Stress neurocircuitry, cortisol, and provoked Th17-related airway inflammation in asthma

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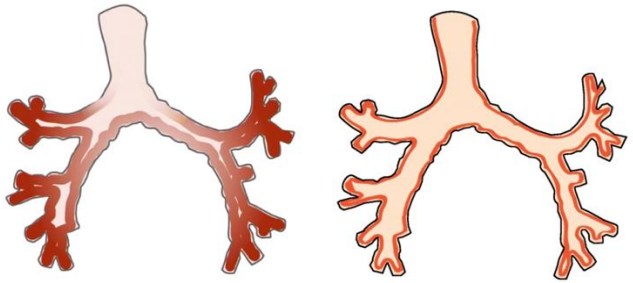
Asthma interacts with the mind

Global Asthma Prevalence: **262 million**

~1200 deaths/day

Higher Stress: more severe, poorly-controlled, treatment-resistant asthma



(Vos et al., The Lancet, 2019; McDonald et al., Eur. Resp. J. 2019; Barnthouse & James, Clin Rev Allergy & Immunol, 2019)

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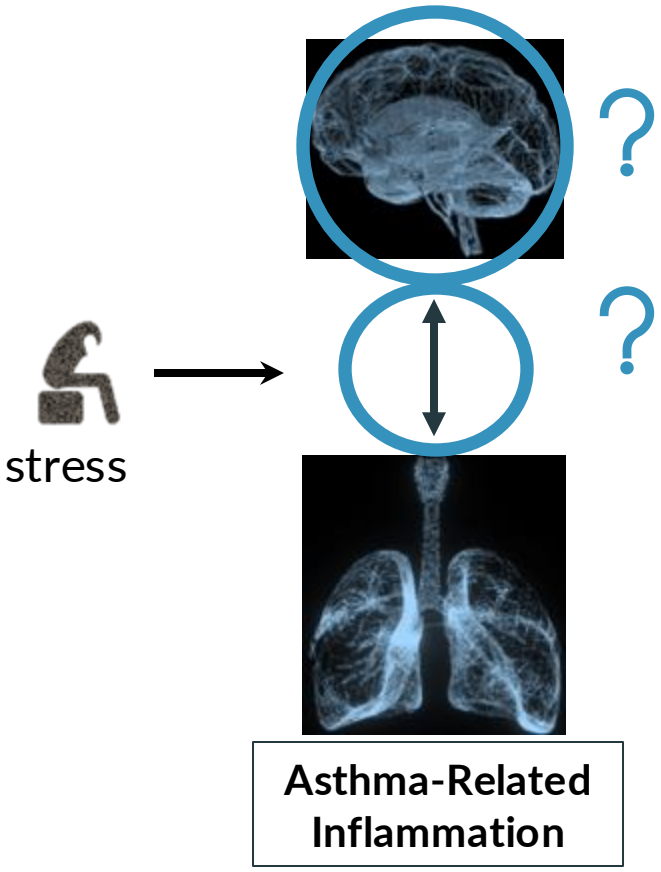
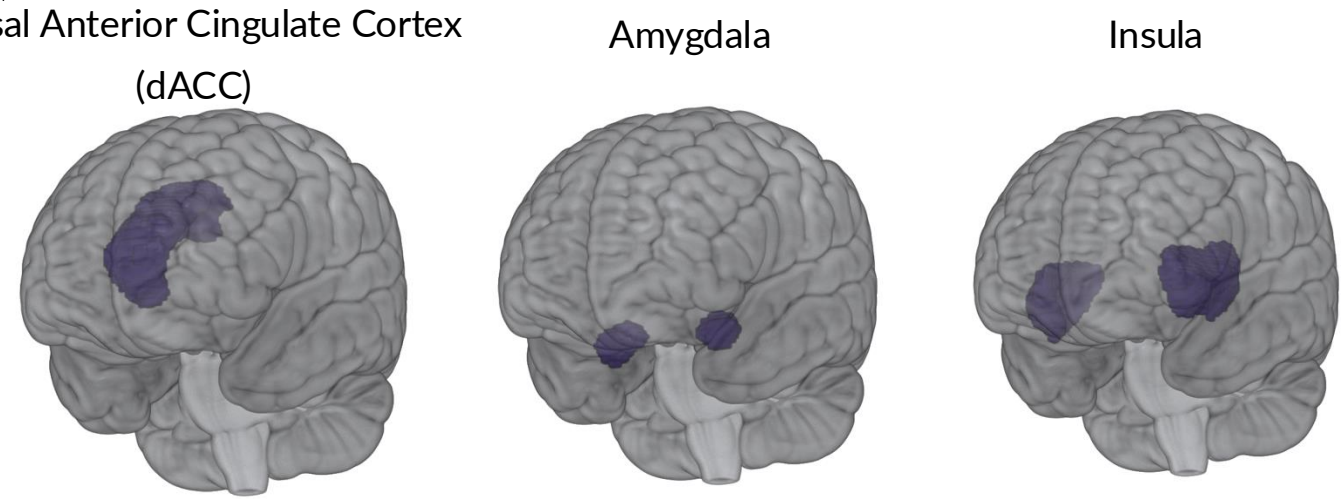
Brain and immune pathways are unknown

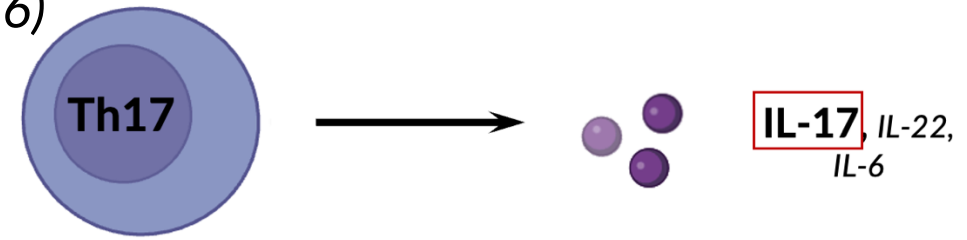


Initial evidence:

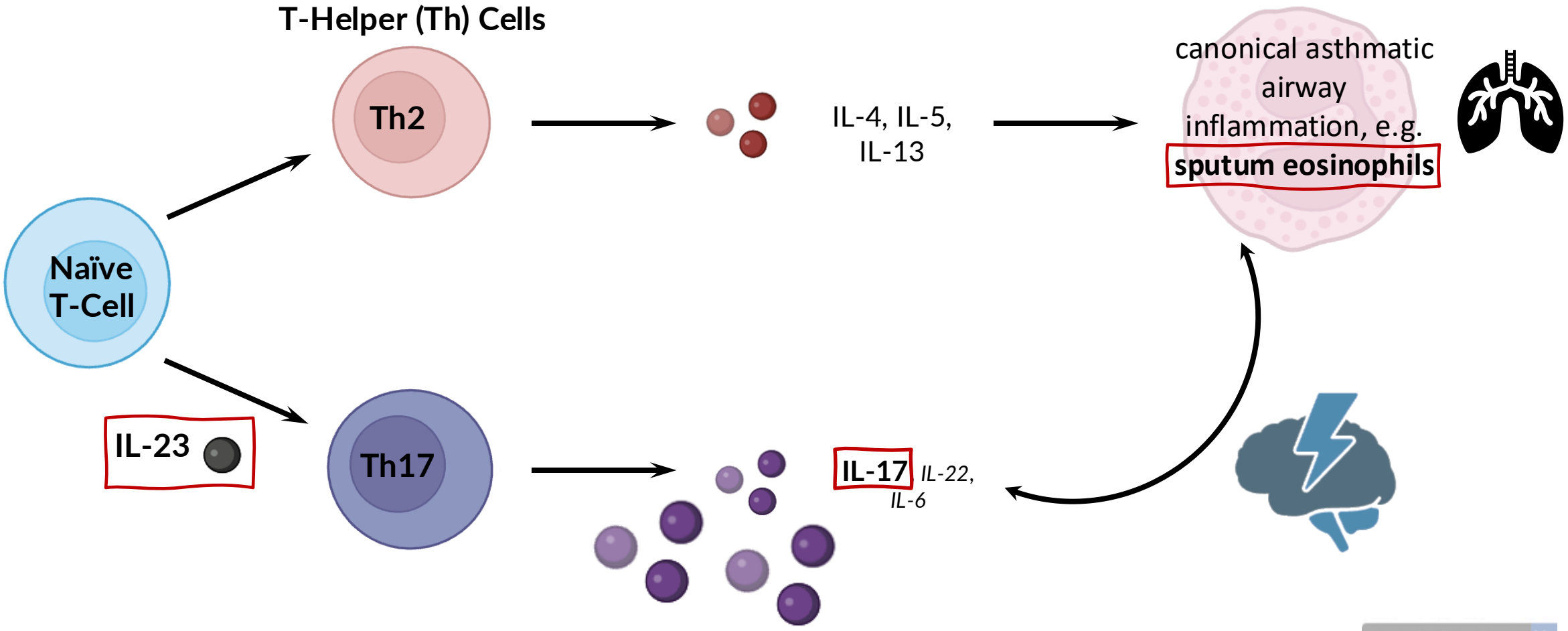
- *Stress/emotion neurocircuitry: salience network (Menon, Brain Mapping 2015)*



- *Immune pathways that trigger asthma symptoms associated with stress (e.g., Th17; Rosenkranz et al., BBI 2016)*



Th2 & Th17-related pathways



Hypothesis: Acute stress will increase provoked airway inflammation

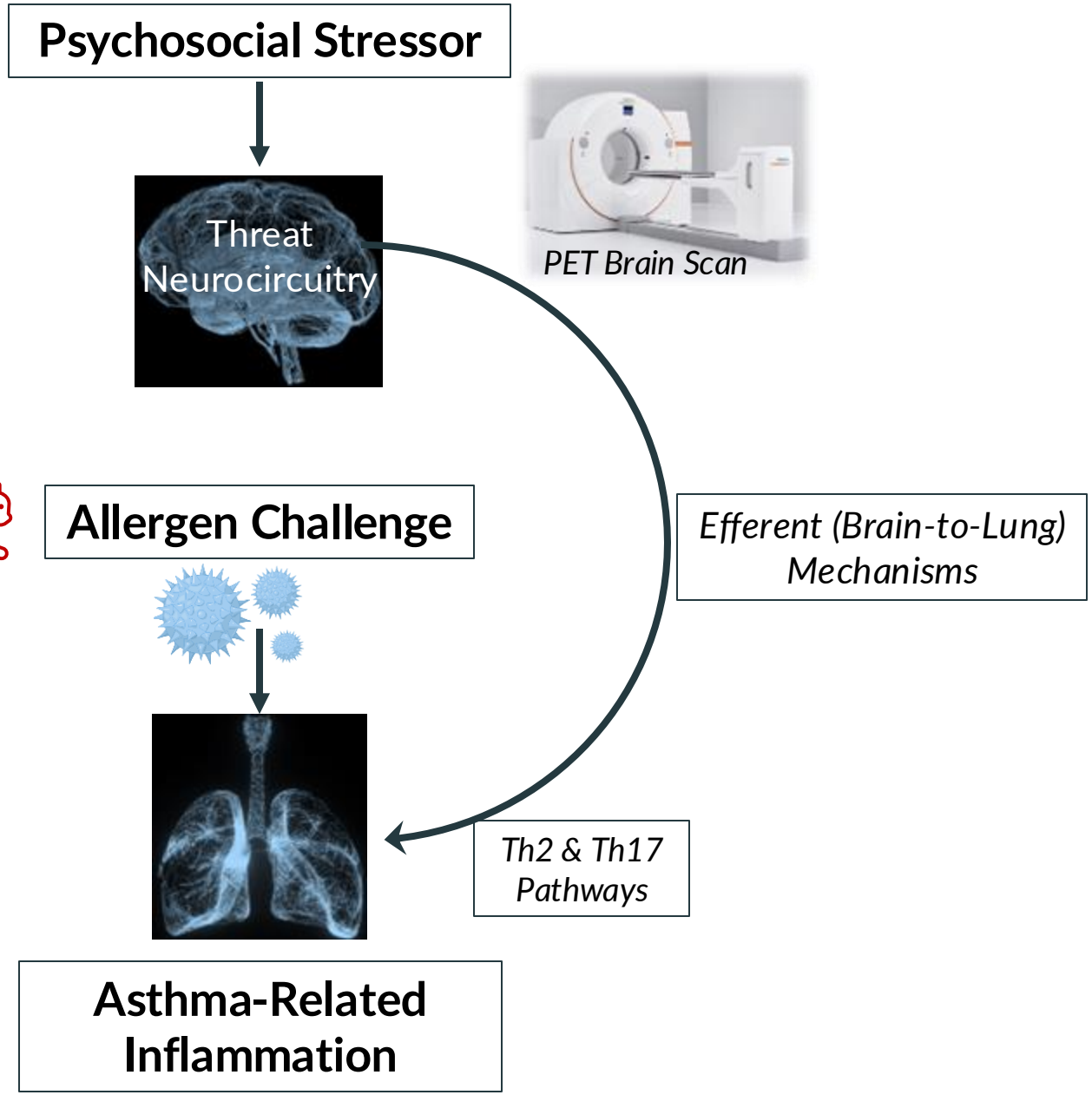
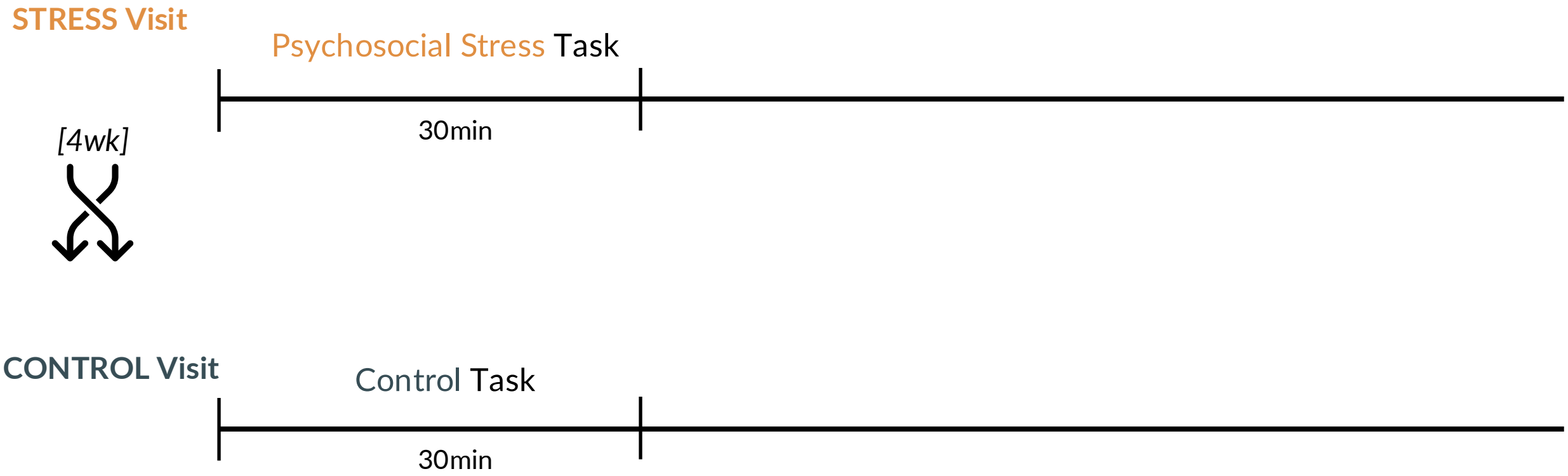


Image: *https://www.siemens-healthineers.com/en-us/molecular-imaging/pet-ct/biograph-vision*

Within-Subjects Design



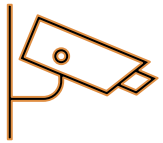
Psychosocial Stress or Control Task

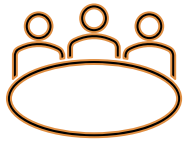
Psychosocial Stress or

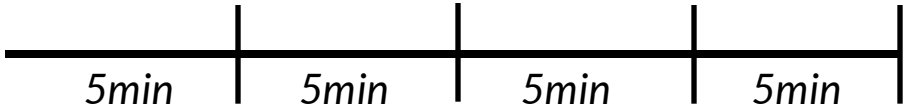
Control Task

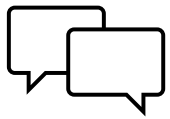
Trier Social Stress Test (TSST)

Control Task

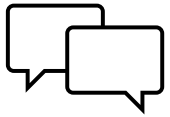








+/-



+/-

Modified

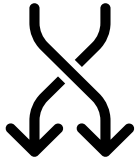
speech math speech math

(*Kern et al., PNEC 2008*)

Within-Subjects Design

STRESS Visit

[4wk]



Psychosocial Stress Task — 30min

PET Brain Scan — 30min

Acute Lung Allergen Challenge — 4hr

Salivary Cortisol Collected *every ~10min*

Th2 & Th17 Airway Inflammation *hourly*

CONTROL Visit

Control Task — 30min

Within-Subjects Design

STRESS Visit

[4wk]

Psychosocial Stress Task (30min) → PET Brain Scan (30min) → Acute Lung Allergen Challenge (4hr)

Salivary Cortisol Collected *every ~10min*

Th2 & Th17 Airway Inflammation *hourly*

CONTROL Visit

Control Task (30min) → PET Brain Scan (30min) → Acute Lung Allergen Challenge (4hr)

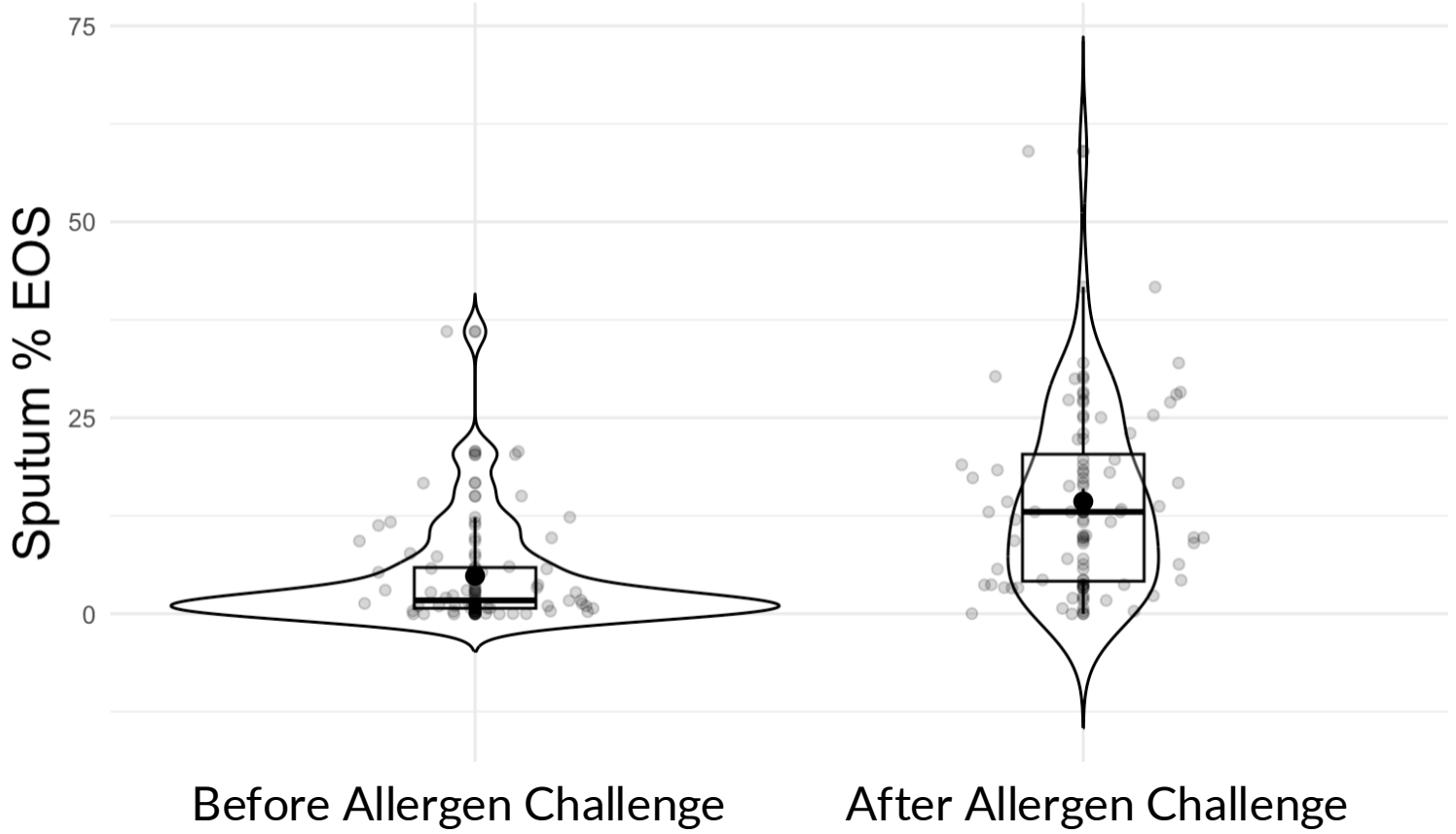
Salivary Cortisol Collected *every ~10min*

Th2 & Th17 Airway Inflammation *hourly*

Participants

- n = 28 (*18 F*)
- Adults ages 19-45y (*Mean 25.9y*)
- Mild asthma; no corticosteroid medications
- 89% White Non-Hispanic
  - *n = 25 White, n = 1 Black/African American, n = 1 Asian, n = 1 multi-racial*

Allergen challenge increases airway inflammation

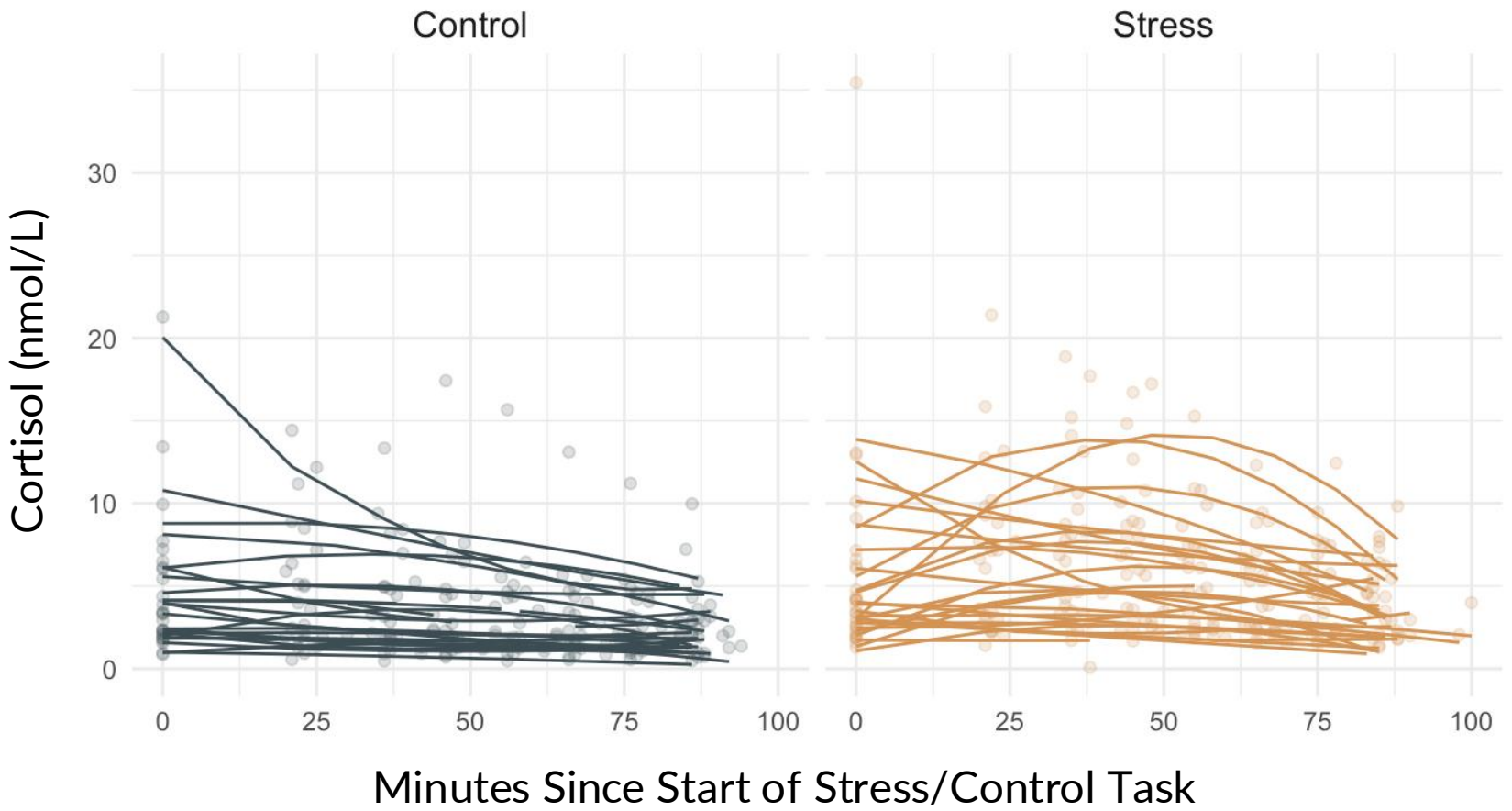


Stats:

$t(23) = 10.37$,

$p < .001$

Acute psychosocial stress increases cortisol

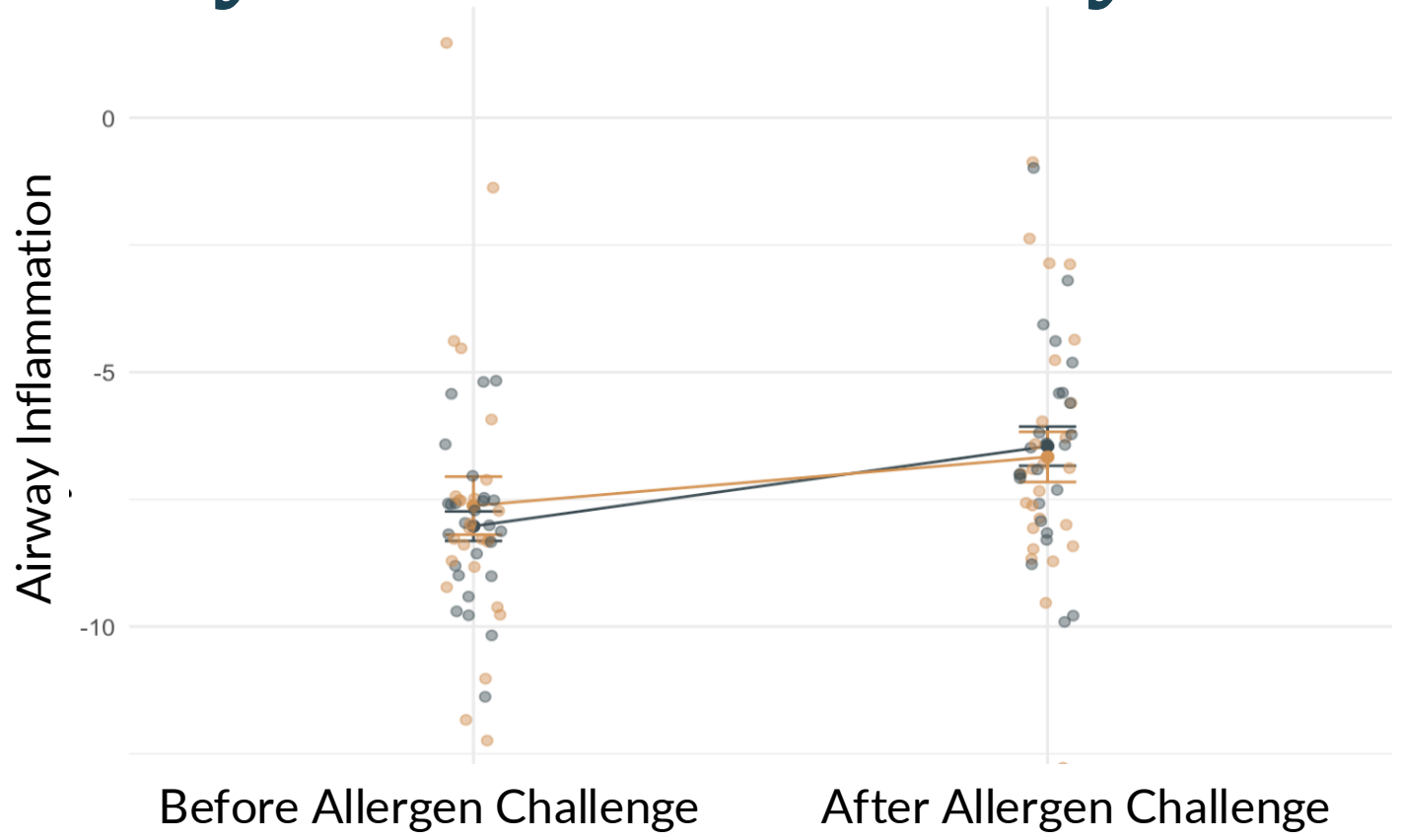


Stats:

$t(24.7) = -3.46$,

$p = .002$

Acute psychosocial stress does not significantly increase airway inflammation

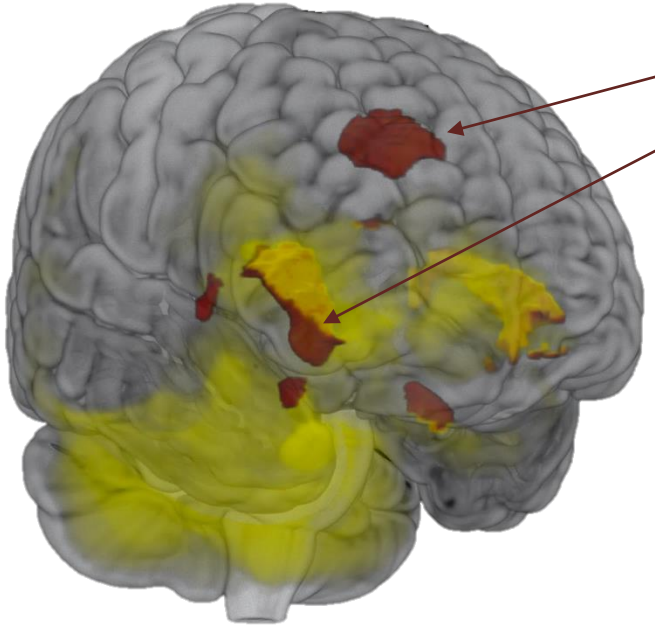


Stats *(condition difference):*

$t(25) = 0.08$,

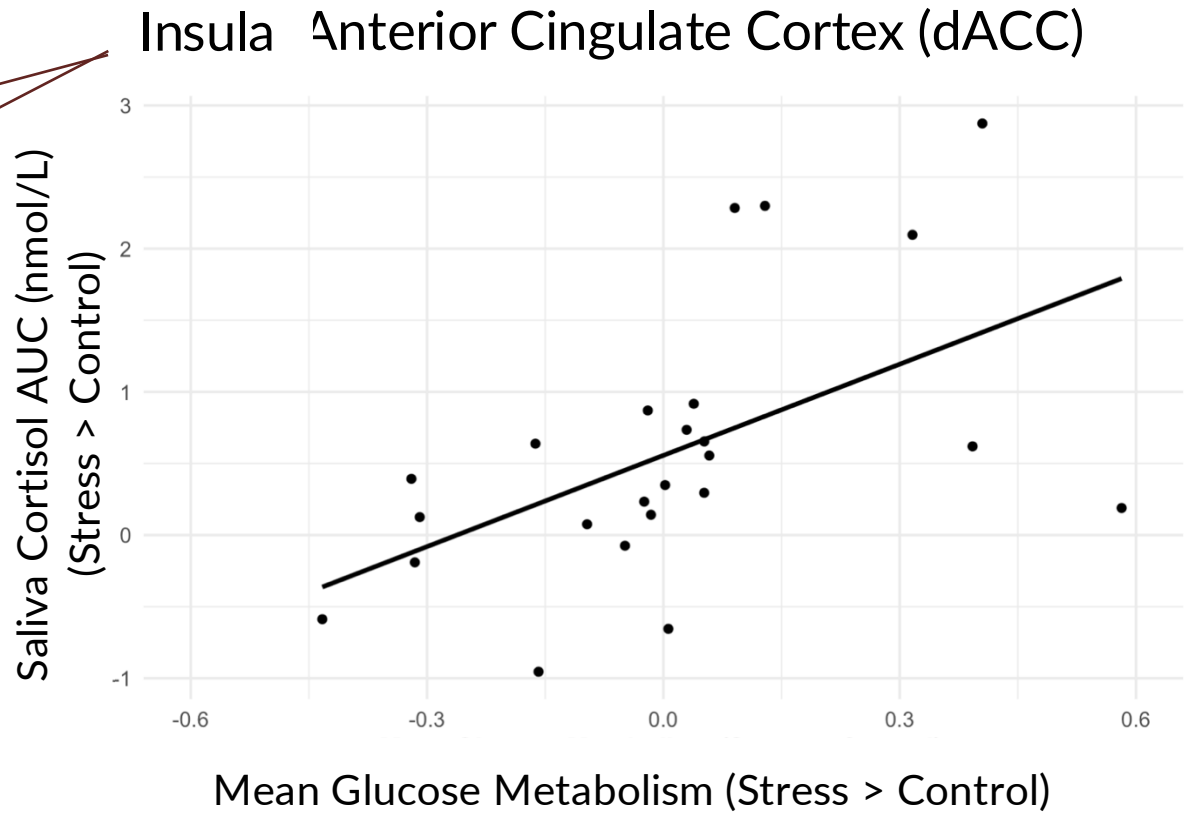
$p = .805$

Cortisol response to psychosocial stress is associated with widespread brain activation

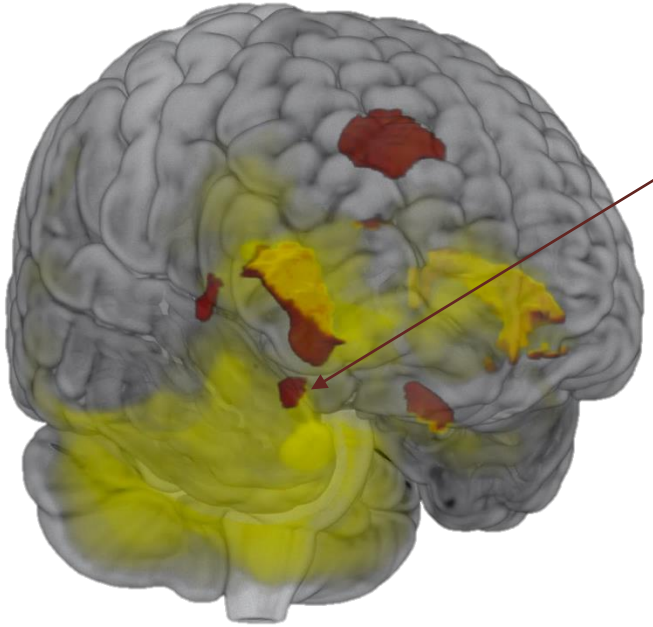


stress > control & greater cortisol response

local Salience Network peaks



Cortisol response to psychosocial stress is associated with widespread brain activation



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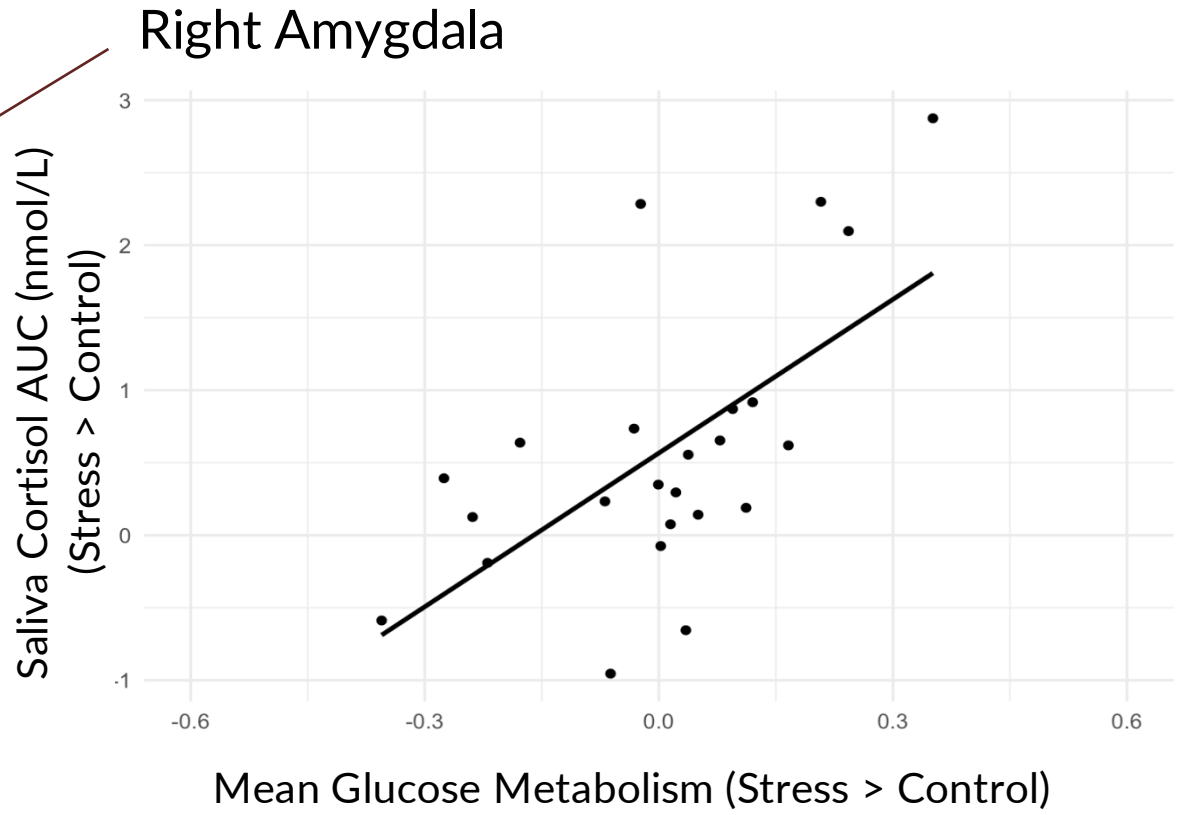
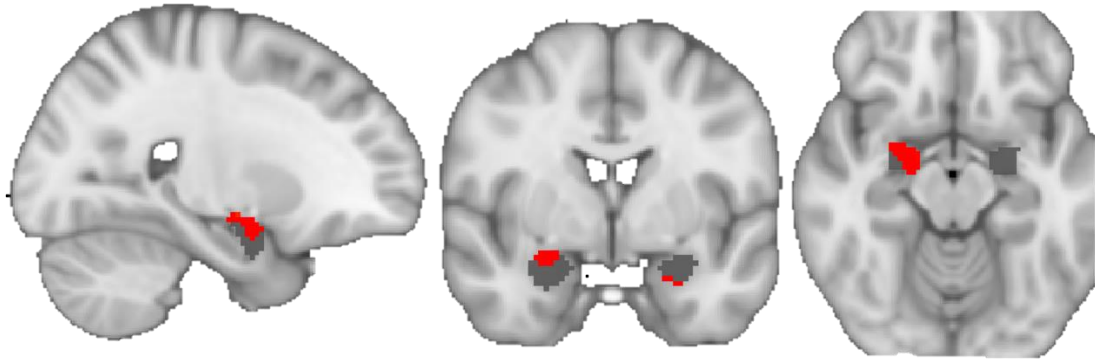
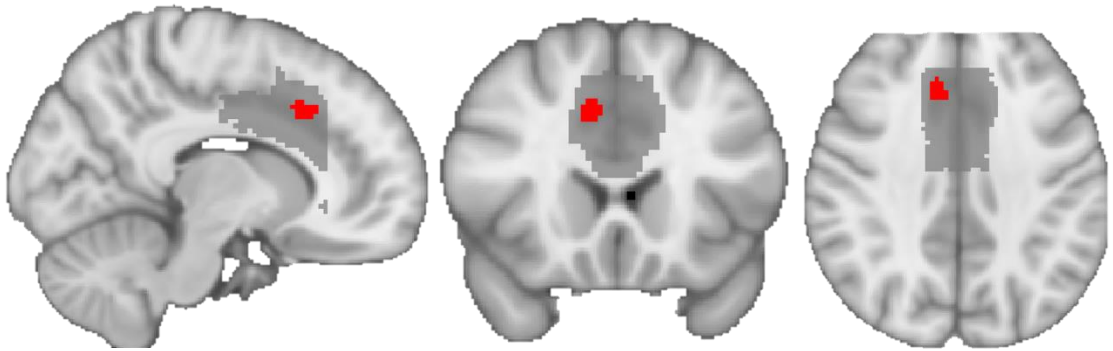


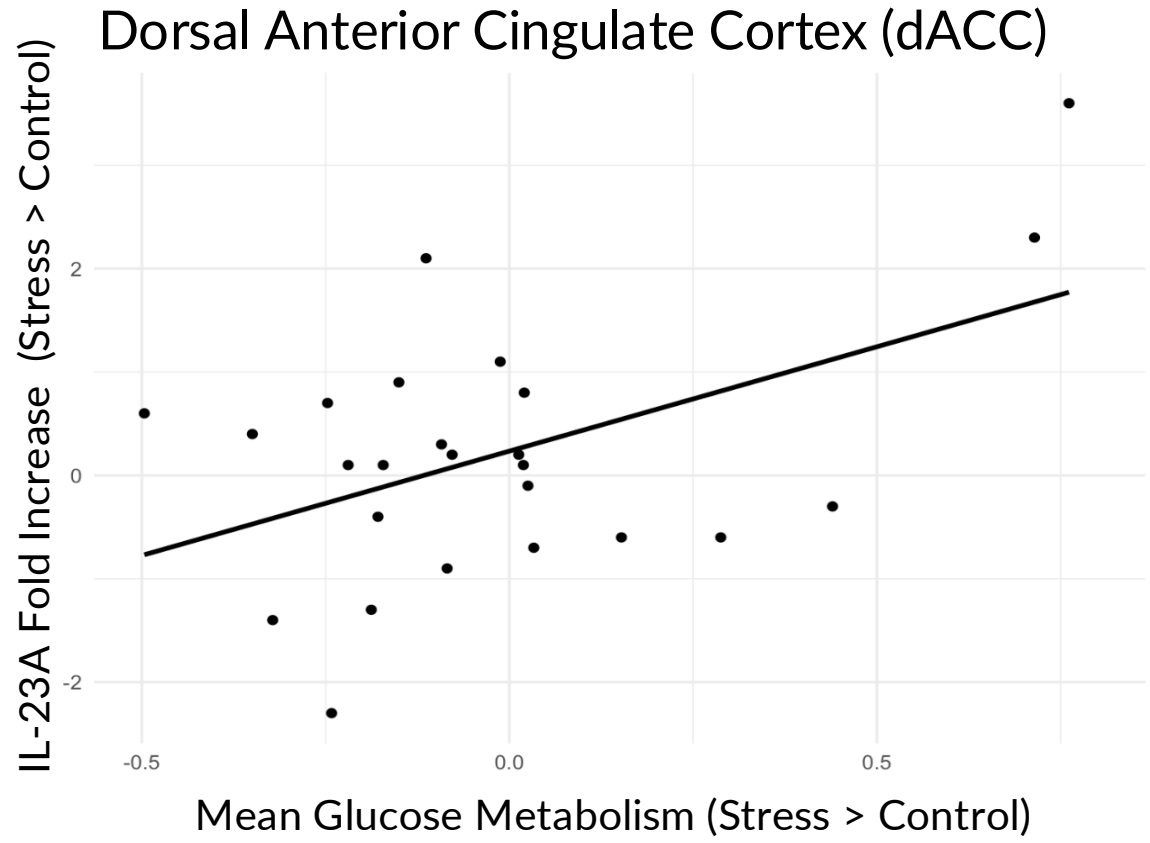
Stress-related salience network activity predicts airway IL-23A mRNA expression

Amygdala

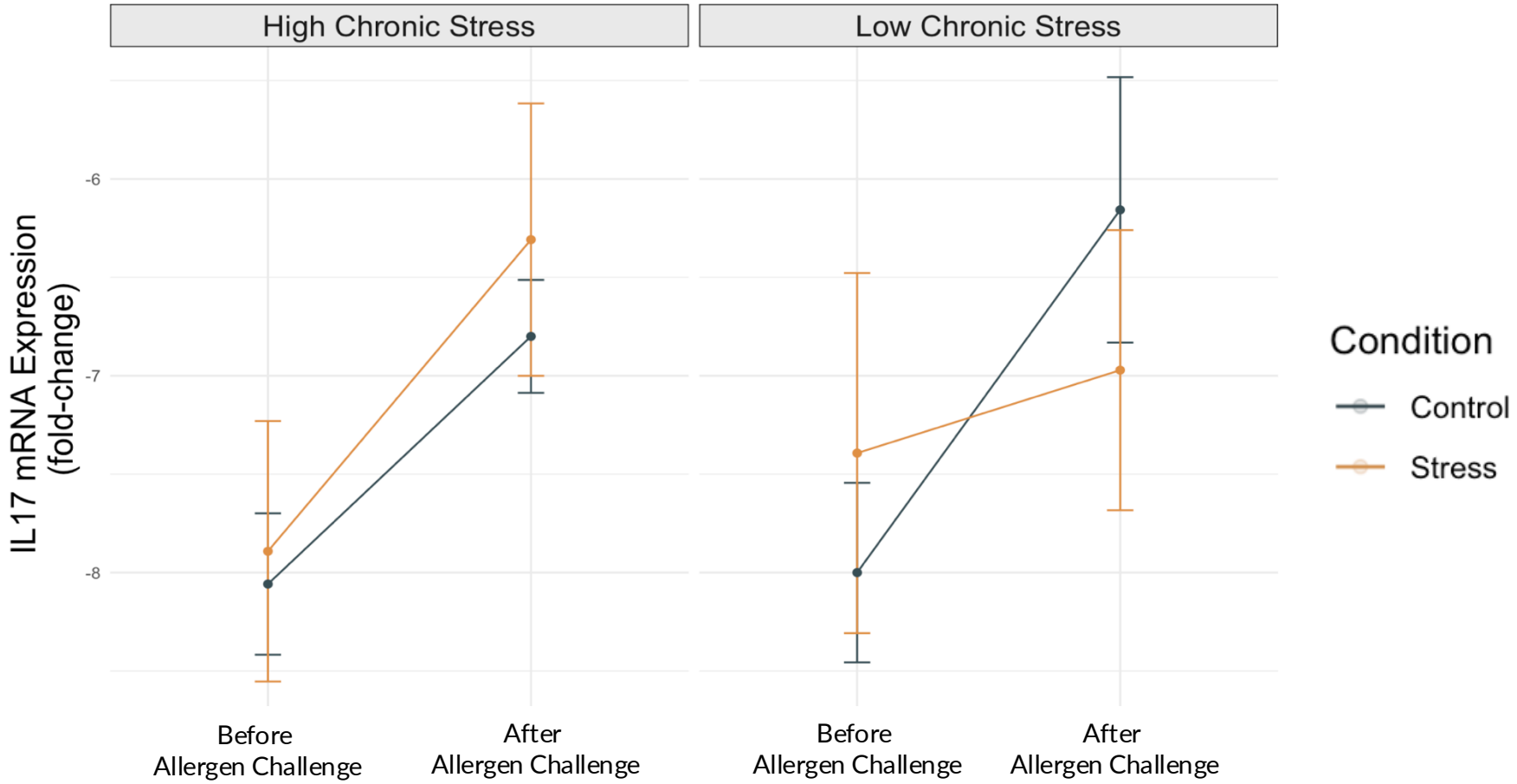


Dorsal Anterior Cingulate Cortex (dACC)



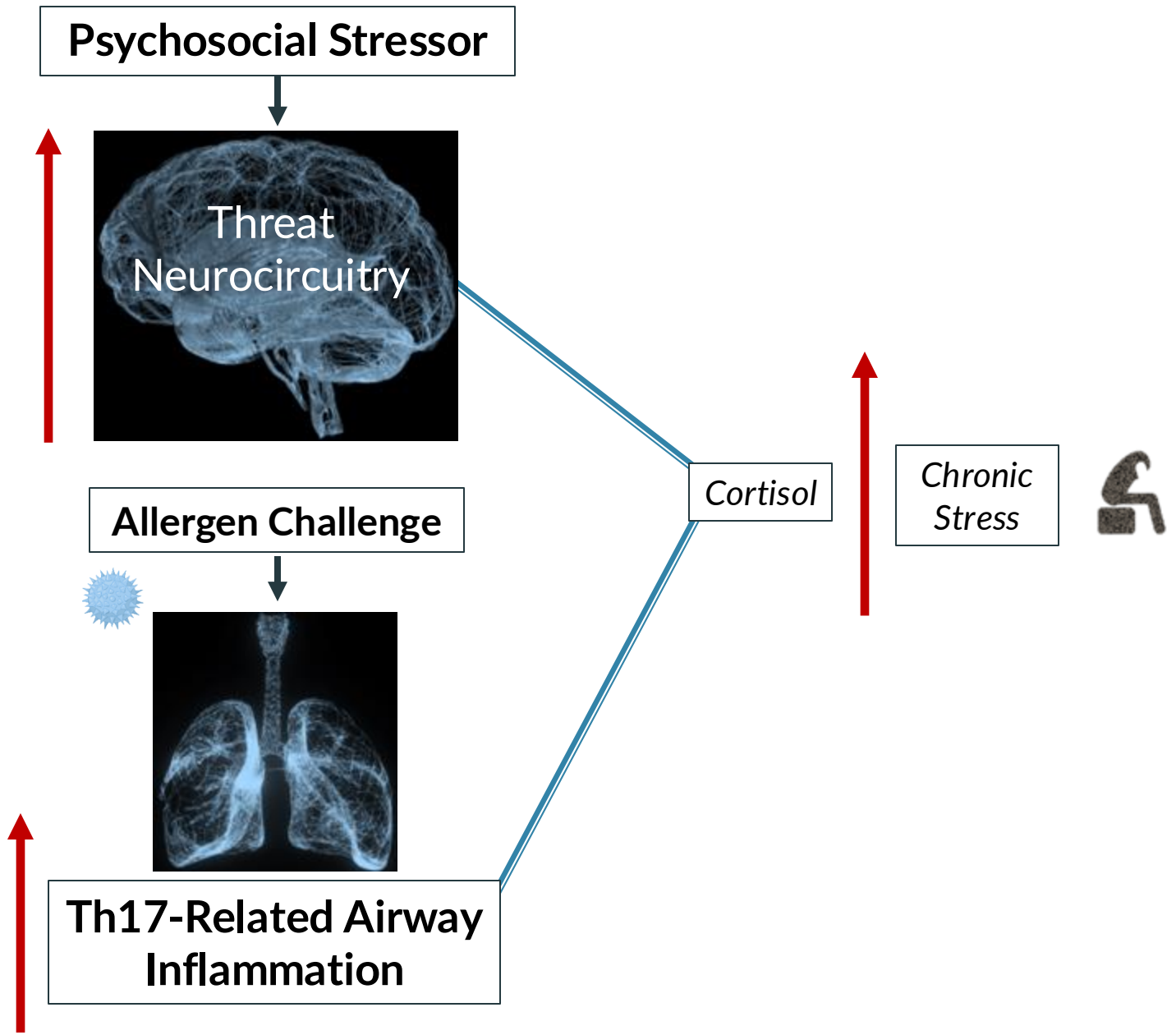


Chronic stress enhances effects of acute psychosocial stress on IL-17A mRNA expression

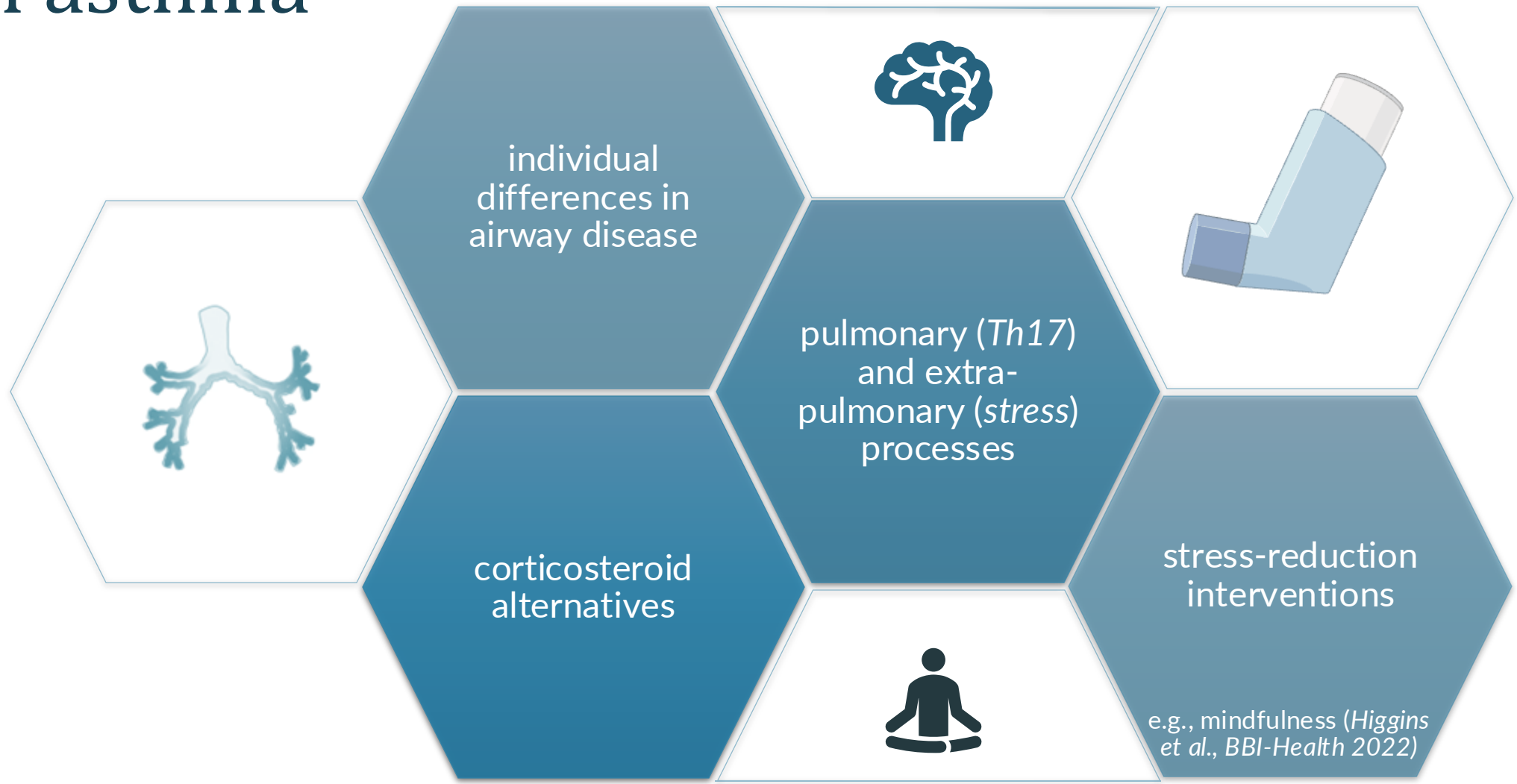


Main Takeaway

Individual differences in acute stress response impact Th17-related inflammation



Need for integrative treatment and prevention in asthma



Gratitude


Melissa Rosenkranz, PhD


Richard Davidson, PhD


William Busse, PhD


Corinna Frye


John Curtin, PhD


Danika Klaus, RN


Stephane Esnault, PhD


Lyn Abramson, PhD

…and many more!

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THANK YOU!

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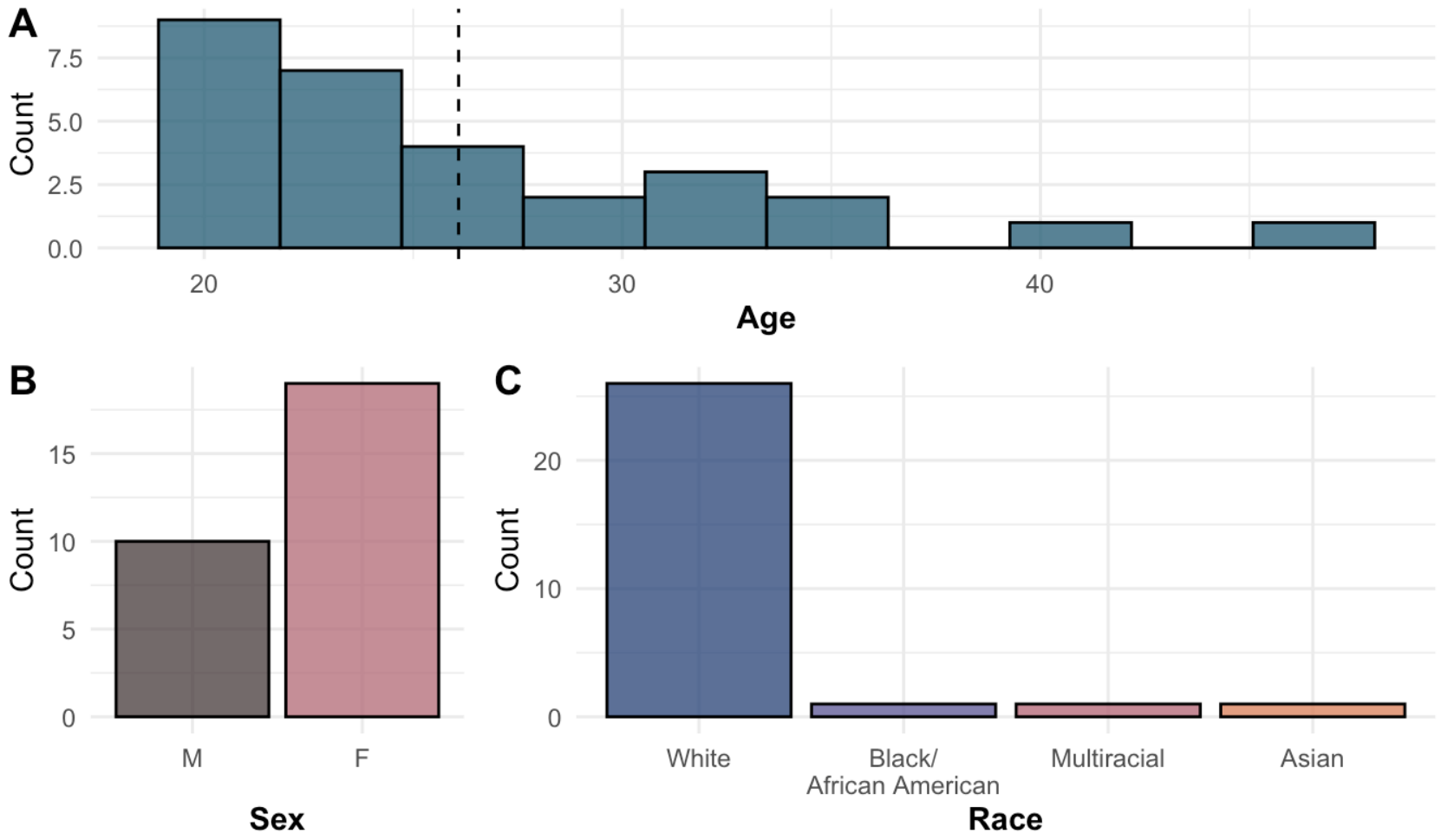
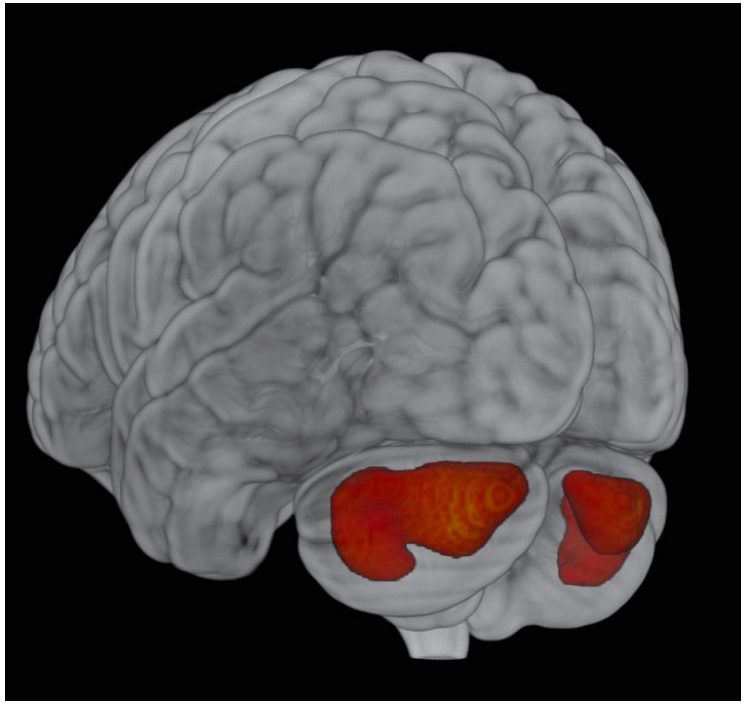
Demographics



Stress is associated with *increased* cerebellum and *decreased* motor / premotor cortex activity



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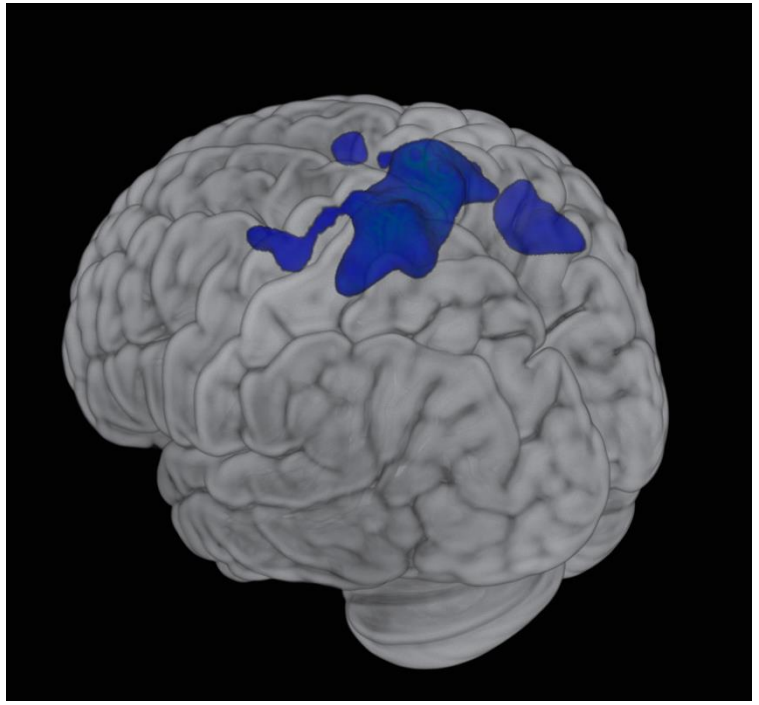
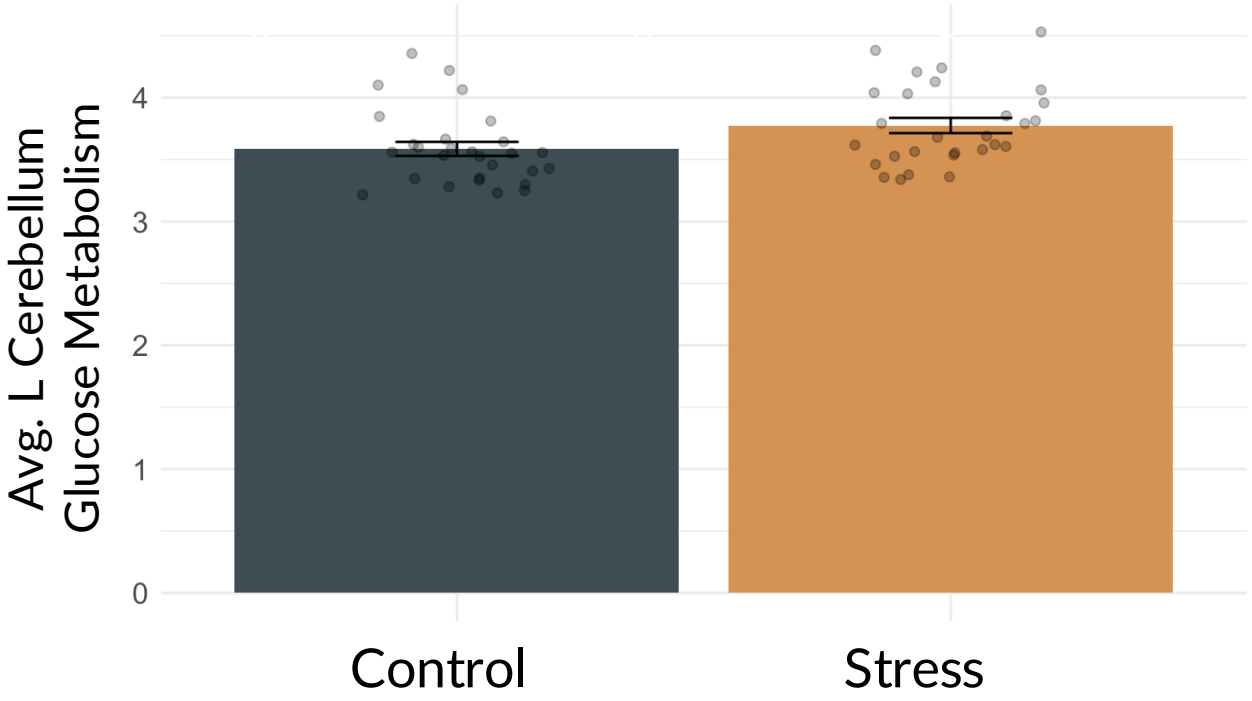


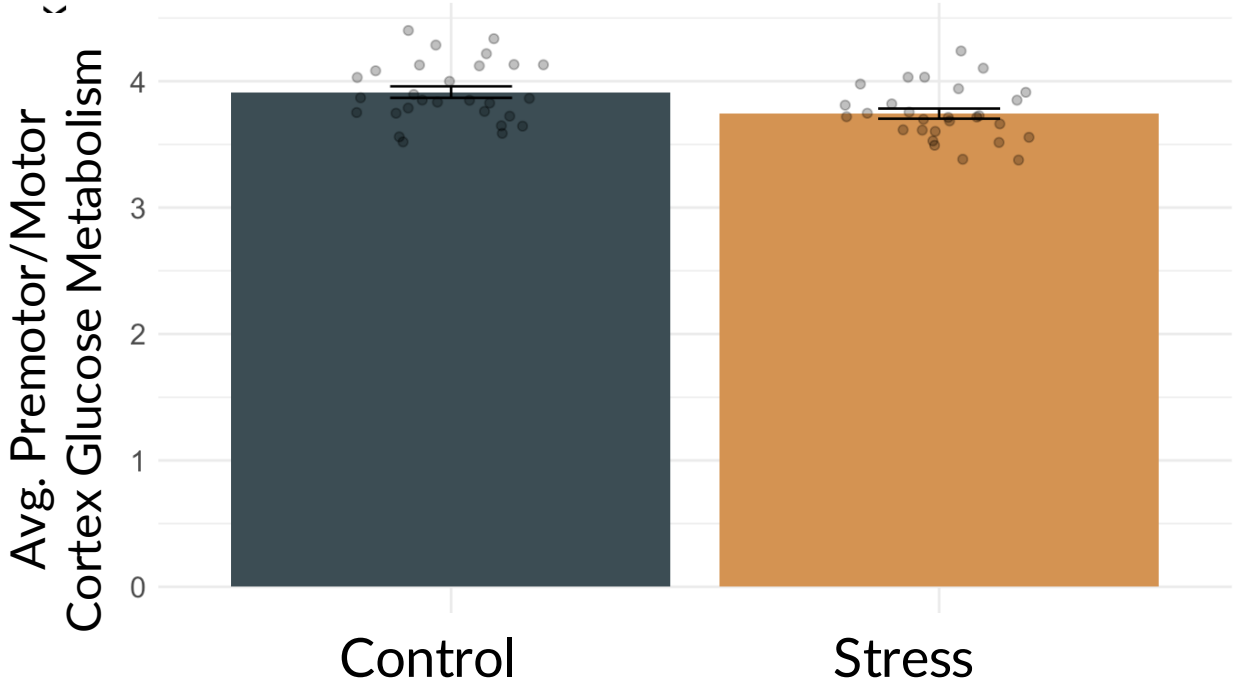
p < .05 corrected

(Nair et al., Brain Commun 2023; Pierce et al., The Cbl 2023; Rosenkranz et al., unpublished)

(Kalin et al., Biol Psychiatry 2005; Metz, Rev Neurosci 2007)

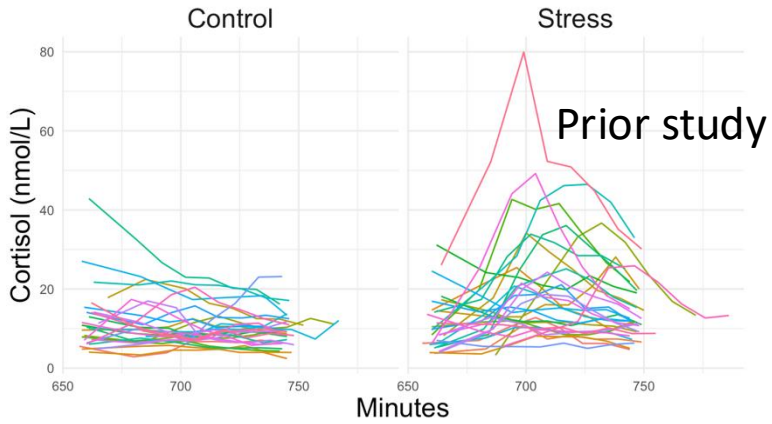
Stress is associated with *increased* cerebellum activity

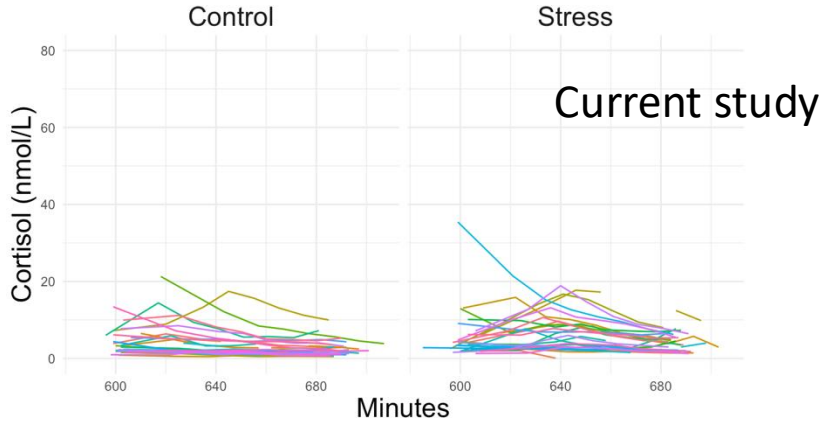




(Baumann & Mattingley, NeuroImage 2012; Nair et al., Brain Commun 2023; Pierce et al., The Cerebellum 2023; Rosenkranz et al., unpublished data)

Why were there no effects of stress on airway inflammation?

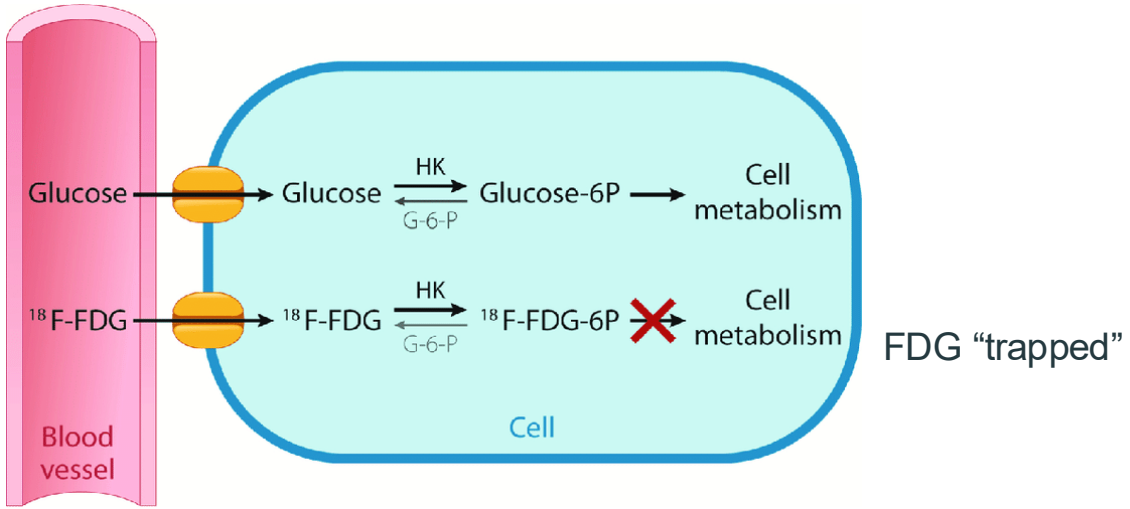




- Less robust acute stress response
- Sympathetic Nervous System moderation
- Acute stress does not prime inflammatory response to allergen challenge in those with *average (not high, not low)* chronic stress

PET

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



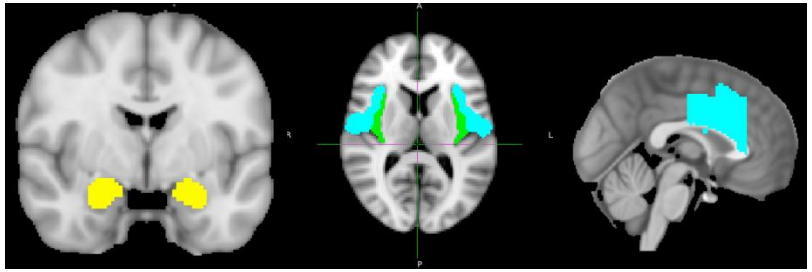
(Rahman et al., 2019)

Analyses: Stress Neurocircuitry

- Whole-Brain

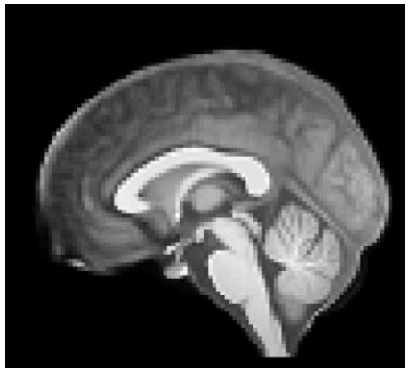
  +

- 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

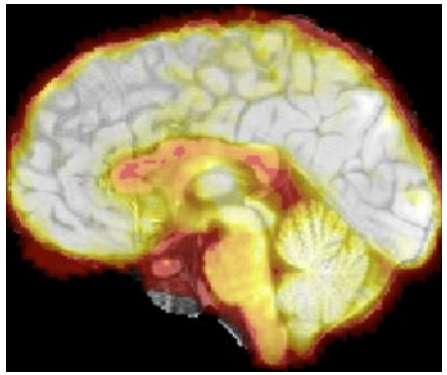


PET Processing

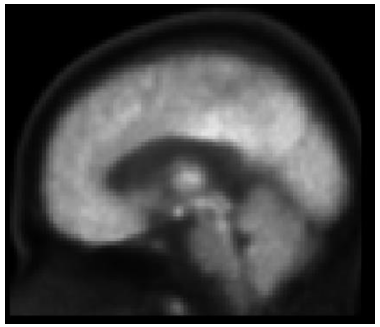
- Processing pipeline optimized for PET-T1 co-registration
  - FSL's FEAT; AFNI; ANTs



Study-specific T1 template



Example co-registration

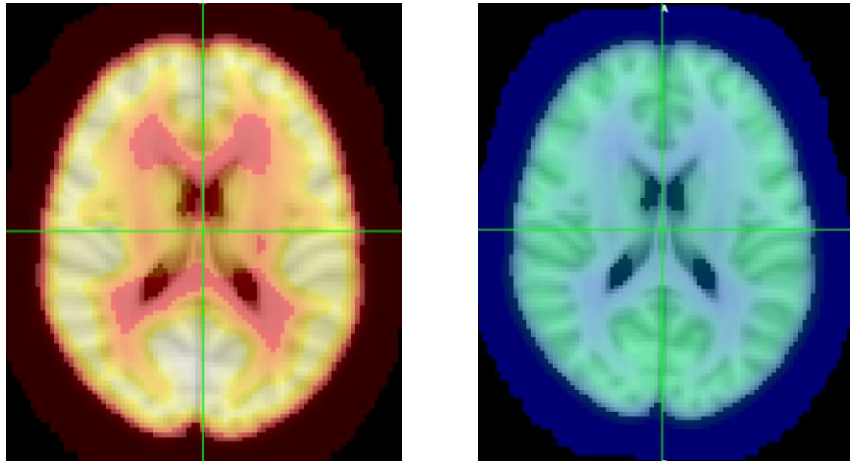


PET template in MNI space

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

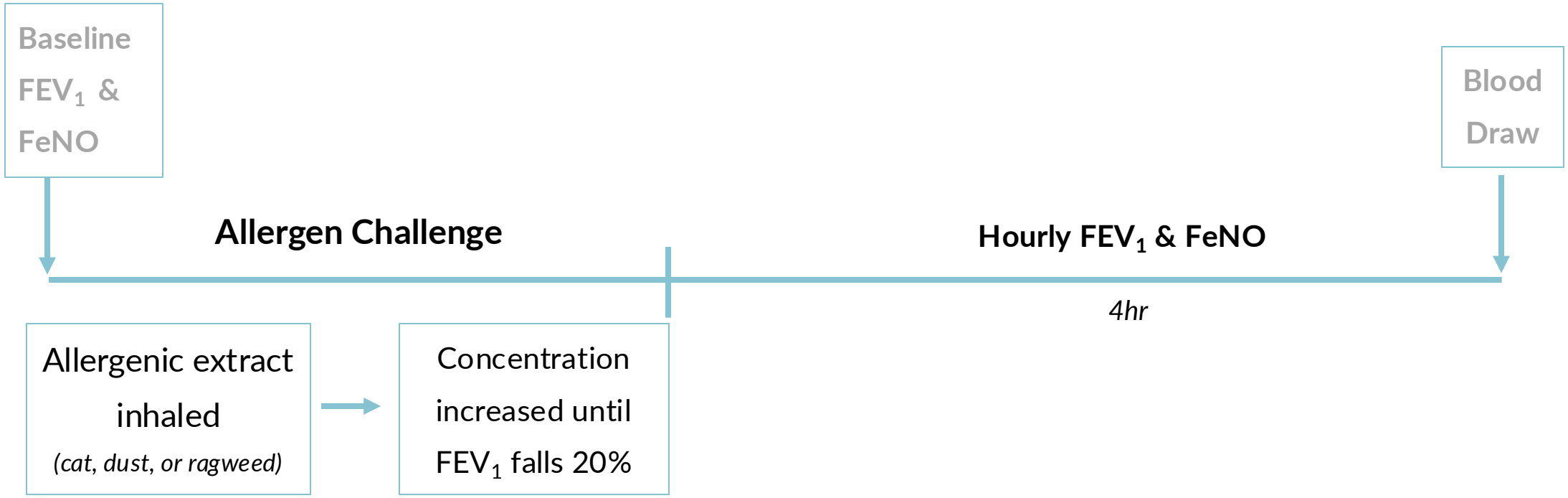
PET Processing

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



Stress — Control

Allergen challenge

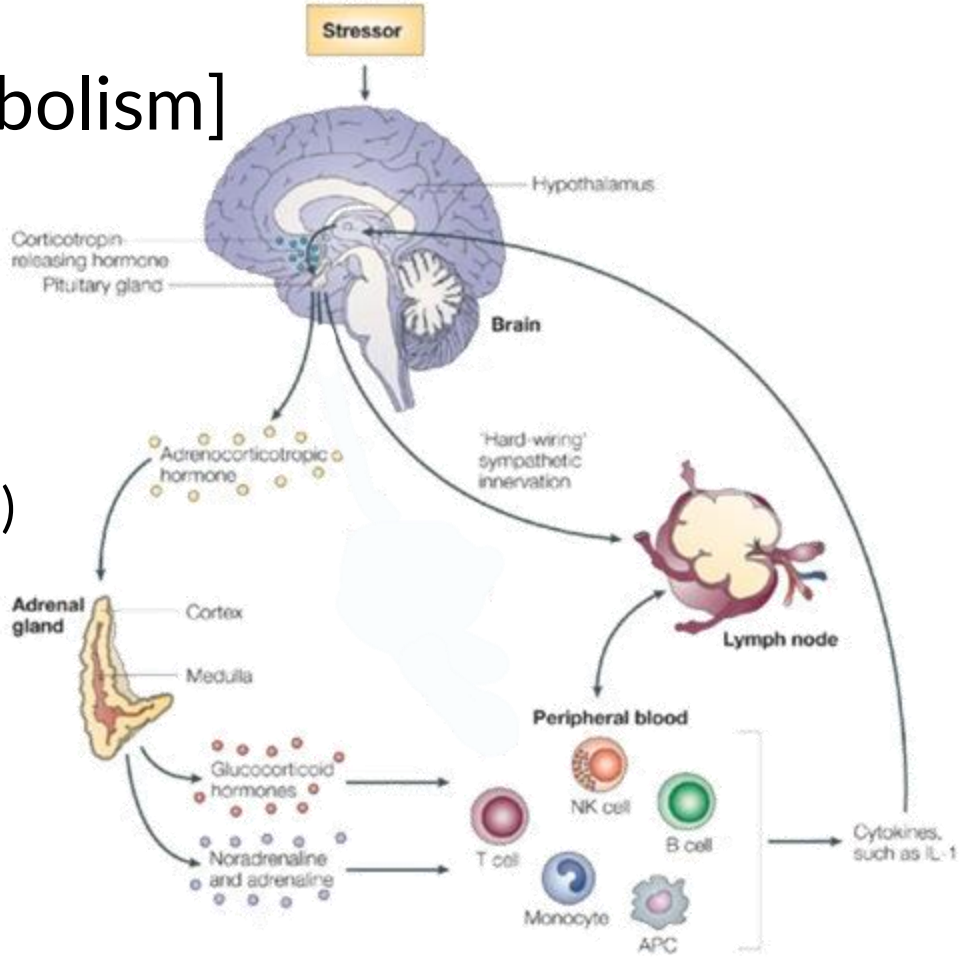


FEV_1: Forced Expiratory Volume (1s) = *Lung Function*

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

Proximal and distal mechanisms

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



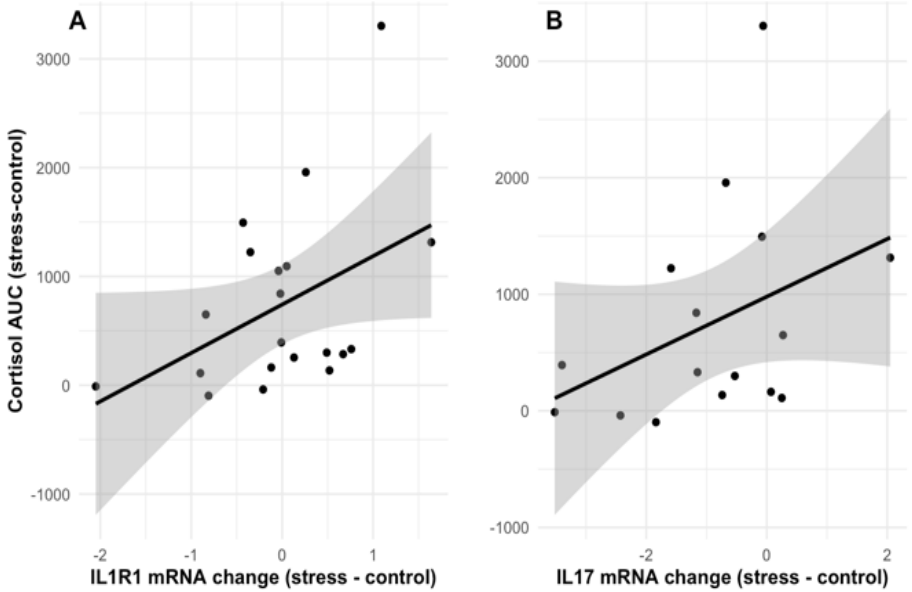
(Glaser & Kiecolt-Glaser, 2005)

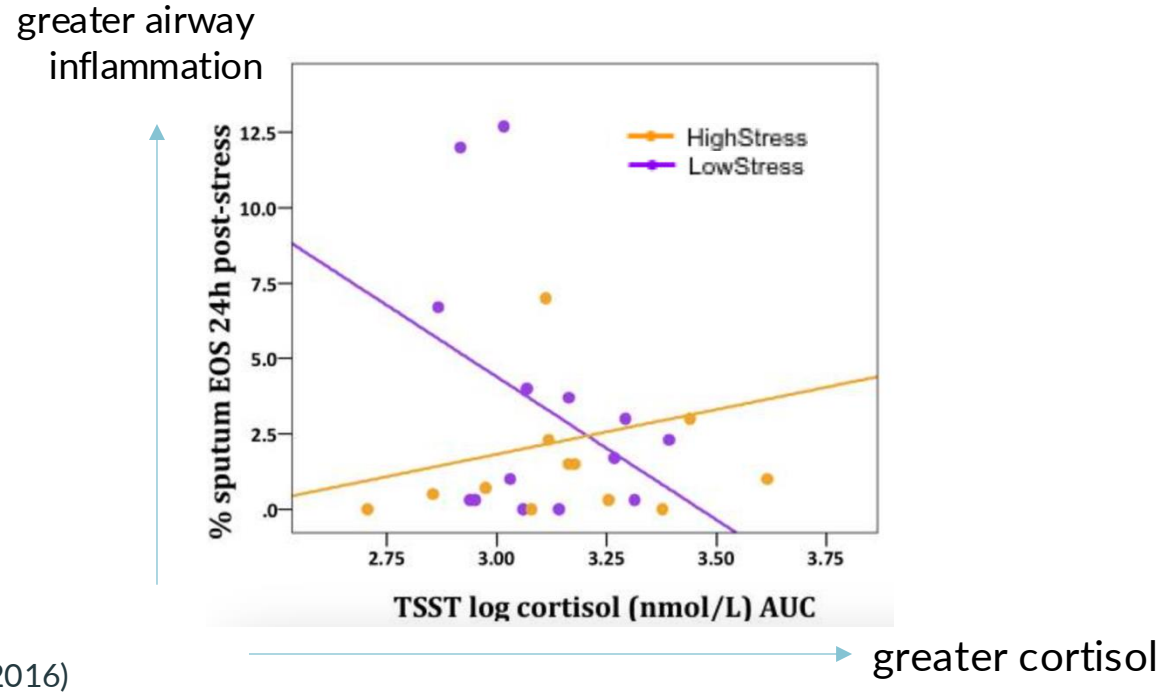
Power: stress neurocircuitry

- Sensitivity Power Analysis:
  - For 80% power (N = 27) at 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)