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# Classical fear conditioning in the anxiety disorders: a meta-analysis ☆

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**Abstract**

Fear conditioning represents the process by which a neutral stimulus comes to evoke fear following its repeated pairing with an aversive stimulus. Although fear conditioning has long been considered a central pathogenic mechanism in anxiety disorders, studies employing lab-based conditioning paradigms provide inconsistent support for this idea. A quantitative review of 20 such studies, representing fear-learning scores for 453 anxiety patients and 455 healthy controls, was conducted to verify the aggregated result of this literature and to assess the moderating influences of study characteristics. Results point to modest increases in both acquisition of fear learning and conditioned responding during extinction among anxiety patients. Importantly, these patient-control differences are not apparent when looking at discrimination studies alone and primarily emerge from studies employing simple, single-cue paradigms where only danger cues are presented and no inhibition of fear to safety cues is required.
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## Introduction

Fear conditioning involves the pairing of a neutral stimulus with an aversive unconditioned stimulus (US). The neutral stimulus initially elicits no emotional reaction, but after repeated pairings with the US, the neutral stimulus becomes a conditioned stimulus (CS) signaling imminent US onset and inducing anxiety associated with the anticipation of the aversive US. Although fear conditioning is generally an adaptive and self-preserving form of learning, such conditioning may become a source of pathology when anxious reactivity to a CS persists in the absence of a CS/US contingency.

Formal theories have implicated fear conditioning in the pathogenesis of anxiety disorders for at least 80 years (Pavlov, 1927; Watson & Rayner, 1920). Renewed enthusiasm for this work (e.g., Gorman, Kent, Sullivan, & Coplan, 2000; Grillon & Morgan, 1999; Pine, 1999) has followed from (1) the introduction of more complex conditioning models accounting for the dynamic context in which fears and anxieties manifest (e.g., Mineka & Zinbarg, 1996), (2) recent findings from basic research in animals delineating specific temporal-lobe circuits engaged by fear conditioning (reviewed by Blair, Schafe, Bauer, Rodrigues, & LeDoux, 2001), and (3) evidence supporting the contributions of similar brain areas to fear learning in humans (e.g., Bechara et al., 1995; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). Clarification of fear-conditioning differences across anxiety patients and healthy controls is likely to benefit future efforts to elucidate the neurobiological loci of clinical anxiety.

The conditioning model of anxiety disorders, as it was originally formulated, asserted that pathological anxiety (neurosis) develops by way of simple classical conditioning (Pavlov, 1927; Watson & Rayner, 1920). Later theorists expanded on this formulation and shifted toward a model in which classically conditioned fear acts as a drive that motivates and reinforces avoidance (Eysenck, 1976, 1979; Eysenck & Rachman, 1965; Miller, 1948; Mowrer, 1947, 1960). Other permutations of this learning theory emphasized the role of incubation of fear (Eysenck, 1979), evolutionarily prepared aversive associations (e.g., Öhman, 1986; Seligman, 1971), failure to inhibit the fear response to safety cues (Davis, Falls & Gewirtz, 2000), associative learning deficits (Grillon, 2002), stimulus generalization (Mineka & Zinbarg, 1996; Watson & Rayner, 1920), and enhanced *conditionability* (Orr et al., 2000; Peri, Ben Shakhar, Orr, & Shalev, 2000) in the formation and persistence of anxiety disorders.

Although learning accounts of pathological anxiety have been the target of much criticism (for reviews, see Rachman, 1977, 1991), this perspective has received wide support from the psychological and psychiatric communities. Over the years, the model has received validation from three sources: (1) the effectiveness of exposure therapy for treating anxiety disorders (e.g., Barlow, 2002; Marks, 1978), (2) findings pointing to increased rates of pathological anxiety among combat and trauma survivors (e.g., Dohrenwend & Shrout, 1981; Green et al., 1990; Lewis & Engle, 1954), and (3) mixed support from retrospective accounts of conditioning precipitants among anxiety patients (for a review, see Rachman, 1991). A further source of validation may potentially emerge from laboratory-based fear-conditioning studies. From 1947 to date, 20 methodologically heterogeneous studies applying lab-based paradigms to compare fear-conditioning processes between anxiety patients and controls have yielded mixed results. The current study provides a meta-analysis of this literature to (i) clarify the overall effect of fear-conditioning differences among anxiety patients and controls and to (ii) explore the extent to

which specific study parameters account for variability in findings across studies. The only existing examination of this literature is a narrative review published in 1959 (Stewart et al., 1959), suggesting a tendency for slower extinction (EXT) among neurotic patients. The current study represents an updated review as well as the first quantitative analysis of this literature.

Given the topic of the current paper, it might be useful to specify what is meant by the emotional state of *fear*. The definition of fear adopted by the current study draws from Davis's (1998) notion that fear is a phasic, apprehensive arousal to an explicit threat of an aversive stimulus dissociable from a more long-term state of *anxiety* elicited by more diffuse threat cues (e.g., contextual cues).

### *Theoretical and empirical support for directional hypotheses*

Prior theories generate specific predictions concerning the relationship between fear conditioning and clinical anxiety. Eysenck (1979) proposed that pathological anxiety results primarily from a failure to extinguish the fear-conditioned response (CR). Eysenck argued that the CR (i.e., an internal state of fear) is "nocive" or uncomfortable and may serve as an aversive US substitute. Thus, reinforcement of the CS may continue during EXT if the CR is elicited by the CS. Of note, Eysenck's theory applies only to conditioning of the Pavlovian B type, whereby the CR largely reproduces the unCR to the US (for a full description of the Pavlovian A and B distinction, see Grant, 1964).

Eysenck's formulation implies that anxiety patients (or susceptible individuals) will acquire stronger fear learning than controls that will result in more reinforcement of the CS in the absence of the US (i.e., stronger CRs during EXT). Such differentially stronger reinforcement of the CS in the absence of the US should then lead to lower rates of EXT among individuals disposed to anxiety disorders. The implications of this theory afford two testable predictions: (a) anxiety patients compared to controls will show larger conditioned fear responses during acquisition (AQC) and (b) anxiety patients vs. controls will show more resistance to EXT. The plausibility of these two predicted outcomes co-occurring is supported by studies reporting positive relations between strength of the CR at AQC and EXT (e.g., Annau & Kamin, 1961; Hilgard & Marquis, 1940).

A more recent theory comes from Davis and colleagues (Davis et al., 2000), who propose that pathological anxiety may result from a failure to inhibit the fear response in the presence of safety signals. This idea receives support from several fear-conditioning experiments including a study reporting fear-potentiated startle (FPS) during exposure to the CS− (CS− is a conditioned stimulus unpaired with the US that functions as a safety signal in aversive learning paradigms) among anxiety patients but not healthy controls (Grillon & Morgan, 1999), a finding of reduced FPS in the presence of safety cues among low but not high anxious participants (Grillon & Ameli, 2001), two studies finding larger electrodermal responses to CS− among anxiety patients vs. controls (Orr et al., 2000; Peri et al., 2000), as well as two studies reporting increased subjective anticipatory anxiety following CS− presentations among anxiety patients vs. controls (Clum, 1969; Hermann, Ziegler, Birbaumer, & Flor, 2002). Because studies in the target literature do not directly compare fear inhibition effects across patients and controls, Davis's theory cannot be directly tested in the current analysis. Nevertheless, as described below, this theory has

implications for levels of discrimination fear conditioning that would be predicted to occur in anxiety patients relative to healthy controls.

During simple conditioning, a single CS is repeatedly paired with the US and within-subject conditioning effects are indexed by subtracting baseline or inter-trial-interval (ITI) levels of arousal from levels of arousal elicited by the CS. In discrimination paradigms, there are generally two CSs. One CS is paired with the US (i.e., CS+) and the other is not (i.e., CS−). Discrimination learning is indexed as the difference between CRs to the CS+ and CS−. If patients do in fact fail to inhibit fear in the presence of safety cues, they should display the fear response to both CS+ and CS−, leading to low levels of discrimination learning even if they actually do condition to the CS+. Conversely, healthy controls should be better able to suppress the fear response during CS− presentations and may therefore show higher rates of discrimination learning. It should be noted that enhanced responding to both CS+ and CS− among patients may also be conceptualized as stimulus generalization, yet either conceptualization (i.e., stimulus generalization or failure to inhibit fear) supports the above predictions regarding discrimination learning.

An opposing prediction for discrimination effects across patients and controls comes from the work of Orr and colleagues who assert that individuals prone to pathological anxiety may be more *conditionable* than their healthy counterparts (Orr et al., 2000; Peri et al., 2000). Here *conditionability* is operationalized as the extent to which responding to the CS+ exceeds CS− during AQC and/or EXT. In contrast with predictions following from Davis's model, this theory predicts heightened discrimination conditioning among anxiety patients at both AQC and EXT and receives some support from empirical tests of the model (Orr et al., 2000; Pitman & Orr, 1986). The competing predictions of models by Davis and Orr will be examined in the current analysis.

Because simple conditioning is not influenced by inhibitory effects (only excitatory conditioning to the CS is measured), and because models by Eysenck and Orr lead to predictions of greater AQC and resistance to EXT of excitatory fear associations among patients, simple fear conditioning is predicted to be stronger in patients vs. controls at both AQC and EXT. Of note, Davis and colleagues' theory proposes only inhibitory mechanisms in the pathogenesis of anxiety disorders and no predictions regarding excitatory learning (e.g., simple conditioning) can be derived from their formulation.

*Phobic anxiety and preparedness*

Seligman (1971) proposed that humans are biologically prepared to form aversive associations to stimuli that have been survival relevant through the course of evolution (e.g., snakes, spiders, closed spaces). This proposition has received much empirical support (for a review, see Mineka & Öhman, 2002) and has become a central component of contemporary learning accounts of phobic anxiety. Unfortunately, "preparedness" effects could not be meta-analyzed in the current study because very few published studies, to date, examine conditioning to prepared stimuli across anxiety patients and healthy controls.

*Summary of directional hypotheses*

Relative to healthy controls, anxiety patients were predicted to display: (a) more overall AQC of fear conditioning, (b) more overall resistance to EXT, (c) more AQC of simple fear

conditioning, and (d) more resistance to EXT of simple fear conditioning. Additionally, we tested the competing predictions regarding discrimination learning with larger and smaller levels of discrimination learning among controls supporting the perspectives of Davis et al. (2000) and Orr et al. (2000), respectively.

### *Exploratory effects to be tested*

In addition to testing the above hypotheses, exploratory analyses were planned to test other consistently reported study qualities that tended to vary across studies (see Tables 3-5 for a complete list of exploratory independent variables). Many of these potential moderators have been shown to influence conditioning phenomena in animal and human samples, yet their relevance to pathological anxiety remains relatively unknown. For this reason, such analyses are exploratory in nature and no a priori predictions were specified.

Although the role of conditioning processes in clinical anxiety is thought to vary by type of anxiety disorder (for a review, see Mineka & Zinbarg, 1996), the limited available data in the target literature precluded testing disorder-specific hypotheses.

## Method

### *Literature search and selection criteria*

Relevant studies were identified primarily through a computerized database search of journal articles and dissertations via PsycLIT and Medline for the years 1920–2003 using the key words *conditioning*, *conditioned*, *anxiety*, *anxious*, *fear*, *phobia*, *phobic*, *panic*, *neurosis*, *patient*, and *disorder*. If the title or abstract of a paper included the search term *conditioning* or *conditioned* together with one of the other key words, the entry was included in an initial pool of potential studies. In addition, reference lists from retrieved articles as well as book chapters and review articles were inspected to generate a list of all possible published studies. Finally, dissertation abstracts were searched and unpublished data were requested from researchers who study fear-conditioning processes in clinical samples, although no unpublished data were retrieved through such solicitations.

These search strategies generated a list of approximately 2400 articles in the English language. Only 45 of these 2400 studies actually conditioned anxiety patients and controls in the laboratory. Many of the other studies were assessments of individuals with subclinical elevations in anxiety, explorations of retrospective accounts of conditioning precipitants, assessments of emotional reactivity to trauma cues among trauma survivors, or theoretical papers and literature reviews.

These 45 articles were retrieved and examined for all of the following inclusion criteria: (a) anxiety patients were compared to healthy controls; (b) anxiety diagnosis, or lack thereof, was established with formal diagnostic assessments (studies testing college students with subclinical elevations in anxiety, in the absence of an anxiety disorder, were excluded); (c) the study examined classical, as opposed to operant, aversive conditioning; (d) the CR was measured via

psychophysiological measures with demonstrated ability to index anxious arousal (e.g., skin-conductance response, FPS); and (e) the CR was not measured via eyelid conditioning.[1]

In total, our search strategies yielded 20 studies suitable for the current analysis. Three of these 20 studies employed *instructed conditioning*, whereby participants are instructed of the CS/US relationship at the outset of the experiment and typically do not experience the temporal pairing of the CS and US. Because past investigations of instructed fear learning demonstrate similar levels of fear AQC when participants do or do not experience the CS/US association (Bridger & Mandel, 1964; Mandel & Bridger, 1973), instructed conditioning studies were included in the current study. Of note, instructed and experienced learning have been found to produce different EXT results (Bridger & Mandel, 1964); however, none of the three instructed conditioning studies assessed EXT of fear learning.

### *Computing effect sizes*

In the current analysis, effect sizes index differences in ACQ or EXT of fear learning between anxiety patients and healthy controls. Positive effect sizes indicate greater conditioned responding among anxiety patients vs. controls (i.e., stronger ACQ or weaker EXT among patients), and negative effect sizes indicate lower levels of conditioned responding among patients vs. controls (i.e., weaker ACQ or stronger EXT among patients).

Effect sizes for individual studies in the current meta-analyses were estimated using the unbiased estimator *d* (Hedges & Olkin, 1985). This index was selected because it corrects for bias in estimation of the population effect size (Hedges & Olkin, 1985). Computer programs such as Meta-Analysis Programs, Version 5.3 (Schwarzer, 1989) and DSTAT (Johnson, 1989) were used to compute all effect size estimates.

When studies reported conditioning results for patients and controls separately, two within-group effect sizes were estimated (i.e., one for patients and one for controls) and the difference between the two was calculated using Cohen's *q* (Cohen, 1988, pp. 109–143). The *q* statistic is not a simple function of the difference between two effect sizes (*d*) because the same difference between effect sizes would result in different outcomes depending on where along the *d* scale the difference occurred. Rather, the effect size *d* is converted to an *r* statistic and then transformed using Fisher's $z(z = \frac{1}{2}\log_e + (1r/1 - r))$. The *q* statistic is the difference between Fisher *z*'s across groups. Cohen applies Fisher's *z* because intervals along the scale remain equal and thus differences of the same magnitude can be detected regardless of the sizes of either *z*. According to Cohen (1988, pp. 109–143), *q* reflects an effect size index comparable to those found in the *d* family of effects and can be converted to *d* by transforming *q* to *r*, and then back to *d*.

In three discrimination studies (i.e., Fayu, 1961; Grillon & Morgan, 1999; Peri et al., 2000), data were available to calculate both discrimination and simple-learning effect sizes. In a fourth discrimination study (Schneider et al., 1999), only data necessary to compute effects of simple learning were reported. In these four instances, simple-conditioning effect sizes reflect simple-conditioning processes elicited within discrimination paradigms. Such simple effects were derived

[1]This final criteria followed from considerable doubts that the USs used for eye blink conditioning are aversive enough to elicit fear conditioning and because eye blink conditioning but not classical fear conditioning involves motor learning (Ramnani, Toni, Josephs, Ashburner, & Passingham, 2000).

by contrasting levels of arousal following the CS+ with baseline levels of arousal (i.e., pre-ACQ or ITI levels) for patients and controls separately.

*Application of the random effects model*

Because studies from the target literature span a 56-year period (1947–2003), the experimental context, instrumentation, and scientific standards are likely to have varied across studies in multiple ways that cannot be gleaned by even the most careful reading of the study report. These unknown study differences are likely to lead to random effects variance that can only be accounted for through the use of a random effects model (REM) (Hedges, 1994). REM was thus applied during aggregation of effects to estimate the effect size delta, as stipulated by Hedges and Olkin (1985, p. 199), with the use of Meta-Analysis Programs, Version 5.3 (Schwarzer, 1989).

*Effect-size aggregation*

Weighted grand means for ACQ, EXT, and each level of a given categorical moderator were computed, whereby individual effect sizes were weighted by an estimate of the inverse of its sampling variance (Hedges & Olkin, 1985, p. 110). Such a weighting scheme gives greater weight to more precise effect-size estimates (Matt & Cook, 1994).

*Independence of error terms*

To maintain independence, only one data point from each sample was included in any given aggregation of effect sizes as recommended by Gleser and Olkin (1994). Because effect sizes for ACQ and EXT often come from the same study, it was necessary to analyze ACQ and EXT data separately for all univariate analyses. The specific steps taken to ensure independence for each effect-size aggregation are noted in Tables 3 and 4.

Additionally, hierarchical linear modeling (HLM) was used to handle dependencies during analyses of moderators for which more than one level was represented in a given study. HLM allows for the analysis of dependent data points by controlling potential autocorrelations through standard error adjustments (Bryk & Raudenbush, 1992).

*Testing the file-drawer problem*

*Estimating fail-safe N*

Fail-safe $N$ was calculated for all effect-size subsets to estimate the number of unpublished studies with effect sizes of zero needed to reduce the aggregated effect below significance (Rosenthal, 1979). Fail-safe $N$ was not computed for effect-size aggregations producing nonsignificant results.

*Visual assessment of funnel plots*

An additional diagnostic for the assessment of publication bias includes the generation of a sample size ($y$-axis) by estimated effect size ($x$-axis) scatterplot for all effects included in analyses

(Light and Pillemer, 1984). Because studies with smaller sample sizes will usually show more variability in effect size, the scatterplot should be the widest at the bottom (i.e., where sample size is smallest) and should progressively narrow as it moves up the *y*-axis (i.e., as the sample size increases) creating a funnel-like shape. Deviations from this expected form indicate file-drawer bias in the target sample of studies.

### *Coding study qualities*

An exhaustive list of study qualities coded categorically and continuously is included in Tables 3 and 5, respectively.

### *Coding validation*

Agreement between raters was assessed with inter-rater reliability (IRR) coefficients. Simple percent agreement rates were computed by dividing items agreed upon by the total number of items coded (i.e., 21). Additionally, reliability of coding was assessed on an item-by-item basis using Cohen's kappa (Cohen, 1960) for categorical data and inter-coder correlations for continuous data as recommended by Orwin (1994). Reliability coefficients of .70 and higher are thought to suffice (Nunnally, 1978), and thus variables with IRRs $\geqslant$.70 were considered for analysis. Discrepancies between coders for variables receiving IRRs $\geqslant$.70 were resolved during coding meetings prior to moderator analyses.

### *Reliability of coding*

The mean percent agreement between raters for all 21 variables across the 20 studies was .92 ($SD = .04$). An item-by-item analysis of IRR yielded a mean kappa of .79 ($SD = .27$) for the six categorical variables and a mean $r$ of .95 ($SD = .14$) for the 15 continuous variables. Additionally, no variables received IRRs $<$.70, and thus all 21 were retained for analysis.

### *Categorical moderator analyses*

Weighted mean effect sizes from different levels of the same moderator were compared with $Q_b$ tests using DSTAT (Johnson, 1989). The $Q_b$ statistic is a between-group homogeneity test derived from formulae found in Hedges and Olkin (1985) that is analogous to a pairwise comparison when there are only two categories in the model.

### *Moderators introducing dependencies reanalyzed with HLM*

Because all effects included in subsets compared via the $Q_b$ statistic must be derived from independent samples to avoid violations of independence, several data points were omitted during $Q_b$ analyses. In order to capitalize on all available data, contrasts including multiple within-study effect sizes were reanalyzed using HLM, a technique capable of handling dependent data by accounting for correlations between observations. HLM, using a repeated measures design, was computed using the SAS mixed model procedure (Littell, Milliken, & Stroup, 1996).

*Continuous moderator analyses*

Separate weighted least-squares analyses (effects weighted by sample size) for ACQ and EXT were conducted to examine the influence of continuous variables on effect sizes. For such analyses, the adjustment to the standard error recommended by Hedges (1994) was applied and 95% confidence intervals for the unstandardized regression coefficients were constructed with these corrected standard errors. A confidence interval not including 0 indicates that the moderator accounts for a significant portion of the variability in effect sizes when alpha is set at .05.

Of note, all meta-analyses were conducted with and without effect sizes estimated only from narrative reports of significance.

*Instructed conditioning studies omitted from three analyses*

Instructed conditioning studies were omitted from continuous moderator analyses testing effects of the number of CS+/US pairings, because during instructed conditioning the CS/US association is formed by a single instruction and thus the number of ACQ trials may be irrelevant. Similarly, analysis of CS and US durations did not include instructed conditioning effects because such effects are likely due to the instructed threat of shock rather than to actual stimulus properties of the CS and US. Finally, analysis of the number of pre-ACQ exposures to the CS and US did not include instructed conditioning effects for the following reason. Pre-ACQ exposures to the CS and US (i.e., unpaired presentations) are thought to counteract the CS/US association acquired during conditioning. During instructed conditioning, such CS and US exposures are counteracted by the instructed CS/US relationship rather than actual CS/US pairings. As a result, effects of CS and US pre-exposures are thought to operate uniquely in instructed vs. traditional conditioning and instructed conditioning effects were thus omitted from these analyses.

## Results

Forty-six effect sizes were computed from the 20 studies in the target literature. Of the 46 effect sizes, 25 (55%) were positive, eight (17%) were negative, and 13 (28%) were zero.

Tables 1 and 2 display effect sizes, confidence intervals, and relevant study characteristics for each study included in the analysis. Tables 3 and 4 display weighted means and associated statistics for each level of all categorical moderators at ACQ and EXT, as well as contrasts comparing different levels of a given moderator. Additionally, Table 5 displays results of weighted least-squares regression analyses of continuous moderators.

*Visual assessment of funnel plot*

The funnel plot including all 46 effect sizes is displayed in Fig. 1. Although the plot roughly takes the form of a "funnel", the lower right-hand side of the plot is more dense than the lower left-hand side, suggesting a publication bias against negative effect sizes from small samples. Such a bias may artificially inflate patient-control conditioning differences estimated by current analyses. The relative vulnerability of aggregated effect sizes to this bias will be reported below by way of fail-safe *N*'s.

Table 1
AQC effect sizes and related parameters

| Study | Dx | *N* (% pt.'s) | Type | CS | US | DV | Contingency | Contiguity | Pre-exposure | | # Trials | | *d* | $d_{combine}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CS | US | ACQ[e] | EXT | | |
| Ashcroft, Guimarães, Wang, and Deakin (1991) | Psychiatric pt.'s with "anxiety states" scoring ⩾2 on the Goldberg clinical interview schedule of observed anxiety and/or depression | 60 (50) | Simp | Tones | WN | SCR | 1.00 | Delay | 10 | 0 | 1 | NA | .18 | — |
| Clum (1969) | "Neurotic inpatients" (diagnostic measure not indicated) | 52 (67) | Disc | Tones | Shock | SCR | .60 | Missing | 15 | 0 | 15 | NA | −.77** | — |
| Fayu (1961) | "Neurotic pt.'s" (diagnostic measure not indicated) | 23 (57) | Disc | Tones | Shock | SCR | .89 | Delay | 2 | 2 | 16 | NA | −.34 | .23 |
| | | 23 (57) | Simp[a] | Tones | Shock | SCR | .89 | Delay | 2 | 2 | 16 | NA | .80 | |
| Grillon, Ameli, Goddard, Woods, and Davis (1994) | Panic disorder (DSM-III-R) | 83 (41) | Disc | Lights | Threat of shock | FPS | NA | Delay | NA | NA | NA | NA | NS | — |
| Grillon and Morgan (1999) | PTSD (DSM-III-R) | 24 (50) | Disc | Lights | Shock | FPS | .80 | Delay | 4 | 0 | 8 | 6 | −.47 | .02 |
| | | 24 (50) | Simp[a] | Lights | Shock | FPS | .80 | Delay | 4 | 0 | 8 | 6 | .52 | |
| Grillon, Morgan, Davis, and Southwick (1998) | PTSD (DSM-III-R) | 65 (52) | Disc | Lights | Threat of shock | FPS | NA | Delay | NA | NA | NA | NA | −.23 | — |
| Halberstam (1961)[f] | "Psychasthenic outpatients"[f] (MMPI) | 36 (50) | Disc | Words | Shock | SCR | 1.00 | Trace | 0 | 2 | 21 | 4 | .30 | — |
| Hermann et al. (2002) | SOPH (ADIS-R; German version) | 33 (42) | Disc | Faces[c] | Odor | SCR | 1.00 | Delay | 10 | 10 | 60 | 25 | .39 | .30 |
| | | 33 (42) | Disc | Faces[c] | Odor | FPS | 1.00 | Delay | 10 | 10 | 60 | 25 | .52 | |
| | | 33 (42) | Disc | Faces[c] | Odor | HR | 1.00 | Delay | 10 | 10 | 60 | 25 | NS | |
| Howe (1957) | "Diagnosed as acute or chronic cases of severe anxiety" (diagnostic measure not indicated) | 120 (50) | Simp | Tones | Shock | SCR | 1.00 | Trace | 4 | 3 | 8 | 8 | .06 | — |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Morgan, Grillon, Southwick, Davis, and Charney (1995) | PTSD (DSM-III-R) | 19 (47) | Disc | Lights | Threat of shock | FPS | NA | Delay | NA | NA | NA | NA | NS | — |
| Orr et al. (2000) | PTSD (DSM-IV) | 33 (45) | Disc | Lights | Shock | SCR | 1.00 | Delay | 5 | 4 | 5 | 10 | .70 | .86 |
| | | 33 (45) | Disc | Lights | Shock | EKG | 1.00 | Delay | 5 | 4 | 5 | 10 | 1.03 | |
| Peri et al. (2000) | PTSD (DSM-III-R) | 66 (55) | Disc | Lights | WN | SCR | .80 | Delay | 2 | 0 | 8 | 6 | .13 | −.07 |
| | | 66 (55) | Disc | Lights | WN | EKG | .80 | Delay | 2 | 0 | 8 | 6 | −.26 | |
| | | 66 (55) | Simp[a] | Lights | WN | SCR | .80 | Delay | 2 | 0 | 8 | 6 | .26 | .25 |
| | | 66 (55) | Simp[a] | Lights | WN | EKG | .80 | Delay | 2 | 0 | 8 | 6 | .23 | |
| Pitman and Orr (1986) | GAD (DSM-III) | 40 (50) | Disc | Faces[b] | Shock | SCR | 1.00 | Delay | 5 | 4 | 5 | 10 | .28 | — |
| Schneider et al. (1999) | SOPH (DSM-IV) | 24 (50) | Simp[a] | Faces[c] | Odor | $fMRI_{amyg}$ | 1.00 | Delay | 10 | 10 | 40 | 20 | .85* | .43 |
| | | 24 (50) | Simp[a] | Faces[c] | Odor | EKG | 1.00 | Delay | 10 | 10 | 40 | 20 | NS | |
| Sloane, Davidson, Staples, and Payne (1965) | "Psychoneurotic inpatients" (chose pt.'s who complained of anxiety obsessions, or fears) | 40 (50) | Simp | Tones | Shock | SCR | .80 | Trace | 0 | 0 | 40 | 20 | 1.21*** | — |
| Thayer, Friedman, Borkovec, Johnsen, and Molina (2000) | GAD (ADIS-R with a severity $\geqslant 4$) | 66 (50) | Disc | Lights | Threat words | EKG | 1.00 | Delay | 0 | 0 | 10 | NA | .49*[d] | — |
| Veit et al. (2002) | SOPH (DSM-IV) | 11(36) | Disc | Faces[c] | Painful pressure | SCR | 1.00 | Delay | 8 | 0 | 16 | 8 | −.91 | — |

*Note*: Contingency = probability of receiving a US in the presence of a CS, minus the probability of receiving a US in the absence of a CS (Alloy & Abramson, 1979); contiguity = the temporal relationship between CS and US during CS/US pairings; CS = conditioned stimulus; US = unconditioned stimulus; DV = dependent variable; ACQ = acquisition; EXT = extinction; $d$ = Hedges' $g$. Positive and negative values signify stronger and weaker levels of AQC among patients vs. controls; $d_{combined}$ = average of within-study $d$'s; PTSD = posttraumatic stress disorder; SOPH = social phobia; GAD = generalized anxiety disorder; Disc = discrimination; Simp = simple; SCR = skin-conductance response; FPS = fear-potentiated startle; EKG = electrocardiogram; $fMRI_{amyg}$ = functional magnetic resonance imaging of the amygdala; NA = not applicable; NS = study reported effect as nonsignificant and the effect was estimated as ".00".

*$p \leqslant .05$. **$p \leqslant .01$. ***$p \leqslant .001$.

[a]Simple-conditioning processes measured within a discrimination paradigm.

[b]Neutral and angry faces averaged together.

[c]Neutral facial expressions.

[d]Effect size estimated from narrative report of "significance" by assigning the effect a $t$ value of 2 as recommended by Hunter and Schmidt (1990).

[e]Number of CS+ trials.

[f]Psychasthenia is perhaps most comparable to obsessive–compulsive disorder (Grivois, Deniker, & Ganry, 1992; Lanteri-Laura, 1994).

Table 2
EXT effect sizes and related parameters

| Study | Dx | *N* (% pt.'s) | Type | CS | US | DV | Contingency | Contiguity | Pre-exposures | | # Trials | | *d* | $d_{combine}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CS | US | ACQ[e] | EXT[e] | | |
| Del-Ben et al. (2001) | Panic disorder (DSM-IV) | 24 (63) | Simp | Tones | WN | SCR | 1.00 | Delay | 10 | 0 | 1 | 10 | NS | — |
| Grillon & Morgan (1999) | PTSD (DSM-III-R) | 24 (50) | Disc | Lights | Shock | Blink | .80 | Delay | 4 | 0 | 8 | 6 | −.59 | — |
| Halberstam (1961) | "Psychasthenic outpatients" (MMPI) | 18 (50) | Disc | Words | Shock | SCR | 1.00 | Trace | 0 | 2 | 21 | 4 | .41 | — |
| Hermann et al. (2002) | SOPH (ADIS-R; German version) | 33 (42) | Disc | Faces[c] | Odor | SCR | 1.00 | Delay | 10 | 10 | 60 | 25 | .32 | .11 |
| | | 33 (42) | Disc | Faces[c] | Odor | FPS | 1.00 | Delay | 10 | 10 | 60 | 25 | NS | |
| | | 33 (42) | Disc | Faces[c] | Odor | HR | 1.00 | Delay | 10 | 10 | 60 | 25 | NS | |
| Howe (1957) | "Diagnosed as acute or chronic cases of severe anxiety" (diagnostic measure not indicated) | 120 (50) | Simp | Tones | Shock | SCR | 1.00 | Trace | 4 | 3 | 8 | 8 | .23 | — |
| Orr et al. (2000) | PTSD (DSM-IV) | 33 (45) | Disc | Lights | Shock | SCR | 1.00 | Delay | 5 | 4 | 5 | 10 | .68 | .29 |
| | | 33 (45) | Disc | Lights | Shock | EKG | 1.00 | Delay | 5 | 4 | 5 | 10 | −.10 | |
| Peri et al. (2000) | PTSD (DSM-III-R) | 66 (55) | Disc | Lights | WN | SCR | .80 | Delay | 2 | 0 | 8 | 6 | −.02 | −.01 |
| | | 66 (55) | Disc | Lights | WN | EKG | .80 | Delay | 2 | 0 | 8 | 6 | .01 | |
| | | 66 (55) | Simp[a] | Lights | WN | SCR | .80 | Delay | 2 | 0 | 8 | 6 | .61 | .46 |
| | | 66 (55) | Simp[a] | Lights | WN | EKG | .80 | Delay | 2 | 0 | 8 | 6 | .31 | |
| Pitman and Orr (1986) | GAD (DSM-III) | 40 (50) | Disc | Faces[b] | Shock | SCR | 1.00 | Delay | 5 | 4 | 5 | 10 | .37 | — |
| Pliszka, Hatch, Borcherding, and Rogeness (1993) | Overanxious disorder (4 or more DSM-III-R symptoms) | 33 (33) | Disc | Lights | WN | SCR | 1.00 | Delay | 0 | 0 | 8 | 4 | .45[d] | .22 |
| | | 33 (33) | Disc | Lights | WN | EKG | 1.00 | Delay | 0 | 0 | 8 | 4 | NS | |
| Schneider et al. (1999) | SOPH (DSM-IV) | 24 (50) | Simp | Faces[c] | Odor | $fMRI_{amyg}$ | 1.00 | Delay | 10 | 10 | 40 | 20 | NS | NS |
| | | 24 (50) | Simp | Faces[c] | Odor | EKG | 1.00 | Delay | 10 | 10 | 40 | 20 | NS | |
| Sloane et al. (1965) | "Psychoneurotic inpatients" (chose pt.'s who complained of anxiety, obsessions, or fears) | 40 (50) | Simp | Tones | Shock | SCR | .80 | Trace | 0 | 0 | 40 | 20 | .99 | — |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Van den Bergh, Stegen, and Van de Woestijne (1997) | Psychosomatic pt.'s (The majority of pt.'s reported as having an anxiety disorder) (DSM-III-R) | 56 (50) | Disc | Odor | $CO_2$ | resp freq | 1.00 | Delay | 0 | 0 | 3 | 2 | .00 | — |

*Note*: Contingency = probability of receiving a US in the presence of a CS, minus the probability of receiving a US in the absence of a CS (Alloy & Abramson, 1979); contiguity = the temporal relationship between CS and US during CS/US pairings; CS = conditioned stimulus; US = unconditioned stimulus; DV = dependent variable; ACQ = acquisition; EXT = extinction; $d$ = Hedges' $g$. Positive and negative values signify more and less conditioned responding among patients vs. controls; $d_{combined}$ = average of within-study $d$'s; PTSD = posttraumatic stress disorder; SOPH = social phobia; GAD = generalized anxiety disorder; Disc = discrimination; Simp = simple; SCR = skin-conductance response; FPS = fear-potentiated startle; EKG = electrocardiogram; $fMRI_{amyg}$ = functional magnetic resonance imaging of the amygdala; NA = not applicable; NS = study reported effect as nonsignificant and the effect was estimated as ".00".

*$p \leqslant .05$.**$p \leqslant .01$.***$p \leqslant .001$.

[a]Simple-conditioning processes measured within a discrimination paradigm.

[b]Neutral and angry faces averaged together.

[c]Neutral facial expressions.

[d]SCR effect size for Pliszka et al. (1993) estimated from narrative report of a "trend" for patients to extinguish less than controls. Here effect size was computed by estimating $p$ as .1.

[e]Number of CS+ trials.

Table 3
Tests of categorical models of study characteristics at AQC

| Categorical variables and relevant contrasts | $k$ | $N$ | $d_+$ (95% CI) | Fail-safe $N$ | $Q_w$ | $Q_b$ |
|---|---|---|---|---|---|---|
| Total AQC[a,b] | | | | | | |
| 1. All within-study ESs averaged[c] | 17 | 795 | .19 (±.21)* | .76 | 31.78** | |
| 2. Simple included over Disc for studies reporting both[d] | 17 | 795 | .25 (±.24)* | 1.45 | 33.96** | |
| Simple vs. Disc[e,f,g,h] | | | | | | |
| Contrast 1 (1 vs. 2) | | | | | | 3.77* |
| 1. Simple[g] | 7 | 357 | .42 (±.28)*** | 8.75 | 11.16 | |
| 2. Disc | 10 | 438 | .08 (±.23) | — | 18.14* | |
| Type of Dependent Measure[c,e,i] | | | | | | |
| Contrast 1 (1 vs. 2) | | | | | | .84 |
| Contrast 2 (1 vs. 3) | | | | | | 1.21 |
| Contrast 3 (2 vs. 3) | | | | | | 3.16 |
| 1. SCR | 8 | 382 | .12 (±.43) | — | 2.32*** | |
| 2. Heart rate | 5 | 222 | .28 (±.38) | — | 06.85 | |
| 3. FPS | 4 | 191 | −.08 (±.27) | — | 0.57 | |
| Type of CS[c,g] | | | | | | |
| Contrast 1 (1 vs. 2) | | | | | | .17 |
| Contrast 2 (A vs. B) | | | | | | .75 |
| Contrast 3 (A vs. C) | | | | | | .06 |
| 1. Visual | 11 | 464 | .20 (±.25) | — | 11.87 | |
| A. Lights | 7 | 356 | .14 (±.21) | — | 06.88 | |
| B. Human faces[j] | 4 | 108 | .26 (±.67) | — | 04.36 | |
| 2. Auditory | 6 | 331 | .18 (±.49) | — | 18.09*** | |
| C. Tones | 5 | 295 | .16 (±.60) | — | 17.80*** | |
| D. Words | 1 | 36 | — | — | — | |
| Type of US[c,g] | | | | | | |
| Contrast 1 (1 vs. 3) | | | | | | .62 |
| Contrast 2 (1 vs. 3A) | | | | | | .00 |
| Contrast 3 (1 vs. 2) | | | | | | 2.07 |
| 1. Shock | 8 | 368 | .23 (±.21)* | 1.60 | 2.46** | |
| 2. Threat of shock | 3 | 167 | −.09 (±.31) | — | 0.50 | |
| 3. No shock | 6 | 260 | .29 (±.42) | — | 05.30 | |
| A. White noise | 2 | 126 | .18 (±.35) | — | 0.00 | |
| B. Odor | 2 | 57 | .56 (±.53)* | .23 | 0.64 | |
| C. Threat words | 1 | 66 | — | — | — | |
| D. Painful pressure | 1 | 11 | — | — | — | |
| Contiguity[c,g,k] | | | | | | |
| Contrast 3 (1 vs. 2) | | | | | | .48 |
| 1. Delay | 13 | 547 | .19 (±.20)* | .27 | 11.89 | |
| 2. Trace | 3 | 196 | .47 (±.67) | — | 08.22* | |

*Note*: $K$ = number of effect sizes; $d_+$ = effect sizes weighted by the reciprocal of their variances; CI = confidence interval; fail-safe $N$ = the number studies with an effect size of ".00" needed to attenuate the average effect size below significance; $Q_w$ = test of within-category homogeneity; $Q_b$ = test of between-category homogeneity analogous to a pairwise comparison; Simple = single cue conditioning; Disc = discrimination conditioning; SCR = skin-conductance response; FPS = fear-potentiated startle; CS = conditioned stimulus; US = unconditioned stimulus; contiguity = the

Table 3 (*continued*)

temporal contiguity of CS and US during CS/US pairings. Delay = type of conditioning with temporal overlapping of CS and US presentations. Trace = type of conditioning with temporal separation between CS offset and US onset. *$p \leqslant .05$.**$p \leqslant .01$.***$p \leqslant .005$.

[a]Aggregation of 17 independent effect sizes.

[b]Results from multiple within-study dependent measures averaged to form a single effect size, except in one case (Schneider et al., 1999) where the effect for one of two DVs estimated from a report of "nonsignificance" was excluded.

[c]Within-study indices of simple and discrimination learning were averaged to form a single effect-size estimate.

[d]Because patient-control differences in discrimination but not simple conditioning may underestimate true patient-control differences in fear learning, the aggregation for total AQC was recomputed after selecting simple over discrimination effects for studies reporting both.

[e]To maintain independence of error terms, this moderator analysis included only one value from a given sample even though some studies had values for more than one level of this moderator.

[f]In the interest of creating more balanced cells for the simple-discrimination contrast, simple-conditioning effects were chosen over discrimination effects for studies with available data for both.

[g]Skin conductance, the dependent measure most frequently used in this literature, was chosen over other dependent measures to increase comparability among studies.

[h]Four of seven simple effects derived from discrimination studies.

[i]In the interest of creating more balanced cells for the skin conductance vs. heart-rate contrast, only heart-rate effects were included for studies reporting both.

[j]Results from Pitman and Orr (1986) averaged across neutral and angry expressions.

[k]Clum (1969) could not be included because he did not report adequate information regarding contiguity.

## *Overall grand mean effects*

### *Acquisition*

The 17 independent effect sizes representing fear-ACQ scores for 399 patients and 396 controls produced a small yet significant grand weighted mean effect size $d_+$ of .19 ($p = .05$), indicating stronger ACQ of fear learning among patients vs. controls. The homogeneity $Q$ for these effect sizes was significant ($Q_w = 31.78$, $p < .01$), indicating that effect sizes in this subset are heterogeneous and likely to come from more than one parent population of effect sizes. As a result, the grand weighted mean is thought to be a less than accurate index of its constituent effect sizes.

After removal of the three effect sizes estimated from narrative reports of significance, the grand weighted mean for ACQ dropped below significance ($d_+ = .17$, $p = .11$, $k = 14$) and the subset remained heterogeneous ($Q_w = 27.43$, $p = .01$).

### *Extinction*

The 12 independent effect sizes reflecting fear-EXT scores for 252 anxiety patients and 259 controls yielded a significant, grand weighted mean $d_+$ of .23 ($p = .006$), demonstrating stronger conditioned responding during EXT among patients relative to healthy controls. Approximately seven studies with null results could be added before the aggregated effect size would drop below significance (fail-safe $N = 7.59$). Additionally, the $Q_w$ statistic revealed homogeneity of effects ($Q_w = 10.49$, $p = .49$), suggesting that all 12 included effect sizes come from a population with a single fixed effect-size parameter. When three effect sizes estimated from narrative reports of results were omitted, the grand weighed mean $d_+$ increased to .25 ($p = .02$; $k = 9$, fail-safe $N = 7.78$) and the subset remained homogeneous ($Q = 9.55$, $p = .30$).

Table 4
Tests of categorical models of study characteristics at EXT

| Categorical variables and relevant contrasts | $k$ | $N$ | $d_+$ (95% CI) | Fail-safe $N$ | $Q_w$ | $Q_b$ |
|---|---|---|---|---|---|---|
| Total EXT[a,b] | | | | | | |
| 1. All within-study ESs averaged[c] | 12 | 511 | .23 (±.18)** | 7.59 | 1.48 | |
| 2. Simple included over Disc for studies reporting both[d] | 12 | 511 | .28 (±.20)** | 11.52 | 12.31 | |
| Simple vs. Disc[e,f,g,h] | | | | | | |
| Contrast 1 (1 vs. 2) | | | | | | .70 |
| 1. Simple[g] | 5 | 274 | .39 (±.35)** | 1.21 | 6.22 | |
| 2. Disc | 7 | 237 | .23 (±.29) | — | 6.44 | |
| Type of dependent measure[c,e,i] | | | | | | |
| Contrast 1 (1 vs. 2) | | | | | | 2.73 |
| 1. SCR | 5 | 242 | .35 (±.25)*** | 4.80 | 4.55 | |
| 2. Heart rate | 5 | 189 | .04 (±.29) | — | .42 | |
| 3. FPS | 1 | 24 | — | — | — | |
| 4. Respiratory rate | 1 | 56 | — | — | — | |
| Type of CS[c,g] | | | | | | |
| Contrast 1 (1 vs. 2) | | | | | | .20 |
| Contrast 2 (A vs. C) | | | | | | .15 |
| 1. Visual | 7 | 253 | .25 (±.29) | — | 5.93 | |
| A. Lights | 4 | 156 | .23 (±.52) | — | 5.40 | |
| B. Human faces[j] | 3 | 97 | .25 (±.40) | — | .52 | |
| 2. Auditory | 4 | 202 | .38 (±.36)* | .46 | 4.55 | |
| C. Tones | 3 | 184 | .40 (±.56) | — | 4.54 | |
| D. Words | 1 | 18 | — | — | — | |
| 3. Olfactory | 1 | 56 | — | — | — | |
| Type of US[c,g] | | | | | | |
| Contrast 1 (1 vs. 3) | | | | | | .11 |
| Contrast 2 (1 vs. 3, 4, and 5) | | | | | | .82 |
| 1. Shock | 6 | 275 | .35 (±.40) | — | 9.43 | |
| 2. Threat of shock | 0 | — | — | — | — | |
| 3. White noise | 3 | 123 | 27 (±.36) | — | .61 | |
| 4. Odor | 2 | 57 | 18 (±.52) | — | .33 | |
| 5. $CO_2$ | 1 | 56 | — | — | — | |
| Contiguity[c,g] | | | | | | |
| Contrast 3 (1 vs. 2) | | | | | | 1.12 |
| 1. Delay | 9 | 333 | .20 (±.22)* | .06 | 6.91 | |
| 2. Trace | 3 | 178 | .44 (±.38)** | 1.02 | 3.78 | |

*Note*: $K$ = number of effect sizes; $d_+$ = effect sizes weighted by the reciprocal of their variances; CI = confidence interval; fail-safe $N$ = the number studies with an effect size of ".00" needed to attenuate the average effect size below significance; $Q_w$ = test of within-category homogeneity; $Q_b$ = test of between-category homogeneity analogous to a pairwise comparison; SCR = skin-conductance response; FPS = fear-potentiated startle; CS = conditioned stimulus; US = unconditioned stimulus. Contiguity = the temporal sequence of CS and US during CS/US pairings. Delay = type of conditioning with temporal overlapping of CS and US presentations. Trace = type of conditioning with temporal separation between CS offset and US onset.
*$p \leqslant .05$.**$p \leqslant .01$.***$p \leqslant .005$.

Table 4 (*continued*)

[a]Aggregation of 12 independent effect sizes.

[b]Results from multiple within-study dependent measures averaged to form a single effect size, except in one case (Pliszka et al., 1993) where the effect for one of two DVs estimated from a report of "nonsignificance" was excluded.

[c]Within-study indices of simple and discrimination learning were averaged to form a single effect-size estimate.

[d]Because patient-control differences in discrimination but not simple conditioning may underestimate true patient-control differences in fear learning, the aggregation for total EXT was recomputed after selecting simple over discrimination effects for studies reporting both.

[e]To maintain independence of error terms, this moderator analysis included only one value from a given sample even though some studies had values for more than one level of this moderator.

[f]In the interest of creating more balanced cells for the simple-discrimination contrast, simple-conditioning effects were chosen over discrimination effects for studies with available data for both.

[g]Skin conductance, the dependent measure most frequently used in this literature, was chosen over other dependent measures to increase comparability among studies.

[h]Two of five simple effects were derived from discrimination studies.

[i]In the interest of creating more balanced cells for the skin conductance vs. heart-rate contrast, only heart-rate effects were included for studies reporting the effects of multiple dependent measures.

[j]Results from Pitman and Orr (1986) averaged across neutral and angry expressions.

### *Acquisition vs. extinction*

Although the overall effect of EXT was more robust than that of ACQ, no difference between ACQ and EXT effects was found using HLM, $F(1, 14) = .93$, $p = .35$.

### *Simple versus discrimination learning*

#### *Acquisition*

Studies measuring simple fear learning yielded a significant weighted mean effect size $d_+$ of .42 ($p < .002$, $k = 7$, fail-safe $N = 8.75$), whereas aggregations of discrimination fear learning resulted in a nonsignificant weighted mean of .08 ($p = .30$, $k = 10$). Simple and discrimination effects were found to be homogeneous ($Q_w = 11.16$, $p = .08$), and heterogeneous ($Q_w = 18.15$, $p = .03$), respectively, implying that the simple but not the discrimination subset was derived from a population with a single fixed effect-size parameter. Following the removal of three discrimination effect sizes estimated from narrative reports of significance, the weighted mean effect of discrimination learning dropped to .02 ($p = .45$, $k = 7$) and the subset remained heterogeneous ($Q_w = 15.07$, $p < .02$). No simple-learning effect sizes were computed from narrative reports of significance and thus no recalculation of the weighted mean was necessary.

Planned contrasts comparing simple and discrimination effect sizes were significant when effects estimated from narrative reports of significance were included ($Q_b = 3.77$, $p = .05$) or excluded ($Q_b = 4.70$, $p = .03$). This finding demonstrates that simple effects, compared to discrimination effects, yielded significantly greater patient-control differences in fear conditioning that are not attributable to inaccuracies from effect-size estimates derived from narrative reports of results. Additionally, HLM revealed a significantly larger effect of simple vs. discrimination learning, $t(17.6) = 3.18$, $p = .005$. That HLM, an analytic technique analyzing all available data points (i.e., independent + dependent data points) yielded a significant

Table 5
Regression results for continuous moderator analyses

| Variable[a] | AQC | | EXT | |
|---|---|---|---|---|
| | *df*[b] | *b* (95% CI) | *df*[b] | *b* (95% CI) |
| Year of publication | 16 | .001 (±.008) | 11 | −.003 (±.010) |
| Demographics | | | | |
| Age | 14 | −.005 (±.022) | 11 | .008 (±.216) |
| Patient | 14 | −.007 (±.025) | 11 | .007 (±.216) |
| Control | 14 | −.002 (±.019) | 10 | .004 (±.020) |
| % Male | 10 | −.199 (±.712) | 9 | .092 (±.907) |
| Patient | 13 | −.331 (±.592) | 9 | .108 (±.846) |
| Control | 11 | −.120 (±.588) | 9 | .108 (±.871) |
| Stimulus duration (s) | | | | |
| CS[c] | 13 | −.007E03 (±.001) | 11 | −.003E03 (±.002) |
| US[c] | 12 | .003E03 (±.001) | 11 | −.003E03 (±.002) |
| # AQC trials | | | | |
| CS+/US pairings[c] | 13 | .009 (±.011) | 11 | .005 (±.010) |
| CS−/US− pairings[c,d] | 12 | −.008 (±.011) | 10 | .001 (±.013) |
| # EXT trials | — | — | 11 | .015 (±.027) |
| # Pre-AQC exposures | | | | |
| CS (latent inhibition)[c] | 13 | .008 (±.052) | 11 | −.001 (±.056) |
| US[c] | 13 | .030 (±.056) | 10 | −.009 (±.056) |
| Contingency[c] | 13 | 1.103 (±1.323) | 10 | −1.212 (±2.05) |

*Note*: *df* = degrees of freedom; *b* = unstandardized regression coefficient ; CI = confidence interval; CS = conditioned stimulus; US = unconditioned stimulus; CS+ = CS paired with the US during AQC; CS− = CS presented in the absence of the US during AQC; contingency = probability of receiving a US in the presence of a CS, minus the probability of receiving a US in the absence of a CS (Alloy & Abramson, 1979).
*$p \leqslant .05$.
[a]Independence of error terms was maintained by averaging within-study effects produced by multiple dependent measures and/or assessment of both simple and discrimination learning.
[b]Degrees of freedom vary by availability of data.
[c]Instructed conditioning studies ($n = 3$) were omitted from this moderator analysis.
[d]Simple learning studies assigned values of zero.

simple-discrimination effect, further supports the simple-discrimination difference present in the target literature.

*Extinction*

Similar to ACQ data, simple conditioning effects yielded a significant weighted mean ($d_+ = .39$, $p = .01$, $k = 5$, fail-safe $N = 1.21$) while discrimination effects did not ($d_+ = .23$, $p = .06$, $k = 7$). Unlike ACQ results, however, effects of discrimination learning at EXT yielded a nonsignificant trend. The test of homogeneity was nonsignificant for simple ($Q_w = 6.22$, $p = .18$) and discrimination effects ($Q_w = 6.44$, $p = .38$), demonstrating homogeneity among effect sizes in

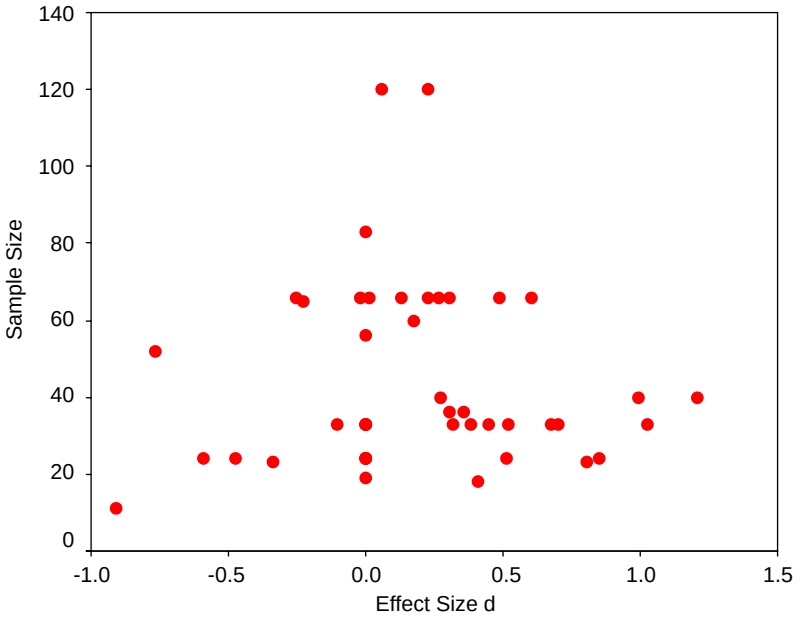


Fig. 1. Funnel plot for all 46 effect sizes.

both subsets. Upon removal of effect sizes estimated from narrative reports of significance, $d_+$ for simple effects rose to .53 ($p < .006$, $k = 3$, fail-safe $N = 16.11$) and $d_+$ for discrimination effects fell to .20 ($p = .12$, $k = 6$). After recalculation of $d_+$, both simple and discrimination subsets remained homogeneous ($p$'s $> .11$).

Although $Q_b$ comparisons revealed no differences between simple and discrimination effects of EXT when effect sizes derived from narrative reports of significance were included ($Q_b = .65$, $p = .42$) or excluded ($Q_b = 1.71$, $p = .19$), HLM yielded a significant difference between simple and discrimination learning when results from narrative reports of significance were included or excluded (both $p$'s $< .03$).

*Grand means for ACQ and EXT were recomputed after selecting simple over discrimination effects for studies reporting both effects*

Owing to the marked reduction in patient-control conditioning differences for discrimination learning and because anxiety patients are thought to have an impaired ability to display discrimination fear learning because of failing to inhibit the fear response in the presence of safety cues (Davis et al., 2000), discrimination effect sizes may underestimate true patient-control conditioning differences. As such, overall mean effect sizes for ACQ and EXT were recomputed after selecting simple over discrimination effects for studies reporting both types of effects. Resulting weighted mean effect sizes ($d_+$) for ACQ and EXT increased to .25 ($p = .02$, $k = 17$, fail-safe $N = 1.45$) and .29 ($p = .003$, $k = 12$, fail-safe $N = 11.52$), respectively. These recomputed mean effect sizes reflect patient-control differences in conditioning that are not affected by the complications introduced by discrimination learning paradigms.

*Results from exploratory analyses*

Because no strong associations between exploratory moderators and effect sizes were found, and for the sake of brevity, results from exploratory analyses will not be described at length but are displayed in Tables 3-5 and are interpreted in the Discussion section.

## Discussion

As predicted, relative to healthy controls anxiety patients displayed stronger overall ACQ and stronger CRs during EXT of fear learning, although both aggregated effects were small. Additionally, the hypothesized effects of simple conditioning were supported by elevations in conditioned responding during both ACQ and EXT of simple conditioning among anxiety patients. Interestingly, patient-control differences in ACQ of simple conditioning (i.e., conditioning requiring only excitatory associations) were significantly larger than such differences in ACQ of discrimination learning (i.e., conditioning requiring both excitatory and inhibitory associations). Similarly, patient-control differences in EXT were significantly larger in simple vs. discrimination conditioning as indicated by HLM results. Contrary to the predictions of the conditionability model of Orr et al. (2000), patients and controls displayed approximately equal ACQ and EXT rates of discrimination learning. Finally, all exploratory moderators were found to contribute nonsignificantly to the variability in patient-control differences in either ACQ or EXT of conditioned fear.

Although overall patient-control differences in ACQ and EXT were significant, the associated effect sizes and fail-safe *N*'s were small (ACQ $d_+ = .19$, fail-safe $N = 0.76$; EXT $d_+ = .23$, fail-safe $N = 7.59$). It is likely that the small size of overall effects is in part due to the collapsing of larger simple effects (ACQ $d_+ = .42$; EXT $d_+ = .39$) with smaller discrimination effects (ACQ $d_+ = .08$; EXT $d_+ = .23$) prior to overall analyses. Consistent with this idea, overall effect sizes increased when selecting simple over discrimination indices for studies reporting both forms of conditioning (ACQ $d_+ = .25$; EXT $d_+ = .28$). Of note, a potential publication bias against medium to large negative effect sizes for studies with small samples was detected via visual assessment of a funnel plot. Such a publication bias may have led to an artificial inflation of aggregated effect sizes in the current study.

*Resistance to EXT or greater initial ACQ?*

Effects of reduced EXT of fear learning among anxiety patients should be interpreted with caution given that target studies operationalized EXT as the average strength of the CR during EXT trials, an index of EXT highly influenced by initial levels of ACQ. Ideally, EXT would be defined as the change in conditioned responding from the start to the end of EXT trials. Alternatively, indices of EXT might be derived with a statistical adjustment for baseline levels of ACQ. For the current analyses, it was not possible to derive such indices without individual subject-level data. Therefore, in the absence of such analyses, the possibility remains that EXT effects reflect initial elevations in ACQ among patients.

*Simple vs. discrimination learning*

The patient-control difference in ACQ of simple conditioning implies greater activation of fear in the presence of danger cues (CS+) among patients, whereas the significantly smaller patient-control difference in ACQ of discrimination learning may imply an impaired ability to suppress the fear response in the presence of safety cues (CS−) among anxiety patients. This interpretation is plausible given several discrimination studies in the target literature finding larger CRs among patients vs. controls to both the CS− and CS+ (Fayu, 1961; Grillon & Morgan, 1999; Orr et al., 2000; Peri et al., 2000), suggesting some combination of stronger excitatory associations and weaker inhibitory associations, respectively, among patients. This associative interpretation of elevated responses to CS+ and CS− among patients is viable given equally strong awareness of the CS/US contingency among patients and controls reported by three of four studies finding CS+/CS− elevations in patients (the fourth study did not report levels of awareness). These results demonstrate that associative learning occurred in both patients and controls, yet patients were unable to inhibit the fear response in the presence of a cue they understood signaled safety (CS−). Such findings are consistent with the theory of pathological anxiety posited by Davis et al. (2000) that implicates abnormalities in inhibitory fear mechanisms among anxiety patients. Of note, this pattern of results also suggests elevated stimulus generalization (i.e., CRs to both CS+ and CS−) among patients. Because the CS+ and CS−, in a given study, share many of the same stimulus properties (e.g., both are colored lights, or both are images of faces), it is possible that patients mistake the CS− for the CS+. Such generalization among patients may be understood as a deficiency to process the safety information that distinguishes the CS− from the CS+ and is thus viewed as being consistent with predictions derived from the model of Davis et al. (2000).

Although the healthy control advantage in discrimination learning (i.e., negative effect size for discrimination learning) predicted by the Davis model was not confirmed, 35% of all discrimination effects were negative, 18% were "0 estimates", and 47% were positive, whereas the corresponding breakdown for simple effects was 0% negative, 10% "0 estimates", and 90% positive. Thus, the pattern of results is consistent with predictions stemming from Davis's model, yet this pattern did not yield a significant result. Of note, the significant effect of simple conditioning does not directly support or contradict the theory by Davis, but rather suggests that an inhibitory account of pathological anxiety does not fully explain patient-control differences in fear conditioning.

While it is true that disparate weighted average effect sizes were generated by different levels of other categorical moderators such as *type of DV* (e.g., heart rate vs. skin conductance) and *contiguity* (i.e., trace vs. delay), only simple-discrimination disparities reached significance at ACQ and EXT. Additionally, unlike disparities produced by other variables, simple-discrimination differences were predicted based on theoretical and empirical rationales. Finally, disparities in levels of moderators such as *type of DV* and *contiguity* are extremely vulnerable to third-variable artifacts resulting from methodological differences across studies in the target literature.

Although this methodological heterogeneity also confers risk of third-variable influence on simple-discrimination comparisons, data from within-study indices of simple and discrimination learning suggest that third variables are not driving the dissociation between simple and discrimination learning. Within-study comparisons are far less subject to third-variable influence because simple and discrimination processes are elicited within a single paradigm and thus

methodological factors remain constant for such comparisons. Three studies for which both simple and discrimination ACQ effect sizes were computed produced the following results: (a) Fayu (1961): $d_{simple} = .80$; $d_{discrim} = -.34$, (b) Grillon and Morgan (1999): $d_{simple} = .52$; $d_{discrim} = -.47$, and (c) Peri et al. (2000): $d_{simple} = .25$; $d_{discrim} = -.07$. Additionally, one study (Peri et al., 2000) yielding simple and discrimination effects at EXT produced a $d_{simple}$ of .46 and a $d_{discrim}$ of $-.01$. That simple-discrimination differences in the predicted direction remain evident when methodological characteristics are held constant suggests that the simple-discrimination dissociation is not the spurious product of third variables.

*Sensitization as a third variable*

It may also be argued that the simple-discrimination dissociation was produced by *sensitization* effects rather than associative learning. In the context of fear and anxiety, sensitization is a time-limited enhancement in responsiveness to fear-relevant or novel stimuli when the fear state is already active (Groves & Thompson, 1970; Öhman & Mineka, 2001). As mentioned earlier, simple conditioning is often assessed by comparing CS+ reactivity before ACQ to levels of reactivity to the CS+ during or after ACQ. Because pre- but not post-ACQ assessments precede exposure to an anxiolytic US, one might expect heightened responding to the CS+ at post- vs. pre-ACQ because of sensitization produced by the US. Discrimination learning is typically assessed by contrasting responses to CS+ and CS−. Because CS+ and CS− are presented after US exposure, responses to both CS types might be elevated by sensitization, which may result in little discrimination learning (i.e., responses to CS+ and CS− equally elevated). According to this alternative, patients will both experience more anxiety to the aversive US and display greater sensitization following US delivery, which may in turn lead to enhanced simple- but reduced discrimination-conditioning among patients.

*Habituation as a third variable*

Relative to individuals with low state anxiety, patients and normals high in state anxiety have been found to display less habituation of the SCR to novel stimuli (Clemens and Selesnick, 1967; Lader and Wing, 1964). It is thus possible that greater responding to the CS+ among patients vs. controls in the target literature (i.e., positive effect of simple conditioning) was due to a relative lack of habituation to the CS+ among patients. Additionally, the failure to find greater discrimination learning among patients may have been due to the lack of SCR habituation to both the CS+ and CS− among patients resulting in approximately equal elevations in SCR to both CS+ and CS− (i.e., little discrimination learning among patients).

Such alternative nonassociative explanations must be seriously considered given the absence of adequate controls for sensitization and habituation in studies included in the target literature. Discrimination paradigms (employed by 15 of 20 target studies) do provide a degree of protection against such nonassociative effects, but the level of protection depends on the outcome of the study. If the CS+ evokes greater conditioned responding relative to the CS−, one can rule out the sensitization and habituation interpretations because both CSs are equally susceptible to such pseudoconditioning effects, yet the CS paired with the US elicited greater responses. If, however, responses to the CS+ and CS− are equally elevated, it is difficult to determine whether such an effect is due to associative or nonassociative mechanisms. More specifically, elevations to the CS+ and CS− may be due to excitatory conditioning and deficits in inhibitory conditioning,

respectively, or both elevations may be due to sensitization and/or habituation. As mentioned previously, the high contingency awareness among patients and controls reported by the majority of studies finding elevated responses to CS+ and CS− among patients, confers viability to an associative interpretation of findings. Nevertheless, nonassociative mechanisms (sensitization and habituation) can only be ruled out if a second experiment comprised of unpaired CS/US presentations accompanies the conditioning experiment. Because CS and US are delivered noncontingently in the unpaired experiment, nonassociative learning to the CS+ and CS− will be evoked independent of associative learning. To the degree to which responses to the CS+ or CS− during the paired study deviate from those elicited during the unpaired study, results from the paired study may be attributed to associative learning. Similarly, to demonstrate stimulus generalization, elevated responses to the CS+ and CS− should be apparent in the paired but not unpaired experiment. Although the associative account of current findings is tenable, future studies contrasting responses to CSs across paired vs. unpaired experiments will provide important confirming or disconfirming results.

*The role of excitatory and inhibitory fear learning in anxiety disorders*

In addition to the plausible evidence for stronger excitatory and weaker inhibitory fear processes among anxiety patients provided by the simple-discrimination dissociation, additional support may derive from the significant overall weighted mean effect sizes found for both ACQ and EXT data. Stronger ACQ of fear learning among patients demonstrates heightened excitatory fear processes, whereas weaker EXT among patients may actually suggest an impairment in inhibitory fear processes. Because fear learning may re-emerge after EXT through CS re-exposure (i.e., spontaneous recovery: Pavlov, 1927), US re-exposure (i.e., reinstatement: Konorski, 1948; Pavlov, 1927), or by introducing a context different from the one in which EXT took place (i.e., renewal: Bouton and Bolles, 1979, 1985), EXT does not constitute an erasure of the CS+/US association but is rather thought to deactivate the association through an inhibitory process (for a review, see Davis et al., 2000). The inhibitory properties of EXT are also supported by evidence of conditioned inhibition produced through EXT (Calton, Mitchell, & Schachtman, 1996; Schachtman, Threlkeld, & Meyer, 2000). Thus, the significant weighted mean effect of EXT may be the result of an impairment in inhibitory fear processes among patients. Of course, the degree to which the EXT effect suggest such inhibitory abnormalities rests on whether the EXT effect reflects stronger resistance to EXT or stronger levels of initial ACQ among patients.

The simple-discrimination dissociation as well as the significant overall effect of both ACQ and EXT may support the idea that excitatory and inhibitory fear processes distinguish individuals with and without an anxiety disorder. Unfortunately, studies in the target literature rarely report the separate effects of excitatory and inhibitory processes. To start, simple-conditioning studies elicit only excitatory processes (i.e., CS+/US associations). Additionally, discrimination studies that assess CRs to both CS+ and CS− operationalize rates of conditioning through a subtraction of CS− from CS+. Thus when patients, relative to controls, show stronger CRs to both the CS+ and CS− and their CS+ vs. CS− differences are close to zero (because both are elevated), it is generally concluded that patients failed to condition. Only when excitatory and inhibitory processes are evaluated separately (as was done when possible in the current meta-analysis) does it appear plausible that patients show more excitatory conditioning to the CS+ but less inhibitory

conditioning to the CS−. It is therefore recommended that future studies apply discrimination paradigms that allow for the assessment of excitatory and inhibitory fear processes. To this end, responding to the CS+ and CS− could each be contrasted to baseline levels of responding. Such baseline measures would ideally be collected during ITIs (rather than at pre-ACQ) to protect against the confounding influence of sensitization and/or habituation processes. FPS but not SCR may be used to assess such ITI levels of responding because electrodermal activity measured in the absence of a stimulus (e.g., during ITI) is referred to as skin-conductance level (SCL), which measures a process related to, yet distinct from phasic SCR. It would therefore be inappropriate to index conditioning as the difference between SCR and SCL but appropriate to index conditioning as the difference in startle magnitudes during ITI vs. CS+ (excitatory association) and ITI vs. CS− (inhibitory association).

*Exploratory results*

*Type of CS*

At ACQ, studies employing human faces as CSs yielded the most substantial effect sizes. Because human faces as opposed to other CSs used in this literature (e.g., colored lights, tones) may have been more associated with aversive events in the evolutionary past, such results may support the idea that evolutionarily prepared CSs yield larger patient-control conditioning differences in the predicted direction. Because the number of studies using faces (or any other prepared stimulus) as CSs is very small ($n = 4$) and because the aggregation of such studies yielded an insignificant result, at best this meta-analysis yields tenuous implications for associations between CS "preparedness" and patient-control differences in fear conditioning.

*Type of US*

The most notable result for *type of US* is the smaller (although not significantly smaller) effect for studies, by Grillon and colleagues, employing threat of shock as the US. In Grillon's threat of shock paradigm, participants learn the CS/US relationship through explicit verbal instruction rather than actually experiencing the temporal contiguity of the CS and US, as is done in all other studies from the target literature. The possibility thus arises that patients and controls have indistinguishable rates of fear learning when assessed via instructed conditioning tasks. This conclusion cannot be made with great confidence because "instructed conditioning" covaries with all other conditioning parameters used by Grillon's group. For example, all studies from this laboratory assess the CR using FPS within discrimination paradigms. Thus, the small effect associated with "threat of shock" may be as likely due to the use of FPS or to the fact that discrimination rather than simple processes are assessed.

*Type of dependent variable*

Although the weighted average effect of ACQ for heart-rate studies trended toward significance ($p = .07$) while the corresponding effect for SCR studies was clearly nonsignificant, this pattern of results switched at EXT, with SCR but not heart-rate studies yielding a significant effect. This switch is in part due to the results of Orr et al. (2000), who found a large, positive heart-rate effect

at ACQ and a small, negative heart-rate effect at EXT. The smaller heart-rate effect at EXT vs. ACQ may also be due to the fact that more "0" estimate effect sizes were included in EXT (three of five effects were "0" estimates) vs. ACQ (one of five were "0" estimates) subsets. Because "0" estimates are likely to underestimate the true effect, heart-rate effects at EXT compared to ACQ are more likely to underestimate the true effect of heart-rate conditioning.

Of note, the weighted average effect of negligible size produced by FPS studies is not thought to indicate that FPS is unable to identify patient-control differences in fear conditioning, but may rather be attributable to the fact that all such studies employed discrimination paradigms. Support for this idea comes from the positive and sizeable nature of the one simple-conditioning effect ($d = .52$) gleaned from these FPS studies. This positive simple effect suggests that FPS is a sensitive index of patient-control differences when assessing simple rather than discrimination learning.

*Latent inhibition*

Another learning phenomenon with potential relevance for pathological anxiety is latent inhibition (Mineka & Zinbarg, 1996), a conditioning effect whereby preconditioning exposure to the CS impairs subsequent conditioning to the CS (Lubow & Moore, 1959; Mackintosh, 1983). This effect has been demonstrated in fear-conditioning paradigms (Dickinson, 1976; Hall & Pearce, 1979; Mineka & Cook, 1986; Pearce, Kaye, & Hall, 1982) illustrating the anxiolytic properties of preconditioning CS exposures. If CS pre-exposures do not attenuate fear learning among individuals predisposed to pathological anxiety, one may have predicted larger patient-control conditioning differences for studies with increasing numbers of CS pre-exposures. This notion was not confirmed by present results, as the number of CS pre-exposures was found to be unrelated to effect sizes.

*Neurobiological implications*

The current results implicate neural circuits underlying the formation and expression of excitatory and inhibitory fear processes in the pathophysiology of anxiety disorders. Evidence from animal studies suggests that excitatory fear associations between the CS+ and US are formed through associative long-term potentiation taking place in the lateral nucleus of the amygdala (see Blair et al., 2001), and expression of such learning is mediated by outputs from the central nucleus of the amygdala (see LeDoux, 1998). The role of the amygdala in human excitatory fear learning is supported by both neuroimaging findings (for a review, see Büchel & Dolan, 2000) and assessments of fear conditioning in brain damaged patients (e.g., Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995).

Although the neurobiological underpinnings of inhibitory fear processes (i.e., conditioned inhibition and EXT) have been less extensively studied, available data suggest the involvement of the lateral septum (Thomas, Yadin, & Strickland, 1991; Yadin & Thomas, 1981) and dorsal central gray (Fendt, 1998) in conditioned inhibition, as well as a role for the sensory cortex (e.g., LeDoux, Romanski, & Xagoraris, 1989; Milad & Quirk, 2002), medial prefrontal cortex (e.g., Morgan, Romanski, & LeDoux, 1993), hippocampus (Schmaltz & Theiosus, 1972), and amygdala-based NMDA transmission (see Davis, 2002) in the EXT of fear learning. Imaging such brain areas across anxiety patients and healthy controls within fear-conditioning paradigms

designed to independently assess excitatory and inhibitory processes may provide useful information regarding the neurobiological basis of anxiety disorders.

*Limitations and future directions*

The primary limitations of the present study result from the paucity of studies in the target literature, the heterogeneity of methodologies applied across studies, and the lack of appropriate controls to protect against nonassociative confounds. The limited data precluded separate analyses of different anxiety diagnoses which may be very important given evidence for disorder-specific conditioning processes (for a review, see Mineka & Zinbarg, 1996). Additionally, the methodological heterogeneity across studies markedly increases the risk of third-variable influence on meta-analytic results. Furthermore, evidence of a modest publication bias against small sample sizes with medium to large negative effect sizes was found, indicating that the file-drawer problem may be artificially increasing the size of aggregated effects reported in the current study. Relatedly, fail-safe *N*'s for effect-size aggregations were small, indicating that significant effect sizes in the current study could be easily reduced below significance with the addition of a few unpublished null results. Finally, due to the absence of adequate controls for sensitization and habituation, nonassociative accounts of patient-control differences cannot be ruled out.

*Type of CS*

An additional limitation stems from the types of CSs used by studies in the target literature. Sixteen of the 20 studies presented colored lights, tones, or fear-irrelevant words as CSs. These CSs cannot be considered evolutionarily prepared because such stimuli have had little adaptive value across phylogeny (Öhman & Mineka, 2001; Seligman, 1971). Clinical and subclinical phobias, on the other hand, are generally formed for stimuli such as heights, closed spaces, blood, and animals (Agras, Chapin, & Oliveau, 1972; Marks, 1969) that are survival relevant in an evolutionary perspective. Using prepared CSs in experimental paradigms may thus be best for eliciting fear processes akin to those associated with phobic anxiety. Conditioning with prepared vs. unprepared stimuli may yield distinct results, as prepared stimuli are associated with faster fear learning, stronger fear responses, and greater resistance to EXT (for a review, see Öhman & Mineka, 2001). It would be interesting to see whether patient-control differences in conditioning are increased, decreased, or unchanged through the use of prepared CSs.

*Type of US*

In addition to the relative absence of prepared CSs in the target literature, existing studies rarely assess conditioned fear using CSs and USs with demonstrated relevance for the disorder under study. For example, threatening facial expressions and stimuli communicating physical threat have been shown to have particular salience for individuals with social anxiety and panic disorder, respectively (e.g., Horenstein & Segui, 1997; Lundh & Öst, 1996; Lundh, Thulin, Czyzykow, & Öst, 1998). Additionally, such axiogenic stimuli as $CO_2$-enriched air and public speaking have been shown to have particular relevance for individuals with panic disorder and social anxiety, respectively (e.g., Davidson, Marshall, Tomarken, & Henriques, 2000; Papp et al., 1997). Only three of the 20 studies meta-analyzed used CSs or USs relevant to the anxiety disorder under study.

Future use of prepared and/or disorder-specific CSs as well as disorder-specific USs would allow for the assessment of learning phenomena that are more analogous to naturally occurring conditioning correlates of pathological anxiety.

*Type of dependent variable*

Another limitation results from the frequent use of SCR to index the CR among studies in the target literature. Although SCR measures an autonomic correlate of sympathetic arousal (i.e., increased hydration of the sweat glands), it has questionable validity for the assessment of fear and anxiety. To start, SCR reflects changes in general arousal that may be associated with a number of different emotional states (for a review, see Cacioppo, Berntson, Larsen, Poehlmann, & Ito, 2000). Additionally, there is reason to believe that SCR is actually an index of attentional processes associated with the orienting reflex (Filion, Dawson, Schell, & Hazlett, 1991; Frith & Allen, 1983; Gray & McNaughton, 2000; Kirby, 1999; Sokolov, 1960). It should be noted that even if SCR primarily measures attention as opposed to emotion, it would still be expected to covary with anxious arousal, as fear-relevant stimuli draw preferential attentional focus (e.g., Carretie, Mercado, Tapia, & Hinojosa, 2001; Öhman, Flykt, & Esteves, 2001).

Measuring conditioned fear with FPS (enhancement of the startle reflex when an organism is in a state of fear or anxiety), as was done by a minority of studies in the target literature (Grillon et al., 1994; Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1998), may be advantageous for a few reasons. FPS is more valence specific than SCR as indicated by findings demonstrating startle attenuation and potentiation by pleasant and unpleasant images, respectively (for a review, see Bradley, Cuthbert, & Lang, 1999). Additionally, the construct validity of FPS as a measure of fear and anxiety is supported by the central role played by amygdaloid "fear circuits" in the potentiation of startle in both animal (e.g., Hitchcock & Davis, 1986) and human studies (Angrilli et al., 1996), as well as demonstrations of reduced and enhanced FPS following administration of anxiolytic (Bitsios, Philpott, Langley, Bradshaw, & Szabadi, 1999; Patrick, Berthot, & Moore, 1996) and anxiogenic agents (Davis, 1979; Davis, Redmond, & Baraban, 1979), respectively (although null relations between anxiolytics and FPS have also been reported; Baas et al., 2002). Finally, FPS allows for the measurement of anxious arousal during ITIs, which may be crucial for the independent assessment of excitatory and inhibitory fear processes (i.e., ITI vs. CS+ and CS−, respectively). Skin-conductance measures taken during ITI (i.e., SCL) cannot be compared to phasic SCRs because SCL and SCR measure distinct electrodermal processes. Thus, FPS but not SCL taken during ITI may be contrasted with responses to CS+ or CS−. Because of the aforementioned value of FPS, it is recommended that the CR be measured via FPS in conjunction with other indices of fear conditioning such as SCR and hear rate.

Finally, it should be mentioned that autonomic correlates of anxious arousal are not synonymous with fear and future fear-conditioning studies should collect self-reported measures of anxiety to lend construct validity to psychophysiological outcome measures.

*Need for prospective studies*

Although the current study attempts to examine conditioned fear as an etiological mechanism of anxiety disorders, the current literature tests individuals with existing disorders and it is

therefore unable to determine whether identified abnormalities predated the onset of the disorder or reflect "disease processes" of pathological anxiety. Studies using longitudinal designs to collect pre- and post-morbid conditioning rates among anxiety-disordered individuals are needed. The high-risk paradigm may be best suited for such a task (e.g., Grillon et al., 1998; Merikangas, Avenevoli, Dierker, & Grillon, 1999), whereby healthy individuals with the greatest likelihood of developing pathological anxiety (e.g., biological offspring of adults with anxiety disorders) would be tracked over time. Pre-morbid conditioning processes could then be compared across individuals who do and do not develop pathological anxiety to identify conditioning precipitants of anxiety disorders.

### *Improving the way ACQ and EXT is calculated*

Both ACQ and EXT of fear learning are generally indexed as the average CR across ACQ and EXT trials, respectively. This is a particularly problematic in the case of EXT. Such measures of EXT actually reflect levels of ACQ as much as they reflect EXT of learning. Computing EXT as the percent change in CR magnitude (from beginning to end of EXT) would provide a better index of EXT because such an index would be less influenced by levels of ACQ. Additionally, operationalizing ACQ as the change over time in CRs would be advantageous in that the learning curve would be captured via analyses.

### *Beyond ACQ and EXT*

Although most conditioning studies of anxiety disorders measure ACQ and/or EXT processes exclusively, several other fear-learning phenomena have been identified in the animal literature that have yet to be tested in anxiety patients (e.g., conditioned inhibition, latent inhibition, post-conditioning inflation/deflation, recovery, reinstatement, and renewal). Although an elaborative discussion of these animal findings is beyond the scope of this paper, such findings illustrate specific learning mechanisms through which conditioned fear may be activated/enhanced (e.g., inflation, recovery, reinstatement, and renewal) and inhibited/reduced (e.g., deflation, conditioned inhibition, latent inhibition). Future studies of such mechanisms across anxiety patients and healthy controls may contribute toward a better understanding of inhibitory and excitatory irregularities in the fear system associated with clinical anxiety.

Additionally, *retention* of conditioning is an important aspect of fear learning that may have special relevance for clinical anxiety (e.g., PTSD), yet very few studies have assessed retention in patient populations (Grillon & Morgan, 1999). Although the majority of trauma survivors (65–94%) display posttraumatic symptoms in the early aftermath of the traumatic event (Rothbaum & Foa, 1993), PTSD develops only in a minority of survivors who retain such symptoms beyond 1 month's time. (American Psychiatric Association, 1994). Given that conditioned fear responding to 'trauma reminders' is a central symptom of PTSD and retention rather than ACQ rates of symptoms are pathoneumonic of the disorder, retention but not ACQ of conditioned fear may be the most important conditioning correlate of PTSD.

An additional benefit of retention stems from the fact that the neurobiology of fear conditioning was largely mapped using animal findings for which levels of ACQ were assessed on a test day separate from the day of training (i.e., assessed retention rather than immediate ACQ).

As such, retention of fear learning in humans may best facilitate neurobiological inferences from the animal to human literatures on conditioned fear.

## Conclusions

The current meta-analysis found significant elevations in levels of conditioned responding during both ACQ and EXT of learned fear among anxiety-disordered individuals. Results implicate two mechanisms as potential mediators of such patient-control conditioning differences: (1) greater excitatory conditioning to danger cues (CS+) among patients vs. controls and (2) impaired inhibitory conditioning to safety signals (CS−) among patients compared to controls. It is therefore recommended that future studies apply discrimination paradigms that allow for the measurement of anxiety during CS+, CS−, and ITI so that contributions of excitatory (CS+ minus ITI) and inhibitory mechanisms (CS− minus ITI) toward the etiology and maintenance of pathological anxiety may be examined independently. Because target studies employed insufficient controls for sensitization and habituation, nonassociative accounts of current findings cannot be rejected. Future studies testing responses to CSs within both paired and unpaired CS/US experiments will contribute importantly towards ruling out nonassociative mechanisms for patient-control differences in conditioning.

Further recommendations for the current literature include future use of prepared and disorder relevant CSs as well as disorder relevant USs, increased use of FPS to index the CR, longitudinal (prospective) assessments of conditioning processes among individuals at risk for anxiety disorders, increased use of change scores rather than absolute levels of conditioned responding to index ACQ and EXT, future investigations of patient-control differences in learning phenomena found to modulate excitatory and inhibitory learning in animals and/or nonclinical human populations (e.g., conditioned inhibition, latent inhibition, US inflation and deflation), and increased focus on retention of conditioned fear.

## References

Agras, W. S., Chapin, H., & Oliveau, D. C. (1972). The natural history of phobia. *Archives of General Psychiatry*, *26*, 315–317.

Alloy, L. B., & Abramson, L. Y. (1979). Judgment of contingency in depressed and non-depressed students: sadder but wiser? *Journal of Experimental Psychology: General*, *108*, 441–448.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.

Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G., & di Paola, F. (1996). Startle reflex and emotion modulation impairment after a right amygdala lesion. *Brain*, *119*, 1991–2000.

Annau, Z., & Kamin, L. J. (1961). The conditioned emotional response as a function of US intensity. *Journal of Comparative and Physiological Psychology*, *54*, 428–432.

* Ashcroft, K. R., Guimarães, F. S., Wang, M., & Deakin, J. F. W. (1991). Evaluation of a psychophysiological model of classical fear-conditioning in anxious patients. *Psychopharmacology*, *104*, 215–219.

*References marked with an asterisk indicate studies included in the meta-analysis.

Baas, J. M., Grillon, C., Bocker, K. B., Brack, A. A., Morgan, C. A., III, Kenemans, J. L., & Verbaten, M. N. (2002). Benzodiazepines have no effect on fear-potentiated startle in humans. *Psychopharmacology*, *161*, 233–247.

Barlow, D. H. (2002). *Anxiety and its disorders: the nature and treatment of anxiety and panic*. New York: The Guilford Press.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, *269*, 1115–1118.

Bitsios, P., Philpott, A., Langley, R. W., Bradshaw, C. M., & Szabadi, E. (1999). Comparison of the effects of diazepam on the fear-potentiated startle reflex and the fear-inhibited light reflex in man. *Journal of Psychopharmacology*, *13*, 226–234.

Blair, H. T., Schafe, G. E., Bauer, E. P., Rodrigues, S. M., & LeDoux, J. E. (2001). Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear-conditioning. *Learning & Memory*, *8*, 229–242.

Bouton, M. D., & Bolles, R. C. (1979). Contextual control of the extinction of conditioned fear. *Learning and Motivation*, *10*, 455–466.

Bouton, M. D., & Bolles, R. C. (1985). *Context, event-memories, and extinction*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1999). Affect and the startle reflex. In M. E. Dawson & A. M. Schell (Eds.), *Startle modification: implications for neuroscience, cognitive Science, and clinical science* (pp. 157–183).

Bridger, W. H., & Mandel, I. J. (1964). A comparison of GSR fear responses produced by threat and electric shock. *Journal of Psychiatric Research*, *2*, 31–40.

Bryk, A. S., & Raudenbush, S. W. (1992). *Hierarchical linear models*. London, England: Sage.

Büchel, C., & Dolan, R. J. (2000). Classical fear-conditioning in functional neuroimaging. *Current Opinion in Neurobiology*, *10*, 219–223.

Cacioppo, J. T., Berntson, G. G., Larsen, J. T., Poehlmann, K. M., & Ito, T. A. (2000). The psychophysiology of emotion. In M. Lewis & J. M. Haviland-Jones (Eds.), *Handbook of emotions* (2nd ed., pp. 173–191).

Calton, J. L., Mitchell, K. G., & Schachtman, T. R. (1996). Conditioned inhibition produced by extinction of a conditioned stimulus. *Learning and Motivation*, *27*, 335–361.

Carretie, L., Mercado, F., Tapia, M., & Hinojosa, J. (2001). Emotion, attention, and the 'negativity bias', studied through event-related potentials. *International Journal of Psychophysiology*, *41*, 75–85.

Clemens, T. L., & Selesnick, S. T. (1967). Psychophysiological method for evaluating medication by repeated exposure to a stressor film. *Diseases of the Nervous System*, *28*, 98–104.

* Clum, G. A. (1969). A correlational analysis of the relationships between personality and perceptual variables and discriminant GSR conditioning. *Journal of Clinical Psychology*, *25*, 33–35.

Cohen, J. (1960). A coefficient of agreement for nominal scales. *Educational and Psychological Measurement*, *20*, 37–46.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed). Hillsdale, NJ: Lawrence Erlbaum Associates.

Davidson, R. J., Marshall, J. R., Tomarken, A. J., & Henriques, J. B. (2000). While a phobic waits: regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. *Biological Psychiatry*, *47*, 85–95.

Davis, M. (1979). Diazepam and flurazepam: effects on conditioned fear as measured with the potentiated startle paradigm. *Psychopharmacology*, *62*, 1–7.

Davis, M. (1998). Are different parts of the extended amygdala involved in fear versus anxiety? *Biological Psychiatry*, *44*, 1239–1247.

Davis, M. (2002). Role of NMDA receptors and MAP kinase in the amygdala in extinction of fear: clinical implications for exposure therapy. *European Journal of Neuroscience*, *16*, 395–398.

Davis, M., Falls, W. A., & Gewirtz, J. (2000). Neural systems involved in fear inhibition: extinction and conditioned inhibition. In M. Myslobodsky & I. Weiner (Eds.), *Contemporary issues in modeling psychopathology* (pp. 113–142).

Davis, M., Redmond, D. E., & Baraban, J. M. (1979). Noradrenergic agonists and antagonists: effects on conditioned fear as measured by the potentiated startle paradigm. *Psychopharmacology*, *65*, 111–118.

* Del-Ben, C. M., Vilela, J. A. A., Hetem, L. A. B., Guimarães, F. S., Graeff, F. G., & Zuardi, A. W. (2001). Do panic patients process unconditioned fear vs. conditioned anxiety differently than normal subjects? *Psychiatry Research*, *104*, 227–237.

Dickinson, A. (1976). Appetitive–aversive interactions: facilitation of aversive conditioning by prior appetitive training in the rat. *Animal Learning and Behavior*, *4*, 416–420.

Dohrenwend, B. P., & Shrout, P. E. (1981). Toward the development of a two-stage procedure for case identification and classification in psychiatric epidemiology. *Research in Community & Mental Health*, *2*, 295–323.

Eysenck, H. J. (1976). The learning theory model of neurosis: a new approach. *Behaviour Research and Therapy*, *14*, 251–267.

Eysenck, H. J. (1979). The conditioning model of neurosis. *Behavioral and Brain Sciences*, *2*, 155–199.

Eysenck, H. J., & Rachman, S. J. (1965). *Causes and cures of neurosis*. London: Routledge & Kegan Paul.

* Fayu, C. (1961). Fear conditioning with normals, neurotics, & schizophrenics. *Acta Psychologica Taiwanica*, *3*, 18–33.

Fendt, M. (1998). Different regions of the periaqueductal grey are involved differently in the expression and conditioned inhibition of fear-potentiated startle. *European Journal of Neuroscience*, *10*, 3876–3884.

Filion, D. L., Dawson, M. E., Schell, A. M., & Hazlett, E. A. (1991). The relationship between skin conductance orienting and the allocation of processing resources. *Psychophysiology*, *28*, 410–424.

Frith, C. D., & Allen, H. A. (1983). The skin conductance orienting response as an index of attention. *Biological Psychology*, *17*, 27–39.

Gleser, L. J., & Olkin, I. (1994). Stochastically dependent effect sizes. In H. Cooper, & L. V. Hedges (Eds.), *The handbook of research synthesis* (pp. 339–355). New York: Russell Sage Foundation.

Gorman, J. M., Kent, J. M., Sullivan, G. M., & Coplan, J. D. (2000). Neuroanatomical hypothesis of panic disorder, revised. *American Journal of Psychiatry*, *157*, 493–505.

Grant, D. A. (1964). Classical and operant conditioning. In A. W. Melton (Ed.), *Categories of human learning*. New York: Academic Press.

Gray, J. A., & McNaughton, N. (2000). *The neuropsychology of anxiety*. New York: Oxford University Press.

Green, B. L., Lindy, J. D., Grace, M. C., Glazerser, G., Leanord, A., Korol, M., & Windget, C. (1990). Buffalo Creek survivors in the second decade: stability of stress symptoms. *American Journal of Orthopsychiatry*, *60*, 43–54.

Grillon, C. (2002). Associative learning deficits increase symptoms of anxiety in humans. *Biological Psychiatry*, *51*, 851–858.

Grillon, C., & Ameli, R. (2001). Conditioned inhibition of fear-potentiated startle and skin conductance in humans. *Psychophysiology*, *38*, 807–815.

* Grillon, C., Ameli, R., Goddard, A., Woods, S. W., & Davis, M. (1994). Baseline and fear-potentiated startle in panic disorder patients. *Biological Psychiatry*, *35*, 431–439.

Grillon, C., Dierker, L., & Merikangas, K. R. (1998). Fear-potentiated startle in adolescent offspring of parents with anxiety disorders. *Biological Psychiatry*, *44*, 990–997.

* Grillon, C., & Morgan, C. A., III (1999). Fear-potentiated startle conditioning to explicit and contextual cues in Gulf War veterans with posttraumatic stress disorder. *Journal of Abnormal Psychology*, *108*, 134–142.

* Grillon, C., Morgan, C. A., III, Davis, M., & Southwick, S. M. (1998). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry*, *44*, 1027–1036.

Grivois, H., Deniker, P., & Ganry, H. (1992). Efficacy of tianeptine in the treatment of psychasthenia. A study versus placebo. *Encephale*, *18*, 591–599.

Groves, P. M., & Thompson, R. F. (1970). Habituation: a dual process theory. *Psychological Review*, *77*, 419–450.

* Halberstam, J. L. (1961). Some personality correlates of conditioning, generalization, and extinction. *Psychosomatic Medicine*, *23*, 67–76.

Hall, G., & Pearce, J. M. (1979). Latent inhibition of a CS during CS–US pairings. *Journal of Experimental Psychology: animal Behavior Processes*, *5*, 31–42.

Hedges, L. V. (1994). Fixed effects models. In H. Cooper, & L. V. Hedges (Eds.), *The handbook of research synthesis* (pp. 285–299). New York: Russell Sage Foundation.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando, FL: Academic Press.

* Hermann, C., Ziegler, S., Birbaumer, N., & Flor, H. (2002). Psychophysiological and subjective indicators of aversive Pavlovian conditioning in generalized social phobia. *Biological Psychiatry*, *52*, 328–337.

Hilgard, E. R., & Marquis, D. G. (1940). *Conditioning and learning*. New York: Appleton-Century.

Hitchcock, J. M., & Davis, M. (1986). Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. *Behavioral Neuroscience*, *100*, 11–22.

Horenstein, M., & Segui, J. (1997). Chronometrics of attentional processes in anxiety disorders. *Psychopathology*, *30*, 25–35.

* Howe, E. S. (1957). GSR conditioning in anxiety states, normals, and chronic functional schizophrenic subjects. *Journal of Abnormal and Social Psychology*, *56*, 183–189.

Hunter, J., & Schmidt, F. (1990). *Methods of meta-analysis: correcting error and bias in research findings*. Newbury Park, CA: Sage.

Johnson, B. T. (1989). *DSTAT: software for the meta-analytic review of research literatures, version 1.11*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Kirby, L. D. (1999). Emotion or attention. The psychological significance of electrodermal activity. *Dissertation Abstracts International Section B: the Sciences and Engineering*, *60*(6-B), 3017.

Konorski, J. (1948). *Conditioned reflexes and neuronal organization*. London: Cambridge University Press.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed trial fMRI study. *Neuron*, *20*, 937–945.

LaBar, K. S., LeDoux, J. E., Spencer, D. D., & Phelps, E. A. (1995). Impaired fear conditioning following unilateral temporal labectomy in humans. *Journal of Neuroscience*, *15*, 6846–6855.

Lader, M. H., & Wing, L. (1964). Habituation of the psycho-galvanic reflex in patients with anxiety states and in normal subjects. *Journal of Neurological and Neurosurgical Psychiatry*, *27*, 210–218.

Lanteri-Laura, G. (1994). Psychasthenia: history and evolution of the P. Janet concept. *Encephale*, *3*, 551–557.

LeDoux, J. (1998). Fear and the brain: where have we been, and where are we going? *Biological Psychiatry*, *44*, 1229–1238.

LeDoux, J. E., Romanski, L., & Xagoraris, A. (1989). Indelibility of subcortical memories. *Journal of Cognitive Neuroscience*, *1*, 238–243.

Lewis, N. D. C., & Engle, B. (1954). *Wartime psychiatry: a compendium of the international literature*. New York: Oxford University Press.

Light, R. J., & Pillemer, D. B. (1984). *Summing up: the science of reviewing research*. Cambridge, MA: Harvard University Press.

Littell, R. C., Milliken, A. G., & Stroup, W. W. (1996). *SAS system for mixed models*. Cary, NC: SAS Institute Inc.

Lubow, R. E., & Moore, A. U. (1959). Latent inhibition: the effect of nonreinforced pre-exposure to the conditional stimulus. *Journal of Comparative and Physiological Psychology*, *52*, 415–419.

Lundh, L. G., & Öst, L. G. (1996). Recognition bias for critical faces in social phobics. *Behaviour Research and Therapy*, *34*, 787–794.

Lundh, L. G., Thulin, U., Czyzykow, S., & Öst, L. G. (1998). Recognition bias for safe faces in panic disorder with agoraphobia. *Behaviour Research and Therapy*, *36*, 323–327.

Mackintosh, N. J. (1983). *Conditioning and associative learning*. Oxford: Oxford University Press.

Mandel, I. J., & Bridger, W. H. (1973). Is there classical conditioning without cognitive expectancy? *Psychophysiology*, *10*, 87–90.

Marks, I. M. (1969). *Fears and phobias*. London: Heinemann.

Marks, I. M. (1978). *Living with fear: understanding and coping with anxiety*. New York: McGraw-Hill.

Matt, G. E., & Cook, T. D. (1994). Threats to the validity of research syntheses. In H. Cooper, & L. V. Hedges (Eds.), *The handbook of research synthesis* (pp. 503–520). New York: Russell Sage Foundation.

Merikangas, K. R., Avenevoli, S., Dierker, L., & Grillon, C. (1999). Vulnerability factors among children at risk for anxiety disorders. *Biological Psychiatry*, *46*, 1523–1535.

Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, *420*, 70–74.

Miller, N. E. (1948). Studies of fear as a learnable drive: I. Fear as motivation and fear reduction as reinforcement in the learning of new responses. *Journal of Experimental Psychology*, *38*, 89–101.

Mineka, S., & Cook, M. (1986). Immunization against the observational conditioning of snake fear in rhesus monkeys. *Journal of Abnormal Psychology*, *95*, 307–318.

Mineka, S., & Öhman, A. (2002). Phobias and preparedness: the selective, automatic, and encapsulated nature of fear. *Biological Psychiatry*, *52*, 927–937.

Mineka, S., & Zinbarg, R. (1996). Conditioning and ethological models of anxiety disorders: stress-in-dynamic-context anxiety models. In D. A. Hope (Ed.), *Nebraska symposium on motivation: Vol. 43. Perspectives on anxiety, panic, and fear*. Lincoln: University of Nebraska Press.

* Morgan, C. A., Grillon, C., Southwick, S. M., Davis, M., & Charney, D. S. (1995). Fear-potentiated startle in posttraumatic stress disorder. *Biological Psychiatry*, *36*, 378–385.

Morgan, M. A., Romanski, L. M., & LeDoux, J. E. (1993). Extinction of emotional learning: contribution of medial prefrontal cortex. *Neuroscience Letters*, *163*, 109–113.

Mowrer, O. H. (1947). On the dual nature of learning: a reinterpretation of "conditioning" and "problem solving". *Harvard Educational Review*, *17*, 102–148.

Mowrer, O. H. (1960). *Learning theory and behavior*. New York: Wiley.

Nunnally, J. C. (1978). *Psychometric theory* (2nd ed.). New York: McGraw-Hill Book Company.

Öhman, A. (1986). Face the beast and fear the face: animal and social fears as prototypes for evolutionary analyses of emotion. *Psychophysiology*, *23*, 123–145.

Öhman, A., Flykt, A., & Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. *Journal of Experimental Psychology: general*, *130*, 466–478.

Öhman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review*, *108*, 483–522.

* Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., & Pitman, R. K. (2000). De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology*, *109*, 290–298.

Orwin, R. G. (1994). Evaluating coding decisions. In H. Cooper, & L. V. Hedges (Eds.), *The handbook of research synthesis* (pp. 139–162). New York: Russell Sage Foundation.

Papp, L. A., Martinez, J. M., Klein, D. F., Coplan, J. D., Norman, R. G., Cole, R., de Jesus, M. J., Ross, D., Goetz, R., & Gorman, J. M. (1997). Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *American Journal of Psychiatry*, *154*, 1557–1565.

Patrick, C. J., Berthot, B. D., & Moore, J. D. (1996). Diazepam blocks fear-potentiated startle in humans. *Journal of Abnormal Psychology*, *105*, 89–96.

Pavlov, I. (1927). *Conditioned reflexes*. London: Oxford University Press.

Pearce, J. M., Kaye, H., & Hall, G. (1982). Predictive accuracy and stimulus associability: development of a model for Pavlovian learning. In M. L. Commons, R. J. Herrnstein, & A. R. Wagner (Eds.), *Quantitative analysis of behavior*, Vol. 3 (pp. 241–255). Cambridge, MA: Ballinger.

* Peri, T., Ben Shakhar, G., Orr, S. P., & Shalev, A. Y. (2000). Psychophysiologic assessment of aversive conditioning in postraumatic stress disorder. *Biological Psychiatry*, *47*, 512–519.

Pine, D. S. (1999). Pathophysiology of childhood anxiety disorders. *Biological Psychiatry*, *46*, 1555–1566.

* Pitman, R. K., & Orr, S. P. (1986). Test of the conditioning model of neurosis: Differential aversive conditioning of angry and neutral facial expressions in anxiety disorder patients. *Journal of Abnormal Psychology*, *95*, 208–213.

* Pliszka, S. R., Hatch, J. P., Borcherding, S. H., & Rogeness, G. A. (1993). Classical conditioning in children with attention deficit hyperactivity disorder (ADHD) and anxiety disorders: a test of Quay's model. *Journal of Abnormal Child Psychology*, *21*, 411–423.

Rachman, S. (1977). The conditioning theory of fear-acquisition: a critical examination. *Behaviour Research and Therapy*, *15*, 375–387.

Rachman, S. (1991). Neo-conditioning and the classical theory of fear acquisition. *Clinical Psychology Review*, *11*, 155–173.

Ramnani, N., Toni, I., Josephs, O., Ashburner, J., & Passingham, R. E. (2000). Learning- and expectation-related changes in the human brain during motor learning. *Journal of Neurophysiology*, *84*, 3026–3035.

Rosenthal, R. (1979). Comment: assumptions and procedures in the file drawer problem. *Psychological Bulletin*, *86*, 638–641.

Rothbaum, B. A., & Foa, E. B. (1993). Subtypes of posttraumatic stress disorder and duration of symptoms. In J. R. Davidson, & E. B. Foa (Eds.), *Posttraumatic stress disorder: DSM-IV and beyond*, Vols. 23–35. Washington, DC: American Psychiatric Press.

Schachtman, T. R., Threlkeld, R., & Meyer, K. (2000). Retention of conditioned inhibition produced by extinction. *Learning and Motivation*, *31*, 283–300.

Schmaltz, L. W., & Theiosus, J. (1972). Acquisition and extinction of a classically conditioned response in hippocampectomized rabbits (*Oryctolagus cuniculus*). *Journal of Comparative and Physiological Psychology*, *79*, 328–333.

* Schneider, F., Weiss, U., Kessler, C., Müller-Gärtner, H. W., Posse, S., Salloum, J. B., Grodd, W., Himmelmann, F., Gaebel, W., & Birbaumer, N. (1999). Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biological Psychiatry*, *45*, 863–871.

Schwarzer, R. (1989). *Meta-analysis programs, version 5.3*. Berlin, Germany: Author.

Seligman, M. E. (1971). Phobias and preparedness. *Behavior Therapy*, *2*, 307–320.

* Sloane, R. B., Davidson, P. O., Staples, F., & Payne, R. W. (1965). Experimental reward and punishment in neurosis. *Comprehensive Psychiatry*, *6*, 388–395.

Sokolov, E. N. (1960). Neuronal models and the orienting reflex. In M. A. B. Brazier (Ed.), *The Central Nervouse System and Behaviour* (pp. 187–276). New York: Josia Macy Jr. Foundation.

Stewart, M. A., Winokur, G., Stern, J. A., Guze, S. B., Pfeiffer, E., & Hornung, F. (1959). Adaptation and conditioning of the galvanic skin response in psychiatric patients. *Journal of Mental Science*, *105*, 1102–1111.

* Thayer, J. F., Friedman, B. H., Borkovec, T. D., Johnsen, B. H., & Molina, S. (2000). Phasic heart period reactions to cued threat and nonthreat stimuli in generalized anxiety disorder. *Psychophysiology*, *37*, 361–368.

Thomas, E., Yadin, E., & Strickland, C. E. (1991). Septal unit activity during classical conditioning: a regional comparison. *Brain Research*, *547*, 303–308.

* Van den Bergh, O., Stegen, K., & Van de Woestijne, K. P. (1997). Learning to have psychosomatic complaints'': Conditioning of respiratory behavior and somatic complaints in psychosomatic patients. *Psychosomatic Medicine*, *59*, 13–23.

* Veit, R., Flor, H., Erb, H., Hermann, C., Lotze, M., Grodd, W., & Birbaumer, N. (2002). Brain circuits involved in emotional learning and antisocial behavior and social phobia in humans. *Neuroscience Letters*, *328*, 233–236.

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology*, *3*, 1–14.

Yadin, E., & Thomas, E. (1981). Septal correlates of conditioned inhibition. *Journal of Comparative and Physiological Psychology*, *95*, 331–340.