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Fear conditioning and extinction in anxious and non-anxious youth: A meta-analysis

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ABSTRACT

Fear conditioning and extinction have been implicated in the etiology and maintenance of anxiety disorders. Most fear conditioning studies have been conducted with adult samples and the few published developmental studies in clinically anxious youth have yielded inconsistent results. The aim of the current review was to use meta-analysis to examine possible differences in fear conditioning and extinction in clinically anxious and non-anxious youth. Seven fear conditioning studies were included in the analysis, with a total of 160 clinically anxious and 166 non-anxious youth. All the studies included in the meta-analysis used a differential conditioning paradigm with at least one or more of the primary dependent variables: self-reported fear, skin conductance response (SCR) and fear potentiated startle (FPS). Similar differential fear acquisition and extinction patterns were observed in anxious and non-anxious individuals. However, anxious youth exhibited stronger fear responses to individual stimuli compared to their non-anxious counterparts. Results in clinically anxious youth resemble those reported in previous studies with clinically anxious adults. Importantly, due to the small number of fear learning studies conducted among youth, these results should be interpreted with caution. Further research is needed so as to better understand fear acquisition and extinction processes in developmental populations. In addition, future studies should focus on other fear-related learning processes such as differences in return of fear, retrieval of fear memory and more subtle differences in fear generalization.

1. Introduction

Anxiety disorders are among the most prevalent form of psychopathology both in youth and adults and can lead to significant distress and functional impairment (Beesdo, Knappe, & Pine, 2009; Kessler et al., 2005). Fear conditioning and extinction paradigms are commonly used to study the behavioral, neural and cognitive processes underpinning these disorders. To date, two meta-analyses compared fear conditioning and extinction in anxious and non-anxious populations (Duits et al., 2015; Lissek et al., 2005). Both found modest differences between groups; however, neither meta-analysis focused on clinically anxious youth. The aim of the current meta-analysis is to address this gap and assess differences between anxious and non-anxious youth in studies using fear conditioning and extinction paradigms.

Classical fear conditioning paradigms are usually comprised of two phases. The first is *fear acquisition*, during which a neutral stimulus (CS) is repeatedly paired with an aversive unconditional stimulus (US), leading to a conditioned response (CR). The neutral stimulus consequently becomes a conditioned stimulus (CS+), eliciting a fearful response even without the US presentation. Following acquisition, the second phase, *fear extinction*, takes place whereby the CS+ is repeatedly presented in the absence of the US. In successful extinction, the CR in response to the CS + declines. In differential conditioning paradigms, which are commonly used in human studies, two CSs are presented. One is paired with the US (danger cue; CS+) while the second is not (safety cue; CS-). These paradigms allow the comparison of excitatory processes to the CS+ and inhibitory processes to the CS-. Differential learning can be computed by subtracting the CR to the CS- from the CR to the CS+ [(CS+) – (CS-)]. In human studies fear conditioning and its extinction are often measured via autonomic activity (e.g., heart-rate, skin conductance (SCR)), modulation of autonomic reflex expressions (e.g., fear potentiated startle (FPS)), neural activity, and self-reported (SR) fear ratings (Duits et al., 2015; Lissek et al., 2005; Lonsdorf et al., 2017).

Impaired fear acquisition and extinction have long been considered key components in the etiology and maintenance of pathological

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anxiety. Two primary processes have been posited to account for possible alterations in these learning processes among anxious individuals. The first highlights excitatory processes and suggests that compared to healthy individuals, anxious individuals exhibit stronger and more rapid fear responses to the CS+ during fear acquisition and extinction. If true, anxious individuals would be expected to show greater differential response in both phases of fear learning (Orr et al., 2000). An alternative explanation focuses on inhibitory processes, suggesting that anxious individuals fail to inhibit fear responses in the presence of safety cues (e.g., CS-). If this were the case, anxious individuals would be expected to have higher fear responses to the CS- and potentially lower differential scores during fear acquisition and extinction (Davis, 2000). Of note, while excitatory processes depict a stronger direct fear response to the CS+, and can solely explain differential learning, inhibitory processes typically depend on additional learning mechanisms. For example, the generalization of fear from the CS + to the CS- or the generalization of fear onto the background context in which fear acquisition occurred. Notably, both of these examples demonstrate the interaction between excitatory and inhibitory processes, which are often intertwined.

Results from two previous meta-analyses in adults provide partial support for the involvement of both processes. The first meta-analysis included 20 studies with 453 anxious and 455 non-anxious adults (Lissek et al., 2005); the second meta-analysis included 44 studies with 963 anxious and 1222 non-anxious adults (Duits et al., 2015). During fear acquisition, in support of the explanation highlighting excitatory processes, Lissek et al. (2005) found that anxious adults had greater excitatory conditioning to danger cues (CS+) compared to their non-anxious peers. In support of the explanation highlighting inhibitory processes, Duits et al. (2015) found group differences in responses to safety cues (CS-), with inhibitory conditioning to the CS- impaired in anxious compared to non-anxious adults. Findings in extinction were more ambiguous. Both Lissek et al. (2005) and Duits et al. (2015) found a stronger fear response to the CS + among anxious as compared to non-anxious adults, which could reflect either excitatory processes (i.e., responding more strongly to threat cues) or an impairment in inhibitory processes (i.e., impaired safety learning). Interestingly, neither meta-analyses found significant group differences in differential learning.

The lack of conclusive support for either excitatory or inhibitory processes in the two adult meta-analyses, in addition to the lack of observed differences that emerged in differential learning, suggests that further research is needed. Moreover, as anxiety is the most prevalent form of pediatric psychopathology (Kessler et al., 2005; Lijster et al., 2017), examining possible differences in fear learning among anxious and non-anxious youth would provide a better understanding of the processes underpinning the development of pediatric anxiety.

And yet, only seven classical fear conditioning studies have been conducted with clinically anxious and non-anxious youth yielding mixed findings. For example, one study found that during fear acquisition the CS+ was rated as more unpleasant than the CS- among anxious but not among non-anxious youth (Craske et al., 2008). In another study, anxious youth did not show differential learning following fear acquisition, while non-anxious youth exhibited expected learning effects (Liberman, Lipp, Spence, & March 2006). In two additional studies, both anxious and non-anxious youth exhibited differential learning following fear acquisition, although the anxious group reported higher overall fear to CS+ (Britton et al., 2013; Lau et al., 2008). Equivocal results also arise for extinction learning. Some studies demonstrated impaired extinction in anxious youth as indicated by higher reported fear levels to the CS + than the CS- (Craske et al., 2008; Liberman et al., 2006), while other studies found that in some measures both anxious and non-anxious children exhibited extinction (Britton et al., 2013; Shechner et al., 2015); in yet another study, both groups failed to show extinction (Lau et al., 2008).

The dearth in fear learning studies among anxious youth is largely due to methodological concerns and ethical challenges. These include choice of proper measures during fear conditioning and extinction (e.g., differences in ability to provide reliable self-reported fear ratings) and the selection of a US potent enough to elicit fear while concurrently developmentally appropriate. Specifically, while most adult fear learning studies use electrical shock as the US, youth fear learning studies typically use aversive sounds as the US (for review, see Shechner, Hong, Britton, Pine, & Fox, 2014). Given the methodological challenges outlined above, it is not surprising that sample sizes in the aforementioned studies were relatively small, yielding inconsistent findings across studies. Moreover, the use of dissimilar dependent measures and the different ways in which these measures were utilized during the respective tasks might also account for differences across studies. The aim of the present meta-analysis is therefore to aggregate and compare fear conditioning and extinction results from several studies conducted with anxious and non-anxious youth.

2. Method

2.1. Selection of studies

Studies were identified by searching the prominent online databases (PubMed, Psychinfo and Web of Science) using the following keywords and their combinations: conditioned, conditioning, fear conditioning in children, pediatric fear conditioning, extinction in children, extinction in pediatric anxiety, fear learning in children, and classical conditioning in children. In addition to the online literature search, a call for unpublished data was sent to major researchers in the field based on available published papers. Studies were selected if they included: 1) youth with an anxiety disorder and a comparison group of non-anxious youth; 2) diagnosis was established based on a validated clinical interview; and 3) differential fear conditioning was used in the study. These inclusion criteria were largely similar to those used in previous meta-analyses conducted with adult samples (Duits et al., 2015; Lissek et al., 2005).

2.2. Effect sizes estimates

Hedges' g was used as an index of effect size. This index was selected as it corrects for bias in estimates of population effect sizes (Hedges & Olkin, 1985). In some cases, it indicated the standardized mean difference in fear responses between anxious and non-anxious individuals, while in other cases it indicated the standardized mean difference in fear responses between the two CSs (CS + vs. CS-). When effect sizes describe the difference between groups, positive values reflect stronger fear responses in the anxious as compared to the non-anxious group. Negative effect sizes indicate larger fear responses in the non-anxious compared to the anxious group. When effect sizes describe the difference between the CSs, positive values indicate stronger fear responses to the CS + versus the CS-, while negative values indicate stronger fear responses to the CS- versus the CS+. In all cases, 95% confidence intervals for the effect sizes were computed.

Effect sizes were calculated separately for both learning phases (fear acquisition and extinction), type of stimulus (CS+; CS-; [(CS+) – (CS-)]), and type of outcome measure (SR, SCR and FPS). In order to maintain independence of errors, only one effect size from each study was included in the final meta-analyses. Specifically, a combined fear index was computed by averaging the effect sizes of each dependent measure used in each study (SR, SCR and FPS). This method allowed us to examine a single, comprehensive fear response outcome. In studies using only a single dependent variable measure, the effect size of the reported measure was used. Effect sizes were computed from raw data received from authors of all seven studies included in the meta-analysis. These data were comprised of means, standard deviations for each measure, and correlations between the CS+ and CS-. When correlations were not available an average of correlations in similar sub groups was used (age, type of group and type of dependent measure).

2.3. Random Effects Model

Data included in this meta-analysis were collected from studies conducted in different locations and times. Accordingly, the experimental circumstances, means, and scientific principles presumably varied across studies in numerous ways that could not be assessed. Thus, a Random Effects Model (REM) was applied to deal with random effects variance (Borenstein, Hedges, Higgins, & Rothstein, 2010).

2.4. Statistical analyses

Statistical analysis was conducted using Comprehensive Meta-Analysis (version 2, 2014). Six meta-analyses were performed to assess differences between anxious and non-anxious youth in fear responses to the CS+, the CS-, and the differences between the CS+ and the CS- (differential learning). These analyses were conducted for fear acquisition and fear extinction separately. When studies included data for both youth and adults, only data pertaining to youth were included in the meta-analyses.

Some studies used multiple questions as self-reported measures of fear. Effect sizes for each measure were computed and are presented in the results section. However, when creating combined effect sizes, only one self-reported measure of fear was used. Specifically, we used a direct assessment of self-reported fear when available. When not available, we used self-reported valence.

2.5. Effect-size aggregation

For each meta-analysis, a weighted grand mean of the combined effect sizes was computed, giving greater weights to more precise effect-size estimates. Specifically, weights were determined by an estimation approximate to the inverse of its sampling variance (Borenstein et al., 2010).

2.6. Publication bias

Publication bias was visually assessed using funnel plots. These plots illustrate a measure of study size (in this case, standard error) as a function of effect size. The presence of bias is indicated by a higher concentration of studies to one side of the mean as compared to the other, as opposed to a symmetric distribution. Additionally, Duval and Tweedie's trim and fill method was used in order to examine how the aggregated effect size would change if bias were to be removed using the insertion of imputed hypothetical studies (Duval & Tweedie, 2000).

3. Results

We identified 7 studies that met inclusion criteria and included 160 anxious youth (*Mean* age = 11.22 years) and 166 non-anxious youth (*Mean* age = 12.66 years). Studies were published between the years 2006 and 2017. The included studies, with their characteristics and corresponding effect sizes, are presented in Table 1 (Britton et al., 2013; Craske et al., 2008; Haddad, Bilderbeck, James, & Lau, 2015; Lau et al., 2008; Liberman et al., 2006; Shechner et al., 2015; Waters, Henry, & Neumann, 2009). In the following sections we first present data on differential learning (CS + minus CS-) and then data on responses to each stimulus separately (CS+,CS-).

3.1. Group differences in differential learning - effect sizes (d difference of CS + minus CS-)

3.1.1. Fear acquisition

For differential learning (CS + minus CS-) during fear acquisition an aggregated small effect size was found for both the anxious [$d = 0.374$, $N = 7$, $p < .001$, $CI_{(95\%)}$ (0.216, 0.533)] and non-anxious groups [$d = 0.356$, $N = 7$, $p < .001$, $CI_{(95\%)}$ (0.206, 0.506)]. The difference between these effect sizes were non-significant, $Q_B = 0.026$, $p = .872$ (see Table 1 and Fig. 1). A Funnel plot depicting the studies distribution is presented in Fig. 3A. Using Trim and Fill, the imputed point estimate was 0.295 [$CI_{(95\%)}$ (0.186, 0.404)] whereas the observed effect size for all studies during acquisition was 0.365.

3.1.2. Extinction

For differential learning (CS + minus CS-) during extinction an aggregated small effect size was found for both the anxious [$d = 0.276$, $N = 7$, $p = 0.001$, $CI_{(95\%)}$ (0.119, 0.433)] and non-anxious youth [$d = 0.209$, $N = 7$, $p = .004$, $CI_{(95\%)}$ (0.068, 0.350)]. The difference between these effect sizes were non-significant, $Q_B = 0.381$, $p = .537$ (see also Table 1 and Fig. 1). Of note, smaller effect sizes in the context of extinction indicate successful extinction. A Funnel plot depicting study distribution is presented in Fig. 3B. Using Trim and Fill, the imputed point estimate was 0.184 [$CI_{(95\%)}$ (0.079, 0.289)] whereas the observed effect size for all studies during extinction that was 0.239.

3.2. Group differences in responses to individual stimuli – effect size of CS+ and CS-

3.2.1. Fear acquisition

During fear acquisition, a significant difference between anxious and non-anxious youth in fear responses to the CS+ was found [$d = 0.415$, $N = 7$, $p = .001$, $CI_{(95\%)}$ (0.179, 0.652)]. Similarly, a significant difference between anxious and non-anxious youth was found in fear responses to the CS- [$d = 0.312$, $N = 7$, $p < .001$, $CI_{(95\%)}$ (0.077, 0.547)]. These effect sizes both indicate that a greater fear response was obtained in the anxious compared to the non-anxious group (see Table 2 and Fig. 2). A Funnel plot depicting study distribution (CS+) is presented in Fig. 3C. Using Trim and Fill, the imputed point estimate was 0.415 similar to the observed effect size for group differences to the CS+. A Funnel plot depicting study distribution to CS- is presented in Fig. 3E. Using Trim and Fill, the imputed point estimate was 0.312 [$CI_{(95\%)}$ (0.077, 0.547)], similar to the observed effect size for group differences to the CS-.

3.2.2. Extinction

During extinction, a significant difference emerged between anxious and non-anxious youth in fear responses to the CS+ [$d = 0.482$, $N = 7$, $p < .001$, $CI_{(95\%)}$ (0.236, 0.728)], with anxious youth demonstrating a greater fear response to the CS + than non-anxious youth. Similarly, a stronger fear response to the CS- among anxious compared to non-anxious youth was also found [$d = 0.371$, $N = 7$, $p = .003$, $CI_{(95\%)}$ (0.124, 0.617)] (see Table 2 and Fig. 2). A Funnel plot depicting study distribution (CS+) is presented in Fig. 3D. Using Trim and Fill, the imputed point estimate was 0.482 [$CI_{(95\%)}$ (0.236, 0.728)], similar to the observed effect size for group differences to the CS+. A Funnel plot depicting study distribution (CS-) is presented in Fig. 3F. Using Trim and Fill, the imputed point estimate was 0.371 [$CI_{(95\%)}$ (0.124, 0.617)], similar to the observed effect size for group differences to the CS-.

4. Discussion

The current meta-analysis examined differences in fear acquisition and extinction among anxious and non-anxious youth. Two major findings emerged. First, comparable differential learning was observed during fear acquisition and extinction in both groups. Second, group differences emerged for fear responses to individual CSs. Anxious compared to non-anxious youth showed elevated fear responses to the CS+ and CS- during both fear acquisition and extinction.

Successful fear acquisition was observed in anxious and non-anxious participants, as indicated by a small differential learning effect (CS + > CS-). This suggests that fear conditioning paradigms used in pediatric research are effective in inducing fear learning. This is

Table 1
Differential learning effect sizes in anxious and non-anxious youth and related characteristics.

Study	Sample characteristics				Stimuli		# Trials			DV	d CS+ vs. CS-			
	Group	N	Ages	Gender							Acquisition		Extinction	
			Mean (SD)	% females	CS	UCS	Pre- ACQ	ACQ	EXT		ANX	NON	ANX	NON
Britton et al. (2013)	ANX	23	13.3 (3.3)	47.8	Two neutral female faces for 8s	Female fearful face + Scream for 3s (95dB)	CS+:4 CS-:4	CS+:10 CS-:10	CS+:8 CS-:8	*S.R.: Fear*	0.76	0.93	0.18	0.69
	NON	42	14.2 (2.6)	54.8						*SCR*	0.59	0.24	0.00	0.00
										FPS	0.68	0.52	0.61	0.57
										Combined	**0.68**	**0.56**	**0.26**	**0.42**
Craske et al. (2008)	ANX	23	TOTAL:	52.2	Pink trapezoid & Cream triangle for 8s	Pure tone for 1s (107dB)	CS+:1 CS-:1	CS+:8 CS-:8	CS+:4 CS-:4	*S.R.: Valence*	0.78	-0.28	0.56	-0.54
	NON	11	9.4 (1.6)	45.5						*SCR*	0.28	0.52	0.10	0.34
										Combined	**0.53**	**0.12**	**0.33**	**-0.10**
Haddad et al. (2015)	ANX	15	15.2 (1.5)	86.7	Two neutral female faces for 6-7s	Female fearful face + Scream (95dB)	CS+:5 CS-:5	CS+:30 CS-:15 Control: 15	N/A	*S.R.: Nervousness*	0.48	0.29	0.15	0.40
	NON	11	15.6 (1.3)	54.5										
Lau et al. (2008)	ANX	16	12.8 (2.5)	56.3	Two neutral female faces for 8s	Female fearful face + Scream for 3s (95dB)	CS+:4 CS-:4	CS+:16 CS-:16	CS+:15 CS-:15	*S.R.: Fear*	0.65	0.42	0.40	0.50
	NON	38	13.9 (2.3)	55.3										
Liberman et al. (2006)	ANX	51	9.7 (1.6)	45.3	Cartoon pictures for 5s	Loud tone for 500 ms	CS+: 1 CS-: 1	CS+:6 CS-:6	CS+:8 CS-:8	*S.R. : Fear*	0.10	0.32	0.26	0.05
	NON	29	10.1 (2.1)	40.0						*SCR*	0.06	0.17	0.36	-0.25
										FPS	N/A	N/A	0.31	-0.19
										Combined	**0.08**	**0.25**	**0.31**	**-0.13**
										Arousal	0.00	0.57	0.16	0.23
Shechner et al. (2015)	ANX	15	11.5 (2.6)	46.7	Blue & yellow bells for 7s	Red bell + Loud noise for 1s (95dB)	CS+:4 CS-:4	CS+:10 CS-:10	CS+:8 CS-:8	*S.R. : Fear .*	0.65	0.22	0.67	0.35
	NON	17	13.0 (2.9)	52.9						*SCR*	0.38	0.16	0.01	0.13
										FPS	0.75	0.91	0.41	0.24
										Combined	**0.60**	**0.43**	**0.36**	**0.24**
Waters et al., (2009)	ANX	17	10.2	47.0	Pink trapezoid & Cream triangle for 8s	Pure tone for 1s (107dB)	CS+:1 CS-:1	CS+:8 CS-:8	CS+:4 CS-:4	*S.R.: Valence*	0.10	0.37	-0.15	0.15
	NON	18	10.2	44.4						*SCR*	0.23	0.35	0.62	-0.01
										Combined	**0.17**	**0.36**	**0.23**	**0.07**
										Arousal	0.34	-0.08	-0.36	-0.11

Note. Pre-ACQ: Pre-acquisition, ACQ: Acquisition. EXT: Extinction, DV: Dependent variables, ANX: Anxious group, NON: Non-anxious group, S.R: Self-report, SCR: Skin conductance response, FPS: Fear potentiated startle, Combined: Averaged of all available DVs.

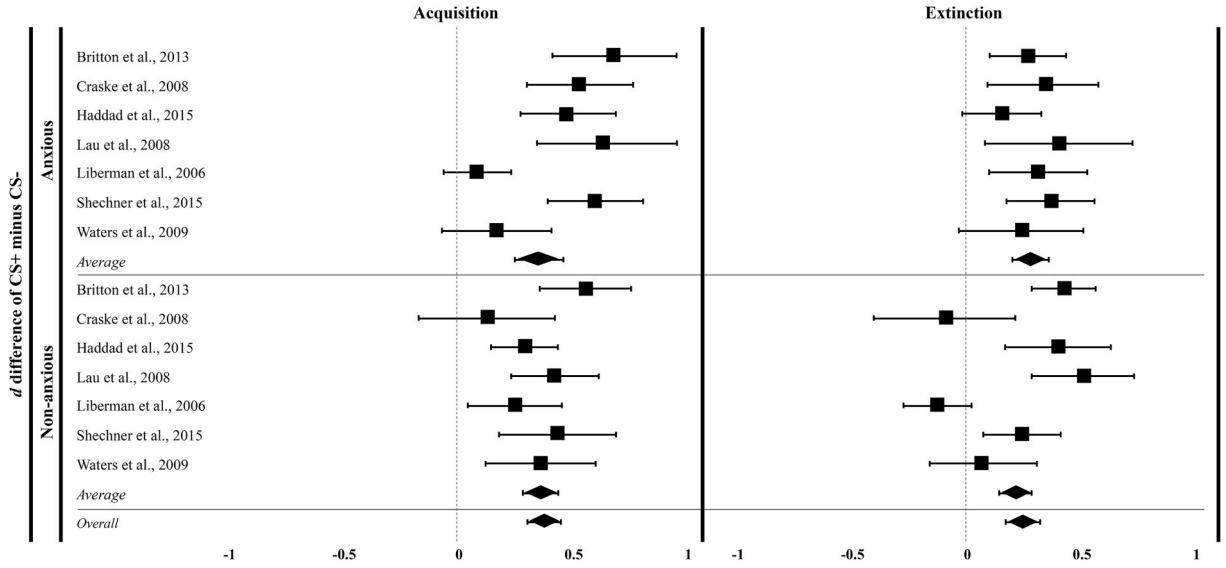

Fig. 1. Group differences in differential learning during fear acquisition and extinction (CS + minus CS-).

important, considering the different types of US used in studies with adults (mainly electric shock) and those used in pediatric studies (mainly loud sounds) (for a comprehensive review, see Shechner et al., 2014). A similar but slightly smaller effect was also evident in extinction, with a small differential learning effect to the CSs also observed (CS+ > CS-). Of note, a differential response did not emerge during extinction in the two previous adult meta-analyses. This could point to a subtle difference between the current youth sample and previous adult samples. However, the observed findings could also stem from differences in fear conditioning paradigms used in adult vs. pediatric studies. For example, extinction in some of the youth studies was relatively short, which could have contributed to the maintained differential learning effect observed in the youth sample. More contemporary fear learning methodology guidelines emphasize the importance of looking at trial-by-trial analyses methods, which could provide a better and more precise understanding of the extinction learning process in future studies (Lonsdorf et al., 2017).

Most importantly, anxious and non-anxious youth showed similar differential learning during fear acquisition and extinction. These results are consistent with those of two meta-analyses examining studies on anxious and non-anxious adults (Duits et al., 2015; Lissek et al., 2005). Specifically, both meta-analyses found no differences in fear

Table 2
Group (anxious vs. non-anxious) effect sizes during acquisition & extinction to individual CSs.

Study	N	# Trials			DV	Acquisition		Extinction	
		Pre-ACQ	ACQ	EXT		CS(+)	CS(-)	CS(+)	CS(-)
Britton et al.(2013)	ANX: 23	CS+:4	CS+:10	CS+:8	*S.R.: Fear*	0.38	0.51	0.44	1.00
	NON: 42	CS-:4	CS-:10	CS-:8	*SCR*	0.33	0.13	0.60	0.63
					FPS	0.05	-0.24	0.33	0.13
					Combined	**0.25**	**0.13**	**0.46**	**0.59**
Craske et al.(2008)	ANX: 23	CS+:1	CS+:8	CS+:4	*S.R.: Valence*	1.00	-0.17	0.90	-0.30
	NON: 11	CS-:1	CS-:8	CS-:4	*SCR*	0.26	0.54	0.65	0.93
					Combined	**0.62**	**0.19**	**0.79**	**0.31**
Haddad et al.(2015)	ANX: 15	CS+:5	CS+:30	N/A	*S.R.: Nervousness*	1.14	0.96	0.75	1.03
	NON: 11	CS-:5	CS-:15						
			Control: 15						
Lau et al.(2008)	ANX: 16	CS+:4	CS+:16	CS+:15	*S.R.: Fear*	0.42	0.19	-0.01	0.15
	NON: 38	CS-:4	CS-:16	CS-:15					
Liberman et al. (2006)	ANX: 51	CS+: 1	CS+:6	CS+:8	*S.R.: Fear*	0.01	0.24	0.37	0.17
	NON: 29	CS-: 1	CS-:6	CS-:8	*SCR*	0.34	0.42	0.48	-0.12
					FPS	N/A	N/A	0.35	-0.19
					Combined	**0.18**	**0.33**	**0.39**	**-0.05**
					S.R.: Arousal	-0.23	0.37	0.03	0.04
Shechner et al.(2015)	ANX: 15	CS+:4	CS+:10	CS+:8	*S.R.: Fear*	0.84	0.31	0.89	0.56
	NON: 17	CS-:4	CS-:10	CS-:8	*SCR*	0.49	0.25	0.36	0.52
					FPS	0.12	0.12	0.06	-0.18
					Combined	**0.48**	**0.23**	**0.44**	**0.30**
Waters et al(2009)	ANX:17	CS+:1	CS+:8	CS+:4	*S.R.: Valence*	-0.29	-0.03	0.44	0.67
	NON: 18	CS-:1	CS-:8	CS-:4	*SCR*	0.93	1.03	0.82	0.15
					Combined	**0.32**	**0.50**	**0.63**	**0.42**
					S.R.: Arousal	0.59	0.14	-0.29	0.02

Note. Pre-ACQ: Pre-acquisition, ACQ: Acquisition. EXT: Extinction, DV: Dependent variables, ANX: Anxious group, NON: Non-anxious group, S.R: Self-reported, SCR: Skin conductance response, FPS: Fear potentiated startle, Combined: Averaged of all available DVs.

acquisition and extinction between anxious and non-anxious adults in differential learning suggesting that these processes may be similar in both groups. Nonetheless, in contrast to the meta-analyses conducted with adults, only a relatively small number of studies have examined fear acquisition and extinction among anxious youth, and further research on these basic fear learning processes is therefore necessary. Further, future studies should focus on additional aspects of fear learning. For example, several studies point to possible group differences in return of fear following successful extinction (Bouton, 2002; Vervliet, Craske, & Hermans, 2013). Given the higher responses observed in anxious youth to both CSs in the current analysis, a greater return of fear could be expected in this population. In addition, other studies have proposed that threat-safety generalization may differ between anxious and non-anxious individuals, with anxious individuals displaying greater fear generalization than their non-anxious peers (Lissek et al., 2014; Vervliet, Baeyens, Van den Bergh, & Hermans, 2013). These studies suggest that between-group differences arise from anxious individuals' tendency to generalize threatening features of a danger cue to other similar stimuli and not merely from difficulties to differentiate between threat and safety cues. Nevertheless, lack of

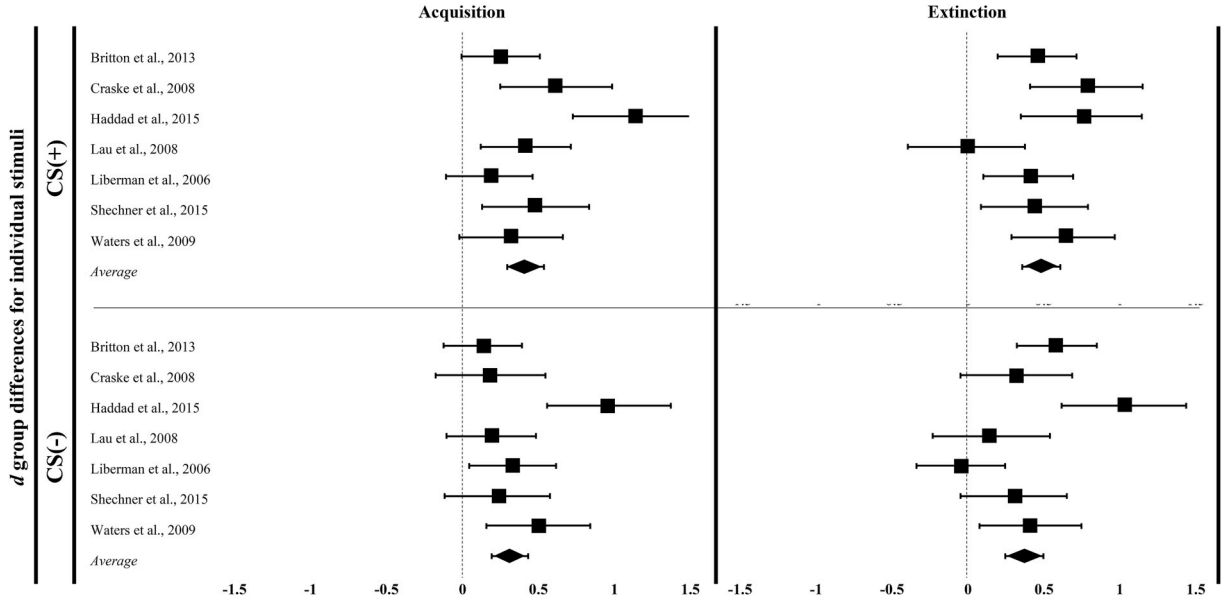

Fig. 2. Group differences in responses to individual stimuli during fear acquisition and extinction.

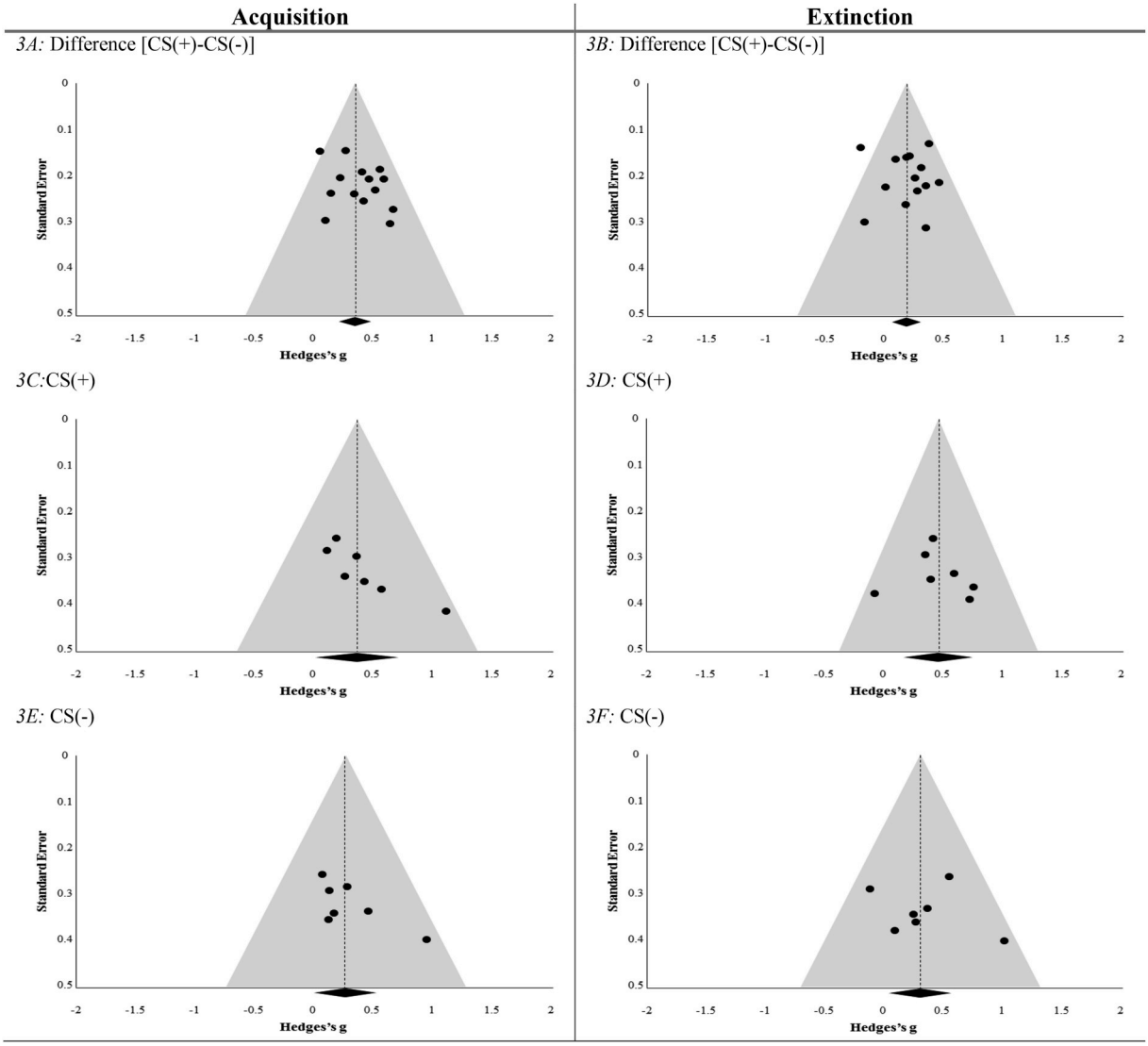

Fig. 3. Funnel plots depicting possible publication bias during fear acquisition and extinction.

differences in differential learning between anxious and non-anxious individuals may also reflect various potential methodological and measurement-related issues, such as relatively short fear learning paradigms and use of only self-report and peripheral psychophysiological measurements. These issues could be addressed, at least to some extent, in future studies through more advanced and sensitive neuroimaging methods (e.g., fMRI, ERP) directly assessing possible neural differences during fear learning, where perturbations may arise in specific brain areas and in connectivity between brain regions.

Unlike differential learning, evidence emerged for differences in fear responses towards individual stimuli (both CS+ and CS-) between anxious and non-anxious youth. These results are similar to the findings of Duits et al. (2015), who reported that anxious adults exhibited an elevated response to the CS- during acquisition and to the CS+ during extinction as compared to non-anxious adults. In contrast to Duits et al. (2015), anxious youth in the current meta-analysis also exhibited an elevated response to the CS+ during acquisition and a higher response to the CS- during extinction. The differences observed across the youth and adult meta-analyses may derive from a tendency to exhibit vigorous responses to stimuli among youth (i.e., excitatory processes to both stimuli), a stronger generalization of the fear related features to the CS- in the youth sample (i.e., impairment in inhibitory processes), or both. In addition, it is possible that anxious youth are more sensitive to threatening contexts than are their typically-developing peers, which could account for the elevation in responding to both CSs observed during fear learning. Further, in contrast to adult studies, where the level of the US aversiveness is determined by each participant prior to beginning fear learning, in youth studies fixed volume-level auditory USs are administered. Therefore, it is possible that the differences in CS responding observed between anxious youth and anxious adults may be due to youth deeming the US as more aversive than their adult counterparts. Importantly, as we did not receive data on subjective US aversiveness ratings for the studies included in our analyses, this explanation should be regarded with caution.

As previously discussed, some theorists suggest that anxious individuals have exacerbated excitatory processing, which would result in heightened responses to the CS+ during both acquisition and extinction (Orr et al., 2000). In contrast, others posit that anxious individuals have greater difficulty in inhibitory processing, which would result in heightened fear responses to safety cues (Davis, Falls, & Gewirtz, 2000). Both hypotheses predict between group differences in differential learning. Hence, the current findings do not fully support either explanation. No group differences were found in differential learning while the major group differences were apparent for individual stimuli (CS+, CS-) during fear acquisition and extinction.

The current study has several notable limitations. First, as noted

previously, a small number of studies were included in the analyses. This was primarily due to very few relevant studies having been conducted with anxious youth. However, as the current meta-analysis includes data from 160 anxious and 166 non-anxious youth, it offers a promising direction for future fear-conditioning studies with clinically anxious youth. Second, the literature on fear conditioning in youth is characterized by inconsistencies in methodology. This includes differences in the questions used to garner self-report data, either in phrasing or the number of questions used. In addition, each study classified the term "youth" differently, resulting in a wide age range. Third, different studies use different methods to analyze data. Some studies divide each response to the CS into separate time windows - for example, categorizing responses into early, middle and late stages following stimulus onset (e.g., Craske et al., 2008; Waters et al., 2009) - whereas others analyze the entire duration of stimulus presentation (e.g., Britton et al., 2013; Shechner et al., 2015). Importantly, in the current study we used only responses that occurred immediately after the CS onset (early), so as to isolate the observed fear response to the CS presentation in a similar way across studies. And yet, this methodological variance across studies makes aggregating findings more challenging (for a comprehensive review on methodological considerations in human fear conditioning studies see Lonsdorf et al., 2017). Last, the combined effect sizes used in the analyses were computed based on the effect sizes of each dependent measure (self-report, SCR and FPS) in each sample. This method allowed us to examine a single comprehensive outcome and to compare our results to two previous meta-analyses conducted with adults. Nonetheless, given that different indices measure different aspects of the fear response, caution is advised when interpreting this combined score. This is even more true given that the combined effect size obtained in each study was comprised based on different combinations of the dependent measures.

Despite its limitations, the current meta-analysis in developmental fear conditioning is the first to synthesize results from clinical pediatric studies and yield findings that are largely consistent with those found in the adult literature. Findings indicate that anxious and non-anxious youth show comparable differential learning in fear acquisition and extinction. However, anxious youth exhibited stronger fear responses to individual CSs compared to non-anxious youth. Though further research is needed so as to better understand fear acquisition and extinction processes in developmental populations, our findings have important implications and can guide future research in examining possible differences in other processes related to fear learning. These processes include return of fear, retrieval of fear memory and more subtle differences in fear generalization across development.

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