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Review

UPDATED META-ANALYSIS OF CLASSICAL FEAR CONDITIONING IN THE ANXIETY DISORDERS

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The aim of the current study was twofold: (1) to systematically examine differences in fear conditioning between anxiety patients and healthy controls using meta-analytic methods, and (2) to examine the extent to which study characteristics may account for the variability in findings across studies. Forty-four studies (published between 1920 and 2013) with data on 963 anxiety disordered patients and 1,222 control subjects were obtained through PubMed and PsycINFO, as well as from a previous meta-analysis on fear conditioning (Lissek et al.[10]). Results demonstrated robustly increased fear responses to conditioned safety cues (CS−) in anxiety patients compared to controls during acquisition. This effect may represent an impaired ability to inhibit fear in the presence of safety cues (CS−) and/or may signify an increased tendency in anxiety disordered patients to generalize fear responses to safe stimuli resembling the conditioned danger cue (CS+). In contrast, during extinction, patients show stronger fear responses to the CS+ and a trend toward increased discrimination learning (differentiation between the CS+ and CS−) compared to controls, indicating delayed and/or reduced extinction of fear in anxiety patients. Finally, none of the included study characteristics, such as the type of fear measure (subjective vs. psychophysiological index of fear), could account significantly for the variance in effect sizes across studies. Further research is needed to investigate the predictive value of fear extinction on treatment outcome, as extinction processes are thought to underlie the beneficial effects of exposure treatment in anxiety disorders. Depression and Anxiety 32:239–253, 2015.

Key words: *anxiety disorders; classical fear conditioning; extinction; meta-analysis*

INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5[1]), anxiety disorders share features of excessive and persistent fear and/or anxiety and related behavioral disturbances (e.g., escape and avoidance) causing significant distress and impairment. Neuroscience-based models presume that emotional responses such as fear and anxiety are grounded in a defense motivational circuit that feeds back to sensory systems, increasing vigilance and information gathering

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(if a threat is expected or detected) and prompting dynamic defensive behavior (e.g., attentive freezing or flight responses). Our understanding of the defense circuitry is primarily based on animal studies that use relatively simple fear-conditioning procedures, subsequently allowing for translational research.[2,3] Although other translational models are feasible as well, human fear-conditioning studies demonstrated that the same neural networks as found in animal studies are activated during fear conditioning. Hyperactivity of amygdala and insula is found in phobic disorders, and in posttraumatic stress disorder (PTSD) hypoactivation in ventromedial prefrontal cortex (vmPFC) during extinction learning.[4,5] These translational findings are very encouraging for using fear-conditioning models to study the development and maintenance of anxiety disorders. In addition, theories of clinical anxiety include abnormalities in conditioned fear as a key etiological feature,[6–9] which was confirmed by a recent meta-analysis of experimental studies evidencing conditioning anomalies across anxiety disorders.[10]

In human fear-conditioning studies, a differential conditioning procedure is often used in which one conditioned stimulus (CS+) is repeatedly paired with an aversive unconditioned stimulus (US) during the acquisition phase, whereas another conditioned stimulus (CS−) is never paired with the US, serving as a conditioned safety cue. Eventually, the CS+ becomes a signal of the US and will itself evoke the associated fear, known as the conditioned response (CR). Extinction of fear usually takes place after repeated exposure to the CS+ in absence of the US, which will lead to a decrease of the CR. The original CS–US association is not erased during extinction of fear, but replaced by a *newly learned* association dependent on the context of extinction.[11,12]

Fear acquisition and fear extinction might comprise independent learning processes. Interestingly, both fear conditioning and extinction mechanisms were demonstrated to be moderately heritable[13] and candidate gene studies suggest that fear acquisition and extinction might to a certain extent be differentially genetically regulated.[14] Thus, individual differences in fear learning and extinction may be independent factors in transforming normal levels of fear to pathological anxiety across the anxiety disorders.

There are two primary ways by which fear conditioning might result in pathological anxiety: (1) enhanced acquisition of the fear response to the CS+ and/or to nonreinforced CS− conditions and (2) reduced fear extinction, or a combination of these processes.[6,7,10,15,16] Prospective studies support the idea that pathological fear conditioning precedes the onset of anxiety disorders, as stronger fear responses to the CS+ and stronger discriminative fear responses (CS+ minus CS−) during extinction have shown to be moderate predictors of the development of posttraumatic stress symptoms in soldiers, firefighters, and policemen before deployment.[17–20]

In 2005, a meta-analysis was published by Lissek et al., which systematically assessed differences in fear acquisition and extinction between patients with anxiety disorders and healthy controls. This meta-analysis included 20 lab-based fear-conditioning studies that had been published between 1920 and 2003, containing data of about 400 anxiety patients and a similar number of control subjects. Results demonstrated a modestly larger level of fear responses to the CS+ (simple learning) in various groups of patients with anxiety disorders compared to control subjects, during both the acquisition ($d = 0.42$, $P < .002$) and extinction of fear ($d = 0.39$, $P = .01$). These findings suggest increased excitatory fear learning during acquisition and increased expression of fear during extinction in anxiety patients compared to controls. No significant differences were found between patients and controls, both during acquisition and extinction, in their ability to discriminate between the CS+ and CS−, in other words, indices of differential conditioning did not differ between patients and healthy controls. Equal difference scores, however, do not mean automatically that patients and controls show comparable response patterns, because patients might show increased fear responses to both CS+ and CS− compared to controls, thereby producing the same discrimination scores.

Patient–control differences in fear responses to the CS− were not measured in the previous meta-analysis. However, several studies found increased fear responses to the CS− during fear acquisition in patients with PTSD[21,22] and social phobia[23] compared to controls, which might be due to a stronger tendency to generalize fear to stimuli resembling the CS+ (because of the many perceptual similarities between the CS+ and CS− employed by studies in this literature), and/or an impaired ability to inhibit fear.

The overall goal of the current meta-analysis was to update and extend the previous meta-analysis because the number of fear-conditioning studies in anxiety patients and controls has more than doubled since 2003. Our extension to the previous meta-analysis was threefold. First, we aimed to systematically examine differences in fear acquisition and extinction between anxiety patients and healthy controls using meta-analyses on all currently existing literature. Second, psychophysiological outcome measures and, as an extension of the previous meta-analysis, verbal report data were included as indices of the conditioned fear response. Third, quantification of patient–control differences in fear reactivity to the CS− was added. A series of meta-analyses were carried out to study patient–control differences in: (1) simple learning during acquisition (intensity of the fear response to the CS+), (2) generalization/inhibition during acquisition (intensity of the fear response to the CS−), (3) discrimination learning during acquisition (fear response to the CS+ minus CS−), (4) simple learning during extinction, (5) generalization/inhibition during extinction, and (6) discrimination learning during extinction. Based on the previous meta-analysis, we hypothesized stronger fear responses to both the CS+ and CS− in patients with various anxiety disorders compared

to controls both during acquisition and extinction. We did not expect patient–control differences in discrimination learning during either acquisition or extinction.

Our second goal was to examine the extent to which study characteristics, for example, the use of subjective versus psychophysiological fear measures, may account for the variability in findings across studies, thereby investigating the sensitivity of various study designs to detect patient–control differences in fear conditioning. In addition, very few studies have directly compared fear conditioning across anxiety disorders. One study demonstrated low excitatory learning during acquisition in PTSD and impaired extinction of fear in patients with panic disorder compared to healthy control subjects.[24] Most studies in anxiety disorders so far have specifically focused on PTSD; theoretically, this disorder fits in very well in a fear-conditioning paradigm, since in PTSD there is a clear stressor preceding the onset of fear symptoms. Considering the overrepresentation of PTSD in fear-conditioning studies, we have chosen to include PTSD diagnosis versus any other anxiety disorder as a factor in the analyses.

METHOD

SELECTION OF STUDIES

The selection of studies up to the year 2003 was covered by Lissek's earlier meta-analysis (published in 2005), and the literature search was not redone for studies for that period. The literature search for studies and dissertations that were published between 2003 and 2013 was primarily performed in PubMed and PsycINFO computerized reference databases. No language restrictions were applied. See also Fig. 1 for the flow chart of our study selection. Similar to the previous meta-analysis by Lissek et al.[10], 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: (*conditioned* OR *conditioning*) AND (*conditioning OR conditioned* OR *anxiety OR anxious* OR *fear* OR *phobia* OR *phobic OR panic* OR *neurosis AND/OR patient OR disorder*). In addition to the online literature search, reference lists of selected papers were screened, and a call for unpublished data was made at the Fifth European Meeting on Human Fear Conditioning in Affligem, Belgium (May, 2013). The literature search resulted in an initial selection of 4,563 studies, after removal of duplicate references (PsycINFO: $N = 3{,}733$; PubMed: $N = 830$). Subsequently, each abstract was examined on the basis of the following inclusion criteria: (1) inclusion of patients with anxiety disorders (as defined according to DSM-IV criteria[25]) and of healthy control subjects; (2) diagnosis of an anxiety disorder was established with formal diagnostic interviewing to ensure the exclusion of studies using subclinical samples; (3) classical, aversive conditioning was examined[1]; (4) subjective (e.g., ratings of valence, anxiety) and/or psychophysiological (e.g., startle response, skin conductance response) outcome measurements were used to index the conditioned fear responses (CR). These inclusion criteria were equal to the criteria used by Lissek et al.[10], but as an extension subjective outcome measures were included. Outcome measures relating to brain imaging (e.g., functional magnetic resonance imaging, positron emission tomography) were considered to be beyond the scope of the current article and were not included in the current meta-analysis.

Finally, 4,468 studies were excluded after the abstracts had been screened, based on the formulated criteria. The remaining 95 studies were screened on the basis of the entire article, resulting in the inclusion of 39 studies that met our inclusion criteria. A request for additional data was sent to corresponding authors, as 31 studies did not provide the statistics that were necessary to reliably calculate (all) effect sizes of interest. Additional statistical details were provided for 21 studies. Therefore, 10 studies had to be excluded from the current meta-analysis as the reported statistics were not sufficient to compute or estimate the effect sizes.

EFFECT SIZE ESTIMATES

Unbiased Cohen's *d* was used as an index of effect sizes, indicating the standardized mean difference in fear responses between patients with anxiety disorders versus controls. Effect sizes were corrected for a potential bias as a result of small sample sizes.[27] By using the common effect size *d*, 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.[28] According to the guidelines of Cohen,[29] an effect size of $d = 0.20$ relates to a small effect, $d = 0.50$ is considered to be a medium effect, and $d = 0.80$ 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 the pooled effect sizes.

To facilitate the merging of effect sizes from the current and previous meta-analysis, effect sizes were computed in a similar way.[10] The formulas as listed in Lipsey and Wilson (2001) were used to calculate the effect sizes per conditioning phase (acquisition, extinction), type of stimulus (CS+; CS−; CS+ minus CS−), and type of outcome measure (e.g., startle response, subjective fear). Fear responses to stimulus types were contrasted with baseline levels and intertrial intervals (ITIs) if available. In the majority of studies that were published after 2003, *d* was calculated by using group means and standard deviations. In one study, the effect size was estimated from the reported *t*-value and corresponding *df* from a *t*-test. Furthermore, as in the previous meta-analysis, the *q* statistic was used to compute within-group effect sizes in papers for which results were reported separately for the patient and control group (see also Lissek et al.[10]).

RANDOM EFFECTS MODEL

A random-effects model was used to account for the heterogeneity within as well as between the included fear-conditioning studies.[27] This model assumes that there is a heterogeneous distribution of true effect sizes, rather than one true effect.[30]

CODING OF STUDY CHARACTERISTICS

Study conditions and characteristics were coded into categorical and continuous variables to study the correlation between these potentially moderating variables and the included effect sizes. The coded categorical variables are listed in Table 1.

A few studies reported effects for more than one level of a categorical variable, for example, there were several PTSD studies that included both a healthy control group and a trauma-exposed control group without PTSD. For these studies, all relevant conditions were coded by including the same study repeatedly in the meta-analysis. Consequently, the number of participants was divided by two, to correct for multiple testing within one group (in this example: the patient

[1]Conditioning studies using eyelid conditioning were not included since these studies primarily focus on investigating associative motor learning processes, rather than fear responses.[26]

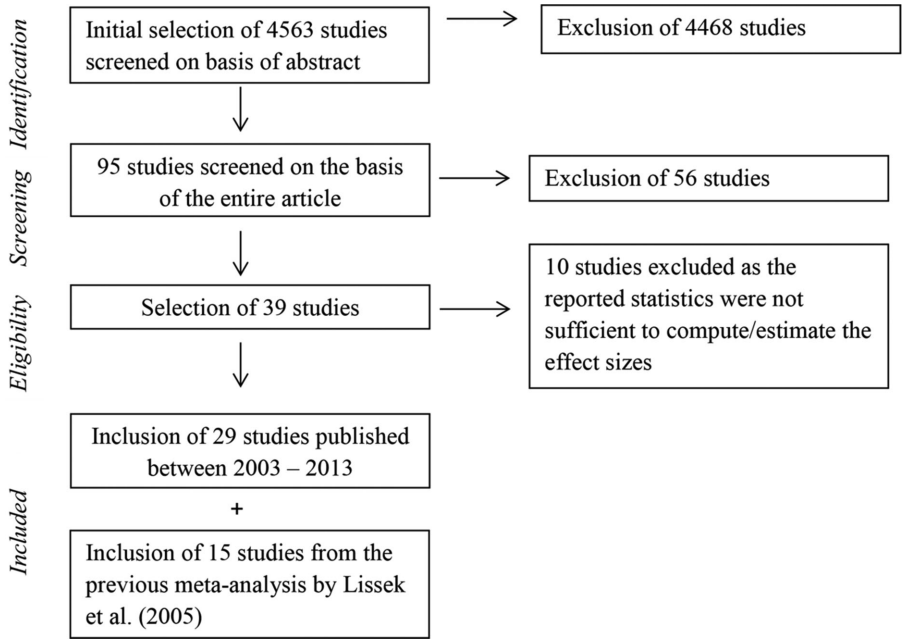

Figure 1. Study selection flow diagram.

TABLE 1. List of the included categorical variables

Categorical variables
Physiological versus subjective outcome measures
Primary diagnosis of posttraumatic stress disorder (PTSD) in the patient group versus any other anxiety disorder[a]
Healthy control group versus trauma-exposed control group
Single cue conditioning paradigm (without a CS−) versus differential paradigm[b]
Disorder-specific US versus nonspecific US
Electric shock US versus other type of US
Effect size was calculated with/without intertrial interval (ITI)[c]

[a]Approximately half of the studies included patients with a PTSD.
[b]Only applicable to analyses of CS+ responding, as only these analyses include both type of conditioning paradigms.
[c]ITI measurements were not available for a significant part of the included data.

TABLE 2. List of the included continuous variables

Continuous variables
Year of publication
Sex ratio (percentage of males)
Mean age of the participants
Stimulus duration of the CS
Stimulus duration of the US
Number of CS trials during habituation
Number of US trials prior to acquisition
Number of CS trials during acquisition
Number of CS trials during extinction (*only applies to the extinction analyses*)
Contingency: probability of US reinforcement in presence of the CS+

sample). These adjustments were implemented in further calculations as well, such as effect size estimates or computed variance. A list of the continuous variables included in the series of meta-analyses is provided in Table 2.

STATISTICAL ANALYSES

Six meta-analyses were carried out to study differences between anxiety patients and control subjects: (1) simple learning during acquisition: fear responses to the CS+ (minus ITI), (2) generalization/inhibition during acquisition: fear responses to the CS− (minus ITI), (3) discrimination during acquisition: fear responses to the CS+ minus CS−, (4) simple learning during extinction: fear responses to the CS+ (minus ITI), (5) generalization/inhibition during extinction: fear responses to the CS− (minus ITI), and (6) discrimination during extinction: fear responses to the CS+ minus CS−.

Statistical multilevel meta-analyses were conducted in Hierarchical Linear and Nonlinear Modeling (HLM), version 6.0.[31] This method is commonly used to deal with multiple effect sizes within studies, as various effect sizes and studies can be included at separate levels in the analyses.[32,33] Furthermore, the inverse sampling variance weight based on the sample size was assigned to the included effect sizes in the regression analyses, as larger samples are associated with more reliable effect sizes. Weighted regression analyses were conducted in HLM to assess whether categorical and continuous study characteristics may account significantly for the variability in effect sizes between studies.[32] In the current meta-analysis, patient–control differences in fear acquisition and extinction were studied while examining the variability that is associated with various potential moderator variables. Within HLM, effect sizes served as level-1 units, categorical variables comprised level-2 units, and level-3 units included the continuous variables. Within the current meta-analysis, k refers to the number of effect sizes, and N reflects the number of studies.

ADDITIONAL ANALYSES

Additional statistical analyses were conducted to control for the influence of outliers and/or influential cases. An outlier was defined as an effect size that is at least two standard deviations above or below the pooled effect size.

Furthermore, the influence of explicit instructions about the CS–US relationship was investigated, as previous studies indicated that the use of instructions might speed up the acquisition and extinction of fear.[34–37] For that reason, all six meta-analyses were repeated without the effect sizes obtained from fully instructed conditioning paradigms.

FILE DRAWER PROBLEM

Potential publication biases were visually assessed by plotting the estimated effect sizes (*x*-axis) and sample sizes (*y*-axis) in scatterplots (one for each of six analyses). Funnel-shaped distributions would support the absence of a publication bias, as smaller studies are assumed to spread more widely at the bottom of the graph whereas larger studies are expected to be more close to the estimated pooled effect size. Furthermore, the fail-safe *N* statistic was calculated for each of six meta-analyses to estimate the number of unpublished studies with null results needed to reduce the calculated effect size below significance.

RESULTS

Forty-four studies, published between 1920 and 2013, were included in the current meta-analysis. Data for approximately 963 patients with anxiety disorders and 1,222 control subjects were combined within the meta-analysis (mean age = 34.6, 49.7% male). The total sample size (including patients and controls) per meta-analysis ranged between 1,070 and 2,383 participants. Table 3 lists all included studies, corresponding effect sizes, and part of the study characteristics.

ACQUISITION

Figure 2A displays average effect sizes of differences in fear responses between patients and controls evoked by CS+ and CS−, and shows patient–control differences in discrimination scores (CS+ and CS−).

Though no significant patient–control differences in fear responses to the CS+ were found, $d = 0.067$, $P = .411$, $N = 35$, $k = 78$, results demonstrated stronger fear responses to the CS− in anxiety patients compared to control subjects, $d = 0.296$, $P < .001$, $N = 26$, $k = 60$, with 95% confidence interval ranging from $d = 0.211$ to $d = 0.381$. Such results indicate increased fear responding to conditioned safety cues in patients with an anxiety disorder. Because safety cues in this literature are perceptually similar to danger cues, such results suggest an enhanced tendency to generalize fear from the CS+ to CS− among those with an anxiety disorder. No significant differences were found with regard to discrimination learning (CS+ minus CS−) between anxiety patients and controls, $d = -0.1541$, $P = .155$, $N = 36$, $k = 76$.

EXTINCTION

During fear extinction, patients with anxiety disorders showed stronger fear responses to the CS+ compared to control subjects, $d = 0.352$, $P = .007$, $N = 18$, $k = 55$ (95% confidence interval: 0.240–0.464), suggesting impaired extinction of conditioned fear to the previously reinforced cue among anxiety patients. No significant patient–control differences were found regarding fear responses to the CS−, $d = 0.126$, $P = .103$, $N = 14$, $k = 43$. There was a marginally significant trend for stronger discrimination learning between CS+ and CS− during extinction in patients compared to controls, $d = 0.147$, $P = .057$, $N = 21$, $k = 59$ (95% confidence interval: 0.036–0.258), suggesting retarded extinction of differential fear conditioning in anxiety patients (see also Fig. 2B).

ADDITIONAL ANALYSES

The removal of single outliers did not result in significant shifts in the pooled effect sizes. Additionally, the exclusion of the fully instructed conditioning paradigms ($N = 4$) did not have a significant influence on the results.

STUDY CHARACTERISTICS

Tables 4 and 5 show the separate regression coefficients for all continuous variables at acquisition and extinction, respectively. The continuous characteristics (included as level-3 units in HLM) did not account for a significant portion of the variability in findings across studies within the regression model. However, weighted regression analysis indicated that the categorical moderator type of control group may account for a significant proportion of the between-study variance in effect sizes during simple learning in the acquisition phase. Follow-up analyses on this effect were conducted within PTSD studies, as only these studies included both type of control groups (healthy vs. trauma-exposed control group). However, no significant influence of type of control group was found on PTSD–control differences in fear responses to the CS+ ($P > .05$).

Finally, none of the categorical study characteristics could account for a significant portion of the variability in findings within the regression model. Tables 6 and 7 display the average effect sizes for each level of all categorical variables at acquisition and extinction, respectively.

FILE DRAWER PROBLEM

Visual assessment of funnel plots provide little evidence for the presence of publication biases, as funnel plots for each of six meta-analyses show a roughly funnel-shaped distribution (see Fig. 3). In addition, fail-safe *N* was calculated to statistically assess the vulnerability of results to publication biases. Fail-safe *N* calculations suggest that 29 nonsignificant effect sizes would be needed to drop any significant pooled effect size from the current meta-analyses below significance.

TABLE 3. Effect sizes per study and outcome measurement

Author	Year	Diagnosis pt.	Control	*N* (% pt.'s)	CS	US	DV	*d* ACQ CS+	*d* ACQ CS−	*d* ACQ CS+ versus CS−	*d* EXT CS+	*d* EXT CS−	*d* EXT CS+ versus CS−
Ashcroft et al.[54]	1991	Psychiatric pt.'s with anxiety states	Healthy	60 (50)	Tones	WN	SCR	0.18	NA	NA	NA	NA	NA
Clum[55]	1969	Neurotic inpatients	Healthy	52 (67)	Tones	Shock	SCR	NA	NA	−0.77	NA	NA	NA
Fayu[56]	1961	Neurotic pt.'s	Healthy	23 (57)	Tones	Shock	SCR	0.80	NA	−0.34	NA	NA	NA
Grillon et al.[45]	1998	PTSD	TE	65 (52)	Lights	Threat of shock	FPS	NA	NA	−0.23	NA	NA	NA
Grillon and Morgan[21]	1999	PTSD	TE	24 (50)	Lights	Shock	FPS	0.52	NA	−0.47	NA	NA	−0.59
Grillon et al.[57]	2008	PD	Healthy	48 (50)	GS	Sound + picture	US exp	−0.52	NA	NA	NA	NA	NA
					GS		Anxiety	0.38	NA	NA	NA	NA	NA
							FPS	−0.10	NA	NA	NA	NA	NA
Grillon et al.[58]	2009	PTSD	Healthy	50 (32)	GS	Sound + picture	Anxiety	−0.26	NA	NA	NA	NA	NA
							FPS	0.26	NA	NA	NA	NA	NA
		GAD	Healthy	52 (35)			Anxiety	0.01	NA	NA	NA	NA	NA
							FPS	−0.97	NA	NA	NA	NA	NA
Halberstam[59]	1961	Psychasthenic outpatients	Healthy	36 (50)	Words	Shock	SCR	NA	NA	0.30	NA	NA	0.41
Hermann et al.[23]	2002	SP	Healthy	33 (42)	Faces	Odor	FPS	NA	NA	0.52	NA	NA	NA
							SCR	NA	NA	0.39	NA	NA	0.32
Howe[60]	1958	Cases of severe anxiety	Healthy	120 (50)	Tones	Shock	SCR	0.06	NA	NA	0.23	NA	NA
Jovanovic et al.[31]	2009	PTSD	TE	55 (49)	GS	Airblast in larynx	US exp	0.19	0.33	−0.28	NA	NA	NA
							FPS	0.09	0.01	−0.00	NA	NA	NA
Jovanovic et al.[41]	2010	PTSD	Healthy	90 (32)	Lights	Airblast in larynx	US exp	0.11	0.26	−0.30	NA	NA	NA
							FPS	0.01	0.22	−0.11	NA	NA	NA
Jovanovic et al.[42]	2010	PTSD	TE	67 (21)	GS	Airblast	FPS	0.29	0.37	−0.09	NA	NA	NA
Jovanovic et al.[61]	2011	PTSD	Healthy	54 (30)	GS	Airblast in larynx	US exp	−0.22	0.27	0.06	NA	NA	NA
							FPS	0.01	0.61	−0.63	NA	NA	NA
Jovanovic et al.[44]	2012	PTSD	Healthy	51 (47)	GS	Airblast in larynx	US exp	−0.96	0.76	1.88	NA	NA	NA
							FPS	−0.64	−0.61	0.24	NA	NA	NA
							SCR	−0.52	−0.63	0.42	NA	NA	NA
Jovanovic et al.[62]	2013	PTSD	Healthy	41 (49)	GS	Airblast	FPS	−0.04	0.49	0.53	−0.27	−0.43	0.20
Kircher et al.[63]	2013	PD	Healthy	84 (50)	GS	WN	Valence	0.39	0.51	−0.10	0.62	0.33	0.26
							Arousal	0.42	0.73	−0.30	0.45	0.63	−0.19
Lau et al.[64]	2008	Combination anxiety disorders	Healthy	54 (30)	Faces	Sound + picture	Anxiety	0.78	0.38	NA	NA	NA	NA

(*Continued*)

TABLE 3. Continued

Author	Year	Diagnosis pt.	Control	*N* (% pt.'s)	CS	US	DV	*d* ACQ CS+	*d* ACQ CS−	*d* ACQ CS+ versus CS−	*d* EXT CS+	*d* EXT CS−	*d* EXT CS+ versus CS−
Liberman et al.[65]	2006	Combination of anxiety disorders	Healthy	80 (64)	Picture	WN	Valence	−0.26	0.09	0.07	−0.45	0.09	−0.54
							Arousal	−0.23	0.37	−0.63	0.03	0.04	−0.07
							Anxiety	0.01	0.24	−0.22	0.37	0.16	0.21
							Control	0.01	0.07	−0.06	0.06	−0.07	0.12
							SCR	0.34	0.42	−0.12	0.49	−0.12	0.64
							FPS	NA	NA	NA	0.35	−0.20	0.58
Linnman et al.[66]	2011	PTSD	TE	43 (44)	Lights	Shock	SCR	1.61	2.21	−0.73	NA	NA	NA
Lissek et al.[67]	2008	SP	Healthy	38 (53)	Faces	comment + face[a]	Valence	0.28	−0.46	0.80	−0.00	−0.62	−0.10
							Arousal	0.14	0.51	−0.29	0.35	0.46	0.44
							Anxiety	0.57	0.23	0.30	0.47	0.02	0.48
							FPS	0.48	−0.66	1.22	−0.43	0.21	−0.66
Lissek et al.[68]	2009	PD	Healthy	48 (50)	Picture	Shock	US exp	−1.20	0.00	−1.20	−1.61	−0.27	−1.46
							Anxiety	0.00	0.38	−0.40	0.25	0.60	−0.66
							FPS	−0.58	0.37	−1.65	−0.15	−0.73	0.88
Lissek et al.[39]	2010	PD	Healthy	38 (50)	GS	Shock	US exp	−2.45	0.13	−2.84	NA	NA	NA
							Anxiety	−0.87	0.69	−1.67	NA	NA	NA
							FPS	0.08	0.20	−0.13	NA	NA	NA
Lissek et al.[40]	2013	GAD	Healthy	48 (46)	GS	Shock	US exp	−1.97	0.23	−2.53	NA	NA	NA
							Anxiety	−0.21	1.31	−1.50	NA	NA	NA
							FPS	0.23	0.71	−0.58	NA	NA	NA
Lueken et al.[69]	2013	PD	Healthy	120 (50)	GS	Tone	Valence	0.46	0.64	−0.18	0.56	0.44	0.11
							Arousal	0.60	0.89	−0.33	0.62	0.70	−0.13
Milad et al.[70]	2008	PTSD	TE	14 (7)	Lights	Shock	SCR	−0.02	−0.01	0.03	0.08	0.00	0.12
Milad et al.[71]	2009	PTSD	TE	31 (52)	Lights	Shock	SCR	0.47	0.48	−0.11	0.46	0.31	0.28
Milad et al.[72]	2013	OCD	Healthy	37 (49)	Lights	Shock	SCR	0.34	0.15	0.19	−0.20	−0.57	0.24
Miller et al.[73]	2011	PTSD	TE	63 (51)	GS	Shock	FPS	−0.01	−0.01	0.01	NA	NA	NA
Nanbu et al.[74]	2010	OCD	Healthy	60 (65)	Lights	Shock	SCR	−0.14	NA	NA	1.56	NA	NA
Norrholm et al.[75]	2011	PTSD	TE	197 (38)	GS	Airblast in larynx	US exp	0.00	0.35	−0.15	0.18	−0.27	0.48
							FPS	0.18	0.16	0.03	0.23	0.20	0.04
Norrholm et al.[76]	2013	PTSD	Healthy	270 (36)	GS	Airblast in larynx	US exp	0.00	0.16	0.01	−0.09	−0.11	0.05
							FPS	0.04	0.16	−0.18	0.32	0.29	0.02
Orr et al.[9]	2000	PTSD	TE	33 (45)	Lights	Shock	SCR	NA	NA	0.70	NA	NA	0.68
							HR	NA	NA	1.03	NA	NA	−0.10
Peri et al.[22]	2000	PTSD	Healthy	66 (55)	Lights	WN	SCR	0.26	NA	0.12	0.64	NA	−0.02
							HR	0.23	NA	−0.25	0.31	NA	0.01
			TE	56 (55)	Lights	WN	SCR	0.38	NA	−0.01	0.73	NA	0.24
							HR	−0.06	NA	−0.25	0.59	NA	−0.43
Pitman and Orr[77]	1986	GAD	Healthy	40 (50)	Faces	Shock	HR	NA	NA	0.28	NA	NA	0.37

(*Continued*)

TABLE 3. Continued

Author	Year	Diagnosis pt.	Control	*N* (% pt.'s)	CS	US	DV	*d* ACQ CS+	*d* ACQ CS−	*d* ACQ CS+ versus CS−	*d* EXT CS+	*d* EXT CS−	*d* EXT CS+ versus CS−
Reeb-Sutherland et al.[78]	2009	Combination of anxiety disorders	Healthy	66 (23)	Color	Airblast in larynx	FPS	−0.50	0.24	−0.58	NA	NA	NA
Schweckendiek et al.[38]	2011	Specific Phobia	Healthy	15 (53)	GS	Picture	SCR	0.02	−0.42	0.45	0.24	−0.42	0.77
							Valence	NA	NA	NA	0.62	−0.31	0.27
							Arousal	NA	NA	NA	−0.27	1.92	−1.39
							Anxiety	NA	NA	NA	0.87	1.02	0.12
							Disgust	NA	NA	NA	0.36	0.15	−1.63
		Specific Phobia	Healthy	15 (53)	GS	Picture[a]	SCR	0.25	NA	0.68	0.48	NA	0.93
							Valence	NA	NA	NA	8.04	NA	5.41
							Arousal	NA	NA	NA	5.03	NA	1.91
							Anxiety	NA	NA	NA	5.35	NA	3.82
							Disgust	NA	NA	NA	0.88	NA	0.47
Sloane et al.[79]	1965	Psychoneurotic inpatients	Healthy	40 (50)	Tones	Shock	SCR	1.21	NA	NA	0.99	NA	NA
Thayer et al.[80]	2000	GAD	Healthy	66 (50)	Lights	Words	HR	NA	NA	0.49	NA	NA	NA
							SCR	0.66	0.30	0.52	0.35	0.15	1.02
Van den Bergh et al.[81]	1997	Psychosomatic pt's (majority with anxiety disorder)	Healthy	56 (50)	Odor	CO_2	Respiratory frequency	NA	NA	NA	NA	NA	0.00
Veit et al.[82]	2002	SP	Healthy	11 (36)	Faces	Pressure	SCR	NA	NA	−0.91	NA	NA	NA
Vriends et al.[83]	2012	Specific Phobia	Healthy	72 (46)	Picture	Sound + picture	Valence	0.26	−0.24	0.45	NA	NA	NA
							Anxiety	0.51	0.38	0.11	NA	NA	NA
Waters et al.[84]	2009	Combination of anxiety disorders	Healthy	35 (49)	GS	Tone	Valence	−0.29	−0.03	−0.27	0.44	0.68	−0.31
							Arousal	0.61	0.15	0.44	−0.30	0.02	−0.26
							FPS	0.61	0.65	−0.05	0.63	0.23	0.40
Wessa et al.[85]	2007	PTSD	TE	29 (48)	GS	Visual cue[a]	Valence	1.09	0.17	0.54	0.85	0.02	0.65
							Arousal	0.98	0.65	0.42	1.20	0.66	0.68
							US exp	0.03	0.87	−0.00	0.97	0.57	0.32
							FPS	−0.34	−0.76	0.03	0.08	0.24	0.97
							SCR	0.49	0.48	−0.11	0.46	0.00	−0.05
			Healthy	29 (48)	GS	Visual cue[a]	Valence	0.89	0.12	0.68	1.17	0.06	0.59
							Arousal	0.96	0.51	0.63	1.26	0.47	0.47
							US exp	0.18	−0.04	1.52	0.92	1.00	−0.63
							FPS	0.09	−0.68	0.71	1.15	0.16	0.11
							SCR	0.66	0.30	0.52	0.35	0.15	1.02

[a]Disorder-specific US.

ACQ, acquisition; EXT, extinction; PD, panic disorder; pt., patient; SP, social phobia; PTSD, posttraumatic stress disorder; GAD, generalized anxiety disorder; TE, trauma-exposed control group; WN, white noise; NA, not applicable; DV, dependent variable; FPS, fear potentiated startle; SCR, skin conductance response; GS, geometric shape; HR, heart rate.

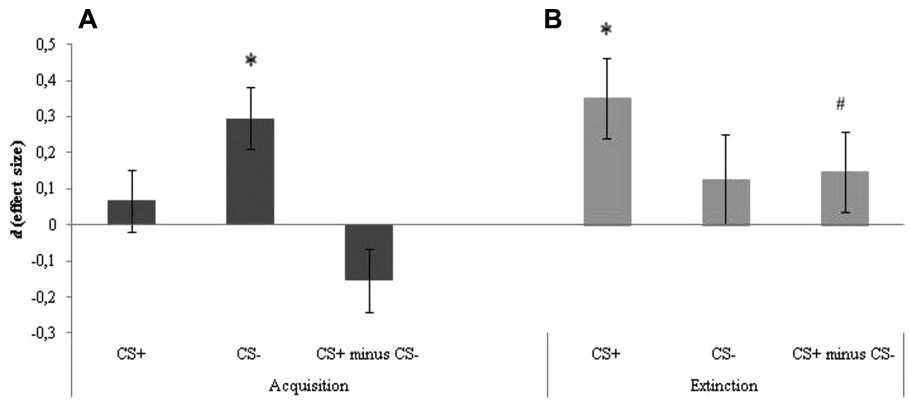

Figure 2. Graphical representation of the effect sizes per stimulus type, reflecting the standardized mean difference in fear responses between anxiety patients minus healthy controls during acquisition (A) and extinction (B). Error bars display the 95% confidence interval. *$P < .05$, #$P = .057$.

DISCUSSION

The results of 44 fear-conditioning studies were combined to update and extend the previous meta-analysis by Lissek et al.[10], thereby aiming to systematically investigate differences in the acquisition and extinction of fear between 963 patients with anxiety disorders and 1,222 control subjects. During acquisition, modestly increased fear responses to the CS− were demonstrated in anxiety patients compared to controls ($d = 0.296$, small effect size). This pattern of overgeneralization has been demonstrated in various groups of anxiety disorder patients (including patients with panic disorder[39] and generalized anxiety disorder[40]). The enhanced fear responses to the CS− could either be interpreted as anxiety patients having a stronger tendency to generalize their learned fear responses more easily to other neutral stimuli resembling conditioned danger cues, or as an impaired ability to inhibit fear to a safety cue in an aversive context.[39–46] A recent neuroimaging study indicates involvement of the hippocampus and vmPFC in responding to stimuli that resemble, but are not, the CS+, areas that have also been implied in extinction.[5] The demonstration of increased fear responses to the CS− indicates that the use of differential paradigms (including both a CS+ and CS−), compared to single cue conditioning paradigms (including CS+ only), has added value for the specification of differences in fear conditioning between anxiety patients and controls.

No support was found for patient–control differences to reinforced cues during acquisition (fear responses to the CS+). This finding may reflect ceiling effects due to the use of aversive USs that provoke similar normative fear reactions in anxiety disordered and healthy individuals.[47] The lack of enhanced CS+ responding is inconsistent with the findings from the previous meta-analysis by Lissek et al.[10]. This discrepancy may have resulted from the small fail-safe *N*'s that were found in the previous meta-analysis, suggesting that the significant pooled effect size from the previous meta-analysis may have dropped below significance due to the inclusion of nonsignificant findings from studies published since the original meta-analysis. Similar to the previous meta-analysis, no differences were found in discrimination learning (differentiation between the CS+ and

TABLE 4. Regression coefficients for all continuous variables at acquisition

	ACQ CS+		ACQ CS−		ACQ CS+ versus CS−	
Variable	*b*	SE	*b*	SE	*b*	SE
Year of publication	−0.024	0.027	−0.027	−0.027	−0.035	0.020
Sex ratio (% males)	−0.003	0.004	−0.005	−0.002	<0.001	0.004
Mean age	−0.002	0.006	0.001	0.005	0.005	0.007
Stimulus duration CS	<0.001	0.756	<−0.001	<0.001	<0.001	<0.001
Stimulus duration US	<0.001	1.324	<−0.001	<0.001	<0.001	<0.001
Number CS trials during habituation	−0.003	0.024	−0.013	0.018	0.001	0.032
Number US trials prior to acquisition	−0.016	0.023	−0.006	0.014	0.011	0.026
Number CS trials during acquisition	0.015	0.015	0.015	0.011	−0.002	0.011
Contingency	<−0.001	0.005	−0.818*	0.343	0.118	0.523

ACQ, acquisition; *b*, regression coefficient; SE, standard error.
*$P < .05$.

TABLE 5. Regression coefficients for all continuous variables at extinction

	EXT CS+		EXT CS−		EXT CS+ versus CS−	
Variable	*b*	SE	*b*	SE	*b*	SE
Year of publication	0.038	0.041	0.061	0.060	−0.03	0.027
Sex ratio (% males)	0.012	0.006	0.008	0.006	−0.002	0.006
Mean age	0.006	0.009	−0.001	0.013	−0.011	0.009
Stimulus duration CS	<0.001	<0.001	<−0.001	<0.001	<0.001	<0.001
Stimulus duration US	<−0.001	<0.001	<−0.001	<0.001	<−0.001	<0.001
Number CS trials during habituation	−0.200*	0.048	−0.005	0.079	−0.055	0.029
Number US trials prior to acquisition	−0.009	0.017	−0.009	0.015	0.012	0.023
Number CS trials during acquisition	0.117	0.028	0.023	0.040	0.013	0.010
Number CS trials during extinction	−0.018	0.018	−0.020	0.019	0.033	0.016
Contingency	−1.146	0.577	−0.001	0.719	−0.790	0.677

EXT, extinction; *b*, regression coefficient; SE, standard error.
*$P < .05$.

CS−) between anxiety patients and controls during fear acquisition.

During extinction, stronger fear responses to the CS+ were found in anxiety patients compared to control subjects ($d = 0.352$, small/medium effect size). Furthermore, patients tended to demonstrate persistent increased differentiation between the CS+ and CS− during extinction ($P = .057$, $d = 0.147$, small effect size). No differences between patients and controls were found in their fear responses to the CS− during fear extinction. Results suggest that patients with anxiety disorders have delayed and/or reduced fear extinction of the excitatory association between the CS+ and US compared to controls. Neuroimaging findings from conditioning studies in anxiety patients allow neural inferences to be drawn from meta-analytic results. Human imaging studies have translated the rodent findings that activation of ventromedial parts of the prefrontal cortex (vmPFC) is instrumental in regulating conditioned fear responding both during extinction training, and during extinction recall.[48,49] Hypoactivation of vmPFC observed in patients with PTSD[50] and phobic fear[4] may be

TABLE 6. Average effect sizes for each level of all categorical variables at acquisition

	ACQ CS+			ACQ CS−			ACQ CS+ versus CS−		
Variable	*k*	*N*	*d* (95% CI)	*k*	*N*	*d* (95% CI)	*k*	*N*	*d* (95% CI)
Outcome measure									
Psychophysiological	40	31	0.14 (±0.12)	26	22	0.23 (±0.12)*	43	33	−0.08 (±0.10)
Subjective	38	19	−0.04 (±0.13)	34	17	0.34 (±0.16)*	33	16	−0.45 (±0.17)
Diagnoses patients									
PTSD	36	16	0.14 (±0.12)	29	13	0.24 (±0.13)*	37	17	−0.09 (±0.12)
Other	42	20	0.04 (±0.12)	31	13	0.31 (±0.14)*	39	19	−0.23 (±0.13)
conditioning paradigm									
Single cue	8	5	0.08 (±0.23)			NA			NA
Discrimination	70	30	0.10 (±0.09)			NA			NA
Type US									
Disorder specific	15	3	0.15 (±0.45)	14	2	0.06 (±0.51)	15	3	0.49 (±0.46)
Nonspecific	63	33	0.06 (±0.09)	45	23	0.34 (±0.01)*	61	34	−0.25 (±0.08)*
Type US									
Shock	19	13	−0.04 (±0.16)	14	8	0.49 (±0.22)*	22	15	−0.44 (±0.16)
No shock	59	22	0.12 (±0.10)	46	18	0.23 (±0.11)*	54	21	−0.03 (±0.10)
Calculation of *d*									
With ITI	17	10	−0.39 (±0.22)	9	7	0.16 (±0.02)			NA
Without ITI	61	30	0.20 (±0.09)*	51	24	0.32 (±0.011)*			NA
Type control group									
Healthy	61	27	0.05 (±0.10)	46	19	0.26 (±0.11)*	56	26	−0.20 (±0.10)
Trauma exposed	17	10	0.30 (±0.18)*	14	8	0.44 (±0.18)	20	12	−0.06 (±0.15)

ACQ, acquisition; NA, not applicable; *k*, number of effect sizes; *N*, number of studies.
*$P < .05$.

TABLE 7. Average effect sizes for each level of all categorical variables at extinction

	EXT CS+			EXT CS−			EXT CS+ versus CS−		
Variable	*k*	*N*	*d* (95% CI)	*k*	*N*	*d* (95% CI)	*k*	*N*	*d* (95% CI)
Outcome measure									
Psychophysiological	24	16	0.34 (±0.13)*	16	12	−0.03 (±0.15)	28	19	0.20 (±0.14)*
Subjective	31	10	0.38 (±0.25)	27	10	0.26 (±0.23)*	31	10	0.12 (±0.18)
Diagnoses patients									
PTSD	21	7	0.34 (±0.16)*	17	6	0.10 (±0.17)	24	9	0.15 (±0.15)
Other	34	11	0.39 (±0.16)*	26	8	0.16 (±0.19)	35	12	0.16 (±0.16)
conditioning paradigm									
Single cue	3	3	0.89 (±0.28)			NA			NA
Discrimination	52	15	0.30 (±0.12)*			NA			NA
Type US									
Disorder specific	19	3	1.17 (±0.53)	14	2	0.19 (±0.51)	19	3	0.73 (±0.53)
Nonspecific	36	16	0.29 (±0.12)*	24	11	0.11 (±0.13)	40	19	0.03 (±0.11)
Type US									
Shock	9	7	0.24 (±0.21)	6	4	−0.12 (±0.34)	11	8	0.01 (±0.24)
No shock	46	11	0.37 (±0.33)*	37	10	0.19 (±0.13)*	48	13	0.15 (±0.13)*
Calculation of *d*									
With ITI	3	2	−0.47 (±0.26)	3	2	−0.13 (±0.26)			NA
Without ITI	52	18	0.41 (±0.12)*	40	14	0.18 (±0.14)*			NA
Type control group									
Healthy	44	15	0.39 (±0.13)*	34	11	0.16 (±0.15)	45	16	0.14 (±0.13)
Trauma exposed	11	5	0.42 (±0.24)*	9	4	0.09 (±0.25)	14	7	0.21 (±0.22)

ACQ, acquisition; EXT, extinction; NA, not applicable; *k*, number of effect sizes; *N*, number of studies.
*$P < .05$.

associated with a deficit in extinction as observed in this meta-analysis. Furthermore, the same areas of vmPFC seem to be involved in both explicitly instructed cognitive emotion regulation of conditioned fear and classical extinction training.[51] Interestingly, one session of cognitive behavioral therapy (CBT) in patients with specific phobia already resulted in strongly enhanced vmPFC activity, reductions of subjective anxiety, and reduced amygdala activity.[4] An important issue that needs to be addressed in future prospective studies is whether reduced extinction performance at baseline may predict poor CBT treatment success.

Results from the current meta-analysis are in line with earlier prospective studies demonstrating that heightened fear responses during extinction might reflect a vulnerability factor for the development of anxiety disorders.[17–20] Interestingly, recent findings indicated that these differences do not persist after treatment, but that instead only those participants (across patient and control group) who reported high anxiety symptoms demonstrated impaired extinction (Duits et al., 2014). Together, these results contribute to our knowledge about whether enhanced excitatory fear conditioning and/or impaired extinction may be a temporary phenomenon that is associated with the anxiety disorder, or whether it reflects a more stable characteristic that may persist regardless of disorder status after treatment. The use of prospective, longitudinal studies is recommended to further examine the course of individual differences in fear conditioning. Findings from the weighted regression analyses indicated that none of the study characteristics, such as the type of fear measure (subjective vs. psychophysiological index of fear) or diagnostic group (PTSD vs. other anxiety disorder), could significantly account for the variance in effect sizes across studies within the regression model. The failure to find a significant influence of moderator variables may have resulted from methodological differences across studies, for example, unequal distribution of moderator variables across studies and the unknown influence of other potential moderator variables that were not included in the current study.

One limitation of the current meta-analysis is the exclusion of fear-conditioning studies that met our inclusion criteria, but did not provide sufficient statistics to calculate the corresponding effect sizes. In 21 of these studies, statistics were subsequently provided by the authors upon request, but of 10 studies no additional data were available. Exclusion of these studies may have resulted in overestimated pooled effect sizes. However, visual and statistical inspection of the file drawer problem did not indicate an upwardly biased effect size, and suggested that at least 29 nonsignificant findings are needed to reduce the current significant findings regarding patient–control differences in fear conditioning below significance. Another limitation concerns the availability of ITI measurements. By taking ITI measurements into account for the calculation of effect sizes, the influence of sensitization and habituation on the pooled effect size

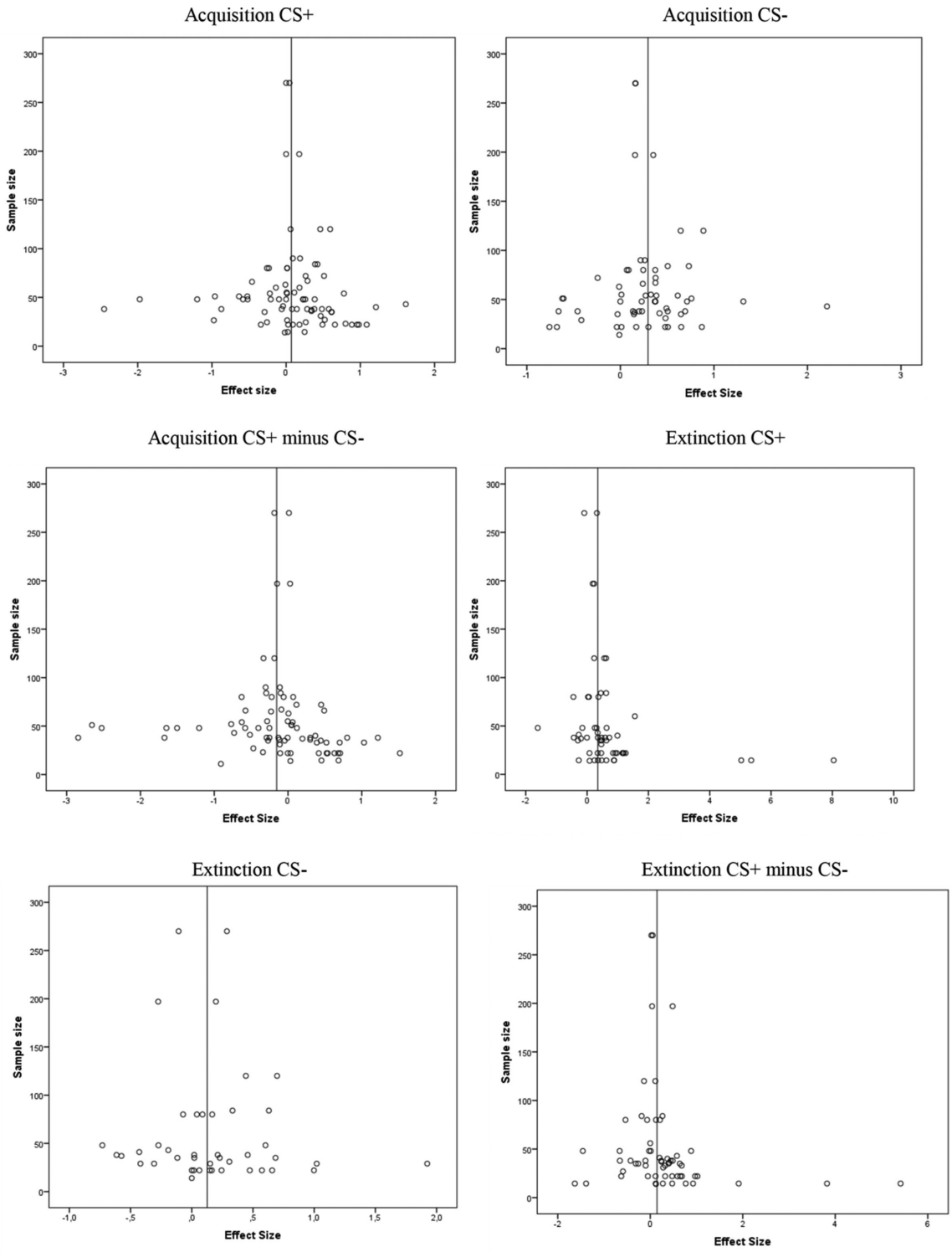

Figure 3. Funnel plots for all six meta-analyses.

can be minimized. However, as these ITI measurements have not been available for each included outcome measurement, this may have led to an overestimation of the pooled effect size.

The current meta-analysis provides a good starting point for the systematic investigation of patient–control differences in acquisition and extinction of cue-specific fear responses. Despite methodological heterogeneity

and different groups of anxiety disorder patients across studies, a small yet robust pattern of overgeneralization of the fear responses to safe cues presented in the potentially threatening context of acquisition was observed. Based on the current data, it was not possible to investigate whether such lack of safety learning is also present in patients with more circumscribed fears such as specific phobias. The research tradition has always been to select patients of a single diagnostic group (mostly PTSD) and then compare—in this case fear conditioning—between one clinical group and a control sample. Future research to investigate differences in fear learning using one single paradigm across the entire anxiety disorder spectrum can overcome this hiatus. Such studies can investigate whether patient groups can be better distinguished based on deficits in fear learning than on the basis of their category of anxiety disorder. This dimensional approach is in line with the NIMH Research Domain Criteria (RDoC) initiative.[52] The second major finding of the current meta-analyses shows that once acquired, fear responses to the CS+ seemed to be more resistant to extinction in patients with anxiety disorders compared to controls. Whether this is due to persistently increased risk perception or a lack in the capacity to down-regulate fear expression needs to be investigated in the future.

RECOMMENDATIONS

Finally, the use of differential paradigms (including both a CS+ and CS−) is recommended to increase the sensitivity to detect patient–control differences. In addition, the use of prospective studies is recommended to study the course of individual differences in fear conditioning, for instance to investigate whether conditionability changes over time or whether it reflects a stable characteristic. Furthermore, the use of prospective studies enables to investigate the predictive value of fear extinction on treatment outcome, as fear extinction and response to exposure treatment (the treatment of choice in anxiety disorders) are likely to be closely related.[12,53]

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