A systematic Review and Meta-Analysis of Fear Conditioning Studies

Paul Arno Wüllenweber

p.a.wullenweber@students.uu.nl

Student number: 6526519

Supervisor: Dr. Evi-Anne van Dis

Second Assessor: Vera Bouwman

Clinical Psychology, Utrecht University

Date: July 17, 2022

Word Count: 4,259

Abstract

Fear conditioning has been described as an important process involved in the etiology of anxiety disorders. The following meta-analysis aimed at examining differences between patients and healthy individuals during acquisition, extinction and the return of fear phase. Four studies (published in 2021 and 2022) with data on 119 individuals with anxiety disorders and 138 controls were obtained after a screening of 672 articles published on PubMed, Embase, PsycINFO, and OpenGrey. None of the studies found significant differences between those individuals with and those without anxiety disorders during acquisition, extinction, and return of fear. One study did find significant differences between patients and healthy controls towards the CS+, but not the CS-, during return of fear. The extent of differences between individuals with anxiety disorders and those without remains somewhat controversial. Further research is necessary to investigate patient-control differences in fear conditioning, which are thought to underlie the pathology of anxiety disorders.

Keywords: anxiety disorders; fear conditioning; reacquistion; meta-analysis;

Introduction

The American Psychiatric Association (APA, 2013) has characterized anxiety disorders by excessive anxiety, avoidance, and worry over a prolonged period of time. There are several types of anxiety disorders, including generalized anxiety disorder, specific phobia, social anxiety disorder, separation anxiety disorder, agoraphobia, panic disorder, and selective mutism (APA, 2013). Epidemiological studies have found anxiety disorders to be the most common of all mental disorders with prevalence rates in Europe at around 14.0 percent in 2010 (Wittchen et al., 2011). Although cognitive-behavioral therapy is highly effective in treating anxiety disorders (Otte, 2011), the return of fear is a common problem (Craske & Mystkowski, 2006). Anxiety disorders are associated with long-term disability and impairment in daily life (World Health Organisation, 2017).

Already early research such as the Little Albert experiment by Watson and Rayner (1920) in the 1920s suggested the crucial role of conditioning within the etiology of anxiety. Ever since there has been a long research tradition investigating the relation between anxiety disorders and conditioning. Research has indicated excessive fear as a hallmark of anxiety disorders, however, whereas anxiety describes a process of general arousal, fear is more specific to a certain threat (Lonsdorf & Merz, 2017). Fear conditioning is defined as pairing a neutral stimulus with an aversive stimulus (unconditioned stimulus; US) causing fear responses (Lissek et al., 2005). By this association, the conditioned stimulus (CS), a formerly neutral stimulus, gets associated with the occurrence of the US, and is able to cause the fear reaction (conditioned response; CR). Contemporary research has yielded in-depth insights into the underlying mechanisms of fear conditioning as the related neural processes (for a review see LeDoux, 2014). In particularly, it can be hypothesized that there are differences in fear conditioning between individuals with and those without anxiety disorders, contributing to

the vulnerability and/or resilience against these conditions. These differences might provide valuable explanations for the development and maintenance of anxiety disorders, improving our understanding thereof, and could potentially be identified as valuable treatment targets.

The return of fear describes the return of an extinguished reaction to a conditioned stimulus (Dirikx et al., 2007), or `an increase of fear from post-treatment to follow-up´ (Vervliet et al., 2013, p. 219). Craske and Mystkowski (2006) found that 19-62% of anxiety patients treated with exposure-based therapies experience a return of fear, indicating a serious challenge to the long-term efficacy of exposure-based treatments. It is assumed that individuals with anxiety-related disorders differ from healthy controls in the amount of return of fear, however, it remains unclear, whether this is due to differences in the process of return of fear itself or due to differences during the acquisition or extinction process. Interestingly, often after the return of fear has been experienced a strong decline in conditioned responses is seen in most patients (Barry et al., 2016). Most research concerning the return of fear is done in animals and it is questionable to which degree this finding can be translated to humans (Hermans et al., 2006). To adjust treatment and improve the prevention of potential relapse it is crucial to improve knowledge regarding these processes.

Research has found fear conditioning to be a valuable lab model providing insights into the etiology and treatment of anxiety disorders (Vervliet et al., 2013). Human (Pavlovian) fear conditioning studies involve a procedure in which during the acquisition phase one neutral stimulus (i.e. a sound) is repeatedly paired with a fear-inducing unconditioned stimulus (US; i.e. a shock). Over time, the now conditioned stimulus (CS) becomes a predictor of the US and will itself evoke the fear reaction (CR; Rescorla, 1968). During extinction of fear, the CS is repeatedly presented without the US, which causes a weaker fear reaction over time. Research has suggested that even after successful extinction the original conditioned

CS-US association remains intact. Hence, there exist two competing meanings of the CS and the original fearful interpretation might be reactivated causing the return of fear (Vervliet et al., 2013; Landkroon et al., 2019), which has been repeatedly observed, also by others. Fear conditioning studies have been conducted with a range of stimuli (CSs, USs), procedures, reconditioning procedures, and fear measures (for an overview see Vervliet et al., 2013).

Previous research has investigated whether there are major differences, such as the presence of certain vulnerability or other involved factors, between individuals with anxiety-related disorders and healthy controls within fear conditioning, involving experimental phases such as acquisition, habituation, generalization, extinction, and reconditioning. Whereas in the past fear conditioning was considered to be a universal process in humans (and animals), only recently attention has emerged to investigate inter-individual differences within this process (Lonsdorf & Merz, 2017).

The assumption that there are further vulnerability factors in persons with anxiety disorders is supported by Lissek et al. (2005) and Duits et al. (2015), who demonstrated that anxiety patients experienced a stronger acquisition of fear compared to healthy controls. When investigating the return of fear it is important to take also the acquisition phase into account because major differences between individuals with anxiety disorders and healthy controls during acquisition might influence later extinction and return of fear. Also, the extent of re-extinction can only be investigated if the acquisition of fear was successful.

A meta-analysis by Duits et al. (2015) has described reduced extinction in individuals with anxiety disorders compared to healthy controls. This result was also found in previous research by Vriends et al. (2011), who additionally investigated the same effect for individuals with high trait anxiety compared to individuals with lower trait anxiety. Impaired discrimination between safe and threatening stimuli has been found to mediate the relationship

between trait anxiety and later return of fear (Staples-Bradley et al., 2016). However, a more recent study by Pöhlchen et al. (2020) did not find any convincing evidence for differences in extinction for persons with anxiety disorders, except for altered startle reactions in those with PTSD. Rattel et al. (2020) suggested that avoidance behavior in those with an anxiety disorder might prevent extinction and thereby maintains the fear. Vervliet et al. (2013) found extinction and the return of fear to be closely associated, therefore it might be especially important to take a look at the extinction phase when discussing the return of fear.

Several manifestations of return of fear may be distinguished from each other. Spontaneous recovery is defined as the `renewal of conditional responding following the passage of time´ (Treanor et al., 2021, p. 691). Return of fear in a context different from the context where extinction has happened is referred to as renewal (Treanor et al., 2021). Reinstatement refers to the `return of conditioned responding that is observed when unpredictable USs are presented after extinction´ (Dirikx et al., 2009, p. 175).

Also, a number of mechanisms has been discussed to underlie the return of fear. For a long time, it has been believed that during extinction the original US-CS conditioning is `extinct´ as suggested by the name of the phase (Rescorla & Wagner, 1972). However, suppression of thoughts might protect the CS-US relationship during extinction, hence facilitating reinstatement (Hennings et al., 2021). Also, other safety behaviors have been shown to prevent fear extinction, which is explained by the patient misattributing the behavior instead of the CS (van Uijen et al., 2018).

A study by Vansteenwegen et al. (2005) found a significant renewal when the extinction context differed from the acquisition and renewal context (ABC renewal), in contrast when the extinction context was the same as the acquisition and renewal context, no return of

fear was observed. Schmajuk et al. (2007) have suggested appraisal processes to underly re-conditioning in this case.

Third, the generalization of fear might be another mechanism involved in renewal. During fear generalization, an originally neutral stimulus is interpreted in a fear-inducing manner `due to both its´ perceptual and/or conceptual similarity to another aversive stimulus´ (Preusser et al., 2017, p. 2545). Due to this mechanism return of fear might occur when the stimulus during re-extinction has some similarities with the original acquisition stimulus.

Fourth, another account explains the return of fear by the activation of the acquisition context, which is referred to as ABA renewal (Vervliet et al., 2013). It is proposed that the CS-US relationship is mediated by the context, hence after acquisition in one context and extinction in a different context, a return of fear can occur when the CS is presented in the original acquisition context again (Dirikx et al., 2009). In particular, after extinction in the assumedly safe context of therapy fear might return as soon as the therapy setting is left and the individual returns to the as unsafe appraised context.

Last, in contrast to the previously mentioned findings, Bouton (2002) explained re-conditioning by the anxious individual acquiring a new fear instead of reactivating an earlier acquired CS-US association. Since other studies have not accounted for this explanation, more research is necessary to compare both accounts. In addition, studies have investigated vulnerability and resilience factors that enhance extinction and prevent the return of fear, as certain attachment styles (i.e., Toumbelekis et al., 2021). Further possible explanations might be that the new fear might reactivate the original conditioning and spontaneous recovery, which haven’t received as much attention as other accounts yet (Vervliet et al., 2013).

The purpose of this thesis is to provide a review of existing fear conditioning studies and a meta-analysis of the effect of conditional responding throughout the experimental pha-

ses (i.e., acquisition, extinction, and return of fear) of the conditioning process. The main objective is to systematically examine the differences in fear conditioning between individuals with anxiety disorders and healthy controls. This appears to be of particular relevance because most fear conditioning studies have been performed in healthy students, however, as described, there might be differences in the underlying processes between persons with anxiety disorders and healthy individuals. Also, it is still not entirely clear why some individuals experience a return of fear after successful extinction, while others do not (Lonsdorf & Merz, 2017). If there are any specific factors contributing to vulnerability to return of fear in individuals with anxiety disorders these might provide relevant targets for treatment and contribute thereby to theory and clinical practice in improving the prevention of relapse in individuals with anxiety disorders.

Most studies have used electrical stimulation or white noise as the US. However, since fear conditioning is more complex and conditioning also might depend on the nature of the stimulus, it is important to take also other stimuli into account (Mineka, & Öhman, 2002). Therefore, systematically examining differences between studies using different US might provide us with further knowledge about the association between stimuli and fear reaction.

Duits et al. (2015) stated in their meta-analyses that the measure of fear would not account for the variance in effect sizes. In contrast, Torrents-Rodas et al. (2014) and Ryan et al. (2021) found that variance is larger in physiological compared to verbal measures. Therefore, it might be important to take the outcome measurement into account when comparing the results of studies with each other.

Thereby, this thesis aims at including a wide range of studies on fear conditioning comparing adult individuals with anxiety-related disorders and healthy controls and in doing so, adding to our current understanding of processes such as acquisition, maintenance, and

treatment of anxiety disorders. It is hypothesized that individuals with anxiety-related disorders relative to healthy controls will report stronger fear responses during acquisition, and extinction, and will experience a more pronounced return of fear compared to healthy controls.

Method

Selection of studies

This meta-analysis was limited to the English language literature. The literature search for studies was performed in PubMed, Embase, PsycINFO, and OpenGrey computerized reference databases. The initial selection of studies was based on a combination of search terms that had to be present in the title and/or abstract of the paper and was related to anxiety (i.e., *fear* or *anxiety disorder*) and conditioning (i.e., *pavlov* or *stimul**).

The following exclusion criteria were used during abstract screening:

1. studies not involving any kind of fear conditioning
2. studies performed only in children, healthy participants, animals, or individuals with other than anxiety disorders
3. secondary analyses, articles that were not based on any study, case reports, and non-experimental studies and reviews
4. studies clearly including no control group were excluded.

Studies were included if individuals received a diagnosis of an anxiety disorder based on a diagnosed structured interview. One study was left out because it included only 15 participants. In addition to persons with anxiety disorders, studies involving individuals with explicitly mentioned elevated symptoms, but no formal diagnoses, were included.

During full-text screening, further criteria were employed. Studies reporting secondary results from the same sample of another study, not involving a comparison group, not in-

cluding the return of fear phase, involving only children, and including other manipulations such as behavioral, cerebral, or medical procedures during fear conditioning were excluded. Studies were furthermore excluded when they did not include the acquisition, extinction, and reacquisition phases based on the full text.

Statistical analysis

Comprehensive Meta-Analysis software, version 3 (Biostat; Borenstein et al., 2013) was used to conduct statistical analyses. Random-effects models were selected in all analyses. Dependent variables were expectancy towards the CS, skin conductance response, pupil dilation, and startle reaction. Sensitivity analysis and funnel plots were inspected for outliers. Results were checked for heterogeneity.

Effect sizes estimates

Hedges' g was used as an index of effect sizes, indicating the standardized mean difference in acquisition, extinction, and return of fear between patients with anxiety disorders versus controls. By using the common effect size *Hedges' g,* data on patient–control differences across studies could be combined and analyzed, even when the dependent variable had not been operationalized in the same way across studies (Lipsey & Wilson, 2001). According to the guidelines of Cohen (1977), an effect size of $g = 0.20$ relates to a small effect, $g = 0.50$ is considered to be a medium effect, and $g = 0.80$ is defined as a large effect. In the current meta-analysis, positive values were assigned to effect sizes reflecting stronger conditioned fear responses in anxiety patients compared to control subjects. Negative effect sizes on the other hand indicate larger fear responses in control subjects versus patients. In addition, 95% confidence intervals for the effect sizes were computed to investigate the significance level of pooled effect sizes.

To facilitate the merging of effect sizes from the current meta-analysis, effect sizes were computed in a similar way. The formulas as listed in Lipsey and Wilson (2001) were used to calculate the effect sizes per conditioning phase (acquisition, extinction, return of fear), and type of stimulus (CS+ and CS−).

Random Effects Model

A random-effects model was used to account for the heterogeneity within as well as between the included fear-conditioning studies (Hedges & Olkin, 1985). This model assumes that there is a heterogeneous distribution of true effect sizes, rather than one true effect (Borenstein et al., 2009).

Publication bias

The presence of potential publication biases was assessed by plotting the estimated effect sizes (x-axis) and sample sizes (y-axis) for each of the analyses. Publication bias would be indicated by funnel-shaped distributions. The number of unpublished studies with null results needed to reduce the calculated effect size below significance was estimated by calculating the fail-N statistics.

Results

Based on the initial search 672 abstracts of studies published between 2011 and 2022 were screened. Finally, 532 of the 672 studies were excluded after checking the abstracts. The remaining 140 studies were screened based on the entire article, finally resulting in the inclusion of 19 studies that met our inclusion criteria. 15 studies did not provide the statistics that were necessary to reliably calculate (all) effect sizes of interest. Figure 1 illustrates the selection process.

Four studies, published between 2021 and 2022, were included in the current meta-analysis. Data for 107 individuals with anxiety-related disorders and 106 control subjects

were analyzed within the meta-analysis. The total sample size of individual studies (including patients and controls) ranged between 36 and 93 participants. Table 1 lists all included studies and part of the study characteristics.

Figure 1

Study selection flow diagram

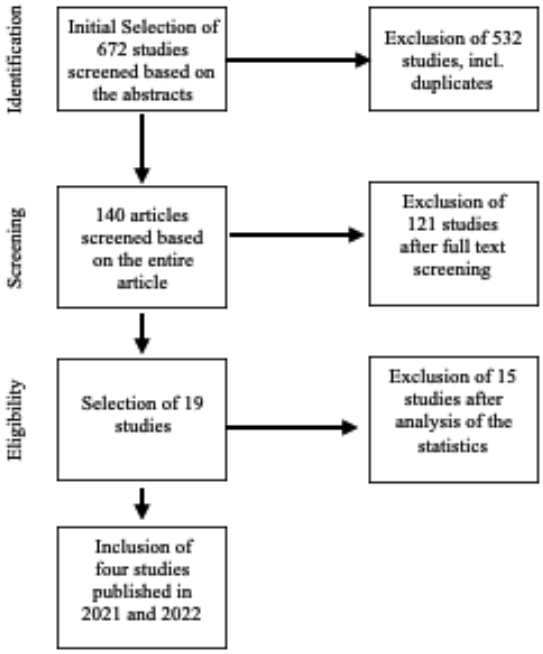

Table 1

Characteristics of the selected Studies

Author	Year	Diagnosis	*N* (% patients)	CS	US	DV	ROF manipulation
Cano	2021	OCD	36 (50%)	photographs	electric shock	SCR	spontaneous recovery
Hennings	2022	PTSD	47 (51%)	pictures of animals and tools	electric shock	SCR, US expectancy ratings	renewal

Table 1

Characteristics of the selected Studies

Author	Year	Diagnosis	*N* (% patients)	CS	US	DV	ROF manipulation
Pöhlchen	2021	OCD	93 (40%)	colored geometrical shapes	electrical shock, airblast	SCR, pupil dilation, startle, subjective ratings	spontaneous recovery
Wake	2021	SAD	80 (50%)	female faces	electric shock, voice	SCR, US expectancy ratings	spontaneous recovery

Note. CS = conditioned stimuli; *US* = unconditioned stimuli; *DV* = dependent variable; *OCD* = obsessive compulsive disorder; *SCR* = skin conductance response; *SAD* = social anxiety disorder, *ROF* = return of fear.

Acquisition

Acquisition was successful in all four studies. Table 2 displays average effect sizes of differences in fear responses between individuals with anxiety-related disorders and controls evoked by the CS (combined) during acquisition. None of the studies found significant ($p < .05$) differences in acquisition between both groups. Overall, patient-control differences towards the CS (combined) were not significant ($g = 0.183$, $p = .146$, $k = 4$). All four papers did find a stimulus effect during acquisition, showing greater responses toward the CS+, compared to the CS-. Inspecting the funnel plot did not reveal any significant outliers. Sensitivity analysis indicated that the removal of any of the studies did not influence the result significantly ($p > .05$). Test for heterogeneity was not significant ($p > .05$).

Table 2

Effect sizes for differences between patients and controls per study during acquisition

Author	Year	*N*	*Hedges´ g*	*standard error*	*p-value*
Cano	2021	36	0.538	.332	.105
Hennings	2022	47	0.267	.288	.355
Pöhlchen	2021	93	0.146	.214	.496
Wake	2021	80	0.014	.221	.949
Overall			0.183	.126	.146

Extinction

Table 3

Effect sizes for differences between patients and controls per study during extinction

Author	Year	*N*	*Hedges´ g*	*standard error*	*p-value*
Cano	2021	36	0.267	.327	.415
Hennings	2022	47	0.177	.300	.556
Pöhlchen	2021	93	0.184	.217	.395
Wake	2021	80	0.181	.217	.413
Overall			0.194	.127	.126

In all four studies, individuals with anxiety-related disorders showed decreased fear reactions after extinction. During fear extinction, again, none of the authors found individuals with anxiety-related disorders to respond stronger towards the CS than healthy controls. The overall effect was not significant ($g = 0.194$, $p = .127$, $k = 4$, $N = 256$). Table 3 presents the effect sizes per study and over all studies. Inspecting the funnel plot did not reveal any significant outliers. Sensitivity analysis indicated that the removal of any of the studies did not influence the result significantly ($p > .05$).

Return of fear

In all four studies individuals with anxiety disorders and those without showed the conditioned reaction to the CS (combined). None of the studies did find significant differences during return of fear between individuals with anxiety disorders and healthy controls ($p > .05$). The overall effect was not significant ($g = 0.187$, $p = .161$, $k = 4$, $N = 256$). Table 4 reports the differences between patients and healthy individuals during return of fear per study. Wake et al. (2021) found a significant stimulus effect ($p < .001$), return of fear was only significant for the CS+.

Inspecting the funnel plot did not reveal any significant outliers. Sensitivity analysis indicated that that the removal of any of the studies did not influence the result significantly ($p > .05$). Test for heterogeneity was not significant.

Table 4

Effect sizes for differences between patients and control per study during return of fear

Author	Year	*N*	*Hedges' g*	*standard error*	*p-value*
Cano	2021	36	0.015	.326	.963
Hennings	2022	47	0.432	.306	.158
Pöhlchen	2021	93	0.247	.254	.331
Wake	2021	80	0.093	.220	.673
Overall			0.187	.133	.161

Discussion

The main aim of this meta-analysis was to systematically examine differences between individuals with anxiety disorders and healthy controls during the fear conditioning phases (i.e., acquisition, extinction, and return of fear). Previous research has found conflicting results regarding patient-control differences, with some studies indicating individuals

with anxiety disorders to show stronger acquisition, experience reduced extinction, and a more pronounced return of fear compared to healthy controls. However, other studies have found these differences to be negligible. The results of four studies were combined to extend and update previous findings regarding these differences. The current meta-analysis combined the results of 119 individuals with anxiety disorders and 138 control subjects. In general, conditioning was successful in all four studies with individuals showing increased anxiety after acquisition, decreased fear responses after extinction, and a return of fear after being confronted with the CS again.

All four studies did find return of fear after successful extinction. This supports previous research demonstrating return of fear to be a common phenomenon and is consistent with the hypothesis that during extinction the once acquired CS-US relationship is not extinguished, but that this relation persists and competes with the newly learned CS-noUS relationship. Return of fear in clinical practice might be more complex than in the paradigms used in the four studies and the effect during return of fear might differ depending on the respective manifestation, for example when comparing ABA to ABC renewal. Therefore, future research should be conducted considering and comparing the distinct manifestations that may provide insights into mechanisms of return of fear and improve our understanding thereof.

Differences during return of fear might be associated with previous differences in acquisition and extinction. Future research investigating this hypothesis might investigate associations between the different phases. No such study exists yet. If such differences exist, one might differentiate between those studies which did find differences in earlier conditioning phases and those which did not. Then it would be possible to look at systematic differences between those studies, for example with regard to the involved conditioning procedure, participants, assessment methods, etc.

During acquisition, none of the studies found significant differences between those with anxiety disorders and those without. This is in line with the previous study by Tinoco-González et al. (2015) but in contrast to others (Lissek et al., 2005; Duits et al., 2015). It should be noted that studies use different fear conditioning procedures, and results might be relatively dependent on the respective task. All four included studies found enhanced CS+ compared to the CS- responding during acquisition which is consistent with previous results by Lissek et al. (2005).

When considering the dependent variables, it should be noted that fear responses were mostly measured using physiological measures. When looking at the meta-analysis by Duits et al. (2015) those studies using physiological measures found relatively small effect sizes compared to other measures of fear. Hence, the effect found might strongly depend on the outcome measurement. In addition, future investigations considering assigned gender at birth and nature of the stimulus (i.e., social vs. non-social, or disorder-specific vs. non-specific) as mediators might be useful to improve our understanding of the specific processes involved in differences between studies.

Taken together, these results add to our current knowledge about fear conditioning. In contrast to our expectations, none of the studies did find any differences between patients and healthy controls in acquisition, extinction, and return of fear. This can be interpreted in several ways: First of all, it should be kept in mind that four studies cannot be considered representative. In the current meta-analysis four studies were included, conducted with individuals diagnosed with PTSD, OCD, and SAD. They did not find significant differences between individuals with and without anxiety disorders during any of the conditioning phases. However, other studies have found such differences, for example during the acquisition and extinction

phase (see the meta-analysis by Duits et al., 2015). If some of these studies would have been included, results at least for acquisition and extinction may have looked differently.

Secondly, this result represents the incoherent results described before and demonstrates the need for further research. The involved studies did not find differences between individuals with anxiety disorders and healthy controls as some studied did before, however, others have, therefore it would be revealing to look at potential differences concerning design and involved patient groups between those studies which did not find differences and those which did. The use of prospective, longitudinal studies is recommended to improve our understanding of differences within these phases and to investigate the course of differences between individuals with anxiety disorders and healthy controls and individuals with anxiety disorders during the conditioning phases. Most studies use a conditioning procedure completed within one day (i.e., Wake et al., 2021), or two days (i.e., Cano et al., 2021), however, in clinical practice, it might be that persons with anxiety disorders relapse after weeks or months, therefore longitudinal designs might enhance the ecological validity of fear conditioning paradigms.

After an extensive screening process, only four studies were included in this meta-analysis. Only studies from 2021 onward were included, research conducted earlier was beyond the scope of this meta-analysis. Nevertheless, it would be interesting if other authors have found different results.

The current meta-analysis might provide a starting point for further systematic investigations of patient-control differences during fear conditioning. An addition to previous research was the comparison of the CS+ and CS-, which was done for the acquisition and extinction phases in the meta-analysis by Duits et al. (2015) but hasn't been applied to the return of fear phase in a meta-analysis.

To conclude, the present thesis compared individuals with anxiety disorders and healthy controls in fear conditioning across four studies concerning responses toward the CS. None of the involved studies found differences in acquisition, extinction, and return of fear, which is inconsistent with previous literature. Therefore, future research is recommended to further clarify these processes in detail.

References

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, (*5th ed.; DSM-5). Arlington, VA Washington, D.C: American Psychiatric Association.

Barry, T. J., Griffith, J.W., Vervliet, B. & Hermans, D. (2016). The role of stimulus specificity and attention in the generalization of extinction. *Journal of Experimental Psychopathology, 7,* pp. 143-152. https://doi.org/10.5127/jep.048615

Borenstein M., Hedges L. V., Higgins, J. P., Rothstein, H. R. (2009). *Introduction to meta-analysis.* Chichester, UK: Wiley.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H. (2013). *Comprehensive Meta-analysis, Version 3.0.* Biostat Inc. https://www.meta-analysis.com/?gclid=EAIaIQobChMI3vatuP3k5QIVqx-tBh2MwQDHEAAYASAAEgLSGfD_BwE. Published 2013. Accessed November 12, 2019.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry, 52*(10), 976–986. https://doi.org/10.1016/s0006-3223(02)01546-9

*Cano, M., Martínez-Zalacaín, I., Giménez, M., Torrents-Rodas, D., Real, E., Alonso, P., Segalàs, C., Munuera, J., Menchón, J. M., Cardoner, N., Soriano-Mas, C., & Fullana, M. A. (2021). Neural correlates of fear conditioning and fear extinction and its association with cognitive-behavioral therapy outcome in adults with obsessive-compulsive disorder. *Behaviour Research and Therapy, 144*, 103927. https://doi.org/10.1016/j.brat.2021.103927

Christiansen, D. M. (2015). Examining sex and gender differences in anxiety disorders. In F. Durbano (Ed.). *A fresh look at anxiety disorders*, (pp. 17-49). InTechOpen. https://doi.org/ 10.5772/60662

Cohen J. (1977). *Statistical Power Analysis for the Behavioral Sciences.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Craske M. G. & Mystkowski, J. (2006). Exposure therapy and extinction: clinical studies. In M. G., Craske, D. Hermans, & D. Vansteenwegen (Eds). *Fear and Learning: Basic Science to Clinical Application* (pp. 217-233). Washington DC: APA Books.

Dirikx, T., Hermans, D., Vansteenwegen, D., Baeyens, F., & Eelen, P. (2007). Reinstatement of conditioned responses in human differential fear conditioning. *Journal of Behavior Therapy and Experimental Psychiatry, 38*(3), 237–251. https://doi.org/10.1016/j.jbtep.2006.04.001

Dirikx, T., Vansteenwegen, D., Eelen, P., & Hermans, D. (2009). Non-differential return of fear in humans after a reinstatement procedure. *Acta Psychologica, 130*(3), 175–182. https://doi.org/10.1016/j.actpsy.2008.12.002

Donner, N. C., & Lowry, C. A. (2013). Sex differences in anxiety and emotional behavior. *Pflügers Archives - European Journal of Physiology, 465*(5), 601-626. https://doi.org/10.1007/s00424-013-1271-7

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., van den Hout, M. A., & Baas, J. M. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety, 32*(4), 239–253. https://doi.org/10.1002/da.22353

Hedges L. V. & Olkin I. (1985). *Statistical Methods for Meta-Analysis*. Orlando: Academic Press.

Hennings, A. C., Bibb, S. A., Lewis-Peacock, J. A., & Dunsmoor, J. E. (2021). Thought suppression inhibits the generalization of fear extinction. *Behavioural Brain Research, 398*, 112931. https://doi.org/10.1016/j.bbr.2020.112931

*Hennings, A. C., McClay, M., Lewis-Peacock, J. A., & Dunsmoor, J. E. (2020). Contextual reinstatement promotes extinction generalization in healthy adults but not PTSD. *Neuropsychologia, 147*, 107573. https://doi.org/10.1016/j.neuropsychologia.2020.107573

Hermans, D., Craske, M. G., Mineka, S., & Lovibond, P. F. (2006). Extinction in human fear conditioning. B*iological Psychiatry, 60*(4), 361–368. https://doi.org/10.1016/j.biopsych.2005.10.006

Landkroon, E., Mertens, G., Sevenster, D., Dibbets, P., &; Engelhard, I. M. (2019). Renewal of conditioned fear responses using a film clip as the aversive unconditioned stimulus. *Journal of Behavior Therapy and Experimental Psychiatry, 65*, 101493. https://doi.org/10.1016/j.jbtep.2019.101493

LeDoux, J. E. (2014). Coming to terms with fear. *Proceedings of the National Academy of Sciences, 111*(8), 2871–2878. https://doi.org/10.1073/pnas.1400335111

Lipsey, M. W. & Wilson D.B. (2001). *Practical meta-analysis*. Thousand Oaks, CA: Sage.

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: A meta-analysis. *Behaviour Research and Therapy, 43*(11), 1391–1424. https://doi.org/10.1016/j.brat.2004.10.007

Lissek, S., Levenson, J., Biggs, A. L., Johnson, L. L., Ameli, R., Pine, D. S., & Grillon, C. (2008). Elevated fear conditioning to socially relevant unconditioned stimuli in social anxiety disorder. *American Journal of Psychiatry, 165*(1), 124–132. https://doi.org/10.1176/appi.ajp.2007.06091513

Lissek, S., Kaczkurkin, A. N., Rabin, S., Geraci, M., Pine, D. S., & Grillon, C. (2014). Generalized anxiety disorder is associated with overgeneralization of classically conditioned fear. *Biological Psychiatry, 75*(11), 909–915. https://doi.org/10.1016/j.biopsych.2013.07.025

Lonsdorf, T. B., & Merz, C. J. (2017). More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans - biological, experiential, temperamental factors, and methodological pitfalls. *Neuroscience & Biobehavioral Reviews, 80*, 703–728. https://doi.org/10.1016/j.neubiorev.2017.07.007

Mineka, S., & Öhman, A. (2002). Phobias and preparedness: The selective, automatic, and encapsulated nature of fear. *Biological Psychiatry, 52*(10), 927–937. https://doi.org/10.1016/s0006-3223(02)01669-4

Otte, C. (2011). Cognitive behavioral therapy in anxiety disorders: Current state of the evidence. *Dialogues Clin. Neurosci., 13*, 413–421.

Pöhlchen, D., Leuchs, L., Binder, F. P., Blaskovich, B., Nantawisarakul, T., Topalidis, P., Brückl, T. M., Norrholm, S. D., Jovanovic, T., Spoormaker, V. I., Binder, E. B., Czisch, M., Erhardt, A., Grandi, N. C., Ilic-Cocic, S., Lucae, S., Sämann, P., & Tontsch, A. (2020). No robust differences in fear conditioning between patients with fear-related disorders and healthy controls. *Behaviour Research and Therapy, 129*, 103610. https://doi.org/10.1016/j.brat.2020.103610

*Pöhlchen, D., Priouret, M., Kraft, M. S., Binder, F. P., Gürsel, D. A., Berberich, G., Koch, K., & Spoormaker, V. I. (2021). Examining differences in fear learning in patients with obsessive-compulsive disorder with pupillometry, startle electromyography and skin conductance responses. *Frontiers in Psychiatry, 12*. https://doi.org/10.3389/fpsyt.2021.730742

Preusser, F., Margraf, J., & Zlomuzica, A. (2017). Generalization of extinguished fear to untreated fear stimuli after exposure. *Neuropsychopharmacology, 42*(13), 2545–2552. https://doi.org/10.1038/npp.2017.119

Rattel, J. A., Miedl, S. F., Liedlgruber, M., Blechert, J., Seidl, E., & Wilhelm, F. H. (2020). Sensation seeking and neuroticism in fear conditioning and extinction: The role of avoidance behaviour. *Behaviour Research and Therapy, 135*, 103761. https://doi.org/10.1016/j.brat.2020.103761

Rescorla, R. A. (1968). Probability of shock in the presence and absence of CS in fear conditioning. *Journal of Comparative and Physiological Psychology, 66*, 1-5.

Rescorla R.A., & Wagner A.R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy (Eds.), *Classical Conditioning II* (pp. 64–99). Appleton-Century-Crofts.

Ryan, K. M., Neumann, D. L., & Waters, A. M. (2021). Does the assessment of different combinations of within-phase subjective measures influence electrodermal responding and between-phase subjective ratings during fear conditioning and extinction experiments? *Biological Psychology, 162*, 108085. https://doi.org/10.1016/j.biopsycho.2021.108085

Schmajuk, N., Larrauri, J., & LaBar, K. (2007). Reinstatement of conditioned fear and the hippocampus: An attentional-associative model. *Behavioural Brain Research, 177*(2), 242–253. https://doi.org/10.1016/j.bbr.2006.11.026

Staples-Bradley, L. K., Treanor, M., & Craske, M. G. (2016). Discrimination between safe and unsafe stimuli mediates the relationship between trait anxiety and return of fear. *Cognition and Emotion, 32*(1), 167–173. https://doi.org/10.1080/02699931.2016.1265485

Tinoco-González, D., Fullana, M. A., Torrents-Rodas, D., Bonillo, A., Vervliet, B., Blasco, M. J., Farré, M., & Torrubia, R. (2015). Conditioned fear acquisition and generalization in generalized anxiety disorder. *Behavior Therapy, 46*(5), 627–639. https://doi.org/10.1016/j.beth.2014.12.004

Torrents-Rodas, D., Fullana, M. A., Bonillo, A., Andión, O., Molinuevo, B., Caseras, X., & Torrubia, R. (2014). Testing the temporal stability of individual differences in the acquisition and generalization of fear. *Psychophysiology, 51*(7), 697–705. https://doi.org/10.1111/psyp.12213

Toumbelekis, M., Liddell, B. J., & Bryant, R. A. (2021). Secure attachment priming protects against relapse of fear in young adults. T*ranslational Psychiatry, 11*(1). https://doi.org/10.1038/s41398-021-01715-x

Treanor, M., Rosenberg, B. M., & Craske, M. G. (2021). Pavlovian learning processes in pediatric anxiety disorders: A critical review. *Biological Psychiatry, 89*(7), 690–696. https://doi.org/10.1016/j.biopsych.2020.09.008

Vansteenwegen, D., Hermans, D., Vervliet, B., Francken, G., Beckers, T., Baeyens, F., & Eelen, P. (2005). Return of fear in a human differential conditioning paradigm caused by a return to the original acquisition context. *Behaviour Research and Therapy, 43*(3), 323–336. https://doi.org/10.1016/j.brat.2004.01.001

van Uijen, S. L., Leer, A., & Engelhard, I. M. (2018). Safety behavior after extinction triggers a return of threat expectancy. *Behavior Therapy*, *49*(3), 450–458. https://doi.org/10.1016/j.beth.2017.08.005

Vervliet, B., Craske, M. G., & Hermans, D. (2013). Fear extinction and relapse: State of the art. *Annual Review of Clinical Psychology, 9*, 215–248. https://doi.org/10.1146/ annurev-clinpsy-050212-185542.

Vriends, N., Michael, T., Blechert, J., Meyer, A. H., Margraf, J., & Wilhelm, F. H. (2011). The influence of state anxiety on the acquisition and extinction of fear. J*ournal of Behavior Therapy and Experimental Psychiatry, 42*(1), 46–53. https://doi.org/10.1016/j.jbtep.2010.09.001

*Wake, S., van Reekum, C. M., & Dodd, H. (2021). The effect of social anxiety on the acquisition and extinction of low-cost avoidance. *Behaviour Research and Therapy, 146*, 103967. https://doi.org/10.1016/j.brat.2021.103967

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. J*ournal of Experimental Psychology, 3*, 1–14. https://doi.org/10.1037/h0069608

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., & Steinhausen, H.-C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology, 21*(9), 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018

Wong, A. H. K., & Beckers, T. (2021). Trait anxiety is associated with reduced typicality asymmetry in fear generalization. *Behaviour Research and Therapy, 138*, 103802. https://doi.org/10.1016/j.brat.2021.103802

World Health Organization (2017). *Depression and other common mental disorders.* World Health Organization. Retrieved May 11, 2022, from https://www.who.int/publications-detail-redirect/depression-global-health-estimates