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The Effect of Extinction Cues on Response Recovery: A Meta-Analysis

El Efecto de Claves de Extinción en la Recuperación de Respuesta: Un Meta-análisis

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A cue presented during Pavlovian extinction may help the recovery of the extinction memory, for which is called an extinction cue (EC). Pavlovian conditioning has been useful as a model of different behavior disorders and extinction as a model for their treatment. Extinguished responses may be recovered under different circumstances, akin to a relapse. Hence, it is important to strengthen extinction memory retrieval. There is contradictory evidence of the effectiveness of ECs to this end. There is also little information about the magnitude of response recovery prevention when using ECs. The magnitude of the ECs effect on response recovery was analyzed by a meta-analysis that considered possible sources of variance in the EC effect. The included studies were gathered mainly through scientific database search engines. Selection criteria included experiments that used a Pavlovian extinction and recovery procedure with an EC test. Effect size was calculated for each relevant experiment. Thirty-seven studies were included. These analyses showed that there is a robust effect of an extinction cue in reducing response recovery, d = 0.71, 95% CI [0.58, 0.85]. This effect is higher when a spontaneous recovery procedure is used and when the experiment is done with non-human animals. Interestingly, the type of control group did not affect the effect size. These results are robust under different statistical analyses, although a publication bias was detected.

Keywords: extinction cue, meta-analysis, Pavlovian conditioning, response recovery

Una clave presentada durante la extinción pavloviana puede contribuir luego a la recuperación de la memoria de extinción, por lo que esta se conoce como clave de extinción (CE). El condicionamiento pavloviano ha sido utilizado como modelo para la comprensión etiológica de diversos trastornos; asimismo, la extinción ha sido utilizada con un modelo para el tratamiento de otros. Las conductas extinguidas pueden recuperarse debido a diferentes motivos, similar a una recaída. Por ello, es importante fortalecer la recuperación de la memoria de extinción. Existe evidencia contradictoria respecto a la eficacia y prevención de las recaídas al utilizar claves de extinción. Se llevó a cabo un meta-análisis justamente sobre la magnitud y las posibles fuentes de varianza del efecto de las CE en la recuperación de respuestas. Los estudios incluidos se recopilaron principalmente a través de buscadores en bases de datos científicas. Los criterios de selección incluyeron experimentos que utilizaron un procedimiento de extinción y recuperación pavloviana con una prueba de CE. Se calculó un tamaño del efecto para cada experimento utilizado. Se incluyeron 37 estudios. El análisis de dichos tamaños del efecto mostró que existe un efecto robusto de las claves de extinción en la reducción de la recuperación de respuestas, d = 0,71, IC del 95% [0,58, 0,85]. Este efecto es mayor cuando se utiliza un procedimiento de recuperación espontánea y cuando el experimento se realiza en animales no humanos. Curiosamente, el tipo de control utilizado no afectó el tamaño del efecto. Estos resultados son robustos bajo diferentes análisis estadísticos, aunque se detectó un sesgo de publicación.

Palabras clave: clave de extinción, condicionamiento pavloviano, metaanálisis, recuperación de respuesta

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An extinction cue (EC) is a stimulus presented during Pavlovian extinction, that may reduce response recovery when introduced later at test. The unconditioned stimulus (US) is formed in Pavlovian conditioning, which is a learned association between an initially neutral stimulus and another relevant event. As the neutral stimulus is paired with the US, the neutral stimulus becomes a conditioned stimulus (CS) and comes to produce a conditioned response (CR). The phenomenon was thoroughly documented by Ivan Pavlov in his *Conditioned Reflexes* (Pavlov, 1927), establishing the foundations of associative learning research.

Pavlovian conditioning has been useful as a conceptual model of the acquisition of anxiety disorders (Laborda et al., 2012; Laborda & Miller, 2013; Papalini et al., 2019; Seligman, 1971). Consequently, fear conditioning has been studied in rats (e.g., Miguez et al., 2015) and humans (e.g., Culver et al., 2011; Dibbets et al., 2008, 2013), where the US it is either a pain-or-startle-inducing stimulus. The resulting conditioning is fear responses to the CS associated with it. Here, fear-response models clinical anxiety. Luckily, the acquired fear can be affected, for example by extinguishing it. Extinction is a relevant related phenomenon, in which presentations of the CS by itself progressively diminishes the CR (Pavlov, 1927). Extinction of conditioned responding is the basic model for exposure therapy, the most reliable treatment for anxiety disorders. For example, a phobic patient could be confronted with his or her fear inducing CSs in exposure therapy, in a progressive and controlled manner, diminishing the fear responses previously elicited by them (Pittig et al., 2016; Wolpe, 1968).

While the reduction of CRs due to extinction has been experimentally reproduced in different species, like rats (e.g., Alfaro et al., 2018; Brooks & Bouton, 1993; Bustamante et al., 2019; González et al., 2016; Miguez et al., 2013, 2014; Miller et al., 2015; San Martín et al., 2018), pigeons (e.g., Brooks, 2000), rabbits (Gormezano et al., 1962), monkeys (Mineka et al., 1984), and humans (e.g., Blass et al., 1984; Diaz et al., 2017; Lira et al., 2016; Quezada et al., 2018), this procedure does not permanently eliminate the learned CRs. The immediate effect of extinction is robust, but there are some situations in which extinguished CRs recover. In brief, CR could recover after a simple time lapse since extinction (i.e., spontaneous recovery; Brooks et al., 2004; Pavlov, 1927) due to a context change from the one in which extinction was conducted (i.e., renewal; Bouton & Ricker, 1994; Willcocks & McNally, 2014), after a new presentation of the US by itself (i.e., reinstatement; Brooks & Fava, 2017; Rescorla & Heth, 1975), and with new pairings of the CS and the US (i.e., reacquisition; Capaldi et al., 2009; Napier et al., 1992). Response recovery fits in behavioral treatment as an explanation of relapses from therapy, for example, a recovery of fear after exposure treatment (Bouton, 1988). Because of this, research have focused on ways to prevent response recovery (i.e., ways to make extinction more enduring).

Several procedures can reduce response recovery (for a review, see Laborda et al., 2011) and the use of ECs is one of them. As previously mentioned, an EC is a stimulus that is presented during Pavlovian extinction, that may reduce response recovery when introduced after extinction. For example, Brooks et al. (2004), used a 15s buzzer as an EC during the extinction of a conditioned ethanol tolerance procedure. The ethanol injection was accompanied with a strobe light as a CS and tolerance (CR) was measured with a tilting plane, with the slipping angle of a rat inside the tilting box as dependent variable. When a rat is tolerant, it slips at a high angle, comparable to a sober state. During extinction of the strobe light (CS), the buzzer (i.e. the EC) was presented in some trials and was then used during a spontaneous recovery test, reducing the recovery of extinguished tolerance.

In this work, we focused on the effect of an EC, when evaluated in situations in which response recovery would be predicted. In some experiments, the effect of the EC on a group of subjects is to reduce response recovery, compared to a group where the EC is not presented or a different stimulus is presented (e.g., Brooks & Bouton, 1993, 1994). The logic behind the EC procedure is to make use of a stimulus that can remind the subject of what was learned during extinction.

Experimental evidence is not consistent about the effectiveness of ECs in preventing response recovery. For example, Dibbets et al. (2012) found more recovery instead of response recovery prevention when using an extinction cue on a renewal paradigm, in contradiction with many other reports (e.g., Brooks & Bouton, 1993, 1994). Dibbets et al. (2012) experiments differ from Brooks and Bouton (1994) in that they were implemented with human participants instead of rats as subjects, and with stimuli shown on a computer screen instead of a magazine training preparation n. Factors such as subject type, experimental paradigm, and response recovery type could explain these mixed results. This produces uncertainty about the generality of the effect of an EC. Because of this, it is important to evaluate the magnitude of an EC effect on response recovery, which can better inform us about the situation of ECs in the grand scheme of prevention of response

recovery. This necessarily relates to the possible therapeutic applications of ECs, since the reduction of relapses can further prolong the long-term effects of therapy.

The goal of this research was to evaluate the integrated magnitude of the EC effect on response recovery. This objective will be addressed through an effect sizes meta-analysis of relevant experiments. The effect size is a standardized measure of the difference between two groups of an experiment, of the dependent variable (Card, 2012). The different effect sizes can be aggregated for a weighted standard effect size of all experiments. Also, analyzing the variability of the effect sizes can test whether its due to sample error or there can be other reasons. A source of variability of the effect sizes is called a moderator variable (Card, 2012). When it comes to experiments, moderators can come from either different parameters or different control techniques. It is hypothesized that the characteristics of each experiment can moderate the EC effect size on response recovery, such as the type of sample used, or the specific experimental paradigm or design used.

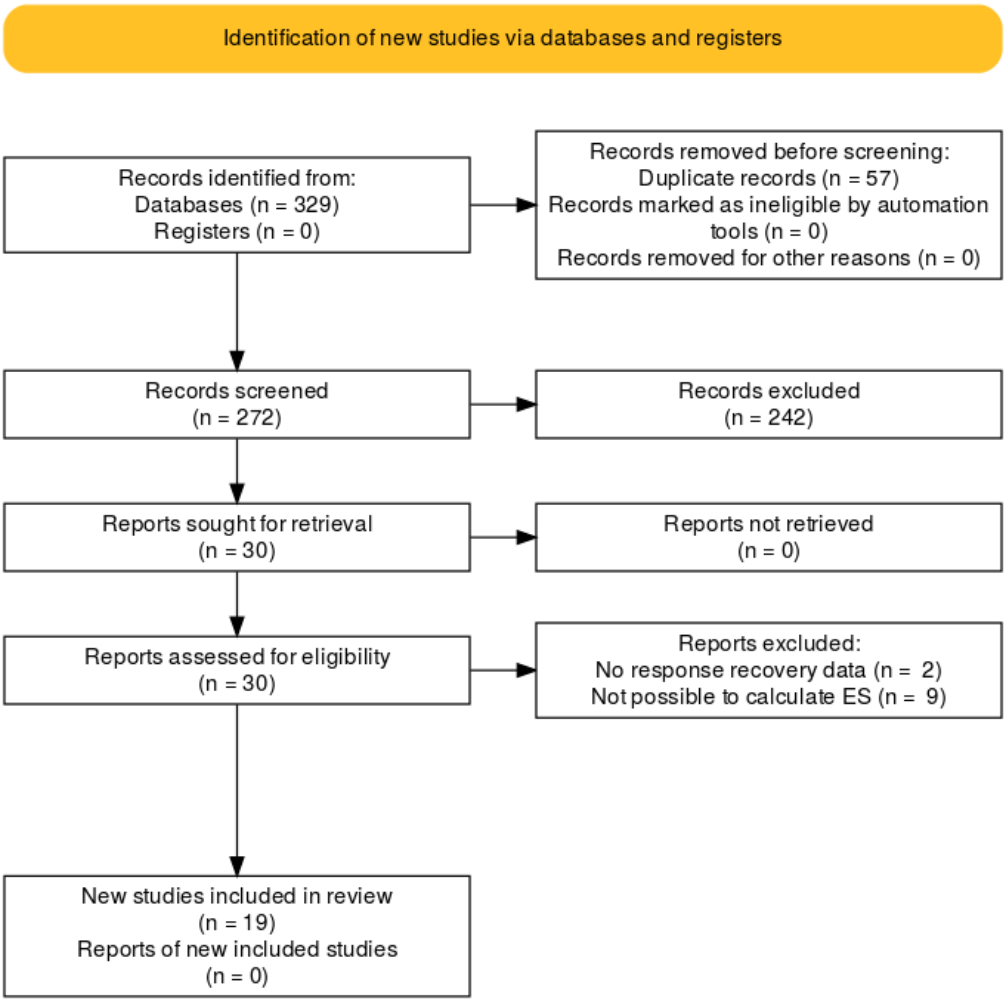
Method

Search and coding strategies

A protocol for this meta-analysis was not published prior to conducting the study. The guidelines from APA (Appelbaum et al., 2018) and the preferred reporting items for systematic review and meta-analysis protocols (Page et al., 2021) were used to guide decision-making in this work. Article search was done using the database search engines ScienceDirect, Scopus, ProQuest, PsycNET, and Web of Science. Prior to searching, three articles were used to define search keywords (i.e., Brooks & Bouton, 1993, 1994; Dibbets et al., 2008), with the strategy of obtaining synonyms of extinction and response recovery used in them. Synonyms obtained for "extinction cue" were "retrieval cue", "safety signal", "recall cue", and "cue from extinction". The synonyms compiled for "response recovery" were "post-extinction effect", "renewed", "ABA-renewal", "ABC-renewal", "spontaneous recovery", "reinstatement", "rapid reacquisition", "reoccurrence", "renewal", "return of fear", "response recovery" and "recovery". Synonyms for "extinction" were also included, to account for possible clinical research that used an extinction-based therapy. The terms used were "extinction training", "exposure therapy", "exposure session", "extinction-based exposure", "exposure treatment" and "ext*". The asterisk is replaced by any letter string by the search engines, which includes conjugations of the verb "(to) extinguish". The keywords in each group were linked with the Boolean operator OR and put between parenthesis, then all three groups were linked together with the Boolean operator AND. Lastly, the keywords were input on a function that searched article title, abstract, and keywords simultaneously, which was present in different forms on each search engine. Searches were done in May 2021 and there was no time restriction for article inclusion. Article search was done by two researchers, with more than two years of experience in the associative learning area, from the experimental psychology laboratory at Universidad de Chile. The same researchers did the screening process from start to finish. Search results were first screened by their titles and abstracts. The studies were selected by one researcher, to be then corroborated by the other. The article screening process is illustrated in Figure 1. The studies were first screened for duplicates and articles about other subjects that passed the keyword filter. After that, each study was examined by title, keywords, and abstract. The same two researchers carried out the coding procedure of the selected articles. Both researchers work in a laboratory dedicated to Pavlovian conditioning research (Lira et al., 2016). Each experiment in each article was coded separately and was considered a data unit. Each researcher coded each experiment by themselves, which were then compared to obtain an agreement rate. Codes included article metadata, experiment characteristics, and parameters of each experimental phase.

Figure 1

Flow Chart showing the Process of Research Article Screening



Note. Each box of the two leftmost columns shows the number of selected articles. The boxes at the rightmost columns show the number of excluded articles due to each screening procedure.

Inclusion and exclusion criteria

The experiments included in the meta-analysis were screened according to the following criteria: a) the concepts of response recovery and ECs are defined from an associative learning point of view, meaning that it uses the terms from the conditioning literature (i.e., CS, CR, EC, etc.) and they assume that cues of the environment govern behavior through associations. b) response recovery and ECs were manipulated as variables experimentally, c) they were published in any year, due to there not being a prior meta-analysis published on the subject, and lastly, d) that they contain enough information for a calculation of the effect size between a group with EC and a control group. Experiments that used an EC that was then tested on a response recovery paradigm were included in the meta-analysis. This means that the experiment conceptualized stimulus exposure as a Pavlovian extinction or used an analogous behavioral treatment, while using treatment reminder cues. This assures conceptual consistency of the variables used in the analysis. Experiments that used a response recovery as a dependent variable, and the presence of the EC as an independent variable, with a corresponding control group were relevant. Operationally, response recovery was considered as spontaneous recovery, renewal, reinstatement, or reacquisition. EC was considered as any stimulus presented during extinction, that was later used in a test. Studies that did not use a measure of response recovery as a dependent variable were not considered, which excluded two studies (see Figure 1). Two other studies were excluded for not enough information for effect size calculation. In general, after article

search, the studies compiled were of three types. The first type is a study implemented with non-human subjects (e.g., rats), with a simple experimental design, or a factorial design, where factors were presence or absence of EC on test and presence or absence of a response recovery procedure (e.g., Experiment 1 of Brooks & Bouton 1994). This factorial design resulted in four groups. In this case, only the two relevant groups were extracted (with response recovery and EC on test, and with response recovery without EC on test) and an effect size was calculated between both. The second type is an experiment implemented with human participants, on a single session, using a computer to present visual stimuli as CSs and strong sounds as USs (e.g., Dibbets & Maes, 2011). In these, the dependent variable were a self-report of US expectancy and physiological measures, like skin conductance. Effect sizes were calculated on only one measure, using an objective physiological measure when possible, and the self-report in experiments were there was no objective physiological data available. The third type is a study implemented on a pre-clinic human sample; in other words, with people who already have a particular conditioned response but do not meet criteria for a clinical diagnose (e.g., spider fear but not phobia). There is no acquisition phase and the extinction is a behavior approach treatment (e.g., Mystkowski et al., 2006). Their dependent variable is a self-reported fear level, from 0 to 100, called a Subjective Units of Distress or SUD. Only some of these experiments report a behavioral approach variable, that was used when possible. SUDs were used otherwise.

Moderators

Regarding moderator variables, the coding of study characteristic allowed experiments to be divided between the subject type they used. This can then be dichotomized between human and non-human animals. Another important aspect of an experiment is the used control group. A control for ECs can be implemented in a few different ways. Some experiments presented the EC during extinction for all subjects. Then, on a response recovery test, they omitted the EC for the control group, this was coded as “No EC during test”. Other experiments presented a different stimulus on test, which could be previously presented on the acquisition phase or be completely novel. This was coded as “Different cue during test”. This code grouped experiments that used a different stimulus during test, which could have different associative histories. The reason for grouping them is that some types of histories are represented by too few studies (e.g., a stimulus presented during acquisition, see Table 1). Lastly, the different response recovery procedures were coded as spontaneous recovery, renewal, reinstatement, and reacquisition. Parameter information was coded as CS, US and EC type, duration, number of presentations per phase, intensity, and number of sessions per phase.

Table 1
List of Compiled Articles with Selected Experiments

Article	Experiment	Species	Response recovery	EC control	ES
Thomas & Sherman (1986)	1	Pigeons	Spontaneous Recovery	No EC on test	3.34
	2	Pigeons	Spontaneous Recovery	No EC on test	0.45
Brooks & Bouton (1993)	2	Wistar rats	Spontaneous Recovery	Acquisition cue on test	0.81
	3	Sprague-Dawley rats	Spontaneous Recovery	No EC on test	1.12
Brooks & Bouton (1994)	1	Wistar rats	ABA Renewal	No EC on test	0.56
	2	Wistar rats	ABA Renewal	Neutral cue on test	0.97
	3	Wistar rats	ABA Renewal	Acquisition cue on test	0.79
Brooks et al. (1999)	1	Wistar rats	Spontaneous Recovery	No EC on test	1.44
	2	Wistar rats	Spontaneous Recovery	No EC on test	1.51
Brooks & Bowker (2001)	1	Wistar rats	Spontaneous Recovery	No EC on test	4.32
	2	Wistar rats	Spontaneous Recovery	No EC on test	1.61
Collins & Brandon (2002)	1	Humans	ABA Renewal	No EC on test	0.27
Brooks et al. (2004)	1	Wistar rats	Spontaneous Recovery	No EC on test	2.15
	2	Wistar rats	Spontaneous Recovery	No EC on test	1.37

(continues)

Table 1 (Conclusion)
List of Compiled Articles with Selected Experiments

Article	Experiment	Species	Response recovery	EC control	ES
Mystkowski et al. (2006)	1	Humans	ABC Renewal	Neutral cue on test	0.45
Dibbets et al. (2008)	1	Humans	ABA Renewal	No EC on test	0.97
Dibbets & Maes (2011)	1	Humans	ABA Renewal	No EC on test	0.09
	2	Humans	ABA Renewal	No EC on test	0.78
Dibbets et al. (2012)	1	Humans	ABA Renewal	No EC on test	-1.57
Dibbets et al. (2013)	1	Humans	ABA Renewal	No EC on test	0.14
Willcocks & McNally (2014)	1	Long-Evan rats	ABA Renewal	No EC on test	0.00
	3	Long-Evan rats	ABA Renewal	No EC on test	-0.12
	4	Long-Evan rats	Reacquisition	No EC on test	1.32
	5	Long-Evan rats	ABA Renewal	Yoked cue on test (to experimental group)	1.82
	6	Long-Evan rats	ABA Renewal	No EC on test	0.52
Bustamante et al. (2016)	1	Humans	ABC Renewal	Acquisition cue on test	1.52
	2	Humans	ABC Renewal	Acquisition cue on test	0.88
Brooks & Fava (2017)	1	Wistar rats	Reinstatement	Neutral cue on test	0.54
Quezada et al. (2018)	1	Humans	ABC Renewal	Neutral cue on test	0.85
	2	Humans	ABC Renewal	Neutral cue on test	0.24
Alfaro et al. (2018)	1	Sprague-Dawley rats	Reacquisition	No EC on test	-0.70
	2	Sprague-Dawley rats	Reacquisition	No EC on test	3.12
	3	Sprague-Dawley rats	Reacquisition	No EC on test	0.45
Bustamante et al. (2019)	1	Sprague-Dawley rats	ABC Renewal	Neutral cue on test	-0.62
	2	Sprague-Dawley rats	ABA Renewal	Neutral cue on test	-0.88
	3	Sprague-Dawley rats	ABA Renewal	Neutral cue on test	-0.49
Nieto et al. (2020)	1	Wistar rats	ABC Renewal	No EC on test	1.31

Note. Each experiment has its respective relevant codes. The animal species used in the experiment, the response recovery type, and the control group type. Each code is presented before re-coding for analysis. ES = effect size.

Statistical method

The analysis data point was the effect size of each experiment in the compiled articles. Only the two groups that contained the elements of interest were coded, that is, a response recovery paradigm, and EC on test and a control of the EC, in studies that had more than one control, or a factorial design of two or more factors. If the factorial design allowed it, the experiment was divided into two-group experiments, keeping the EC-no-EC difference between groups, as well as maintaining the independence of the observations. On practice, this means that only contrasts between two groups were considered. This posed a difficulty as factorial ANOVAS for factorial designs, make use of post-hoc tests or planned comparisons, and this data is seldom reported. In these cases, the figures of the articles were analyzed through specialized software to extract the exact data values that were used to make them (Rohatgi, 2019). This allowed to obtain means and standard error of each group, which could be used to directly compute an effect size between groups of interest. The effect size was calculated using the free online tool Practical Meta-Analysis Effect Size Calculator (Wilson, n.d.). Risk of low internal validity of the studies was addressed by including only experimental studies, that allows to better isolate interest variables, preserving internal validity. Standardized mean differences were calculated for each experiment and then synthetized using a weighted

mean effect size method under a fixed effects model and under a random effects model, to assess results robustness using different statistical assumptions. Calculations were made in Microsoft Excel by inputting the relevant formulas in each cell in a spreadsheet. The Q statistic was used to assess homogeneity.

Results

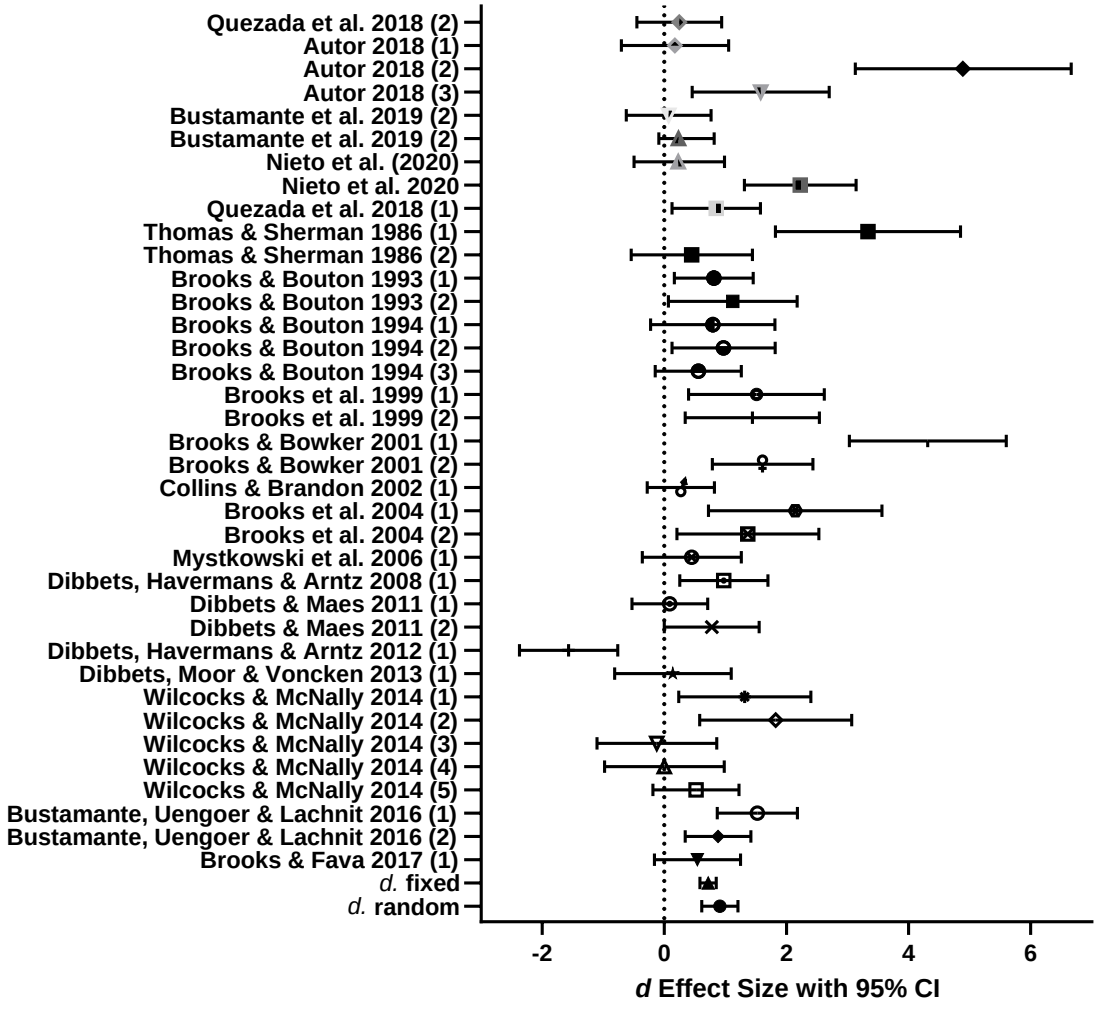
The total number of articles found in the database search was 330. Thirty articles were selected as potential inclusions (see Table 1 for final inclusions). On detailed examination, 11 articles were excluded (see Table 2), 9 for not having enough information for ES calculations and 2 for not recording or reporting response recovery data. Thirty-seven experiments were extracted and coded of the 19 articles remaining. All effect sized used are shown in Figure 1. Inter-coder agreement rate was 88.97 %. Mean weighted effect size for all experiments coded, was high both under a fixed effects model, d = 0.71, 95 %CI [0.58, 0.85], and under a random effects model, d = 0.9, 95 % CI [0.61, 1.20]. These similar effect sizes suggest that statistic assumptions do not affect conclusions about the magnitude of the effect size. The homogeneity test result, under a fixed effects model, was Q = 159.65, which is higher than critical value of 52.19 with df = 37, which rejects the null hypothesis that effect size variability is due to sampling error alone. In other words, the mean weighted effect size is not homogenic. Effect sizes for all articles reviewed and mean weighted effect sizes are shown in Figure 2.

Table 2
List of Compiled Articles that Were Excluded

Article	Reason for exclusion
McTavish et al. (2012)	No response recovery data
Culver et al. (2011)	No response recovery data
Brooks (2000)	Not possible to calculate ES
Stasiewicz et al. (2007)	Not possible to calculate ES
Vansteenwegen et al. (2006)	Not possible to calculate ES
Gámez & Bernal-Gamboa (2019)	Not possible to calculate ES
Hornstein et al. (2018)	Not possible to calculate ES
Nieto et al. (2017)	Not possible to calculate ES
Shin & Newman (2018)	Not possible to calculate ES
Bernal-Gamboa et al. (2021)	Not possible to calculate ES
Brooks (2021)	Not possible to calculate ES

Moderator analysis show the sources of variability. The analysis of animal species grouped together pigeon experiments (i.e., Experiment 1 of Brooks, 2000) with rats for an “animal” category, the other being “humans”. The analysis of response recovery type grouped the different types of renewal experiments into one “renewal” category. Lastly, the control group type that were different from omitting the EC on test were diverse and represented by only a few experiments each (e.g., two experiments used an acquisition paired cue, two experiments presented a neutral cue on test and one experiment used a yoked cue to the experimental group, see Table 1), so they were grouped together as “Different cue on test”. The α probability level was set at 0.05.

Figure 2
Forest Plot of Selected Experiments



Note. Multiple experiments of the same paper are numbered. Error bars indicate 95 % CI for the effect size of that experiment. Dotted line marks the "no effect" boundary. At the bottom, mean weighted effect sizes are shown under fixed and random effects models.

The result of the animal species moderator analysis was a Q_{within} of 151.5 with a corresponding $Q_{between}$ of 8.14, which is greater than the critical value of 3.84 with $df = 1$. The null hypothesis that the variance between human and non-human subjects is due to sampling error alone is rejected. In other words, there is a significant difference between humans and non-human animals. The weighted mean effect size is higher for the non-human subjects. The result of the response recovery moderator analysis was a Q_{within} of 137.86, with a corresponding $Q_{between}$ of 21.79, which is higher than the critical value of 7.81, with $df = 3$. This means that the variance between effect sizes of experiments that used reacquisition, spontaneous recovery and renewal is not due to sampling error alone, and is different among the three conditions, being higher for spontaneous recovery. Lastly, the results for the control type moderator analysis were a Q_{within} of 157.49, with a corresponding $Q_{between}$ of 2.15, which is lower than the critical value of 3.84 with $df = 1$. This means that the effect sizes between experiments with no EC on test and experiments with a different cue on test are due to sampling error alone and are not different between them. The weighted mean effect size for each condition of all moderators analyzed are summarized on Table 3. Other aspects of the experiments were analyzed but yielded no important effect or pattern. The results of control type are reported due to theoretic importance.

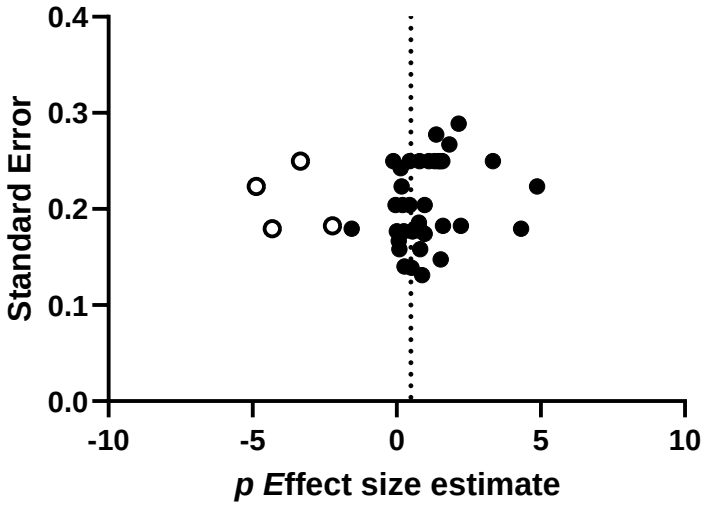
Table 3
Summary of Moderator Analysis

Moderator	Group	Mean effect size	Q between value	Critical Q value
Species	Humans	0.49		
	Non-Humans	0.88	8.14	3.84
Response recovery type	Spontaneous Recovery	1.32		
	Renewal	0.53		
	Reacquisition	0.85		
	Reinstatement	0.54	21.70	7.81
Control group type	No EC on test	0.81		
	Different cue on test	0.61	2.15	3.84

Note. Each moderator group have its respective effect size. Q between value is the contrast Q value, and the critical Q value is what is compared against. A Q between value higher than the critical means that the null hypothesis of between group variance due to sampling error only is rejected.

Publication bias was assessed using the trim and fill method, where effect sizes are plotted against their standard error. The plot is then trimmed of effect sizes until it is symmetrical and finally the same number of studies are added to the plot with an inverted value to show a theoretical symmetric distribution of effect sizes when there is no publication bias. Using the *R* statistic, 5 studies were trimmed. After this correction effect size was lower but still robust, $d = 0.59$, 95% CI [0.45, 0.73]. When 5 studies were filled, the effect size was similar, $d = 0.54$, 95% CI [0.41, 0.67]. This suggests that there is some degree of publication bias in the results, but when more studies are filled, the effect of EC still is large and positive. A funnel plot showing the result of this analysis can be seen in Figure 3.

Figure 3
Funnel Plot with Effect Sizes of the Experiments Included



Note. In black, the data obtained from experiments. In white, the data estimated to be missing for a symmetrical funnel. The black dots show an asymmetry towards the right, suggesting some level of publication bias.

Discussion

The articles compiled show that EC research have been an active field of study within the Pavlovian conditioning field. This research synthesis examined the effect sizes of all relevant experiments published searching for a mean effect size and possible variance sources. Both fixed and random effects calculated *d* were high. To represent the impact of EC on recovery, consider that the mean effect size—under a fixed effects model—can be interpreted as that about 79 % of a group with EC will be below the fear relapse mean of a control group without EC (or a different cue), for example. This suggests a considerable effect of EC on response recovery.

The effect of an EC on the response recovery of the analyzed experiments are not homogeneous, they are moderated by mainly two factors: Firstly, the experiments that use spontaneous recovery have a more pronounced effect of the EC. Secondly, the experiments done with non-human animals also have a higher effect of EC. Notably, the type of control group used did not affect the magnitude of the effect of ECs on response recovery.

The use of non-human animal may have a higher effect size due to more controlled conditions, compared to experiments with human participants. Not all human samples were pre-clinic, which can contribute to greater variability and smaller effect size. A pre-clinic sample have the advantage that they have an already established Pavlovian conditioning (e.g., of fear to the phobia object). The experiments are done about this conditioning. In these cases, the exposure procedure effect size may itself be smaller, because they are not complete therapy treatments. Consequently, the difference between a group who relapses and a group who prevents the relapse is smaller. Comparing experiments with this type of sample and others where a Pavlovian conditioning is established experimentally results interesting. This type of research is of much lower volume, as reflected on the compiled experiments of this meta-analysis. Obtaining generalizing conclusions about human sample type is not possible with this data.

A main limitation of the results is that the research includes only published studies, which could imply greater positive bias. Methodological measures were implemented to reduce the effect of positive bias on results with different statistical assumptions and bias analysis. After corrections, the effect of ECs on extinction were still high.

Relatedly, some moderator variables were represented only by few studies, which also limits conclusions. The low representativity of different moderators can be attributed to low variety of different experimental paradigms in the literature on the topic of response recovery prevention (e.g., reacquisition and reinstatement are underrepresented with only one data point each, compared to spontaneous recovery and renewal). The results of this meta-analysis may reflect the state of the literature, showing that there are gaps allowing more complete results. Interactions between moderators could be explored with a more varied research in the area.

A second important limitation is that 11 possible inclusions ended up being excluded. Out of a possible sample of 30 articles, more than a third of them could not be included due to the impossibility of obtaining an effect size. Still, all the excluded articles contain a favorable result of ECs, which is worth mentioning. This does not strengthen the metanalytic conclusion but shows that the literature on the topic at large points in a similar direction.

The applicability of these results for therapy is limited, due to the greater number of experiments with non-human animals. A good venue of research can be spontaneous recovery on human participants, which is minimally represented in the compiled experiments and only in non-human animals. Moderator analysis showed a disparity between animal subjects and human participants; however, the spontaneous recovery experiments were only implemented with animal subjects. This makes it difficult to separate the effect of spontaneous recovery from the animal research, pressing to produce more spontaneous recovery research on humans. The results of these experiments can give better information about whether the EC is useful as a therapy reminder over time, more than a strategy to generalize therapy to different contexts. Spontaneous recovery is an ecologically valid model of relapse in humans, meaning that it more closely resembles a relapse after a time lapse following treatment. The metanalytic results point to spontaneous recovery as the stronger beneficiary of ECs, but this interpretation is muddied by it only representing animal experiments.

ECs are experimentally effective, but the aspects that favor their response recovery prevention capacity are not yet clear, which may result in an area of interest for further research. An effective tool of response

recovery, like what ECs seems to be, will be beneficial for both enrichment of associative models of learning and applications on therapy techniques based on such models.

References

Alfaro, F., Navarro, V. M., Laborda, M. A., Betancourt, R., & Miguez, G. (2018). Rol de estímulos asociados a las claves de extinción en la recuperación de respuesta. *Psykhe*, *28*(1), 1-15. https://doi.org/10.7764/psykhe.28.1.1282

Appelbaum, M., Cooper, H., Kline, R., Mayo-Wilson, E., Nezu, A., & Rao, S. (2018). Journal article reporting standards for quantitative research in psychology: The APA publications and communications board task force report. *American Psychologist*, *73*(1), 3-25. https://doi.org/10.1037/amp0000191

Bernal-Gamboa, R., Mason, T. A., Nieto, J., & Gámez, A. M. (2021). An analysis of extinction-cue features in the reduction of operant behavior relapse. *The Psychological Record*, *72*, 65-73. https://doi.org/10.1007/s40732-021-00472-z

Blass, E. M., Ganchrow, J. R., & Steiner, J. E. (1984). Classical conditioning in newborn humans 2-48 hours of age. *Infant Behavior and Development*, *7*(2), 223-235. https://doi.org/10.1016/S0163-6383(84)80060-0

Bouton, M. E. (1988). Context and ambiguity in the extinction of emotional learning: implications for exposure therapy. *Behaviour Research and Therapy*, *26*(2), 137-149. https://doi.org/10.1016/0005-7967(88)90113-1

Bouton, M. E., & Ricker, S. T. (1994). Renewal of extinguished responding in a second context. *Animal Learning & Behavior*, *22*(3), 317-324. https://doi.org/10.3758/BF03209840

Brooks, D. C. (2000). Recent and remote extinction cues reduce spontaneous recovery. *Quarterly Journal of Experimental Psychology Section B: Comparative and Physiological Psychology*, *53*(1), 25-58. https://doi.org/10.1080/027249900392986

Brooks, D. C. (2021). Spontaneous recovery can be prevented in appetitive conditioning with rats. *Learning and Motivation*, *75*, Article 101734. https://doi.org/10.1016/j.lmot.2021.101734

Brooks, D. C., & Bouton, M. E. (1993). A retrieval cue for extinction attenuates spontaneous recovery. *Journal of Experimental Psychology: Animal Behavior Processes*, *19*(1), 77-89. https://doi.org/10.1037/0097-7403.19.1.77

Brooks, D. C., & Bouton, M. E. (1994). A retrieval cue for extinction attenuates response recovery (renewal) caused by a return to the conditioning context. *Journal of Experimental Psychology: Animal Behavior Processes*, *20*(4), 366-379. https://doi.org/10.1037/0097-7403.20.4.366

Brooks, D. C., & Bowker, J. L. (2001). Further evidence that conditioned inhibition is not the mechanism of an extinction cue's effect: A reinforced cue prevents spontaneous recovery. *Animal Learning & Behavior*, *29*(4), 381-388. https://doi.org/10.3758/BF03192903

Brooks, D. C., & Fava, D. A. (2017). An extinction cue reduces appetitive Pavlovian reinstatement in rats. *Learning and Motivation*, *58*, 59-65. https://doi.org/10.1016/j.lmot.2017.04.002

Brooks, D. C., Palmatier, M. I., Garcia, E. O., & Johnson, J. L. (1999). An extinction cue reduces spontaneous recovery of a conditioned taste aversion. *Animal Learning & Behavior*, *27*(1), 77-88. https://doi.org/10.3758/BF03199433

Brooks, D. C., Vaughn, J. M., Freeman, A. J., & Woods, A. M. (2004). An extinction cue reduces spontaneous recovery of ataxic ethanol tolerance in rats. *Psychopharmacology*, *176*(3-4), 256-265. https://doi.org/10.1007/s00213-004-1882-y

Bustamante, J., Martín, C. S., Laborda, M. A., & Miguez, G. (2019). An extinction cue does not necessarily prevent response recovery after extinction. *Learning and Motivation*, *67*, Article 101576. https://doi.org/10.1016/j.lmot.2019.101576

Bustamante, J., Uengoer, M., & Lachnit, H. (2016). Reminder cues modulate the renewal effect in human predictive learning. *Frontiers in Psychology*, *7*, Article 1968. https://doi.org/10.3389/fpsyg.2016.01968

Capaldi, E. J., Martins, A. P. G., & Altman, M. (2009). Memories of reward and nonreward regulate the extinction and reacquisition of both excitatory and inhibitory associations. *Learning and Motivation*, *40*(3), 259-273. https://doi.org/10.1016/j.lmot.2009.04.002

Card, N. A. (2012). *Applied meta-analysis for social science research*. The Guilford press.

Collins, B. N., & Brandon, T. H. (2002). Effects of extinction context and retrieval cues on alcohol cue reactivity among nonalcoholic drinkers. *Journal of Consulting and Clinical Psychology*, *70*(2), 390-397. https://doi.org/10.1037/0022-006X.70.2.390

Culver, N. C., Stoyanova, M., & Craske, M. G. (2011). Clinical relevance of retrieval cues for attenuating context renewal of fear. *Journal of Anxiety Disorders*, *25*(2), 284-292. https://doi.org/10.1016/j.janxdis.2010.10.002

Díaz, M. C., Quezada, V. E., Navarro, V. M., Laborda, M. A., & Betancourt, R. (2017). The effect of massive extinction trials on the recovery of human fear conditioning. *Revista Mexicana de Psicología*, *34*(1), 5-12. https://www.redalyc.org/pdf/2430/243056045001.pdf

Dibbets, P., Havermans, R., & Arntz, A. (2008). All we need is a cue to remember: The effect of an extinction cue on renewal. *Behaviour Research and Therapy*, *46*(9), 1070-1077. https://doi.org/10.1016/j.brat.2008.05.007

Dibbets, P., Havermans, R. C., & Arntz, A. (2012). Partial presentation of an extinction cue enhances renewal in an ABA paradigm. *The Open Psychology Journal*, *5*(1), 11-19. https://doi.org/10.2174/1874350101205010011

Dibbets, P., & Maes, J. H. R. (2011). The effect of an extinction cue on ABA-renewal: Does valence matter? *Learning and Motivation*, *42*(2), 133-144. https://doi.org/10.1016/j.lmot.2010.12.003

Dibbets, P., Moor, C., & Voncken, M. J. (2013). The effect of a retrieval cue on the return of spider fear. *Journal of Behavior Therapy and Experimental Psychiatry*, *44*(4), 361-367. https://doi.org/10.1016/j.jbtep.2013.03.005

Gámez, A. M., & Bernal-Gamboa, R. (2019). The reoccurrence of voluntary behavior in humans is reduced by retrieval cues from extinction. *Acta Psychologica*, *200*, Article 102945. https://doi.org/10.1016/j.actpsy.2019.102945

González, V. V., Navarro, V., Miguez, G., Betancourt, R., & Laborda, M. A. (2016). Preventing the recovery of extinguished ethanol tolerance. *Behavioural Processes*, *124*, 141-148. https://doi.org/10.1016/j.beproc.2016.01.004

Gormezano, I., Schneiderman, N., Deaux, E., & Fuentes, I. (1962). Nictitating membrane: Classical conditioning and extinction in the albino rabbit. *Science*, *138*(3536), 33-34. https://doi.org/10.1126/science.138.3536.33

Hornstein, E. A., Haltom, K. E. B., Shirole, K., & Eisenberger, N. I. (2018). A unique safety signal: Social-support figures enhance rather than protect from fear extinction. *Clinical Psychological Science*, *6*(3), 407-415. https://doi.org/10.1177/2167702617743002

Laborda, M. A., McConnell, B. L., & Miller, R. R. (2011). Behavioral techniques to reduce relapse after exposure therapy. In T. R. Schachtman & S. S. Reilly (Eds.), *Associative learning and conditioning theory: Human and non-human applications* (pp. 79-103). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199735969.003.0025

Laborda, M. A., Miguez, G., Polack, C. W., & Miller, R. R. (2012). Animal models of psychopathology: Historical models and the Pavlovian contribution. *Terapia Psicológica*, *30*(1), 45-59. https://doi.org/10.4067/S0718-48082012000100005

Laborda, M. A., & Miller, R. R. (2013). Preventing return of fear in an animal model of anxiety: Additive effects of massive extinction and extinction in multiple contexts. *Behavior Therapy*, *44*(2), 249-261. https://doi.org/10.1016/j.beth.2012.11.001

Lira, D., Bustamante, J., Quezada, V. E., Laborda, M. A., & Miguez, G. (2016). Crónica del laboratorio de psicología experimental: Prof. Ronald Betancourt Mainhard (1999-2016). *Cuadernos de Neuropsicologia, Panamerican Journal of Neuropsychology*, *10*(2), 23-41. https://www.cnps.cl/index.php/cnps/article/view/233

McTavish, F. M., Chih, M.-Y., Shah, D., & Gustafson, D. H. (2012). How patients recovering from alcoholism use a smartphone intervention. *Journal of Dual Diagnosis*, *8*(4), 294-304. https://doi.org/10.1080/15504263.2012.723312

Miguez, G., Martínez, G., & Betancourt, R. (2013). Reinstauración de la tolerancia al etanol: la función del contexto. *Revista de Psicología*, *22*(1), 4-12. https://doi.org/10.5354/0719-0581.2013.27712

Miguez, G., Soares, J. S., & Miller, R. R. (2015). The role of test context in latent inhibition of conditioned inhibition: Part of a search for general principles of associative interference. *Learning and Behavior*, *43*(3), 228-242. https://doi.org/10.3758/s13420-015-0175-0

Miguez, G., Witnauer, J. E., Laborda, M. A., & Miller, R. R. (2014). Trial spacing during extinction: The role of context-US associations. *Journal of Experimental Psychology: Animal Learning and Cognition*, *40*(1), 81-91. https://doi.org/10.1037/a0033203

Miller, R. R., Laborda, M. A., Polack, C. W., & Miguez, G. (2015). Comparing the context specificity of extinction and latent inhibition. *Learning & Behavior*, *43*(4), 384-395. https://doi.org/10.3758/s13420-015-0186-x

Mineka, S., Davidson, M., Cook, M., & Keir, R. (1984). Observational conditioning of snake fear in rhesus monkeys. *Journal of Abnormal Psychology*, *93*(4), 355-372. https://doi.org/10.1037/0021-843X.95.4.307

Mystkowski, J. L., Craske, M. G., Echiverri, A. M., & Labus, J. S. (2006). Mental reinstatement of context and return of fear in spider-fearful participants. *Behavior Therapy*, *37*(1), 49-60. https://doi.org/10.1016/j.beth.2005.04.001

Napier, R. M., Macrae, M., & Kehoe, E. J. (1992). Rapid reacquisition in conditioning of the rabbit's nictitating membrane response. *Journal of Experimental Psychology: Animal Behavior Processes*, *18*(2), 182-192. https://doi.org/10.1037//0097-7403.18.2.182

Nieto, J., Mason, T. A., Bernal-Gamboa, R., & Uengoer, M. (2020). The impacts of acquisition and extinction cues on ABC renewal of voluntary behaviors. *Learning and Memory*, *27*(3), 114-118. https://doi.org/10.1101/lm.050831.119

Nieto, J., Uengoer, M., & Bernal-Gamboa, R. (2017). A reminder of extinction reduces relapse in an animal model of voluntary behavior. *Learning and Memory*, *24*(2), 76-80. https://doi.org/10.1101/lm.044495.116

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, Article 71. https://doi.org/10.1136/bmj.n71

Papalini, S., Lange, I., Bakker, J., Michielse, S., Marcelis, M., Wichers, M., Vervliet, B., van Os, J., Van Amelsvoort, T., Goossens, L., & Schruers, K. (2019). The predictive value of neural reward processing on exposure therapy outcome: Results from a randomized controlled trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 339-346. https://doi.org/10.1016/J.PNPBP.2019.02.002

Pavlov, I. P. (1927). *Conditioned reflexes* (G. V. Anrep, Ed.). Oxford University Press.

Pittig, A., van den Berg, L., & Vervliet, B. (2016). The key role of extinction learning in anxiety disorders. *Current Opinion in Psychiatry*, *29*(1), 39-47. https://doi.org/10.1097/YCO.0000000000000220

Quezada, V., Laborda, M. A., Díaz, M. C., Navarro, V. M., Mallea, J., Repetto, P., Orellana, G., & Mainhard, R. B. (2018). Extinction cues do not reduce recovery of extinguished conditioned fear in humans. *International Journal of Psychology and Psychological Therapy*, *18*(1), 39-53. https://www.ijpsy.com/volumen18/num1/481.html

Rescorla, R. A., & Heth, C. D. (1975). Reinstatement of fear to an extinguished conditioned stimulus. *Animal Behavior Processes*, *104*(1), 88-96. https://doi.org/10.3758/BF03209977

Rohatgi, A. (2019). *WebPlotDigitizer*. https://automeris.io/WebPlotDigitizer

San Martín, C., Diaz, F., Cañete, A., Laborda, M. A., & Miguez, G. (2018). Readquisición de la tolerancia asociativa al etanol: el efecto de la extinción masiva. *Avances En Psicología Latinoamericana*, *36*(2), 419-429. https://doi.org/10.12804/revistas.urosario.edu.co/apl/a.5727

Seligman, M. E. P. (1971). Phobias and preparedness. *Behavior Therapy*, *2*(3), 307-320. https://doi.org/10.1016/S0005-7894(71)80064-3

Shin, K. E., & Newman, M. G. (2018). Using retrieval cues to attenuate return of fear in individuals with public speaking anxiety. *Behavior Therapy*, *49*(2), 212-224. https://doi.org/10.1016/j.beth.2017.07.011

Stasiewicz, P. R., Brandon, T. H., & Bradizza, C. M. (2007). Effects of extinction context and retrieval cues on renewal of alcohol-cue reactivity among alcohol-dependent outpatients. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*, *21*(2), 244-248. https://doi.org/10.1037/0893-164X.21.2.244

Thomas, D. R., & Sherman, L. (1986). An assessment of the role of handling cues in "spontaneous recovery" after extinction. *Journal of the Experimental Analysis of Behavior*, *46*(3), 305-314. https://doi.org/10.1901/jeab.1986.46-305

Vansteenwegen, D., Vervliet, B., Hermans, D., Beckers, T., Baeyens, F., & Eelen, P. (2006). Stronger renewal in human fear conditioning when tested with an acquisition retrieval cue than with an extinction retrieval cue. *Behaviour Research and Therapy*, *44*(12), 1717-1725. https://doi.org/10.1016/j.brat.2005.10.014

Willcocks, A. L., & McNally, G. P. (2014). An extinction retrieval cue attenuates renewal but not reacquisition of alcohol seeking. *Behavioral Neuroscience*, *128*(1), 83-91. https://doi.org/10.1037/a0035595

Wilson, D. B. (n.d.). *Practical meta-analysis effect size calculator [Online calculator]*.

Wolpe, J. (1968). Psychotherapy by reciprocal inhibition. *Conditional Reflex: A Pavlovian Journal of Research & Therapy*, *3*(4), 234-240. https://doi.org/10.1007/BF03000093

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