Social Cognitive and Affective Neuroscience, 2024, **19**(1), nsae065
DOI: https://doi.org/10.1093/scan/nsae065
Advance Access Publication Date: 9 October 2024
Original Research – Neuroscience

A preliminary study of threat-anticipatory responding in Latina youth: associations with age, anxiety, and cortical thickness

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Abstract

Variation in prefrontal cortex neuroanatomy has been previously associated with elevated physiological responses to anticipated aversive events. The extent to which such associations extend beyond the specific ecology of treatment-seeking youth from upper-middle socioeconomic backgrounds is unknown. The current study tests the replicability of neuroanatomical correlates of anticipatory responding and the moderating roles of age and anxiety severity in a community sample of Latina girls, a historically underrepresented group exhibiting high levels of untreated anxiety. Forty pre-adolescent Latina girls ($M_{Age} = 10.01$, s.d. = 1.25, range = 8–12 years) completed a structural magnetic resonance imaging scan. Participants also completed a differential threat and safety learning paradigm, during which skin conductance and subjective fear responding were assessed. Anxiety severity was assessed via the *Screen for Child Anxiety Related Emotional Disorders*. Ventromedial prefrontal cortex thickness was associated with reduced physiological responsivity to anticipated threat. Age- and anxiety-dependent associations emerged between dorsomedial prefrontal cortex thickness and individual differences in subjective fear responding to anticipated threat. This preliminary study extends work on neuroanatomical contributions to physiological threat responsivity to a community sample of Latina youth and highlights potential considerations for early identification efforts in this population when threat neurocircuitry is still developing.

Keywords: threat learning; safety learning; structural MRI; skin conductance responses; Latina youth

The anticipation of threat engages conserved neural circuitry evolved to facilitate adaptive defensive responding (LeDoux 2012, Fanselow 2018). Perturbations in this circuitry can generate excessive anticipatory responding, a core feature of anxiety disorders (Grupe and Nitschke 2013, Hamm 2020, Abend 2023). Characterizing perturbations in threat responding in children is of particular interest, as individual differences in threat anticipation and anxiety arise early (Merikangas et al. 2010, Dvir et al. 2019), during a period when threat-relevant neurocircuitry is still developing (Shin and Liberzon 2010, Casey et al. 2015).

A growing evidence base identifies age, anxiety, and brain structure as important determinants of elevated threat anticipation (Mineka and Zinbarg 2006, Craske et al. 2008, Gao et al. 2010, Hartley et al. 2011, Shechner et al. 2014, Fullana et al. 2018, Abend et al. 2020, 2021, Michalska et al. 2022). Notably, most of this work has focused on physiological and subjectively reported indices of anticipatory threat responding in treatment-seeking youth from relatively high socioeconomic backgrounds, limiting the representativeness of samples. Further, methodological tools in neuroscientific and physiological research are often subject to biases against certain phenotypes (e.g. hair texture, and skin color) shared by marginalized racial and ethnic groups (Webb et al. 2022) and have, in part, contributed to a vast and systemic underrepresentation of these groups in studies of threat and safety learning (Kredlow et al. 2018, La Scala et al. 2023). As such, the extent to which previous findings on threat anticipation extend to ethno-racially and socioeconomically diverse populations remains unclear. To address this significant gap directly and shift the field toward a more equitable standard of research, the current study focused on a community-based sample of pre-adolescent Latina girls to replicate prior work and investigate the influence of age, anxiety symptoms, and prefrontal cortical thickness on children's physiological and subjective indices of anticipatory threat responding to potential but not immediately present threats.

Received: 28 December 2023; **Revised**: 19 April 2024; **Accepted**: 8 October 2024

Threat and safety learning

Neurocircuitry has evolved to enable rapid learning of threat associations following encounters with danger (LeDoux 2014). Through threat conditioning, a neutral stimulus (i.e. a conditioned stimulus, CS+) acquires the capacity to elicit fear responses in anticipation of danger after being paired with an intrinsically aversive event (i.e. an unconditioned stimulus, US) (Pavlov 1927, Fanselow 2018). Threat conditioning facilitates early detection of potential danger (Beckers et al. 2013) and promotes defensive responding (Fanselow 2018, Abend 2023). Through extinction, such conditioned anticipatory responding is attenuated if the stimulus no longer predicts the occurrence of threat (Milad and Quirk 2012). In some experimental paradigms, a second, nonreinforced conditioned stimulus (CS–), never paired with the US, serves as a learned safety signal (Rogan et al. 2005, Michalska et al. 2016, 2019, Glenn et al. 2020, 2021, Mullins et al. 2021). Safety signal learning tests for the active inhibition of threat in the presence of safety. An individual's learning can be measured in various ways, including their subjective perceptions of fear of the CS+, CS–, and US, as well as peripheral indices of arousal, including skin conductance response (Lonsdorf et al. 2017).

Associations between anxiety and anticipatory responding

Anxiety disorders are among the most prevalent forms of childhood psychopathology (Anderson et al. 1987, Moreno et al. 2010), and rates increase as children enter adolescence (Ford et al. 2003, Canino et al. 2004, Beesdo et al. 2009), frequently persisting into adulthood (Bruce et al. 2005). A prominent feature of anxiety disorders is excessive responding in anticipation of threats (Lissek et al. 2005, Mineka and Zinbarg 2006, Michalska et al. 2018, 2023, Abend 2023), which can interfere with normal functioning (American Psychiatric Association 2013). Indeed, prominent theoretical frameworks implicate threat and safety learning perturbations in the cause and maintenance of excessive threat responding in anxiety (Barlow 2002, Mineka and Oehlberg 2008). Whereas evidence suggesting that anxious youth discriminate between threat and safety cues differently than nonanxious youth during threat conditioning (i.e. acquisition of threat contingencies) remains inconclusive (see Dvir et al. 2019 for a meta-analysis), mounting research nonetheless suggests that anxious youth exhibit global alterations in threat and safety learning. For example, relative to typically developing youth, anxious youth display increased subjective fear (Lau et al. 2008) and skin conductance responding (Craske et al. 2008, Abend et al. 2020) to both threat and safety cues during threat and safety learning and are, likewise, more resistant to threat extinction (Dvir et al. 2019, Abend et al. 2022). More broadly, anxious individuals also show greater physiological responding across several threat-anticipatory states (e.g. Grupe and Nitschke 2013). Delineating the mechanisms that underlie associative learning of threat and safety can clarify the processes that forge the development of both normative fear and pathological anxiety.

Development of anxiety in Latinx youth

Mental health disparities among Latinx youth have escalated in recent years (Substance Abuse and Mental Health Services Administration 2018). Compared to their white peers, Latinx youth report more anxiety symptoms and have higher rates of anxiety diagnoses (39.0% versus 30.5%; Ginsburg and Silverman 1996, Varela et al. 2004, Georgiades et al. 2018). Rates among Latina adolescents, in particular, have significantly increased, representing a critical health disparity (McLaughlin et al. 2007). A recent study with Latinx high school students found that two-thirds of Latinx adolescents reported symptoms that were clinically significant for anxiety and over half for posttraumatic stress disorder (Capps et al. 2020). At the same time, Latinxs are less likely to receive treatment and experience more barriers to accessing care compared to their white counterparts (Lagomasino et al. 2005, Gudiño et al. 2009, Dixon De Silva et al. 2020), thus escalating the Latinx population's experiences of health disparities.

Problematically, most work on threat anticipation and anxiety has not included Latinxs and other people of color (see Martínez et al. 2014, for a notable exception), limiting inferences about the generalizability of extant findings and the implications they may have for addressing mental health disparities. The current study extends prior work by focusing on a sample of Latina girls, an understudied group exhibiting higher levels of untreated anxiety compared to other ethnic groups (Pina and Silverman 2004, McLaughlin et al. 2007, Anderson and Mayes 2010, Georgiades et al. 2018). Determining the extent to which previous results on anxiety and physiological, subjective, and neural correlates of anticipatory threat responding generalize to Latina youth will set the stage for future work examining sociocultural influences like cultural stress, ethnic–racial discrimination, and cultural strengths and competencies on these processes (Vargas and Willis 1994, Brown et al. 2007, Mullins et al. 2024a, 2024b).

Neural correlates of anticipatory responding

Conditioned threat-anticipatory responding relies in part on prefrontal cortex function and structure (Kolb 1974, Zbrozyna and Westwood 1991, Morgan et al. 1993, Milad et al. 2005, Pessoa 2009, Etkin et al. 2011, Hartley et al. 2011, Shackman et al. 2011, Fullana et al. 2016, 2018, Winkelmann et al. 2016, Marin et al. 2017, Abend et al. 2021). Within the medial prefrontal cortex, the *dorsal* region (i.e. dorsomedial prefrontal cortex, dmPFC) is believed to be involved in the appraisal and expression of negative emotions, including fear, whereas the *ventral* region (i.e. ventromedial prefrontal cortex, vmPFC) is involved in the implicit regulation of these emotions (Alexander et al. 2020, Kenwood et al. 2022) and these respective roles are believed to be consistent across species (Quirk and Mueller 2008, Sierra-Mercado et al. 2011, Mullins and Michalska 2023). Prior functional work shows dmPFC activation correlates with *increased* anticipatory threat responding (Mechias et al. 2010, Klumpers et al. 2015, Chavanne and Robinson 2021) and vmPFC activation correlates with *reduced* anticipatory threat responding (Phelps et al. 2004, Schiller et al. 2008, Marin et al. 2017). Even though research on structural underpinnings of anticipatory threat responding is scarce, there is some agreement that increased vmPFC cortical thickness is associated with reduced threat responding (Milad et al. 2005, Hartley et al. 2011, Winkelmann et al. 2016). Specifically, vmPFC cortical thickness is related to reduced skin conductance responding to a conditioned stimulus after it no longer predicts potential threat. Less is known about structural correlates of dmPFC thickness.

Only one study, to our knowledge, has examined contributions of dmPFC cortical thickness to anticipatory threat responding. Abend et al. (2020) observed an inverse association between cortical thickness in a broad prefrontal cortex region that subsumed aspects of the dmPFC and the magnitude of skin conductance responding during threat and safety learning, as well as moderating effects of age and anxiety in other cortical regions. These

Table 1. Anticipated findings, supporting evidence, and results.

Hypothesis	Supporting evidence	Finding
Age would be associated with skin conductance and subjective fear **responding**.	Block et al. 1970, Gao et al. 2010, Michalska et al. 2016, Abend et al. 2020[a]	Age was not directly associated with skin conductance or subjective fear responding.
Anxiety symptoms would be positively associated with skin conductance and subjective fear responding.	Craske et al. 2008, Lau et al. 2008, Abend et al. 2020	**Anxiety symptoms were positively associated with subjective fear responding**. No association with skin conductance responding emerged.
vmPFC thickness would be inversely associated with skin conductance and subjective fear responding.	Milad et al. 2005, Hartley et al. 2011, Winkelmann et al. 2016	vmPFC thickness was inversely associated with skin conductance responding. No association with subjective fear responding emerged.
dmPFC thickness would be inversely associated with skin conductance and subjective fear **responding**.	Abend et al. 2020	dmPFC thickness was not directly associated with skin conductance or subjective fear responding.
Age and anxiety would moderate associations between cortical thickness and skin conductance and subjective fear **responding such that associations would grow more strongly negative with increasing age and more strongly positive with increasing anxiety**.	Abend et al. 2020[a]	**dmPFC thickness and subjective fear responding were negatively associated for older children** with high and mean levels of anxiety, **but not for children in any other age group** at any other anxiety levels. No moderating effect of age or anxiety on the association between vmPFC thickness and skin conductance or subjective fear responding emerged.

Bold text indicates aspects of Abend et al. (2020) intended for replication.
[a]Abend et al. (2020) observed an inverse association between age and skin conductance responding and moderating effects of age and anxiety on the association between cortical thickness and skin conductance responding in regions that excluded the vmPFC and dmPFC.

findings suggest a role of the dmPFC in regulating anticipatory responses to potential danger that is reflected in morphological features of the cortex and identify age and anxiety as key factors to consider in thickness-response associations. This study was conducted with a sample ranging widely in age (8–50 years), approximately half of which was treatment-seeking and did not focus on discrete cortical regions, limiting the potential for more nuanced inferences about developing associations between brain structure and threat responding during more distinct developmental periods. The current study tests the broad replicability of these effects in a sample of pre-adolescent Latina girls, an understudied group with already disproportionately high rates of anxiety that is at the cusp of a developmental transition known for even sharper increases in anxiety disorder prevalence rates (Reardon et al. 2009). We examine more targeted prefrontal regions of interest, the vmPFC and dmPFC, given their differential roles in threat and safety learning, and explore both physiological and subjective indices of anticipatory responding, considering the limited concordance between these distinct facets of responsivity (LeDoux and Pine 2016, Michalska et al. 2022, Taschereau-Dumouchel et al. 2022). We contend this investigation may be informative for the derivation of more developmentally sensitive intervention and prevention efforts targeting anxiety, specifically in youth who remain underrepresented in this branch of research.

The current preliminary study

To estimate independent and interactive associations of development, anxiety, and brain structure with physiological and subjective indices of children's threat responding, the current preliminary study examined child age and anxiety symptoms, as well as cortical thickness assessed via a structural magnetic resonance imaging (MRI) scan, in conjunction with children's skin conductance and subjective fear responding recorded during a well-validated laboratory-based threat and safety learning paradigm (Lau et al. 2011, Britton et al. 2013, Michalska et al. 2017, Glenn et al. 2021). We tested five a priori hypotheses outlined in Table 1. First, child age would be associated with skin conductance and subjective fear responding during threat and safety learning. Because findings are mixed with regards to the direction of these associations (Block et al. 1970, Gao et al. 2010, Michalska et al. 2016, Abend et al. 2020), we did not make specific predictions about the direction of effects. Second, child anxiety symptoms would be positively associated with skin conductance and subjective fear responding during threat and safety learning. Third, vmPFC thickness would be inversely associated with skin conductance and subjective fear responding during threat and safety learning. Fourth, dmPFC thickness would be inversely associated with skin conductance and subjective fear responding during threat and safety learning. Fifth, age and anxiety would moderate associations between cortical thickness and skin conductance and subjective fear responding such that associations would grow more strongly negative with increasing age and more strongly positive with increasing anxiety severity.

We complement and extend prior work in several ways. First, threat and safety learning research has often focused on early childhood and adulthood. In the current study, we add to a growing body of work focused on the development of anticipatory threat responding in pre-adolescence, enabling potentially more nuanced inferences about threat responding processes prior to a period of significantly heightened anxiety risk during which threat neurocircuitry undergoes significant structural and functional developments (Herting et al. 2012, Gee et al. 2013, Newman et al. 2016). Second, we study a community-based sample consisting of primarily Mexican-origin Latina girls, a group at heightened risk for anxiety (McLaughlin et al. 2007) that has been underrepresented in research on threat anticipation (see Martínez et al. 2014 for a notable exception). Third, we evaluate both physiological and subjective indices of anticipatory responding. Because physiological measures of fear and anxiety often correlate weakly with subjective experiences (LeDoux and Pine 2016, Michalska et al. 2022, Taschereau-Dumouchel et al. 2022), perhaps in part because subjective reports require introspective skills that develop with age, identifying ways in which these indices are differentially implicated during threat and safety learning may inform a deeper understanding of anxiety disorders and their treatment across development.

Methods

Participants

Participants included 55 Latina girls (M_{Age} = 9.95, s.d. = 1.33, range = 8–13 years) residing in the Inland Empire Region of Southern California. Of these 55 participants, 5 were missing structural brain data due to failure to complete a scan, 10 were missing physiological data due to technical difficulties (N = 2) or task abortion (N = 8), and 2 were missing subjective fear ratings due to data collection errors. The task abortion rate in the current sample (18%) was comparable to other work with subclinical samples (14%) utilizing the same threat and safety learning paradigm (Shechner et al. 2015). Participants with complete data did not differ from participants with incomplete data as to age, $t(53) = -0.513$, $P = .610$, annual household income, $t(16.40) = -1.220$, $P = .240$, anxiety, $t(53) = -0.504$, $P = .616$, mean cortical thickness, $t(48) = 0.600$, $P = .551$, overall physiological responding during threat and safety learning, $t(43) = -1.023$, $P = .312$, or overall subjective fear responding during threat and safety learning, $t(51) = -0.617$, $P = .540$. Where Levene's test indicated unequal variances, degrees of freedom were corrected, and t-values were recalculated using unpooled variances. Analyses utilized only participants with complete data for all study variables. As such, the final sample included 40 Latina girls (M_{Age} = 10.01, s.d. = 1.25, range = 8–12 years).

Participants were recruited via fliers in outpatient mental health clinics and local hospitals, and the University of California, Riverside Psychology Department shared database of child participants. Participant eligibility was determined by phone screening with a parent. Children were eligible for participation if they were conversant in English, age 8–13 years, self-identified as Latina, were premenstrual, had no contraindications for neuroimaging, and did not meet any exclusionary criteria. Due to a recruitment error, two participants were postmenstrual at study entry. As menstruation or pubertal status per se was not the focus of the present study, their data were retained in analyses. Exclusionary criteria for children were active use of any psychoactive substance (including use of any selective serotonin reuptake inhibitor within the past month or fluoxetine within the past 6 months), current suicidal ideation or psychiatric diagnosis of Tourette's syndrome or obsessive-compulsive disorder, or lifetime history of mania or psychosis. On average, families had household incomes ($25 000–$39 999) below the median annual household income in the USA ($67 521; United States Census Bureau 2020).

Procedures

Data for the present analyses were collected at participants' first of several laboratory assessments as part of an ongoing longitudinal study of socioemotional development. Upon participant arrival, written parent consent and child assent were obtained. During the laboratory session, children completed a structural MRI scan, as well as a battery of self-report questionnaires assessing demographics, behavior, anxiety, and other mental health outcome measures not reported here. They also completed a laboratory-based differential threat and safety learning paradigm, during which physiological and subjective fear responding was assessed. At the end of the laboratory session, participants were compensated with a gift card and a small prize. The Institutional Review Board approved all study procedures.

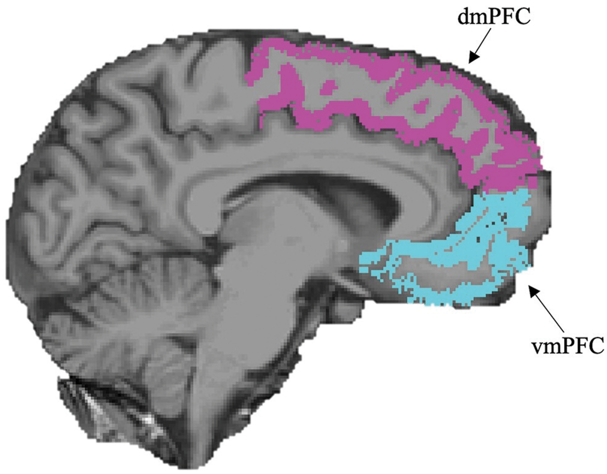

Figure 1. Using Freesurfer Version 6.0.0 (https://surfer.nmr.mgh.harvard.edu), thickness measurements for the left and right ventromedial prefrontal cortex (vmPFC, Freesurfer label: medial orbitofrontal) and left and right dorsomedial prefrontal cortex (dmPFC, Freesurfer label: superior frontal) were extracted. For visualization in FMRIB Software Library (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), the sample subject Freesurfer labels were converted to cortical masks and overlaid on a sagittal view of the Freesurfer provided brain mask as the underlay.

Measures

Brain imaging, data processing, and analysis

MRI scans were acquired on a 3-Tesla Siemens Magnetom Prisma scanner (Siemens, Malvern, PA) with a 32-channel receive-only head coil at the University of California, Riverside Center for Advanced Neuroimaging. Participants completed a T1-weighted magnetization-prepared rapid conditioning gradient-echo scan (MPRAGE) with the following parameters: 208 sagittally acquired 0.80 mm slices; 320 × 300 matrix; 0.8 mm^3 isotropic voxels; flip angle = 8°; field of view (FOV) = 256 × 240 mm, repetition time (TR) = 2400 ms, echo time (TE) = 2.72 ms, inversion time (TI) = 1060 ms. Using Freesurfer Version 6.0.0 (https://surfer.nmr.mgh.harvard.edu), T1 images were processed, cortical surface reconstruction was performed, and thickness measurements for the left and right vmPFC (Freesurfer label: medial orbitofrontal) and left and right dmPFC (Freesurfer label: superior frontal) were extracted (Powers et al. 2017). Left and right thicknesses were averaged to assess mean thickness for each region (Fig. 1) and global mean cortical thickness measurements, which were employed as nuisance covariates, were also extracted.

Child anxiety symptoms

Participants completed the forty-one item *Screen for Child Anxiety Related Emotional Disorders* (SCARED; Birmaher et al. 1999) to provide continuous measures of anxiety disorder symptoms across five domains: panic/somatic, generalized anxiety, separation anxiety, social phobia, and school phobia. For each item, children indicated on a 3-point Likert scale (0 = *Not true or hardly ever true* to 2 = *Very true or often true*) the extent to which each was true for them. Responses were summed across all items, as well as within

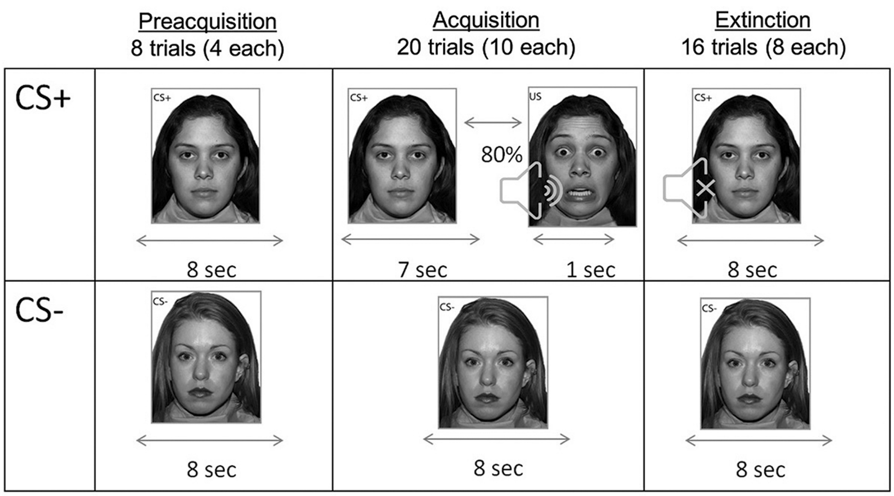

Figure 2. During the preacquisition phase of the threat and safety learning paradigm, children passively viewed neutral faces of two women, the CS, in the absence of the US. During the acquisition phase, one woman, the CS+, predicted the US, a 1 second image of a fearful face paired with a scream, while the other woman, the CS–, did not. During the extinction phase, the CS+ and CS– were presented repeatedly in the absence of the US.

each subdomain. The SCARED demonstrated strong internal consistency in the current sample with a Cronbach's α of 0.92 and 82.5% of the sample met diagnostic criteria for an anxiety disorder (≥25).

Threat and safety learning

To assess threat and safety learning, participants completed a differential threat conditioning and extinction paradigm (Fig. 2) validated in pediatric populations (Lau et al. 2011, Britton et al. 2013, Michalska et al. 2017, Glenn et al. 2021).

Task instructions

Participants were accompanied by a researcher into a dark room illuminated by a single night light. They were asked to sit at a computer and place a pair of headphones over their ears. They were told that a series of pictures would appear on the screen and at times they would see a mildly unpleasant face and hear a mildly unpleasant sound. Prior to the start of the paradigm, participants were reassured that nothing in the study would hurt them in any way and that the researcher would be present in the back of the room for the duration of the task.

Task description

The trace conditioning paradigm consisted of a *preacquisition* phase, an *acquisition* phase, and an *extinction* phase. In each phase, a series of approximately 4 × 6 inch black and white photos were presented on screen. During preacquisition, which consisted of eight trials, children passively viewed neutral faces of two women, one at a time, in the absence of the US. During acquisition, which consisted of 20 trials, one woman, assigned to be the CS+, predicted the US, a 1 second image of a fearful expression of that woman paired with a loud, aversive 95 dB scream, while the other woman, the CS–, did not. The two faces were counterbalanced for CS+ and CS– assignment. During these paired trials, the CS+ was presented first, then disappeared and was replaced by the US, which co-terminated with the scream. The CS+ was followed by the US with an 80% reinforcement schedule. Participants were told they could learn to predict when the US would occur but were not informed of the CS-US contingency. During extinction, which consisted of 16 trials, the CS+ and CS– were presented repeatedly in the absence of the US. Throughout all three phases, the CS+ and CS– were presented for 7–8 s (7 s when paired with the US, 8 s when unpaired), followed by an interstimulus interval of a blank gray screen for 8–21 seconds ($M = 15$ s). Presentation order of the CS types and interstimulus intervals was pseudo-randomized (two different orders counterbalanced across participants). We note the current study did not habituate participants to the aversive noise prior to the start of the experiment, in line with previous work employing this paradigm (Lau et al. 2011, Britton et al. 2013, Michalska et al. 2017, Abend et al. 2020, Glenn et al. 2021, Mullins et al. 2021). This decision was guided by an effort to avoid attenuation of the aversiveness of the US (Abend et al. 2020), which would reduce the capacity for the procedure to induce conditioned fear. The task was presented using E-prime Version 2.0.10 (https://pstnet.com/products/e-prime/).

Skin conductance response

Skin conductance responding indexed participants' physiological responding to the CS+ and CS– across the three phases of the threat and safety learning task (Lonsdorf et al. 2017). Skin conductance responding was recorded from two Ag/AgCl electrodes from the middle and ring finger of the nondominant hand, using a Biopac MP160 system (EDA100C; Biopac Systems, Goleta, CA, USA) together, with AcqKnowledge 4.3 (Biopac Systems, Goleta, CA, USA) software. Skin conductance was sampled continuously at 2000 Hz. Skin conductance response amplitude to each CS+ and CS– was determined by the difference between baseline activity (minimum amplitude within 0–1 seconds prior to stimulus onset) to peak activity (maximum amplitude within 1–5 s following stimulus onset). Raw values for each trial were expressed as a percent change from that trial's baseline value with the following equation: Skin Conductance Response = % Signal Change from Baseline = [(Maximum Amplitude − Minimum Amplitude)/Minimum Amplitude] * 100 (Balderston and Helmstetter 2010, Michalska et al. 2017, 2019). Trial-level skin conductance responding to the conditioned and unconditioned stimuli appears in Fig. 3a and Fig. 3b, respectively. In line with previous work (Michalska et al. 2017, 2019, Mullins et al. 2021), outliers were determined by computing the global skin conductance response average across all trials and both CS types for each participant. Individual trials that deviated more than ±2 s.d. from the global average were

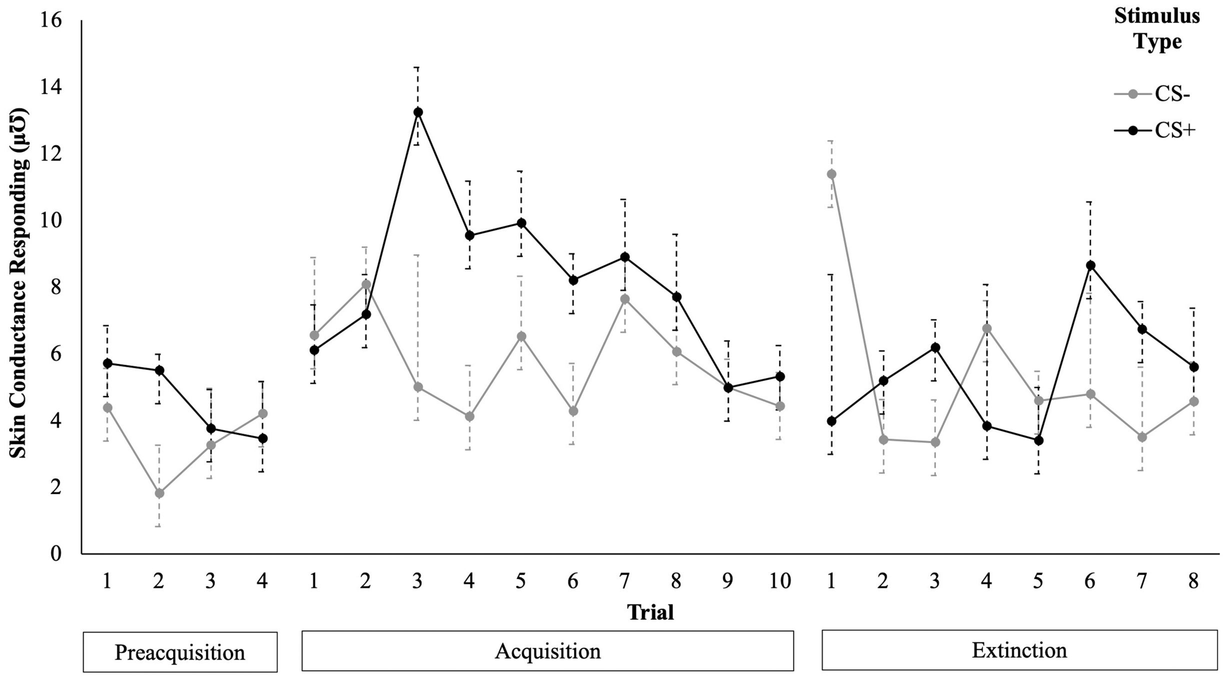

Figure 3a. Trial-by-trial skin conductance responding to the paired (CS+) and unpaired (CS-) conditioned stimuli during preacquisition, acquisition, and extinction phases. Error bars represent standard error.

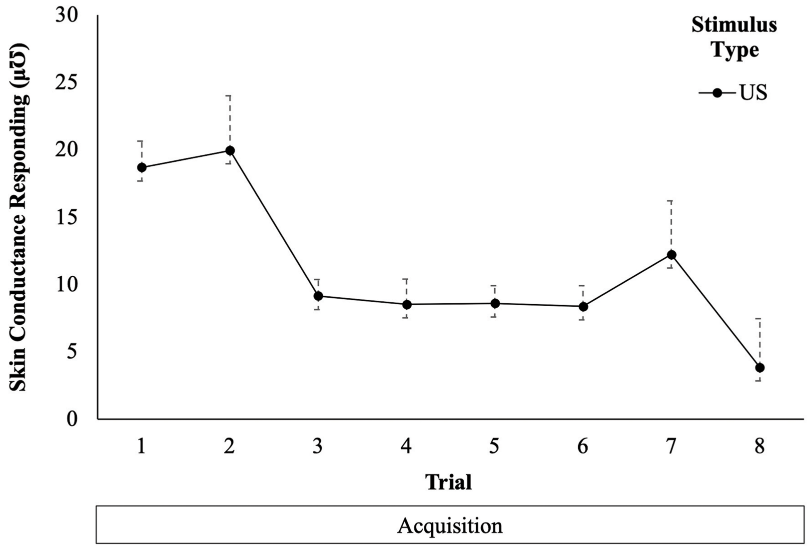

Figure 3b. Trial-by-trial skin conductance responding to the unconditioned stimulus (US) during the acquisition phase. Error bars represent standard error.

considered artifacts and replaced with that participant's respective upper (+2 *SD*) or lower (−2 s.d.) limit value. As has been recommended in previous work (Boucsein 2012), we ensured that for each subject, outliers did not make up >20% of trials. Percent signal change values were averaged within stimulus types and phases to assess skin conductance responding to the CS+ (paired or unpaired) and CS− during preacquisition, acquisition, and extinction. Across these three phases, averaged responding to both stimulus types assessed overall anticipatory responding (i.e. *Overall Skin Conductance Response*), averaged responding to the CS+ assessed anticipatory responding to threat (i.e. *Skin Conductance Response to Threat*), and averaged responding to the CS− assessed anticipatory responding to safety (i.e. *Skin Conductance Response to Safety*).

Subjective fear response

Subjective fear ratings indexed participants' subjective fear responding to the CS+ and CS− across the three phases of the threat and safety learning task. Prior to preacquisition, participants were shown a picture of each CS and asked to rate on a 10-point Likert scale how anxious they were when they viewed it (1 = *Not at all anxious* to 10 = *Extremely anxious*). The preacquisition phase was followed immediately by the acquisition phase, after which participants completed this question a second time.

Then, the extinction phase began at the end of which participants completed this question a third and final time. Across these three phases, averaged responses to both stimulus types assessed overall anticipatory responding (i.e. *Overall Subjective Fear Response*), averaged responses to the CS+ assessed anticipatory responding to threat (i.e. *Subjective Fear Response to Threat*), and averaged responses to the CS− assessed anticipatory responding to safety (i.e. *Subjective Fear Response to Safety*).

Data analysis

First, skin conductance response data were analyzed with a repeated-measures analysis of variance (ANOVA), with phase (preacquisition, acquisition, extinction) and CS type (CS+, CS−) as within-subject factors. Next, subjective fear ratings were analyzed with a repeated-measures ANOVA, with phase and CS type as within-subject factors. In cases where the assumption of sphericity was violated, Huynh–Feldt corrections were applied. To probe tested interactions, post hoc *t*-tests were performed for skin conductance responding to the CS+ and CS− within each phase, and then subjective fear responding to the CS+ and CS− within each phase. For all analyses, statistical significance was set to $\alpha = 0.05$. All analyses were conducted in SPSS Version 27 (https://www.ibm.com/spss).

Based on the prior study by Abend et al. (2020), we first tested main effects of prefrontal cortical thickness, age, anxiety, and their interaction on *Overall Skin Conductance Response*. Because physiological responses and subjective experiences are thought to tap into distinct facets of fear and anxiety (LeDoux and Pine 2016, Michalska et al. 2022, Taschereau-Dumouchel et al. 2022), we also separately tested main and interaction effects of cortical thickness, age, and anxiety on *Overall Subjective Fear Response*. Finally, because children's ability to differentiate between threatening and non-threatening stimuli grows more efficient with age (Pine et al. 2009, Michalska et al. 2016) and is an important predictor of anxiety trajectories (Shechner et al. 2014, Waters 2017), we tested main and interaction effects on *Skin Conductance Response to Threat, Subjective Fear Response to Threat, Skin Conductance Response to Safety*, and *Subjective Fear Response to Safety*.

To examine main and interactive effects of cortical thickness, age, and anxiety on children's anticipatory responding during threat and safety learning, moderated linear regression analyses were conducted with the PROCESS macro in SPSS (Hayes 2013). Separate regression models were conducted for each outcome of interest. In the first model, *Overall Skin Conductance Response* was regressed onto vmPFC thickness, age, anxiety, the product of vmPFC thickness and age, the product of vmPFC thickness and anxiety, and the product of vmPFC thickness, age, and anxiety. In the second model, *Overall Subjective Fear Response* was regressed onto vmPFC thickness, age, anxiety, the product of vmPFC thickness and age, the product of vmPFC thickness and anxiety, and the product of vmPFC thickness, age, and anxiety. The following four models repeated these analyses with *Skin Conductance Response to Threat, Subjective Fear Response to Threat, Skin Conductance Response to Safety*, and *Subjective Fear Response to Safety* as separate outcome variables. Six final regression models tested main and interaction effects of dmPFC thickness, age, and anxiety on *Overall Skin Conductance Response, Overall Subjective Fear Response, Skin Conductance Response to Threat, Subjective Fear Response to Threat, Skin Conductance Response to Safety*, and *Subjective Fear Response to Safety* as separate outcome variables.

In sum, 12 moderated linear regression models were conducted, one for each outcome (i.e. *Overall Skin Conductance Response, Overall Subjective Fear Response, Skin Conductance Response to Threat, Subjective Fear Response to Threat, Skin Conductance Response to Safety, Subjective Fear Response to Safety*) and cortical thickness predictor (i.e. vmPFC, dmPFC) combination. All variables were continuous and mean-centered prior to analysis, and the estimated effects are reported as unstandardized regression coefficients. To address any non-normality in the distribution of the outcomes, the models were estimated using bootstrapped samples (bootstrap $N = 5000$) to produce 95% bias-corrected confidence intervals (BC CI) around the parameter estimates. Effects were determined to be significant at $P < .05$ if the upper and lower limits of the CIs did not contain zero. For significant interactions, each outcome was examined across three levels (average, +1 s.d., −1 s.d.) of each predictor variable. To account for multiple tests, Bonferroni corrections were applied.

Results

Descriptive statistics appear in Table 2, and bivariate correlations appear in Table 3.

Skin conductance response to conditioned threat cues

A repeated-measures ANOVA testing the phase by CS type effect on skin conductance responding yielded a significant main effect of phase, $F(1.59, 62.17) = 3.48$, $P = .047$. Post-hoc *t*-tests revealed that skin conductance responding was greater during acquisition relative to preacquisition, $t(39) = -3.86$, $P < .001$, but not extinction, $t(39) = 1.30$, $P = .101$. A significant main effect of CS type also emerged, $F(1, 39) = 8.32$, $P = .006$, with post-hoc *t*-tests revealing that skin conductance responding was greater to the CS+ relative to the CS− across all phases, $t(39) = -2.89$, $P = .003$. Unexpectedly, there was no significant phase by CS type interaction, $F(2, 78) = 2.05$, $P = .136$. For completeness, follow-up paired-samples *t*-tests were conducted with each phase. These tests indicated greater response to the CS+ relative to the CS− during acquisition, $t(39) = -3.52$, $P = .001$, but not during preacquisition, $t(39) = -2.00$, $P = .052$, or extinction, $t(39) = -0.158$, $P = .875$ (Fig. 4). While the absence of a significant phase by CS type interaction was unexpected, the overall qualitatively observed pattern for skin conductance responding indicates partial conditioning followed by extinction.

Subjective fear ratings of conditioned threat cues

A repeated-measures ANOVA testing the phase by CS type effect on subjective fear responding yielded a significant main effect of phase, $F(2, 74) = 7.82$, $P = .001$. Post-hoc *t*-tests revealed that subjective fear responding was greatest during acquisition relative to preacquisition, $t(37) = -3.67$, $P < .001$, and extinction, $t(38) = 1.99$, $P = .027$. A significant main effect of CS type also emerged, $F(1, 37) = 6.21$, $P = .017$, with post-hoc *t*-tests revealing that subjective fear responding was greater to the CS+ relative to the CS− across all phases, $t(39) = -3.24$, $P = .001$. These main effects were qualified by a significant phase by CS type effect, $F(1.75, 64.85) = 12.75$, $P < .001$. Paired-sample *t*-tests indicated greater subjective fear responding to the CS+ relative to the CS− during acquisition, $t(38) = -4.05$, $P < .001$, but not during preacquisition, $t(38) = 0.20$, $P = .846$, or extinction, $t(38) = 1.73$, $P = .092$ (Fig. 5). This pattern indicates successful conditioning followed by extinction of the threat contingency in subjective fear responding.

vmPFC thickness and anticipatory responding

The first set of moderated linear regression analyses examined whether anticipatory responding during threat and safety

Table 2. Descriptive statistics for key study variables.

Variables	M	SD	Minimum	Maximum	N
Age	10.01	1.25	8.22	12.66	40
Anxiety	38.20	15.61	4.00	71.00	40
Cortical thickness	2.81	0.08	2.67	2.97	40
vmPFC thickness	2.71	0.16	2.38	3.14	40
dmPFC thickness	3.36	0.15	2.85	3.63	40
Overall skin conductance response	5.45	4.07	0.51	18.34	40
Skin conductance response to threat	6.06	3.95	0.64	18.55	40
Skin conductance response to safety	4.84	4.59	0.38	22.29	40
Overall subjective fear response	3.70	1.88	1.00	7.67	40
Subjective fear response to threat	4.19	2.37	1.00	10.00	40
Subjective fear response to safety	3.18	1.84	1.00	8.00	40

Table 3. Bivariate correlations among key study variables.

		1	2	3	4	5	6	7	8	9	10	11
1	Age											
2	Anxiety	0.06										
3	Cortical thickness	–0.37	0.23									
4	vmPFC thickness	–0.13	0.03	0.32*								
5	dmPFC thickness	–0.06	0.26	0.68†	0.01							
6	Overall skin conductance response	–0.02	–0.14	0.09	–0.14	0.15						
7	Skin conductance response to threat	–0.04	–0.18	0.08	–0.20	0.22	0.94†					
8	Skin conductance response to safety	0.00	–0.09	0.08	–0.07	0.09	0.96†	0.81†				
9	Overall subjective fear response	0.10	0.35*	–0.05	0.11	–0.03	–0.12	–0.13	–0.10			
10	Subjective fear response to threat	–0.10	0.33*	0.01	0.06	0.01	–0.08	–0.09	–0.07	0.92†		
11	Subjective fear response to safety	0.33*	0.28	–0.12	0.15	–0.07	–0.14	–0.15	–0.11	0.86†	0.59†	

The P-values of Pearson correlation analysis are shown. Results are listed for the variables of interest using a P-value < .05.
*P < .05,
†P < .001.

learning varied as a function of vmPFC thickness, age, and anxiety symptoms. All analyses covaried for mean cortical thickness.

Overall anticipatory responding (CS+, CS–)

When examining children's *Overall Skin Conductance Response*, no main or interaction effects of vmPFC thickness, age, or anxiety emerged, all P's > .115. When examining children's *Overall Subjective Fear Response*, a main effect of anxiety was observed, b = 0.06, P = .018, 95% BC CI [0.0102, 0.1004] such that subjective fear ratings were greater for children with higher anxiety. No main effects of age or vmPFC thickness nor any interaction effects on children's *Overall Subjective Fear Response* emerged, all P's > .310.

Anticipatory responding to threat (CS+)

When examining children's *Skin Conductance Response to Threat*, a main effect of vmPFC thickness was observed, b = –11.16, P = .041, 95% BC CI [–21.8271, –0.4840] such that physiological responsivity was reduced with increasing cortical thickness (Fig. 6). No main effects of age or anxiety or interaction effects on children's *Skin Conductance Response to Threat* emerged, all P's > .090. When examining children's *Subjective Fear Response to Threat*, a main effect of anxiety was observed, b = 0.07, P = .024, 95% BC CI [0.0094, 0.1227], such that subjective fear ratings were greater for children with higher anxiety. No main effects of age or vmPFC thickness or interaction effects on children's *Subjective Fear Response to Threat* emerged, all P's > .120.

Anticipatory responding to safety (CS–)

When examining children's *Skin Conductance Response to Safety*, no main or interaction effects of vmPFC thickness, age, or anxiety emerged, all P's > .291. When examining children's *Subjective Fear Response to Safety*, a main effect of anxiety was observed, b = 0.04, P = .034, 95% BC CI [0.0037, 0.0855], such that subjective fear ratings were greater for children with higher anxiety. No main effects of age or vmPFC thickness or interaction effects on children's *Subjective Fear Response to Safety* emerged, all P's > .089.

dmPFC thickness and anticipatory responding

The second set of moderated linear regression analyses examined whether anticipatory responding during threat and safety learning varied as a function of dmPFC thickness, age, and anxiety. All analyses covaried for mean cortical thickness.

Overall anticipatory responding (CS+, CS–)

When examining children's *Overall Skin Conductance Response*, no main or interaction effects of dmPFC thickness, age, or anxiety emerged, all P's > .208. When examining children's *Overall Subjective Fear Response*, a main effect of anxiety was observed, b = 0.05, P = .023, 95% BC CI [0.0072, 0.0896] such that subjective fear ratings were greater for children with higher anxiety. No main effects of age or dmPFC thickness or interaction effects on children's *Overall Subjective Fear Response* emerged, all P's > .052.

Anticipatory responding to threat (CS+)

When examining children's *Skin Conductance Response to Threat*, no main or interaction effects of dmPFC thickness, age, or anxiety emerged, all P's > .187. When examining children's *Subjective Fear Response to Threat*, a three-way interaction between dmPFC thickness, age, and anxiety was observed, $\Delta R^2 = 0.129$, P = .017. dmPFC thickness and *Subjective Fear Response to Threat* were

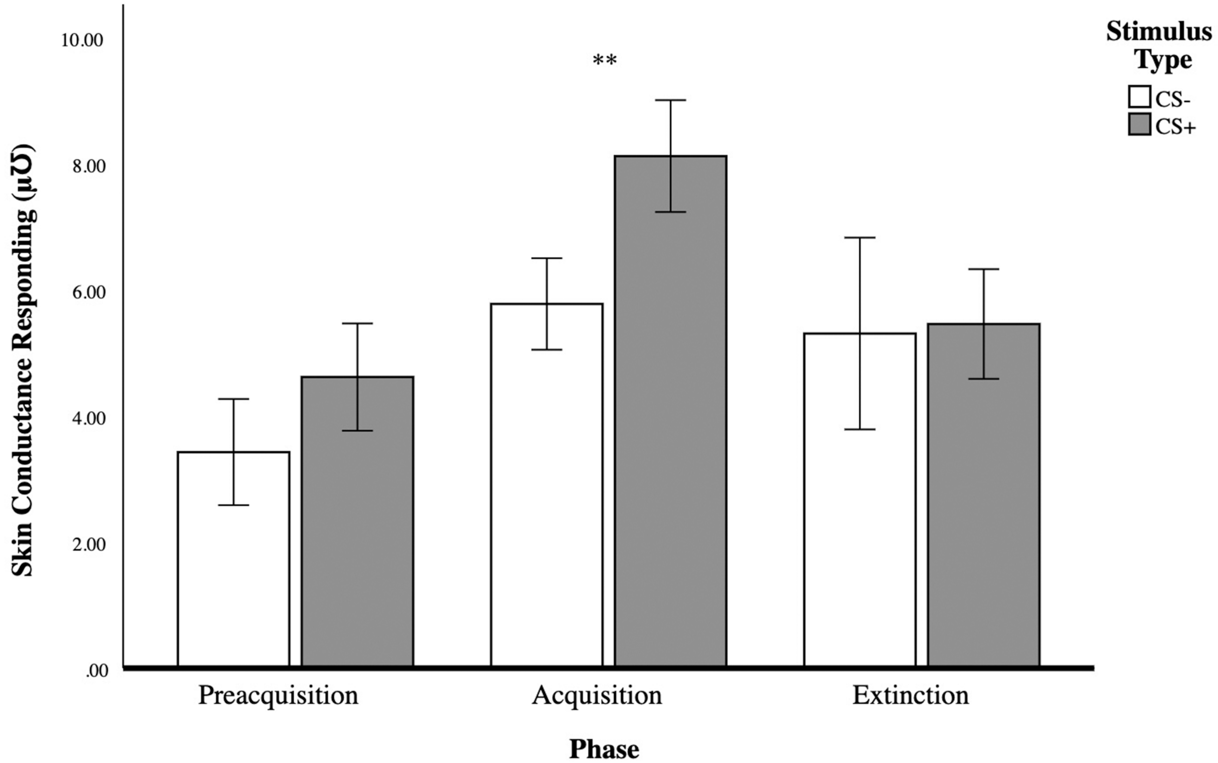

Figure 4. Skin conductance responding to the paired (CS+) and unpaired (CS–) conditioned stimuli during preacquisition, acquisition, and extinction phases. Error bars represent standard error. *P < .05, **P < .01, ***P < .001.

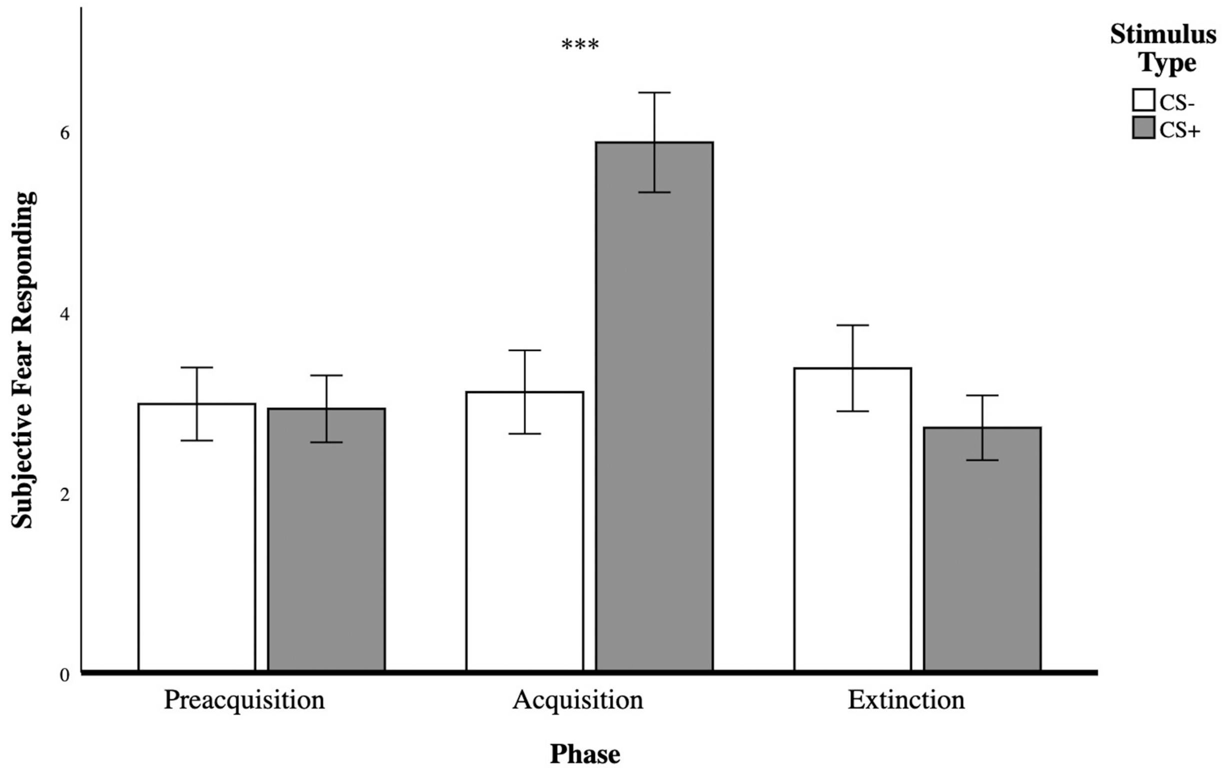

Figure 5. Subjective fear responding to the paired (CS+) and unpaired (CS–) conditioned stimuli during preacquisition, acquisition, and extinction phases. Error bars represent standard error. *P<.05, **P <.01, ***P < .001.

negatively associated for older children with high, $b = -28.98$, $P = .005$, 95% BC CI [−48.2670, −9.6956], and mean, $b = -11.34$, $P = .043$, 95% BC CI [−22.3174, −0.3664] levels of anxiety (Fig. 7). No significant associations between dmPFC thickness and *Subjective Fear Response to Threat* were observed for any other age groups at any other levels of anxiety, all $ps > 0.099$. A main effect of

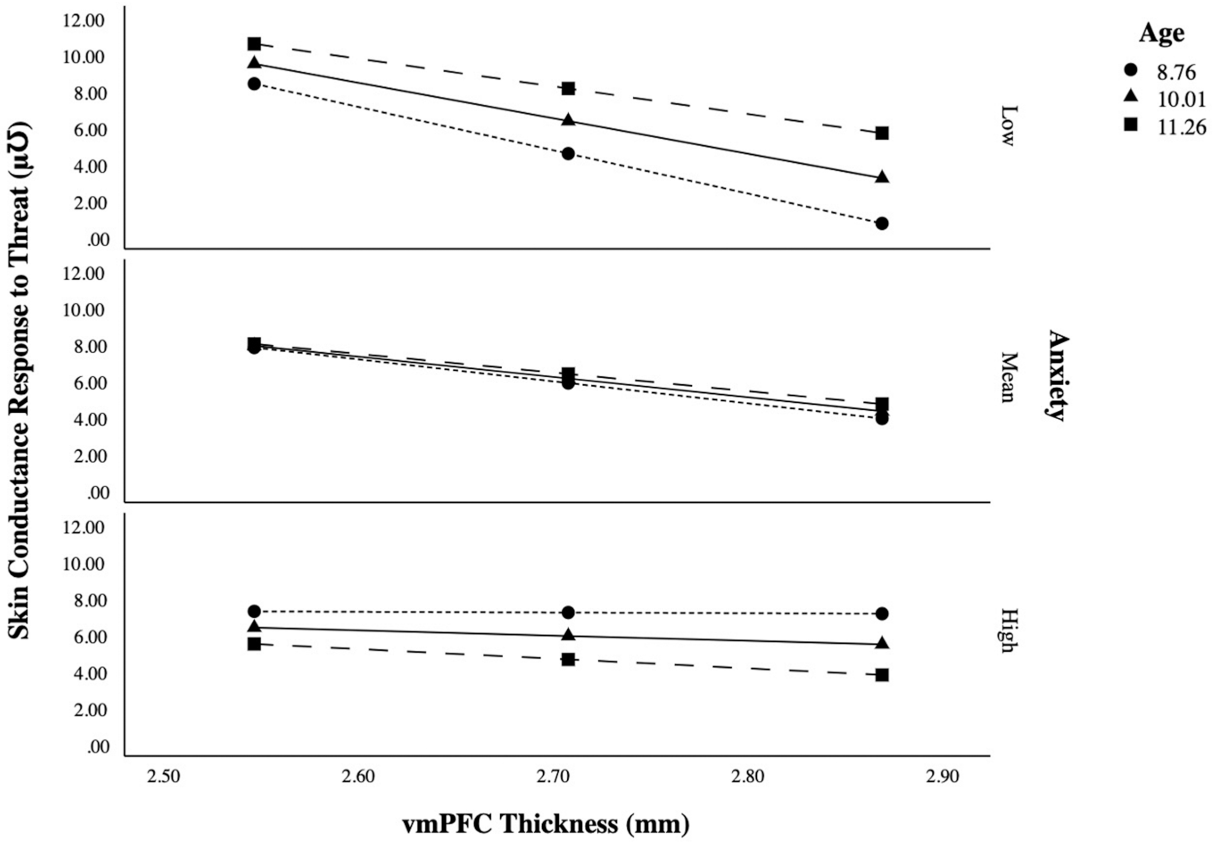

Figure 6. A main effect of vmPFC thickness on skin conductance responding to threat was observed, b = −11.16, P = .041, 95% BC CI [−21.8271, −0.4840].

anxiety on children's *Subjective Fear Response to Threat* also emerged, $b = 0.06$, $P = .019$, 95% BC CI [0.0107, 0.1101], but no main effect of age, nor any two-way interaction effects were observed, all P's > .054.

Anticipatory responding to safety (CS–)

When examining children's *Skin Conductance Response to Safety*, no main or interaction effects of dmPFC thickness, age, or anxiety emerged, all P's > .266. When examining children's *Subjective Fear Response to Safety*, no main or interaction effects of dmPFC thickness, age, or anxiety emerged, all P's > .055.

Bonferroni corrections

Bonferroni corrections were applied to the twelve regression analyses testing main and interaction effects of cortical thickness, age, and anxiety on anticipatory responding. With an adjusted significance level of $P < .004$, previously observed main and interaction effects were no longer significant. We note that these analyses were meant as a preliminary examination of threat anticipation in an understudied population and are intended to guide future replications in larger, demographically diverse samples.

Discussion

Four key findings emerged from this preliminary study of conditioned threat-anticipatory responding in Latina girls. First, contrary to our predictions, child age did not uniquely influence participants' physiological or subjective fear responding during threat and safety learning. Second, child anxiety symptoms were positively associated with subjective fear responding during threat and safety learning. Third, vmPFC thickness was inversely associated with skin conductance responding during threat and safety learning. Fourth, dmPFC thickness, age, and anxiety interacted to predict subjective fear responding during threat and safety learning, such that dmPFC thickness and skin conductance responding were inversely associated for older children with high and mean levels of anxiety, but not for children in any other age group at any other anxiety levels.

Contrary to our first hypothesis, child age in our sample was not directly associated with skin conductance or subjective fear responding during threat and safety learning. While extensive work has demonstrated the magnitude of anticipatory physiological responding to threat increases throughout childhood (Block et al. 1970, Gao et al. 2010, Michalska et al. 2016) and then begins to decrease in adulthood (Abend et al. 2020), we observed no effect of age on threat responsivity in the current sample. We attribute this discrepancy with prior work to the age range of our sample. While a more targeted age range enables potentially more nuanced understandings of the development of threat and safety learning, it also may limit the ability to observe the age effects typical of larger samples with a larger age distribution (Abend et al. 2020). Alternatively, pubertal development, rather than age, may contribute to threat and safety learning processes, such that higher pubertal status is related to an increased physiological responding to threat (Stenson et al. 2021). The current sample was premenstrual at study entry (except two erroneously recruited participants), which may explain the absence of any effects of age. Indeed, participant age in the present study was highly correlated with pubertal status, a developmental marker previously found to interact with anxiety in predicting variation in threat-relevant neuroanatomy (Glenn et al. 2022). As such, continued research, specifically with pre-adolescent samples, is necessary to better

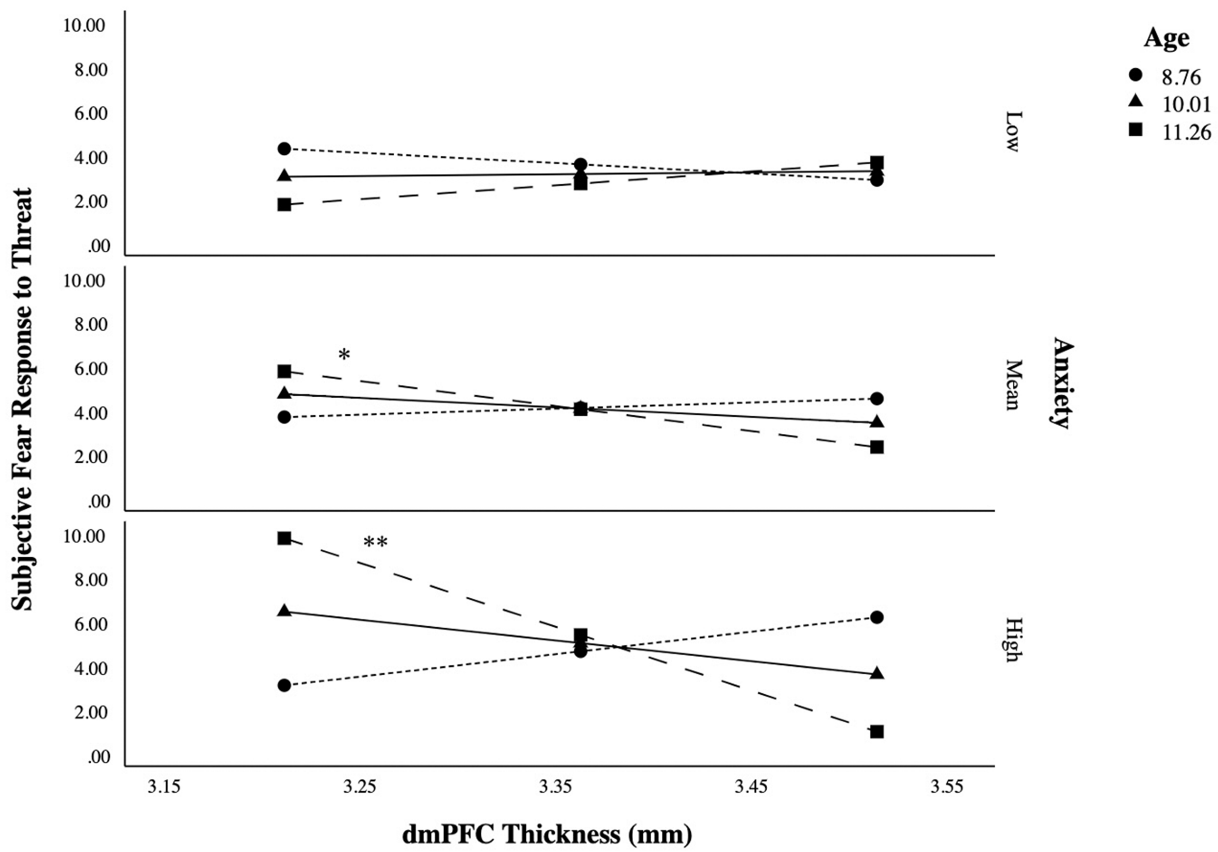

Figure 7. A three-way interaction between dmPFC thickness, age, and anxiety, on children's subjective fear responding to threat was observed, $\Delta R^2 = 0.129$, $P = .017$. dmPFC thickness and subjective fear responding to threat were negatively associated only for older children with high, $b = -28.98$, $P = .005$, 95% BC CI [−48.2670, −9.6956], and mean, $b = -11.34$, $P = .043$, 95% BC CI [−22.3174, −0.3664] levels of anxiety. *$P < .05$, **$P < .01$, ***$P < .001$.

understand how anticipatory responding to threat continues to develop past middle childhood.

In partial support of our second hypothesis, even though anxiety symptom severity was not associated with physiological responding during threat and safety learning, it predicted elevated subjective fear responding. The latter is consistent with previous work using the same paradigm demonstrating higher self-reported fear of each CS type among anxious relative to nonanxious participants (Abend et al. 2020). Heightened response to the CS− has been hypothesized to reflect anxiety-related aberrations in safety learning (Grupe and Nitschke 2013, Tanovic et al. 2018, Mullins et al. 2021), and heightened response to CS+ has been hypothesized to reflect enhanced threat learning (Orr et al. 2000). Both patterns of anticipatory responding indicate some form of perturbations in learning, and both were observed in the current study when examining subjective fear specifically.

In partial support of our third hypothesis, a significant association between vmPFC cortical thickness responding and skin conductance responding, but not subjective fear responding, emerged during threat and safety learning. Specifically, increased cortical thickness was associated with reduced physiological responding to conditioned threat stimuli. This finding is consistent with both functional and structural neuroimaging implicating vmPFC in threat and safety learning (Phelps et al. 2004, Milad et al. 2005, Schiller et al. 2008, Hartley et al. 2011, Winkelmann et al. 2016, Marin et al. 2017) and supports the possibility that thickness of this cortical tissue plays a role in regulating responsivity to conditioned threat cues (Myers-Schulz and Koenigs 2012, Kenwood et al. 2022). Contrary to our fifth hypothesis, age and anxiety did not interact with vmPFC thickness to predict children's skin conductance responding during threat and safety learning. Whereas previous work has demonstrated age- and anxiety-dependent associations between cortical thickness and skin conductance responding in a broad region of the PFC (Abend et al. 2020), these findings did not extend to more targeted regions, the vmPFC, in our sample. Given the posterior to anterior progression of brain development (Gogtay et al. 2004, Bethlehem et al. 2022), age and anxiety may moderate associations between cortical thickness and physiological responding to threat as the vmPFC matures, though continued research is needed.

Our fourth hypothesis, that dmPFC thickness would be inversely associated with skin conductance and subjective fear responding during threat and safety learning, was not supported. Functional neuroimaging work highlights the role of the dmPFC in learning that a stimulus is threatening after repeated pairings with an aversive event, finding associations between increased activation in dmPFC and elevated responsivity to threat (Mechias et al. 2010, Klumpers et al. 2015, Chavanne and Robinson 2021). However, no study to date has investigated structural correlates of the dmPFC in isolation (though see Abend et al. 2020). In the current study, we observed no main effects of dmPFC thickness on skin conductance responding or subjective fear responding. However, in partial support of our fifth hypothesis, dmPFC thickness, age, and anxiety interacted to predict subjective anticipatory responding to threat stimuli, such that thickness and subjective fear responding were inversely associated for older children with high and mean levels of anxiety but not for children in any other age groups at any other anxiety levels. This result suggests that previous findings of inverse associations between broad regions of the PFC, which subsumed the dmPFC, and physiological responding during threat and safety learning (Abend et al. 2020) may extend to subjective indices and points to age and anxiety as important factors to consider in this association.

The current preliminary findings should be considered in the context of several limitations. First, sample size was modest, potentially reducing statistical power, particularly for interaction effects, and precluding analyses of individual differences within the sample. Although analyses utilized bootstrapping techniques to mitigate this limitation, we hope that researchers in the field will be encouraged by these findings to ascertain larger study samples. Indeed, recruiting and retaining members of underrepresented groups in longitudinal research poses conceptual and methodological challenges (Outram et al. 2022, Fisher-Hoch et al. 2023), calling for a strategic plan to increase representation of such populations in neuroscientific research. Second, this was a cross-sectional design examining associations between neural measures and concurrent anxiety symptoms in a community sample. Longitudinal studies extending this work and comparing neural correlates of anticipatory threat responding between nonanxious, subclinical, and treatment-seeking clinical samples could provide a more complete understanding of causal developmental pathways between brain structure, threat responsivity, and anxiety severity. Such studies are currently underway in our lab. Third, while conditioning was successful in the context of subjective reports of fear, participants demonstrated only partial conditioning as measured by physiology. Therefore, future work on stimulus characteristics that elicit different effects with regard to responsivity, could further contribute to our understanding of individual variation in threat and safety learning and subsequent associations with anxiety.

Several strengths mitigate these limitations to some extent and offer preliminary data about the role of cortical thickness, age, and anxiety in children's responsivity to threat. First, our study adds to a growing body of work focused on the development of anticipatory responding in pre-adolescence. Relative to work in children and adults, the current investigation enables potentially more nuanced inferences about threat and safety learning processes during an important yet understudied developmental period. The transition to adolescence is marked by stark increases in the prevalence of anxiety disorders (Reardon et al. 2009), as well as significant structural and functional changes to threat neurocircuitry (Gee et al. 2013, Herting et al. 2012, Newman et al. 2016). As such, studies of these processes in pre-adolescence provide a unique opportunity to alter anxiety trajectories and prevent long-term psychiatric morbidity.

Second, we explore both physiological and subjective indices of anticipatory responding. Physiological and subjective measures represent distinct facets of fear and anxiety (LeDoux and Pine 2016, Michalska et al. 2022, Taschereau-Dumouchel et al. 2022) and, thus, should be differentially probed in threat and safety learning research. Elucidating ways in which these indices are uniquely implicated during threat and safety learning may inform a more thorough understanding of anxiety disorders and their treatment.

Third, the current preliminary study is one of the first to examine anticipatory threat responding in a Latina sample, an understudied group at an increased risk for anxiety compared to other racial and ethnic groups (Pina and Silverman 2004, McLaughlin et al. 2007, Anderson and Mayes 2010, Georgiades et al. 2018). Because anxiety in childhood is associated with an increased risk for psychopathological sequelae later in development (Pine et al. 1998, Gregory et al. 2007, Beesdo et al. 2009), identifying factors that moderate individual-level risk for alterations in threat and safety learning may inform prevention efforts targeting long-term mental health outcomes, specifically in underrepresented youth. We hope that our initial findings encourage clinical researchers to extend this work to clinical samples within and outside the underrepresented Latina population.

Latinxs make-up one of the largest and fastest growing ethnoracially minoritized groups in the USA (Noe-Bustamante and Flores 2019). Given these individuals face unique challenges that may contribute to the development and maintenance of anxiety and are also less likely to receive treatment due, in part, to barriers to accessing care (Lagomasino et al. 2005, Gudiño et al. 2009, Dixon De Silva et al. 2020), their vast underrepresentation in neuroscientific and physiological research on threat and safety learning is particularly problematic (Kredlow et al. 2018, Webb et al. 2022, La Scala et al. 2023). As such, determining the extent to which previous work on anxiety and physiological and neural correlates of threat responding generalize to Latina youth will set the stage for future work that examines structural and sociocultural influences on these processes (Díaz et al. 2024, Mullins et al. 2024a, 2024b). We view the current preliminary study, which replicates a subset of previously documented effects of anxiety and cortical thickness on anticipatory threat responding, as a guide for future confirmatory work as we take steps to shift the field toward more equitable research standards.

Conflict of interest

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or National Science Foundation.

Funding

Research reported in this publication was supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health award (NIMHD F31MD018279) awarded to J.L.M. and by a National Science Foundation CAREER Award (NSF 2239067) awarded to K.J.M.

Data availability

Data concerning this manuscript may be made available by the corresponding author upon reasonable request.

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Social Cognitive and Affective Neuroscience, 2024, 19(1), nsae065, DOI: https://doi.org/10.1093/scan/nsae065, Advance Access Publication Date: 9 October 2024, Original Research – Neuroscience

Received: 28 December 2023; **Revised**: 19 April 2024; **Accepted**: 8 October 2024