Challenging the Brain and Lungs: Impacts of acute stress on the brain, cortisol, and inflammatory responses in asthma

Estelle Higgins

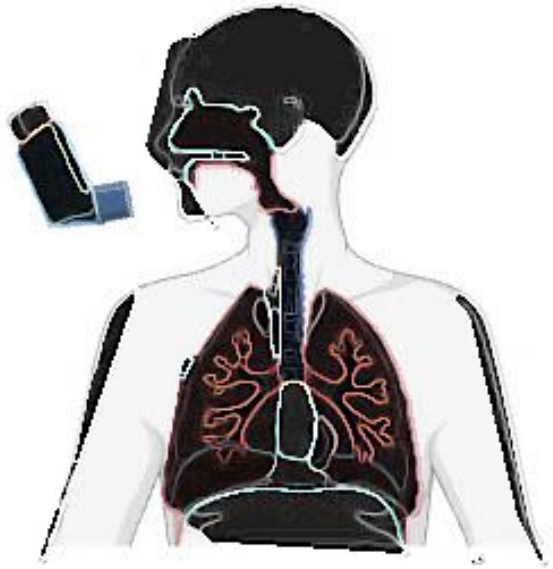
First-Year Project

November 10, 2023

Overall Roadmap

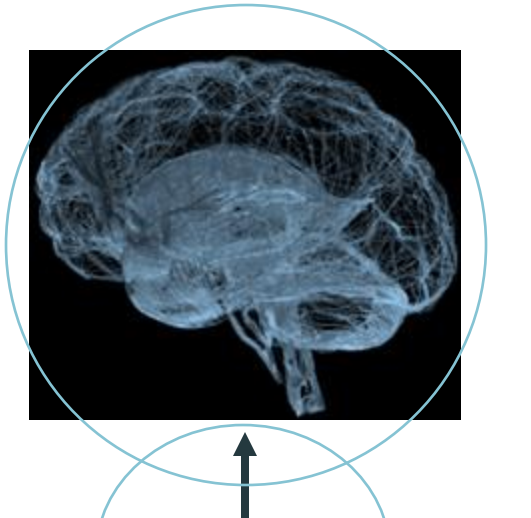
Overall Roadmap

Background



Background

stress

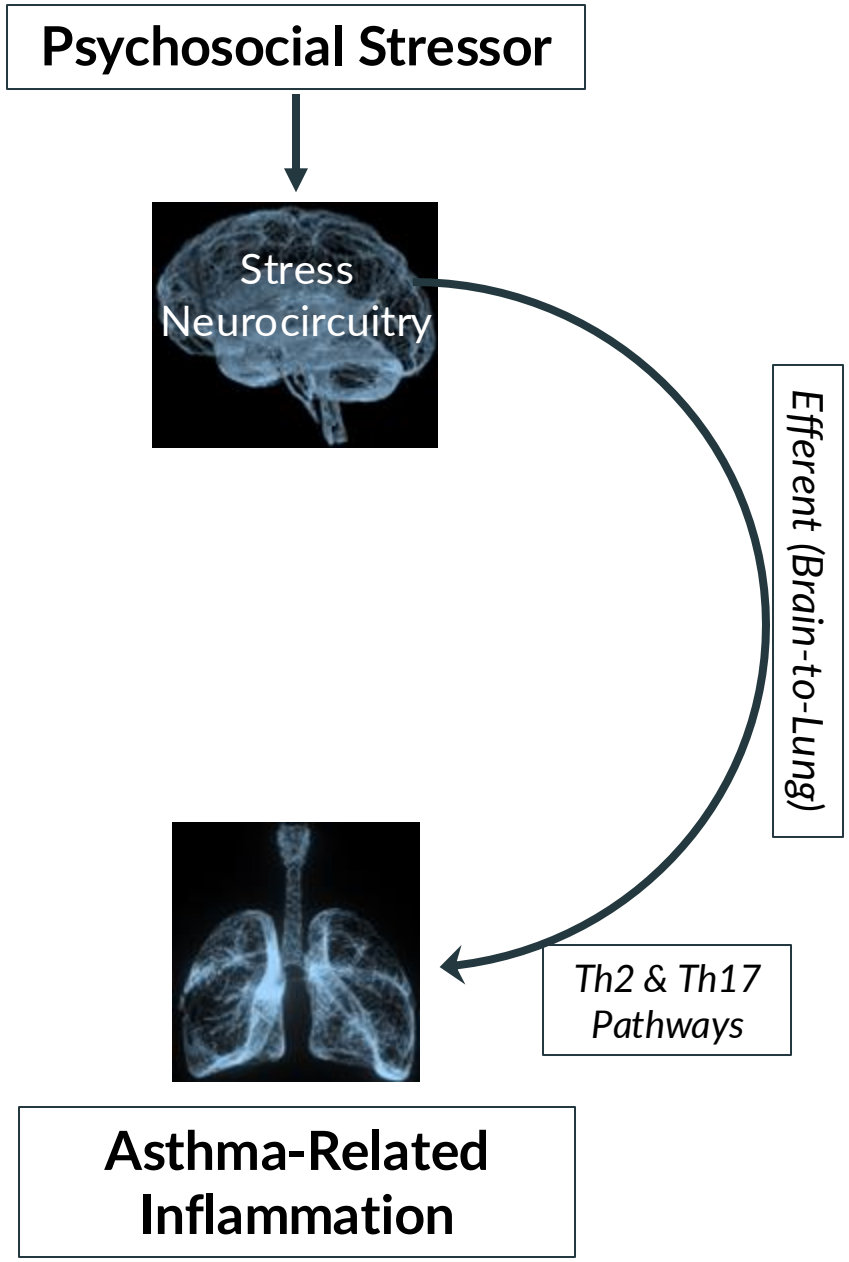


Asthma-Related Inflammation

Initial evidence:

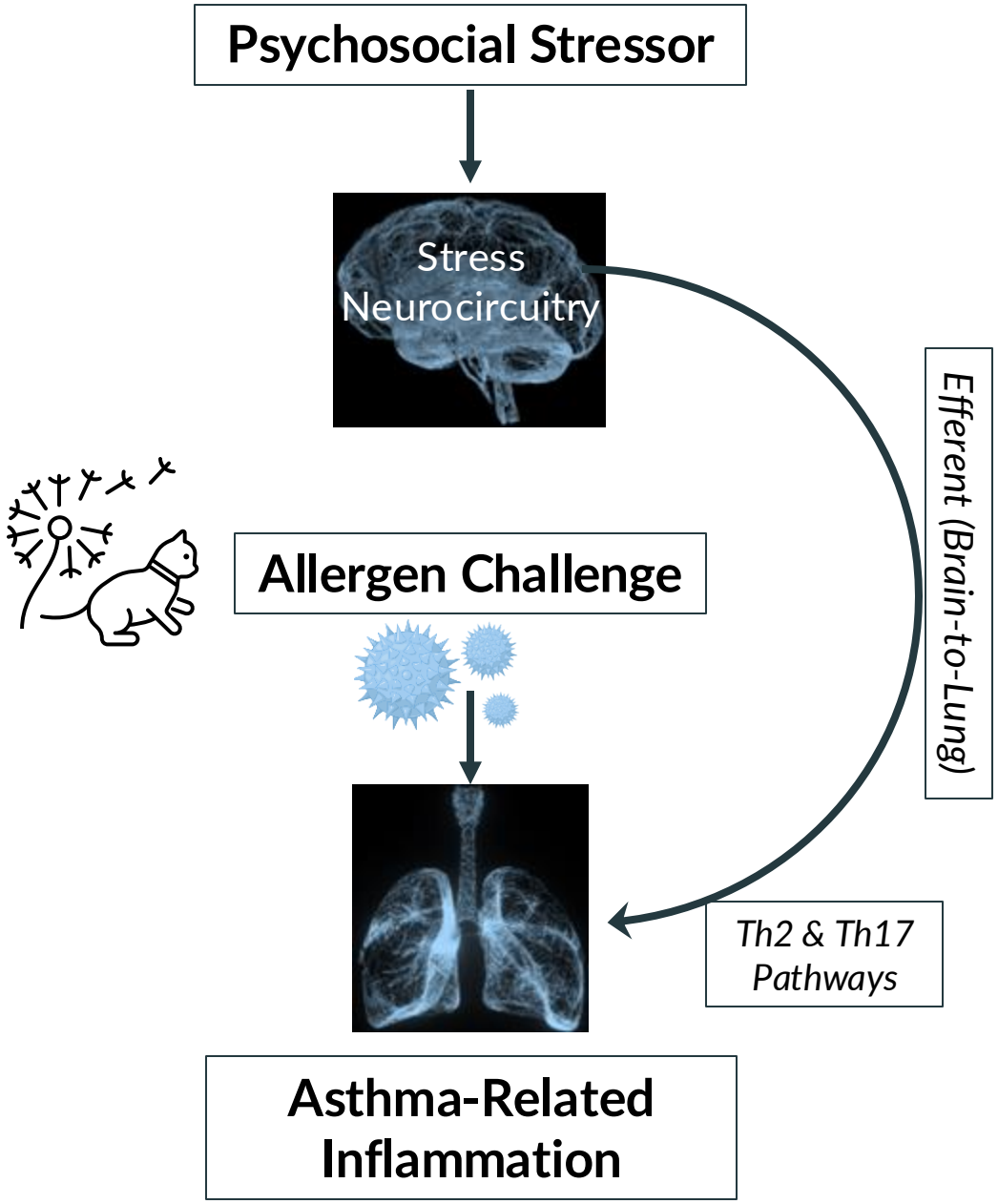
- *Stress/Emotion Neurocircuitry*
- *Th2 & Th17 Pathways*

Background: Motivation



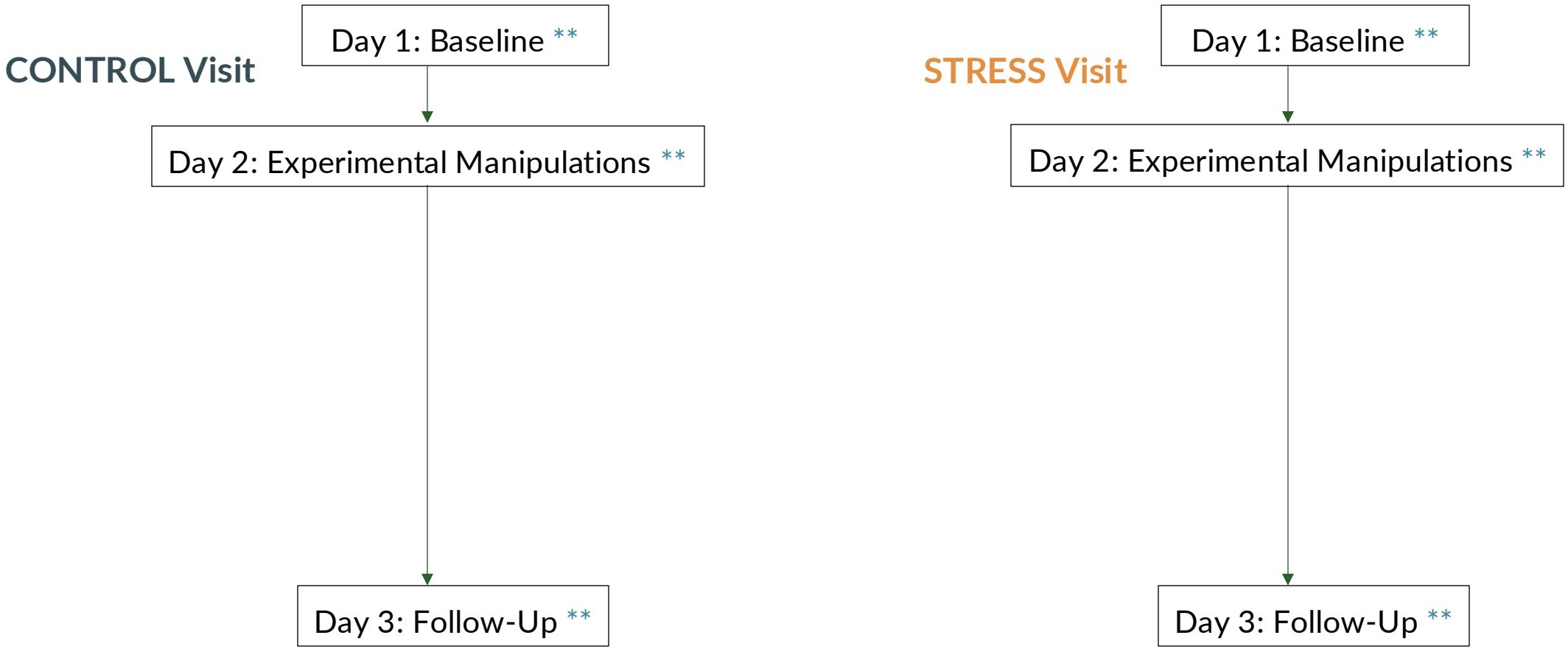
(Rosenkranz et al., Brain Behav Immun 2016)

Hypotheses


Psychosocial Stressor
Stress Neurocircuitry
Efferent (Brain-to-Lung)
Allergen Challenge
Th2 & Th17 Pathways
Asthma-Related Inflammation


Background
Methods
Results
Conclusions

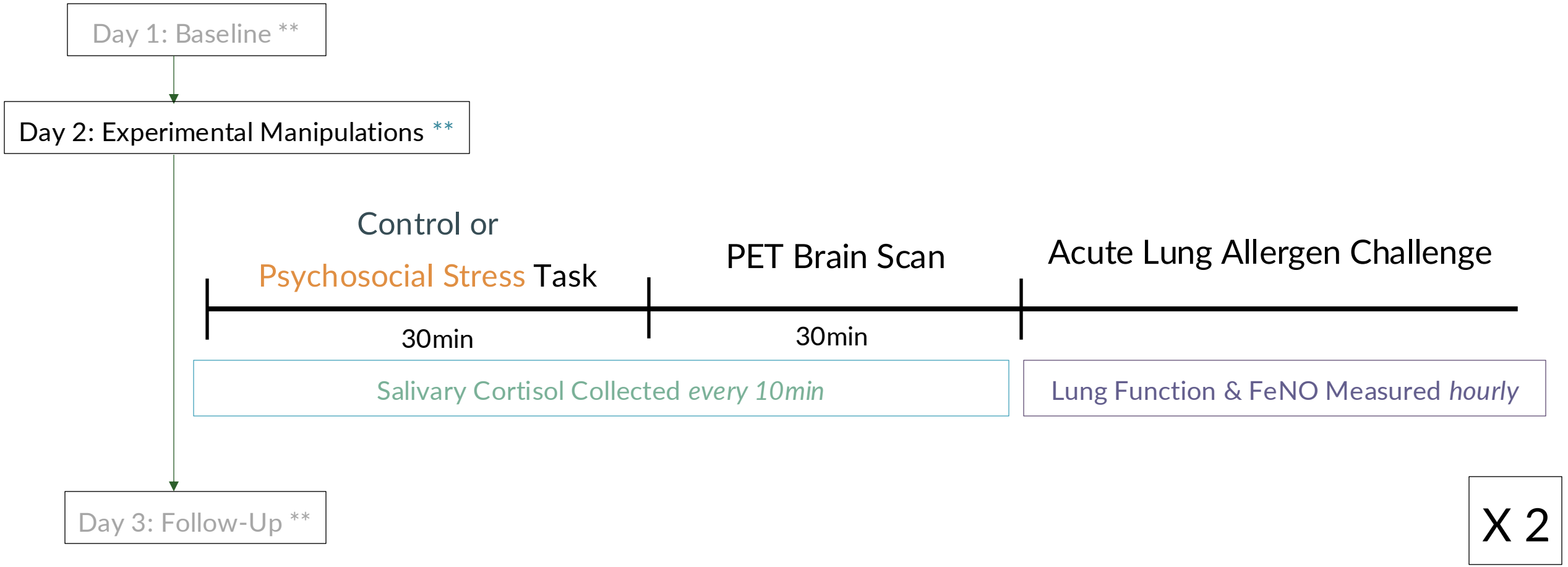
Study Design



*[4wk between **randomized** stress/control visit order]*

**** Airway inflammation measured (daily)**

Experimental Manipulations Day



** Airway inflammation measured (daily)

Analyses

- N = 28 (18 F); within-subject
  - *Target N = 50 not reached due to COVID-19*

PRIMARY OUTCOMES	MODERATORS	COVARIATES
TH2 Inflammation: Sputum & Eosinophils (EOS) Fraction of Exhaled Nitric Oxide (FeNO)	Perceived Stress Cortisol Area Under the Curve (AUC)	Antigen Dose
TH17 Inflammation: Interleukin (IL)-17, IL-1R1, IL-23A mRNA expression		
Brain Glucose Metabolism *Whole-brain and regions of interest*		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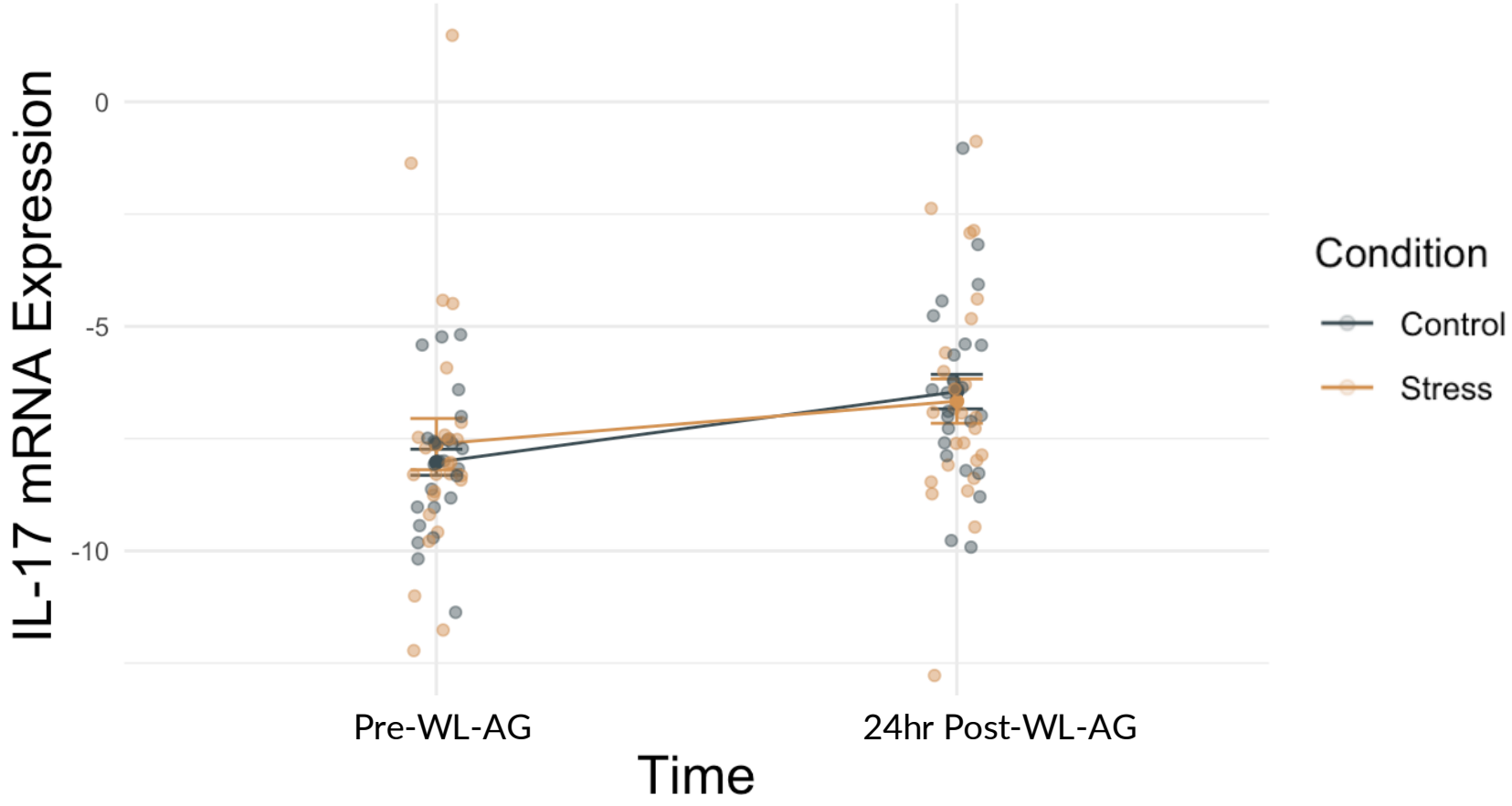
Acute stress does not significantly increase Airway Inflammation

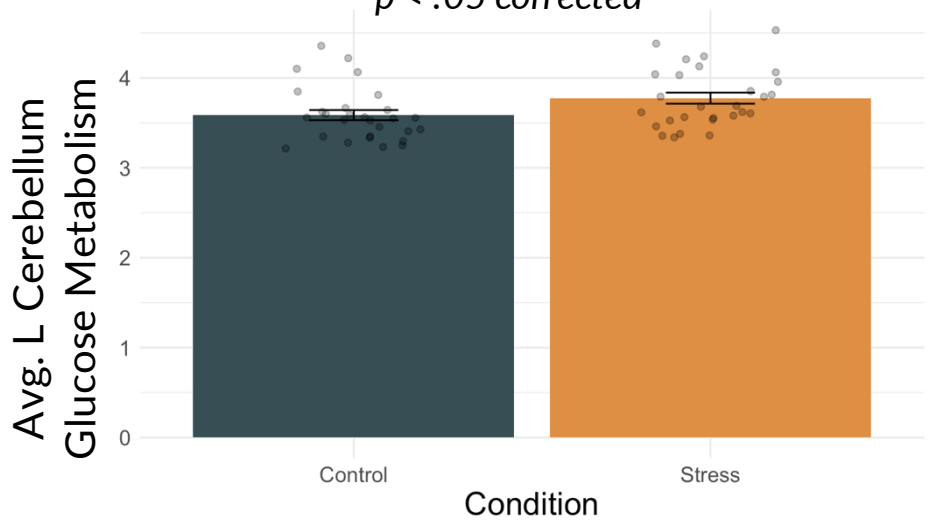


*MODEL: lmer(IL17 ~ time.c*condition.c + (1 + time.c*condition.c | subid))*

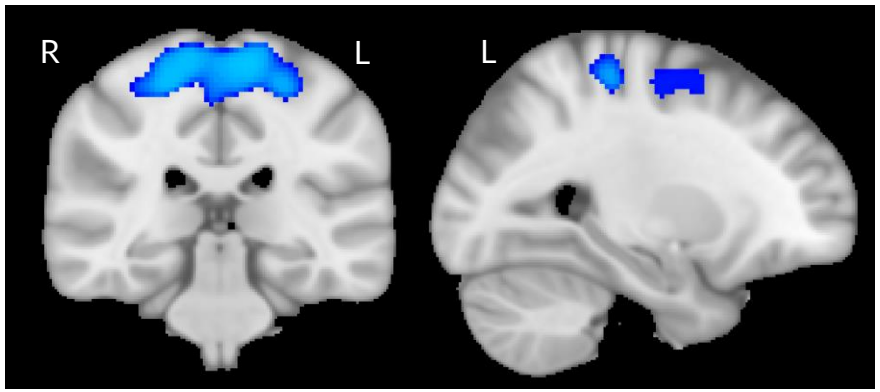
Glucose Metabolism:

Stress *Increases* Cerebellum

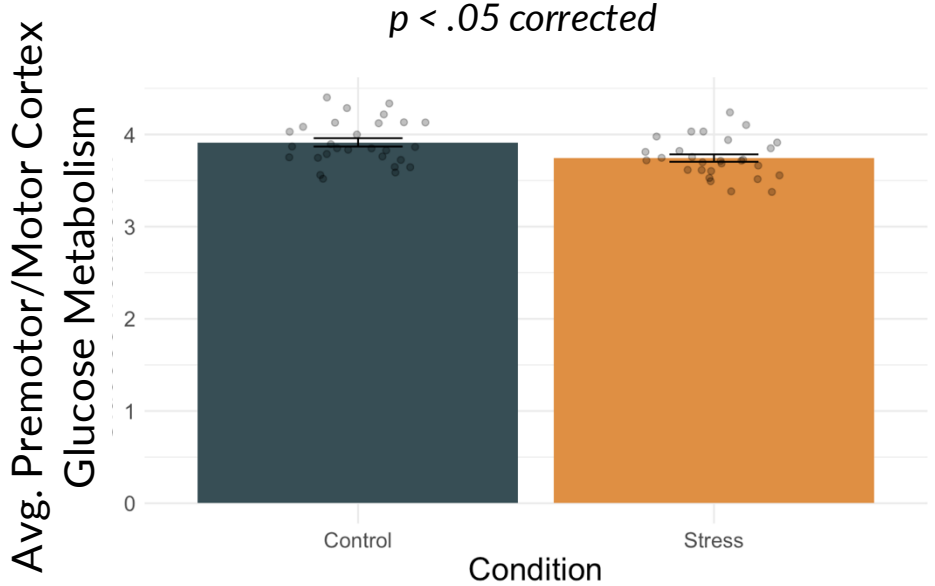
p < .05 corrected



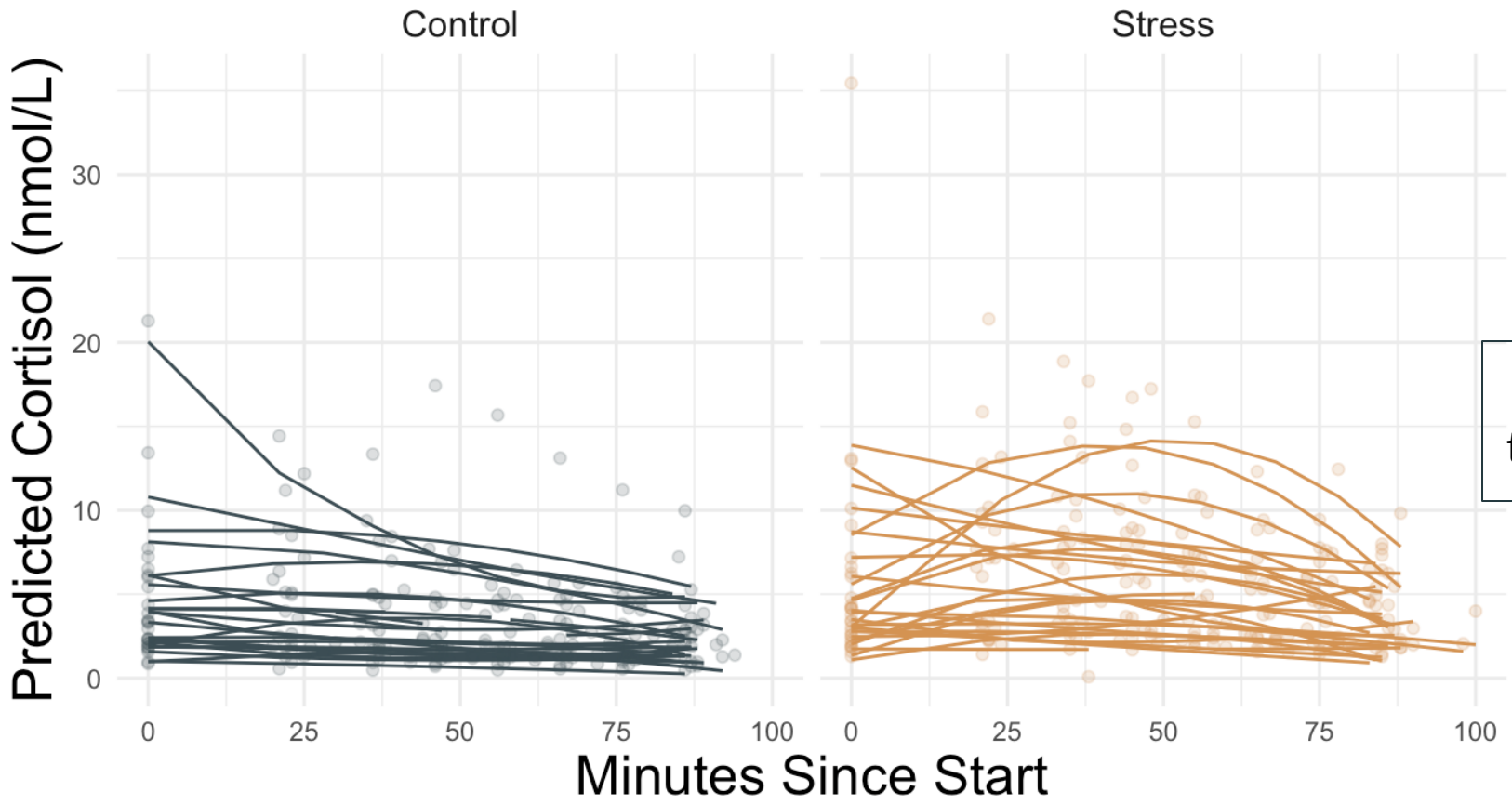
Stress *Decreases* Motor Cortex



p < .05 corrected



Acute Stress Increases Cortisol

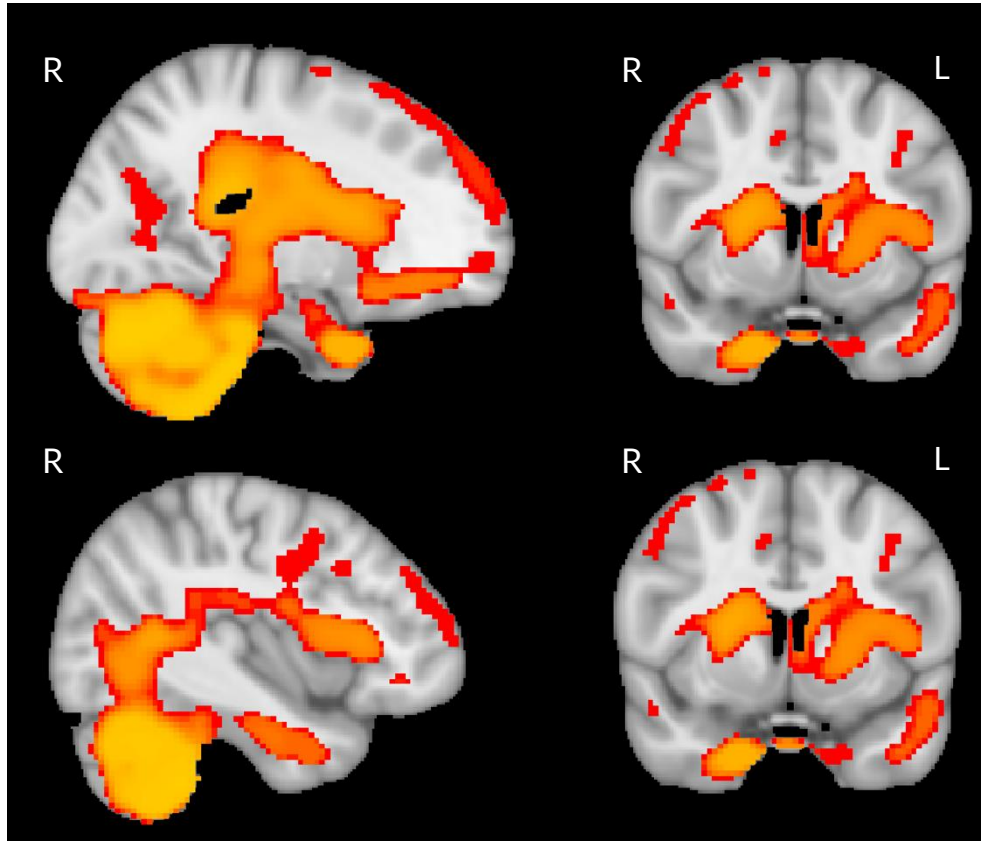


Stats:

t(27) = -2.78, p = .01

*MODEL: lmer(cortisol ~ minutes*condition.c + minutes^2*condition.c + (1 + minutes*condition.c + minutes^2*condition.c || subid))*

Cortisol Response to Stress is Associated with Widespread Brain Activity



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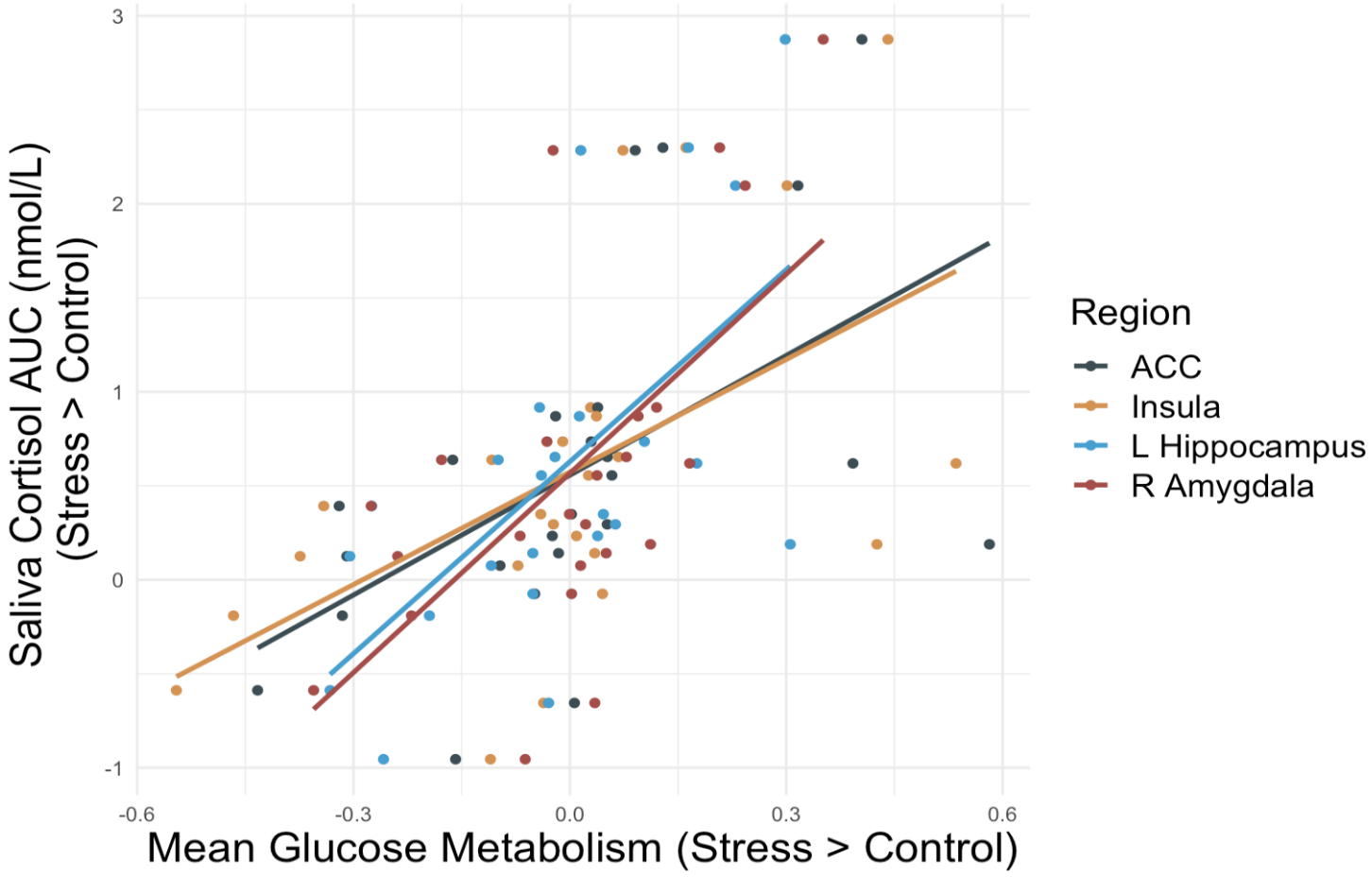
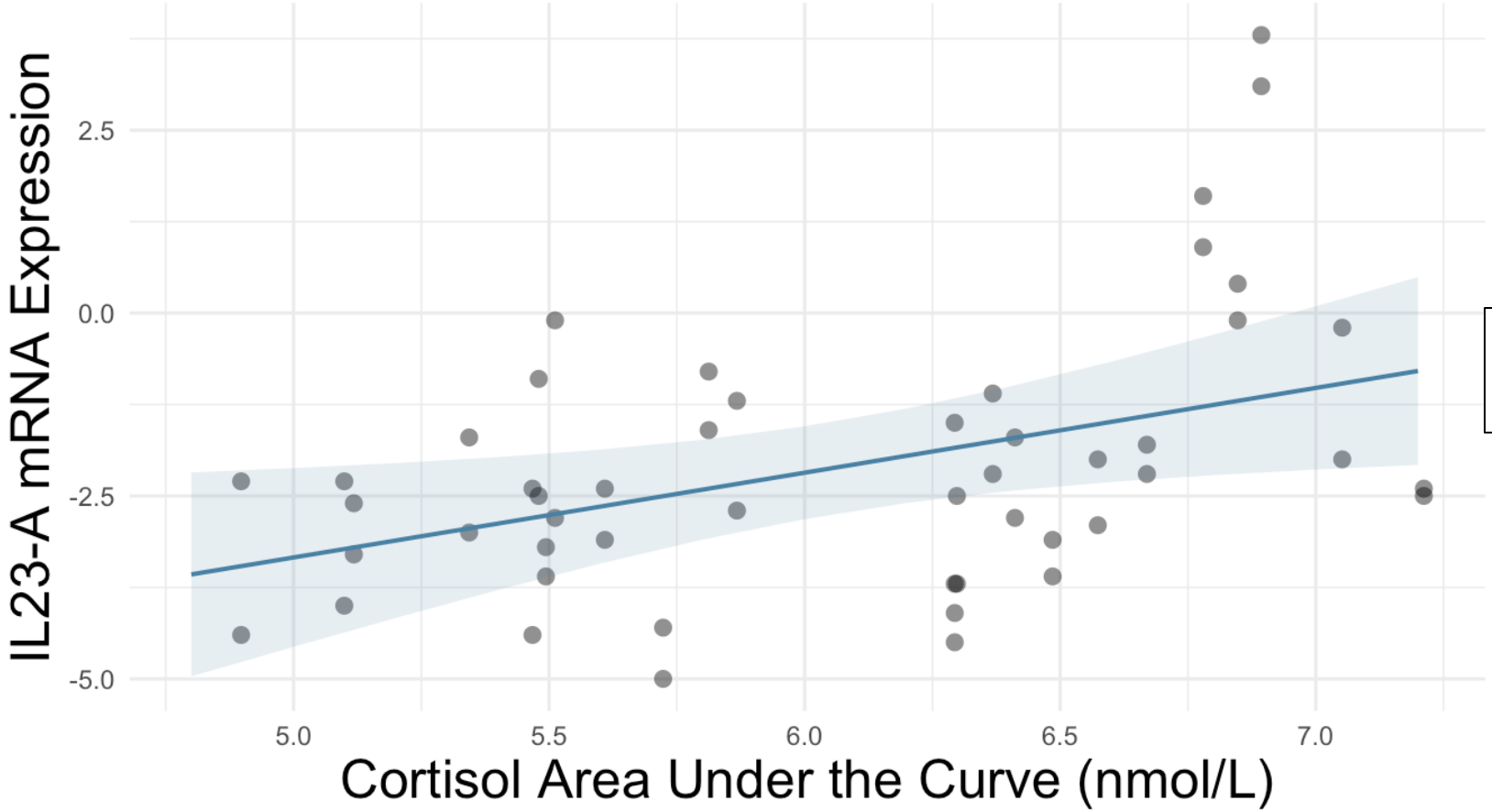


Stress-Induced Cortisol Correlates with IL-23A mRNA Expression

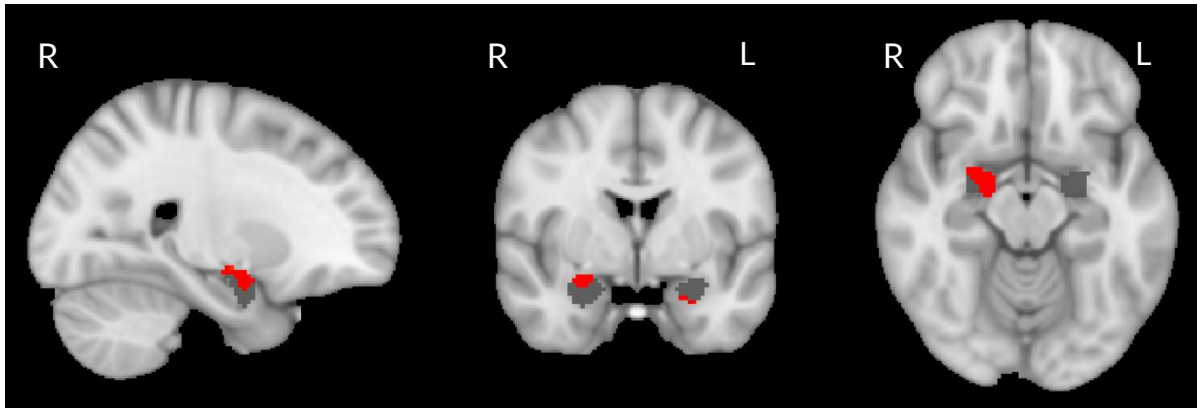


Stats
t(22.1) = 2.38, p = .003

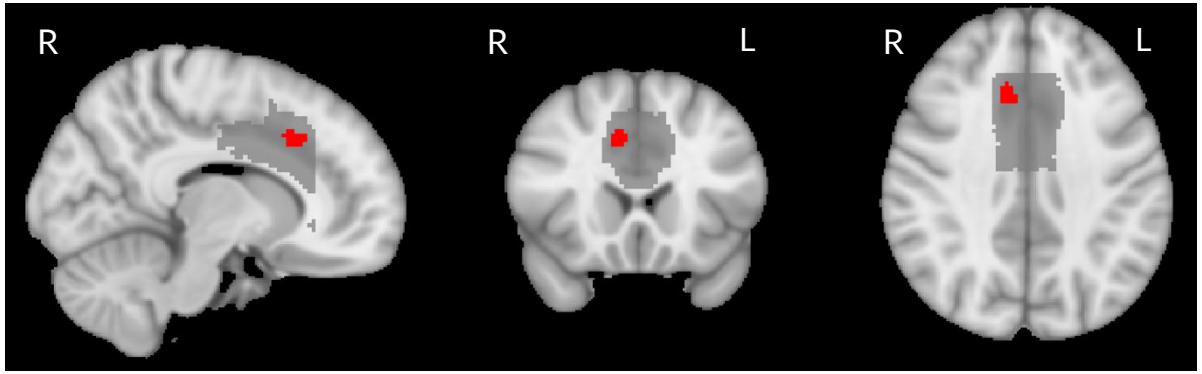
*MODEL: lmer(IL23A ~ time.c*cortisol AUCg + allergen.dose + (1 + time.c | subid) in stress condition only*

Stress-Related Salience Network Activity Predicts IL-23A mRNA Expression

AMYGDALA

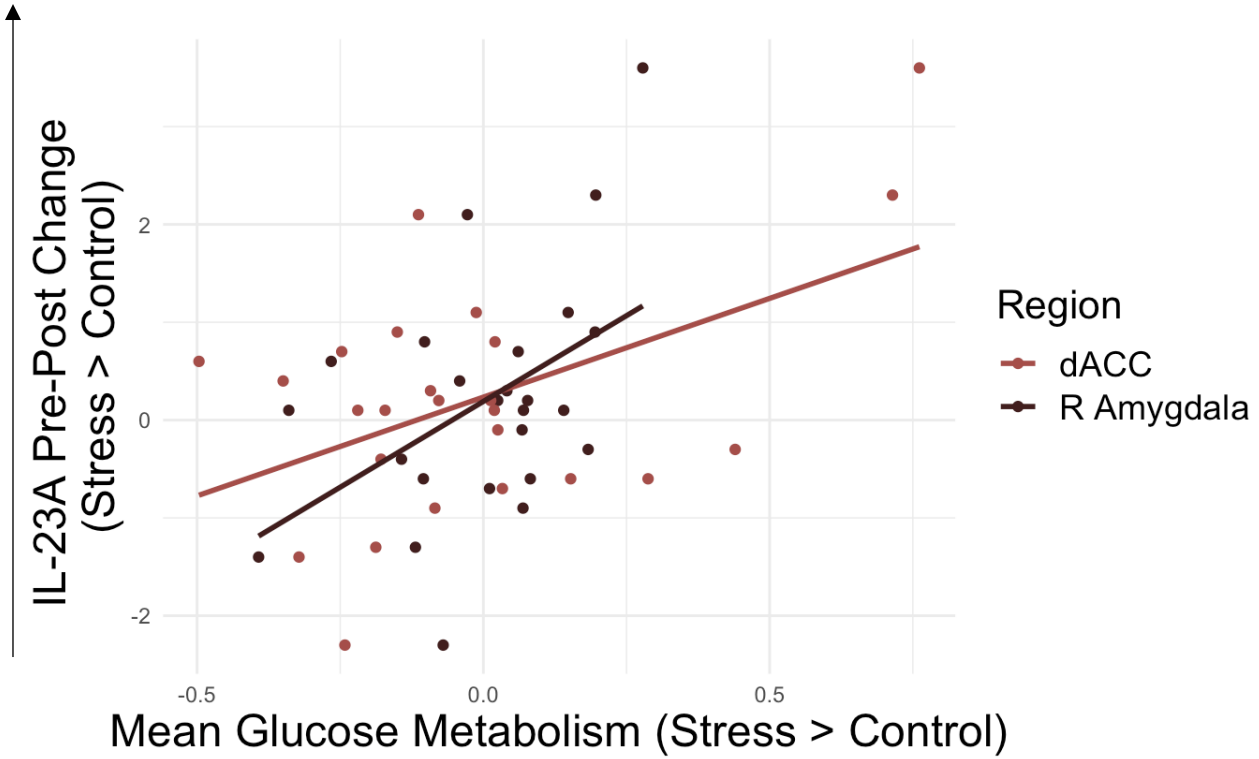


ANTERIOR CINGULATE



p < .05 corrected

Greater increase in inflammation, in stress vs control

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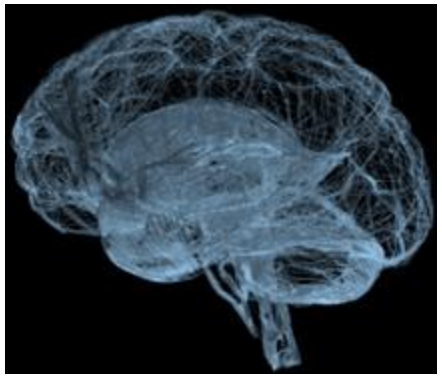
Conclusions

- Acute stress did not significantly alter airway inflammatory response
- Psychosocial stress caused greater glucose metabolism in the cerebellum and less in the motor cortex
- Stress-evoked cortisol was associated with glucose metabolism across the brain, including in the salience network
- Stress-related salience network activity predicted IL-23A mRNA expression

Conclusions

cortisol



stress

Asthma-Related Inflammation

Conclusions

stress

cortisol → descending pathways

airway inflammation

mind-body interventions?

=> targeted, personalized treatments

(Higgins et al., Brain Behav Immun-Health 2022)

Gratitude

Center for healthyminds
UNIVERSITY OF WISCONSIN–MADISON

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

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** first-year project committee*


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*Richard Davidson, PhD **


*Lyn Abramson, PhD **


*John Curtin, PhD **


Stephane Esnault, PhD


William Busse, PhD


Danika Klaus, RN

…and many more!

References - update!!

- Higgins, E. T., Davidson, R. J., Busse, W. W., Klaus, D. R., Bednarek, G. T., Goldman, R. I., Sachs, J., & Rosenkranz, M. A. (2022). Clinically relevant effects of Mindfulness-Based Stress Reduction in individuals with asthma. Brain, Behavior, & Immunity - Health, 25, 100509. https://doi.org/10.1016/j.bbih.2022.100509
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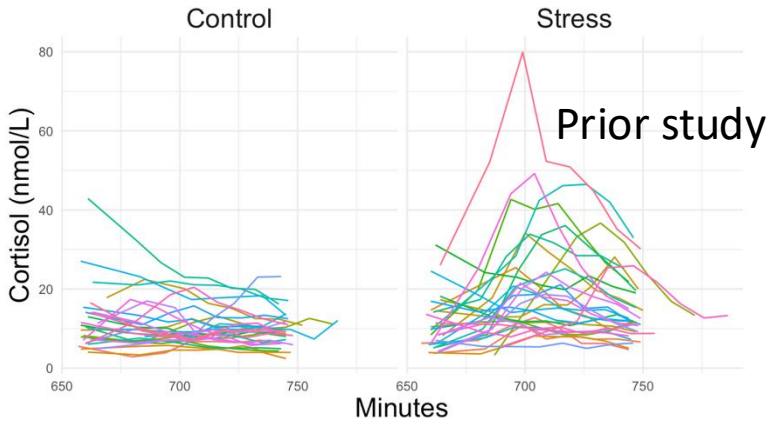
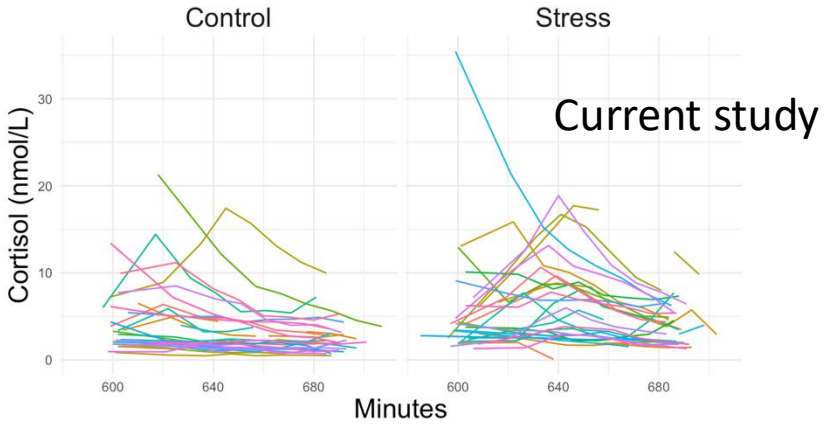
Alternative Explanations

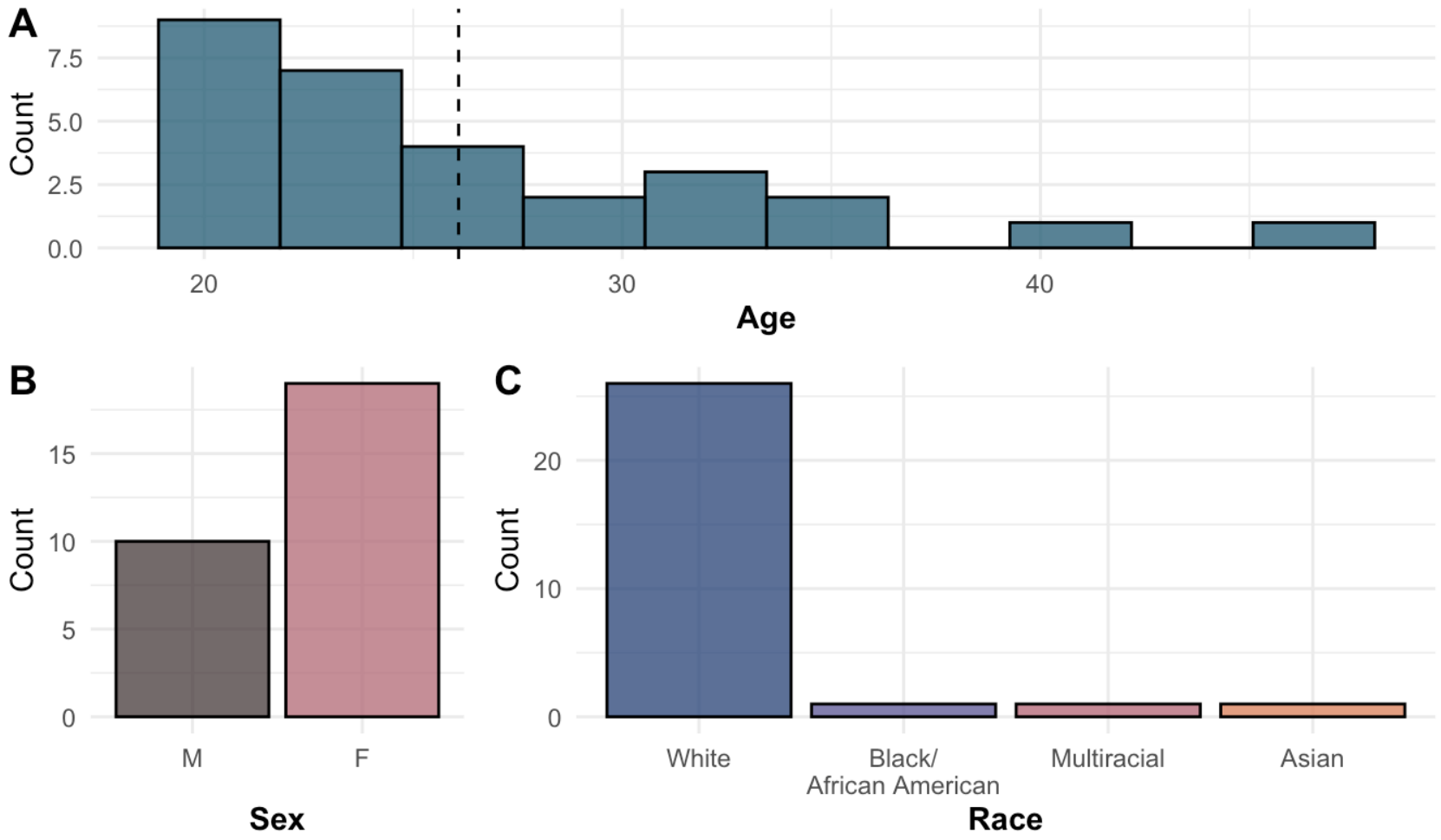




Alternative explanations:

- Less robust acute stress response
- Sympathetic Nervous System moderation
- Acute stress does not prime inflammatory response to allergen challenge in those with moderate chronic stress

Demographics



TH17 Cells

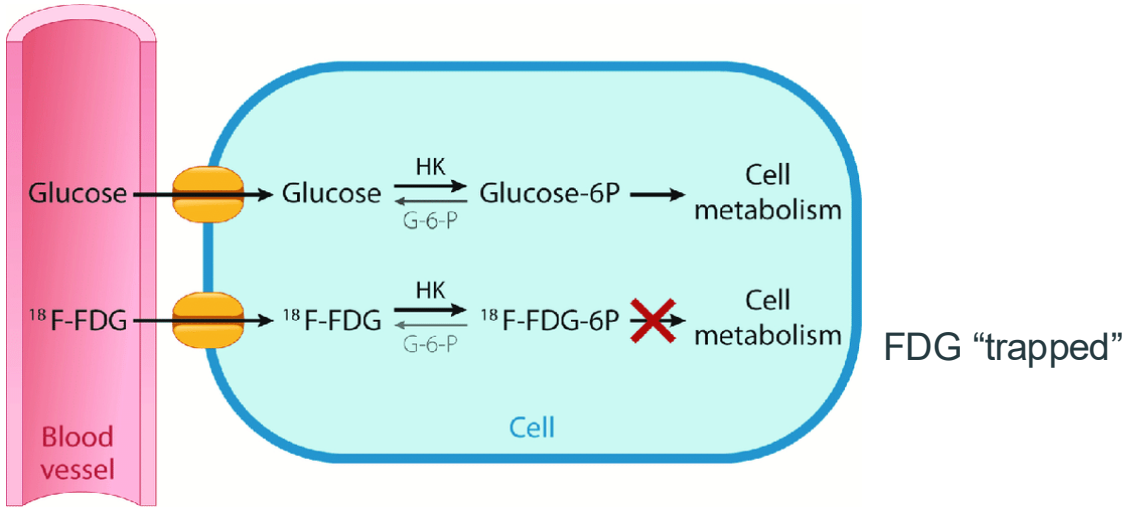
- Adaptive (Humoral) Immune System [autoimmune disease] → IL-17 (neutrophils)
  - Associated with depression
- Differentiation: requires IL-6 and TGFβ; promoted by TNF-a, IL-1β, IL-21, IL-23
- Stress → ↑ IL-1β

Asthma:

- IL-17 in severe asthma … role in mild asthma?
- Modulates Th2 responses
- EOS release IL-1β → IL-17 expression

PET

- Brain Glucose Metabolism: fluoro-18-deoxyglucose (FDG)-Positron Emission Tomography (PET)
  - Venous FDG injection → [uptake time: TSST] → Scan



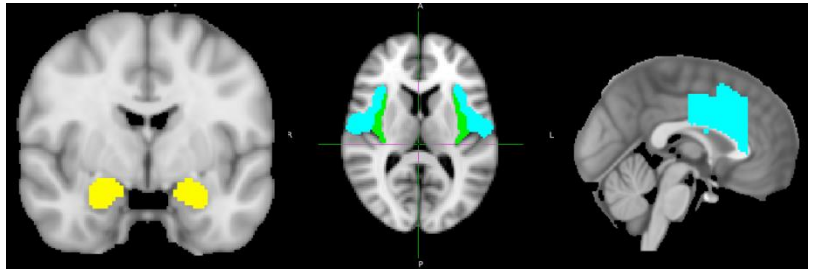
(Rahman et al., 2019)

Analyses: *stress neurocircuitry*

- Whole-Brain

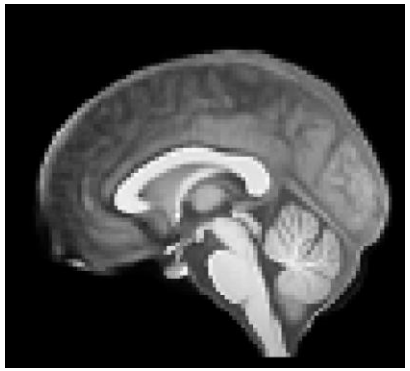
  +

- a priori ROIs
  - amygdala, infula/frontal opercular cortex (IFOC), dorsal anterior cingulate cortex (dACC)
- Paired t-tests with FSL's randomise
- Regressions with FSL's randomise
  - PET image with cortisol and inflammatory biomarkers

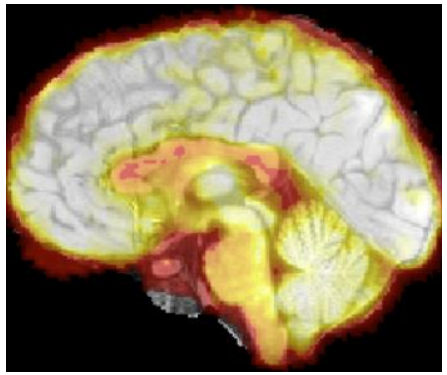


PET Processing

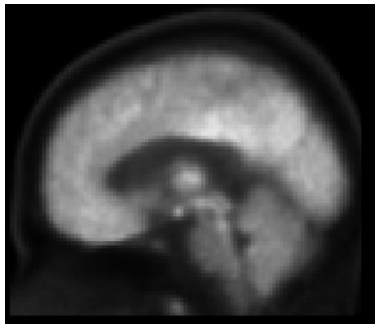
- Processing pipeline optimized for PET-T1 co-registration
  - FSL's FEAT; AFNI; ANTs



Study-specific T1 template



Example co-registration

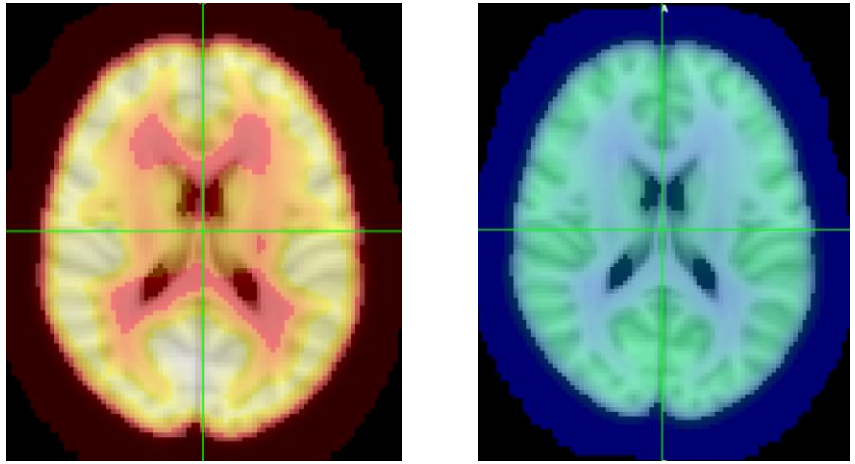


PET template in MNI space

  - 2 subjects missing T1; co-registered to PET template in MNI space

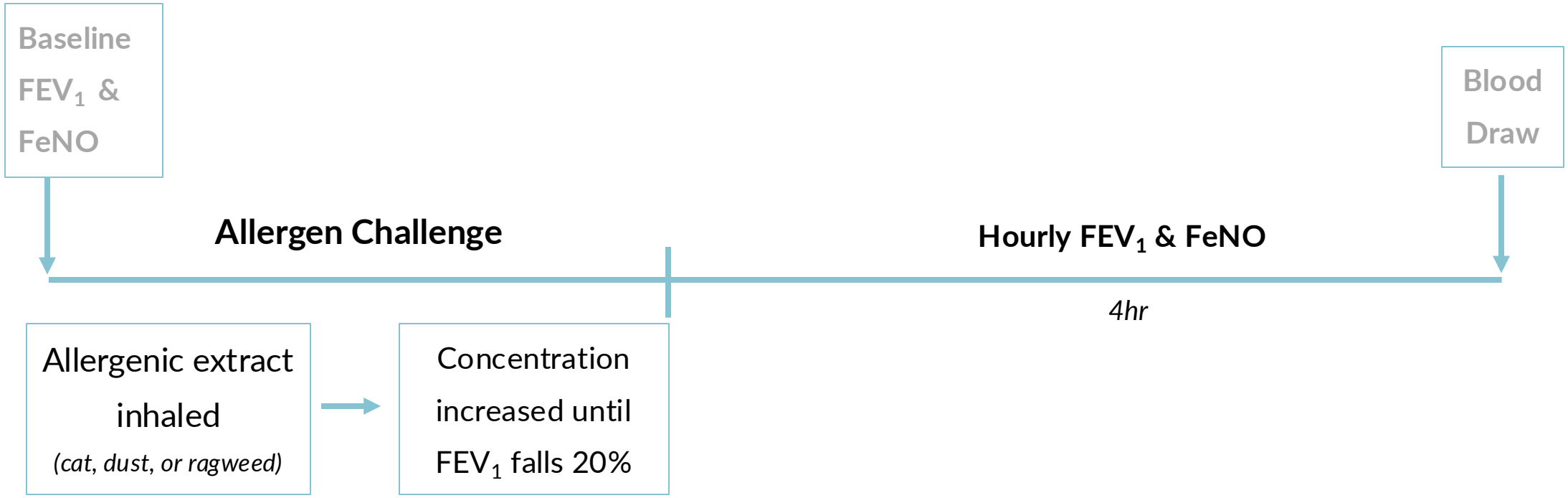
PET Processing

- 4D scaled, smoothed PET images co-registered to T1 template in MNI space: merge by condition
- Stress minus Control



Stress — Control

Allergen Challenge



FEV_1: Forced Expiratory Volume (1s) = *Lung Function*

FeNO: Fraction of Exhaled Nitric Oxide = *Airway Inflammation*

Allergen Challenge Dose Conversion

- For safety, dose varied by challenge and by person
  - Ragweed Pollen (n = 5); Cat (n = 12); or Dust Mite (n = 12)

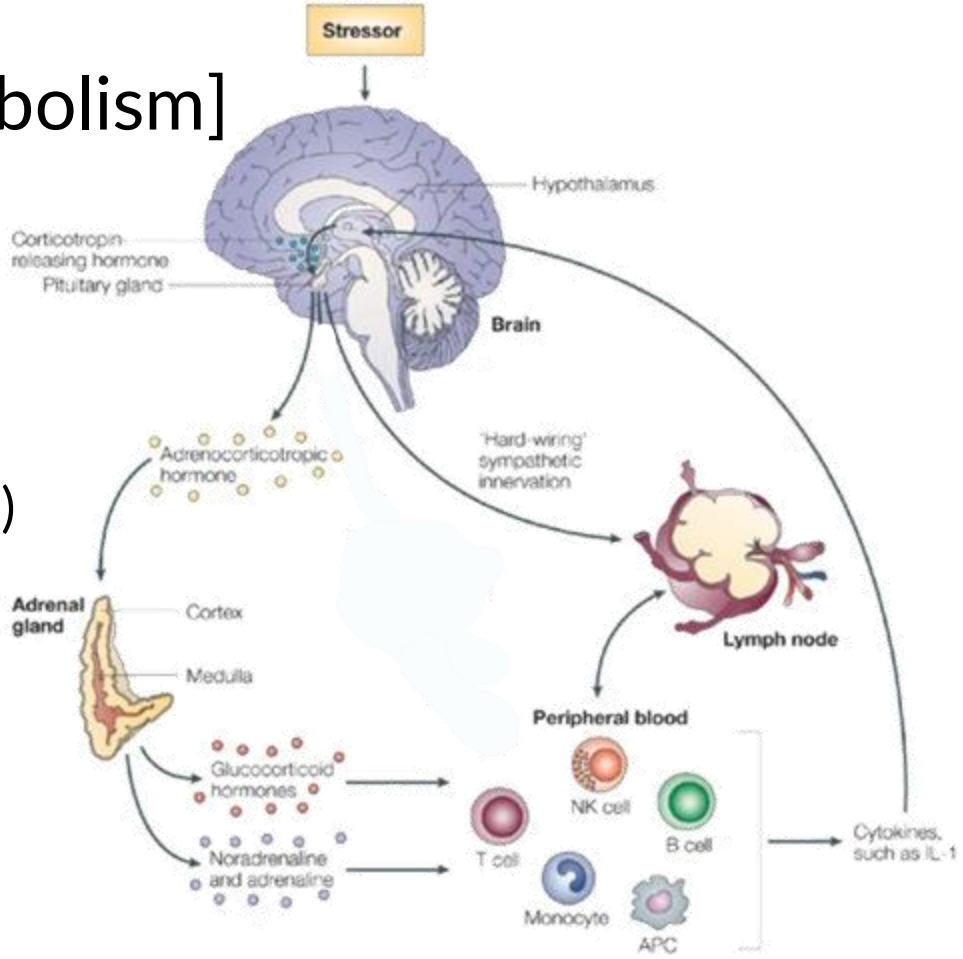
- Nonlinear least squares to extract optimal parameters used in conversion equation

Ragweed Equivalent Dose =

$$0.004 \times (\text{Cat/Dust dose}) + .00002 \times (\text{Cat/Dust dose})^2 - .00000002 \times (\text{Cat/Dust dose})^3$$

Proximal & Distal Measures

- Distal Mechanism: brain [glucose metabolism]
  - In-Between Mechanisms: brainstem
- Proximal Mechanisms:
  - HPA Axis
  - Sympathetic Nervous System
  - Neurogenic Inflammation (Sensory Neuropeptides)



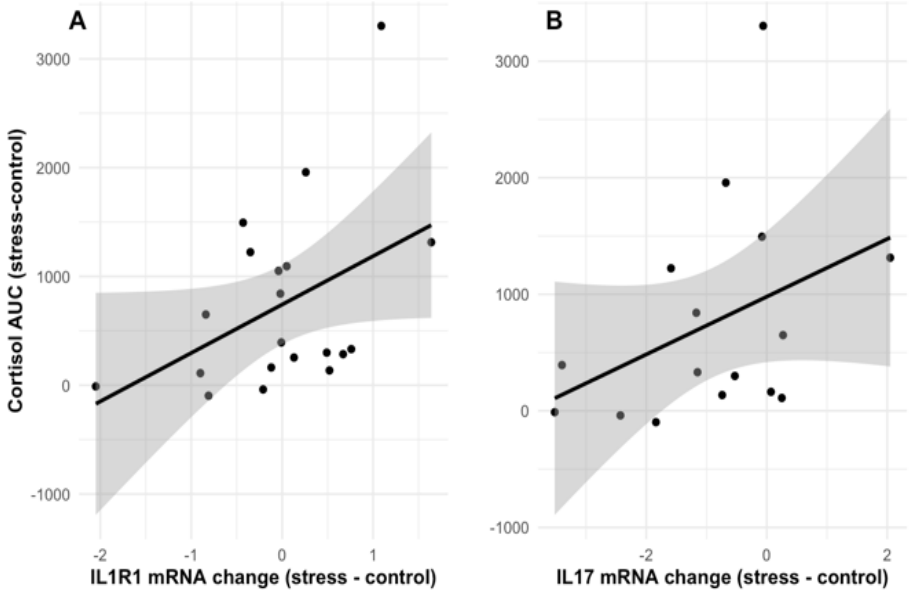
(Glaser & Kiecolt-Glaser, 2005)

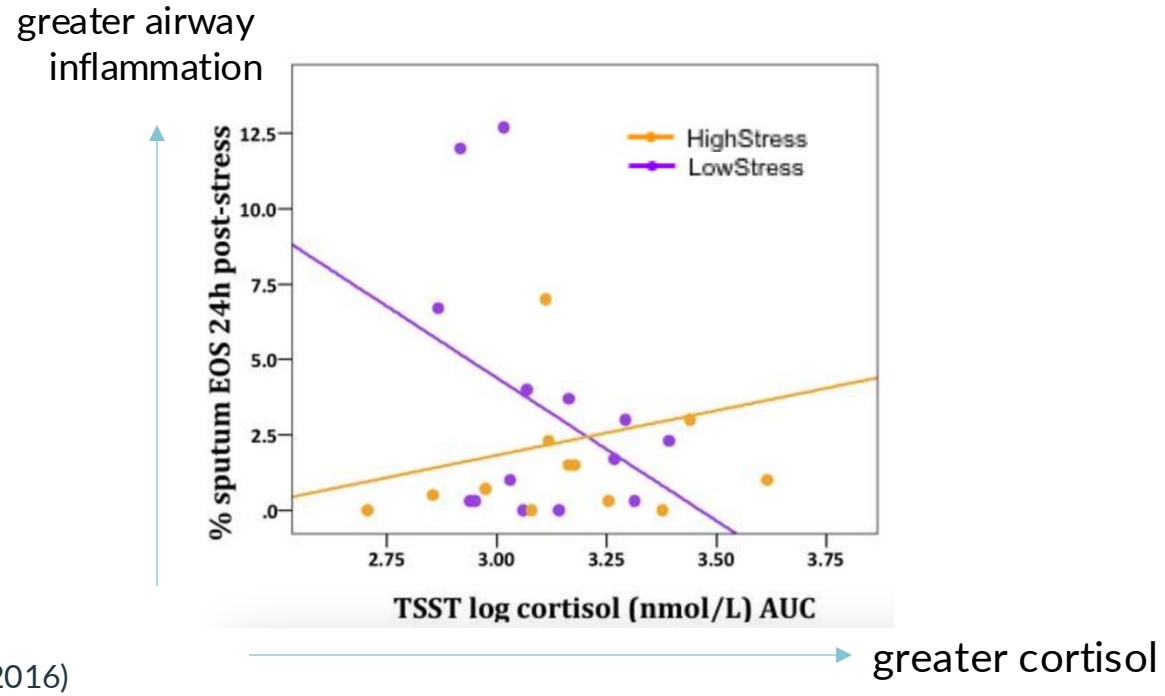
Power: Stress Neurocircuitry

- Sensitivity Power Analysis:
  - For 80% power (N = 27) at α = .05:
  - **Medium Effect Size *d* = .56**

Prior Evidence

- Psychosocial Stressor ⟶ Increased Cortisol, associated with Airway Inflammation Biomarkers
  - Th17 path (IL-17A, IL-1R1)
  - Th2 path (EOS) moderated by chronic stress

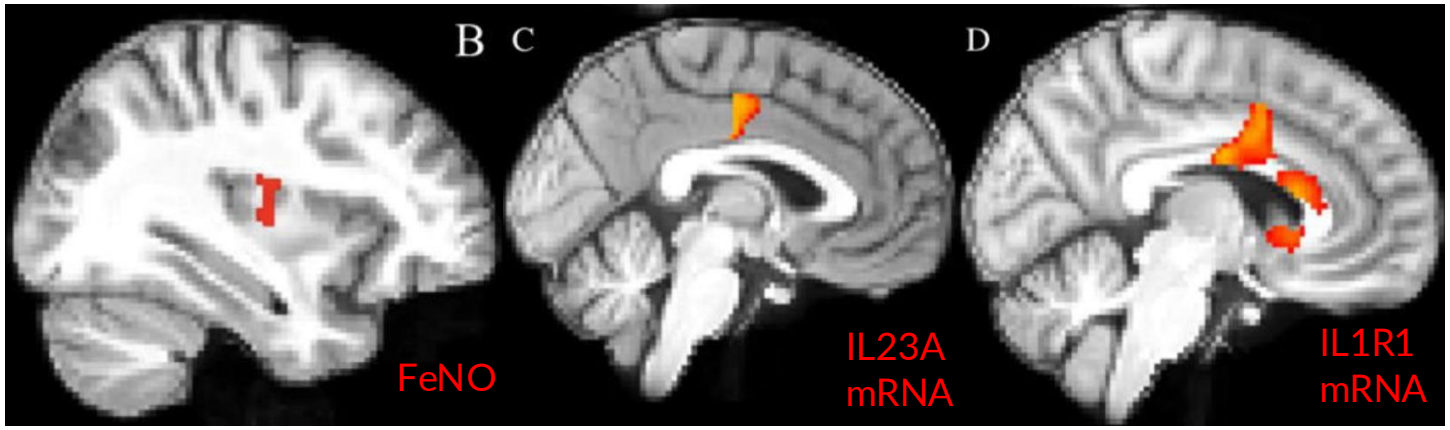




(Rosenkranz et al., 2016)

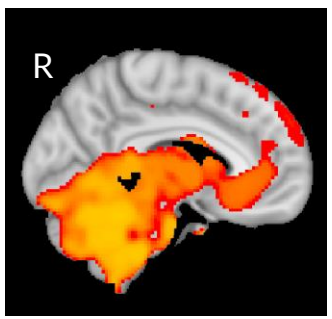
Prior Evidence

- Psychosocial Stressor ⟶ Stress Neurocircuitry Activation associated with Airway Inflammation Biomarkers
  - Th2 pathway (FeNO) & Th17 cell mRNA (IL23A, IL1R1)

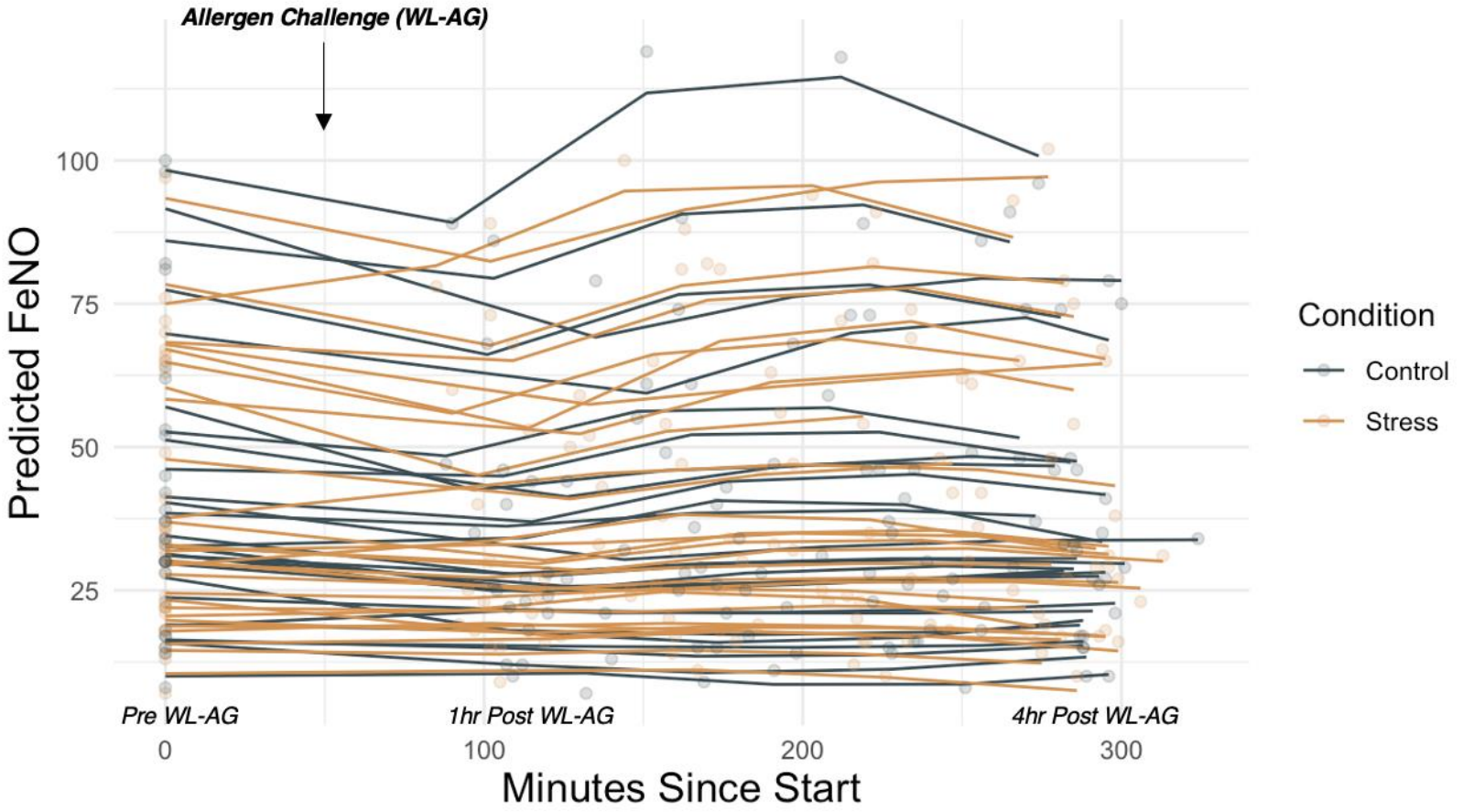


(Rosenkranz et al.,

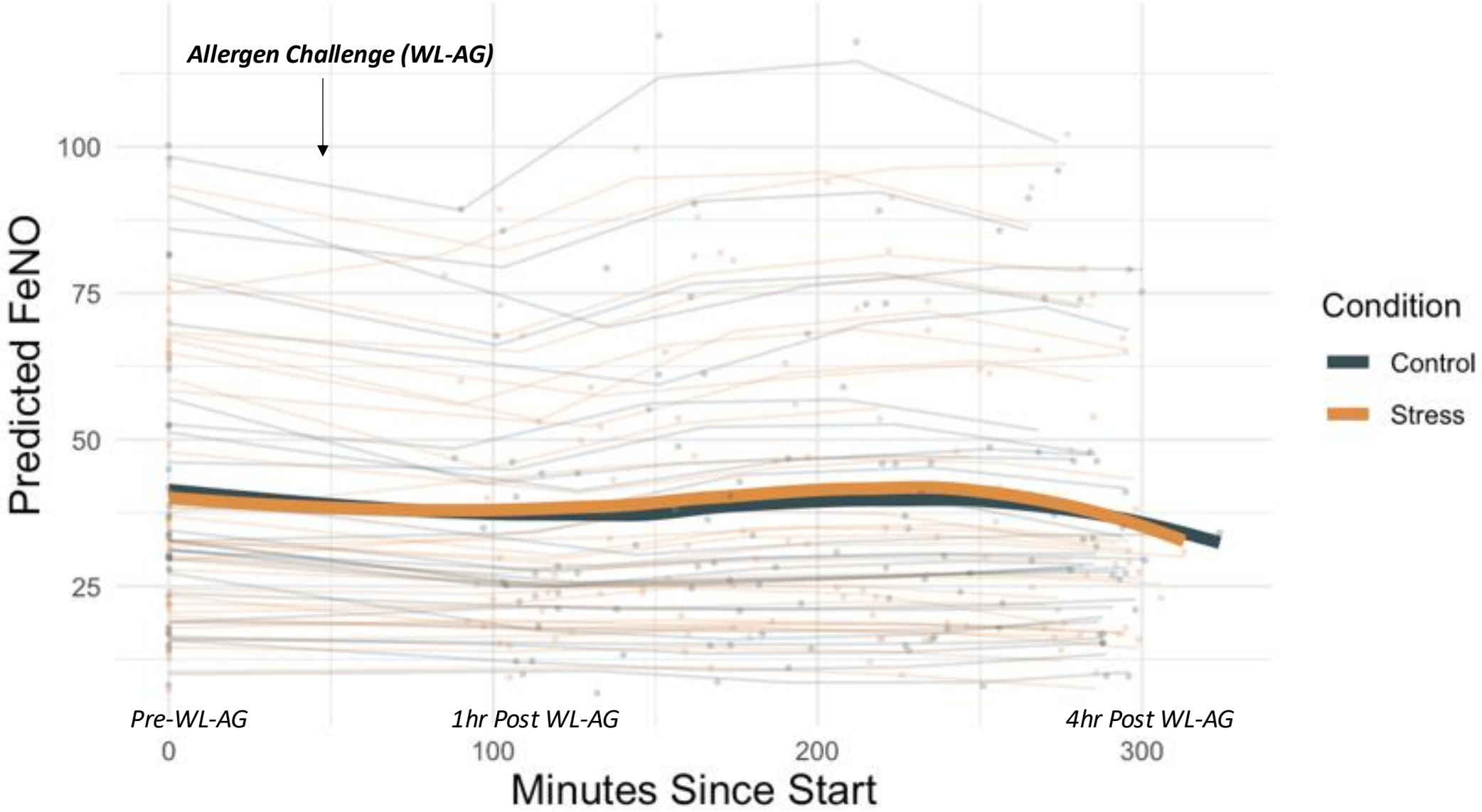
Cortisol



Acute stress does not significantly increase Airway Inflammation



*MODEL: lmer(cortisol ~ minutes * condition.c + minutes^2 * condition.c + (1 + minutes * condition.c + minutes^2 * condition.c || subid))*


Allergen Challenge (WL-AG)
Predicted FeNO
100
75
50
25
Pre-WL-AG
1hr Post WL-AG
4hr Post WL-AG
0
100
200
300
Minutes Since Start
Condition
Control
Stress