


Exposure to unpredictable childhood environments is associated with amygdala activation during early extinction in adulthood

Jessica M. Duda^a, Taylor J. Keding^a, Sahana Kribakaran^{a,b}, Paola Odriozola^c, Elizabeth R. Kitt^a, Emily M. Cohodes^a, Sadie J. Zacharek^d, Sarah McCauley^e, Jason T. Haberman^a, Jutta Joormann^a, Dylan G. Gee^{a,*} 

^a Department of Psychology, Yale University, New Haven, CT, USA

^b Yale School of Medicine, Yale University, New Haven, CT, USA

^c Department of Psychology, University of California Los Angeles, Los Angeles, CA, USA

^d Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA

^e Silberman School of Social Work at Hunter College, New York, NY, USA

ARTICLE INFO

Keywords:

Childhood adversity
Caregiving
Unpredictable stress
Extinction learning
Amygdala
fMRI

ABSTRACT

Early adversity can alter the maturation and function of neural regions that support affective functioning, including threat and safety learning. A growing body of cross-species research has specifically focused on the role of unpredictability in childhood environments in shaping affective functioning; however, the links between childhood unpredictability and neural function related to extinction learning in adulthood remain unclear. In this study, we probed the association between childhood unpredictability, extinction learning, and neural activation in four regions implicated in extinction learning in healthy young adults ($N = 45$; aged 18–30 years). Results revealed that adults exposed to more unpredictable childhood environments showed greater basolateral amygdala activity to the former (i.e., extinguished) threat cue during early, but not late, extinction, including when controlling for current anxiety and childhood trauma exposure. An exploratory analysis showed that exposure to unpredictable caregiving, but not distal unpredictability (e.g., unpredictability of the physical home or community), specifically drove findings in the amygdala. Childhood unpredictability was not associated with activity in the other regions of interest or with skin conductance response during extinction. These findings add to a growing literature on longstanding impacts of unpredictable caregiving environments, with implications for promoting healthy neurodevelopment and targeted clinical interventions.

1. Introduction

Early life adversity has well-established effects on neurodevelopmental trajectories related to affective functioning (Gee, 2021; Heim and Nemeroff, 2001; Sheridan and McLaughlin, 2020; Tottenham, 2014). Cross-species evidence suggests that exposure to unpredictable environments in early life can exert distinct effects on development (Glynn and Baram, 2019) from other features of adverse environments (e.g., environmental harshness or deprivation; Ellis et al., 2009; McLaughlin et al., 2021). Even after accounting for other exposures to early adversity, children who experience more unpredictability in their early environments show higher rates of anxiety and depression into adulthood (Ross et al., 2016; Spadoni et al., 2022; Wang et al., 2023). Early unpredictability may also have a sex-dependent association with

post-traumatic stress disorder (PTSD) symptoms, with women but not men showing greater PTSD symptoms in adulthood following exposure to unpredictable childhood environments (Spadoni et al., 2022). Further, the predictability of prenatal and early life environments has been shown to shape maturation of neural circuitry involved in affective learning and memory (Bolton et al., 2018; Glynn and Baram, 2019; Jirsaraie et al., 2023; Johnson et al., 2018; Molet et al., 2016). According to theoretical work, chronic exposure to stressful and unpredictable environments may also hinder learning from safety cues via increasing expectations of threat—a potentially adaptive response to uncertain, threatening contexts (Kaye and Krystal, 2020; Kube et al., 2020; Wilkinson et al., 2017). However, despite considerable work investigating the effects of early life adversity (e.g., maltreatment, community violence, poverty) on threat processing and its neural underpinnings (e.

* Corresponding author at: Department of Psychology, Yale University, 100 College Street, New Haven, CT 06510, USA.

E-mail address: dylan.gee@yale.edu (D.G. Gee).

<https://doi.org/10.1016/j.dcn.2025.101578>

Received 31 October 2024; Received in revised form 12 May 2025; Accepted 20 May 2025

Available online 31 May 2025

1878-9293/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

g., Hein and Monk, 2017; McCrory et al., 2011; Weissman et al., 2022), little research has investigated the specific effects of early environmental unpredictability on the neural circuitry involved with extinction learning. Understanding the impact of early environmental statistics on neural function during extinction represents an important area of study given the well-established role of altered extinction learning in anxiety-related pathology (Craske et al., 2018; Milad et al., 2014; Singewald and Holmes, 2019).

Considerable theoretical work proposes that environmental unpredictability in early life alters threat processing into adulthood. For example, predictive processing theories propose that prolonged exposure to unpredictable, stressful environments spurs the development of meta-level expectations (“priors”) of threat, facilitating threat perception and reducing the integration of external safety cues (Kaye and Krystal, 2020; Kube et al., 2020; Wilkinson et al., 2017). Drawing from the decision-making literature, environmental unpredictability can be considered analogous to the concept of “expected uncertainty”—environments with stochastic or noisy contingencies (Soltani and Izquierdo, 2019). Exposure to expected uncertainty is thought to reduce the influence of external cues on learning (Wilkinson et al., 2017). Indeed, in cases of expected uncertainty, information is inherently noisier and less informative, such that it is adaptive to reduce learning rates from external cues (Griffin and Fletcher, 2017; Soltani and Izquierdo, 2019; Wilkinson et al., 2017). For these reasons, individuals may increase expectations (and perceptions) of threat and reduce learning from disconfirmatory external evidence (e.g., evidence of safety) after prolonged exposure to unpredictable, stressful environments during development. Still, further empirical work is needed to investigate this theorized relationship between exposure to unpredictable early environments and reduced learning from evidence of safety.

Extinction learning tasks are commonly applied to model learning about safety in formerly threatening environments. A standard extinction learning task consists of two phases: 1) the acquisition phase, in which an aversive unconditioned stimulus (US; e.g., noise, shock) is paired with a positive conditioned stimulus (CS+; e.g., a shape) while another stimulus is unpaired (the negative conditioned stimulus or CS-); and 2) the extinction phase, wherein neither CS is paired with the US (Lebois et al., 2019). Extinction learning is operationalized as the change in the conditioned response across extinction, which can be assessed via physiological measures such as skin conductance response (SCR). These tasks are often paired with functional magnetic resonance imaging (fMRI) to probe the neural circuitry involved in threat and safety learning.

Extinction learning involves neural circuitry including the ventromedial prefrontal cortex (vmPFC), hippocampus, basolateral amygdala (BLA), dorsal anterior cingulate cortex (dACC), and anterior insula (Fullana et al., 2018; Phelps and LeDoux, 2005; Singewald and Holmes, 2019; Suarez-Jimenez et al., 2020). Indeed, a meta-analysis of healthy participants revealed consistent involvement of the dACC and anterior insula during both extinction learning and recall, while activation of the vmPFC, dorsolateral prefrontal cortex, and hippocampus most consistently emerged when comparing response to the former (i.e., extinguished) CS+ and unextinguished CS+ (rather than the safety cue) during extinction recall (Fullana et al., 2018). The amygdala has also been consistently implicated in associative learning and threat conditioning (Krabbe et al., 2018), and amygdala activation correlates with conditioned threat responding during early extinction (Phelps et al., 2004). Further, projections from the vmPFC to the basolateral amygdala have been shown to facilitate formation of extinction memories (Bloodgood et al., 2018; Bukalo et al., 2015; Singewald and Holmes, 2019), and stimulation of the medial PFC (mPFC) and mPFC-amygdala pathway in animal models facilitates extinction learning (Bukalo et al., 2015; Milad and Quirk, 2002). Preclinical work has also revealed that identical mPFC neurons are activated during extinction learning and later recall, indicating an involvement in forming memories of extinction (Milad and Quirk, 2002; Phelps et al., 2004; Phelps and

LeDoux, 2005).

Prior work has shown that trauma exposure interferes with extinction learning and the function of underlying neural circuitry. Trauma-exposed populations with PTSD demonstrate attenuated extinction learning (VanElzakker et al., 2014), yet potentiated learning of new aversive cues (Handy et al., 2018; Kleim et al., 2012). Further, trauma-exposed populations with PTSD show altered activity in the dACC, hippocampus, BLA, and vmPFC during extinction (Garfinkel et al., 2014; Milad et al., 2009; Rougemont-Bücking et al., 2011; Sripada et al., 2013; Suarez-Jimenez et al., 2020). Specifically, PTSD is associated with vmPFC and hippocampal hypoactivation during extinction learning (Rougemont-Bücking et al., 2011; Shvil et al., 2013; Suarez-Jimenez et al., 2020), and greater dACC activation during both extinction learning and recall (Milad et al., 2009; Rougemont-Bücking et al., 2011). Exposure to maltreatment in childhood has been found to augment amygdala responsiveness to threat into adulthood (Hein and Monk, 2017; McCrory et al., 2011), and individuals with PTSD often show increased amygdala activation during extinction learning (Garfinkel et al., 2014; Milad et al., 2009; Suarez-Jimenez et al., 2020; but see Shvil et al., 2014). While the effects of trauma exposure on these processes are relatively well-established, the impact of early environmental unpredictability on neural function during extinction remains unknown.

1.1. Present study

Building on theoretical work proposing that statistical regularities over development shape later threat processing (e.g., Wilkinson et al., 2017), as well as evidence that exposure to unpredictable environments impacts neural development (e.g., Glynn and Baram, 2019; Granger et al., 2021), we investigated associations between early life unpredictability and the physiological and neural correlates of extinction learning. First, we hypothesized that greater exposure to unpredictable childhood environments would be associated with weaker extinction of initial fear responses, operationalized as less attenuation of SCR in response to the extinguished threat cue (i.e., former CS+) in early but not late extinction. Second, we hypothesized that childhood unpredictability would be associated with altered activity in four *a priori* regions of interest (ROIs) to the extinguished threat cue (i.e., blunted vmPFC and hippocampus activity, greater dACC and BLA activity), especially in early versus late trials of extinction. Because we were interested in whether childhood unpredictability was associated with altered extinction learning and neural function above and beyond exposure to childhood trauma, we planned to follow up on any significant findings with a sensitivity analysis including childhood trauma as a covariate. Finally, in an exploratory analysis, we tested whether specific dimensions of early unpredictability differentially related to neural function during extinction for any significant findings.

2. Methods

2.1. Sample and procedures

We initially recruited 67 healthy unmedicated young adults (ages 18–30 years) from the greater New Haven area through flyers and online advertisements as part of a larger study investigating the neural correlates of conditioned inhibition via safety cue learning (Kribakaran et al., 2022; Meyer et al., 2019; Odriozola et al., 2024). Participants completed a clinical interview to rule out current psychopathology (the Anxiety and Related Disorders Interview Schedule for DSM-5; Brown and Barlow, 2014), self-report measures of childhood unpredictability (Glynn et al., 2019) and childhood trauma (Bernstein et al., 2003), and an affective learning task during fMRI and SCR data collection (Meyer et al., 2019). Exclusion criteria included MRI contraindications (e.g., metallic implants, pacemakers, claustrophobia, possible pregnancy), chronic medical illness, neurological disorders, current

psychopathology, and use of psychotropic medications. One participant was excluded due to an incidental finding identified during scanning. Prior to analyses, two participants with excessive motion were excluded (mean absolute translational or rotational motion in any of the 6 rigid directions of greater than 0.2 or 2°, respectively; mean relative motion above 0.2 mm; greater than 15 % of data regressed out as a motion outlier; Power et al., 2012). Motion was assessed using mean framewise displacement, in line with Power et al. (2012). The subsample of participants who met inclusion criteria and completed the measure of childhood unpredictability ($N = 45$) was the focus of analyses (see Table 1 for demographic characteristics). All participants provided informed consent. The institutional review board at Yale University approved all study procedures. Data, materials, and analysis code are available via emailing the corresponding author.

2.2. Assessment of childhood unpredictability

Childhood unpredictability was assessed using the Questionnaire of Unpredictability in Childhood (QUIC; Glynn et al., 2019), a 38-item scale designed to capture chronic exposure to unpredictable environments prior to age 18. Example items include “At least one of my parents had punishments that were unpredictable” and “I changed schools frequently.” A portion of the items that Glynn et al. (2019) deemed more applicable to younger children asked participants to focus on experiences before age 12, such as “I had a bedtime routine” or “My parents kept track of what I ate.” Responses are presented in a dichotomous (“yes”, “no”) format and summed to create five subscales, with higher scores representing more unpredictable environments: 1) parental monitoring and involvement (capturing unpredictability of parental involvement and family routines; e.g., “My family ate a meal together most days,” “At least one of my parents regularly kept track of my school progress”), 2) parental unpredictability (capturing unpredictability of parental mood and behavior; e.g., “At least one of my parents was unpredictable,” “One of my parents could go from calm to furious in an instant”), 3) parental environment (capturing unpredictability of family structure and events; e.g., “At least one of my parents changed jobs frequently,” “My parents got divorced”), 4) physical environment (capturing unpredictability of the childhood home and school environment; e.g., “In my house things I needed were often misplaced so that I could not find them,” “I changed

Table 1
Sample demographic information.

Variable	<i>n</i>	%
Sex assigned at birth		
Male	14	31.1
Female	31	68.9
Race and ethnicity		
Asian	9	19.6
Black or African American	7	15.2
Hawaiian/Pacific Islander	0	0.0
Hispanic/Latine	4	8.7
Non-Hispanic White	26	56.5
Childhood adversity measure	<i>M</i> (<i>SD</i>)	Range (Min - Max)
QUIC (total score)	4.8 (4.8)	0–21
Parental monitoring/involvement	0.8 (1.4)	0–7
Parental unpredictability	2.4 (2.5)	0–9
Parental environment	0.8 (1.3)	0–6
Physical environment	0.6 (1.0)	0–4
Safety/security	0.2 (0.5)	0–3
CTQ	31.0 (7.7)	25–69

Note. Sample demographic information. Final sample $N = 45$. Age: $M = 22.4$ years, $SD = 3.6$ years, range = 18–30 years. Racial categories include multiracial participants and thus add to $N > 45$. The QUIC subscales have a differing number of items: parental monitoring/involvement - 9 items, parental unpredictability - 12 items, parental environment - 7 items, physical environment - 7 items, safety and security - 3 items. Thus, a higher average value does not necessarily indicate a higher level of relative endorsement. CTQ: Childhood Trauma Questionnaire; QUIC: Questionnaire of Unpredictability in Childhood.

schools frequently”), and 5) safety and security (capturing unpredictability of food, resources, and safety in the home; e.g., “There was a period of time when I often worried that I was not going to have enough food to eat,” “There was a period of time when I did not feel safe in my home”). The QUIC demonstrates good to excellent internal consistency (Cronbach’s α 0.84–0.92; Glynn et al., 2019) and showed good internal consistency in this sample ($\omega = .87$).

2.3. Assessment of childhood trauma

The Childhood Trauma Questionnaire (CTQ) – Short Form is a 28-item self-report questionnaire divided into five subscales assessing exposure to neglect (physical and emotional) and abuse (emotional, physical, and sexual) during childhood. Responses are reported on a 5-point Likert-type scale (1: “never true”, 5: “very often true”). Example items include “People in my family hit me so hard that it left bruises or marks.” The CTQ demonstrates strong internal consistency, discriminant validity, and structural validity, although studies on test-retest reliability of the short form are more limited (Gerdner and Allgulander, 2009; Saini et al., 2019). A CTQ total score was calculated via summing the five subscale scores (Crow and Levy, 2019). The scale showed excellent internal consistency in this sample ($\omega = .95$).

2.4. Affective learning task

Blood-oxygen-level-dependent (BOLD) activity during extinction learning was assessed via fMRI as part of a broader affective learning task (Fig. 1). Geometric shapes of different colors served as the conditioned stimuli (CS), and an aversive metallic white noise (Neumann et al., 2008) delivered at 95–100 decibels served as the unconditioned stimulus (US). An acquisition phase (~6.5 min) was followed by a testing phase adapted from an AX+ /BX- task to assess conditioned inhibition via learned safety (two runs of ~7 min each; results reported in Kribakaran et al., 2022; Meyer et al., 2019; Odriozola et al., 2024). Next, participants completed the extinction learning phase (~4.5 min). During the extinction phase (the focus of these analyses), participants were presented with the former threat cue (former CS+, which was no longer paired with the US) and the safety cue (CS-, which was never paired with the US). Finally, in a reversal phase (~6.5 min), contingencies of the former threat and safety cues were reversed, such that the former safety cue was now reinforced by the US on 50 % of trials (yielding the new CS+), while the former threat cue remained unreinforced by the US (yielding a CS-). These phases were administered continuously during fMRI data collection.

2.5. Physiological data acquisition and analysis

To assess extinction learning, skin conductance data were collected during fMRI scanning with Biopac (<https://www.biopac.com/>) and recorded with AcqKnowledge software (<https://www.biopac.com/product/acqknowledge-software/>). Two independent raters visually inspected the data and excluded participants showing excessive motion or other data distortions. The data were then analyzed with the PsychoPhysiological Modeling MATLAB toolbox using a general linear model to produce reconstructed values (Bach and Friston, 2013). These reconstructed values served as the primary measure of extinction learning in this study. Participants were removed if they did not show sufficient learning during acquisition, lacked a sustained physiological response to the task, or had missing data due to acquisition issues, leaving a final subsample of $N = 29$ with skin conductance data. Additional information about data processing and exclusions is available in the Supplemental Materials.

2.6. fMRI acquisition, preprocessing, and analyses

fMRI data were collected during the affective learning task on a 3 T

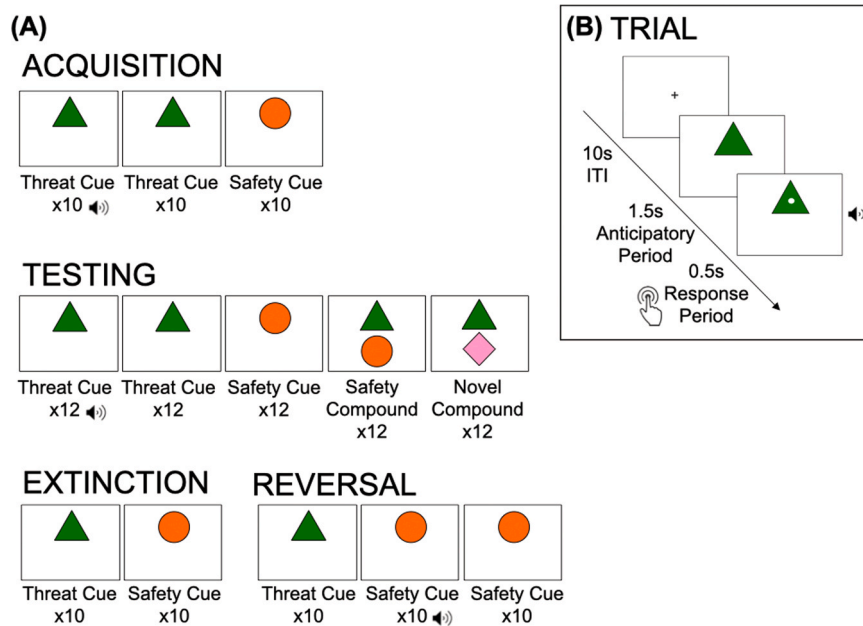


Fig. 1. Affective learning task design.

Note. A) During the acquisition phase, participants were shown two stimulus types: one shape was paired with an aversive sound (unconditioned stimulus [US]) on 50 % of the trials to yield a threat cue (conditioned stimulus [CS+]), and the other shape was not reinforced, yielding a safety cue (CS-). During the testing phase, participants were presented with a reinforced threat cue, unreinforced threat cue, safety cue, safety compound (threat and safety cues presented simultaneously), and novel compound (threat and novel cues presented simultaneously). Results from the testing phase are reported elsewhere (Kribakaran et al., 2022; Meyer et al., 2019; Odriozola et al., 2024). These analyses focus on the extinction phase, in which the former threat cue was not reinforced with the US (yielding a former CS+), and the former CS- continued to be unreinforced. Finally, in the reversal phase, the contingencies of the former threat and safety cues were reversed, such that the former safety cue was now reinforced by the US on 50 % of trials (yielding the new CS+), while the former threat cue remained unreinforced by the US (yielding a CS-). B) An example trial with timing information. ITI (intertrial interval): participants waited for 10 s between trials. Anticipatory period: the cue (e.g., threat, safety) was presented for 1.5 s. Response period: A dot was presented on the shape and participants were asked to press a button when they saw the dot. In reinforced trials, the US occurred during the response period. Figure reproduced from Odriozola et al. (2024).

Siemens Magnetom Prisma scanner. Preprocessing was conducted with the Human Connectome Project (HCP) minimal processing pipeline with the HCP Pipelines BIDS app (v 3.17.14). First-level analyses were conducted with the fMRI Expert Analysis Tool version 6.00 (FEAT), using FSL's Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL, fsl.fmrib.ox.ac.uk/fsl/) version 5.11. Stimulus event timings (i.e., the full two seconds combining the anticipatory and response periods for the former threat cue [CS+] and safety cue [CS-] conditions) were convolved with a double-gamma canonical hemodynamic response function, with temporal derivatives for each predictor as a confound term. Timeseries were high-pass filtered with a 90-s cutoff, estimated with the `cutoffcalc` function in FEAT, and prewhitened in FMRIB's Improved Linear Model (FILM). For further information about MRI acquisition, preprocessing, and analyses, see the [Supplemental Materials](#). ROIs were anatomically defined and included the bilateral dACC (Automated Anatomic Labeling Atlas 3; Rolls et al., 2020), bilateral anterior vmPFC (derived from Mackey and Petrides, 2014), bilateral anterior hippocampus (obtained from Hindy and Turk-Browne, 2016), and bilateral BLA (Juelich Histological Atlas; Amunts et al., 2005). To measure BOLD activity, mean percent signal change was extracted using these anatomical masks for each ROI and stimulus type (former CS+ and CS-). Regions of interest are shown in [Figure S1](#) of the [Supplemental Materials](#).

2.7. Analyses

Prior to analyses, outliers defined as > 3 standard deviations from the mean were removed for all adversity, clinical, physiological (SCR), and neuroimaging variables. This process resulted in the removal of two participants' datapoints for hippocampal activation and skin conductance to the former CS+, and one datapoint for each of the following

variables: BLA and dACC activation to the CS- and former CS+, hippocampal activation to the CS-, childhood unpredictability (QUIC), and childhood trauma (CTQ). Participants with an outlying datapoint on a given variable were only removed from analyses if that variable was present. Pearson correlations were conducted between variables of no interest (age, sex assigned at birth, scanner site) and variables of interest (BOLD activity, SCR). Gender identity was also collected but did not differ from sex assigned at birth in this sample. Only sex assigned at birth was significantly associated with the variables of interest and thus was included in subsequent analyses.

To test for changes in SCR and BOLD activity across early versus late extinction, linear mixed-effects models were conducted with the *nlme* package in RStudio (Pinheiro et al., 2023). First, to assess whether childhood unpredictability was associated with weaker fear extinction (Hypothesis 1), mixed-effects models were conducted predicting SCR to each stimulus type (former CS+ and CS-) during extinction, with fixed effects of childhood unpredictability (QUIC), stage (early versus late trials), their interactions, and sex assigned at birth, and a random intercept for subject. To test the relationship between unpredictability and BOLD activity in each ROI during extinction (vmPFC, dACC, hippocampus, BLA; Hypothesis 2), mixed-effects models were conducted predicting percent signal change for each ROI and stimulus type (former CS+ and CS-) versus the intertrial interval, with fixed effects of unpredictability, extinction stage, their interactions, and sex assigned at birth, and a random intercept for subject. Multiple comparisons correction was performed using Benjamini-Hochberg false-discovery rate correction to balance specificity and preservation of power (Benjamini and Hochberg, 1995; Singh and Dan, 2006). To determine whether childhood unpredictability was associated with altered neural function during extinction learning above and beyond childhood trauma exposure, a sensitivity analysis was performed with childhood trauma exposure (CTQ) added as

a covariate in all significant models. Finally, to better understand any significant associations between childhood unpredictability (QUIC total score) and a variable of interest, exploratory Pearson correlations were conducted between the outcome variable and each subscale of the QUIC. For these subscale analyses, Bonferroni correction was applied for multiple comparisons to be conservative given the exploratory nature of these analyses.

3. Results

3.1. Psychophysiology

A mixed-effects model showed no significant differences in skin conductance by extinction stage (early versus late trials) or stimulus type (former threat cue versus safety cue), $ps > .201$. Contrasting with Hypothesis 1 (greater childhood unpredictability will be associated with weaker decrease in SCR to the former threat cue in early but not late extinction), linear mixed-effects models revealed no significant effects of childhood unpredictability or its interactions with stage (early vs. late trials) on skin conductance to either stimulus (former threat cue, safety cue) during extinction, $ps > .429$. As a check of overall task efficacy, skin conductance data during extinction learning were visualized (Fig. 2). Participants showed nominally greater skin conductance during early trials of extinction, especially to the former threat cue, indicating threat-related physiological changes in the expected directions.

3.2. Functional activity

Linear mixed-effects models were conducted predicting functional activity to the former CS+ versus baseline for each ROI during extinction with childhood unpredictability, stage of extinction (early versus late trials), and their interactions, controlling for sex assigned at birth. Partially supporting Hypothesis 2 (childhood unpredictability will be associated with blunted vmPFC and hippocampal activity and greater dACC and BLA activity to the former threat cue during fear extinction, especially in early versus late trials), results showed a significant interaction between childhood unpredictability and stage of extinction predicting BLA activity, $t(41) = -3.16$, FDR-corrected $p = .012$. Post-hoc linear models revealed that higher childhood unpredictability was

associated with greater BLA activity to the former threat cue in early extinction, $t(41) = 3.07$, $p = .004$, but not late extinction, $t(40) = -1.78$, $p = .083$ (Fig. 3). Childhood unpredictability and its interactions with stage were not associated with altered activity of the vmPFC, dACC, or hippocampus to the former threat cue, FDR-corrected $ps > .707$, nor any ROI to the safety cue, FDR-corrected $ps > .390$.

3.3. Sensitivity analysis

Given evidence that childhood trauma may contribute to perceived environmental unpredictability and is associated with altered neural processing of threat (Hein and Monk, 2017; Maner et al., 2022), we tested whether unpredictability-related alterations in BLA activity during extinction remained significant even after accounting for childhood trauma. Thus, a mixed-effects model predicting BLA activity to the former threat cue versus the intertrial interval was conducted with childhood unpredictability, stage of extinction (early versus late trials), and their interactions, and childhood trauma and sex assigned at birth as covariates. Results revealed a significant interaction between childhood unpredictability and stage of extinction predicting BLA activity, $t(40) = -2.95$, $p = .005$, even when controlling for childhood trauma. Post-hoc linear models run separately by stage showed that when accounting for childhood trauma, unpredictability was differentially associated with greater BLA activity in early extinction, $t(39) = 2.61$, $p = .013$, but not late extinction, $t(38) = -1.82$, $p = .076$. Results also held when adding trait anxiety as a covariate (see Supplemental Materials), suggesting that these findings could not be explained by current anxiety symptoms.

3.4. Basolateral amygdala activity by childhood unpredictability type

As an exploratory follow-up analysis, we examined whether findings in the BLA were driven by exposure to unpredictability that was more proximal (e.g., unpredictable caregiving) versus more distal (e.g., socioeconomic factors or physical environment; Ugarte and Hastings, 2023). To this end, Pearson correlations were run between BLA activity and each subscale of the QUIC, applying Bonferroni correction for multiple comparisons (Bonferroni-corrected $\alpha = .01$). Of note, results of the safety/security subscale should be interpreted with caution due to low endorsement of these items. Only the parental unpredictability subscale—assessing the degree to which the child could predict caregivers' moods and behavior—was associated with heightened BLA activity during early extinction, $r(42) = .41$, $p = .005$ (Fig. 4). Associations between BLA activity and other aspects of caregiving (parental monitoring and involvement, which assesses predictability of caregiver routines; and parental environment, which captures predictability of parental jobs and relationships) did not survive Bonferroni correction, $ps > .015$. The subscales capturing distal unpredictability factors related to the physical environment (e.g., moving frequently) and safety/security (e.g., unpredictable family finances) were unrelated to BLA activity, $ps > .473$.

4. Discussion

This study was the first to our knowledge to investigate the effects of the predictability of the early life environment on neural function during extinction learning in human adults. While we did not find an effect of exposure to unpredictable environments in childhood on physiological markers of threat responding, or vmPFC, dACC, or hippocampal activity in extinction, the findings revealed an association between childhood unpredictability and BLA function during extinction, a region critically implicated in threat learning and detection (Barad et al., 2006; Öhman, 2005; Phelps and LeDoux, 2005). Specifically, we found that adults reporting more unpredictable childhood environments showed greater activity of the BLA in early (but not late) extinction, in line with hypotheses. Given evidence that BLA cellular activity and BOLD activity

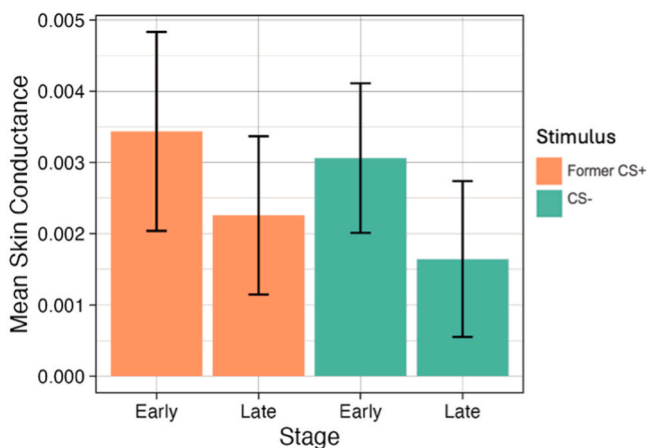


Fig. 2. Skin conductance response during extinction by task stage and stimulus type.

Note. Graph depicts mean skin conductance response during extinction separated by stimulus [former (i.e., extinguished) threat cue, safety cue] and by early versus late trials of extinction. There were no significant differences in skin conductance response by stimulus type or stage of extinction. Former (i.e., extinguished) CS+: Conditioned stimulus that was paired with threat during the acquisition phase but is not reinforced during extinction; CS-: Conditioned stimulus without threat.

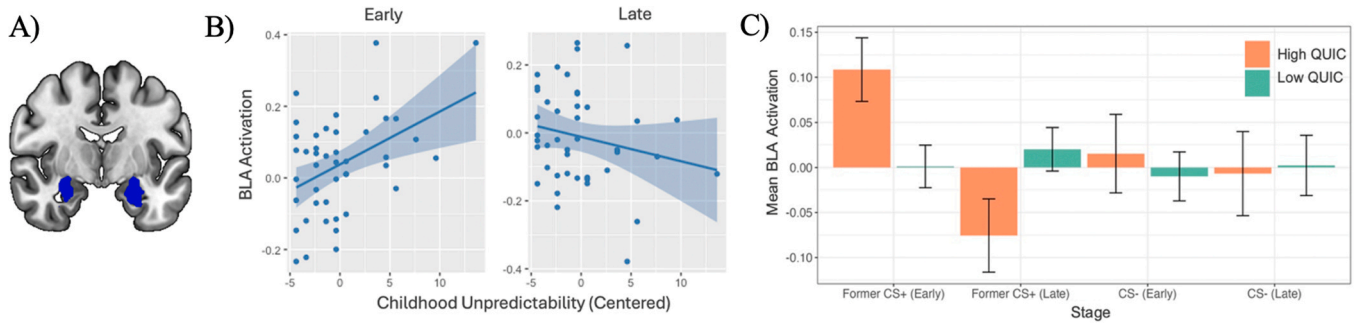


Fig. 3. Exposure to unpredictable early life environments is associated with greater BLA activity to the former threat cue during early versus late extinction. *Note.* A) Basolateral amygdala (bilateral) region of interest (Amunts et al., 2005); B) BLA activity to the former (i.e., extinguished) CS+ by childhood unpredictability and stage of extinction. Graph depicts a significant interaction between childhood unpredictability (QUIC) and stage (early versus late extinction) predicting BOLD activity (percent signal change to the former CS+ versus the intertrial interval) in the BLA, $t(41) = -3.16$, FDR-corrected $p = .012$. C) BLA activity by stimulus, stage of extinction, and childhood unpredictability. Graph depicts mean BOLD activation (percent signal change) for the BLA for each stimulus type (former CS+, CS-) during early and late extinction. Participants are divided into high and low childhood unpredictability groups via a median split for visualization purposes only (all analyses were conducted with childhood unpredictability as a continuous variable). BLA: Basolateral amygdala (bilateral); CS+: Conditioned stimulus with threat (aversive sound); CS-: Conditioned stimulus without threat; Former (i.e., extinguished) CS+: Conditioned stimulus that was paired with threat during the acquisition phase but is not reinforced during extinction; QUIC: Questionnaire of Unpredictability in Childhood.

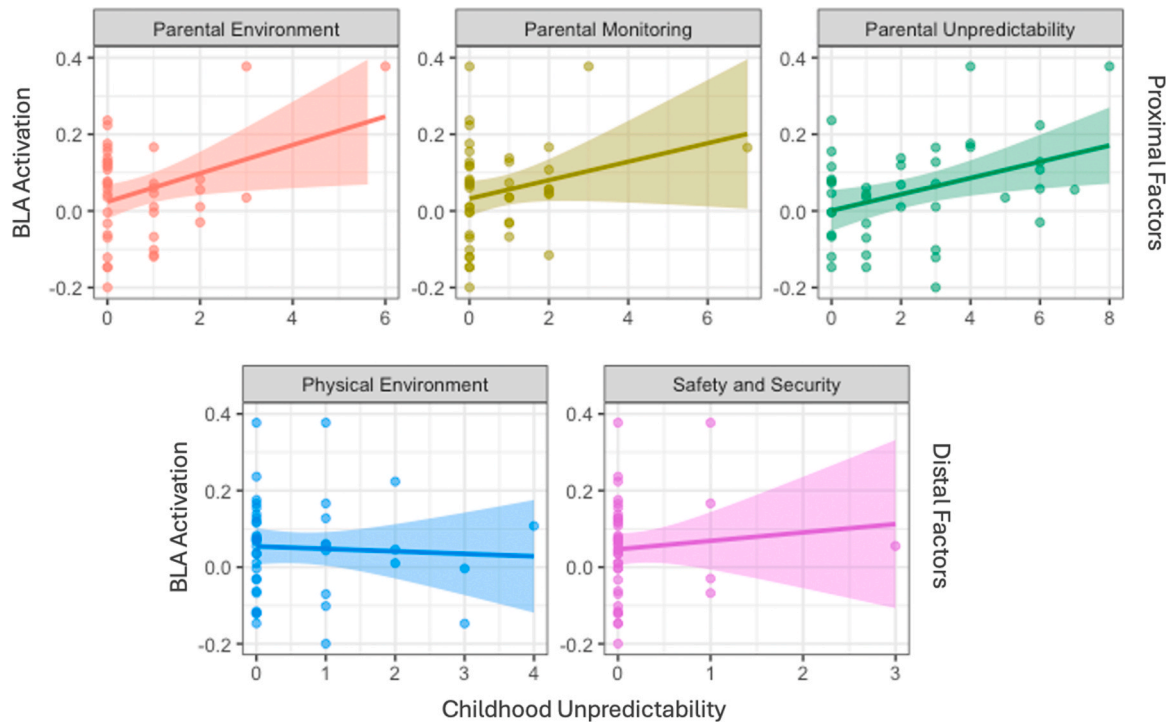


Fig. 4. BLA Activity to the former threat cue in early extinction by childhood unpredictability subscale. *Note.* Graphs depict associations between each subscale of the Questionnaire of Unpredictability in Childhood and BLA activity (percent signal change to former threat cue versus the intertrial interval) in early extinction. Higher parental unpredictability was associated with heightened BLA activity during early extinction, $r(42) = .41$, $p = .005$, which survived Bonferroni correction ($\alpha = .01$). Associations with parental environment ($r(42) = .36$, $p = .015$) and parental monitoring ($r(42) = .27$, $p = .074$) did not survive Bonferroni correction. Physical environment was unrelated to BLA activity, $r(42) = .010$, $p = .950$, as was safety and security, $r(42) = .11$, $p = .474$, although the truncated distribution of the safety and security items limits interpretation of this subscale in the current study. BLA: Basolateral amygdala (bilateral).

are correlated with the degree of threat conditioning and extinction learning (Barad et al., 2006; France et al., 2022), these results may reflect initially weaker extinguishing of neural reactivity to threat among adults exposed to greater unpredictability in early life. (We note that there was a pattern of childhood unpredictability associated with a possible decrease in amygdalar response to threat in later extinction trials, but this pattern was not significant so we have not interpreted it here.) The amygdala is thought to be involved in prediction error-driven computations and adjusting learning rates to volatility (Piray and Daw,

2021); current findings in early extinction could suggest that prolonged exposure to unpredictability in childhood may alter neural responsiveness to subsequent shifts in environmental contingencies (in this case, the shift of the CS+ from a threatening to neutral stimulus). Interestingly, we observed these associations between the childhood environment and amygdala function in a non-clinical sample of adults, suggesting that the early environment may exert effects on neural functioning that persist across the lifespan, even in adults without psychopathology. Indeed, the amygdala undergoes considerable postnatal

development and may be differentially vulnerable to environmental conditions in early life (Hein and Monk, 2017).

Importantly, childhood unpredictability was associated with altered amygdala activity in early extinction even when controlling for childhood trauma, suggesting that an unpredictable early environment may exert dissociable effects from other forms of adversity on the functioning of threat-related circuitry. This finding aligns with past research showing that early unpredictability is associated with altered cognitive development and increased risk of psychopathology into adulthood, beyond the effects of childhood maltreatment and other forms of early life adversity (Davis et al., 2017; Maner et al., 2022; Spadoni et al., 2022). Still, little research has previously disentangled the effects of unpredictability and trauma on neural functioning. It is particularly important to account for trauma exposure when examining amygdala function, as both childhood maltreatment and broader trauma exposure in adulthood have been reliably connected to amygdala hyperreactivity to affective cues across the lifespan (Hein and Monk, 2017; McCrory et al., 2011; Shin et al., 2004; Suarez-Jimenez et al., 2020). The current study shows that even after accounting for trauma, the predictability of a child's environment may exert separable effects on amygdala function during extinction in adulthood.

Exploratory analyses revealed a specific association between caregiver unpredictability and altered amygdala function, whereas more distal unpredictability factors such as unpredictability of the physical home and community were not related to amygdala function during extinction. These findings may have important implications for treatment, as the consistency of parental behavior and routines could be directly targeted through clinical interventions. Additionally, predictable caregiving may serve as a buffer between more distal forms of unpredictability and developmental outcomes (Ugarte and Hastings, 2023). Future studies should empirically examine the potential buffering role of predictable caregiving for children exposed to structural adversities to inform intervention. Further, distal unpredictability factors, such as housing insecurity, may directly increase the risk of unpredictable caregiving due to strain placed on families (Bess et al., 2023). Policies that increase access to stable housing, food, childcare, and other social programs could provide needed resources to boost the predictability of caregiving and of children's environments more broadly (Glynn et al., 2024).

Based on theoretical work suggesting that unpredictable threat exposure may increase expectations of threat and hinder safety learning (Kaye and Krystal, 2020; Wilkinson et al., 2017), we also hypothesized that childhood unpredictability would be associated with weaker extinguishing of fear responses assessed with skin conductance. Contrary to hypotheses, we did not find associations between environmental unpredictability and extinction learning. There are several possible explanations for these findings. First, given the small sample size for SCR analyses ($N = 29$), limited power may have contributed to these null results. Second, past research suggests a possible dissociation between SCR and amygdala activation during extinction. Specifically, Milad et al. (2009) found that people with PTSD exhibit greater amygdala activation during extinction (but not extinction recall), yet greater skin conductance during extinction recall (but not extinction). Thus, it is possible that amygdala activity and skin conductance may correlate with distinct components of threat and safety learning, or be differentially sensitive to environmental stressors. Third, the non-clinical nature of the current sample excluded participants with PTSD or anxiety disorders, who may have shown more exaggerated fear responses (Shvil et al., 2013). Even so, some research has shown that trauma-exposed individuals with PTSD show potentiated startle responses but not altered skin conductance (Glover et al., 2011); unpredictable childhood environments may exert similar effects on threat and extinction learning that would be better captured with other methods (e.g., acoustic startle).

The present study benefits from several key strengths. First, the study is the first to our knowledge to empirically investigate the association between the predictability of a child's environment and later extinction

learning. This research helps to bridge a gap between theoretical work, which proposes that chronic exposure to unpredictable stress alters later learning about threat and safety (Wilkinson et al., 2017), and empirical science. Second, this study is one of the first to probe the effects of early environmental unpredictability on the neural circuitry involved with threat processing, an important area of study given evidence that these regions are sensitive to the early environment (Hein and Monk, 2017). Third, these findings are an important step in disentangling the effects of environmental unpredictability and harshness (Ellis et al., 2009), allowing for a more specific examination of the differential effects of early life environmental unpredictability on neural development. Fourth, impaired extinction learning is widely used as a clinical endophenotype for anxiety disorders (Craske et al., 2018; Singewald and Holmes, 2019), and exposure to unpredictable early environments has been linked to later development of anxiety pathology (Spadoni et al., 2022). Future work in clinical samples could build on our findings to probe BLA function during extinction as a possible link between early unpredictability and anxiety disorders.

Despite these strengths, several important limitations should be considered. First, the SCR analyses relied on a smaller subset of the participants due to well-documented causes of missingness in skin conductance analyses (low SCR signal, technical issues, and/or failure to sustain threat learning; Kribakaran et al., 2022; Lonsdorf et al., 2017; Meyer et al., 2019). Second, although the final sample was larger than the median sample size for fMRI studies ($N = 45$ versus $N = 28.5$; Grady et al., 2020; Poldrack et al., 2017), the sample size was modest. Expanding this work into a larger sample with a range of psychopathology is indicated. The small sample also limits power to test for moderation by sex, an important consideration given prior evidence of sex-dependent associations between early unpredictability and mental health outcomes (Spadoni et al., 2022). Third, the study assessed participants' childhood environment via retrospective self-report measures. Reliance on self-report measures can increase risk of biased reporting, including both overreporting and hesitancy to disclose painful memories (McKinney et al., 2009; Rosenman et al., 2011). Still, self-report measures of childhood experiences, including trauma, have been shown to be quite stable across time and only marginally influenced by current mood state (Goltermann et al., 2023; Yancura and Aldwin, 2009). In fact, recent research indicates that subjective reports of childhood adversity are more predictive of psychopathology than objective measures (e.g., court records; Danese and Widom, 2021), highlighting the importance of *perceptions* of early life environment on outcomes. Finally, applying a measure that separately probes childhood unpredictability at different developmental stages (e.g., infancy, toddlerhood, childhood, adolescence) will be well-positioned to identify sensitive periods of neural development related to vulnerability to environmental unpredictability.

In sum, exposure to unpredictable environments in childhood is differentially associated with altered neural function during extinction into adulthood, over and above the effects of childhood trauma. Adults exposed to unpredictable early environments show heightened activity of the BLA during early extinction, possibly reflecting attenuated extinction of neural reactivity to threat. Further, these findings are specifically tied to unpredictable caregiving, rather than unpredictability of the physical environment. This research adds to a growing body of work implicating the predictability and consistency of caregiver signals in childhood on developmental trajectories (Davis et al., 2017; Glynn and Baram, 2019; Noroña-Zhou et al., 2020).

Childhood environments that are fragmented and unpredictable are distinct from other forms of early life adversity, such as poverty, abuse, or neglect, yet have received comparatively much less empirical attention. Future studies are indicated that investigate environmental unpredictability, extinction learning, and its neural correlates longitudinally to clarify the mechanisms through which environmental inconsistency alters the function of neural circuitry involved in threat processing and extinction learning. Future research should also expand

on these findings within clinical populations, especially in a sample with anxiety or trauma-related disorders such as PTSD, to determine whether altered amygdala responsiveness during extinction learning links early unpredictability with psychopathology. Crucially, caregiving predictability (e.g., the consistency of parental signals or behavior) is modifiable and could represent a key target for clinical intervention. In the future, this work may inform the development and refinement of interventions that promote consistent caregiving for children, with the goal of supporting healthy cognitive and neural development.

CRedit authorship contribution statement

Duda Jessica M.: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Keding Taylor J.:** Methodology, Data curation. **Kribakaran Sahana:** Methodology, Investigation, Data curation, Conceptualization. **Odrizola Paola:** Methodology, Investigation, Data curation, Conceptualization. **Kitt Elizabeth R.:** Investigation, Formal analysis, Data curation. **Cohodes Emily M.:** Methodology, Investigation, Conceptualization. **Zacharek Sadie J.:** Software, Investigation, Formal analysis. **McCauley Sarah:** Investigation, Data curation. **Haberman Jason T.:** Methodology, Investigation. **Joormann Jutta:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Gee Dylan G.:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Funding

This work was supported by a National Institutes of Health (NIH) Director's Early Independence Award (DP5OD021370) to D.G.G., Brain & Behavior Research Foundation (National Alliance for Research on Schizophrenia and Depression; NARSAD) Young Investigator Award to D.G.G., Jacobs Foundation Early Career Research Fellowship to D.G.G., National Science Foundation (NSF) CAREER Award (BCS-2145372) to D.G.G., NIMH National Research Service Award (NRSA; F30MH124271) to S.K., the National Science Foundation (NSF) Graduate Research Fellowship Program awards (DGE1122492) to P.O., a Scholar Award granted by the International Chapter of the Philanthropic Educational Organization (P.E.O. Foundation) to P.O., and the Society for Clinical Child and Adolescent Psychology (Division 53 of the American Psychological Association) Richard "Dick" Abidin Early Career Award and Grant to D.G.G.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank everyone who helped with project design, set-up, data collection, and data processing on this project. We gratefully acknowledge Dr. Tyrone D. Cannon for his helpful feedback about this work. We also thank Qingyang Ma for her assistance with literature reviews and interest in learning new imaging techniques.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.dcn.2025.101578](https://doi.org/10.1016/j.dcn.2025.101578).

Data Availability

Data will be made available on request.

References

- Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N.J., Habel, U., Schneider, F., Zilles, K., 2005. Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anat. Embryol.* 210 (5), 343–352. <https://doi.org/10.1007/s00429-005-0025-5>.
- Bach, D.R., Friston, K.J., 2013. Model-based analysis of skin conductance responses: Towards causal models in psychophysiology. *Psychophysiology* 50 (1), 15–22. <https://doi.org/10.1111/j.1469-8986.2012.01483.x>.
- Barad, M., Gean, P.-W., Lutz, B., 2006. The role of the amygdala in the extinction of conditioned fear. *Biol. Psychiatry* 60 (4), 322–328. <https://doi.org/10.1016/j.biopsych.2006.05.029>.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B* 57 (1), 289–300.
- Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluwalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl.* 27 (2), 169–190. [https://doi.org/10.1016/S0145-2134\(02\)00541-0](https://doi.org/10.1016/S0145-2134(02)00541-0).
- Bess, K.D., Miller, A.L., Mehdipani, R., 2023. The effects of housing insecurity on children's health: a scoping review. *Health Promot. Int.* 38 (3), daac006. <https://doi.org/10.1093/heapro/daac006>.
- Bloodgood, D.W., Sugam, J.A., Holmes, A., Kash, T.L., 2018. Fear extinction requires infralimbic cortex projections to the basolateral amygdala. *Transl. Psychiatry* 8 (1), 1–11. <https://doi.org/10.1038/s41398-018-0106-x>.
- Bolton, J.L., Molet, J., Regev, L., Chen, Y., Rismanchi, N., Haddad, E., Yang, D.Z., Obenaus, A., Baram, T.Z., 2018. Anhedonia following early-life adversity involves aberrant interaction of reward and anxiety circuits and is reversed by partial silencing of amygdala corticotropin-releasing hormone gene. *Biol. Psychiatry* 83 (2), 137–147. <https://doi.org/10.1016/j.biopsych.2017.08.023>.
- Brown, T., Barlow, D., 2014. Anxiety and related disorders interview schedule for DSM-5 (ADIS-5)-adult and lifetime version: Clinician Manual. Oxford University Press.
- Bukalo, O., Pinard, C.R., Silverstein, S., Brehm, C., Hartley, N.D., Whittle, N., Colacicco, G., Busch, E., Patel, S., Singewald, N., Holmes, A., 2015. Prefrontal inputs to the amygdala instruct fear extinction memory formation. *Sci. Adv.* 1 (6), e1500251. <https://doi.org/10.1126/sciadv.1500251>.
- Craske, M.G., Hermans, D., Vervliet, B., 2018. State-of-the-art and future directions for extinction as a translational model for fear and anxiety. *Philos. Trans. R. Soc. B: Biol. Sci.* 373 (1742), 20170025. <https://doi.org/10.1098/rstb.2017.0025>.
- Crow, T.M., Levy, K.N., 2019. Adult attachment anxiety moderates the relation between self-reported childhood maltreatment and borderline personality disorder features. *Personal. Ment. Health* 13 (4), 239–249. <https://doi.org/10.1002/PMH.1468>.
- Danese, A., Widom, C.S., 2021. The subjective experience of childhood maltreatment in psychopathology. *JAMA Psychiatry* 78 (12), 1307–1308. <https://doi.org/10.1001/jamapsychiatry.2021.2874>.
- Davis, E.P., Stout, S.A., Molet, J., Vegetabile, B., Glynn, L.M., Sandman, C.A., Heins, K., Stern, H., Baram, T.Z., 2017. Exposure to unpredictable maternal sensory signals influences cognitive development across species. *Proc. Natl. Acad. Sci.* 114 (39), 10390–10395. <https://doi.org/10.1073/pnas.1703444114>.
- Ellis, B.J., Figueredo, A.J., Brumbach, B.H., Schlomer, G.L., 2009. Fundamental dimensions of environmental risk. *Hum. Nat.* 20 (2), 204–268. <https://doi.org/10.1007/s12110-009-9063-7>.
- France, J.M., Reda, M., Marusak, H.A., Riser, M., Wiltshire, C.N., Davie, W.M., Grasser, L.R., Wanna, C.P., Stenson, A.F., Ely, T.D., Norrholm, S.D., Stevens, J.S., Jovanovic, T., 2022. Anxiety, fear extinction, and threat-related amygdala reactivity in children exposed to urban trauma. *J. Exp. Psychopathol.* 13 (4), 20438087221132501. <https://doi.org/10.1177/20438087221132501>.
- Fullana, M.A., Albajes-Eizaguirre, A., Soriano-Mas, C., Vervliet, B., Cardoner, N., Benet, O., Radua, J., Harrison, B.J., 2018. Fear extinction in the human brain: a meta-analysis of fMRI studies in healthy participants. *Neurosci. Biobehav. Rev.* 88, 16–25. <https://doi.org/10.1016/j.neubiorev.2018.03.002>.
- Garfinkel, S.N., Abelson, J.L., King, A.P., Sripada, R.K., Wang, X., Gaines, L.M., Liberzon, I., 2014. Impaired contextual modulation of memories in PTSD: an fMRI and psychophysiological study of extinction retention and fear renewal. *J. Neurosci.* 34 (40), 13435–13443. <https://doi.org/10.1523/JNEUROSCI.4287-13.2014>.
- Gee, D.G., 2021. Early adversity and development: parsing heterogeneity and identifying pathways of risk and resilience. *Am. J. Psychiatry* 178 (11), 998–1013. <https://doi.org/10.1176/appi.ajp.2021.21090944>.
- Gerdner, A., Allgulander, C., 2009. Psychometric properties of the Swedish version of the Childhood Trauma Questionnaire—Short Form (CTQ-SF). *Nord. J. Psychiatry* 63 (2), 160–170. <https://doi.org/10.1080/08039480802514366>.
- Glover, E.M., Phifer, J.E., Crain, D.F., Norrholm, S.D., Davis, M., Bradley, B., Ressler, K.J., Jovanovic, T., 2011. Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. *Depress Anxiety* 28 (12), 1058–1066. <https://doi.org/10.1002/da.20880>.
- Glynn, L.M., Baram, T.Z., 2019. The influence of unpredictable, fragmented parental signals on the developing brain. *Front. Neuroendocrinol.* 53. <https://doi.org/10.1016/j.yfrne.2019.01.002>.
- Glynn, L.M., Stern, H.S., Howland, M.A., Risbrough, V.B., Baker, D.G., Nievergelt, C.M., Baram, T.Z., Davis, E.P., 2019. Measuring novel antecedents of mental illness: the questionnaire of unpredictability in childhood. *Neuropsychopharmacology* 44 (5), 876. <https://doi.org/10.1038/S41386-018-0280-9>.
- Glynn, L.M., Liu, S.R., Lucas, C.T., Davis, E.P., 2024. Leveraging the science of early life predictability to inform policies promoting child health. *Dev. Cogn. Neurosci.* 69, 101437. <https://doi.org/10.1016/j.dcn.2024.101437>.

- Goltermann, J., Meinert, S., Hülsmann, C., Dohm, K., Grotegerd, D., Redlich, R., Waltemate, L., Lemke, H., Thiel, K., Mehler, D.M.A., Enneking, V., Borgers, T., Repple, J., Gruber, M., Winter, N., Hahn, T., Brosch, K., Meller, T., Ringwald, K.G., Dannlowski, U., 2023. Temporal stability and state-dependence of retrospective self-reports of childhood maltreatment in healthy and depressed adults. *Psychol. Assess.* 35 (1), 12–22. <https://doi.org/10.1037/pas0001175>.
- Grady, C.L., Rieck, J.R., Nichol, D., Rodrigue, K.M., Kennedy, K.M., 2020. Influence of sample size and analytic approach on stability and interpretation of brain-behavior correlations in task-related fMRI data. *Hum. Brain Mapp.* 42 (1), 204–219. <https://doi.org/10.1002/hbm.25217>.
- Granger, S.J., Glynn, L.M., Sandman, C.A., Small, S.L., Obenaus, A., Keator, D.B., Baram, T.Z., Stern, H., Yassa, M.A., Davis, E.P., 2021. Aberrant maturation of the uncinate fasciculus follows exposure to unpredictable patterns of maternal signals. *J. Neurosci.* 41 (6), 1242–1250. <https://doi.org/10.1523/JNEUROSCI.0374-20.2020>.
- Griffin, J.D., Fletcher, P.C., 2017. Predictive processing, source monitoring, and psychosis. *Annu. Rev. Clin. Psychol.* 13, 265–289. <https://doi.org/10.1146/annurev-clinpsy-032816-045145>.
- Handy, J.D., Avcu, P., Ko, N., Ortiz, A., Doria, M.J., Servatius, R.J., 2018. Facilitated acquisition of the classically conditioned eyeblink response in active duty military expressing posttraumatic stress disorder symptoms. *Behav. Brain Res.* 339, 106–113. <https://doi.org/10.1016/j.bbr.2017.11.014>.
- Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry* 49 (12), 1023–1039. [https://doi.org/10.1016/S0006-3223\(01\)01157-X](https://doi.org/10.1016/S0006-3223(01)01157-X).
- Hein, T.C., Monk, C.S., 2017. Research review: neural response to threat in children, adolescents, and adults after child maltreatment – a quantitative meta-analysis. *J. Child Psychol. Psychiatry* 58 (3), 222–230. <https://doi.org/10.1111/jcpp.12651>.
- Hindy, N.C., Turk-Browne, N.B., 2016. Action-based learning of multistate objects in the medial temporal lobe. *Cereb. Cortex* 26 (5), 1853–1865. <https://doi.org/10.1093/cercor/bhv030>.
- Jirsaraie, R.J., Palma, A.M., Small, S.L., Sandman, C.A., Davis, E.P., Baram, T.Z., Stern, H., Glynn, L.M., & Yassa, M.A. (2023). Prenatal exposure to maternal mood entropy is associated with a weakened and inflexible salience network in adolescence. *Biol. Psychiatry. Cognitive Neurosci. Neuroimaging*, S2451-9022(23)00215-X. (<https://doi.org/10.1016/j.bpsc.2023.08.002>).
- Johnson, F.K., Delphech, J.-C., Thompson, G.J., Wei, L., Hao, J., Herman, P., Hyder, F., Kaffman, A., 2018. Amygdala hyper-connectivity in a mouse model of unpredictable early life stress. *Transl. Psychiatry* 8 (1), 49. <https://doi.org/10.1038/s41398-018-0092-z>.
- Kaye, A.P., Krystal, J.H., 2020. Predictive processing in mental illness: hierarchical circuitry for perception and trauma. *J. Abnorm. Psychol.* 129 (6), 629–632. <https://doi.org/10.1037/ABN0000628>.
- Kleim, B., Ehring, T., Ehlers, A., 2012. Perceptual processing advantages for trauma-related visual cues in post-traumatic stress disorder. *Psychol. Med.* 42 (1), 173. <https://doi.org/10.1017/S0033291711001048>.
- Krabbe, S., Gründemann, J., Lüthi, A., 2018. Amygdala inhibitory circuits regulate associative fear conditioning. *Biol. Psychiatry* 83 (10), 800–809. <https://doi.org/10.1016/j.biopsych.2017.10.006>.
- Kribakaran, S., Odriozola, P., Cohodes, E.M., McCauley, S., Zacharek, S.J., Hodges, H.R., Haberman, J.T., Pierre, J.C., Gee, D.G., 2022. Neural circuitry involved in conditioned inhibition via safety signal learning is sensitive to trauma exposure. *Neurobiol. Stress* 21, 100497. <https://doi.org/10.1016/j.ynstr.2022.100497>.
- Kube, T., Berg, M., Kleim, B., Herzog, P., 2020. Rethinking post-traumatic stress disorder—a predictive processing perspective. *Neurosci. Biobehav. Rev.* 113, 448–460. <https://doi.org/10.1016/J.NEUBIOREV.2020.04.014>.
- Lebois, L.A.M., Seligowski, A.V., Wolff, J.D., Hill, S.B., Ressler, K.J., 2019. Augmentation of extinction and inhibitory learning in anxiety and trauma-related disorders. *Annu. Rev. Clin. Psychol.* 15, 257. <https://doi.org/10.1146/ANNUREV-CLINPSY-050718-095634>.
- Lonsdorf, T.B., Menz, M.M., Andreatta, M., Fullana, M.A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Römer, S., Shiban, Y., Schmitz, A., Straube, B., Merz, C.J., 2017. Don't fear "fear conditioning": Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neurosci. Biobehav. Rev.* 77, 247–285. <https://doi.org/10.1016/j.neubiorev.2017.02.026>.
- Mackey, S., Petrides, M., 2014. Architecture and morphology of the human ventromedial prefrontal cortex. *Eur. J. Neurosci.* 40 (5), 2777–2796. <https://doi.org/10.1111/ejn.12654>.
- Maner, J.K., Hasty, C.R., Martinez, J.L., Ehrlich, K.B., Gerend, M.A., 2022. The role of childhood unpredictability in adult health. *J. Behav. Med.* 1–12. <https://doi.org/10.1007/s10865-022-00373-8>.
- McCrory, E.J., Brito, S.A.D., Sebastian, C.L., Mechelli, A., Bird, G., Kelly, P.A., Viding, E., 2011. Heightened neural reactivity to threat in child victims of family violence. *Curr. Biol.* 21 (23), R947–R948. <https://doi.org/10.1016/j.cub.2011.10.015>.
- McKinney, C.M., Harris, T.R., Caetano, R., 2009. Reliability of self-reported childhood physical abuse by adults and factors predictive of inconsistent reporting. *Violence Vict.* 24 (5), 653. <https://doi.org/10.1891/0886-6708.24.5.653>.
- McLaughlin, K.A., Sheridan, M.A., Humphreys, K.L., Belsky, J., Ellis, B.J., 2021. The value of dimensional models of early experience: thinking clearly about concepts and categories. *Perspect. Psychol. Sci.* 16 (6), 1463–1472. <https://doi.org/10.1177/1745691621992346>.
- Meyer, H.C., Odriozola, P., Cohodes, E.M., Mandell, J.D., Li, A., Yang, R., Hall, B.S., Haberman, J.T., Zacharek, S.J., Liston, C., Lee, F.S., Gee, D.G., 2019. Ventral hippocampus interacts with prefrontal cortex during inhibition of threat response via learned safety in both mice and humans. *Proc. Natl. Acad. Sci.* 116 (52), 26970–26979. <https://doi.org/10.1073/pnas.1910481116>.
- Milad, M.R., Quirk, G.J., 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 420 (6911), 70–74. <https://doi.org/10.1038/nature01138>.
- Milad, M.R., Pitman, R.K., Ellis, C.B., Gold, A.L., Shin, L.M., Lasko, N.B., Zeidan, M.A., Handwerker, K., Orr, S.P., Rauch, S.L., 2009. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol. Psychiatry* 66 (12), 1075–1082. <https://doi.org/10.1016/J.BIOPSYCH.2009.06.026>.
- Milad, M.R., Rosenbaum, B.L., Simon, N.M., 2014. Neuroscience of fear extinction: implications for assessment and treatment of fear-based and anxiety related disorders. *Behav. Res. Ther.* 62, 17–23. <https://doi.org/10.1016/j.brat.2014.08.006>.
- Molet, J., Maras, P.M., Kinney-Lang, E., Harris, N.G., Rashid, F., Ivy, A.S., Solodkin, A., Obenaus, A., Baram, T.Z., 2016. MRI uncovers disrupted hippocampal microstructure that underlies memory impairments after early-life adversity. *Hippocampus* 26 (12), 1618–1632. <https://doi.org/10.1002/hipo.22661>.
- Neumann, D.L., Waters, A.M., Westbury, H.R., 2008. The use of an unpleasant sound as the unconditional stimulus in aversive Pavlovian conditioning experiments that involve children and adolescent participants. *Behav. Res. Methods* 40 (2), 622–625. <https://doi.org/10.3758/BRM.40.2.622>.
- Norona-Zhou, A.N., Morgan, A., Glynn, L.M., Sandman, C.A., Baram, T.Z., Stern, H.S., Davis, E.P., 2020. Unpredictable maternal behavior is associated with a blunted infant cortisol response. *Dev. Psychobiol.* 62 (6), 882–888. <https://doi.org/10.1002/dev.21964>.
- Odriozola, P., Kribakaran, S., Cohodes, E.M., Zacharek, S.J., McCauley, S., Haberman, J.T., Quintela, L.A., Hernandez, C., Spencer, H., Pruessner, L., Caballero, C., Gee, D.G., 2024. Hippocampal involvement in safety signal learning varies with anxiety among healthy adults. *Biol. Psychiatry Glob. Open Sci.* 4 (1), 155–164. <https://doi.org/10.1016/j.bpsgos.2023.05.007>.
- Öhman, A., 2005. The role of the amygdala in human fear: automatic detection of threat. *Psychoneuroendocrinology* 30 (10), 953–958. <https://doi.org/10.1016/j.psyneuen.2005.03.019>.
- Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron* 48 (2), 175–187. <https://doi.org/10.1016/j.neuron.2005.09.025>.
- Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E., 2004. Extinction learning in humans: role of the Amygdala and vmPFC. *Neuron* 43 (6), 897–905. <https://doi.org/10.1016/j.neuron.2004.08.042>.
- Pinheiro, J., Bates, D., & R. Core Team. (2023). nlme: Linear and Nonlinear Mixed Effects Models (Version R package version 3.1-162) [Computer software]. (<https://CRAN.R-project.org/package=nlme>).
- Piray, P., Daw, N.D., 2021. A model for learning based on the joint estimation of stochasticity and volatility. *Article 1 Nat. Commun.* 12 (1). <https://doi.org/10.1038/s41467-021-26731-9>.
- Poldrack, R.A., Baker, C.I., Durnez, J., Gorgolewski, K.J., Matthews, P.M., Munafò, M.R., Nichols, T.E., Poline, J.-B., Vul, E., Yarkoni, T., 2017. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat. Rev. Neurosci.* 18 (2), 115–126. <https://doi.org/10.1038/nrn.2016.167>.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59 (3), 2142–2154. <https://doi.org/10.1016/j.neuroimage.2011.10.018>.
- Rolls, E.T., Huang, C.-C., Lin, C.-P., Feng, J., Joliet, M., 2020. Automated anatomical labelling atlas 3. *NeuroImage* 206, 116189. <https://doi.org/10.1016/j.neuroimage.2019.116189>.
- Rosenman, R., Tennekoon, V., Hill, L.G., 2011. Measuring bias in self-reported data. *Int. J. Behav. Healthc. Res.* 2 (4), 320–332. <https://doi.org/10.1504/IJBHR.2011.043414>.
- Ross, L.T., Hood, C.O., Short, S.D., 2016. Unpredictability and symptoms of depression and anxiety. *J. Soc. Clin. Psychol.* 35 (5), 371–385. <https://doi.org/10.1521/jscp.2016.35.5.371>.
- Rougemon-Bücking, A., Linnman, C., Zeffiro, T.A., Zeidan, M.A., Lebron-Milad, K., Rodriguez-Romaguera, J., Rauch, S.L., Pitman, R.K., Milad, M.R., 2011. Altered processing of contextual information during fear extinction in PTSD: an fMRI study. *CNS Neurosci. Ther.* 17 (4), 227–236. <https://doi.org/10.1111/J.1755-5949.2010.00152.X>.
- Saini, S.M., Hoffmann, C.R., Pantelis, C., Everall, I.P., Bousman, C.A., 2019. Systematic review and critical appraisal of child abuse measurement instruments. *Psychiatry Res.* 272, 106–113. <https://doi.org/10.1016/J.PSYCHRES.2018.12.068>.
- Sheridan, M.A., McLaughlin, K.A., 2020. Neurodevelopmental mechanisms linking ACEs with psychopathology. *Adverse Childhood Experiences: Using Evidence to Advance Research, Practice, Policy, and Prevention.* Elsevier Academic Press, pp. 265–285. <https://doi.org/10.1016/B978-0-12-816065-7.00013-6>.
- Shin, L.M., Orr, S.P., Carson, M.A., Rauch, S.L., Macklin, M.L., Lasko, N.B., Peters, P.M., Metzger, L.J., Dougherty, D.D., Cannistraro, P.A., Alpert, N.M., Fischman, A.J., Pitman, R.K., 2004. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch. Gen. Psychiatry* 61 (2), 168–176. <https://doi.org/10.1001/archpsyc.61.2.168>.
- Shvil, E., Rusch, H.L., Sullivan, G.M., Neria, Y., 2013. Neural, psychophysiological, and behavioral markers of fear processing in PTSD: a review of the literature. *Curr. Psychiatry Rep.* 15 (5), 358. <https://doi.org/10.1007/s11920-013-0358-3>.
- Shvil, E., Sullivan, G.M., Schafer, S., Markowitz, J.C., Campeas, M., Wager, T.D., Milad, M.R., Neria, Y., 2014. Sex differences in extinction recall in posttraumatic stress disorder: a pilot fMRI study. *Neurobiol. Learn. Mem.* 113, 101–108. <https://doi.org/10.1016/j.nlm.2014.02.003>.

- Singewald, N., Holmes, A., 2019. Rodent models of impaired fear extinction. *Psychopharmacology* 236 (1), 21–32. <https://doi.org/10.1007/S00213-018-5054-X>.
- Singh, A.K., Dan, I., 2006. Exploring the false discovery rate in multichannel NIRS. *NeuroImage* 33 (2), 542–549. <https://doi.org/10.1016/j.neuroimage.2006.06.047>.
- Soltani, A., Izquierdo, A., 2019. Adaptive learning under expected and unexpected uncertainty. *Article 10 Nat. Rev. Neurosci.* 20 (10). <https://doi.org/10.1038/s41583-019-0180-y>.
- Spadoni, A.D., Vinograd, M., Cuccurazzu, B., Torres, K., Glynn, L.M., Davis, E.P., Baram, T.Z., Baker, D.G., Nievergelt, C.M., Risbrough, V.B., 2022. Contribution of early-life unpredictability to neuropsychiatric symptom patterns in adulthood. *Depress Anxiety* 39 (10–11), 706–717. <https://doi.org/10.1002/da.23277>.
- Sripada, R.K., Garfinkel, S.N., Liberzon, I., 2013. Avoidant symptoms in PTSD predict fear circuit activation during multimodal fear extinction. *Front. Hum. Neurosci.* 7, 672. <https://doi.org/10.3389/FNHUM.2013.00672/BIBTEX>.
- Suarez-Jimenez, B., Albajes-Eizaguirre, A., Lazarov, A., Zhu, X., Harrison, B.J., Radua, J., Neria, Y., Fullana, M.A., 2020. Neural signatures of conditioning, extinction learning, and extinction recall in posttraumatic stress disorder: a meta-analysis of functional magnetic resonance imaging studies. *Psychol. Med.* 50 (9), 1442–1451. <https://doi.org/10.1017/S0033291719001387>.
- Tottenham, N., 2014. The importance of early experiences for neuro-affective development. *Curr. Top. Behav. Neurosci.* 16, 109. https://doi.org/10.1007/7854_2013_254.
- Ugarte, E., Hastings, P.D., 2023. Assessing unpredictability in caregiver–child relationships: Insights from theoretical and empirical perspectives. *Dev. Psychopathol.* 1–20. <https://doi.org/10.1017/S0954579423000305>.
- VanElzakker, M.B., Kathryn Dahlgren, M., Caroline Davis, F., Dubois, S., Shin, L.M., 2014. From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and anxiety disorders. *Neurobiol. Learn. Mem.* 113, 3–18. <https://doi.org/10.1016/J.NLM.2013.11.014>.
- Wang, Z., Cao, X., Zheng, X., Chen, Y., Zhu, J., 2023. Abnormalities in brain structure following childhood unpredictability: A mechanism underlying depressive and anxiety symptoms. *Psychol. Med.* 1–9. <https://doi.org/10.1017/S0033291723001526>.
- Weissman, D.G., Rosen, M.L., Colich, N.L., Sambrook, K.A., Lengua, L.J., Sheridan, M.A., McLaughlin, K.A., 2022. Exposure to violence as an environmental pathway linking low socioeconomic status with altered neural processing of threat and adolescent psychopathology. *J. Cogn. Neurosci.* 34 (10), 1892–1905. https://doi.org/10.1162/jocn_a_01825.
- Wilkinson, S., Dodgson, G., Meares, K., 2017. Predictive processing and the varieties of psychological trauma. *Front. Psychol.* 8, 1840. <https://doi.org/10.3389/FPSYG.2017.01840/BIBTEX>.
- Yancura, L.A., Aldwin, C.M., 2009. Stability and change in retrospective reports of childhood experiences over a 5-year period: findings from the davis longitudinal study. *Psychol. Aging* 24, 715–721. <https://doi.org/10.1037/a0016203>.