# Fronto-Amygdala Connectivity Moderates the Association of Inflammation with Negative Affective Reactivity to Daily Stress in Adolescents

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## BACKGROUND

**Adolescence** is marked by heightened affective reactivity to daily stressors.

- High NA and blunted PA linked to psychopathology onset
- Factors driving individual variability remain unclear.

**Two biological systems are potential mechanisms:**

### Peripheral inflammation

- Pro-inflammatory cytokines sensitize cortico-limbic circuits and alter neurotransmission; linked to greater affective reactivity in adults
- Untested in adolescents for momentary stress-affect dynamics

### Fronto-amygdala connectivity

- Lateral PFC (DLPFC, VLPFC) supports emotion regulation via cognitive control and reappraisal
- More positive LPFC–amygdala coupling reflects less efficient downregulation; predicts psychopathology

**These systems likely interact.** Inflammatory cytokines disrupt PFC dopamine signaling, suggesting CRP and fronto-amygdala FC ***jointly*** shape stress reactivity.

***Critically, no prior study has integrated peripheral inflammation, task-based neural function, and naturalistic stress-affect dynamics using ecological momentary assessment (EMA) in adolescents.***

## METHODS

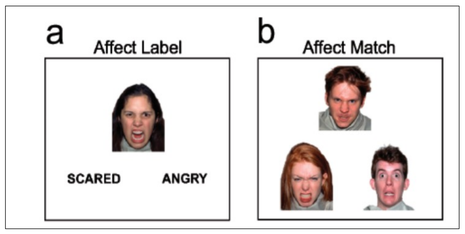
| N = 124 | N = 85 | N = 68 |
|---|---|---|
| **EMA** | **+ Inflammation** | **+ Task fMRI** |
| *3,416 prompts* | *2,352 prompts* | *1,910 prompts* |

**Blood Draw**

**C-Reactive Protein (CRP)**
**Finger-prick** dried blood spots
*Luminex singleplex assay*
**Log-transformed + Z-scored**
Batch + BMI controlled

**fMRI Scan**

**Affect-Labeling Task fMRI**
**Implicit emotion regulation**
*NimStim faces · 3T GE scanner*
**PPI: Neg Label > Neg Match**
Amygdala → DLPFC + VLPFC ROIs




≤ 5 days

**EMA Burst**

**14-Day EMA Burst**
**3×/day × 14 days** (MetricWire)
**Stress:** event Y/N → 0–100 slider
**Affect:** 9 items, 0–100 sliders
NA (5) · PA (4)

DAILY PROMPTS — Morning — Afternoon — Evening

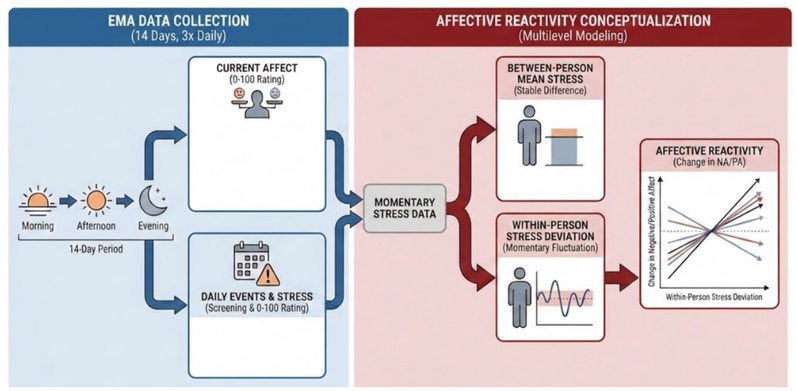
**Data Analysis.** Two-level mixed-effects models (lme4); within- vs. between-person stress; random intercepts + slopes; LRT model building; Johnson-Neyman moderation probing.

## HYPOTHESES

**H1** Higher systemic inflammation (CRP) is associated with greater affective reactivity to daily stressors.

**H2** This association is stronger in adolescents with more positive LPFC-amygdala connectivity during implicit emotion regulation.

## RESULT 1: REACTIVITY = STRESS → NEGATIVE AFFECT




### Within-person stress increases predict elevated negative affect across all three samples.

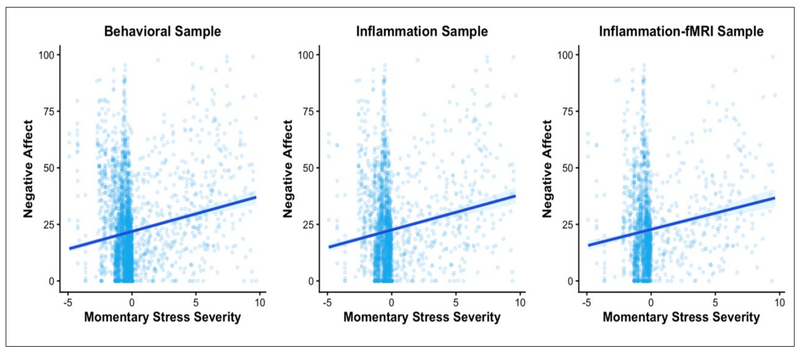



**Figure 2.** Within-person associations of momentary stress and NA across the three nested samples. Lines reflect the fixed effect from the multilevel model; bands are 95% CIs.

- Within-person stress to NA: B = 1.48, p < .001
- Between-person mean stress to NA B = 8.97, p < .001
- PA showed no significant association with stress (all ps > .21)

## RESULT 2: CRP POTENTIATES REACTIVITY

### Higher inflammation is associated with stronger within-person stress-NA coupling.

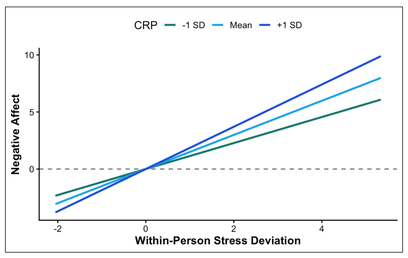



**Figure 3.** Fitted slopes at low (−1 SD), mean, and high (+1 SD) CRP. Stress deviations scaled in 10-point units; slope = expected change in NA (0–100) per 10-point increase in stress.

**Simple slopes (within-person stress to NA)**

| | | |
|---|---|---|
| Low CRP (−1 SD) | **B = 1.14** | *p < .001* |
| Mean CRP | **B = 1.50** | *p < .001* |
| High CRP (+1 SD) | **B = 1.85** | *p < .001* |

**Johnson-Neyman:** CRP significantly moderated stress reactivity across the ***entire observed range*** of CRP values.

## REGIONS OF INTEREST

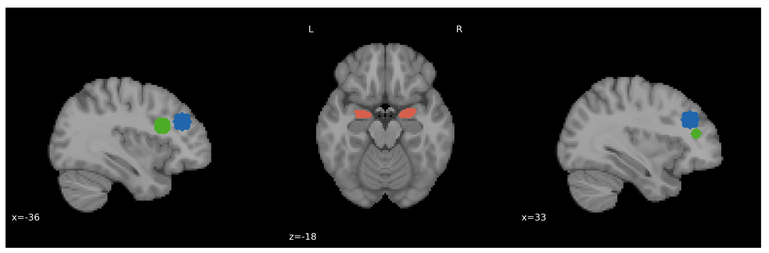



**Figure 1.** DLPFC ROIs (blue; Burklund et al., 2014: L −36, 36, 27; R 33, 33, 30); VLPFC ROIs (green; Pozzi et al., 2021: L −40, 16, 24; R 42, 40, 16); bilateral amygdala seeds (red; Harvard-Oxford 50%). All coordinates in MNI152 standard space.

## RESULT 3: DLPFC × CRP × STRESS

### CRP-related potentiation of stress reactivity depends on DLPFC–amygdala connectivity.

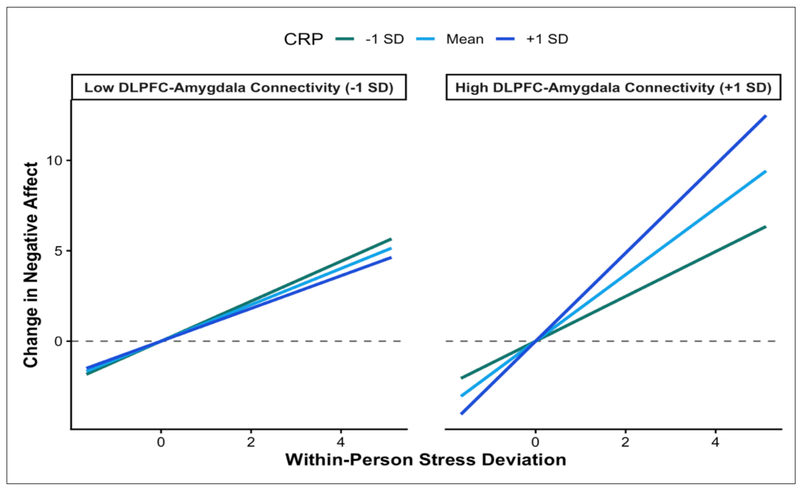



**Figure 4.** Predicted Δ NA from full multilevel model at low (−1 SD) and high (+1 SD) DLPFC=amygdala FC, by CRP level.

At **high** DLPFC-amygdala FC, higher CRP yields a steeper slope.
At **low** FC, slopes do not differ by CRP.
*Adding three-way interactions improved fit over the main-effects model: $\chi^2(7) = 18.57$, $p = .010$.*

- **Stress × CRP × DLPFC–Amygdala FC** B = 34.99, SE = 16.43, t = 2.13, ***p = .039***
- **Stress × CRP × VLPFC–Amygdala FC** B = −11.04, SE = 19.66, t = −0.56, *p = .58*

## DISCUSSION

### Evidence for a multilevel pathway

Inflammation and DLPFC-amygdala connectivity jointly shape adolescents' negative affective responses to everyday stress.

### Specificity to the DLPFC

More positive DLPFC-amygdala coupling may reflect a less efficient regulatory configuration that is especially vulnerable to inflammatory perturbation.

### Importance of naturalistic designs

This multilevel approach strengthens ecological and construct validity over studies that rely on retrospective self-report measures or a single level of analysis.

### Limitations

- Cross-sectional design.
- CRP is a broad-spectrum marker of systemic inflammation, we cannot distinguish among specific inflammatory pathways.

### Clinical implications

Adolescents with both elevated CRP and high DLPFC-amygdala FC may represent a subgroup at heightened risk for stress-related psychopathology, and a candidate target for either anti-inflammatory or regulation-focused interventions.

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