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

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FYP Symposium 2023

Overall Roadmap

Background → Methods → Results → Conclusions

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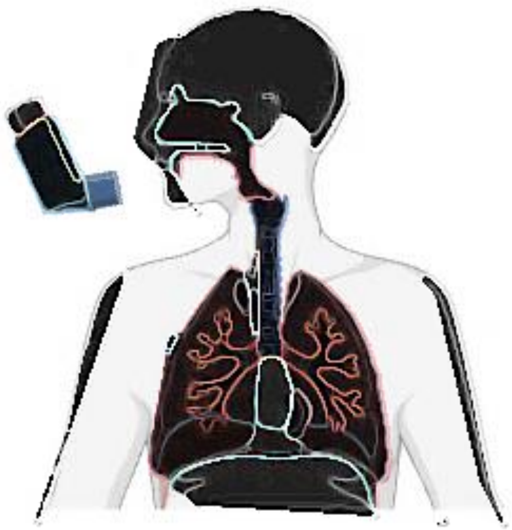
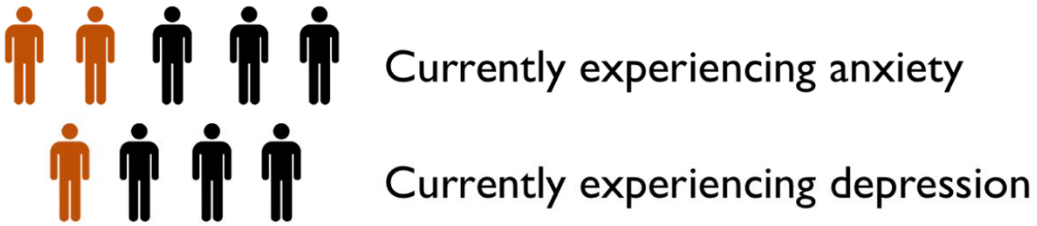
Background → Methods → Results → Conclusions

Asthma interacts with the mind

U.S. Asthma Prevalence:
24,963,874
(~8%)



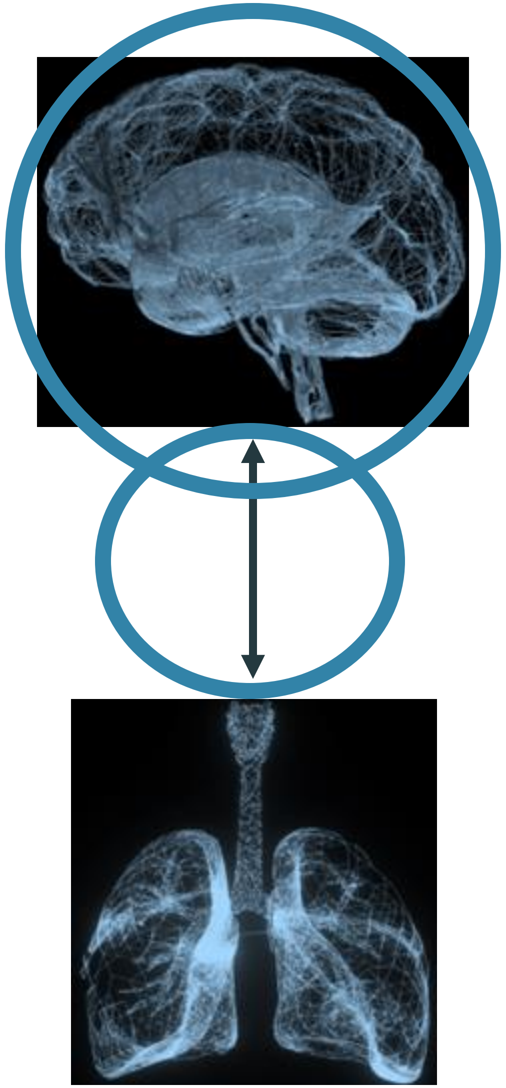
With Severe Asthma:



(CDC, 2023; McDonald et al., Eur. Resp. J. 2019; Severe Asthma Toolkit, 2019)

Brain and immune pathways are unknown

stress



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Asthma-Related Inflammation

Initial evidence:

- *Stress/emotion neurocircuitry; Salience Network*

- *Immune pathways that trigger asthma symptoms (e.g., Th17)*

Motivation: Acute stress increases markers of airway inflammation

(Rosenkranz et al., Brain Behav Immun 2016)

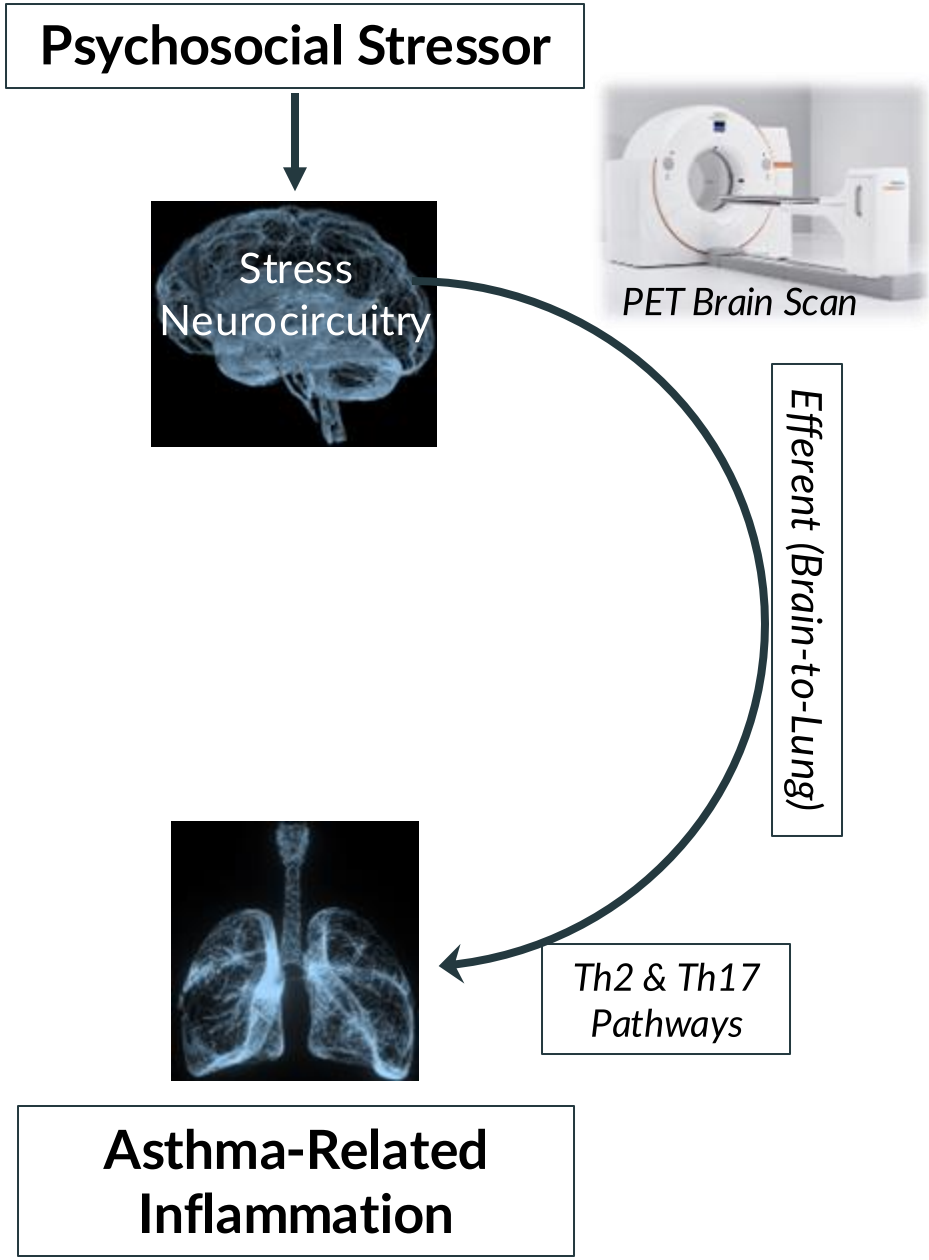


Image: *https://www.siemens-healthineers.com/en-us/molecular-imaging/pet-ct/biograph-vision*

Hypothesis: Acute stress will increase *<u>provoked</u>* airway inflammation

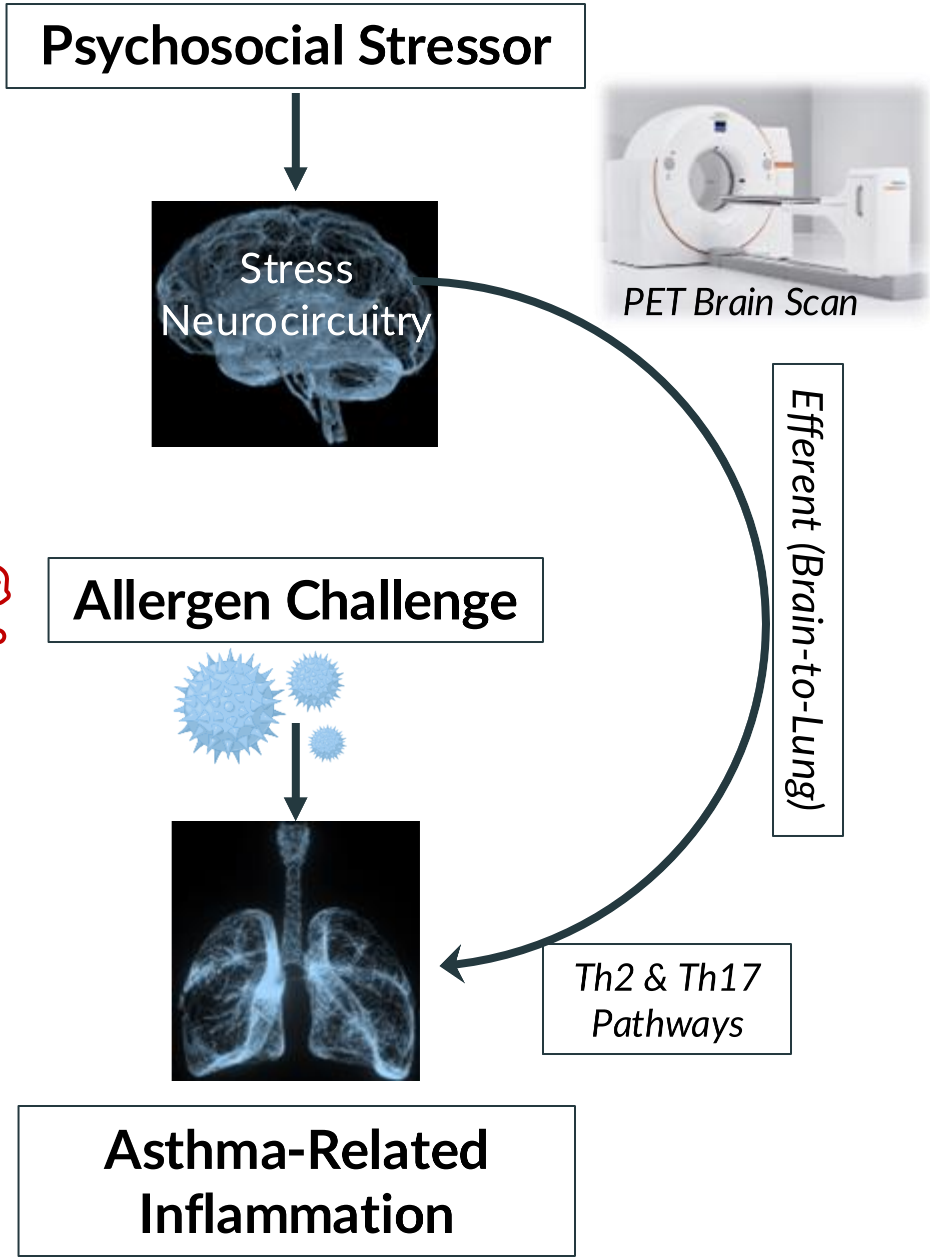


Image: *https://www.siemens-healthineers.com/en-us/molecular-imaging/pet-ct/biograph-vision*

Background

Methods

Results

Conclusions

Within-Subjects Design

STRESS Visit

Psychosocial Stress Task

30min

[4wk]

Control Task

30min

CONTROL Visit

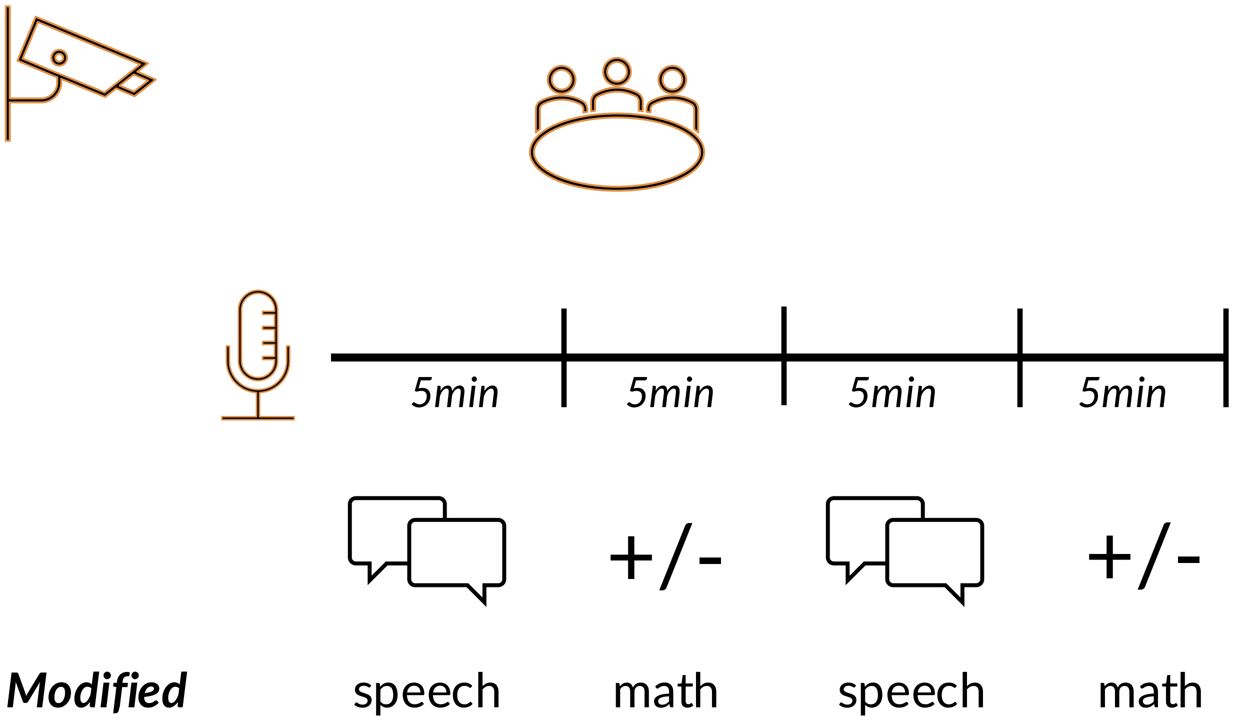
Control or Psychosocial Stress Task

Psychosocial Stress or

Control Task

Trier Social Stress Test (TSST)

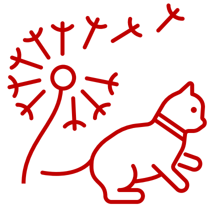
Control Task



(Kern et al., PNEC 2008)

Within-Subjects Design

STRESS Visit



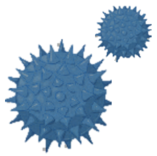
Psychosocial Stress Task	PET Brain Scan	Acute Lung Allergen Challenge
30min	30min	4hr
Salivary Cortisol Collected *every ~10min*		Lung Function & Inflammation *hourly*

CONTROL Visit

Control Task	PET Brain Scan	Acute Lung Allergen Challenge
30min	30min	4hr
Salivary Cortisol Collected *every ~10min*		Lung Function & Inflammation *hourly*

Analyses: linear mixed models & permutation regressions (brain)

- N = 28 (*18 F*), 19-45y

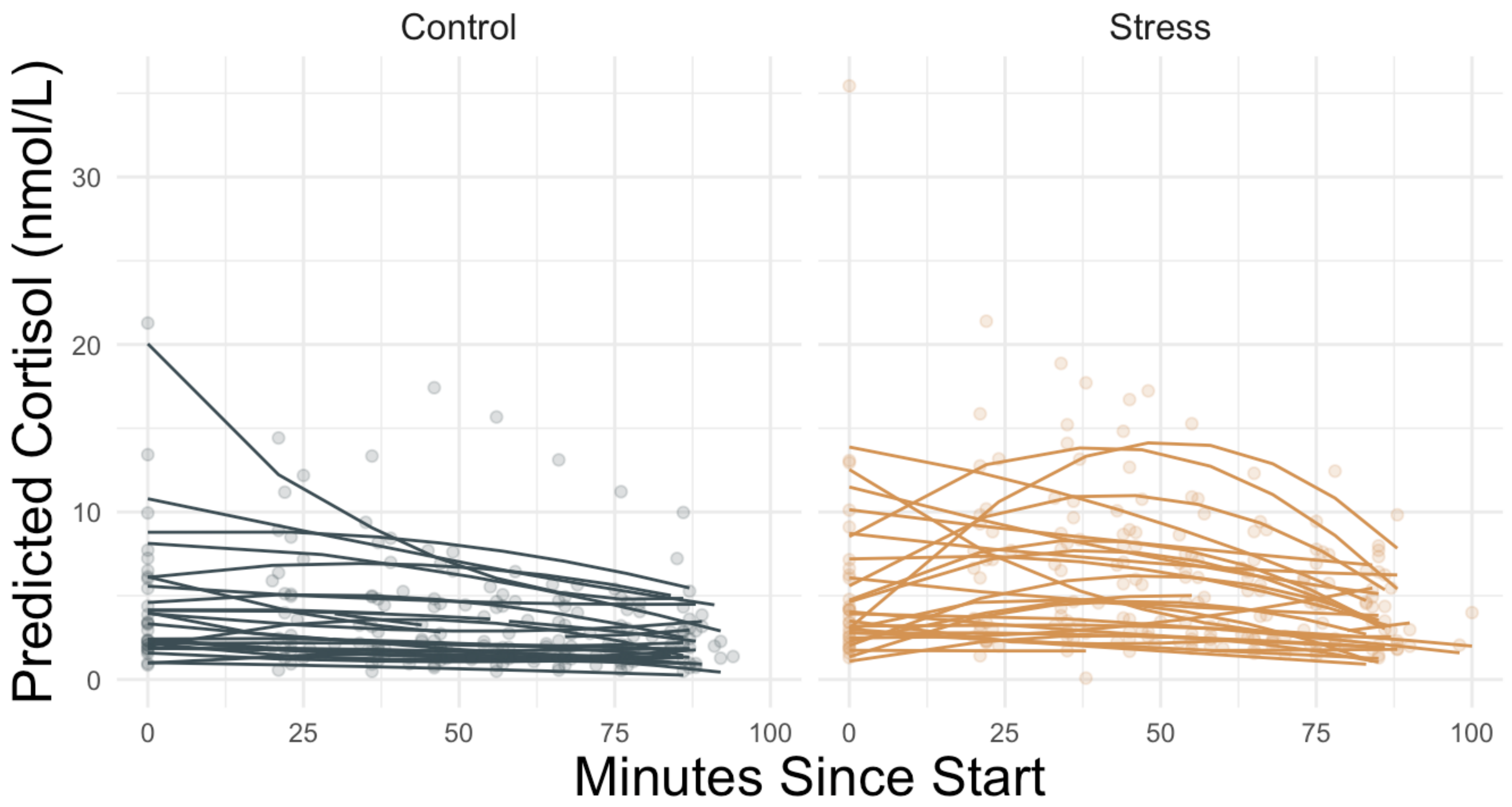


PET Brain Scan

PRIMARY OUTCOMES	MODERATORS	COVARIATES
Inflammatory Biomarkers (Airway): *Immune cells involved in airway tightening and asthma response*	Perceived Stress Cortisol	Antigen Dose
Brain Glucose Metabolism *Index of brain activity during stress*		

Background Methods **Results** Conclusions

Stress increases cortisol



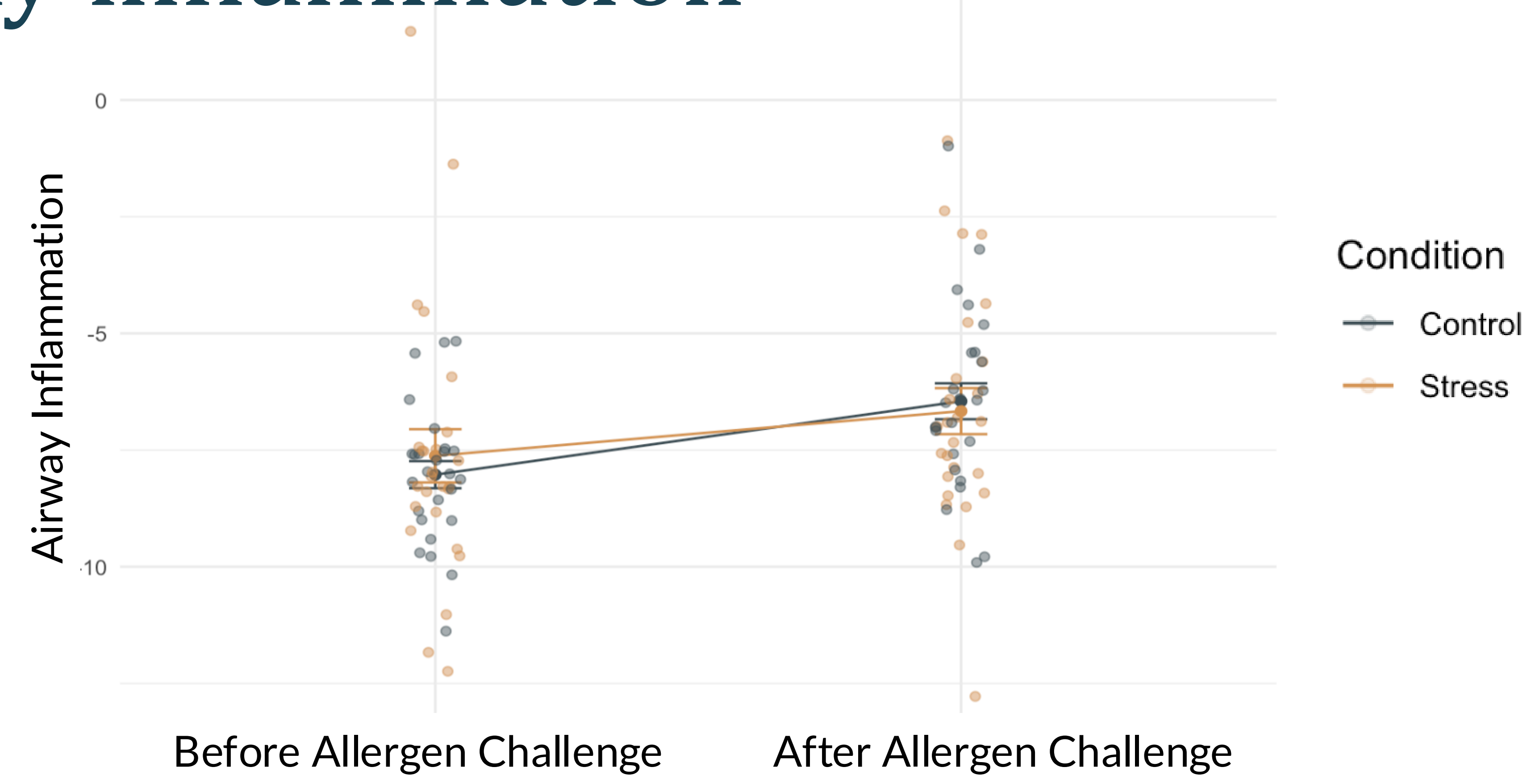
<u>Stats:</u>

$t(24.7) = -3.46$,

$p = .002$

*MODEL: lmer(cortisol ~ minutes*condition.c + minutes²*condition.c + (1 + minutes*condition.c + minutes²*condition.c || subid))*

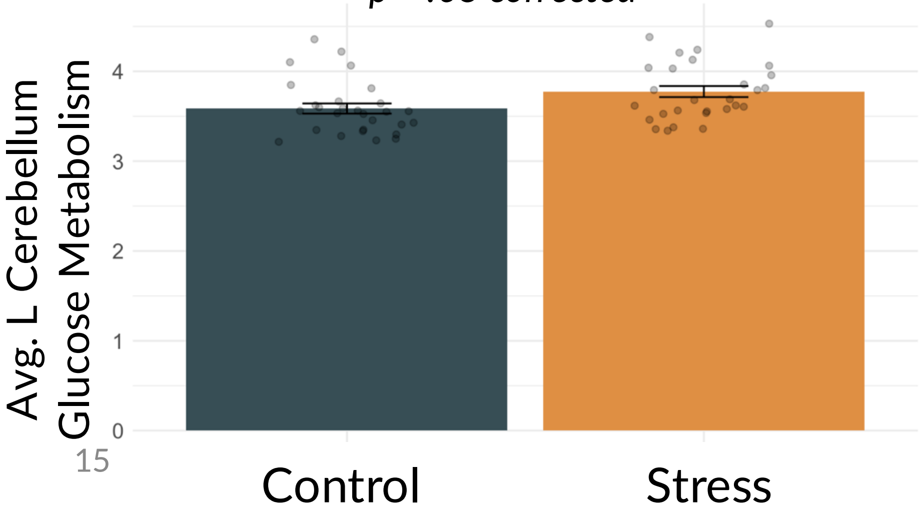
Stress does not significantly increase airway inflammation



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

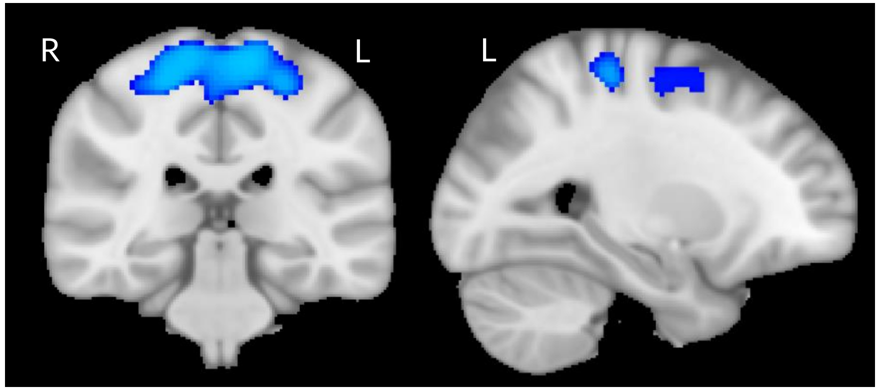
Stress is associated with *increased* cerebellum activity

p < .05 corrected

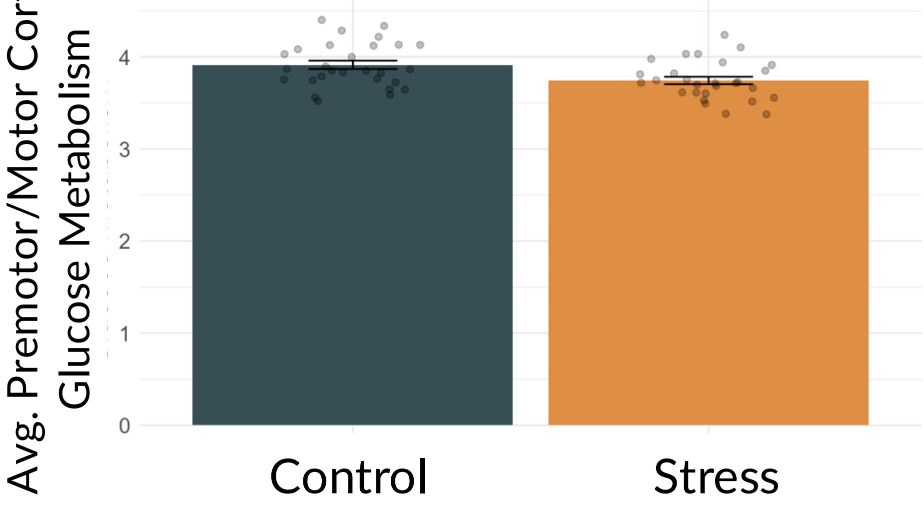


- Baumann & Mattingley, NeuroImage 2012
- Pierce et al., The Cerebellum 2023
- Nair et al., Brain Commun 2023
- Rosenkranz et al., unpublished data

Stress is associated with *decreased* motor/premotor cortex activity

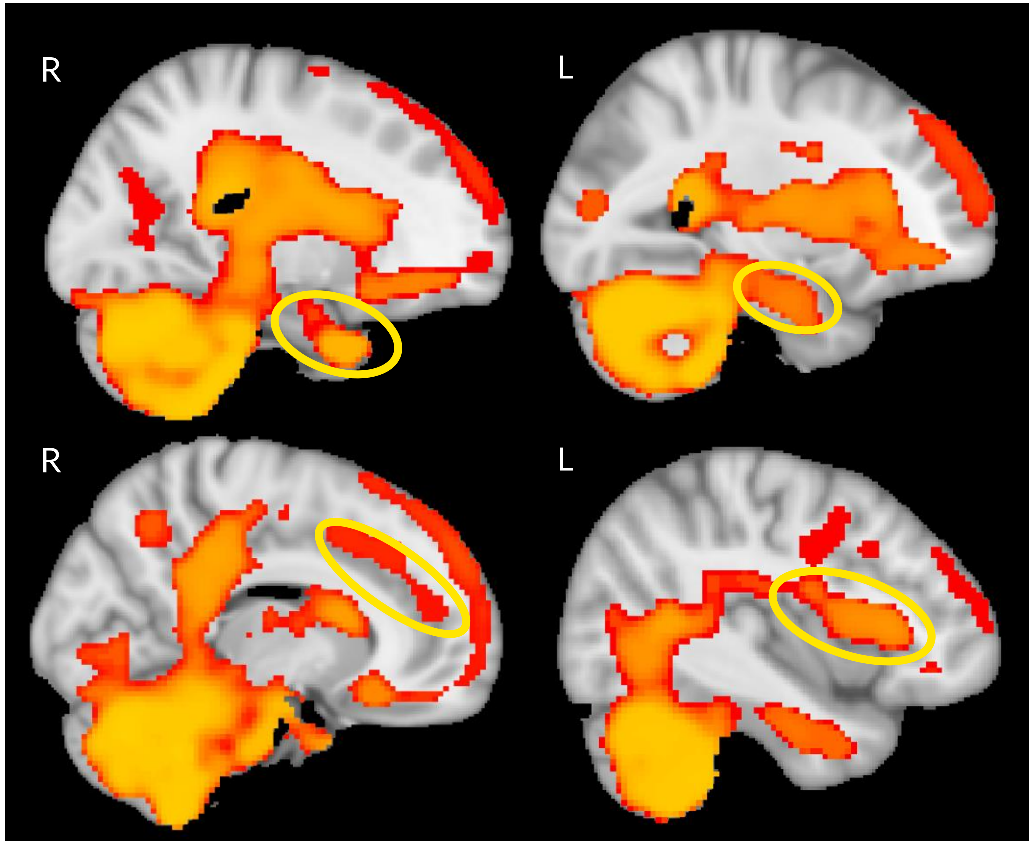


p < .05 corrected

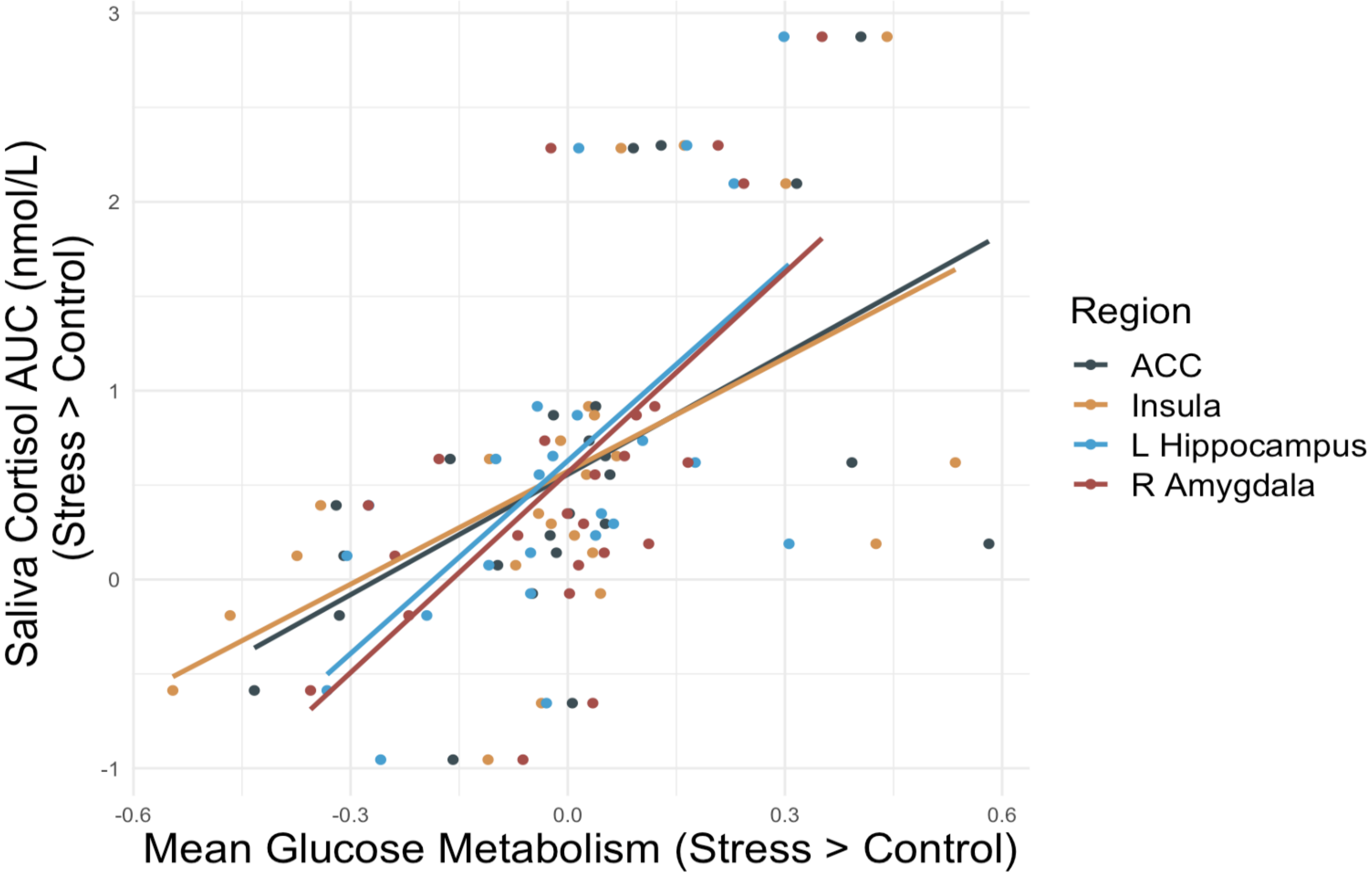


- Metz, Rev Neurosci 2007
- Kalin et al., Biol Psychiatry 2005

Cortisol response to stress is associated with brain response to stress

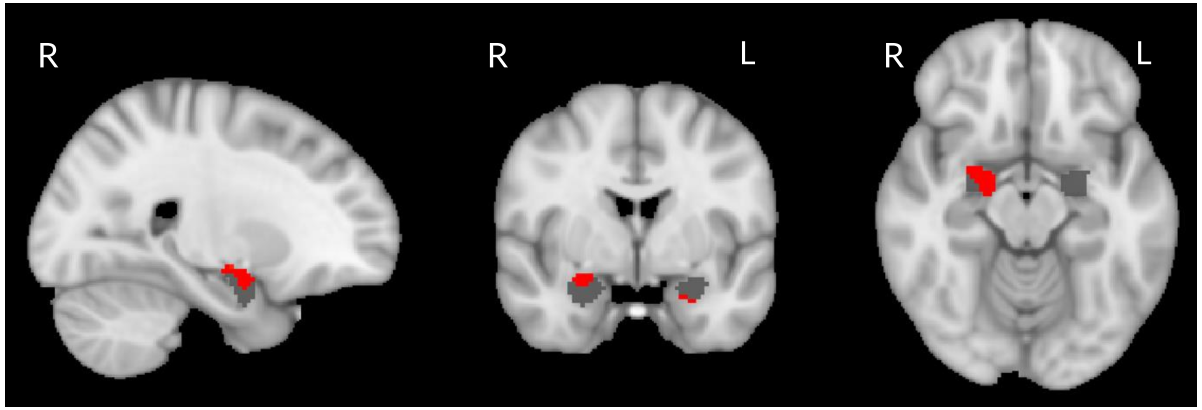


p < .05 corrected

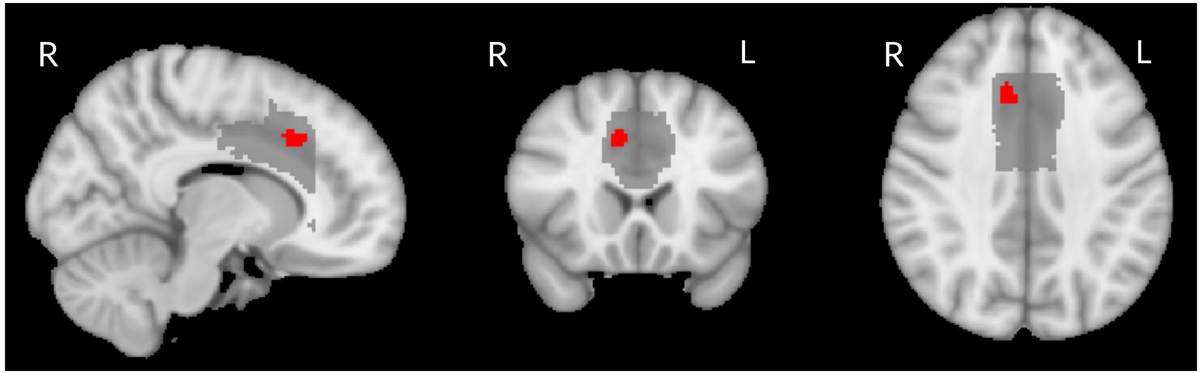


Stress-related salience network activity predicts airway inflammation

Amygdala



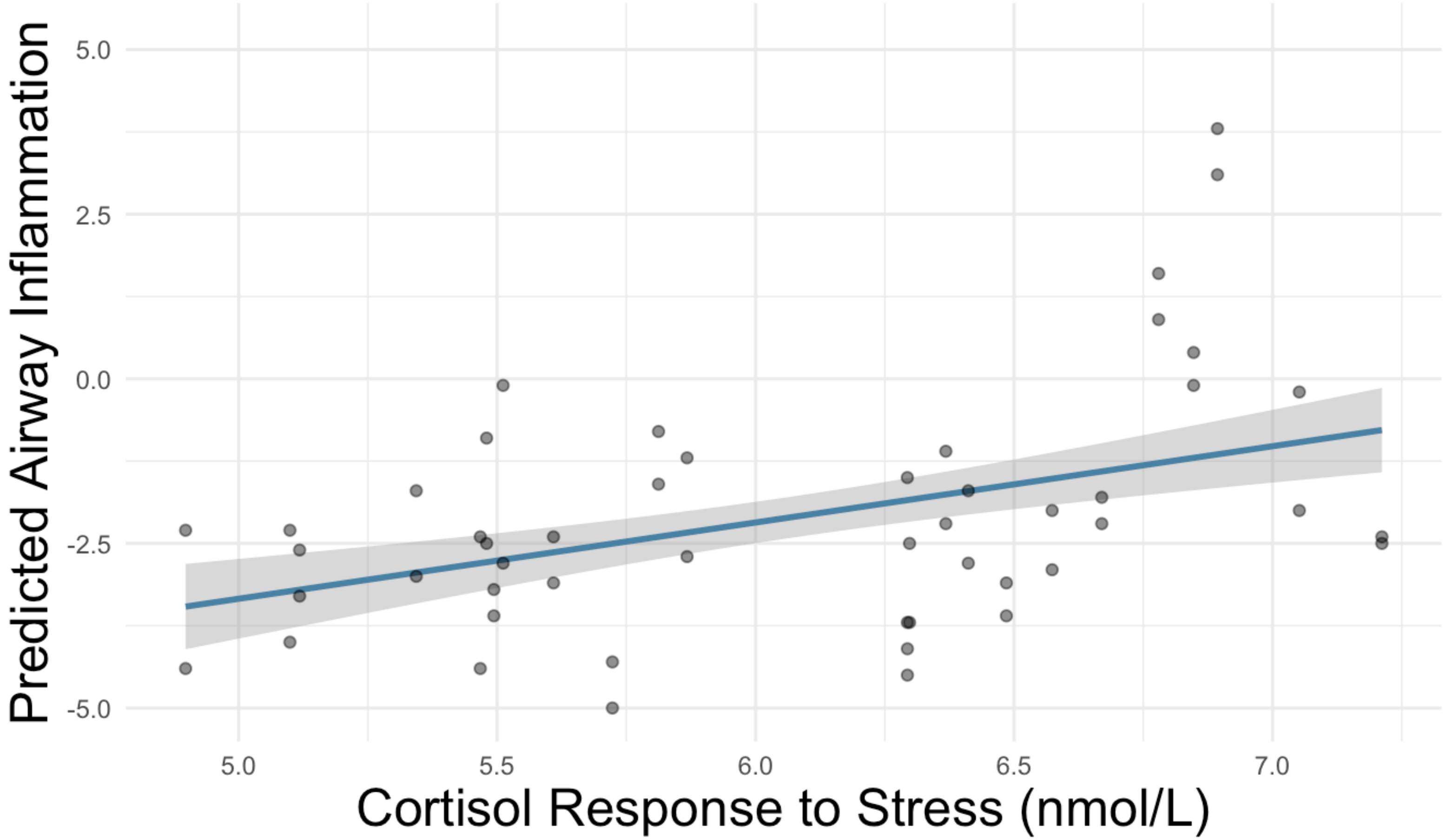
Dorsal Anterior Cingulate Cortex (dACC)



p < .05 corrected

Greater increase in inflammation, in stress vs control

Stress-induced cortisol correlates with airway inflammation

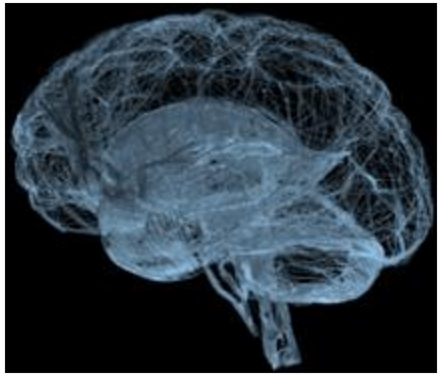


Stats
$t(22.1) = 2.38$, $p = .003$

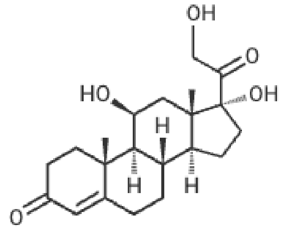
*LINEAR MIXED MODEL: lmer(IL23A ~ time.c*cortisol AUCg + allergen.dose + (1 + time.c | subid) in stress condition only*

Background Methods Results **Conclusions**

Stress-sensitive asthma phenotype?

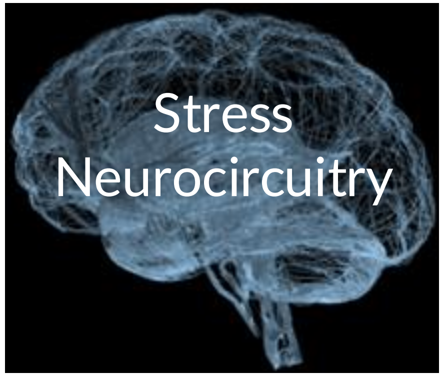


- Acute stress did not increase inflammatory response to challenge *in the whole group*



- *Variability in stress response* associated with inflammatory response:
  - **More robust cortisol and brain responses to stress were associated with stronger inflammatory responses**
    - *Subpopulation with stress-sensitive asthma phenotype?*

Need for integrative treatment and prevention in asthma

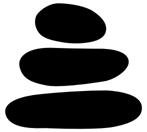


stress & cortisol

Asthma-Related Inflammation

=> targeted, personalized interventions and prevention

e.g., mind-body interventions



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

Gratitude

* *first-year project committee*

*Melissa Rosenkranz, PhD **

*Richard Davidson, PhD **

*Lyn Abramson, PhD **

*John Curtin, PhD **

Stephane Esnault, PhD

William Busse, PhD

Danika Klaus, RN

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…and many more!

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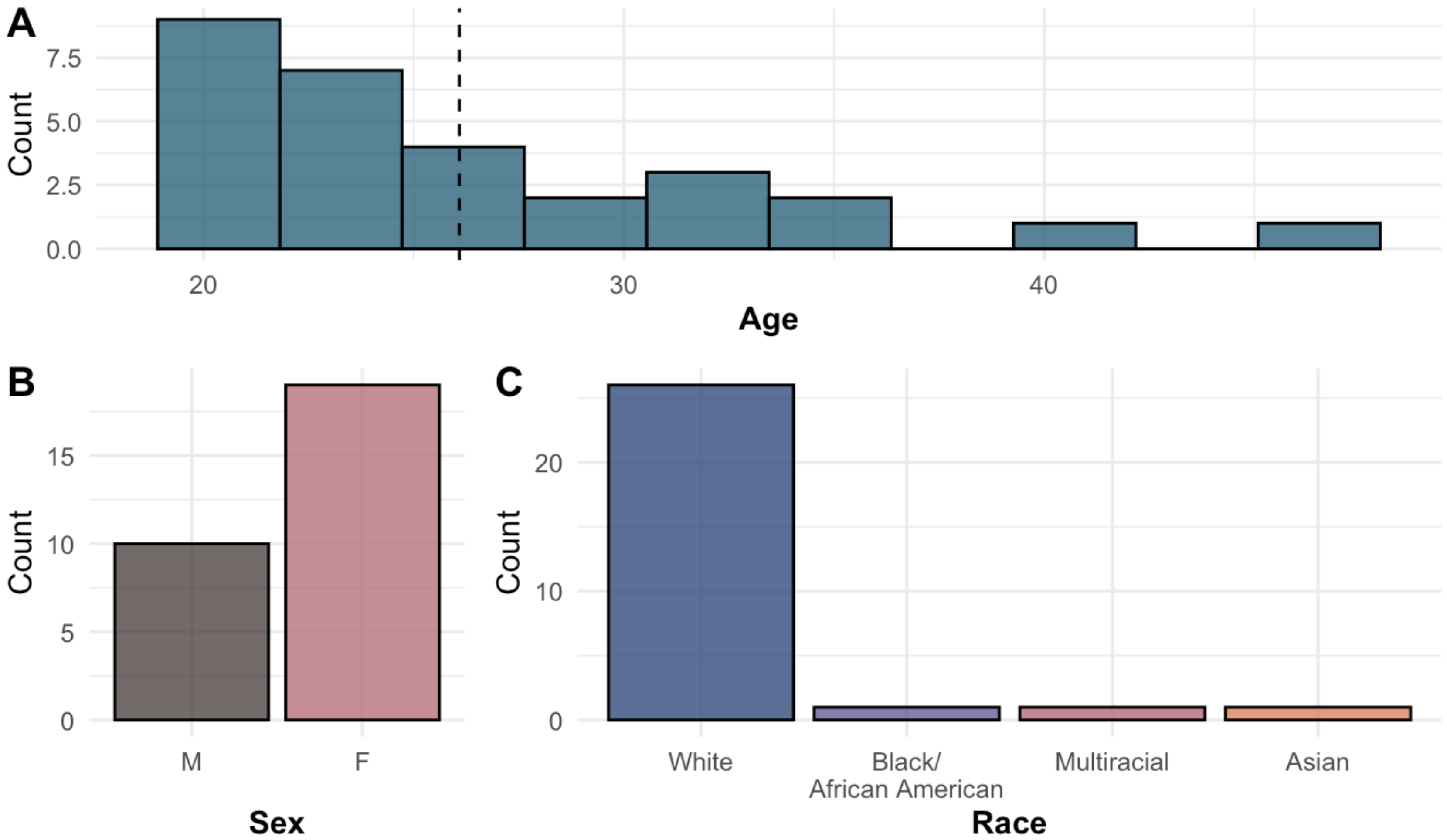
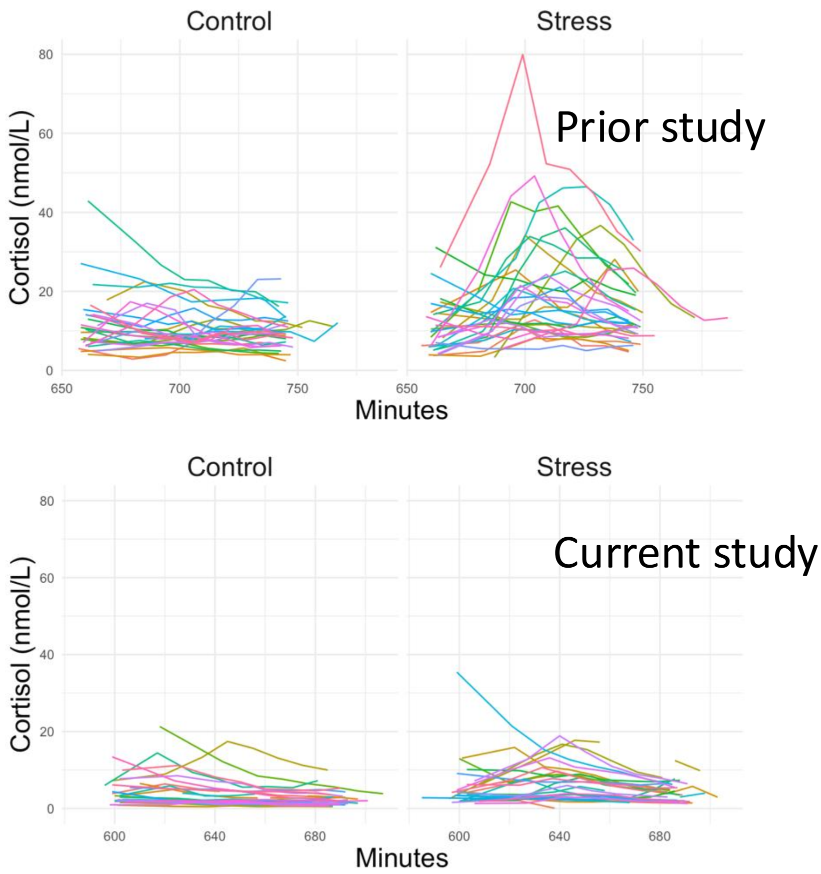
Questions?

Demographics



Why were there no effects of stress on airway inflammation?



- Less robust acute stress response
- Sympathetic Nervous System moderation
- Acute stress does not prime inflammatory response to allergen challenge in those with *average (not high, not low)* chronic stress

TH17 Cells

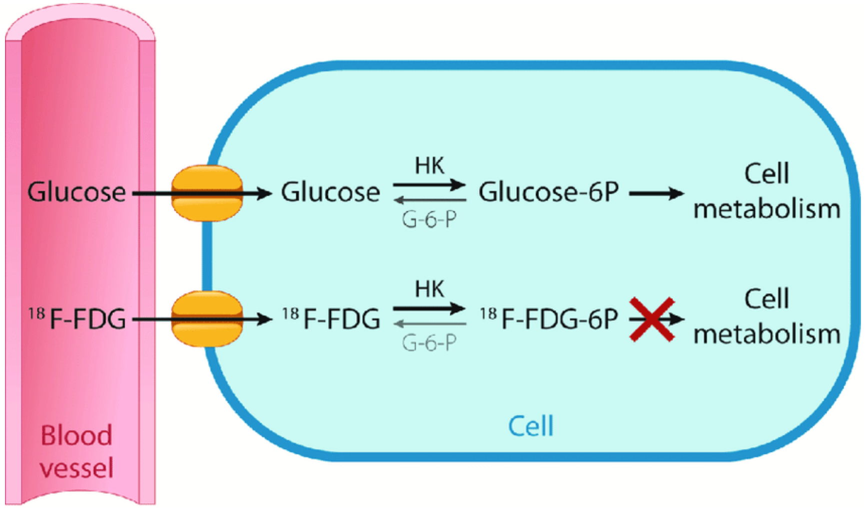
- Adaptive (Humoral) Immune System [autoimmune disease] → IL-17 (neutrophils)
  - Associated with depression
- Differentiation: requires IL-6 and TGFβ; promoted by TNF-a, IL-1β, IL-21, IL-23
- Stress → ↑ IL-1β

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



FDG “trapped”

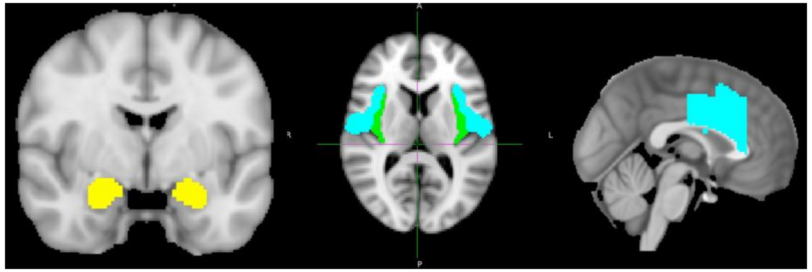
(Rahman et al., 2019)

Analyses: Stress Neurocircuitry

- Whole-Brain

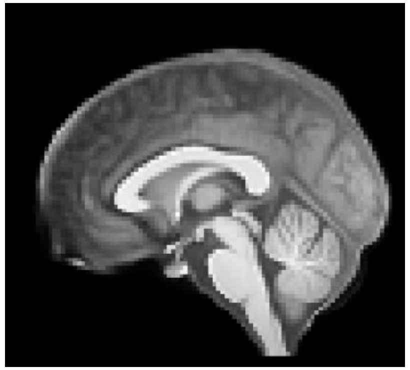
  +

- 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

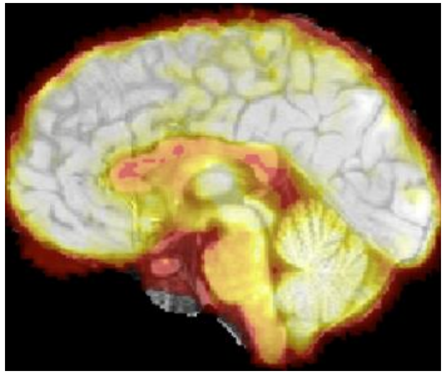


PET Processing

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

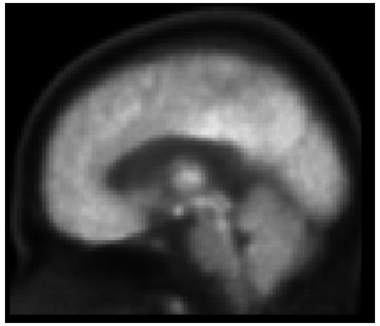


Study-specific T1 template



Example co-registration

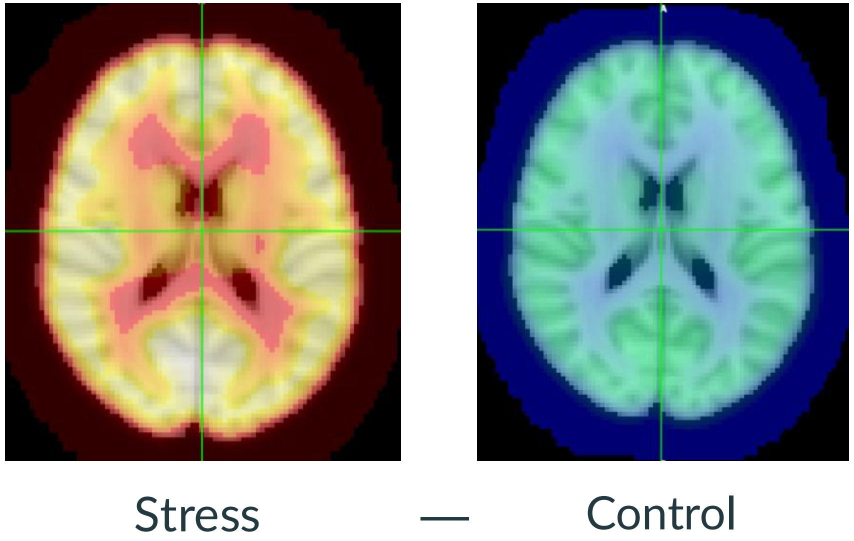
- 2 subjects missing T1; co-registered to PET template in MNI space



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



Allergen challenge

Baseline FEV_1 & FeNO

Allergen Challenge

Hourly FEV_1 & FeNO

Blood Draw

4hr

Allergenic extract inhaled
(cat, dust, or ragweed)

→

Concentration increased until FEV_1 falls 20%

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)

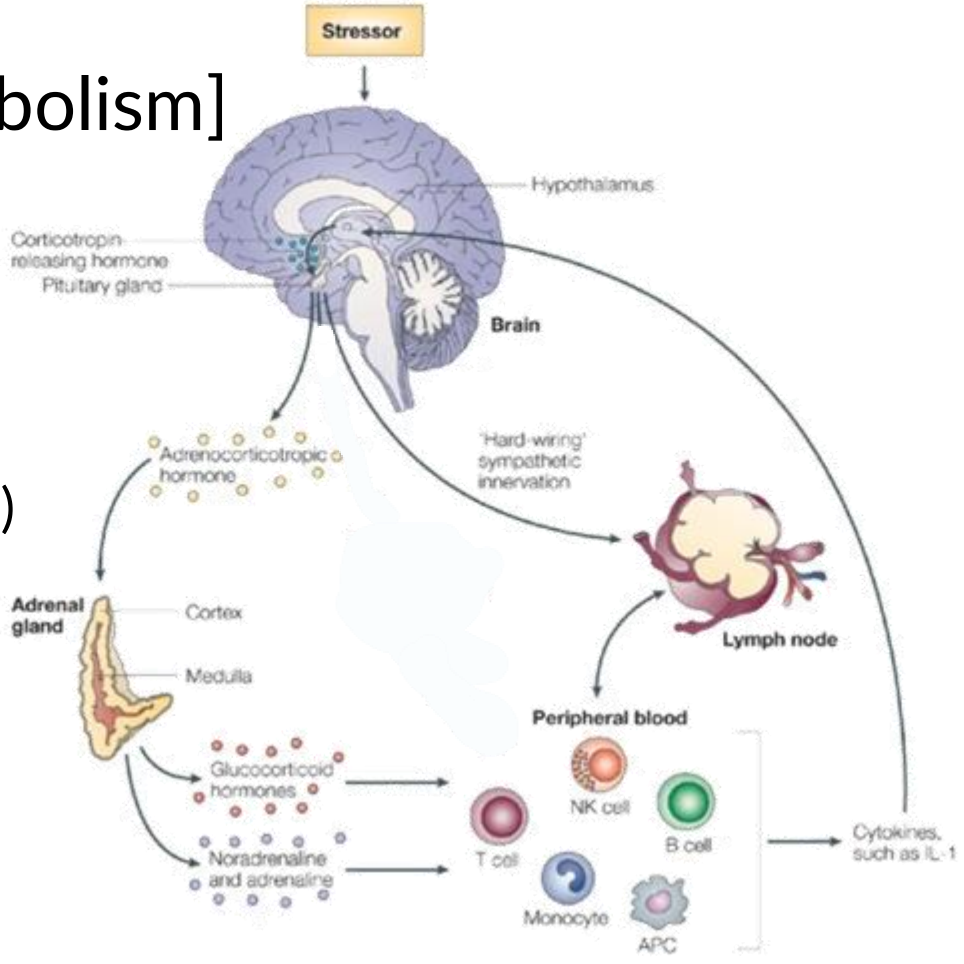
- Nonlinear least squares to extract optimal parameters used in conversion equation

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 and distal mechanisms

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



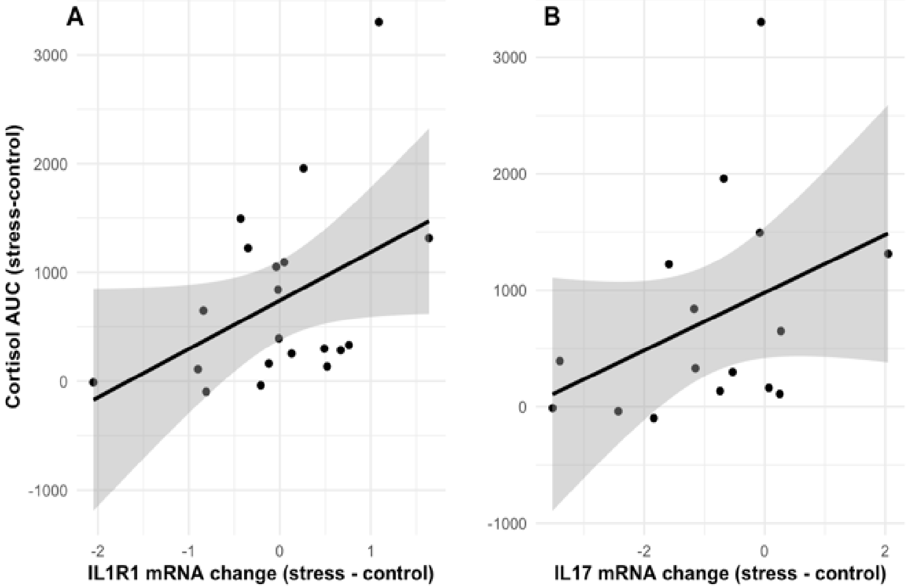
(Glaser & Kiecolt-Glaser, 2005)

Power: stress neurocircuitry

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

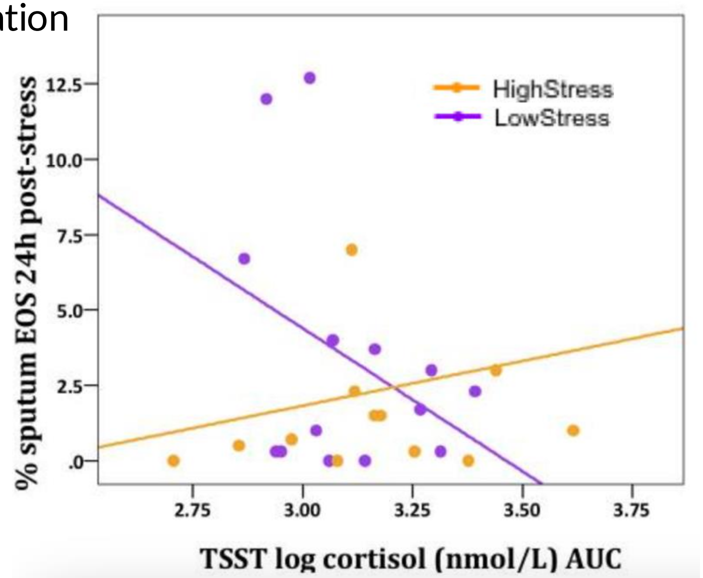
Prior evidence

- Psychosocial Stressor ⟶ Increased Cortisol, associated with Airway Inflammation Biomarkers
  - Th17 path (IL-17A, IL-1R1)



- Th2 path (EOS) moderated by chronic stress

greater airway inflammation



greater cortisol

(Rosenkranz et al., 2016)