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Major stress in early childhood strengthens the association between peripheral inflammatory activity and corticostriatal responsivity to reward

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ABSTRACT

Background: Severe, chronic stress during childhood accentuates vulnerability to mental and physical health problems across the lifespan. To explain this phenomenon, the neuroimmune network hypothesis proposes that childhood stressors amplify signaling between peripheral inflammatory cells and developing brain circuits that support processing of rewards and threats. Here, we conducted a preliminary test of the basic premises of this hypothesis.

Methods: 180 adolescents (mean age = 19.1 years; 68.9 % female) with diverse racial and ethnic identities (56.1 % White; 28.3 % Hispanic; 26.1 % Asian) participated. The Childhood Trauma Interview was administered to quantify early adversity. Five inflammatory biomarkers were assayed in antecubital blood — C-reactive protein, tumor necrosis factor-a, and interleukins-6, −8, and −10 — and were averaged to form a composite score. Participants also completed a functional MRI task to measure corticostriatal responsivity to the anticipation and acquisition of monetary rewards.

Results: Stress exposure and corticostriatal responsivity interacted statistically to predict the inflammation composite. Among participants who experienced major stressors in the first decade of life, higher inflammatory activity covaried with lower corticostriatal responsivity during acquisition of monetary rewards. This relationship was specific to participants who experienced major stress in early childhood, implying a sensitive period for exposure, and were evident in both the orbitofrontal cortex and the ventral striatum, suggesting the broad involvement of corticostriatal regions. The findings were independent of participants' age, sex, racial and ethnic identity, family income, and depressive symptoms.

Conclusions: Collectively, the results are consistent with hypotheses suggesting that major stress in childhood alters brain-immune signaling.

1. Introduction

Over the last twenty years, research has yielded increasingly robust evidence that severe, chronic stress during childhood accentuates vulnerability to mental and physical health problems across the lifespan (Miller et al., 2011). This phenomenon has been documented in experimental studies of animals (Kruschinski et al., 2008; Avitsur et al., 2006; Andersson et al., 2009; Barr et al., 2009; Peña et al., 2017), tightly controlled prospective analyses of humans (Chandan et al., 2020; McLaughlin et al., 2012; Montez & Hayward, 2014; Murphy et al., 2017; van den Berg et al., 2011), and quasi-experimental analyses of policy shifts (Aizer et al., 2016; Costello et al., 2010). The convergence of evidence across these approaches supports the conclusion that childhood stress, when severe and chronic, can have a causal influence on health

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outcomes. This risk is particularly apparent for mood disorders, post-traumatic stress disorder, and cardiometabolic diseases (Danese et al., 2017; Suglia et al., 2018; Teicher et al., 2021).

These observations have generated interest in elucidating mechanisms that connect childhood stress to subsequent illness. However, formulating a viable mechanistic account of this phenomenon has proven challenging, because a successful model must answer two difficult questions. How does childhood stress elevate risk for such a broad array of seemingly unrelated health problems? And how do these risks unfold over the (often) lengthy incubation period that separates exposure and disease? To address these questions, the neuroimmune network (NIN) hypothesis (Nusslock & Miller, 2015) draws upon preclinical and translational evidence showing that even under normal conditions, brain circuits involved in emotion generation and regulation are engaged in bidirectional communication with peripheral immune cells that mediate inflammation (Miller & Raison, 2016; Schiller et al., 2021; Weber et al., 2017; Haroon et al., 2012; Weber et al., 2017). The framework goes on to suggest that major childhood stressors accentuate this communication by initiating positive feedback loops between periphery inflammatory activity and brain circuitries involved in threat and reward processing. As a consequence of this enhanced communication, stress-exposed children are presumed to display a sustained brain-immune phenotype, marked by low-grade inflammatory activity, heightened threat responsivity, and dampened reward processing. Together, these features are thought to contribute to mental and physical health problems across the lifespan.

There is considerable preclinical and translational evidence to support the constituent propositions of the NIN hypothesis (Eisenberger et al., 2017; Miller & Raison, 2016; Schiller et al., 2021; Weber et al., 2017; Chiang et al., 2022; Haroon et al., 2012; McLaughlin et al., 2019; Weber et al., 2017). However, most of the evidence in humans is from studies connecting stress with either brain development or inflammatory activity, but not both. In fact, just a handful of studies have considered the relationships amongst all three constructs (Chat et al., 2022; Kraynak et al., 2019; Miller et al., 2021). One study of midlife adults found that childhood physical abuse was associated with more low-grade inflammation in adulthood, which in turn was associated with lower functional connectivity of corticolimbic brain regions (Kraynak et al., 2019). While this paper did not report behavioral outcomes, lower connectivity of these regions would presumably manifest in higher threat responsivity. Another study considered a key assumption of the NIN framework, that the strength of the relationship between inflammatory activity and brain responsivity would vary with stress exposure. Consistent with this hypothesis, it observed that among children living in poverty, low-grade inflammation was related to more amygdala responsivity to threatening facial expressions, and more ventral striatal (VS) responsivity to monetary rewards (Miller et al., 2021). The strength of these associations declined as children's socioeconomic conditions improved.

These findings raise several questions. First, the available studies consider specific kinds of adversity, including poverty, maltreatment, and neighborhood violence. This is a sensible approach given these stressors' high prevalence and health implications (Koball et al., 2020; Wildeman et al., 2014). However, children experience other severe chronic stressors – e.g., parental loss – and it remains unclear whether these adversities also moderate the relationship between inflammatory activity and brain responsivity to threat and/or reward. Second, extant studies provide limited insights about developmental timing, and whether sensitive periods exist during which stressors are more likely to strengthen these relationships. Stressors in early childhood, relative to the middle and later stages, seem to have the more durable consequences for many subsequent neural and immune functions (Miller et al., 2011; Boyce et al., 2021; Tottenham & Galván, 2016). However, the nervous and immune systems both evolved to "learn" from experience, and continue to do so across the lifespan, implying that later stress could also amplify their communication.

Finally, the study of children yielded a surprising finding for reward - among those living in poverty, inflammation was *positively* associated with VS responsivity (Miller et al., 2021). This pattern runs counter to evidence from experimental paradigms indicating that inflammation blunts reward seeking and sensitivity (Eisenberger et al., 2010; Capuron et al., 2012; Draper et al., 2018). To explain the inconsistency, the authors drew on theory (Eisenberger et al., 2017; Inagaki et al., 2015) suggesting that inflammation's consequences for VS responsivity is context-dependent. In situations where a reward is highly salient for well-being and/or safety - as money would be for low-income youth - inflammation is thought to increase VS activity in a manner that facilitates approach behavior. However, in settings where that reward is not salient, inflammation has the opposite effect, reducing VS activity and inhibiting approach behavior. Presumably, this tendency would have been adaptive in ancestral settings, increasing the likelihood that people with infections and injuries navigated towards stimuli that facilitated recovery, and away from those which did not.

Here, we further consider the context-dependence scenario, assessing history of major stress, inflammatory activity, and responsivity to monetary reward in a relatively affluent sample. Expanding on previous work, we use a task that differentiates between anticipation and consumption of a reward, and that quantifies involvement of both cortical and subcortical brain regions. Although many brain regions respond to rewards, the VS and orbitofrontal cortex (OFC) are key. In broad terms, the VS assesses the hedonic value of stimuli, and the OFC integrates this judgment with competing goals, motivations, and desires (Berridge et al., 2009; Haber & Knutson, 2010). Drawing on the NIN framework, we predicted that (1) inflammation would be inversely associated with corticostriatal responsivity to reward and (2) this relationship would be strongest among participants with a history of major stressors. We also hypothesized that stressors experienced during earlier stages of childhood would moderate these brain-immune associations more strongly than stressors experienced later.

2. Methods

2.1. Participants

The Brain, Motivation, and Personality Development (BrainMAPD) study investigated risk for depression and anxiety in late adolescence and early adulthood (Young et al., 2021). It was performed at two sites, Northwestern University in Evanston, Illinois and the University of California, Los Angeles (UCLA). The Institutional Review Boards of both universities approved the protocol. Participants were 272 individuals (183 female, mean age = 19.16 years, SD = 0.52), all of whom gave written informed consent. They were selected from a larger screening sample of 2461 individuals to represent a broad range of scores on self-reported threat and reward sensitivity (details on Online Supplement). Exclusion criteria were lack of right-handed dominance, not fluent in English, traumatic brain injury, MRI contraindications, pregnancy, color blindness, lifetime psychotic symptoms or bipolar I disorder, clinically significant substance use disorder in past 6 months, and antipsychotic medications.

Complete data were available from 209 participants. We subsequently excluded 29 participants because of technical difficulties (n = 17) or excessive motion (n = 12) during fMRI, leaving a sample of 180. Included and excluded participants were similar on self-identified racial identity (p's = 0.29-0.54), family income (p =.78) and major early stressors (p =.32). However, included participants were 0.2 years older (p =.08) and more likely to have experienced major stressor in later childhood (56 % vs. 44 %; p =.10).

2.2. Major life stressors

To quantify major childhood stressors, research assistants administered the Childhood Trauma Interview (Fink et al., 1995). Before

starting all of the research assistants underwent extensive training, during which they achieved high levels of reliability with experienced judges, using a set of gold-standard interviews from earlier projects. The interview covered 6 stressor domains - caregiver separations/losses/neglect; emotional, physical, and sexual abuse; and witnessing violence. For each stressor, interviewers rate severity from 1 (minimal or mild) to 6 (very extreme or sadistic). Following earlier methodological analyses of the CTI (Vrshek-Schallhorn et al., 2014), stressors were categorized as minor (rating of 1–2) or major (rating of 3–6), and occurring in earlier (ages 0–8) or later (ages 9–18) stages of childhood.

The distribution of stressors was zero-inflated and right-skewed. In early childhood, 58.9 % of the sample had 0 major stressors, and 30.0 % had 1–2. During later childhood, the parallel values were 43.9 % and 41.1 %. Given these distributions, we computed binary variables reflecting any exposure to major stressors during each period. Although this approach precluded modeling graded effects of stress, it was preferable to mis-estimating effects for the small number of cases with multiple stressors. Nonetheless, we ran sensitivity analyses with alternative versions of these variables.

2.3. Monetary incentive delay task

Participants completed two runs of the Monetary Incentive Delay (MID) task (Samanez-Larkin et al., 2007) (**Figure S1**). First, a circle cue signaling a reward trial (participant might Win $0.00, Win $1.50, or Win $5.00) or a square cue indicating a loss trial (participant might Lose $0.00, Lose $1.50, or Lose $5.00) was presented for 2 s. Then, a jittered fixation was presented followed by a solid white square. Participants were instructed to make a button response when the solid white square was still on the screen to either win money (reward trials) or avoid losing money (loss trials). Feedback detailing the amount of money won or lost was given for 2 s on each trial. Finally, a jittered fixation cross was presented for 2 s, 4 s, or 6 s as an intertrial interval. The initial target duration was calculated from each participant's mean hit reaction time on a practice run. The target duration then dynamically updated to maintain difficulty, so participants accurately hit the target on 66 % of trials. Each of the six trial types was presented 16 times in random order, totaling 96 trials, across two runs.

2.4. MRI acquisition and preprocessing

Data were acquired using a Siemens Prisma 3.0 T MRI scanner with a 64-channel head coil. Identical scanners and sequences were used at the two sites. Structural 3D axial MPRAGE images were acquired (0.8 mm thick; TR = 2300 ms; TE = 3.03 ms; FOV = 256x256; Matrix = 160x160; Flip Angle = 7∘; 192 slices). Functional runs utilized a gradient echo EPI sequence covering 64 axial slices (2.0 mm thick; TR = 2050 ms; TE = 25 ms; FOV = 208x208mm; Matrix = 104x104; Flip Angle = 76∘; Multiband acceleration Factor = 2). Functional data were first assessed for outlier volumes (75th percentile + 1.5 time interquartile range) based on framewise displacement [average of rotation and translation parameter differences, using weighted scaling (Power et al., 2012) as implemented in the fslmotionoutliers function]. Participant data with either run exceeding 10 % outliers were not included in group analyses. Outlier volumes were censored in first level analyses by including a regressor with a single time point corresponding to each outlying volume. fMRI data were processed with FEAT (FMRI Expert Analysis Tool) Version 6.00nusing standard procedures. Participants with > 10 % outlier volumes in either run, as identified by the fslmotionoutliers function, were excluded (additional details in Online Supplement).

Regressors of interest for the anticipation phase included: win $0.00, win $1.50, win $5.00, lose $0.00, lose $1.50, lose $5.00. Regressors of interest for the outcome phase included: gain (hit: win $1.50, win $5.00), nongain (miss: win $1.50, win $5.00), loss (miss: lose $1.50, lose $5.00), and nonloss (hit: lose $1.50, lose $5.00). Regressors of noninterest included: neural activation to the target, temporal derivatives, six motion regressors, and regressors to censor outlying volumes. Anticipation was the period after participants saw the cue signifying the possibility to win or lose money but had not yet responded to the target square (2 s). The outcome phase was the period after participants received feedback indicating whether they won or lost money for that trial (2 s). The target was the onset of the solid white square where participants were instructed to make a button response, followed by 2 s. First-level voxel-wise *z*-statistics were generated for each participant, contrasting anticipation of reward (i.e., Win $0.50, Win $5.00) vs non-reward (i.e., Win $0.00), anticipation of loss (i.e., Lose $0.50, Lose $5.00) vs non-loss (i.e., Lose $0.00), outcome of gain vs no-gain, and outcome of loss vs no-loss (Samanez-Larkin et al., 2007).

For analyses, we extracted separate parameter estimates reflecting neural activation during the anticipation and outcome periods. Guided by a recent *meta*-analysis (Oldham et al., 2018), we generated 8 mm spheres around peak activation coordinates in the left and right VS for the anticipation and outcome periods. We then took the average activation across these spheres to compute a separate bilateral VS region-of-interest (ROI) for each period. OFC analyses focused exclusively on the outcome period, as this region is not activated during anticipation (Oldham et al., 2018). We averaged activation across three 8 mm spheres to compute a single OFC ROI for the outcome period (Fig. 1).

2.5. Low-Grade inflammation

Serum harvested from antecubital venipuncture was assayed for five biomarkers of low-grade inflammation: C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin10 (IL-10), and tumor necrosis factor-α (TNF-α). CRP was measured by high-sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer. The average intra- and inter-assay coefficients of variation were 2.5 % and 5.6 %. The cytokines were measured in duplicate by electrochemiluminescence on a SECTOR Imager 2400A (MesoScale Discovery) with a Human Pro-Inflammatory 4-Plex Ultra-Sensitive assay (MesoScale Discovery; (Fu et al., 2010). Intra-assay coefficients of variation ranged from 3.02 % (IL-6) to 4.22 % (IL-10) and inter-assay coefficients from 5.84 % (TNF-α) to 8.53 % (IL-8).

Most biomarkers were skewed and/or kurtotic, so we normalized their distributions by natural-log transformation. We then standardized these values (mean = 0; SD = 1), and averaged the *z*-scores into a composite (Cronbach's α = 0.57) with higher scores reflecting more inflammation. The composite has two advantages: Conceptually, it reflects the integrated nature of inflammation, entailing multiple signaling molecules, and statistically it substantially reduces the frequency of false-positive results. A confirmatory factor analysis of this single-factor model provided good fit (CFI = 0.98, RMSEA = 0.04, SRMR = 0.032) and, in sensitivity analyses we used a latent variable derived from it to consider alternative definitions of inflammation.

2.6. Depression as alternative explanation

To evaluate depression's role, we estimated secondary models with covariates reflecting participants' self-reports of the intensity of current symptoms (from the Inventory to Diagnose Depression; (Zimmerman & Coryell, 1987), and current psychotropic medication use (yes/no). We considered using diagnoses from the Structured Clinical Interview for DSM-V, but decided against it because only 6 participants had a current depressive episode.

2.7. Statistical approach

Hypotheses were tested in linear regression equations, using Model 1 of PROCESS v3.4 (Hayes, 2018) in SPSS 28.0. The outcome was the inflammation composite. All of the models included a set of demographic covariates that have established association with childhood adversity, brain development, and inflammatory activity (Chiang et al.,

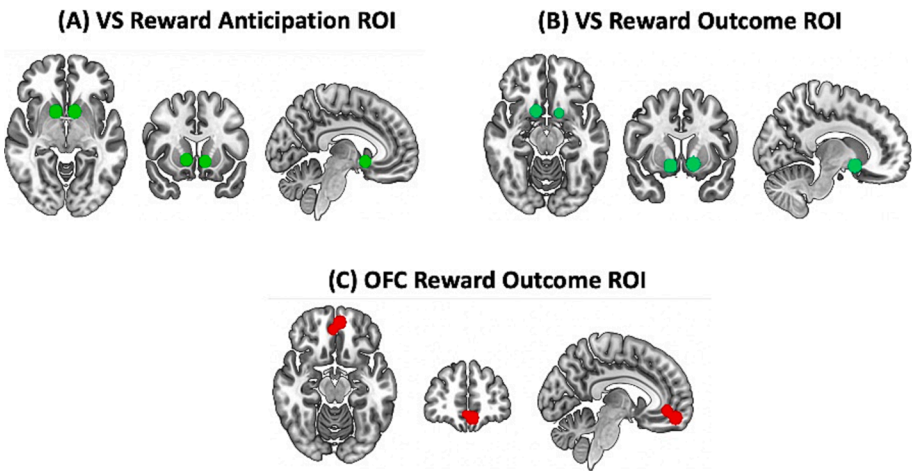

Fig. 1. Ventral striatum (VS) and orbitofrontal cortex (OFC) regions-of-interests. The VS region-of-interest (ROI) used in analyses of the anticipation (panel A) and outcome (panel B) phases of the Monetary Incentive Delay Task. The OFC ROI used in analyses of the outcome phase (panel C). For the VS, we averaged activation across the left and right spheres to form separate bilateral ROIs for the anticipation and outcome periods. For the OFC, we averaged activation across the three spheres in the orbitofrontal cortex to form a single ROI for the outcome phase. OFC analyses focused exclusively on the outcome period because it is not reliably activated during reward anticipation (Oldham et al., 2018).

2022; McLaughlin et al., 2019). They were site, age, sex, racial and ethnic identity, and participant reports of annual family income. By adjusting for these covariates, we reduce the chances that any associations observed reflect their influence, rather than the predictors of interest. Each model also contained predictors reflecting major life stress (explicitly modeled as a binary variable), corticostriatal responsivity, and a product term reflecting these variables' interaction. The NIN hypothesis stipulates that in such a model, a statistical interaction should emerge, where major stress increases the strength of the association between inflammatory activity and corticostriatal responsivity. All *p* values are based on two-tailed tests.

3. Results

Table 1 describes the sample. The majority self-identified as female (68.9 %) and White (56.1 %), although a substantial proportion endorsed Asian race (26.1 %) and/or Hispanic (28.3 %) ethnicity. On the whole, the sample was fairly affluent, with 48.3 % reporting annual household income above $100,000. A substantial proportion reported experiencing major stress during early (ages 0–9; 41.1 %) and later (9–18; 56.1 %) childhood. In bivariate analyses, early stress was unrelated to corticostriatal responsivity during both phases of the fMRI task (*p*'s = 0.17-0.82). Later stress exposure was associated with higher OFC responsivity during the reward outcome phase, $F(1,179) = 4.40$, $p = .03$), but not with VS responsivity during either phase (*p*'s = 0.57-0.81). Depressive symptoms were generally mild and only 3.3 % had a current depressive episode.

3.1. Early childhood stress

Table 2 shows conditional regression models for early childhood stress, separately for each of the 3 ROIs of corticostriatal responsivity (VS Reward Anticipation, VS Reward Outcome, OFC Reward Outcome). In all models, White participants had higher inflammation scores compared with Black (by 0.46 to 0.51 SD units) and Asian (by 0.35 to 0.39 SD units) participants. The White and Hispanic-identifying participants had similar inflammation scores. Inflammation was higher among participants who had experienced major early adversity (by 0.15 to 0.17 SD units) relative to those who had not. None of the other covariates was related to inflammation.

As predicted, there were significant interactions between early stress and corticostriatal responsivity. These interactions were evident for both OFC ($p = .01$; $\Delta R^2 = 0.03$) and VS ($p = .03$; $\Delta R^2 = 0.02$) responsivity during the reward outcome phase, but not the VS responsivity during anticipation ($p = .77$; $\Delta R^2 = 0.0004$). To decipher the interactions, we stratified the sample by early stress, then plotted the simple slopes (Fig. 2). As hypothesized, corticostriatal responsivity was inversely associated with inflammation scores among participants who had experienced major early stress. Specifically, each 1 SD increase in OFC responsivity during the outcome phase was associated with a 0.34 SD lower inflammation score (95 % CI = -0.62,-0.06, $p = .02$). The parallel figure for VS responsivity was 0.51 SD (95 % CI = -0.92,-0.10, $p = .02$). However, among participants without early stress, the slopes relating corticostriatal responsivity to inflammation were not significantly

Table 1
Characteristics of the analytic sample ($n = 180$).

Characteristic	Number	Percent	Mean	SD
Age, years			19.15	0.51
Self-identified sex, female	124	68.89		
Self-identified race, White	101	56.11		
Self-identified race, Asian	47	26.11		
Self-identified race, Black	14	7.78		
Self-identified race, multiracial	15	8.33		
Self-identified ethnicity, Hispanic (any race)	51	28.33		
Annual family income < $49,999	49	27.22		
Annual family income $50,000 - $99,999	44	24.44		
Annual family income > $100,000	87	48.33		
Inventory to Diagnose Depression (0–32)			4.62	4.21
Psychotropic medication	16	8.89		
Current major depression	6	3.33		
Major stressor - early (ages 0–8)	74	41.11		
Major stressor - later (ages 9–18)	101	56.11		
Ventral striatum response - reward anticipation			0.42	0.33
Orbitofrontal cortex response - monetary reward			0.35	0.39
Ventral striatum response - monetary reward			0.31	0.29
Low-grade Inflammation composite			0.00	0.52
C-reactive protein (mg/L)			1.83	2.89
Interleukin-6 (pg/mL)			0.94	0.90
Interleukin-8 (pg/mL)			7.02	2.96
Interleukin-10 (pg/mL)			1.87	3.28
Tumor necrosis factor-α (pg/mL)			4.07	0.93

Table 2
Results of conditional regression models testing neuroimmune network hypothesis, with low-grade inflammation as outcome ($n = 180$).

	Model 1: VS Reward Anticipation			Model 2: OFC Reward Outcome			Model 3: VS Reward Outcome		
	B	95 % CI	p	B	95 % CI	p	B	95 % CI	p
Site (Northwestern)	0.12	−0.03, +0.27	0.11	0.12	−0.03, +0.27	0.11	0.11	−0.04, +0.26	0.17
Age (years)	0.00	−0.14, +0.15	0.92	0.02	−0.13, +0.16	0.82	0.05	−0.10, +0.21	0.49
Sex (female)	0.07	−0.08, +0.23	0.36	0.07	−0.08, +0.23	0.36	0.06	−0.10, +0.20	0.47
Race (Multi-racial)	0.13	−0.14, +0.40	0.34	0.13	−0.14, +0.40	0.34	0.17	−0.10, +0.44	0.22
Race (Asian)	−0.38	−0.60, −0.20	0.0001	−0.35	−0.53, −0.18	0.0001	−0.39	−0.57, −0.21	0.0001
Race (Black)	−0.49	−0.77, −0.21	0.0007	−0.46	−0.74, −0.18	0.001	−0.51	−0.79, −0.24	0.0004
Ethnicity (Hispanic)	−0.06	−0.23, +0.12	0.54	−0.06	−0.23, +0.11	0.49	−0.02	−0.20, +0.15	0.80
Household income (annual)	−0.00	−0.04, +0.03	0.89	−0.00	−0.04, +0.03	0.87	0.00	−0.03, +0.04	0.83
Major early stressor (yes)	0.17	+0.01, +0.32	0.04	0.16	+0.01, +0.31	0.04	0.15	+0.00, +0.31	0.05
Corticostriatal reactivity	−0.11	−0.45, +0.23	0.54	0.13	−0.12, +0.38	0.32	0.08	−0.23, +0.40	0.61
Stressor x Reactivity	0.07	−0.38, +0.52	0.77	−0.47	−0.84, −0.10	0.01	−0.59	−1.11, −0.07	0.03
Intercept	−0.18	−2.99, +2.63	0.90	−0.38	−3.14, +2.38	0.79	−1.06	−3.90, +1.78	0.47

Note. Results of conditional regression models predicting low-grade inflammation from covariates, major early stressor, corticostriatal reactivity, and the interaction of the latter two variables. Categorical variables coded as follows: sex (male = 0, female = 1), race and ethnicity (does not identify as = 0, does identify as = 1), and major early stressor (absent = 0, present = 1). For race and ethnicity, referent is Non-Hispanic Whites.

different from zero (OFC slope = 0.13, CI = -0.12,+0.38, p =.32; VS slope = 0.08, 95 % CI = -0.23,+0.40, p =.61). Fig. 3 illustrates these patterns using scatterplots of covariate-adjusted individual data points.

3.2. Sensitivity and specificity analyses

To evaluate depression's role in the observed interactions, the models were re-estimated with covariates reflecting the intensity of depressive symptoms and use of psychotropic medications. In all models, symptoms were positively associated with inflammation, with p values approaching significance (OFC: B = 0.02, CI = 0.00,+0.04, p =.06; VS: B = 0.02, CI = -0.01,+0.04, p =.08). Medication's relationship with inflammation was non-significant (p's > 0.39). Nonetheless, the interactions between early stress and corticostriatal responsivity in the outcome phase were still evident (OFC: p =.009; $\Delta R^2 = 0.03$; VS: p =.02; $\Delta R^2 = 0.03$) when depression and medication were included.

Based on suggestions from a reviewer, we further expanded the list of covariates to include adiposity (measured via body mass index) and anxiety (measured via the anxious arousal scale of the Mood and Anxiety Symptom Questionnaire (Watson et al., 1995). In all models adiposity and anxiety were positively associated with the inflammation composite (p values from 0.027 to 0.037). However, even with these covariates added to the models, the observed interactions between early stress and corticostriatal responsivity remained significant for the OFC and VS during the outcome phase (OFC: p =.03; $\Delta R^2 = 0.02$; VS: p =.03; ΔR^2 = 0.02).

There are different approaches to aggregating inflammatory biomarkers. Although we weighted each biomarker equally, others recommend using empirically-derived weighting schemes (Moriarity et al., 2021). Thus, we re-estimated models after representing inflammation as an empirically-weighted latent variable, derived from the single-factor confirmatory factor analysis described in Methods. Patterns were highly similar. Specifically, interactions between early stress and corticostriatal responsivity were significant for OFC (p =.011) and VS (p =.028) during the outcome phase, but not for VS during anticipation (p =.39).

Because early stress had a zero-inflated, right-skewed distribution, we transformed it into a binary variable reflecting presence vs. absence. To determine whether the interactions observed were an artifact of this approach, we re-estimated models with an alternative version of this variable, where participants were grouped into categories reflecting 0, 1, 2, or 3 + major adversities. (The percentage of the sample who fell into these categories was 59, 18, 12, and 11, respectively.) In these revised models, the interactions between early stress and neural responsivity to reward were still observed. The effect sizes associated with the interactions were slightly larger, in fact, although the p values were slightly larger, reflecting the small number of participants in the 2 and 3 + categories (OFC: p =.06; $\Delta R^2 = 0.03$; VS: p =.05; $\Delta R^2 = 0.05$).

To determine whether these patterns were specific to reward, we re-estimated models adjusting for activation in the same ROI during the outcome phase of monetary loss trials. The magnitude of the interactions reported above was unchanged (OFC: p =.01; $\Delta R^2 = 0.03$; VS: p =.02; $\Delta R^2 = 0.03$). Finally, we conducted exploratory whole-brain analyses to examine whether early life stress and inflammation were related to brain activity during the reward outcome phase outside our ROIs in the corticostriatal circuit (see Supplementary Materials).

3.3. Later childhood stress

Table S1 shows parallel models for later childhood stress. Again, inflammation was significantly higher among White compared with Black (by 0.46 to.50 SD units) and Asian (by 0.36 to 0.37 SD units) participants, though not Hispanic participants (by 0.02-0.06 SD units). Most importantly, the major stress x corticostriatal responsivity interaction was non-significant in all three models (VS anticipation: p =.18; $\Delta R^2 = 0.01$; OFC outcome: p =.72; $\Delta R^2 = 0.00$; VS outcome: p =.76; $\Delta R^2 = 0.00$).

The significant interactions we observed for early, but not later, stressors implies the existence of a sensitive period. To evaluate this possibility further, we compared the magnitude of the interactions using Fisher's test after transforming coefficients into z-scores. The major stress x OFC reward outcome coefficient was significantly larger for adversity in early vs. later childhood ($z = 2.09$, p =.03). For the VS interaction, this difference approached significance ($z = 1.81$, p =.07). We also considered the possibility of dose effects, i.e., whether corticostriatal responsivity and inflammation activity would be even more strongly related among those who experienced both early and later stressors. However, in these models all of the three-way interactions (early stress by later stress by neural responsivity) were not significant (p's = 0.24—27).

4. DISCUSSION

In trying to understand how childhood adversity influences subsequent health, many studies have considered the role of brain development or inflammatory activity (Chiang et al., 2022; McLaughlin et al., 2019), but just a handful integrate both of these constructs (Chat et al., 2022; Kraynak et al., 2019; Miller et al., 2021). We sought to fill that knowledge gap here, and observed that inflammatory activity and corticostriatal responsivity were most strongly related among participants who experienced major early stressors. This pattern is consistent with a key assumption of the NIN framework, specifically that childhood stress

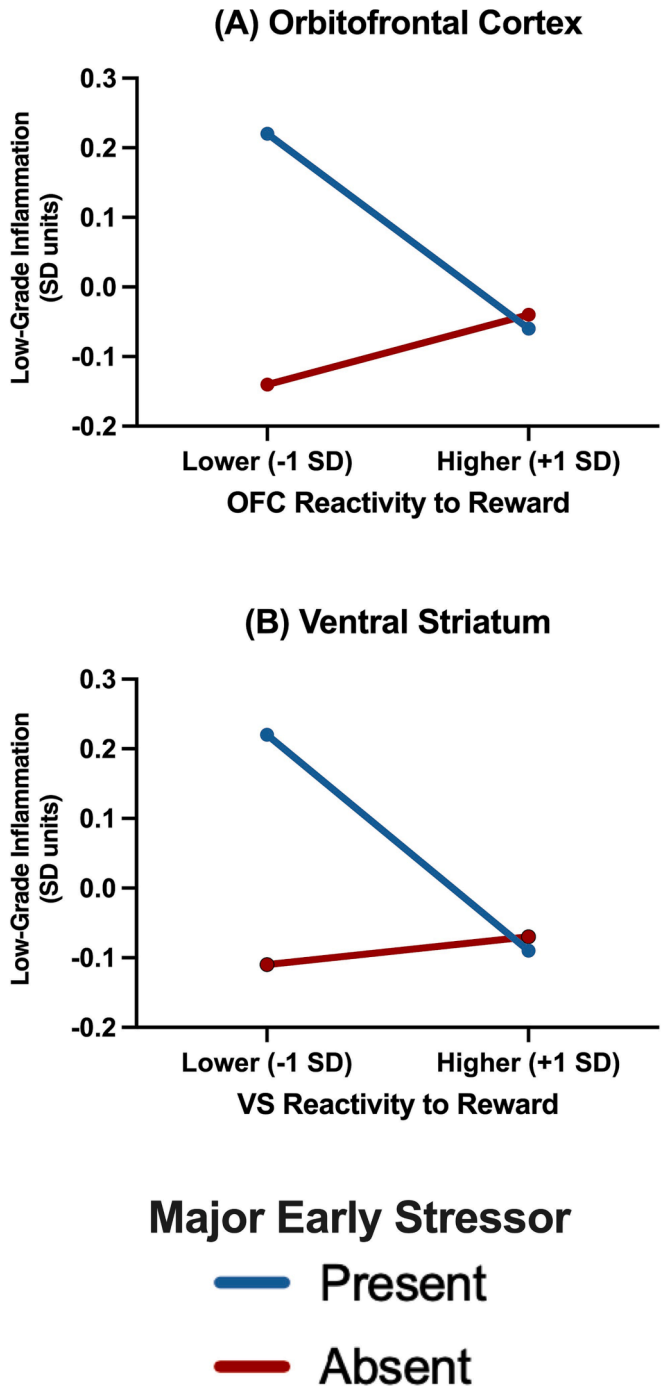

Fig. 2. Early stress interacts with corticostriatal responsivity to predict inflammation. Among participants who experienced to major stressors in early childhood, corticostriatal responsivity to monetary reward during the outcome phase was inversely associated with scores on the inflammation composite. However, these variables were unrelated among participants without major stress in early childhood. This pattern was evident in both the OFC (upper panel) and the VS (lower panel).

strengthens the relationship between inflammatory activity and corticostriatal responsivity. Of course, given this study's observational design, strong inferences about brain-immune communication are not feasible, a point we address more fully below.

The paper's findings also help clarify several other issues regarding the connections among childhood adversity, brain development, and inflammatory activity. First, as the Introduction noted, studies have yielded inconsistent findings regarding the direction of the relationship between inflammation and reward-related brain responsivity, with reports of both positively (Miller et al., 2021; Chat et al., 2022; Inagaki et al., 2015) and negatively (Eisenberger et al., 2010; Capuron et al., 2012) valanced associations. To explain this variability, Eisenberger et al. proposed a matching hypothesis based on the motivational salience of a reward in a given context (Eisenberger et al., 2017). The results of our study are consistent with the matching scenario. The sample here was middle- and upper-class, with an average family income over $100,000. Only a small fraction (14 %) had incomes near the poverty threshold. For these participants, the task's small monetary rewards would likely have little motivational salience. Thus, under the matching scenario, one would expect inflammation to dampen corticostriatal responsivity.

The study also clarifies issues related to the nature and timing of childhood stressors as they relate to brain development and inflammatory activity. As we noted, previous studies in this area have focused on maltreatment (Kraynak et al., 2019), poverty (Miller et al., 2021), and neighborhood violence (Chat et al., 2022). While these are common adversities with health consequences, contemporary youth are exposed to other major stressors. Thus, we asked whether a similar pattern would be apparent when a broader category of major stressors was considered. It was, suggesting the possibility that the processes specified in the NIN framework are influenced by a wider group of severe, chronic, stressors than previously appreciated. In future research, it will be important to expand the scope of major stressors considered, and include common exposures like peer bullying and racial discrimination.

With regard to timing, we observed that major stressors in the first decade of life accentuated the relationship between later corticostriatal responsivity and inflammatory signaling, and did so more strongly than major stressors later in childhood. These patterns are consistent with a sensitive period scenario, where exposures in the first decade of life are especially potent. Similar observations emerged in a long-term prospective study, which found that males exposed to major stressors between school entry and grade 3 had lower VS responsivity to monetary reward when they reached early adulthood (Hanson et al., 2016). For stressors experienced later in childhood, or in adolescence, the associations with subsequent responsivity were significantly weaker. Obviously, the correlational nature of both studies precludes strong inferences about the presence of sensitive periods for stress exposure. Future research could supply firmer conclusions regarding this issue by tracking brain development in youth who received policy interventions (e.g., cash transfers, nutrition supplements) at different stages of development (Hoynes et al., 2016).

Finally, these results clarify aspects of reward-related brain function that are most germane to adversity and inflammation. Like an earlier study (Miller et al., 2021), we found the relationship between inflammation and VS responsivity was strongest among participants exposed to major early stress. Extending these results, we observed the same pattern in the OFC. Collectively, these findings imply that major childhood stress heightens the capacity of inflammatory signals to modulate functioning of both the VS, which assesses hedonic value, and the OFC, which integrates this judgment with competing goals and desires (Berridge et al., 2009; Haber & Knutson, 2010). Our findings also suggest these patterns are specific to receiving rewards (at least in the VS). Why they are not evident during the anticipation phase is unclear; based on other studies (Eisenberger et al., 2017; Treadway et al., 2019), we expected them to be. Future research should investigate this issue.

When interpreting these findings, several limitations are important to consider. First, although the NIN framework specifies causal hypotheses, this study's observational design only provides a weak test of these predictions. It is difficult to envision a decisive test of the framework's key assumptions in humans, because randomly assigning children to significant early-life stress would be unethical. The best approach would likely involve an experimental manipulation of early-life stress in an animal model, e.g., repeated social defeat. This would be a rigorous and valuable addition to the literature. Second, we

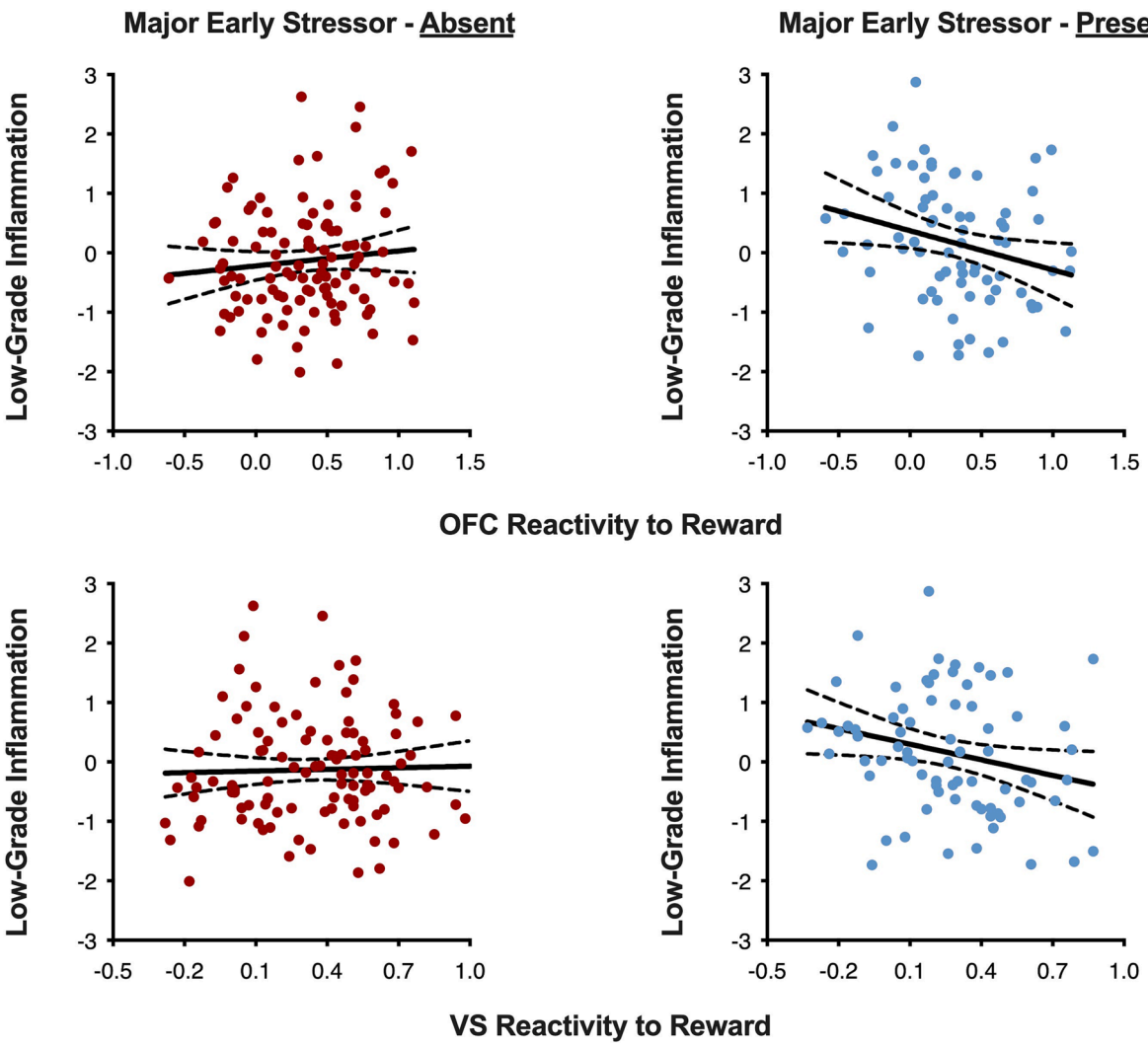

Fig. 3. Granular depictions of interaction. These scatterplots depict the relationship between corticostriatal responsivity to monetary reward during the outcome phase and scores on the inflammation composite. There were significant inverse associations between these variables for participants who had been exposed to major life stress during early childhood in both orbitofrontal (upper right panel) and ventral striatal (lower right panel). However, these associations were not evident for participants without major stress in early childhood (upper and lower left panels). Each scatterplot depicts a best-fitting regression line with 95% confidence intervals around it. Values are adjusted for covariates.

assessed corticostriatal responsivity to a single reward – money – and did not consider threat, which is pivotal to the NIN framework, or other types of rewards (e.g., social). We did, however, observe that the magnitude of the interaction between early stress and corticostriatal responsivity was unchanged when we adjusted for activation in the same ROI during monetary loss trials. This suggests that, among individuals with childhood adversity, inflammation is uniquely associated with corticostriatal reactivity to reward, as opposed to loss, cues. Third, we did not perform ROI analyses of other brain regions involved in reward (e.g., insula, medial PFC, caudate, putamen), categorize the nature of stressors (e.g., threat vs. deprivation), or evaluate the specificity of individual inflammatory biomarkers. Though interesting, these issues are of secondary interest here, and evaluating them would dramatically escalate false discovery risks. We conduct exploratory whole-brain analyses, however, to examine whether early life stress and inflammation were related to brain activity outside our corticostriatal ROIs (see Supplemental Materials). Fourth, because health outcomes were not included in the analyses, we remain uncertain about any clinical implications of the patterns observed. Finally, because there is no technology available to non-invasively monitor brain-immune crosstalk, we had to infer its occurrence indirectly via covariation of inflammatory activity and neural responsivity.

Despite these limitations, these findings are consistent with the NIN framework's central hypothesis - that stress in childhood amplifies crosstalk between inflammation and corticostriatal circuitry that supports reward processing. If substantiated with the kind of studies outlined above, these findings will facilitate deeper understanding how early-life stress, acting through the brain and immune system, contribute to a diverse set of health problems.

5. Author contributions

Dr. Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Miller, Craske, Zinbarg, and Nusslock *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* Miller and Nusslock *Critical revision of the manuscript for intellectual content:* Carroll, Craske, Zinbarg, Chat, and Vinograd. *Statistical analysis:* Miller, Carroll, Zinbarg.

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CRediT authorship contribution statement

Gregory E. Miller: . **Ann L. Carroll:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Casey C. Armstrong:** Data curation, Formal analysis, Methodology, Software, Writing – review & editing. **Michelle G. Craske:** Funding acquisition, Methodology, Supervision, Writing – review & editing. **Richard E. Zinbarg:** Conceptualization, Formal analysis, Funding acquisition, Writing – review & editing, Supervision. **Susan Y. Bookheimer:** Funding acquisition, Investigation, Methodology, Supervision. **Iris Ka-Yi Chat:** . **Meghan Vinograd:** Data curation, Investigation, Supervision, Writing – review & editing. **Katherine S. Young:** Data curation, Methodology, Resources, Supervision, Writing – review & editing. **Robin Nusslock:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft.

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.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.01.013.

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