Childhood Stress, Grown-up Brain Networks:

Corticolimbic Correlates of Threat-related Early Life Stress and Adult Stress Response

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**Supplementary Methods**

**Participants**

Participants were recruited using internet advertisements and flyers placed in public areas and local clinics, and from other research groups at McLean Hospital; recruitment were targeted to women, ages 18 to 45, who either had (or had not) experienced stressful life events in childhood, and who either did (or did not) have major depressive disorder (MDD). Recruitment was designed to capture a sample reflective of the racial, ethnic, socioeconomic diversity of the Boston area; experimental variables did not covary with race, ethnicity, socioeconomic status, or education (*p*s>0.10). The present sample was drawn from an ongoing study with distinct, non-overlapping experimental objectives and analyses that will be reported elsewhere. The larger, ongoing study features a clinical screening session plus three experimental sessions: a functional magnetic resonance imaging session, a positron emission tomography session, and a session in which participants are exposed to a social-evaluative stress manipulation while an electroencephalogram is recorded. Participants have the option to decline participation in one of the three experimental sessions. Data for the present report were drawn from the clinical screening session, the fMRI session, and the stress exposure session. One goal of the ongoing study is to investigate the effects of a low-dose dopamine agonist on reward sensitivity; accordingly, approximately half of the participants in the present sample received the drug amisulpride prior to the MRI scan, while the other half received placebo. Drug/placebo administration was given so that plasma concentration would peak during the task-based fMRI component of the protocol, which occurred after the resting state scan investigated in the current analyses. Amisulpride is a D2/D3 receptor antagonist with particularly high affinity for mesolimbic pathways (Admon *et al.*, 2017, Schoemaker *et al.*, 1997), and we had no hypotheses regarding effects of amisulpride on corticolimbic circuits. However, to ensure that the pharmacological manipulation was unrelated to the present findings, we performed analyses to test the effects of the pharmacological manipulation on the experimental variables of corticolimbic static or dynamic RSFC, or associations between the pharmacological manipulation and ELS severity or cortisol AUC. Results indicated that drug status was not significantly associated with amygdala-DLPFC static RSFC, β=-0.01, F(56)<0.01, *p*=0.94, or amygdala-rACC dynamic RSFC, β<-0.01, F(56)<0.01, *p*=0.95. Drug status was also not significantly associated with ELS severity, β=-0.11, F(56)=0.75, *p*=0.39, or cortisol reactivity (AUC) at a subsequent research session, β=-0.05, F(38)=0.08, *p*=0.78. Thus, although amisulpride affects dopamine-rich striatal regions (Admon *et al.*, 2017) that strongly project to the prefrontal cortex, in the current study, administration of a single, low dose of amisulpride did not modulate functional connectivity involving the prefrontal cortex. As mentioned above, it is also important to consider that the drug administration was timed in order to reach maximal plasma level of the drug during an fMRI task rather than the resting state scan. As a result, only procedures relevant to the experimental goals of the present study are reported in the main text.

**Measures**

**Severity of early life stress*.*** An examination of deprivation-related ELS was beyond the scope of the present study, however, nine participants reported some form of limited caregiving during childhood in their TAQ interview; therefore, analyses were repeated excluding these participants. Because such exclusion did not alter the significance or pattern of effects we report on analyses including the full sample. In addition, although severity of threat-related ELS was not related to recency, *r*(70)=0.06, p=0.69, or age of onset, *r*(70)=-0.13, p=0.38, of ELS events this does not preclude an effect of ELS onset on brain network functioning or acute stress reactivity. Although investigation of other dimensions of ELS was beyond the scope of the present study, these may be interesting directions for future study.

**Maastricht Acute Stress Task.** As session three, participants completed the Maastricht Acute Stress Test (MAST; (Smeets *et al.*, 2012)). The MAST is a laboratory stress paradigm that combines several well-validated stress manipulations (Dickerson and Kemeny, 2004) by repeatedly exposing participants to cold pressor interspersed with periods of serial subtraction in front of two critical evaluators. During periods of cold pressor exposure, participants were instructed to immerse the left hand up to the wrist in ice water (1–3°C). Cold pressor exposure was repeated five times in a fixed order with duration of exposure varying between 60s-90s; onset of each exposure was controlled by a computer (thus, introducing some degree of uncontrollability). Between periods of water immersion, participants were asked to subtract the value of 17 serially from 2,043. Participants completed four blocks of serial subtraction in a fixed order, with the duration of each block varying between 45-90s. Throughout the cold pressor exposure and blocks of serial subtraction, participants were monitored by two experimenters (one male, one female) who were aloof and unsmiling in demeanor, and who provided error feedback when the participant made a mistake in subtraction (“*Incorrect. Start over at 2043*”) but no positive feedback or encouragement. Finally, to prolong the effect of the stress manipulation, at the end of the last exposure, participants were informed that their performance failed to meet the requisite threshold and that the task would be repeated following administration of remaining experimental procedures (however, later in the session, participants were informed that repeating the task would not be necessary). Saliva samples were collected at 5 time points: on average across participants, -102 min (before stressor), +12 min following onset of stressor, +28 min, +38 min (relief), +80 min. Participants had a 10- to 20-minute acclimation period from arrival at the laboratory to the first collection of salivary cortisol.

**Analyses**

**Resting-state functional connectivity analyses.** Conservative and well-established procedures was performed for motion correction and denoising, consistent with previous studies and guidelines (Kaiser *et al.*, 2016, Power *et al.*, 2015).

***Head motion and artifact detection.*** Prior research has demonstrated that estimates of functional connectivity are especially sensitive to motion (Laumann  *et al.*, 2016, Power *et al.*, 2015); therefore, conservative motion correction procedures were performed using SPM12 to assess head motion by translation and rotation in *x, y, z* directions; and Artifact Detection Tools (ART, [www.nitrc.org/projects/artifact\_detect/](http://www.nitrc.org/projects/artifact_detect/)) to calculate time points of significant head motion or fluctuations in the magnetic field (>0.5 mm motion from previous frame, global mean intensity >3 SD from mean intensity across functional scans) for each participant. Using output from ART, we modeled outlier images in each participant’s first-level general linear model. In addition, composite estimates of motion outliers were covaried in group-level analyses.

**Denoising.** Denoising of the timeseries was performed with the CONN toolbox (<https://www.nitrc.org/projects/conn/>; (Whitfield-Gabrieli and Nieto-Castanon, 2012)) and CompCor (Behzadi *et al.*, 2007) to estimate physiological noise from white matter and cerebrospinal fluid for each participant using principal component analysis. The first five components were regressed out of each subject’s functional data on the first level of analysis (together with motion and outlier regressors). Next, for static connectivity analyses, a band-pass filter of 0.009–0.10 Hz was applied to the time series; for dynamic connectivity analyses, a band-pass filter of 0.0278–0.10 Hz was applied. These ranges were selected to remove high-frequency activity related to cardiac and respiratory activity (Cordes *et al.*, 2001), and low-frequency activity in the range of scanner drift (<0.009 Hz) or with a period that exceeds the duration of sliding windows (<0.0278 Hz) (Leonardi and Van De Ville, 2015). These corrections yielded, at each voxel, a residual BOLD time course that was used for subsequent analyses.

**Supplementary Results**

**Post-hoc Analyses to Characterize Associations Between Threat-Related ELS and RSFC**

**Dynamic resting-state functional connectivity analysis*.*** As a post-hoc test to clarify the underlying patterns of correlation across sliding windows that contributed to group differences in dynamic RSFC, we computed descriptive statistics to examine the frequency of positive or negative correlations between the seed ROI (amygdala) and the region of effect (here, rACC). Specifically, for each participant, we calculated the proportion of windows in which (Fisher’s z-transformed Pearson) correlations between the seed ROI and the region of effect fell within particular ranges: high negative (z<−0.5), moderate negative (−0.5<z<−0.25), low/uncorrelated (−0.25<z<0.25), moderate positive (0.25<z<0.5), and high positive (z>0.5). Results are displayed in Figure S2.

**Test of moderating effects of type of threat-related ELS*.*** Post-hoc analyses were also performed to investigate whether the association between threat-related ELS severity and either static corticolimbic RSFC (between bilateral amygdala and DLPFC) or dynamic corticolimbic RSFC (between bilateral amygdala and rACC) differed as a function of type of threat-related ELS. Partial correlations (controlling for age and motion composite scores) were performed between static amygdala-DLPFC RSFC and severity of peer aggression, severity of sexual abuse, severity of parental domestic conflict, or severity of parental verbal or physical abuse; next, the Meng procedure (Meng *et al.*, 1992) was used to test for significant differences in these correlation. Partial correlations and Meng tests among correlations were repeated for dynamic amygdala-rACC RSFC and each type of threat-related ELS. Results failed to detect significant differences between the correlations of each type of threat-related ELS severity and either static or dynamic corticolimbic RSFC; Z values ranged from 0.026 (*p*=0.98) to 1.15 (*p*=0.13). However, the absence of significant moderator effects should be interpreted with caution given that the sample sizes of participants reporting a specific type of threat-related ELS were modest (e.g., ranging from n=19 participants reported exposure to peer aggression to n=35 participants reported exposure to parental verbal or physical abuse) and the majority (73%) of participants reporting exposure to threat-related ELS reported multiple types of exposure (Table 1, main text).

**Repeat analyses considering ELS as a categorical variable**. In the present study, we chose to take a dimensional approach to the construct of early life stress, rather than dichotomizing the sample into those who reported any ELS versus those who reported no ELS. When analyses are repeated using a dichotomized ELS variable (any ELS = +1, n=52; no ELS = -1, n=18), compared with individuals with no ELS history, those reporting any ELS exhibited decreased (more negative) static RSFC between bilateral amygdala and DLPFC, β=-0.42, F(66)=13.05, p=0.001, and increased (more variable) dynamic RSFC between bilateral amygdala and rACC, β=0.45, F(66)=16.12, p<0.001. These patterns are consistent with original analyses in which ELS is entered as a continuous variable.

**Post-hoc Analyses Focused on Depression**

**Experimental effects controlling for depression.** The experimental aims of the present study were focused on neural and physiological correlates of childhood stress exposure. Therefore, as noted in the main text, recruitment efforts aimed to balance participants’ exposures to threat-related ELS across diagnostic status (i.e., recruit women with a history of high-severity threat-related ELS both who do, or who do not, have current major depressive disorder), and diagnostic status was controlled in all analyses (MDD status contrast-coded). These procedures were designed to avoid confounding effects of depression (the most common psychiatric disorder associated with ELS, (Andersen, 2015)), but in a sample that represents the range of psychiatric health outcomes for women with a history of threat-related ELS. In support of the idea that experimental effects were not driven by depression, all experimental effects were detected when controlling for psychiatric (MDD) status in statistical models (all changes in β<0.10; all experimental effects also remained significant when controlling for severity of depressive symptoms, as measured by the Beck Depression Inventory, 2nd Ed. (Beck *et al.*, 1996)).

**Moderating effects of depression.** Next, analyses were performed to investigate whether depression moderated the experimental effects; i.e., although such effects remained significant when controlling for depression (as confirmed by the analyses above) it remains possible that experimental effects vary in their strength between individuals with or without MDD. Regression analyses failed to provide evidence for a moderating effect of MDD status on the associations between ELS severity and static corticolimbic RSFC, between either static or dynamic corticolimbic RSFC and cortisol response to stress, or the indirect effect of ELS severity on cortisol response via static corticolimbic RSFC (all *p*s >0.55). (However, given the more modest sample size available for cortisol reactivity, results of those moderation analyses should be interpreted with caution). MDD status did moderate the association between ELS severity and dynamic corticolimbic RSFC, dynamic β=-0.22, F(64)=2.17, *p*=0.03, and follow-up regression analyses showed that the association between ELS severity and dynamic corticolimbic RSFC was stronger among non-MDD than MDD individuals (β=0.65, F(30)=24.35, *p*<0.01 versus β=0.33, F(64)=2.88, *p*=0.09). These patterns support an interpretation in which increased dynamic RSFC between amygdala and medial prefrontal cortex has compensatory effects for psychiatrically healthy individuals.

**Main effects of depression.** It is also possible that the alterations in corticolimbic functioning that were observed as a function of threat-related ELS severity may also have independent associations with psychiatric health, e.g., MDD status or depression symptom severity. When MDD group was separately regressed on either static or dynamic corticolimbic RSFC (controlling for age, motion outliers, and threat-related ELS severity), no differences were observed between depressed versus non-depressed participants: static β=-0.04, F(65)=0.12, *p*=0.74; dynamic β=-0.15, F(65)=1.82, *p*=0.18. Next, (mean-deviated) BDI symptom severity was separately regressed on static or dynamic corticolimbic RSFC (controlling for age, motion outliers, and threat-related ELS severity); these analyses revealed that lower severity of depressive symptoms was related to higher dynamic variability in RSFC between amygdala and rACC, β=-0.22, F(65)=3.85, *p*=0.05, (but no effects of symptom severity on static RSFC: β=-0.04, F(65)=0.12, *p*=0.74). (Differences in results of regressions that included BDI symptom severity versus MDD status may be related to enhanced statistical power of continuous relative to dichotomous predictors.) Together, these results provide some evidence that among women with varying exposure to childhood stress, elevated dynamic flexibility in a corticolombic circuit linking amygdala with rACC is related to psychiatric resilience in the form of decreased symptoms of depression. However, neither MDD group nor BDI symptom severity had significant main effects on cortisol AUC (controlling for age, motion, and threat-related ELS severity), β=0.16, F(35)=1.05, *p*=0.31, and β=0.05, F(35)=0.08, *p*=0.78.

**Post-hoc Analyses Focused on Other Psychiatric History**

Out of the full sample (n=70), approximately half (n=36) met criteria for current MDD; out of those meeting criteria for current MDD, a subset (n=15) also reported a current anxiety disorder (see main text, Table 1). Although the group of participants with anxiety disorders was too small to support analyses examining moderating effects of anxiety, experimental analyses were repeated controlling for anxiety disorders (anxiety present = +1, anxiety absent = -1) in addition to MDD. The addition of anxiety as a covariate failed to alter the pattern or significance of effects in any experimental analyses (i.e., all changes in β<0.15, all *p*s for experimental effects remain <0.05).

**Post-hoc Analyses Testing Experimental Effects Within Groups Defined By Psychiatric Diagnosis**

As noted above, post-hoc analyses failed to indicate that experimental effects were moderated by or covaried with psychiatric history (depression, anxiety). However, for completeness and at the request of a reviewer, we also performed within-group analyses within groups defined by depression status (current MDD versus no history of MDD) or anxiety status within the depressed group (current MDD with anxiety versus current MDD with no history of MDD) to evaluate each key area of the analyses: 1) the association between ELS severity and amygdala-DLPFC static RSFC, 2) the association between ELS severity and amygdala-rACC dynamic RSFC, 3) the association between amygdala-DLPFC static RSFC and cortisol response (AUC) (controlling for ELS severity, as in mediator regressions), 4) the interaction of amygdala-DLPFC static RSFC and amygdala-rACC dynamic RSFC in predicting cortisol response (AUC) (controlling for ELS severity, as in mediator regressions). All analyses controlled for age and outlier volumes, as in all other experimental analyses. The results of these within-group analyses are reported below. Of note, although not all within-group effects are significant (as we would expect, given that small samples lead to instability of effects and reduced statistical power), the directions of effect for specific analyses are consistent across subgroups defined by psychiatric status. This consistency, together with the absence of moderator effects of psychiatric status in experimental analyses, encourage us to believe that ELS severity effects are not driven by psychiatric status in the present sample.

1) Association between ELS severity and amygdala-DLPFC static RSFC:

* among non-depressed subjects: **β= -0.52**, F(30)=12.45, p<0.01
* among depressed subjects: **β= -0.38**, F(32)=4.03, p=0.05
* among depressed subjects without anxiety: **β= -0.33**, F(15)=1.28, p=0.27
* among depressed subjects with anxiety: **β= -0.58**, F(13)=5.90, p=0.03

2) Association between ELS severity and amygdala-rACC dynamic RSFC:

* among non-depressed subjects: **β= 0.65**, F(30)=24.35, p<0.01
* among depressed subjects: **β= 0.33**, F(32)=2.88, p=0.09
* among depressed subjects without anxiety: **β= 0.58**, F(15)=4.68, p=0.04
* among depressed subjects with anxiety: **β= 0.11**, F(13)=0.14, p=0.71

3) Association between amygdala-DLPFC static RSFC and cortisol AUC:

* among non-depressed subjects: **β= 9.24**, F(8)=17.29, p<0.01
* among depressed subjects: **β= 1.38**, F(18)=0.20, p=0.66
* among depressed subjects without anxiety: **β= 4.27**, F(6)=1.82, p=0.22
* among depressed subjects with anxiety: **β= 9.71**, F(4)=0.31, p=0.61

3) Interaction between amygdala-DLPFC static RSFC and amygdala-rACC dynamic RSFC in statistically predicting cortisol AUC:

* among non-depressed subjects: **β= -8.97**, F(8)=17.68, p<0.01
* among depressed subjects: **β= -1.02**, F(18)=0.11, p=0.74
* among depressed subjects without anxiety: **β= -2.89**, F(6)=0.95, p=0.37
* among depressed subjects with anxiety: **β= -10.37**, F(4)=0.34, p=0.59

**Post-hoc Power Analysis for Mediated Effects.** We performed a post-hoc power analysis to evaluate the likelihood of observing (1) the effect of ELS severity on static or dynamic corticolimbic RSFC (observed partial η2 = 0.24, partial η2 = 0.26; available n=70); (2) the effect of static amygdala-DLPFC RSFC on cortisol response, controlling for ELS severity and other covariates (age, motion outliers) (the b path of the mediation model; observed partial η2 = 0.16; available n=42); and (3) the moderating effect of dynamic amygdala-rACC RSFC on the association between static amygdala-DLPFC RSFC and cortisol response, controlling for ELS severity and other covariates (age, motion outliers) (moderation of the b path, observed partial η2 = 0.15; available n=42). Based on these estimates, and using the R pwr package, we estimate that the power in the present study for these analyses ranged from 70-72% [analyses 2-3] to >95% [analyses 1].

**Response to the MAST**

**Cortisol response.** A repeated-measures analysis of variance (ANOVA) was performed to confirm that the stress manipulation elicited a significant physiological (cortisol) response; the repeated factor was time, and the dependent variable was log-transformed salivary cortisol (age was included as a covariate, for consistency with experimental analyses). This analysis revealed a significant non-linear (cubic) effect of time on cortisol, F(1,37)=7.55, *p*<0.01 (Figure S3A).

**Subjective emotional response.** Next, a repeated-measures ANOVA was performed to examine the effect of the stress manipulation on subjective response to stress, as measured with visual analogue mood scale (VAMS) ratings of negative affect (summed across (item 1) feeling friendly versus hostile, (item 2) feeling relaxed versus tense, and (item 3) feeling happy versus sad). (Analyses controlled for age, motion outliers, and MDD status). Significant linear, F(1,37)=22.48, *p*<0.01, cubic, F(1,37)=69.79, *p*<0.01, quadratic, F(1,37)=15.60, *p*<0.01, and fourth-order, F(1,37)=46.10, *p*<0.01, effects were observed (Figure S3B). After adding static and dynamic corticolimbic RSFC, and their interaction, to the model, the linear and quadratic main effects of time remained significant (see main text) and the linear effect of time was moderated by dynamic amygdala-rACC, F(34)=3.62, *p*=0.06 (see main text). Follow-up partial correlations revealed that higher dynamic amygdala-rACC RSFC was related to significantly lower post-stress hostility at the time point corresponding with peak cortisol response to stress (time 3, +28 min post-stress), *r*(37)=-0.38, *p*=0.02. Dynamic amygdala-rACC RSFC was non-significantly related to decreased sadness, *r*(37)=-0.24, *p*=0.14, and tension, *r*(37)=-0.23, *p*=0.16, at this time point (time 3, +28 min post-stress). Together, these findings support the effectiveness of the stress manipulation in eliciting a physiological (cortisol) and an emotional (negative mood) response, and suggest associations between intrinsic corticolimbic dynamics and emotional functioning.

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**Figure S1.** Early life stress (ELS) severity was associated with stronger negative static resting-state functional connectivity (RSFC) between bilateral amygdala and regions of dorsolateral prefrontal cortex (DLPFC; displayed in main text), and stronger positive RSFC between bilateral amygdala and areas of left (k=208, peak *p*<0.001, MNI coordinates -40, -60, 6) and right (k=231, peak *p*<0.001, MNI coordinates 46, -74, 0) occipital cortex (OCC). *Note:* Displayed is posterior view of brain. Voxelwise RSFC analyses thresholded at peak *p*<0.005, two-sided t-test, FWE corrected *p*<0.05. Analyses controlled for age and motion outliers.

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**Figure S2. Descriptive summary of resting-state functional connectivity between amygdala and rostral anterior cingulate cortex, across sliding windows.** Displayed are the correlations between early life stress severity (ELS) and proportions of windows in which (Fisher’s z-transformed Pearson) correlations between the seed ROI and the region of effect fell within particular ranges: high negative (z<−0.5), moderate negative (−0.5<z<−0.25), low/uncorrelated (−0.25<z<0.25), moderate positive (0.25<z<0.5), and high positive (z>0.5). ELS severity was significantly positively correlated with proportion of windows in which functional connectivity between amygdala and rACC was strongly positive (z>0.5). *Note*: *p*<0.05\*

 

**Figure S3. Physiological and subjective response to a social-evaluative stress manipulation.** Across the group, participants exhibited a robust response to stress in the form of **(A)** nonlinear (cubic) cortisol response to the stress, peaking at 28 minutes post-stress exposure; and (B) linear and nonlinear (quadratic, cubic, fourth-order) increases in self-reported negative affect (hostility, sadness, and tension) using a visual analogue mood scale (VAMS), also peaking 28 minutes post-stress exposure.

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