Psychological Medicine

cambridge.org/psm

Late positive potential reveals sustained threat contingencies despite extinction in adolescents but not adults

Gil Shner-Livne[1], Nadav Barak[1], Ido Shitrit[1], Rany Abend[2] and Tomer Shechner[1]

[1]School of Psychological Sciences and the Integrated Brain and Behavior Research Center, University of Haifa, Haifa, Israel and [2]Baruch Ivcher School of Psychology, Reichman University, Herzliya, Israel

Original Article

Cite this article: Shner-Livne G, Barak N, Shitrit I, Abend R, Shechner T (2024). Late positive potential reveals sustained threat contingencies despite extinction in adolescents but not adults. *Psychological Medicine* 1–12. https://doi.org/10.1017/S0033291724001314

Received: 11 December 2023
Revised: 23 March 2024
Accepted: 9 May 2024

Keywords:
adolescence; anxiety; extinction; late positive potential; threat learning

Corresponding author:
Gil Shner-Livne;
Email: gilshner.gs@gmail.com

Abstract

Background. Major theories link threat learning processes to anxiety symptoms, which typically emerge during adolescence. While this developmental stage is marked by substantial maturation of the neural circuity involved in threat learning, research directly examining adolescence-specific patterns of neural responding during threat learning is scarce. This study compared adolescents and adults in acquisition and extinction of conditioned threat responses assessed at the cognitive, psychophysiological, and neural levels, focusing on the late positive potential (LPP), an event-related potential (ERP) component indexing emotional valence.

Method. Sixty-five adults and 63 adolescents completed threat acquisition and extinction, 24 h apart, using the bell conditioning paradigm. Self-reported fear, skin conductance responses (SCR), and ERPs were measured.

Results. Developmental differences emerged in neural and psychophysiological responses during threat acquisition, with adolescents displaying heightened LPP responses to threat and safety cues as well as heightened threat-specific SCR compared to adults. During extinction, SCR suggested comparable reduction in conditioned threat responses across groups, while LPP revealed incomplete extinction only among adolescents. Finally, age moderated the link between anxiety severity and LPP-assessed extinction, whereby greater anxiety severity was associated with reduced extinction among younger participants.

Conclusions. In line with developmental theories, adolescence is characterized by a specific age-related difficulty adapting to diminishing emotional significance of prior threats, contributing to heightened vulnerability to anxiety symptoms. Further, LPP appears to be sensitive to developmental differences in threat learning and may thus potentially serve as a useful biomarker in research on adolescents, threat learning, and anxiety.

Introduction

Acquisition and extinction of threat contingencies are key learning mechanisms implicated in the onset and maintenance of anxiety disorders (Mineka & Oehlberg, 2008; Pittig, Treanor, LeBeau, & Craske, 2018). Specifically, influential developmental theories of anxiety link heightened risk for its emergence during adolescence to age-dependent maturational changes in threat learning neural circuitry (Casey, Glatt, & Lee, 2015; Jovanovic, Nylocks, & Gamwell, 2013; Kitt, Odriozola, & Gee, 2023). Nevertheless, despite the potential utility of such neurobiological theories for clinical research on anxiety etiology and treatment, very limited empirical research examines them. To begin bridging this gap, we used event-related potentials (ERPs) to test whether adolescents, relative to adults, indeed show distinct, age-dependent patterns of neural responses to learned threats.

Anxiety symptoms typically emerge during adolescence (Beesdo, Knappe, & Pine, 2009; Kessler et al., 2005) and reflect a persistent tendency toward excessive, impairing defensive responses to potential threats (American Psychiatric Association, 2022). If not treated early, anxiety often becomes chronic, incurs considerable personal and societal costs, and confers increased risk for additional psychopathology. Despite high prevalence and considerable negative outcomes, current first-line treatments for anxiety, like cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs), often show limited efficacy particularly among youth (Rapee, Creswell, Kendall, Pine, & Waters, 2023). While these treatments are effective in reducing anxiety, compared to no-treatment or waitlist conditions (James, Reardon, Soler, James, & Creswell, 2020), they do not consistently result in substantial improvements for many adolescents. Incomplete understanding of the mechanisms giving rise to anxiety symptoms impedes research on improving therapeutic approaches.

Prominent developmental theories of anxiety link the emergence of anxiety to age-dependent perturbations in threat learning processes, encompassing the acquisition and

extinction of threat contingencies. These theories posit that adolescence is characterized by sensitivity to variations in threat learning, increasing the risk of developing anxiety disorders. Specifically, adolescents tend to overgeneralize learned threat to safety cues, as indicated by self-reports, physiological responses, and avoidance behaviors (Klein, Berger, Vervliet, & Shechner, 2021; Skversky-Blocq, Pine, & Shechner, 2021; Skversky-Blocq, Shmuel, Waters, & Shechner, 2022b). Less effective differentiation between learned threat and safety cues has also been demonstrated in attention allocation during direct (Klein et al., 2021) and observational threat learning paradigms (Skversky-Blocq, Shmuel, Cohen, & Shechner, 2022a). More broadly, physiological arousal to both threat and safety-acquired cues is higher among adolescents than adults (Linton & Levita, 2021). Extinction of threat contingencies likewise appears to be age-specific, with studies reporting attenuated extinction learning among adolescents compared to adults and children, indicated by persistent physiological responding (Pattwell et al., 2012) and negative valence attributed to conditioned threat cues (Waters, Theresiana, Neumann, & Craske, 2017). Moreover, in a study on anxiety patients and healthy controls, anxiety was associated with sustained physiological fear responses during extinction in youth but not adults (Abend et al., 2022). Together, the findings across multiple levels of measurement support theories that adolescence is associated with distinct threat learning patterns, which may contribute to heightened sensitivity to developing anxiety symptomatology.

Neurobiological theories further link the substantial maturation processes the neural circuitry involved in threat learning undergoes during early childhood and adolescence to anxiety vulnerability (Casey et al., 2015; Jovanovic et al., 2013; Kitt et al., 2023). Specifically, variations in maturation of key threat circuitry nodes, such as the amygdala and ventromedial prefrontal cortex (vmPFC), and pathways between them, are posited to influence threat acquisition and extinction processes, rendering adolescents more susceptible to maintenance of acquired fear memories. A few functional magnetic resonance imaging (fMRI) studies have examined developmental differences in neural responding during extinction processes (Ganella, Drummond, Ganella, Whittle, & Kim, 2018; Morriss, Christakou, & van Reekum, 2019; Pattwell et al., 2012). Findings reveal that compared to adults, adolescents show reduced extinction and impaired extinction recall, linked to altered vmPFC activation. Comparing anxiety patients and healthy controls in youth and adult samples, Gold et al. (2020) found youth exhibited distinct, anxiety-dependent amygdala-vmPFC connectivity during extinction recall, and also differed from adults in neural activation patterns when rating fear of threat cues and assessing memory of threat contingencies. Moreover, structural MRI work finds that volume of the amygdala and additional subcortical structures moderates associations between extinction learning and anxiety severity in adults but not youths (Abend et al., 2022).

EEG and ERP research offers several important, complementary advantages to fMRI research. While the MRI environment itself might induce an increase in state anxiety (Mutschler et al., 2014), measuring EEG is generally less fear-inducing. Moreover, ERP offers high temporal resolution which may uncover specific aspects of the conditioned threat response. One ERP component in which threat learning may manifest is the late positive potential (LPP), observed ~300–400 milliseconds following cue onset and lasting several hundred milliseconds, with a maximal parietal topography (Danon-Kraun et al., 2021; Dennis & Hajcak, 2009; Weinberg & Hajcak, 2011). LPP is believed to index the emotional significance of stimuli (Hajcak & Foti, 2020; Schupp & Kirmse, 2021). Indeed, fMRI work on the processing of emotional stimuli links neural activation in 'limbic' circuitry nodes, such as the amygdala and insula, to LPP amplitude in youth (Bunford, Kujawa, Fitzgerald, Monk, & Phan, 2018) and adults (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; MacNamara, Rabinak, Kennedy, & Phan, 2018). LPP could therefore provide a more direct way to track the brain's responses to threats as these change during acquisition and extinction of threat contingencies.

Previous research establishes the relevance of LPP for indexing threat learning in adults, with increased LPP amplitude in response to conditioned threat (CS+) relative to safety (CS−) cues during acquisition, and a gradual decrease in amplitude over extinction trials (Bacigalupo & Luck, 2018; Cheng, Jackson, & MacNamara, 2022; Ferreira de Sá, Michael, Wilhelm, & Peyk, 2019; Paiva et al., 2020; Panitz, Hermann, & Mueller, 2015; Seligowski et al., 2018, 2021; Sperl, Wroblewski, Mueller, Straube, & Mueller, 2021). Importantly, LPP responses during extinction were shown to diminish more slowly than corresponding psychophysiological responses, suggesting LPP may be less susceptible to simple habituation effects (Bacigalupo & Luck, 2018; Sperl et al., 2021). Because LPP may show less habituation than psychophysiological readouts, it may serve as a more direct and accurate index of neural responses to threat contingencies (Bacigalupo & Luck, 2018).

Only two studies to date have assessed LPP in youth during a classical learning task. One assessed a community sample of adolescents and found differential LPP responses towards the conditioned stimulus (CS) during an extinction recall task, a week following extinction, suggesting it as a promising index of return of fear (Danon-Kraun et al., 2021). The second study revealed enhanced differential LPP among anxious compared to non-anxious adolescents, one week after extinction, underlining LPP's ability to reveal anxiety-related differences in extinction learning (Klein et al., 2023). However, no study to date has directly compared youth and adult samples in terms of LPP during threat acquisition and extinction, thus limiting the ability to make strong inferences on adolescence-specific effects.

Here, we examined threat learning processes in typically developing adolescents and adults, measured during both threat acquisition and extinction and indicated by LPP, skin conductance response (SCR), and self-reported fear. By extending the extinction phase, as well as including a 24-h interval between acquisition and extinction to allow consolidation of learning, our study is uniquely positioned to identify subtle differences in the slower process of threat extinction assessed in the lab (Treanor, Rosenberg, & Craske, 2021). Identifying neural markers of developmental differences in threat learning and, critically, extinction processes implicated in the pathogenesis of anxiety disorders – could be pivotal in enhancing clinical approaches to anxiety, informing both the timing and method of intervention (Pittig et al., 2018).

We had three a-priori preregistered hypotheses (https://osf.io/y79s2). First, we hypothesized that while both age groups (adolescents, adults) would exhibit successful differential threat acquisition and a reduction in these responses during extinction in all measures, adolescents would demonstrate a slower extinction than adults, as indicated by differential LPP. Second, we hypothesized that adolescents would display overall higher psychophysiological arousal than adults, evidenced by increased SCR during acquisition and extinction (Abend et al., 2020; Linton & Levita,

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

2021). Third, we hypothesized that trait anxiety levels would be associated with increased differential threat acquisition and impaired extinction in both age groups (Klein, Abend, Shmuel, & Shechner, 2022; Klein, Shner, Ginat-Frolich, Vervliet, & Shechner, 2020). Of note, we preregistered six hypotheses; for clarity, hypotheses 1,2,3, and 5 in the preregistration were combined to form the first hypothesis presented here.

In addition to our a-priori hypotheses, we conducted several exploratory analyses. Building on previous research indicating extinction impairments among anxious youth (Klein et al., 2023), we explored potential interactions among age, anxiety levels, and extinction during the later stages of learning. We also investigated potential associations between differential threat learning manifesting in LPP and differential threat responses manifesting in psychophysiological and self-report indices.

Method

Preregistration

The study hypotheses, sample size design, procedure, and data analysis plan were preregistered on the Open Science Framework prior to data collection (https://osf.io/y79s2).

Participants

Participants included 65 adults (M_{age} = 24.83 years, S.D. = 3.45, range:18.08–34.62 years; 55.4% females) and 63 adolescents (M = 15.03 years, S.D. = 1.65, range:12.19–17.91 years; 57.1% females). Of these, three participants (one adult and two adolescents) aborted during threat acquisition, and nine (five adults and four adolescents) did not return to the lab for a second visit. Overall, 59 adults and 57 adolescents completed both visits (for complete demographic and clinical characteristics, see online Supplementary Table S1). Participants were recruited through online advertisements and received modest compensation. Before the experiment, adult participants and legal guardians of the adolescent participants signed a consent form, and adolescents signed assent forms.

No significant differences emerged between adults and adolescents in gender, anxiety symptom severity (SCARED/SCARRED), or sleep duration or quality between visits, all $ps > 0.075$. Adolescents reported greater intolerance of uncertainty (Intolerance of Uncertainty Scale, IUS) than adults, $t(124) = -2.288$, $p = 0.024$ (see online Supplementary Table S1). Information on pubertal development of the adolescent sample is presented in the online Supplemental Materials.

Procedure

The study consisted of two experimental lab visits. On visit 1, participants completed the habituation and differential threat acquisition phases of the bell threat learning task (Shechner et al., 2015). On the next day, participants returned for a second visit and underwent threat extinction followed by self-report questionnaires. All experimental phases included electroencephalogram (EEG) and SCR measurements. All procedures received IRB approval (316/21).

Threat learning task

The habituation phase consisted of eight trials presenting a grey-colored animated bell, with each trial lasting seven seconds; see online Supplementary Fig. S1. Next, participants underwent three blocks of threat acquisition, each comprised of 10 presentations of the CS+ and 10 presentations of the CS−, in pseudorandomized order. Blue and yellow bells served as the CSs, counterbalanced as CS+ and CS−. Each CS was presented for seven seconds in each trial. In 60% of the trials, immediately following the CS+ (i.e. at the end of the 7th second), a 1-second-long unconditioned stimulus (US) consisting of a picture of the same-colored bell ringing paired with a loud alarm sound at 95 dB was presented. Trials (across all experimental phases) were separated by an inter-trial interval (ITI), in which participants observed a white fixation cross on a black background, varying randomly in length between 10 and 12 s. Following the three threat acquisition blocks, participants rated their unpleasantness when encountering the US using a Likert scale ranging from 0 (not at all unpleasant) to 10 (extremely unpleasant). The acquisition phase lasted ∼20–25 min.

Because extinction learning tends to occur more slowly than threat acquisition, the extinction phase was designed to be twice as long as the acquisition phase (Treanor et al., 2021). Immediately prior to the start of the extinction phase, we presented the CS+ paired with the US as a reminder of the previously learned association. Thereafter, participants completed six consecutive blocks of extinction, each consisting of 10 CS+ and 10 CS− presentations using a procedure similar to that of acquisition, but without US delivery at any point (online Supplementary Fig. S1a, S1b in Supplemental Materials). The extinction phase lasted ∼40–45 min. Participants were not explicitly informed about the CS + -US contingency at any stage of the learning task.

Measures

Self-report questionnaires

Fear ratings. Fear levels ('How afraid are you of this bell?') were assessed for each CS separately, prior to acquisition ('pre-acquisition', i.e. before the presentation of any stimulus) and extinction ('pre-extinction', i.e. before the reminder trials preceding the extinction phase) and following each block, using a Likert scale ranging from 1 (not at all afraid) to 10 (extremely afraid). Threat expectancy levels ('How likely is it for this bell to ring?') were also assessed and are reported in online Supplemental Materials.

Screen for Child Anxiety Related Emotional Disorders (SCARED). The SCARED questionnaire is a commonly used self-report measure assessing anxiety symptoms in youth (Birmaher et al., 1997). It consists of 41 items assessing anxiety symptoms, each rated on a 3-point Likert scale (0–2), with total anxiety scores ranging 0–82. Internal consistency in our study was α = 0.91. Total scores were converted into Z scores in the adolescent sample for comparability with the adult sample (Abend et al., 2020).

Screen for Adult Anxiety Related Disorders (SCAARED). The SCAARED questionnaire is an adaptation of the SCARED questionnaire to assess anxiety symptoms in adults (Angulo et al., 2017). It features 44 items rated similarly to the SCARED, with total scores ranging 0–88. Internal consistency in our study was $\alpha = 0.94$. Total scores were likewise converted into Z scores in the adult sample.

Duration and Quality of Sleep between Visits. Given that acquisition and extinction were conducted on separate days, and night sleep is critical for consolidation of learning (Treanor et al., 2021), participants reported sleep duration between visits

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

1 and 2 and ranked their subjective quality of sleep on a 4-point Likert scale, ranging from 0 (very bad) to 3 (very good).

Skin conductance response (SCR)

Skin conductance was recorded continuously at 500 Hz using an 8-slot Bionex system (Mindware Technologies Ltd., OH, USA) and two isotonic gel electrodes placed on participants' left palm (i.e. hypothenar and thenar muscles).

We used MindWare data analysis software (Version 3.0.25). Responses to the CSs were calculated on a trial-by-trial basis as the difference between trough-to-peak amplitude, between 500 ms and 7 s following CS onset. SCR threshold was set at 0.01; scores <0.01, or negative changes, were counted as zero. A square-root transformation was then applied to normalize SCR scores (Lonsdorf et al., 2019). Finally, SCR data were averaged per stimulus type (CS+, CS−), block, and phase (acquisition, extinction). Temperature in the experiment room was kept consistent across participants (20°–22° Celsius).

Electroencephalogram (EEG)

EEG was recorded using a g.Nautilus RESEARCH 32 g.SCARABEO (g.tec, medical engineering GmbH, Austria) wearable headset with 32 Ag/AgCl electrodes. Electrodes were placed according to the standard 10–20 international system. All EEG data processing and analysis were performed in MATLAB (v. R2022a) using the toolboxes for EEGLAB version 2022.1 (Delorme & Makeig, 2004) and ERPLAB version 9.00 (Lopez-Calderon & Luck, 2014). For more information on EEG preprocessing, see online Supplemental Materials.

Late positive potential (LPP). ERP segments were averaged separately per stimulus type (CS+, CS−), experimental block (1–6), and phase (acquisition/extinction). In line with prior work, LPP was extracted in a time window of [400, 1000 ms] following stimulus onset in a parietal site (Pz) (Danon-Kraun et al., 2021; Dennis & Hajcak, 2009; Klein et al., 2023; Weinberg & Hajcak, 2011). To ensure enough trials to calculate reliable LPP, we used the averaged LPP score in all three acquisition blocks and the averaged LPP score for blocks (1,2) (3,4) and (5,6) extinction in our statistical analyses.

Statistical analysis

All analyses were preregistered (https://osf.io/y79s2). Our primary analyses focused on developmental differences in differential threat acquisition and extinction in all measures. For the acquisition phase and the extinction phase, we used repeated-measures analyses of covariance (RM-ANCOVAs) of LPP, SCR, and self-reported fear. Stimulus (CS+, CS) and block were within-subject factors, age group (adolescents, adults) was a between-subjects factor, and anxiety level (*Z* scores of SCARED/SCAARED) was entered as a continuous covariate. In follow-up analyses, to facilitate interpretation, we divided participants into low- and high-anxiety groups based on a median split in each age group (adults, adolescents). Greenhouse–Geisser or Huynh-Feldt corrections were applied as needed.

In additional analyses, we examined the moderating effect of age on the association between anxiety levels (SCARED/SCAARED *Z* scores) and magnitude of extinction learning (differences between CS+ and CS− at final stages of extinction), using Model 1 in the SPSS Hayes macro-PROCESS (Preacher & Hayes, 2004).

Finally, we used Pearson's correlations to explore associations among LPP, SCR, self-reported fear, and threat expectancy, anxiety levels, and age.

Results

Threat acquisition

Self-reported fear

RM-ANCOVA of reported fear towards the conditioned cues with Stimulus (CS+, CS−) × Block (pre-acquisition, block 1, block 2, block 3) × Age (adolescents, adults) × Anxiety levels (continuous), yielded a three-way interaction of Stimulus × Block × Anxiety level, $F_{(2.208,\ 262.806)} = 5.986$, $p = 0.002$, $\eta_p^2 = 0.048$. Follow-up analysis indicated that a two-way interaction of Stimulus × Block emerged in both high- and low-anxiety groups, $F_{(2.716,\ 179.229)} = 94.071$, $p < 0.001$, $\eta_p^2 = 0.588$, and $F_{(1.621,\ 87.539)} = 36.114$, $p < 0.001$, $\eta_p^2 = 0.401$, respectively. To further examine self-reported fear of the CSs, we corrected for four multiple comparisons in each group (high- and low-anxiety levels) according to pre-acquisition and three acquisition blocks (Bonferroni-corrected for four tests; corrected alpha = 0.013). In line with our first hypothesis, both groups reported comparable fear of the CS+ and CS− in pre-acquisition, but differential fear (CS+ > CS−) was evident during the three subsequent blocks of threat acquisition (all $ps < 0.001$), indicating successful threat learning (see Fig. 1a). Further analyses showed that in line with our third hypothesis, individuals with high-anxiety symptoms reported more fear of the CS+ than those with low-anxiety symptoms following the first, second, and third block of acquisition, $t(123) = -3.79$, $p < 0.001$, $t(123) = -4.36$, $p < 0.001$, and $t(120) = -2.77$, $p < 0.001$, respectively, but not in pre-acquisition $t(118.56) = -1.99$, $p = 0.049$. No differences in self-reported fear of the CS− emerged during pre-acquisition or across acquisition; all $ps \geqslant 0.173$.

A main effect of anxiety also emerged, $F_{(1,119)} = 12.43$, $p = 0.001$, $\eta_p^2 = 0.095$, with follow-up analyses indicating that highly anxious participants reported overall higher levels of fear towards conditioned cues across the acquisition phase ($M = 3.44$, S.D. = 1.27) than those with low self-reported anxiety ($M = 2.65$, S.D. = 1.27). Additional lower-order effects are reported in online Supplementary Table S4 in the supplemental materials.

Skin conductance response (SCR)

RM-ANCOVA of SCR with Stimulus (CS+, CS−) × Block (block 1, block 2, block 3) × Age (adolescents, adults) × Anxiety (continuous) yielded a two-way interaction of Stimulus × Age, $F_{(1,107)} = 6.02$, $p = 0.016$, $\eta_p^2 = 0.053$. In line with our first hypothesis, both adults, $F_{(1,62)} = 48.62$, $p < 0.001$, $\eta_p^2 = 0.440$, and adolescents, $F_{(1,57)} = 105.07$, $p < 0.001$, $\eta_p^2 = 0.648$, displayed successful threat acquisition (main effect of CS, CS+ > CS−). The source of this two-way interaction is likely derived from the stronger differential acquisition effect among adolescents than adults (see Fig. 1b; for a detailed presentation of developmental difference in SCR across acquisition blocks, see online Supplementary Fig. S3 in Supplemental Materials). In line with our second hypothesis, a main effect of age emerged, $F_{(1,107)} = 6.76$, $p = 0.011$, $\eta_p^2 = 0.059$, whereby adolescents exhibited overall greater SCR across the acquisition phase ($M = 0.34$, S.D. = 0.20) than adults ($M = 0.24$, S.D. = 0.20).

We noted a two-way interaction of Stimulus × Block, $F_{(1.83,\ 195.06)} = 23.99$, $p < 0.001$, $\eta_p^2 = 0.183$, suggesting a gradual decrease in the difference between the CSs across acquisition due to habituation. However, follow-up analyses indicated that differential SCR remained significant during the first, $t(122) = 12.57$, $p < 0.001$, second, $t(121) = 7.73$, $p < 0.001$, and third, $t(112) = 7.82$, $p < 0.001$, blocks of acquisition. Additional lower-order effects are reported in online Supplementary Table S4 in the supplemental materials.

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

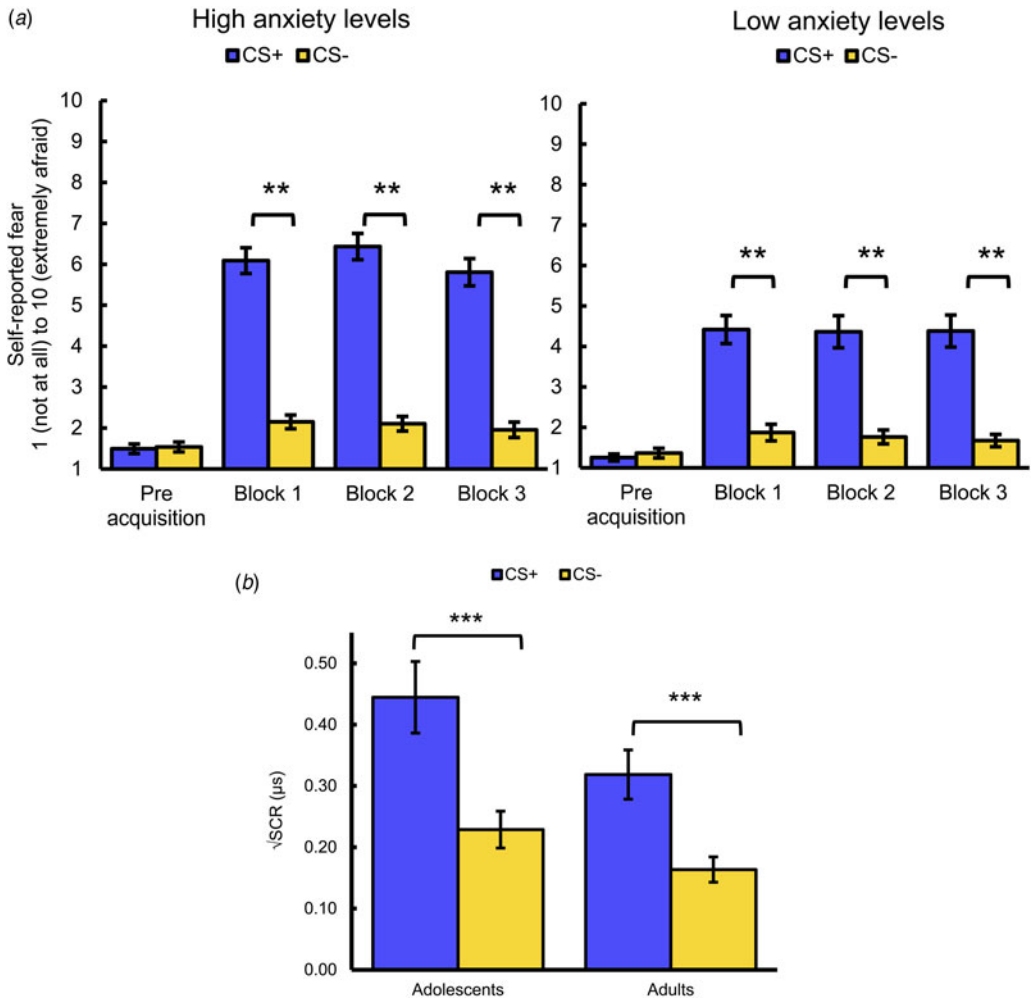

Figure 1. (a) Differences in self-reported fear towards the CS+ and the CS− across acquisition learning among individuals with high and low anxiety levels, measured by SCARED/SCAARED questionnaires' *Z* scores. (b) Developmental differences in SCR during CS+ and the CS− trials across acquisition learning.
Note: Error bars represent the standard error of the mean.
A. CS+, conditioned threat cue; CS−, conditioned safety cue; $^{*}p < 0.013$ after correcting for multiple comparisons; $^{**}p < 0.001$.
B. SCR, Skin conductance response. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Additional analyses of SCR to the US indicated that adults exhibited greater habituation than adolescents across acquisition blocks (online Supplementary Fig. S4, Supplemental Materials).

Late positive potential (LPP)

LPP temporal dynamics and topographic activation across the scalp are presented in Fig. 2. The RM-ANCOVA of LPP mean amplitude testing the Stimulus × Age × Anxiety effect, yielded a main effect of Stimulus, $F_{(1,95)} = 27.30$, $p < 0.001$, $\eta_p^2 = 0.223$. In line with the first hypothesis, participants exhibited enhanced LPP response to the CS+ ($M = 5.55$, S.D. = 2.49) compared to the CS− ($M = 4.41$, S.D. = 2.63), suggesting threat acquisition manifests in this component. Further, a main effect of Age emerged, $F_{(1,95)} = 35.95$, $p < 0.001$, $\eta_p^2 = 0.275$, suggesting greater LPP amplitude across CSs in adolescents ($M = 6.38$, S.D. = 2.31) relative to adults ($M = 3.57$, S.D. = 2.32); see Fig. 2. Additional analyses on the effects of age are presented in the online Supplemental Materials. No other effects were observed.

To summarize, in line with our first hypothesis, the results indicated successful threat acquisition across self-reported fear, SCR, and LPP in adolescents and adults. Notably, developmental differences emerged at psychophysiological and neural levels. Supporting our second hypothesis, adolescents displayed heightened SCR responses to both threat and safety cues, but contrary to our hypothesis, they also demonstrated stronger threat differentiation in SCR. Additionally, adolescents showed heightened LPP responses to both threat and safety cues. Finally, supporting our third hypothesis, individuals with higher anxiety levels exhibited greater differential self-reported fear during acquisition irrespective of their age group. However, anxiety moderation was not observed in other threat-related indices, as initially expected. All significant results for threat acquisition are presented in online Supplementary Table S4 in Supplemental Materials.

Threat extinction

Self-reported fear

RM-ANCOVA of reported fear towards conditioned cues with Stimulus (CS+, CS−) × Block (pre-extinction, block 1, block 2, block 3, block 4, block 5, block 6) × Age (adolescents, adults) × Anxiety, yielded a significant Stimulus × Block × Anxiety interaction, $F_{(2.14,\ 239.65)} = 4.01$, $p = 0.017$, $\eta_p^2 = 0.035$. Participants with

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

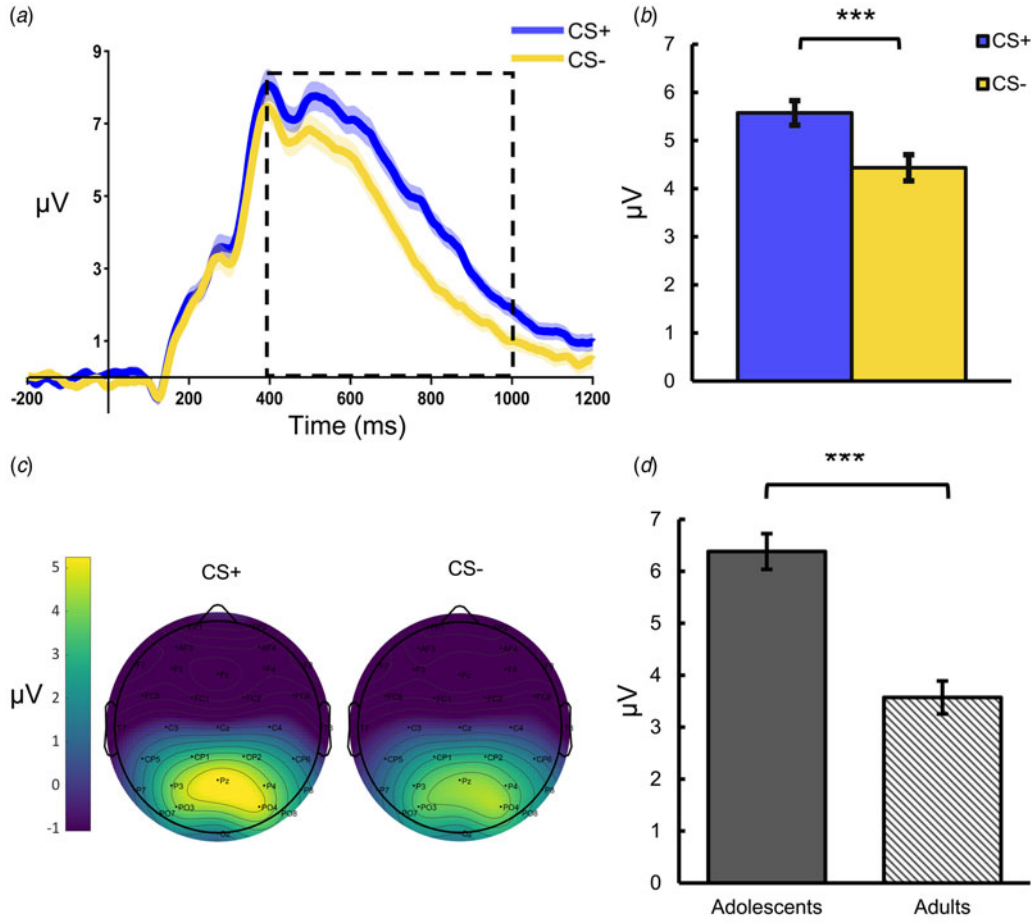

Figure 2. (a) Grand-average ERP waveforms at the Pz electrode, across all participants, during CS+ and CS− trials. (b) Difference in LPP during CS+ and CS− trials across acquisition: activity at Pz electrode between 400 and 1000 ms following stimulus onset, across all participants (c) Grand-average LPP topographic maps of the LPP, across all participants, during CS+ and CS− trials between 400 and 1000 ms following stimulus onset. (d) Developmental differences in overall LPP averaged across both CSs, and all acquisition blocks (400–1000 ms).
Note: Error bars represent the standard error of the mean. Dashed rectangle denotes the time window used for statistical analyses of LPP (400–1000 ms).
$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

low- and high-anxiety levels exhibited a significant Stimulus × Block interaction, $F_{(2.43,\ 126.22)} = 10.21$, $p < 0.001$, $\eta_p^2 = 0.164$, and $F_{(1.91,\ 116.07)} = 43.16$, $p < 0.001$, $\eta_p^2 = 0.414$, respectively. Follow-up *t* tests comparing differential responses to CSs (CS+ v. CS−) in extinction blocks (Bonferroni-corrected for seven tests; corrected alpha = 0.007) indicated complete diminishing of differential self-reported fear (CS+ not different than CS−) earlier in the low-anxiety group (blocks 5–6; $ps \geqslant 0.012$) than in the high-anxiety group (block 6, $p = 0.009$); see Fig. 3a. A lower-order main effect of block was also observed (see online Supplemental Materials). Additional lower-order effects are reported in online Supplementary Table S5 in the supplemental materials.

Skin conductance response (SCR)

RM-ANCOVA of SCR testing the Stimulus × Block × Age × Anxiety effect yielded a significant Stimulus × Block interaction, $F_{(2.93,255.14)} = 19.77$, $p < 0.001$, $\eta_p^2 = 0.185$. Follow-up *t* tests examining differential SCR (CS+ v. CS−) per block (Bonferroni-corrected for six tests, alpha = 0.0083) indicated a gradual decrease in differential response across extinction but without complete extinction (all $ps \leqslant 0.006$), in contrast to our initial hypothesis; see Fig. 3b. A lower-order main effect of block was also observed (see online Supplemental Materials). Other lower-order effects are reported in online Supplementary Table S5 in the supplemental materials.

Late positive potential (LPP)

The RM-ANCOVA testing the Stimulus × Block × Age × Anxiety effect yielded a significant Stimulus × Block × Age interaction, $F_{(2,172)} = 3.16$, $p = 0.045$, $\eta_p^2 = 0.035$. To reveal the source of this three-way interaction, we ran follow-up analyses comparing differential LPP for adolescents and adults, in each of the three extinction blocks (blocks 1&2, blocks 3&4, and blocks 5&6).

Blocks 1&2. RM-ANOVA with Stimulus (CS+, CS−) × Age (adolescents, adults) revealed a main effect of stimulus, showing participants demonstrated greater LPP towards the CS+ ($M = 3.91$, S.D. = 2.84) than the CS− ($M = 3.05$, S.D. = 2.51), $F_{(1,88)} = 10.14$, $p = 0.002$, $\eta_p^2 = 0.103$. A main effect of age emerged, $F_{(1,88)} = 16.94$, $p < 0.001$, $\eta_p^2 = 0.161$, suggesting adolescents ($M = 4.38$, S.D. = 2.17) demonstrated overall greater LPP than adults ($M = 2.50$, S.D. = 2.16) during the first block of extinction. The Stimulus × Age interaction was not significant, $F_{(1,88)} = 0.18$, $p = 0.674$, $\eta_p^2 = 0.002$.

Block 3&4. RM-ANOVA with Stimulus (CS+, CS−) × Age (adolescents, adults) revealed a main effect of stimulus, suggesting participants demonstrated greater LPP towards the CS+

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

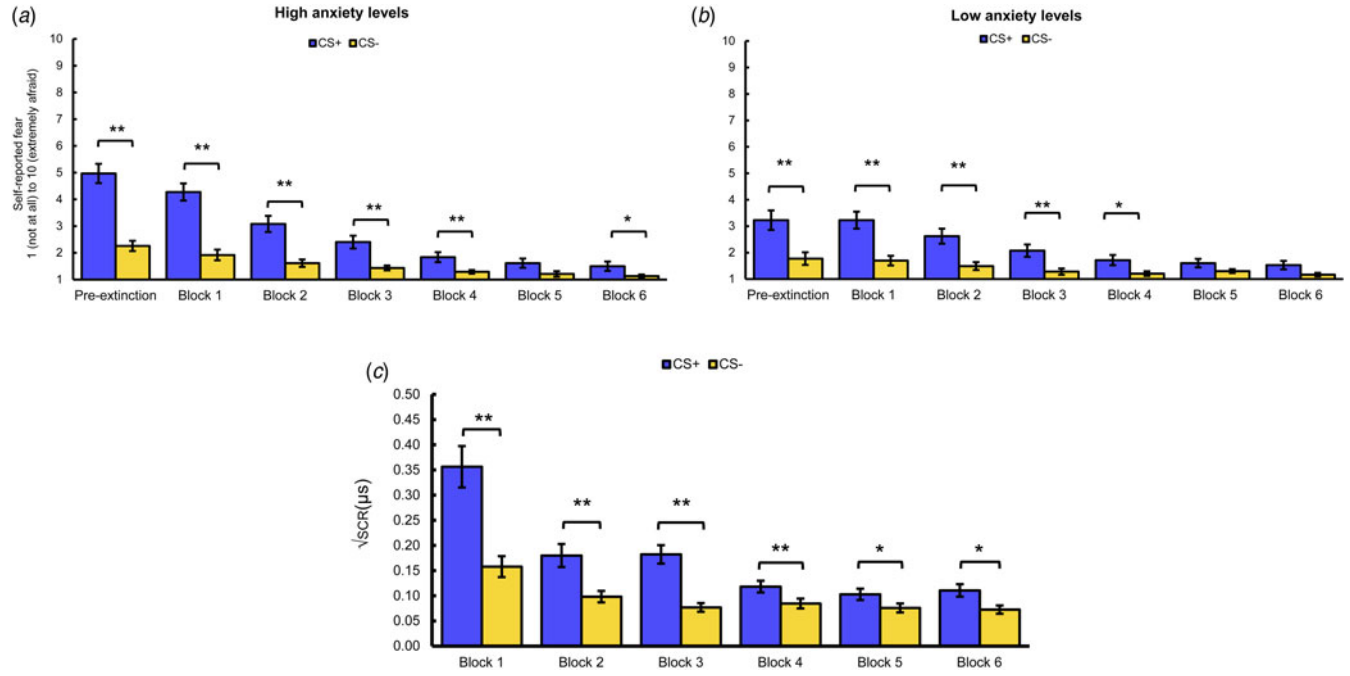

Figure 3. (a) Differences in self-reported fear towards the CS+ and CS− across extinction blocks among individuals with high and low anxiety levels, measured by SCARED/SCAARED questionnaires' *Z* scores. (b) Differences in SCR during CS+ and CS− trials across extinction blocks.
Note: Error bars represent the standard error of the mean. SCR, Skin conductance response.
A. $^{*}p < 0.007$ after correcting for multiple comparisons; $^{**}p < 0.001$.
B. $^{*}p < 0.008$ after correcting for multiple comparisons; $^{**}p < 0.001$.

($M = 3.61$, S.D. = 2.90) than the CS− ($M = 2.51$, S.D. = 2.51), $F_{(1,89)} = 17.44$, $p < 0.001$, $\eta_p^2 = 0.164$. A main effect of age emerged, $F_{(1,89)} = 5.06$, $p = 0.027$, $\eta_p^2 = 0.054$, suggesting adolescents ($M = 3.59$, S.D. = 2.36) demonstrated overall greater LPP than adults ($M = 2.47$, S.D. = 2.35) during the second block of extinction. The Stimulus × Age interaction was not significant, $F_{(1,89)} = 1.27$, $p = 0.262$, $\eta_p^2 = 0.014$.

Block 5&6. RM-ANOVA with Stimulus (CS+, CS−) × Age (adolescents, adults) revealed a two-way interaction, $F_{(1,88)} = 5.55$, $p = 0.021$, $\eta_p^2 = 0.059$. Follow-up analysis for each age group revealed a main effect of stimulus only among adolescents, $F_{(1,47)} = 11.70$, $p = 0.001$, $\eta_p^2 = 0.199$, with greater LPP towards the CS+ ($M = 4.11$, S.D. = 3.06) than the CS− ($M = 2.52$, S.D. = 3.29), even during the last blocks of extinction, thus supporting our first hypothesis. In contrast, adults showed no main effect of stimulus, $F_{(1,41)} = 0.92$, $p = 0.344$, $\eta_p^2 = 0.022$, suggesting complete extinction of the threat contingencies. For waveform and topographical presentations of the LPP across extinction, see Fig. 4. Additional lower-order effects are reported in online Supplementary Table S5 in the supplemental materials.

To summarize, in line with our first hypothesis, adolescents and adults showed comparable extinction learning as indexed by self-reported fear and SCR. Contrary to our hypothesis, participants did not exhibit complete extinction as indexed by SCR. Confirming our second hypothesis, developmental differences emerged at the neural level, with persistent differential LPP responses in adolescents compared to adults. Finally, supporting our third hypothesis, individuals with higher anxiety levels demonstrated slower extinction, particularly in self-reported fear, but this anxiety effect was not observed in other threat-related measures. All significant results for threat extinction are presented in online Supplementary Table S5 in Supplemental Materials.

Moderating effect of age on the association between anxiety levels and extinction learning

In addition to the pre-registered analyses above, we examined exploratory moderation models to assess the possible moderating effect of age on the association between anxiety severity (measured by SCARED/SCAARED *Z* scores) and the extent of threat extinction learning. The latter was quantified for all dependent variables as the difference between responses to CS+ and CS− during the final block of extinction. To maximize the sensitivity of the moderation analyses, we used age as a continuous variable. For LPP, results revealed a significant age moderation effect, $B = -0.208$, $F_{(1,84)} = 11.71$, $p = 0.001$. Post-hoc analyses showed more severe anxiety was associated with diminished extinction in the youngest group (one standard deviation below the mean age; 14.15 years), $B = 2.34$, $t = 4.63$, $p < 0.001$, and middle group (around the mean age; 19.55 years), $B = 1.22$, $t = 3.43$, $p < 0.001$, but not the older group (one standard deviation above the mean age; 24.94 years), $B = 0.10$, $t = 0.21$, $p = 0.835$; see Fig. 5.

No moderation effects emerged for self-reported fear or SCR, all $ps \geqslant 0.476$. These results suggest that age-dependent associations between anxiety severity and extinction learning manifest in LPP amplitude.

Association between self-reports, psychophysiological measures, and neural measures during threat acquisition and extinction

We conducted exploratory correlation analyses to assess associations among the dependent variables (self-reports, psychophysiological measures, neural measures) during acquisition and

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

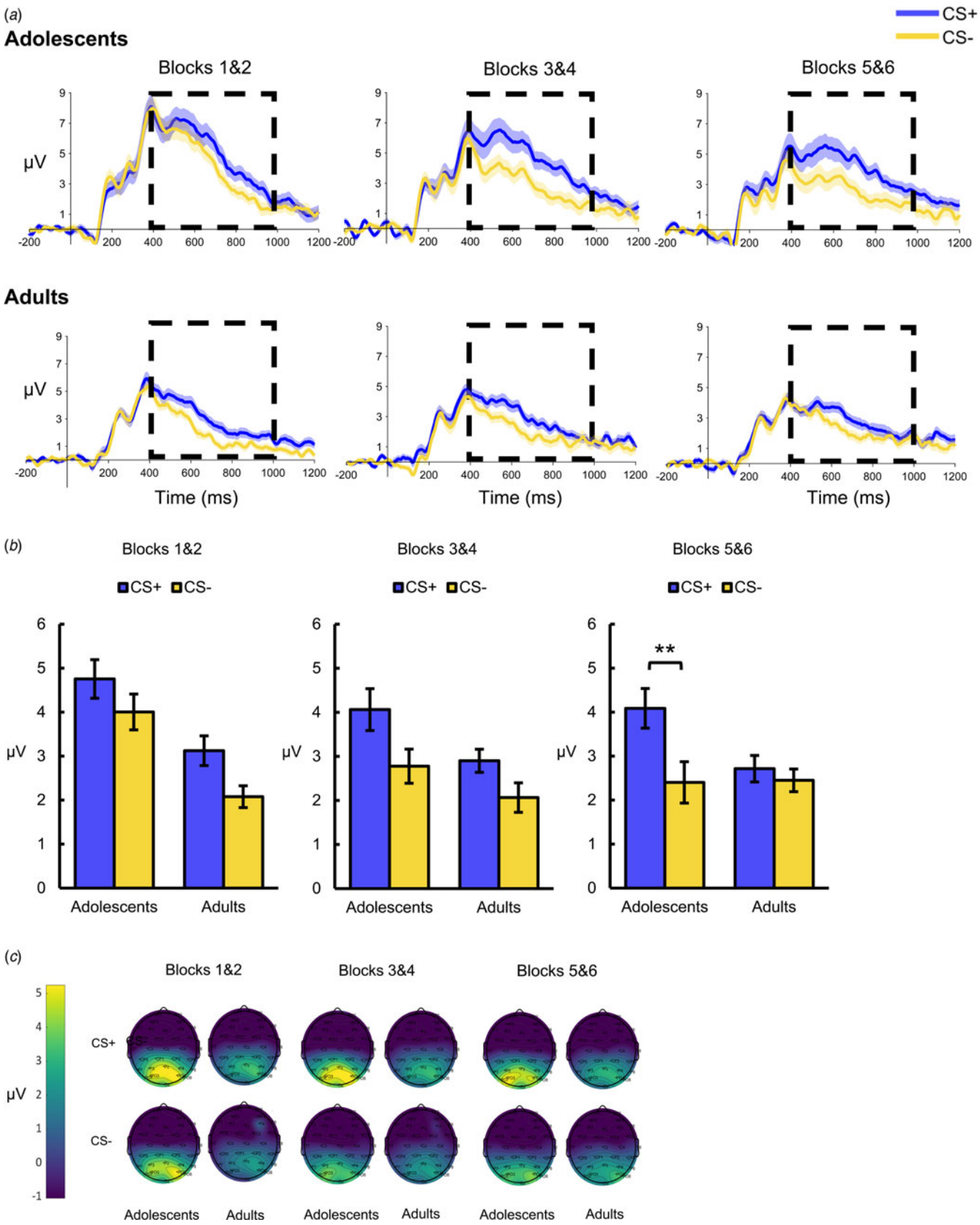

Figure 4. (a) Grand-average ERP waveforms at the Pz electrode, among adolescents and adults, during CS+ and CS− trials, across extinction blocks. (b) Differences in LPP during CS+ and CS− trials across extinction blocks among adolescents and adults: activity at Pz electrode between 400 and 1000 ms following stimulus onset. Error bars represent the standard error of the mean (c) Grand-average topographic presentation of the LPP among adolescents and adults, during CS+ and CS− trials between 400 and 1000 ms following stimulus onset across extinction blocks.
Notes: Dashed rectangle denotes the time window used for statistical analyses of LPP (400–1000 ms).
*$p < 0.017$ after correcting for multiple comparisons; **$p < 0.001$.

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

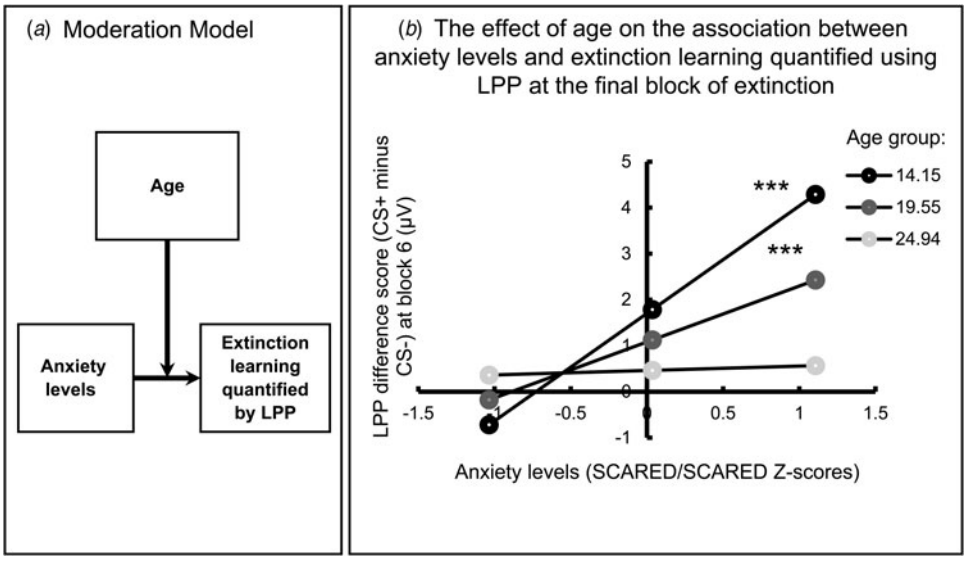

Figure 5. (a) Moderation model: association between anxiety levels (SCARED/SCAARED *Z* scores) and extinction learning quantified using LPP difference score ((CS+)–(CS−)) at the final block of extinction, moderated by age. (b) Post-hoc analysis: correlations between anxiety levels and LPP difference score at the end of extinction are moderated by age.
Notes: SCARED, Screen for Child Anxiety Related Emotional Disorders; SCAARED, Screen for Adult Anxiety Related Disorder, LPP: Late Positive Potential.
$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

extinction. Notable among these were significant correlations among self-reported fear, SCR, and LPP elicited by threat (CS+) during extinction ($ps \leqslant 0.036$), suggesting convergence in responses across cognitive, psychophysiological, and neural levels during extinction (online Supplementary Tables S6 and S7, Supplemental Materials). We emphasize that these findings are strictly exploratory and meant to guide future research.

Discussion

This study examined differences between adolescents and adults in their responses to conditioned threat, assessed at cognitive, psychophysiological, and neural levels, focusing on extinction deficits as indicated by LPP. Supporting our first hypothesis, both adolescents and adults showed threat differentiation in LPP during acquisition indicated by enhanced responses towards the CS+ compared to the CS−, in line with prior work in adults (Bacigalupo & Luck, 2018; Ferreira de Sá et al., 2019; Panitz et al., 2015; Seligowski et al., 2018; Sperl et al., 2021). This suggests differential threat acquisition is evident already in adolescents as indexed by LPP. Moreover, adolescents in our sample exhibited overall enhanced LPP compared to adults, possibly suggesting increased general context-dependent sensitivity to potential threat cues in this age group (Abend, 2023). The overall heightened LPP responses that emerged during acquisition are in line with the findings of a recent magnetoencephalogram (MEG) study, showing overall enhanced activation among adolescents compared to adults during fear learning and generalization in time windows parallel to the LPP (Roesmann et al., 2022). A similar main effect of age was identified in a study examining developmental differences in early ERP components during a fear learning task (Linton & Levita, 2021). These findings may reflect hyper-sensitivity to contexts of potential threat (e.g. probabilistic threat learning) among adolescents across different neural indices. At the same time, it is important to note that additional factors may have contributed to this age effect, such as a non-specific elevation in general arousal or attention levels among adolescents; alternatively, non-neural factors, such as skull thickness, could contribute to the observed higher neural amplitude in adolescents (Segalowitz, Santesso, & Jetha, 2010). Future work comparing age groups may wish to take such factors into consideration.

Alongside developmental differences in neural responses to threat cues, supporting our second hypothesis, adolescents exhibited a general elevated psychophysiological arousal to conditioned cues compared to adults, as well as greater threat-specific arousal, contrary to our initial expectations. Adolescents also demonstrated relatively slower habituation and sustained arousal to the US. Such findings are in line with previous results suggesting adolescents show overall higher SCR (i.e. to both threat and safety cues) than adults during threat acquisition (Linton & Levita, 2021; Skversky-Blocq et al., 2022b) and increased differential SCR during acquisition (Abend et al., 2020). Slower habituation to the US among adolescents may reflect increased sensitivity and diminished ability to regulate psychophysiological arousal to aversive events in this age group, possibly contributing to stronger conditioning effects that are generalized to all conditioned cues. This, in turn, may contribute to the emergence of anxiety in adolescents. This explanation is supported by the extinction phase in which no US was presented, and age group differences in gradual decreases or differential SCR were no longer apparent. Age differences in LPP and elevated SCR may also be partially explained by a developmental difference in intolerance of uncertainty (IUC). While it was only a secondary measure in this study, we found adolescents reported higher IUC than adults (see online Supplemental Materials, Table S1). As IUC has been suggested to contribute to the development and maintenance of anxiety (Morriss, Zuj, & Mertens, 2021; Osmanağaoğlu, Creswell, & Dodd, 2018), future work could focus on the role of IUC in the context of an uninstructed threat learning paradigm which inherently involves some uncertainty as to the occurrence of the aversive outcome (US).

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press

In line with our first hypothesis, developmental differences in LPP emerged during threat extinction. Unlike adults who showed a decrease in LPP differential responses until full extinction, adolescents showed persistent differential LPP responses, suggesting difficulty in extinguishing the learned threat contingency. Our finding for extinction in LPP is similar to previous studies reporting diminished LPP responses until complete extinction among adults (Cheng et al., 2022; Ferreira de Sá et al., 2019; Sperl et al., 2021). Lack of complete extinction in adolescents may indicate difficulty adapting to changes in the emotional significance of the threatening cue when it no longer predicts any actual danger. A related developmental study reported that during extinction, adolescents did not show diminished early visual differential responses as measured by the N1 component, but adults did (Linton & Levita, 2021). Moreover, an fMRI study focusing on developmental differences in extinction found adolescents, but not adults, showed increased amygdala activation towards the CS+ compared to the CS−, even during prolonged extinction learning (Morriss et al., 2019).

From a clinical perspective, our study provides support to theories linking adolescence-specific perturbations in threat extinction and anxiety symptoms (Casey et al., 2015). Specifically, we found higher anxiety levels in adolescents were linked to less effective extinction, as revealed by sustained threat differentiation in LPP through the end of the extinction phase. Prior complementary imaging work found anxiety-related activations in key nodes of the fear circuitry differed in youth and adults (Gold et al., 2020). Stronger retention of conditioned threat responses in youth may therefore reflect an adaptive characteristic; it has been hypothesized to support survival at an age when the individual is biologically prepared to leave familial safety and attain reproductive success (Casey et al., 2015). However, individual variations in resistance to extinction may also lead to anxiety vulnerability, as many threat contingencies that were acquired incidentally and should have been normatively extinguished remain intact. Along these lines, in a recent study, clinically anxious adolescents exhibited sustained LPP differentiation compared to non-anxious counterparts during a delayed extinction task, and enhanced LPP differentiation was associated with poorer outcomes in exposure-based therapy (Klein et al., 2023). Thus, our findings underscore adolescence as a specific developmental period susceptible to variations in threat extinction which may impact both anxiety vulnerability and response to treatment. Treatment approaches that address this issue may therefore be warranted, although it is important to emphasize that additional research is needed to replicate and extend our findings to clinical populations.

Our findings suggest that while the decrease in psychophysiological response during extinction was comparable in adolescents and adults, LPP revealed distinct age-related extinction patterns. In line with prior research highlighting different facets of threat responses across various measures (Klein et al., 2022; Newsome, Ruiz, Gold, Pine, & Abend, 2023), our results emphasize that SCR, reflecting arousal in preparation for behavioral action, and LPP, a correlate of the emotional significance of a stimulus, quantify different aspects of the fear response mechanisms (Abend, 2023; Bacigalupo & Luck, 2018). The relatively sustained differential LPP we found for adolescents but not adults suggests a potentially more sensitive measure for exploring age-related differences during extinction learning.

The study had several limitations. The threat learning task was extended to accommodate EEG recording (requiring a larger number of trials) and SCR measures (necessitating a longer ITI). This extended timeframe might have made it challenging for some participants to maintain focus, resulting in increased movements and artifacts; indeed, approximately 20% of participants were excluded due to artifactual data and technical issues. This may have been related to the experimental design and may have limited our ability to detect certain statistical effects, particularly given our complex models and multiple variables. Furthermore, repeated exposure to the US could also lead to habituation, impacting learning (Abend et al., 2022). At the same time, the task design enabled the integration of multiple measures, allowed the consolidation of acquisition (over a 24-h period), and afforded a longer extinction period, consistent with recent recommendations (Treanor et al., 2021). Finally, we averaged the LPP trials across acquisition blocks and every two blocks during extinction to enable a sufficient signal-to-noise ratio. However, doing so hindered direct comparisons with SCR and self-reports that were analyzed using block-by-block design. This is an inherent limitation when integrating different physiological measures, particularly EEG, which require different numbers of trials to achieve a valid measure.

In conclusion, our results underline the capacity of LPP to capture developmental differences in threat learning, with the potential to identify neural processes that render adolescents more susceptible to heightened fear responses and thus vulnerability to anxiety symptomatology. This is particularly relevant given the growing evidence of distinct LPP responses among anxious adolescents and their predictive value in exposure-based treatment outcomes (Klein et al., 2023). These findings encourage a continued focus on the LPP in the context of clinical research on pediatric anxiety and its treatment.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724001314

Acknowledgements. The study was funded by the Israel Science Foundation (ISF-920/19, TS) and the Brain & Behavior Research Foundation (Young Investigator award, RA).

Competing interests. The authors declare no conflict of interest.

References

Abend, R. (2023). Understanding anxiety symptoms as aberrant defensive responding along the threat imminence continuum. *Neuroscience and Biobehavioral Reviews*, *152*(July 2022), 105305. doi: 10.1016/j.neubiorev.2023.105305

Abend, R., Burk, D., Ruiz, S. G., Gold, A. L., Napoli, J. L., Britton, J. C., … Averbeck, B. B. (2022). Computational modeling of threat learning reveals links with anxiety and neuroanatomy in humans. *ELife*, *11*, 1–30. doi: 10.7554/eLife.66169

Abend, R., Gold, A. L., Britton, J. C., Michalska, K. J., Shechner, T., Sachs, J. F., … Pine, D. S. (2020). Anticipatory threat responding: Associations with anxiety, development, and brain structure. *Biological Psychiatry*, *87*(10), 916–925. doi: 10.1016/j.biopsych.2019.11.006

American Psychiatric Association. (2022). Anxiety disorders. In *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). Washington, DC, American Psychiatric Association. doi: 10.1176/appi.books.9780890425787.x05_Anxiety_Disorders

Angulo, M., Rooks, B. T., Gill, M. K., Goldstein, T., Sakolsky, D., Goldstein, B., … Birmaher, B. (2017). Psychometrics of the screen for adult anxiety related disorders (SCAARED) – A new scale for the assessment of DSM-5 anxiety disorders. *Psychiatry Research*, *253*(August 2016), 84–90. doi: 10.1016/j.psychres.2017.02.034

Bacigalupo, F., & Luck, S. J. (2018). Event-related potential components as measures of aversive conditioning in humans. *Psychophysiology*, *55*, e13015. doi: 10.1111/psyp.13015

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *Psychiatric Clinics of North America*, *32*(3), 483–524. doi: 10.1016/j.psc.2009.06.002

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. K. (1997). The Screen for Child Anxiety Related Emotional Disorders (SCARED): Scale construction and psychometric characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(4), 545–553. doi: 10.1097/00004583-199704000-00018

Bunford, N., Kujawa, A., Fitzgerald, K. D., Monk, C. S., & Phan, K. L. (2018). Convergence of BOLD and ERP measures of neural reactivity to emotional faces in children and adolescents with and without anxiety disorders. *Biological Psychology*, *134*(August 2017), 9–19. doi: 10.1016/j.biopsycho.2018.02.006

Casey, B. J., Glatt, C. E., & Lee, F. S. (2015). Treating the developing versus developed brain: Translating preclinical mouse and human studies. *Neuron*, *86*(6), 1358–1368. doi: 10.1016/j.neuron.2015.05.020

Cheng, Y., Jackson, T. B., & MacNamara, A. (2022). Modulation of threat extinction by working memory load: An event-related potential study. *Behaviour Research and Therapy*, *150*(July 2021), 104031. doi: 10.1016/j.brat.2022.104031

Danon-Kraun, S., Horovitz, O., Frenkel, T., Richter-Levin, G., Pine, D. S., & Shechner, T. (2021). Return of fear following extinction in youth: An event-related potential study. *Developmental Psychobiology*, *63*(7), e22189. doi: 10.1002/dev.22189

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Dennis, T. A., & Hajcak, G. (2009). The late positive potential: A neurophysiological marker for emotion regulation in children. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *50*(11), 1373–1383. doi: 10.1111/j.1469-7610.2009.02168.x

Ferreira de Sá, D. S., Michael, T., Wilhelm, F. H., & Peyk, P. (2019). Learning to see the threat: Temporal dynamics of ERPs of motivated attention in fear conditioning. *Social Cognitive and Affective Neuroscience*, *14*(2), 189–203. doi: 10.1093/scan/nsy103

Ganella, D. E., Drummond, K. D., Ganella, E. P., Whittle, S., & Kim, J. H. (2018). Extinction of conditioned fear in adolescents and adults: A human fMRI study. *Frontiers in Human Neuroscience*, *11*(January), 1–13. doi: 10.3389/fnhum.2017.00647

Gold, A. L., Abend, R., Britton, J. C., Behrens, B., Farber, M., Ronkin, E., … Pine, D. S. (2020). Age differences in the neural correlates of anxiety disorders: An fMRI study of response to learned threat. *American Journal of Psychiatry*, *177*(5), 454–463. doi: 10.1176/appi.ajp.2019.19060650

Hajcak, G., & Foti, D. (2020). Significance?& significance! empirical, methodological, and theoretical connections between the late positive potential and P300 as neural responses to stimulus significance: An integrative review. *Psychophysiology*, *57*(7), 1–15. doi: 10.1111/psyp.13570

James, A. C., Reardon, T., Soler, A., James, G., & Creswell, C. (2020) Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, *2020*(11). doi: 10.1002/14651858.CD013162.pub2.

Jovanovic, T., Nylocks, K., & Gamwell, K. L. (2013). Translational neuroscience measures of fear conditioning across development: Applications to high-risk children and adolescents. *Biology of Mood & Anxiety Disorders*, *3*(1), 17. doi: 10.1186/2045-5380-3-17

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of. *Archives of General Psychiatry*, *62*(June), 593–602. Retrieved from http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.62.6.593

Kitt, E. R., Odriozola, P., & Gee, D. G. (2023). *Extinction learning across development: neurodevelopmental changes and implications for pediatric anxiety disorders*. doi: 10.1007/7854_2023_430

Klein, Z., Abend, R., Shmuel, S., & Shechner, T. (2022). Unique associations between conditioned cognitive and physiological threat responses and facets of anxiety symptomatology in youth. *Biological Psychology*, *170*(March), 108314. doi: 10.1016/j.biopsycho.2022.108314

Klein, Z., Berger, S., Vervliet, B., & Shechner, T. (2021). Fear learning, avoidance, and generalization are more context-dependent for adults than adolescents. *Behaviour Research and Therapy*, *147*(October), 103993. doi: 10.1016/j.brat.2021.103993

Klein, Z., Shner, G., Ginat-Frolich, R., Vervliet, B., & Shechner, T. (2020). The effects of age and trait anxiety on avoidance learning and its generalization. *Behaviour Research and Therapy*, *129*(March), 103611. doi: 10.1016/j.brat.2020.103611

Klein, Z., Shner-livne, G., Danon-kraun, S., Ginat-frolich, R., Pine, D. S., & Shechner, T. (2023). *Enhanced late positive potential to conditioned threat cue during delayed extinction in anxious youth*. doi: 10.1111/jcpp.13814

Linton, S. R., & Levita, L. (2021). Potentiated perceptual neural responses to learned threat during Pavlovian fear acquisition and extinction in adolescents. *Developmental Science*, *24*(5), e13107. doi: 10.1111/desc.13107

Liu, Y., Huang, H., McGinnis-Deweese, M., Keil, A., & Ding, M. (2012). Neural substrate of the late positive potential in emotional processing. *Journal of Neuroscience*, *32*(42), 14563–14572. doi: 10.1523/JNEUROSCI.3109-12.2012

Lonsdorf, T. B., Klingelhöfer-Jens, M., Andreatta, M., Beckers, T., Chalkia, A., Gerlicher, A., … Merz, C. J. (2019). Navigating the garden of forking paths for data exclusions in fear conditioning research. *ELife*, *8*, 1–36. doi: 10.7554/eLife.52465

Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, *8*(1 APR), 1–14. doi: 10.3389/fnhum.2014.00213

MacNamara, A., Rabinak, C. A., Kennedy, A. E., & Phan, K. L. (2018). Convergence of fMRI and ERP measures of emotional face processing in combat-exposed U. S. military veterans. *Psychophysiology*, *55*(2), e12988. doi: 10.1111/psyp.12988

Mineka, S., & Oehlberg, K. (2008). The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta Psychologica*, *127*(3), 567–580. doi: 10.1016/j.actpsy.2007.11.007

Morriss, J., Christakou, A., & van Reekum, C. M. (2019). Multimodal evidence for delayed threat extinction learning in adolescence and young adulthood. *Scientific Reports*, *9*(1), 1–10. doi: 10.1038/s41598-019-44150-1

Morriss, J., Zuj, D. V., & Mertens, G. (2021). The role of intolerance of uncertainty in classical threat conditioning: Recent developments and directions for future research. *International Journal of Psychophysiology*, *166*(February), 116–126. doi: 10.1016/j.ijpsycho.2021.05.011

Mutschler, I., Wieckhorst, B., Meyer, A. H., Schweizer, T., Klarhöfer, M., Wilhelm, F. H., … Ball, T. (2014). Who gets afraid in the MRI-scanner? Neurogenetics of state-anxiety changes during an fMRI experiment. *Neuroscience Letters*, *583*, 81–86. doi: 10.1016/j.neulet.2014.09.021

Newsome, P., Ruiz, S. G., Gold, A. L., Pine, D. S., & Abend, R. (2023). Fear-potentiated startle reveals diminished threat extinction in pathological anxiety. *International Journal of Psychophysiology*, *183*(February 2022), 81–91. doi: 10.1016/j.ijpsycho.2022.11.011

Osmanağaoğlu, N., Creswell, C., & Dodd, H. F. (2018). Intolerance of uncertainty, anxiety, and worry in children and adolescents: A meta-analysis. *Journal of Affective Disorders*, *225*(July 2017), 80–90. doi: 10.1016/j.jad.2017.07.035

Paiva, T. O., Almeida, P. R., Coelho, R. C., Pasion, R., Barbosa, F., Ferreira-Santos, F., … Marques-Teixeira, J. (2020). The neurophysiological correlates of the triarchic model of psychopathy: An approach to the basic mechanisms of threat conditioning and inhibitory control. *Psychophysiology*, *57*(8), 1–18. doi: 10.1111/psyp.13567

Panitz, C., Hermann, C., & Mueller, E. M. (2015). Conditioned and extinguished fear modulate functional corticocardiac coupling in humans. *Psychophysiology*, *52*(10), 1351–1360. doi: 10.1111/psyp.12498

Pattwell, S. S., Duhoux, S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D., … Lee, F. S. (2012). Altered fear learning across development in both mouse and human. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(40), 16318–16323. doi: 10.1073/pnas.1206834109

Pittig, A., Treanor, M., LeBeau, R. T., & Craske, M. G. (2018). The role of associative fear and avoidance learning in anxiety disorders: Gaps and directions for future research. *Neuroscience and Biobehavioral Reviews*, *88*(March), 117–140. doi: 10.1016/j.neubiorev.2018.03.015

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers*, *36*(4), 717–731. doi: 10.1002/jcp.28952

Rapee, R. M., Creswell, C., Kendall, P. C., Pine, D. S., & Waters, A. M. (2023) Anxiety disorders in children and adolescents: A summary and overview of the literature. *Behaviour Research and Therapy*, *168*(July), 104376. doi: 10.1016/j.brat.2023.104376.

Roesmann, K., Wessing, I., Kraß, S., Leehr, E. J., Klucken, T., Straube, T., & Junghöfer, M. (2022). Developmental aspects of fear generalization – A MEG study on neurocognitive correlates in adolescents versus adults. *Developmental Cognitive Neuroscience*, *58*(May), 101169. doi: 10.1016/j.dcn.2022.101169

Schupp, H. T., & Kirmse, U. M. (2021). Case-by-case: Emotional stimulus significance and the modulation of the EPN and LPP. *Psychophysiology*, *58*(4), e13766. doi: 10.1111/psyp.13766

Segalowitz, S. J., Santesso, D. L., & Jetha, M. K. (2010). Electrophysiological changes during adolescence: A review. *Brain and Cognition*, *72*(1), 86–100. doi: 10.1016/j.bandc.2009.10.003

Seligowski, A. V., Bondy, E., Singleton, P., Orcutt, H. K., Ressler, K. J., & Auerbach, R. P. (2018). Testing neurophysiological markers related to fear-potentiated startle. *Psychiatry Research*, *267*, 195–200. doi: 10.1016/j.psychres.2018.06.023

Seligowski, A. V., Reffi, A. N., Phillips, K. A., Orcutt, H. K., Auerbach, R. P., Pizzagalli, D. A., & Ressler, K. J. (2021). Neurophysiological responses to safety signals and the role of cardiac vagal control. *Behavioural Brain Research*, *396*, 112914. doi: 10.1016/j.bbr.2020.112914

Shechner, T., Britton, J. C., Ronkin, E. G., Jarcho, J. M., Mash, J. A., Michalska, K. J., … Pine, D. S. (2015). Fear conditioning and extinction in anxious and nonanxious youth and adults: Examining a novel developmentally appropriate fear-conditioning task. *Depression and Anxiety*, *32*(4), 277–288. doi: 10.1002/da.22318

Skversky-Blocq, Y., Pine, D. S., & Shechner, T. (2021). Using a novel paradigm to examine observational fear-learning across development. *Depression and Anxiety*, *38*(7), 731–738. doi: 10.1002/da.23152

Skversky-Blocq, Y., Shmuel, S., Cohen, O., & Shechner, T. (2022a). Looking fear in the face: Adults but not adolescents gaze at social threat during observational learning. *International Journal of Psychophysiology*, *182* (April), 240–247. doi: 10.1016/j.ijpsycho.2022.11.004

Skversky-Blocq, Y., Shmuel, S., Waters, A. M., & Shechner, T. (2022b). Observational extinction reduces fear and its retention among adolescents and adults. *Behaviour Research and Therapy*, *159*(February), 104207. doi: 10.1016/j.brat.2022.104207

Sperl, M. F. J., Wroblewski, A., Mueller, M., Straube, B., & Mueller, E. M. (2021). Learning dynamics of electrophysiological brain signals during human fear conditioning. *NeuroImage*, *226*, 117569. doi: 10.1016/j.neuroimage.2020.117569

Treanor, M., Rosenberg, B. M., & Craske, M. G. (2021). Pavlovian learning processes in pediatric anxiety disorders: A critical review. *Biological Psychiatry*, *89*, 690–696. doi: 10.1016/j.biopsych.2020.09.008

Waters, A., Theresiana, C., Neumann, D., & Craske, M. (2017). Developmental differences in aversive conditioning, extinction, and reinstatement: A study with children, adolescents, and adults. *Journal of Experimental Child Psychology*, *159*, 263–278. doi: 10.1016/j.jecp.2017.02.012

Weinberg, A., & Hajcak, G. (2011). The late positive potential predicts subsequent interference with target processing. *Journal of Cognitive Neuroscience*, *23*(10), 2994–3007. doi: 10.1162/jocn.2011.21630

https://doi.org/10.1017/S0033291724001314 Published online by Cambridge University Press