75 mg/kg	60 min	3	10

B ***Animal - Appetitive Study Characteristics cont.***

Study Information					Conditioning Procedures cont.								
First Author(s)	**Year**	**Exp #**	**Effect Size/ Direction**	**Reinforcement Schedule**	**Total Reinforced Acquisition**	**Duration of memory retrieval (min)**	**Time between Retrieval and Extinction (min)**	**Duration of Extinction Trials**	**# of Extinction Trials/Day**	**# of Extinction Days**	**Total Extinction**	**Time between Acquisition and Extinction (memory age)**	**Time between Extinction and Test**
Flavell	2011	1a	Large/+**	100%	180 min	10	60	70 min	1	1	70 min	24h	6 tests across 20 days
Flavell	2011	1b	Large/+*	100%	180 min	10	60	70 min	1	1	70 min	24h	27 days
Ma	2012	1a	Moderate/+	50%	225 min	15	10	45 min	0.5 (1 every other day)	10–14	225 – 315 min	72h	72h
Ma	2012	1b	Small/+	50%	225 min	15	10	45 min	0.5 (1 every other day)	10–14	225 – 315 min	72h	1 week
Ma	2012	1c	Small/+	50%	225 min	15	10	45 min	0.5 (1 every other day)	10–14	225 – 315 min	72h	4 weeks
Millan	2013	1	Large/+*	100% (w/ 24 sec timeout)[b]	7 sessions	10	70	60 min	1	4	240 min	24h	no info
Millan	2013	4	Large/−*	100% (w/ 24 sec timeout)[b]	7 sessions	10	70	60 min	1	4	240 min	24h	no info
Olshavsky, Song	2013	1a	Small/+	100%	56 trials	.17	60	N/A	18	1	18 trials	24h	24h
Olshavsky, Song	2013	1b	Large/+**	100%	56 trials	.17	60	N/A	18	1	18 trials	24h	21 days
Sartor	2013	1	Large/+**	50%	180 min	3	60	15 min	1	Variable[c]	Variable	24h	24h
Xue	2012	5	Large/+*	100% (w/ 40 sec timeout)[b]	30 sessions (max 600 infusions)	15	10	60 min	3	Variable[c]	Variable	24h	24h
Xue	2012	6	Large/+**	100% (w/ 40 sec timeout)[b]	30 sessions (max 600 infusions)	15	10	60 min	3	Variable[c]	Variable	24h	28 days
Xue	2012	7	Large/+*	100% (w/ 40 sec timeout)[b]	30 sessions (max 600 infusions)	15	10	60 min	3	Variable[c]	Variable	24h	24h

Notes.

* $p<0.05$

** $p<0.01$

[a] Our analyses combine effect sizes of rats from both the orienter and non-orienter categorizations.

[b] Nosepokes were reinforced with the US 100% in these studies, however there was a timeout period after each nosepoke in which the drug was not available.

[c]Extinction procedures were conducted daily until extinction criteria were met.

Table 3

A *Human - Fear Study Characteristics*

Study Information					Study Design		Participant Characteristics		Conditioning Procedures				
First Author(s)	**Year**	**Exp #**	**Effect Size/ Direction**	**n**	**Test Type**	**Between- or Within-Subjects Design**	**Mean Age**	**% Female**	**CS**	**Conditioned Learning Relevant?**	**US**	**US Duration (msec)**	**US Intensity**
Agren, Engman	2012	N/A	Large/+*	33	Reacquisition	Between	24.6	57.6	Photo of neutral environment with lamp lit in either red or blue	N	Shock	500	Up to 5mA
Agren, Furmark	2012	N/A	Large/+	20	Reinstatement	Between	24.0	50.0	Photo of neutral environment with lamp lit in either red or blue	N	Shock	500	Up to 5mA
Golkar	2012	1	Small/+	19	Reinstatement	Within	27.2	52.6	fearful male faces	Y	Shock	100	No info
Golkar	2012	2	Small/−	20	Reinstatement	Within	26.3	55.0	Colored squares	N	Shock	100	No info
Kindt	2013	1a	Small/−	40	Reinstatement	Between	21.1	67.5	Pictures of spiders	Y	Shock	2	No info
Kindt	2013	1b	Small/−	40	Reacquisition	Between	21.1	67.5	Pictures of spiders	Y	Shock	2	No info
Meir Drexler	2014	1a	Moderate/+	39	Spontaneous Recovery	Between	23.9	48.7	Pictures of aversive animals in context (frame)	Y	Shock	100	No info
Meir Drexler	2014	1b	Small/−	39	Renewal	Between	23.9	48.7	Pictures of aversive animals in context (frame)	Y	Shock	100	No info
Oyarzun	2012	1	Large/+**	17	Reinstatement	Within	23.4	66.7	Colored squares	N	Aversive sounds	N/A	N/A
Schiller	2010	1a	Moderate to large/+*	42	Spontaneous Recovery	Between	23.6	63.1	Colored squares	N	Shock	200	10V–60V
Schiller	2010	1b	Moderate to large/+	19	Reinstatement	Between	23.6	63.1	Colored squares	N	Shock	200	10V–60V
Schiller	2010	2	Moderate to large/+	21	Reinstatement	Within	22.8	55.6	Colored squares	N	Shock	200	10V–60V
Schiller	2013	1	Large/+**	19	Reinstatement	Within	26.0	52.6	Colored squares	N	Shock	200	20V–60V

A ***Human - Fear Study Characteristics***

Study Information					Study Design		Participant Characteristics		Conditioning Procedures				
First Author(s)	**Year**	**Exp #**	**Effect Size/ Direction**	**n**	**Test Type**	**Between- or Within-Subjects Design**	**Mean Age**	**% Female**	**CS**	**Conditioned Learning Relevant?**	**US**	**US Duration (msec)**	**US Intensity**
Soeter	2011	IIa	Small/+	40	Spontaneous Recovery	Within	21.8	72.5	Pictures of spider or gun (CS+) or mug (CS−)	Y	Shock	2	≥1 mA
Soeter	2011	IIb	Small/−	40	Reinstatement	Within	21.8	72.5	Pictures of spider or gun (CS+) or mug (CS−)	Y	Shock	2	≥1 mA
Soeter	2011	IIc	Small/−	40	Reacquisition	Within	21.8	72.5	Pictures of spider or gun (CS+) or mug (CS−)	Y	Shock	2	≥1 mA

B ***Human - Fear Study Characteristics cont.***

Study Information				Conditioning Procedures cont.								
First Author(s)	**Year**	**Exp #**	**Effect Size, Direction**	**# of Acquisition Trials**	**Reinforcement Schedule**	**# of Reinforced Acquisition Trials**	**Duration of memory retrieval (seconds)**	**Time between Retrieval and Extinction (min)**	**# of Extinction Trials**	**Time between Acquisition and Extinction (Memory Age)**	**Time between Extinction and Test**	**Expectancy Ratings Utilized?**
Agren, Engman	2012	N/A	Large/+*	16	100%	16	120	10	8	24h	24h	N
Agren, Furmark	2012	N/A	Large/+	16	100%	16	120	10	8	24h	72h	N
Golkar	2012	1	Small/+	12	50%	6	6	10	12	24h	24h	N
Golkar	2012	2	Small/−	12	50%	6	6	10	12	24h	24h	N
Kindt	2013	1a	Small/−	8	75%	6	8	10	12	24h	24h	Y (During)
Kindt	2013	1b	Small/−	8	75%	6	8	10	12	24h	24h	Y (During)
Meir Drexler	2014	1a	Moderate/+	16	75%	12	30	10	8	24h	24h	Y (During)
Meir Drexler	2014	1b	Small/−	16	75%	12	30	10	8	24h	48h	Y (During)
Oyarzun	2012	1	Large/+**	16	38%	6	4	10	10	24h	24h	N

B *Human - Fear Study Characteristics cont.*

Study Information				Conditioning Procedures cont.								
First Author(s)	**Year**	**Exp #**	**Effect Size, Direction**	**# of Acquisition Trials**	**Reinforcement Schedule**	**# of Reinforced Acquisition Trials**	**Duration of memory retrieval (seconds)**	**Time between Retrieval and Extinction (min)**	**# of Extinction Trials**	**Time between Acquisition and Extinction (Memory Age)**	**Time between Extinction and Test**	**Expectancy Ratings Utilized?**
Schiller	2010	1a	Moderate to large/+*	16	38%	6	4	10	11	24h	24h	N
Schiller	2010	1b	Moderate to large/+	16	38%	6	4	10	11	24h	1 year	N
Schiller	2010	2	Moderate to large/+	13	38%	5	4	10	11	24h	24h	N
Schiller	2013	1	Large/+**	13	38%	5	8	10	11	24h	24h	N
Soeter	2011	IIa	Small/+	5	80%	4	8	10	10	24h	24h	Y (End)
Soeter	2011	IIb	Small/−	5	80%	4	8	10	10	24h	24h	Y (End)
Soeter	2011	IIc	Small/−	5	80%	4	8	10	10	24h	24h	Y (End)

Notes.

* $p<0.05$

** $p<0.01$

Table 4

Summary of Main Effects and Moderation Effects for Animal Fear, Animal Appetitive, and Human Fear Paradigms

Outcome/moderator	Animal - Fear	Animal - Appetitive	Human - Fear
Main Effects			
Overall effect	g = 0.21, n = 34	**g = 0.89***, n = 13**	**g = 0.40**, n = 16**
Test Type	χ^2 = 2.30	**χ^2= 7.85***	χ^2 = 3.17
- Spontaneous recovery	g = 0.45^{t}	**g = 1.00****	**g = 0.53***
- Reinstatement	g = −0.47	**g = 0.96*****	**g = 0.42****
- Renewal	g = 0.34	g = 1.22^{t}	g = −0.19
- Reacquisition	g = 0.17	g = −1.02	g = 0.36
Moderators			
Study design			
Between vs. within subject	-	-	B = 0.06
- Between	-	-	**g = 0.43***
- Within	-	-	g = 0.37^{t}
Participant characteristics			
Age	-	-	B = 0.04
Gender	-	-	B = −0.01
Housed alone vs. together	**B = 0.81***	-	n/a
- Housed alone	**g = 0.78***	-	n/a
- Housed together	g = −0.20	-	n/a
Number animals housed together	**B = −0.19*****	B = −0.09	n/a
Conditioning procedures			
Stimuli			
Fear-relevant vs. fear-irrelevant	n/a	n/a	**B = −0.64*****
- Fear-relevant	n/a	n/a	g = 0.02
- Fear-irrelevant	n/a	n/a	**g = 0.66*****
Context vs. cued conditioning	B = 0.51	B = −0.75	-
- Context	g = 0.64	g = 0.46	-
- Cued	g = 0.14	**g = 1.20*****	-
Shock duration	B = 0.45	n/a	**B = 2.31*****
Shock intensity	B = 1.50^{t}	n/a	-
Type of US (Food vs. Drug)	n/a	B = 0.09	n/a
- Food	n/a	g = 0.95^{t}	n/a
- Drug	n/a	**g = 0.86****	n/a
Timing of procedures			
Number of acquisition trials	B = 0.02	-	**B = 0.08****
Reinforcement schedule	-	-	B = −0.00
Number of reinforced acquisition trials	-	-	B = 0.03

Outcome/moderator	Animal - Fear	Animal - Appetitive	Human - Fear
Number of extinction trials	*B* = −0.00	-	*B* −0.12
Duration of retrieval (post-retrieval extinction group)	*B* = −0.00	*B* = 0.02	*B* = 0.00
Time between retrieval and extinction (post-retrieval extinction group)	*B* = −0.00	*B* = −0.34	-
Hours between acquisition and post-retrieval extinction/extinction (24 vs. 48 hrs)	*B* = −0.61	-	-
- 24hrs	*g* = 0.32	-	-
- 48hrs	*g* = −0.29	-	-
Hours between post-retrieval extinction/extinction and test (24 vs. 48 hrs)	*B* = −0.65	-	-
- 24hrs	*g* = 0.26	-	-
- 48hrs	*g* = −0.24	-	-
Time between post-retrieval extinction/extinction and test (short delay vs. long delay)	***B* = 0.66***	*B* = 0.00	-
- Short delay	*g* = 0.12	***g* = 0.93****	-
- Long delay	***g* = 0.78***	***g* = 0.94****	-
Expectancy ratings	n/a	n/a	***B* = −0.59****
- Expectancy ratings	n/a	n/a	*g* = 0.00
- No expectancy ratings	n/a	n/a	***g* = 0.59*****

Notes. Significant findings are presented in bold.

^{t} p ≤ .08,

* p < .05,

** p < .01,

*** p < .001.

"-" indicates inconsistency of methods or insufficient variation within methods for adequate examination of the moderator.