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Unique associations between conditioned cognitive and physiological threat responses and facets of anxiety symptomatology in youth

Zohar Klein [a], Rany Abend [b], Shahar Shmuel [a], Tomer Shechner [a,*]

[a] School of Psychological Sciences and the Integrated Brain and Behavior Research Center, University of Haifa, Israel

[b] Emotion and Development Branch, National Institute of Mental Health, Bethesda, MD 20892, USA

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ABSTRACT

This study examined associations between anxiety symptomatology and cognitive and physiological threat responses during threat learning in a large sample of children and adolescents. Anxiety symptomatology severity along different dimensions (generalized anxiety, separation anxiety, social anxiety, and panic symptoms) was measured using parental and self-reports. Participants completed differential threat acquisition and extinction using an age-appropriate threat conditioning task. They then returned to the lab after 7–10 days to complete an extinction recall task that also assessed threat generalization. Results indicated that more severe overall anxiety was associated with greater cognitive and physiological threat responses during acquisition, extinction, and extinction recall. During acquisition and extinction, all anxiety dimensions manifested greater cognitive threat responses, while panic, separation anxiety, and social anxiety symptoms, but not generalized anxiety, were related to heightened physiological threat responses. In contrast, when we assessed generalization of cognitive threat responses, we found only generalized anxiety symptoms were associated with greater threat response generalization. The study provides preliminary evidence of specificity in threat responses during threat learning across youth with different anxiety symptoms.

1. Introduction

Excessive responses to potential threats are central features of anxiety symptomatology, encompassing aberrant threat appraisal and physiological arousal (American Psychiatric Association, 2013). Studies examining how these cognitive and physiological responses to threat are learned commonly use threat conditioning paradigms. Despite the emergence of anxiety symptoms in youth, previous threat conditioning research has focused primarily on differences between anxious and non-anxious adults. Moreover, the extant developmental studies have considered anxious youth as one homogeneous group, although it is not known whether distinct anxiety symptom dimensions (i.e., generalized anxiety, separation anxiety, social anxiety, and panic symptoms) are specifically associated with aberrant cognitive and physiological threat responses. Here, we begin to examine specificity in associations between symptom severity across anxiety dimensions and cognitive and physiological threat responses in youth during threat learning.

Human responses to potential threats typically manifest as anticipatory physiological responses reflected in changes in levels of somatic arousal and as cognitive responses reflected in conscious subjective fear states (DSM; LeDoux & Pine, 2016). Major developmental theories link perturbations in learning threat-anticipatory responses to the emergence of anxiety symptoms (Casey, Glatt, & Lee, 2015; Pine, 2007). To test such theories, threat learning processes are commonly assessed using threat conditioning paradigms. These enable the examination of conditioned threat responses in well-controlled laboratory settings. Specifically, during *threat acquisition*, a neutral stimulus (conditioned stimulus; CS+) begins to signal threat through repeated pairing with an aversive stimulus (unconditioned stimulus; US), while a safety cue (CS-) is not reinforced. During *threat extinction*, the CS+ is repeatedly presented in the absence of the US, and participants learn to extinguish their conditioned threat responses. During *extinction recall,* the retention of extinction learning over time is assessed, while stimulus-related *generalization* examines threat response to stimuli resembling the conditioned threat cues. Several theories ascribe a role to perturbations in these learning-related processes in the emergence and maintenance of anxiety symptoms (for a review, see Pittig, Treanor, LeBeau, & Craske, 2018).

Despite the emergence of anxiety symptoms in early development

* Correspondence to: School of Psychological Sciences and the Integrated Brain and Behavior Research Center, University of Haifa, Abba Hushi 199, Mt Carmel, Haifa, Israel.

E-mail address: tshechner@psy.haifa.ac.il (T. Shechner).

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(Beesdo, Knappe, & Pine, 2009; Kessler et al., 2005), most of the empirical work on threat conditioning has been conducted with adult samples (Treanor, Rosenberg, & Craske, 2021, Shechner, Hong, Britton, Pine, & Fox, 2014). Meta-analyses of such studies indicate anxiety is not associated with differential responses to the CSs but rather with stronger responses to the safety cue during acquisition and stronger responses to the threat cue during extinction learning (Duits et al., 2015; Lissek et al., 2005). Some studies have examined the role of age and development in threat learning and related processes. Compared to adults, adolescents show attenuated extinction learning and recall (Ganella, Drummond, Ganella, Whittle, & Kim, 2018; Pattwell et al., 2012) and greater threat generalization as indicated by cognitive (ratings), physiological (SCR), and behavioral (avoidance) measurements (Klein, Berger, Vervliet, & Shechner, 2021; Schiele et al., 2016). Such age-related differences might be related to structural and functional changes in brain maturation that occur from adolescence through adulthood (Morriss, Christakou, & Van Reekum, 2019).

Only a few studies have considered clinically anxious and non-anxious youth (see meta-analysis by Dvir, Horovitz, Aderka, & Shechner, 2019; Abend et al., 2020). These have consistently found pediatric anxiety to be associated with stronger conditioned responses to both threat and safety cues during acquisition and extinction, manifesting in excessive cognitive threat appraisal and physiological responses. A handful of studies have examined extinction recall and generalization processes in youth, suggesting impaired extinction retention in anxious compared to non-anxious youth (Craske et al., 2008; Treanor et al., 2021). Finally, one study reported that following threat acquisition, youth with anxiety showed excessive generalization of fear appraisal (El-Bar, Laufer, Yoran-Hegesh, & Paz, 2017). Together, the initial evidence generally links pediatric anxiety symptoms with excessive cognitive and physiological threat responses during threat learning.

A shortcoming of prior work on pediatric populations is that anxiety severity has been assessed overall without considering different symptom dimensions. This may be incongruent with the distinct manifestation of specific anxiety symptoms. Namely, generalized anxiety symptoms are primarily characterized by excessive cognitive response to threat in the form of chronic and uncontrollable worry that may be experienced across a variety of contexts (Olatunji, Broman-Fulks, Bergman, Green, & Zlomke, 2010). Panic symptoms are characterized by excessive autonomic arousal in response to stimuli or events conferring risk of imminent threat (Brown & McNiff, 2009). In contrast, social anxiety and separation anxiety symptoms are context-specific, with specific worries and physiological responses elicited in social and separation situations.

A handful of studies in adult populations have investigated the association between specific anxiety symptom dimensions and differential threat learning. These studies have shown that panic (Lissek et al., 2009; Lissek et al., 2010; Neueder, Andreatta, & Pauli, 2019), generalized anxiety (Lissek et al., 2014), and social anxiety symptoms (Hermann, Ziegler, Birbaumer, & Flor, 2002; Lissek et al., 2008) are generally associated with aberrant threat learning. While some similarities in threat responses exist across anxiety dimensions, certain differences emphasize the importance of examining the specific features of each dimension. One recent study directly compared threat learning processes for adult patients with panic and patients with generalized anxiety (Cooper, Grillon, & Lissek, 2018). Although both groups showed similar levels of aberrant discrimination in self-reported risk ratings during initial learning, sustained impairments that were demonstrated in later phases of learning were associated only with generalized anxiety patients.

To the best of our knowledge, no previous studies with youth have examined the associations between specific anxiety dimensions and threat learning. A recent study used a network analysis approach to examine the network structure of anxiety symptoms in a large sample of children and adolescents (Abend et al., 2021). Results revealed the centrality of excessive cognitive and physiological threat responses in this inter-connected structure. However, it is not yet clear whether severity along these anxiety dimensions differentially covaries with cognitive and physiological threat responses elicited during threat learning.

Identifying specific links between different anxiety symptoms and types of threat responses in youth has two major potential implications. First, threat conditioning is a widely-used translational model for understanding the development of anxiety psychopathology (Craske, Hermans, & Vervliet, 2018). However, understanding of the nature of the different types of threat responses and how these are linked to specific anxiety manifestations is limited. The establishment of such links could inform us on individual differences in symptom manifestation and how these relate to experiencing aversive events. This, in turn, could improve our understanding of anxiety etiology and promote evidence-based diagnostic conceptualization. This approach is in line with recent quantitative conceptualizations of psychopathology that propose to augment clinical assessments with multilevel analysis of psychological and biological systems, such as the Research Domain Criteria (RDoC; Insel et al., 2010) and HiTOP (Kotov et al., 2017).

Second, understanding the cognitive and physiological mechanisms underlying threat extinction learning and recall could guide prevention programs and clinical interventions. For example, understanding that a specific group of symptoms is predominantly associated with cognitive biases rather than physiological arousal could facilitate tailoring treatment plans to the specific needs of the patient. Importantly, such insights may be of particular utility in youth, given the emergence of anxiety symptoms in childhood and adolescence (Beesdo et al., 2009; Kessler et al., 2005) and the need for early intervention and prevention (Chronis-Tuscano, Danko, Rubin, Coplan, & Novick, 2018).

Here, we examine the association between anxiety symptomatology severity along different dimensions and threat acquisition, extinction, extinction recall, and generalization in a large sample of children and adolescents. All youth completed a threat conditioning paradigm in the lab and a standard anxiety inventory assessing anxiety symptom severity along different dimensions (generalized anxiety, separation anxiety, social anxiety, and panic symptoms). In line with previous studies, we hypothesized that overall severity of anxiety symptoms would be associated with excessive cognitive and physiological threat responses to both threat and safety cues in the context of threat acquisition and extinction (for an example, see Dvir et al., 2019), and also with attenuated extinction recall and elevated generalization (for an example, see El-Bar et al., 2017). Based on clinical observations and experimental findings in adults, we further hypothesized that unique associations between anxiety dimensions and aberrant cognitive and physiological threat responses would emerge. Specifically, severity of panic symptoms would be associated with excessive physiological threat responses, while severity of generalized anxiety symptoms would be associated with excessive cognitive threat responses (for an example, see Cooper et al., 2018). Moreover, we expected severity in social anxiety and separation anxiety symptoms would be associated with both excessive physiological and excessive cognitive threat responses. Finally, we hypothesized the severity of generalized anxiety symptoms would be associated with over-generalization of threat appraisal during extinction recall.

2. Methods

2.1. Participants

A community sample of 136 children and adolescents (ages 7–17 years; Mage = 10.67 years, SD = 1.96; 50% females; all self-identified as Israeli Jews) was recruited mainly through social media to take part in research on fear and anxiety. Youth and their parents signed informed assent and consent prior to participation. The study received ethical approval from the university's Institutional Review Board. Exclusion criteria included psychotropic medications, history of head injuries, previous or current diagnosis of schizophrenia, autism spectrum disorders, bipolar disorder, or eating disorders assessed during a phone screening. Participants were compensated with a modest gift certificate. Overall, 136 youths participated in the first part of the study (Visit 1). Three participants quit the threat conditioning task during Visit 1. Twenty participants (15%) did not come back for the second part of the study (Visit 2). Therefore, 113 participants completed the two experimental visits of the study. Of note, participants who dropped out and participants who completed the study did not differ in age ($p = .881$), gender ($p = .241$), or anxiety levels ($p = .642$).

2.2. Procedure

The study had two experimental sessions. In Visit 1, participants and their parents signed consent and assent forms and received a verbal explanation of the study from the experimenter. Thereafter, parents filled out self-report questionnaires. Next, youth were seated in front of a 19″ monitor in a sound-proofed room and completed the bell differential threat conditioning and extinction tasks, while cognitive (i.e., self-reported fear) and psychophysiological (i.e., SCR) responses were collected. Finally, participants completed the screen for child anxiety related emotional disorders (SCARED) questionnaire. In Visit 2, participants returned to the lab 7–10 days following Visit 1 and performed the extinction recall and generalization task, while cognitive (i.e., threat appraisal) responses were collected.

2.3. Instruments and measurements

2.3.1. Anxiety severity

Participants' anxiety symptoms in the past three months were assessed using the SCARED (Screen for Child Anxiety Related Emotional Disorders), a child- and parent-report measure, comprising 41 items indexing four main symptom dimensions as specified by DSM5: panic/somatic symptoms (13 items; e.g., "When I get anxious, I feel dizzy"), generalized anxiety symptoms (9 items; e.g., "I worry about how well I do things"), separation anxiety symptoms (8 items; e.g., "I am afraid to be alone in the house"), and social anxiety symptoms (7 items; e.g., "I feel shy with people I don't know well") (American Psychiatric Association, 2013). Respondents rate the frequency of each item using a 3-point Likert scale from 0 (not true or hardly ever true) to 2 (very true or often true). Total scores range from 0 to 82; higher scores indicate higher levels of anxiety (Birmaher et al., 1997, 1999). The reliability and validity of the overall scores and the subscales scores have been established in clinical and community samples (Behrens, Swetlitz, Pine, & Pagliaccio, 2019; Birmaher et al., 1997, 1999; Hale, Raaijmakers, Muris, & Meeus, 2008; Hale, Crocetti, Raaijmakers, & Meeus, 2011). In our study, Cronbach's alpha for total SCARED-Child report was 0.90, with values for the dimensions ranging between 0.76 and 0.78; Cronbach's alpha for total SCARED-Parent report was 0.94, with values of the dimensions ranging between 0.85 and 0.92.

Participants and their parents completed the self-reported and parental versions of the SCARED, respectively. An average score was computed for each participant to mitigate reported.

discrepancies (Behrens et al., 2019). This self-reported and parental-reported combined SCARED score for each anxiety dimension was used in the statistical analysis (see Table 1).

2.3.2. Experimental tasks

2.3.2.1. Visit 1: threat acquisition and extinction. The bell differential threat learning task is an established task that yields differential conditioning and extinction in youth (see Ginat-Frolich, Gendler, Marzan, Tsuk, & Shechner, 2019; Ginat-Frolich, Klein, Katz, & Shechner, 2017; Klein, Shner, Ginat-Frolich, Vervliet, & Shechner, 2020; Shechner et al., 2015). Pictures of blue and yellow cartoon bells serve as the conditioned stimuli (CSs) (see Fig. 1A). Participants are told that during the task, they will hear an unpleasant sound, and if they pay attention, they will be able to predict when the sound will occur. In each trial, one bell is presented in the center of a computer screen for eight seconds. During *pre-acquisition*, each bell is presented four times. Thereafter, during threat *acquisition*, each bell is presented ten times. During this phase, one bell (CS+: conditioned threat cue) is paired with a 1-second aversive sound played at 95 dB (unconditioned stimulus; US) at an 80% reinforcement rate delivered via headphones. The US is administered at second 7 and co-terminates with cue offset. The second bell is never paired with the US (CS-: conditioned safety cue). During threat *extinction*, each bell is presented eight times in the absence of the US. The order of the bells in each phase is pseudorandomized into four versions, with the color and order of the CSs counterbalanced between participants. Following each phase of Visit 1 (i.e., pre-acquisition (phase 1), acquisition (phase 2), and extinction (phase 3)), cognitive threat responses were assessed by rating the level of fear in response to each CS using a Likert scale ranging from 1 (not at all afraid) to 10 (extremely afraid).

Table 1
Demographic and anxiety symptom variables across participants.

Whole Sample (N = 133)	Mean (SD)	Minimum	Maximum
Demographics			
Age	10.67 (1.96)	7.66	16.90
Sex - No. of females (% of sample)	67 (50.37%)	–	–
Average of SCARED combined score			
Overall SCARED score	19.49 (10.30)	3	56.5
Panic symptoms score	3.04 (2.98)	0	16
Generalized anxiety symptoms score	5.60 (3.29)	0.5	16.5
Separation anxiety symptoms score	4.62 (3.12)	0	15
Social anxiety symptoms score	5.31 (3.01)	0	13

Note: SCARED = Screen for Child Anxiety-Related Emotional Disorders

2.3.2.2. Visit 2: extinction recall and generalization. The extinction recall and generalization task took place 7–10 days ($M = 7.43$ days) after Visit 1. The task consists of five bell morphs ranging in perceptual similarity from the CS- to the CS+ (CS-, GS25%, GS50%, GS75%, CS+) (see Fig. 1B). Each morph is presented twice for eight seconds in two blocks; morph order is randomized within each block. Cognitive threat responses were assessed by participants' ratings of how unpleasant each morph was, ranging from 0 (not at all) to 6 (very much).

2.3.3. Psychophysiology

Skin conductance was recorded continuously throughout the experimental phases in Visit 1 using two isotonic gel electrodes placed on the left palm (i.e., hypothenar and thenar muscles) with an 8 Slot Bionex system at a sampling rate of 25 Hz (MindWare Technologies Ltd., www.mindwaretech.com, Westerville, Ohio, USA) and Mindware acquisition software (Version 3.0.13, MindWare Technologies Ltd.). In line with recent recommendations, SCR to each stimulus was scored on a trial-by-trial basis as the difference between trough-to-peak amplitude at 500 ms and 5 s after stimulus onset (Kuhn, Gerlicher, & Lonsdorf, 2021; Lonsdorf et al., 2019). SCR threshold was set at 0.01 microsiemens; therefore, all scores below 0.01 microsiemens, as well as negative changes, were scored as zero and included in analyses. We used a square root transformation to normalize scores for each participant in each trial (Lonsdorf et al., 2019). Thereafter, SCR data were averaged per stimulus (CS+, CS-) and per phase (pre-acquisition, acquisition, extinction) for each participant.

2.4. Statistical analysis

To analyze the association between the severity of overall anxiety, as well as along each dimension and threat acquisition, extinction, and extinction recall, we used a separate repeated-measures ANCOVA (see below) for total SCARED score and for each anxiety dimension score

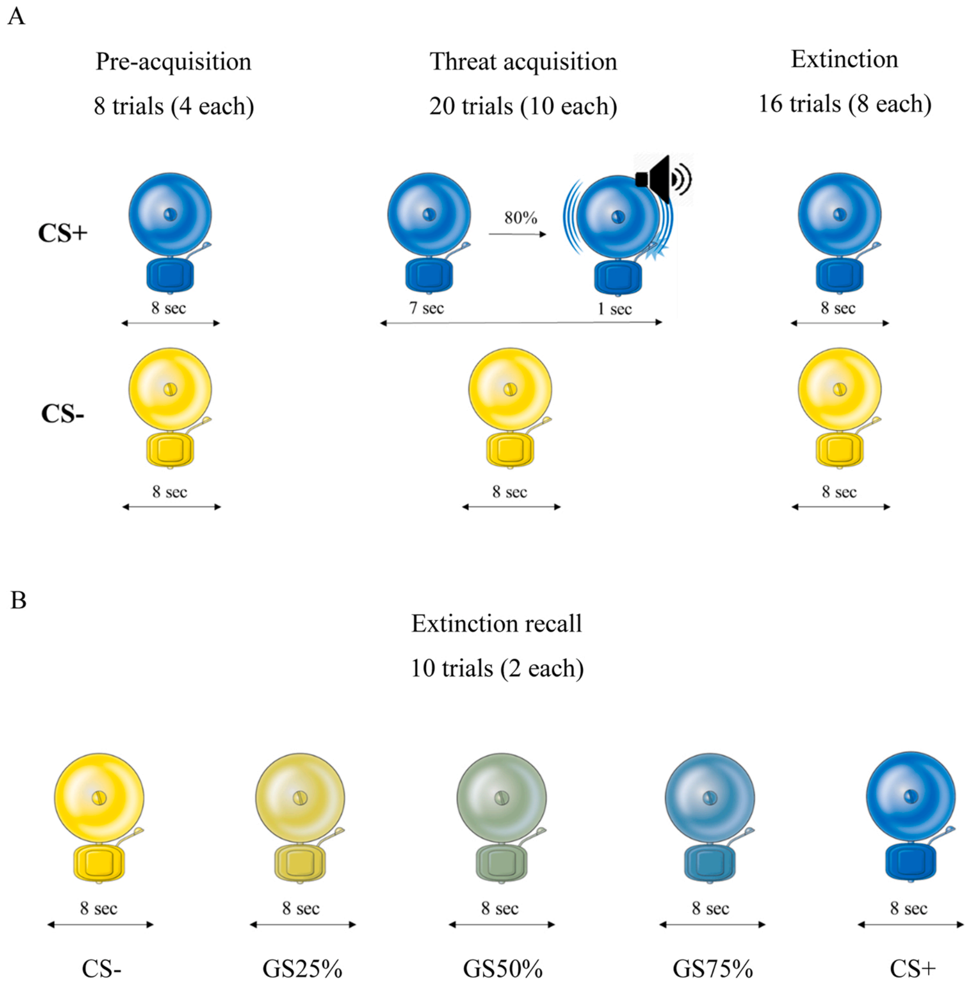

Fig. 1. Overview of experimental phases in the threat conditioning task. A. Visit 1: pre-acquisition phase, threat acquisition phase, and extinction phase. B. Visit 2: extinction recall and generalization task. Note: CS+ = conditioned threat cue; CS- = conditioned safety cue; GS = generalization stimulus.

(panic symptoms, generalized anxiety symptoms, separation anxiety symptoms, social anxiety symptoms) whereby these were used as continuous variables. We subsequently performed complementary analyses with all four anxiety dimensions as covariates to examine specificity across the different anxiety dimensions and dependent variables.

In addition, we used linear regression analyses to quantify the specific associations (β-coefficients) between anxiety severity and self-

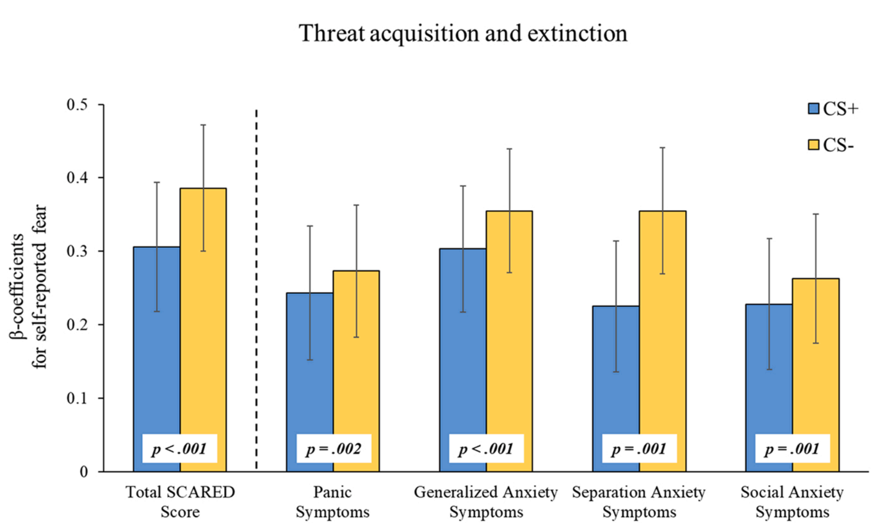

Fig. 2. Bar plot showing the standardized beta coefficients reflecting overall and each anxiety dimension score's association with self-reported fear rating during the threat learning task (averaged across threat acquisition and extinction). Error bars represent one standard error. *P*-values at the bottom of the bars represent main effect of each dimension of anxiety symptoms on CS+ and CS− combined.

reported fear (Fig. 2) and SCR (Fig. 3) during threat acquisition and extinction, and between anxiety severity and self-reported threat appraisal during extinction recall (Fig. 4).

For cognitive threat responses (self-reported fear) and physiological responses (SCR) during threat acquisition and extinction (Visit 1), we used Phase (acquisition, extinction) and Stimulus (CS+, CS-) as within-subject factors. For cognitive threat responses during the extinction recall and generalization task (Visit 2), Stimulus (CS-, GS25%, GS50%, GS75%, CS+) was the within-subject factor. All analyses included participants' age as a covariate.

In supplemental analyses (see supplemental materials), we compared participants with high and low symptom scores on the different dimensions. Specifically, we divided participants into low (below the 20th percentile) and high (above the 80th percentile) anxiety groups based on their scores for each anxiety dimension of the SCARED; these groups were then used as between-subject factors in analyses (see Table S1 in supplemental materials for demographic information).

As anxiety symptoms are highly comorbid across anxious individuals, we examined the effect of symptom severity comorbidity burden on the dependent variables. Each anxiety dimension was divided into high and low levels of severity based on a median split. Thereafter, we calculated a comorbidity index for each participant: low levels of anxiety in all four dimensions were scored as 0 (non-anxious, n = 33), high levels in one or two anxiety dimensions were scored as 1 (low anxiety comorbidity, n = 46), and high levels in three or four anxiety dimensions were scored as 2 (high anxiety comorbidity, n = 47). We used a repeated-measures ANOVA to assess the impact of anxiety comorbidity on cognitive and physiological responses during threat acquisition and extinction and on cognitive threat responses during extinction recall and generalization.

All statistical analyses were conducted using SPSS (version 25). We assumed a significance level of 0.05. Greenhouse-Geisser corrections were applied when Mauchly's test of sphericity was significant, and all follow-up analyses used Bonferroni correction for multiple comparisons.

3. Results

For each dependent variable (cognitive responses, physiological responses), we first present the results without considering anxiety severity to inform on general task effects; then, we examine the effects of overall anxiety and each anxiety dimension severity on responses in line with our hypotheses. For descriptive statistics, see Table 2.

3.1. Threat acquisition and extinction (visit 1)

3.1.1. Cognitive responses: self-reported fear

A Phase (acquisition, extinction) × Stimulus (CS-, CS+) RM-ANCOVA yielded a significant two-way interaction of Phase × Stimulus, $F(1, 125) = 41.08$, $p < .001$, $\eta_p^2 = .25$. Following threat acquisition, participants rated greater fear of the CS+ than of the CS-, $F(1, 128) = 115.78$, $p < .001$, $\eta_p^2 = .47$. Following extinction, CS differences diminished but were still significant, $F(1, 127) = 26.37$, $p < .001$, $\eta_p^2 = .17$. Importantly, participants showed a decrease in self-reported fear to the CS+ from acquisition to extinction, $F(1, 125) = 45.28$, $p < .001$, $\eta_p^2 = .27$, in line with a threat extinction process.

3.1.1.1. Overall anxiety severity. A Phase × Stimulus × Overall anxiety severity RM-ANCOVA yielded a significant effect of overall anxiety severity on self-reported fear, $F(1, 123) = 19.47$, $p < .001$, $\eta_p^2 = .14$. Participants with a higher total SCARED score reported greater self-reported fear across phases and CSs.

3.1.1.2. Panic symptom severity. A Phase × Stimulus × Panic symptom severity RM-ANCOVA yielded a significant effect of panic symptoms on self-reported fear, $F(1, 123) = 9.77$, $p = .002$, $\eta_p^2 = .07$. Participants with a higher panic symptom score reported greater self-reported fear across phases and CSs.

3.1.1.3. Generalized anxiety symptom severity. A Phase × Stimulus × Generalized anxiety symptom severity RM-ANCOVA yielded a significant effect of generalized anxiety symptoms on self-reported fear, $F(1, 123) = 20.57$, $p < .001$, $\eta_p^2 = .14$. Participants with a higher generalized anxiety symptom score reported greater self-reported fear across phases and CSs.

3.1.1.4. Separation anxiety symptom severity. A Phase × Stimulus × Separation anxiety symptom severity RM-ANCOVA yielded a significant effect of separation anxiety symptoms on self-reported fear, $F(1, 123) = 10.78$, $p = .001$, $\eta_p^2 = .08$. Participants with a higher separation anxiety symptom score reported greater self-reported fear across phases and CSs.

3.1.1.5. Social anxiety symptom severity. A Phase × Stimulus × Social anxiety symptom severity RM-ANCOVA yielded a significant effect of

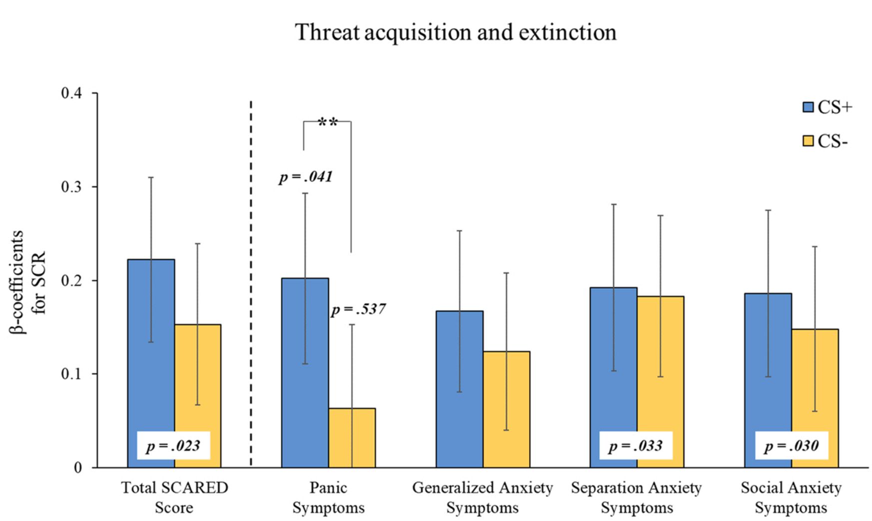

Fig. 3. Bar plot showing the standardized beta coefficients reflecting overall and each anxiety dimension score's association with skin conductance response during the threat learning task (averaged across threat acquisition and extinction). Error bars represent one standard error. *P* values at the bottom of the bars represent main effect of each dimension of anxiety symptoms on CS+ and CS− combined, while *p* values at the top of the bars represent the effect on each stimulus separately.

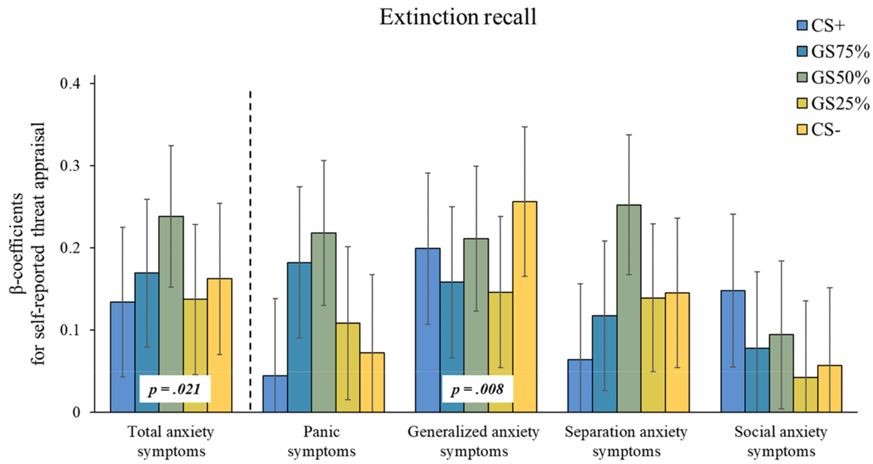

Fig. 4. Bar plot showing the standardized beta coefficients reflecting overall and each anxiety dimension score's association with self-reported threat appraisal during extinction recall and generalization task. Error bars represent one standard error. *P* values at the bottom of the bars represent main effect of each dimension of anxiety symptoms on all stimuli combined.

Table 2
Descriptive statistics.

Whole Sample (N = 133)	Mean (SD)
Cognitive Responses: Self-Reported Fear (visit 1)	
Acquisition CS+	4.54 (3.15)
Acquisition CS-	1.79 (2.06)
Extinction CS+	2.99 (2.69)
Extinction CS-	1.98 (2.35)
Physiological Responses: SCR (visit 1)	
Acquisition CS+	0.49 (0.47)
Acquisition CS-	0.29 (0.30)
Extinction CS+	0.41 (0.30)
Extinction CS-	0.31 (0.25)
Cognitive Responses: Self-Reported Threat Appraisal (visit 2)	
Extinction Recall CS+	2.30 (1.97)
Extinction Recall GS75	1.65 (1.55)
Extinction Recall GS50	1.48 (1.67)
Extinction Recall GS25	1.49 (1.60)
Extinction Recall CS-	1.52 (1.65)

Note: CS+ = conditioned threat cue; CS- = conditioned safety cue; GS = generalization stimulus; SCR = skin conductance response; visit 1 = threat acquisition and extinction task; visit 2 = extinction recall and generalization task.

social anxiety symptoms on self-reported fear, $F(1, 123) = 10.58$, $p = .001$, $\eta_p^2 = .08$. Participants with a higher social anxiety symptom score reported greater self-reported fear across phases and CSs.

3.1.1.6. All anxiety dimensions as covariates. A Phase × Stimulus RM-ANCOVA with Panic, Generalized, Separation, and Social anxiety symptom severity as covariates yielded a significant effect of generalized anxiety symptoms on self-reported fear, $F(1, 120) = 4.53$, $p = .035$, $\eta_p^2 = .04$. Only generalized anxiety symptom severity was associated with greater self-reported fear across phases and CSs, when controlling for all other anxiety dimensions.

Together, results indicate that severity of overall anxiety, as well as all anxiety dimensions, was associated with greater cognitive threat responses across phases and CSs (see Fig. 2). After controlling for the other anxiety dimensions, only generalized anxiety symptom severity was associated with greater cognitive threat responses.

3.1.2. Physiological responses: skin conductance response (SCR)

A Phase (acquisition, extinction) × Stimulus (CS-, CS+) RM-ANCOVA of SCR yielded a significant Phase × Stimulus interaction, $F(1, 120) = 12.99$, $p < .001$, $\eta_p^2 = .10$. During threat acquisition, participants showed greater SCR to the CS+ than to the CS-, $F(1, 123) = 55.19$, $p < .001$, $\eta_p^2 = .31$. CS differences diminished during extinction, but were still significant, $F(1, 123) = 26.11$, $p < .001$, $\eta_p^2 = .18$, with participants showing a decrease in response to the CS+ from acquisition to extinction, $F(1, 121) = 7.67$, $p = .006$, $\eta_p^2 = .06$.

3.1.2.1. Overall anxiety severity. A Phase × Stimulus × Overall anxiety severity RM-ANCOVA yielded a significant effect of overall anxiety severity on SCR, $F(1, 118) = 5.33$, $p = .023$, $\eta_p^2 = .04$. Participants with a higher total SCARED score showed greater SCR across phases and CSs.

3.1.2.2. Panic symptom severity. A Phase × Stimulus × Panic symptom severity RM-ANCOVA yielded a two-way interaction of Stimulus × Panic symptom severity, $F(1, 118) = 7.80$, $p = .006$, $\eta_p^2 = .06$. Follow-up analysis revealed a significant effect of panic symptom severity on SCR to the CS+ , $F(1, 119) = 4.29$, $p = .041$, $\eta_p^2 = .03$, but not to the CS-, $F(1, 119) = 0.38$, $p = .537$, $\eta_p^2 = .001$. Thus, more severe panic symptoms were associated with greater physiological response to the CS+ but not to the CS-.

In addition, to examine potential differences between phases, we compared participants' SCR to CSs in each phase separately (i.e., acquisition and extinction). We found CS+ /CS- differentiation in SCR was evident during both acquisition, $F(1, 121) = 4.34$, $p = .039$, $\eta_p^2 = .03$, and extinction, $F(1, 121) = 5.77$, $p = .018$, $\eta_p^2 = .05$.

3.1.2.3. Generalized anxiety symptom severity. A Phase × Stimulus × Generalized Anxiety symptom severity RM-ANCOVA did not yield any significant effects.

3.1.2.4. Separation anxiety symptom severity. A Phase × Stimulus × Separation anxiety symptom severity RM-ANCOVA yielded a significant effect of separation anxiety symptom severity on SCR, $F(1, 118) = 4.63$, $p = .033$, $\eta_p^2 = .04$. Participants with a higher separation anxiety symptom score showed greater SCR across phases and CSs.

3.1.2.5. Social anxiety symptom severity. A Phase × Stimulus × Social anxiety symptom severity RM-ANCOVA yielded a significant effect of social anxiety symptom severity on SCR, $F(1, 118) = 4.83$, $p = .030$, $\eta_p^2 = .04$. Participants with a higher social anxiety symptom score showed greater SCR across phases and CSs.

3.1.2.6. All anxiety dimensions as covariates. A Phase × Stimulus RM-ANCOVA with Panic, Generalized, Separation, and Social anxiety symptom severity as covariates yielded a two-way interaction of Stimulus × Panic symptom severity, $F(1, 115) = 5.77$, $p = .018$, $\eta_p^2 = .05$. Only panic symptom severity was associated with differential SCR between the CS+ and the CS- across phases, when controlling for all other anxiety dimensions.

Together, the results indicate that overall anxiety severity, separation anxiety, and social anxiety symptom severity were associated with a greater physiological response across phases and CSs, while panic symptom severity was associated with greater physiological response specifically to the threat but not to the safety cue, and generalized anxiety symptom severity was not associated with physiological responses at all (see Fig. 3). After controlling for all other anxiety dimensions, only panic symptom severity was associated with greater physiological response specifically to the threat but not to the safety cue.

3.2. Extinction recall and generalization (visit 2)

3.2.1. Cognitive responses: self-reported threat appraisal

Cognitive responses to threat generalization were assessed by participants' ratings of how unpleasant each presented morph was 7–10 days following extinction. A Stimulus (CS-, GS25%, GS50%, GS75%, CS+) RM-ANCOVA yielded a significant main effect of stimulus, $F(4, 448) = 10.11$, $p < .001$, $\eta_p^2 = .08$, indicating increased cognitive responses with increasing perceptual similarity to the CS+ .

3.2.2. Overall anxiety severity

A Stimulus × Overall anxiety severity RM-ANCOVA yielded a significant effect of overall anxiety severity, $F(1, 110) = 5.48$, $p = .021$, $\eta_p^2 = .05$. Participants with a higher total SCARED score reported greater cognitive responses during extinction recall across stimuli (i.e., CSs and GSs).

3.2.3. Panic symptom severity

A Stimulus × Panic symptom severity RM-ANCOVA did not yield any significant effects.

3.2.4. Generalized anxiety symptom severity

A Stimulus × Generalized anxiety symptom severity RM-ANCOVA yielded a significant effect of generalized anxiety symptom severity, $F(1, 110) = 7.30$, $p = .008$, $\eta_p^2 = .06$. Participants with a higher generalized anxiety symptom score reported greater cognitive responses during extinction recall across stimuli.

3.2.5. Separation anxiety symptom severity

A Stimulus × Separation anxiety symptom severity RM-ANCOVA did not yield any significant effects.

3.2.6. Social anxiety symptom severity

A Stimulus × Social anxiety symptom severity RM-ANCOVA did not yield any significant effects.

3.2.7. All anxiety dimensions as covariates

A Phase × Stimulus RM-ANCOVA with Panic, Generalized, Separation, and Social anxiety symptom severity as covariates yielded a marginal effect of generalized anxiety symptoms on threat appraisal, $F(1, 107) = 3.66$, $p = .058$, $\eta_p^2 = .03$. Only generalized anxiety symptom severity was associated with greater cognitive responses during extinction recall across stimuli, while controlling for all other anxiety dimensions.

Together, the results indicate that overall anxiety severity and generalized anxiety symptom severity were associated with greater cognitive responses across all stimuli. The severity of panic symptoms, separation anxiety symptoms, and social anxiety symptoms was not associated with cognitive threat responses during extinction recall (see Fig. 4). After controlling for all other anxiety dimensions, generalized anxiety symptom severity was still associated with greater cognitive threat generalization during extinction recall.

3.3. Association between age and threat generalization

As noted, participants' age was considered as a covariate in all the above analyses. No main effects or interactions were observed for age in cognitive and physiological responses during the threat acquisition and extinction phases (Visit 1). However, during the extinction recall phase (Visit 2), a two-way interaction of Stimulus × Age emerged, $F(4, 444) = 5.70$, $p < .001$, $\eta_p^2 = .05$. Follow-up regression analysis using age to predict cognitive responses of each stimulus separately (CS-, GS25%, GS50%, GS75%, CS+) indicated an association between age and cognitive threat responses of the GS50%, $F(1, 111) = 10.22$, $p = .002$, $R^2 = -.31$, but not the other stimuli (CS-, GS25% GS75%, CS+) (see Fig. 5).

3.4. High versus low symptom severity

To complement the primary analyses using anxiety as a continuous dimension, we also compared high (above the 80th percentile in the sample) and low (below the 20th percentile) participants on each anxiety dimension. This supplemental analysis determined the presence or absence of anxiety as two dichotomous groups in line with the categorical approach to psychopathology. Our main results when we used anxiety severity as a continuous variable were replicated using high and low categorical groups. To be specific, all anxiety dimensions were associated with greater cognitive responses. Moreover, panic symptoms, but not generalized anxiety, were associated with greater physiological responses. Finally, generalized anxiety symptoms were associated with greater threat generalization. For more information, see supplemental materials (see Fig. S1, S2 and S3 in supplemental materials).

3.5. The effect of symptom severity comorbidity

3.5.1. Cognitive responses: self-reported fear during threat acquisition and extinction

A Phase (acquisition, extinction) × Stimulus (CS-, CS+) × Comorbid severity (non- anxious, low comorbidity, high comorbidity) RM-ANCOVA yielded a significant main effect of comorbid severity, $F(2, 122) = 6.34$, $p = .002$, $\eta_p^2 = .09$. Self-reported fear across phases and CSs increased as a function of symptom severity comorbidity. Follow-up tests revealed participants in the high comorbidity group reported greater self-reported fear than both low anxious participants ($p = .003$) and participants in the low comorbidity group ($p = .035$).

3.5.2. Physiological responses: self-reported fear during threat acquisition and extinction

A Phase (acquisition, extinction) × Stimulus (CS-, CS+) × Comorbid severity (non- anxious, low comorbidity, high comorbidity) RM-ANCOVA yielded a significant main effect of comorbid severity, $F(2, 117) = 5.74$, $p = .004$, $\eta_p^2 = .09$. SCR across phases and CSs increased as a function of symptom severity comorbidity. Follow-up tests revealed participants in the high comorbidity group showed greater SCR only compared to low anxious participants ($p = .003$).

3.5.3. Cognitive responses: self-reported threat appraisal during extinction recall

A Stimulus (CS-, GS25%, GS50%, GS75%, CS+) × Comorbid severity (non-anxious, low comorbidity, high comorbidity) RM-ANCOVA yielded a significant main effect of comorbid severity, $F(2, 109) = 3.48$, $p = .034$, $\eta_p^2 = .06$. Self-reported threat appraisal across stimuli increased as a function of symptom severity comorbidity. Follow-up

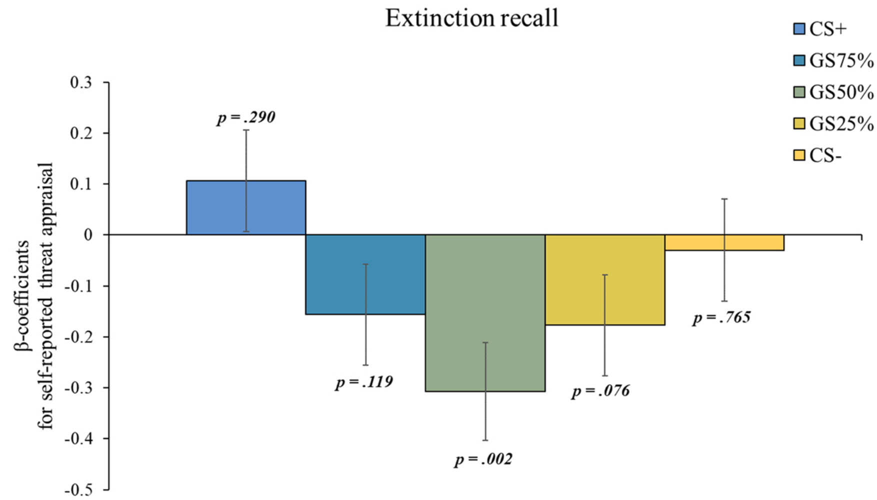

Fig. 5. Bar plot showing the standardized beta coefficients of participants' age on cognitive threat responses during extinction recall phase. Error bars represent one standard error. *P* values represent the effect of age on each stimulus separately.

tests revealed participants in the high comorbidity group reported greater self-reported threat appraisal only compared to low anxious participants ($p = .034$).

Together, the results indicate that anxiety comorbid severity was associated with greater cognitive and physiological responses, as well as increased threat generalization, during threat learning (see Fig. S4 in supplemental materials).

4. Discussion

In a sample of children and adolescents with mixed anxiety symptomatology, we examined the specificity of associations between symptom severity along different anxiety dimensions and cognitive and physiological threat responses during threat learning. Three major findings emerged. First, overall anxiety severity was associated with greater cognitive and physiological responses to threat and safety cues during threat acquisition and extinction and also with elevated threat generalization during extinction recall. Second, all anxiety dimensions were associated with greater cognitive responses, while panic, separation anxiety, and social anxiety symptoms, but not generalized anxiety, were related to heightened physiological responses during threat acquisition and extinction. Finally, only generalized anxiety symptoms were associated with greater threat generalization during extinction recall. Together, these findings suggest that while some threat response facets are common across anxiety dimensions, other unique associations exist between threat learning processes and specific features of each dimension in youth.

Across the whole sample, participants exhibited successful differential threat acquisition manifested by greater cognitive and physiological threat responses to the threat cue (CS+) than the safety cue (CS-). Following extinction, participants showed a decreased response to the CS+ in both measurements, although the difference between CSs did not fully diminish. Other studies have also reported partial differential extinction among youth (Lau et al., 2008; Shechner et al., 2015). This finding might result from an insufficient number of trials during extinction learning (i.e., eight trials) (Lonsdorf et al., 2017; Ryan, Zimmer-Gembeck, Neumann, & Waters, 2019). Alternatively, it could indicate some degree of impaired extinction learning in this age group. Recent structural and functional imaging studies have begun to reveal age differences in threat extinction learning at the neural level (Linton & Levita, 2021; Morriss et al., 2019). Specifically, age-related changes in amygdala-mPFC circuitry during adolescence have been hypothesized to render this age group vulnerable to the emergence and maintenance of anxiety.

Importantly, overall anxiety severity was associated with greater cognitive and physiological responses across CSs and phases. These results are consistent with a recent meta-analysis (Dvir et al., 2019) and a large clinical youth sample (Abend et al., 2020), indicating comparable differential threat learning among anxious and non-anxious youth. These findings suggest excessive responding with more severe anxiety may reflect biases in cue-based information processing, thus generating responses to threat that do not depend on threat learning per se. Therefore, the threat learning paradigm could reflect a context of uncertain potential threat in which such biases manifest in response to specific cues, leading to excessive responding in both the cognitive and physiological domains. We also found anxiety severity was associated with greater threat generalization to novel ambiguous stimuli. This elevated threat generalization may be driven by an interpretation bias, a tendency to misinterpret ambiguous situations, which has been suggested as a vulnerability factor in childhood anxiety disorders (Ginat-Frolich & Shechner, 2020; Gonzalez et al. 2017; Waters, Wharton, Zimmer-Gembeck, & Craske, 2008). Our finding is consistent with previous studies where anxious individuals exhibited greater fear generalization, both among adults (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Haddad, Pritchett, Lissek, & Lau, 2012) and among youth (El-Bar et al., 2017; Klein et al., 2020).

Prior theory and empirical work suggest the excessive expression of cognitive (e.g., worry) and physiological (e.g., changes in autonomic arousal) responses to threat are central in anxiety symptoms. Our findings extend previous work by demonstrating specific links between symptom severity of distinct anxiety dimensions and conditioned cognitive and physiological threat responses. Specifically, cognitive responses were enhanced across all anxiety dimensions during threat acquisition and extinction. However, physiological responses showed unique patterns across different dimensions. Panic symptom severity, which encompasses excessive physiological and somatic responses to threat, was associated with greater physiological response, specifically to the threat cue (CS+). Generalized anxiety symptom severity, operationalized as cognitive responses to threat, was not associated with physiological response magnitude. Separation and social anxiety symptoms, which were assessed without specificity of response dimension, were associated with greater general conditioned physiological responding. These findings begin to uncover specificity in the link between physiological symptom dimensions of anxiety and excessive physiological responding to threat, but not safety, in a laboratory setting. This is in line with previous studies finding panic-disorder patients experience anxiety reductions in safe situations, such as being at home, or when using safety behaviors, but not in situations of potential threat (Funayama et al., 2013; Salkovskis, Clark, Hackmann, Wells, & Gelder, 1999). Moreover, we observed the association between panic symptom severity and elevated SCR for the threat cue but not the safety cue during both threat acquisition and extinction learning. Thus, participants with more severe physiological and somatic symptoms expressed resistance to extinction, evident in their excessive physiological threat responses. This finding is consistent with prior findings in adults with panic disorder (Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007) is suggestive of a specific link between panic symptoms and deficit in physiological adaptation to a changing environment among youth.

Importantly, our findings suggest a degree of specificity in the associations between severity of reported symptoms and threat responses associated with threat learning. Namely, the severity of cognitive symptoms, captured by the generalized anxiety subscale, was associated with the magnitude of subjective fear, whereas the severity of physiological symptoms, captured by the panic subscale, was associated with the magnitude of SCR (Brown & McNiff, 2009). The lack of association between severity of generalized anxiety symptoms and physiological threat responses in our youth sample is in line with a previous study with adults, where individuals with and without generalized anxiety disorder exhibited similar SCR levels during threat acquisition (Yassa, Hazlett, Stark, & Hoehn-Saric, 2012).

Interestingly, only generalized anxiety symptoms, encompassing primarily cognitive responses to threat, were associated with greater cognitive threat generalization during extinction recall. Studies of adults similarly found generalized anxiety disorder patients showed greater threat generalization than non-anxious controls (Lissek et al., 2014; Tinoco-González et al., 2015). However, in contrast to our results, another study found greater generalization among adult patients with panic disorder (Lissek et al., 2010). A possible explanation of the incongruent findings is that we examined generalization following threat acquisition and extinction, while this latter study followed threat acquisition alone (Lissek et al., 2010). Hence, panic symptoms are likely to be associated with threat generalization, but extinction learning might diminish this association. In contrast, generalized anxiety symptoms are associated with increased threat generalization even following extinction learning.

In line with other studies, we observed a negative correlation between age and threat generalization (Klein et al., 2021; Reinhard et al., 2021; Schiele et al., 2016). Specifically, age was negatively associated with cognitive threat responses of the ambiguous GS50% but not the other stimuli (i.e., CS-, GS25%, GS75% and CS+). Age-related differences in threat response to ambiguous cues could be explained by various developmental factors, specifically by neural maturation and its cognitive related functions (Gold et al., 2020; Hein et al., 2018; Morriss et al., 2019; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014). Cortical brain regions that mature relatively late in development, such as the prefrontal cortex (Giedd et al., 2015; Tamnes et al., 2017), may be essential for inhibiting threat responses to ambiguous cues (Dymond et al., 2015; Lissek et al., 2014). Taken together, results from this large sample support previous findings of the effects of anxiety levels and age on overgeneralization of threat, and they expand those findings by demonstrating a link between generalized anxiety symptoms and threat overgeneralization in youth.

Our findings have implications for understanding the specific components of threat response, namely physiological and cognitive responses, as these relate to different facets of anxiety symptomatology throughout development. Because anxiety emerges early in life, a better understanding of specific links between aspects of aberrant threat learning and anxiety dimensions could potentially inform us more precisely on pathological mechanisms and improve clinical interventions. For example, youth with prominent physiological symptoms may benefit more from interventions that include a greater emphasis on psychophysiological components (e.g., biofeedback, body sensations, etc.) than youth affected primarily by cognitive symptoms such as excessive worry. Moreover, interventions targeting threat generalization could be more relevant for youth with predominantly cognitive symptoms than youth suffering from other anxiety symptoms. These examples are consistent with a transdiagnostic approach to psychotherapy, conceptualizing impairments along multiple diagnostic dimensions as related constructs, and providing a core set of treatment skills to address these dimensions (García-Escalera et al., 2020; Marchette & Weisz, 2017). Clinical research provides preliminary support for the notion that transdiagnostic protocols for youth are at least as efficacious in treating anxiety as traditional anxiety-specific treatment protocols and may even produce greater gains in treatment response at follow-up (Kennedy, Bilek, & Ehrenreich-May, 2019).

An important caveat for the interpretation of our results is that youth in our sample reported high levels of symptoms in more than one anxiety dimension. A large multi-site study similarly found pediatric anxiety symptoms manifested along multiple, correlated domains (Abend et al., 2021). While this complicates the identification of unique associations between anxiety dimensions and threat learning processes, comorbid symptomatology is in line with typical symptom presentation and accords with recent conceptualizations of psychopathology (HiTOP; Kotov et al., 2017). Our results add to the literature by showing greater comorbidity, i.e., more severe anxiety along multiple dimensions, is associated with greater cognitive and physiological threat responses. Hence, greater comorbidity appears to manifest as a general amplifier of threat response.

Other limitations of the study should be noted as well. First, the sample's age range was relatively large (7–17 years). This could have resulted in participants at different biological and psychological developmental stages being included in a single group. Yet this age range allowed us to examine age effects on threat learning and its generalization. Second, due to technical limitations, we did not record psychophysiology measures during extinction recall; future work could benefit from recording both cognitive and physiological threat responses throughout the study. Finally, the participant sample consisted of community members with a wide range of anxiety severity. Future studies should extend this work to patient populations and examine the extent to which these findings generalize to pathological anxiety.

To the best of our knowledge, this study is the first to examine links between different facets of anxiety symptomatology and conditioned cognitive and physiological responses to threat in a large sample of youth. We provide preliminary support for links between symptom expression along different dimensions of anxiety and excessive threat responses, as indicated by emotion-related cognitive biases and physiological arousal. These processes offer glimpses of perturbations in information processing more broadly and their subsequent impact on normative and pathological developmental trajectories. Our findings could set the stage for future studies examining specific effects of anxiety symptoms on such biases and identifying potential targets for early interventions among children and adolescents.

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Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2022.108314.

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