



Fueling the fire in the lung-brain axis: The salience network connects allergen-provoked TH17 responses to psychological stress in asthma

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ABSTRACT

Background: Asthma, a highly prevalent chronic inflammatory disease of the airways, results in an average of 10 deaths per day in the U.S., and psychological stress hinders its effective management. Threat-sensitive neuro-circuitry, active during psychological stress, may intensify airway inflammatory responses and contribute to poor clinical outcomes. However, the neural mechanisms and descending pathways connecting acute stress and inflammatory responses to allergen exposure remain poorly understood. We hypothesized that stress-induced engagement of the salience network would prime Th17 immune pathways and potentiate airway inflammation. **Methods:** We measured brain glucose metabolism during the Trier Social Stress Test (TSST) and a non-stressful control task using [¹⁸F]fluorodeoxyglucose positron emission tomography (PET) in 28 adults (18F) with asthma. Salivary cortisol was collected to quantify physiological stress responses. Before and after airway provocation with a whole-lung allergen challenge (WL-AG), airway inflammation was assessed using fraction of exhaled nitric oxide (FeNO), sputum % eosinophils, and expression of Th17-related cytokine mRNA in the airway.

Results: As expected, the WL-AG increased all inflammatory biomarkers. Acute stress significantly increased salivary cortisol ($t(27.3) = -27.3, p < 0.01$), but did not significantly affect airway inflammation overall. Instead, more robust cortisol responses to stress predicted increased glucose metabolism in the amygdala, insula, and dorsal anterior cingulate cortex, key nodes in the salience network, as well as increased IL-23A mRNA expression ($t(22.1) = 2.38, p = 0.026$) and FeNO ($t(21.5) = 2.17, p = 0.041$). Moreover, differential increases in amygdala and dACC glucose metabolism predicted differential increases IL-23A mRNA expression following WL-AG. In addition, compared to low chronic stress, high chronic stress was associated with enhanced IL-17A mRNA expression in response to acute stress and WL-AG.

Conclusions: Individual differences in salience network and cortisol responses to acute stress predict enhanced allergen challenge-provoked Th17-related responses, advancing our understanding of the efferent arm of the lung-brain axis in asthma. This work underscores the importance of translational research for the development of novel interventions that target stress-sensitive brain and immune pathways.

1. Introduction

Affecting ~ 8 % of the U.S. population (Centers for Disease Control and Prevention (CDC), 2023), asthma is a chronic inflammatory disease

characterized by episodic and recurrent respiratory symptoms (Holgate et al., 2015). Despite several pharmacological treatment options, asthma remains poorly managed in 30–50 % of patients with moderate to severe asthma (Czira et al., 2022), causing an average of 10 deaths per day in

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the U.S., with higher rates in women and Black Americans (CDC, 2023). An insufficient understanding of the role of the mind and brain in asthma exacerbation contributes to these poor clinical outcomes.

Psychological distress may substantively contribute to individual differences in asthma pathobiology and compromise effective disease management. Mood and anxiety disorders are more prevalent in asthma (Stanescu et al., 2019) and associated with more severe symptoms and poorer disease control (Fong et al., 2022; Leander et al., 2014). Daily ecological momentary assessments reveal that greater exposure to acute stressors is linked to more severe airway inflammation and asthma symptoms (Jenkins et al., 2024; Dunton et al., 2016). Moreover, individuals with asthma and higher stress levels are less responsive to treatment (Brehm et al., 2015). Although some evidence has linked emotion-related neural reactivity with asthma (e.g., Rosenkranz et al., 2005, 2012, 2018, 2022; Ritz et al., 2019), the contributions of the central nervous system to disease expression in asthma remain insufficiently characterized. In particular, the neural circuits and descending pathways through which psychological stress impacts airway inflammation are largely unknown. The comorbidities between asthma and psychological dysfunction highlight the need for more comprehensive treatment strategies (Agusti et al., 2016). Nonetheless, current clinical care often overlooks extrapulmonary factors. Understanding these mechanisms is essential to identifying novel behavioral and pharmacological treatment targets to reduce asthma exacerbations and improve clinical outcomes.

In asthma, allergen exposure causes airway constriction and the migration of immune cells to the airways (Fahy, 2015; Holgate et al., 2015). In most asthma patients, airway inflammation is dominated by a T helper-2 (Th2) response, characterized by increased eosinophils (EOS) in the blood and airways and increased release of airway nitric oxide (Holgate et al., 2015). While prior research examining stress-related contributions to airway inflammation has focused on Th2 mediators (e.g., Chen & Miller, 2007; Liu et al., 2002; Rosenkranz et al., 2016), recent work implicates T helper-17 (Th17)-associated pathways (Allgire et al., 2021). A Th17 response is typically associated with neutrophilic asthma but is also synergistic with Th2 responses (Wakashin et al., 2008). For instance, EOS synthesize and release IL-1 β , increasing the production of IL-17A (Esnault et al., 2012, 2019). At the same time, IL-23 expression in the airway increases eosinophil recruitment and Th2 cytokine production, in addition to neutrophilic inflammation (Wakashin et al., 2008). Indeed, the combination of Th2 and Th17 responses is linked to more severe asthma (Irvin et al., 2014; Wakashin et al., 2008).

Importantly, prior studies support a connection between Th17 immune activity and psychological distress. Outside the context of chronic inflammatory disease, cytokines driving Th17 responses, including IL-1 β , IL-23, and IL-6, reliably increase following psychological stress in animals and humans (Brydon et al., 2005; Kim & Jones, 2010; Steptoe et al., 2007). In asthma, Th17 responses are associated with stress and depressive-like behavior in rodent models (Oyamada et al., 2021; Sato et al., 2023) and humans (Y. Chen et al., 2011; Davami et al., 2016; Zhu et al., 2016). However, the descending pathways involved in emotion-related modulation of these inflammatory responses in the airway remain largely unknown.

Our group has previously linked asthma-related outcomes, particularly Th17 activity, with threat-related salience network activation (Rosenkranz et al., 2018, 2022; Dill-McFarland et al., 2024). The salience network, which includes the anterior cingulate cortex (ACC), insula-frontal opercular cortex (IFOC), and amygdalae, is a set of threat-sensitive regions involved in anticipating, processing, and responding to physiologically relevant stimuli (Menon, 2015; Mesulam & Mufson, 1982; Seeley, 2019; Vogt, 2015). Previously, we showed that psychosocial stress-induced activity in the amygdala (Rosenkranz et al., 2022), ACC, and IFOC (Rosenkranz et al., 2018) was associated with subsequent priming in both Th2- and Th17-related pathways. This priming was observed in the absence of allergen exposure, suggesting that

exposure to allergen during heightened stress would elicit more robust responses.

In the current study, we built on this previous approach with the addition of an inflammatory provocation following the psychosocial stressor. We once again combined [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) with a laboratory stressor. We then used allergen challenge to provoke airway inflammation, in adults with asthma, to investigate the brain networks engaged by psychological stress that predict changes in airway inflammatory responses to allergen challenge. Based on our prior work, we hypothesized that the descending influence of stress-sensitive neurocircuitry—primarily the salience network—would be associated with the potentiation of inflammatory responses to allergen. Specifically, we predicted that Th17 cells via IL-17/IL-1 β signaling would contribute to this potentiation, alongside canonical Th2 pathways.

2. Materials & Methods

2.1. Participants

Thirty-six adults ages 19–45y (Mean = 25.92y; 25 female) with a physician diagnosis of mild asthma were enrolled. Inclusion criteria included FEV₁ \geq 70 % at baseline and 12 % reversibility or PC20 response to methacholine \leq 8.0 mg/ml. Participants had stable asthma, were free from inhaled or oral corticosteroids and respiratory infection within 1mo of screening and were not receiving immunotherapy. Exclusion criteria included incompatibility with the MRI or PET environments, major medical problems including autoimmune or inflammatory conditions other than asthma, history of neurological disorder, bipolar or psychotic disorders, head trauma, night shift work, current smoker status, or pregnancy. Participants taking limited psychotropic medications, including antidepressants at stable doses, were included. Eight participants withdrew due to scheduling conflicts or were lost to contact. Twenty-eight participants (18 female) had complete PET data and are included in analyses reported here.

2.2. Study design

Participants completed a three-day set of visits twice, once with the stress condition and once with the control condition, separated by a minimum of four weeks. Condition order was randomized, and those administering the allergen challenge were blind to condition. For each set of visits, day 1 included baseline vitals, spirometry, and sputum induction, from which measures of asthma-related inflammation were derived. The experimental stress or control manipulation and allergen challenge took place on day 2 (Fig. 1), within 72 h of day 1. An indwelling venous catheter was inserted into the antecubital vein for administration of the PET tracer, then participants completed questionnaires and watched a valence-neutral video. Immediately before PET tracer injection, participants provided saliva for assessment of baseline cortisol level. After tracer injection, participants performed the laboratory stress or control task, followed by acquisition of PET data approximately 35 m after tracer injection. PET data were acquired for approximately 40 mins, followed by allergen challenge. Participants returned 24 h later (day 3) for post-challenge assessments including sputum collection. The University of Wisconsin-Madison's Health Sciences Institutional Review Board approved the protocol (ID 2016–0021).

2.2.1. Stress and control tasks

The TSST is a well-validated stress induction procedure consisting of a 5-minute impromptu speech and 5-minute mental arithmetic task, performed in front of a video camera, microphone, and panel of two unsympathetic judges. To accommodate the bulk of FDG uptake, an additional 5-minute verbal task and 5-minute mental arithmetic task were added, for a total duration of 30 min. This extended TSST has been

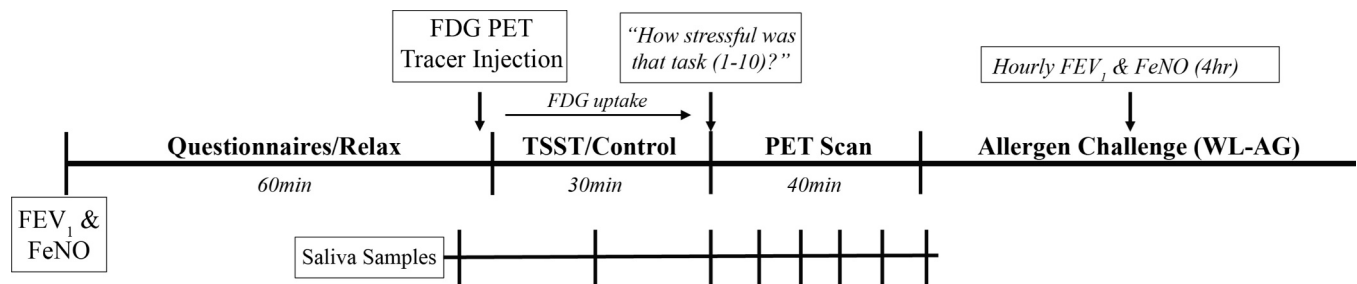


Fig. 1. Study design. Timing of experimental procedures completed on Day 2.

previously validated (Kern et al., 2008; Rosenkranz et al., 2016). The validated control condition was identical to the stress condition, but with stressful elements removed and task difficulty reduced. See [Supplementary materials](#) for full participant instructions for both tasks.

2.2.2. Physiological & Self-Report stress responses

To quantify hypothalamic–pituitary–adrenal (HPA) axis responses, saliva was collected using a Salivette (Sarstedt, Inc.; Nümbrecht, Germany) before, during, and immediately after the stress and control tasks. In total, eight samples were collected: one before FDG injection, one halfway through the task, one immediately after task completion, one every 10 min during the PET scan, and one final post-scan sample. Concentration of cortisol in saliva was quantified with standard assay techniques, using a commercially available bioluminescence immunoassay (CLIA; IBL-Hamburg, Hamburg, Germany) and reagents from Roche Diagnostics (Indianapolis, IN, USA). Intra-assay and inter-assay coefficients of variation were 6.54 and 7.47, respectively. Missing values that were not baseline, peak, or final samples were interpolated using linear interpolation. As an index of cortisol output, area under the curve with respect to ground (AUC_G) was computed within each condition (stress and control) for each participant as described previously (Pruessner et al., 2003). Cortisol AUC_G values were log-transformed to normalize their distribution. To measure perceived stress, participants were asked: “How stressful was that task, on a scale of 1 to 10?” immediately following the TSST and control task. For neuroimaging analyses, difference scores were computed by subtracting cortisol AUC_G and perceived stress values during the control condition from those during the stress condition within each participant.

2.2.3. Brain imaging

Participants were familiarized with the imaging environment before data acquisition. For localization of the PET signal, anatomical T1-weighted MRI images were acquired on a 3.0-T MR750 scanner with a 32-channel head coil. A 3D magnetization-prepared rapid gradient echo (3D MPRAGE) used with the following parameters: inversion time 256 ms, 256x256 in-plane resolution, 192x1mm sagittal slices, 256 mm FOV. To quantify regional cerebral glucose metabolism, PET scans were collected with a Siemens ECAT EXACT HR + PET scanner in 3D mode (Brix et al., 1997), using 5–7 mCi of [¹⁸F]fluorodeoxyglucose (FDG). A dynamic time series sequence of six 5-minute FDG emission frames was acquired. A 6-minute transmission scan was then acquired for attenuation correction. An iterative reconstruction algorithm (4 iterations, 16 subsets) was used for FDG image reconstruction and included a 4 mm Gaussian filter post-reconstruction (ECAT version 7.2.2 software) with corrections for random events, dead time, attenuation, and scanner normalization. The final images had dimensions of 128x128x63, corresponding to voxel dimensions of 2.57x2.57x2.43 mm³.

The preprocessing pipeline used a combination of Oxford Centre for Functional Magnetic Resonance Imaging of the Brain’s Software Library’s (FMRIB FSL) FEAT (Woolrich et al., 2001); Analysis of Functional Neuroimaging (AFNI, Cox, 1996); and Advanced Normalization Tools (ANTs, Avants et al., 2011) to optimize coregistration. Preprocessing steps included motion-correction, skull-stripping, image co-

registration, intensity normalization, image scaling, spatial normalization, and smoothing. See [Supplementary Materials](#) for details.

2.2.4. Lung function & FeNO

Lung function was measured according to American Thoracic Society (ATS) standards (American Thoracic Society, 1995) at each visit using spirometry and quantified as forced expiratory volume in the first second of effort (FEV₁). Fraction of exhaled nitric oxide (FeNO) is a non-invasive biomarker of eosinophilic airway inflammation that predicts risk for exacerbation and airflow obstruction (Dweik et al., 2011). FeNO was measured in breath condensate following ATS guidelines at a flow rate of 50 mL/s with a rapid-response chemiluminescent analyzer (NIOX System; Aerocrine, Solna, Sweden, Silkoff et al., 2004).

2.2.5. Sputum inflammatory measures

Sputum induction occurred on days 1 and 3 of each set of visits, 24hr before and 24hr after allergen challenge, as described previously (Rosenkranz et al., 2016). To index type-2 (T2) inflammation, differentials (300 cells per slide) were reported as the percentage of eosinophils. RNA was recovered from sputum samples to quantify cytokine gene expression. Total RNA was extracted using the RNeasy Mini Kit (Qiagen, Valencia, CA). The reverse transcription (RT) reaction was performed using the Superscript III system (Invitrogen/Life Technologies, Grand Island, NY, USA). Transcription of genes defining the IL-1β/IL-17 pathway, including IL-17A, IL-1β (IL1R1), and IL23A, was measured, in addition to exploratory transcripts IL-5, IL-6, IL-10, IL-13, CCL2, IFN-γ, and CX3CR1 using SYBR Green Master Mix (SABiosciences, Frederick, MD, USA) and primers designed to span an exon-exon-junction for qPCR, as described previously (Evans et al., 2018). Primers’ sequences are reported in [Supplementary Material Table S1](#). Reported data are inverted ΔΔCt values using the comparative cycle threshold method with the reference gene β-glucuronidase (GUSB). Prior to experimental RT-qPCR, standard curves and primer efficiencies were determined, resulting in > 90 % efficiencies for each gene. For neuroimaging analyses, regressors for differential change in gene expression were computed by subtracting pre-WL-AG from post-WL-AG in the control condition, from that of the stress condition.

2.2.6. Whole-Lung allergen challenge (WL-AG)

After completion of each PET scan, allergen (Standardized Short Ragweed Pollen [RW, Greer Labs], n = 5; Cat [Fel d1; Bayer Allergy Products], n = 12; or Dust Mite [Dermatophagoides farinae; Miles Allergy Products], n = 12) was administered via breath-actuated nebulizer. Baseline spirometry was performed before the challenge was initiated with 5 breaths of saline diluent, and participants inhaled increasing concentrations of allergen extract, until FEV₁ decreased by 20 % relative to baseline. To ensure safety, the dose of allergen administered was not consistent across conditions and instead was based on that which caused a 20 % fall in FEV₁. Hourly FeNO and spirometry measures were collected for 4hr following the challenge.

2.3. Statistical analyses

2.3.1. Data analysis

Linear mixed effects models were used to regress primary airway inflammatory indices (sputum % EOS, FeNO, and $\Delta\Delta\text{Ct}$ values of IL-17A, IL-1R1, and IL23A mRNA) on condition (stress and control), time (pre- and post-allergen challenge), and the condition x time interaction. Participant was included as a random factor to account for repeated measures. Time, condition, and a condition x time interaction were included as random effects. In separate models, perceived stress and cortisol AUCg were included as moderators with time (pre- and post-WL-AG), to predict inflammatory outcomes in the stress condition only. Time was included as a random effect and participant as a random factor. All models with inflammatory outcomes included allergen dose as a covariate. Brauer & Curtin's (2018) recommendations were followed to address model convergence warnings.

2.3.2. Neuroimaging analysis

To examine stress-induced changes in glucose metabolism, one-sample *t*-tests were conducted on stress minus control difference images using non-parametric permutation tests with FSL's Randomise with 5000 permutations (Winkler et al., 2014). To assess relationships between glucose metabolism and physiological outcomes, voxelwise pairwise correlations between stress-minus-control PET difference images and peripheral outcome difference scores (stress minus control) were performed using FSL's Randomise, with 5000 permutations (Winkler et al., 2014). All analyses with inflammatory markers included stress-minus-control allergen dose difference score as a covariate. For all analyses, threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons (Smith & Nichols, 2009).

Neuroimaging analyses were performed across the whole brain and within *a priori*-specified regions of interest (ROIs). ROIs included bilateral amygdalae defined based on the Harvard-Oxford Structural Atlas (Craddock et al., 2012); dorsal ACC (dACC) as defined by Shackman et al. (2011); and IFOC comprising the Harvard-Oxford-defined insula, central and frontal operculum, and lateral orbitofrontal cortex with medial boundaries of the insula. The IFOC ROI was selected based on the co-activation of these regions in our prior work and cytoarchitectonic continuity (Craig, 2009; Morecraft et al., 2015).

2.3.3. Exploratory analyses

Acute stress potentiates inflammatory responses in those with higher levels of chronic stress (E. Chen et al., 2006; Rosenkranz et al., 2016; Steptoe et al., 2007). Therefore, exploratory analyses examined the moderating effect of baseline chronic stress on the impact of acute stress on inflammatory responses to airway challenge, with the recognition that these analyses would be underpowered. Chronic stress was measured at baseline using the UCLA Life Stress Interview for adults (LSI; Hammen, 1991). Models regressed primary airway inflammatory measures on the LSI score x condition x time interaction and all lower-order effects. Condition, time, and their interaction were included as random effects, with participant as a random factor.

Primary cytokine and cell differential outcomes were selected based on results from our prior work and evidence of their involvement in asthma-related inflammation and psychological distress. Considering the heterogeneity of inflammatory phenotypes in asthma, other immune pathways may also play an important role in the mind-brain-lung interactions under investigation here. Therefore, additional exploratory inflammatory outcomes included sputum percent neutrophils and mRNA expression of IL-5, IL-13, IL-6, IL-10, TNF- α , CCL-2, and CX3CR1.

2.3.4. Outliers & false discovery rate correction

Influential outliers were determined according to Cook's distance for level-two fixed effects using the `hlm_influence` and `dotplot_diag` functions from the `HLMdiag` package in R (Loy & Hofmann, 2014). Cook's distance distributions were examined, and analyses were run with and

without participants identified as influential outliers according to `dotplot_diag`'s internally calculated cutoff ($3 \times \text{IQR}$; (Loy & Hofmann, 2014; R Core Team, 2023). Unless noted, results did not change when outliers were removed, and reported results exclude significant outliers. The Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was used to correct for false discovery rate across families defined by *a priori*-hypothesized inflammatory outcomes (i.e., FeNO, sputum % EOS, and IL-17A, IL-23A, and IL-1R1 mRNA expression) as implemented with the "p.adjust" function from the stats package in R (R Core Team, 2022). This correction provides a gain in power relative to familywise error rate correction (Benjamini & Hochberg, 1995).

3. Results

3.1 Demographics.

Of participants included in final analyses ($N = 28$), 25 identified as Non-Hispanic White, and one each as Non-Hispanic Black/African American, Asian, and multi-racial. Mean age of asthma onset was 10.8y (range 0.8–38.5y), with an average disease duration of 15.3y (range 3–33y). See Table 1 for details.

3.1. Confirmation of stress induction by TSST

To evaluate the effectiveness of the TSST and control tasks, mixed effects models with perceived stress or salivary cortisol as outcomes were evaluated. In cortisol models, time (in minutes) was modeled as a continuous variable with eight data points, and a quadratic trend for time and its interaction with condition were added as fixed and random effects. The TSST increased perceived stress ($B = 2.7$, $t(53.6) = -5.77$, $p < 0.001$) and salivary cortisol AUCg ($B = 0.55$, $t(24) = -2.92$, $p = 0.0075$) compared to the control condition. Additionally, salivary cortisol followed a significant quadratic pattern in which levels increased then decreased across the measurement period associated with the TSST relative to the control condition ($B = -0.097$, $t(27.3) = -2.78$, $p = 0.0097$; Fig. 2). This trend reflects the expected physiological reactivity to and recovery from acute stress.

3.2. Confirmation of induction of airway inflammation by allergen challenge

As expected, WL-AG increased expression of all airway inflammatory outcomes relative to baseline, except sputum percent neutrophils which did not change and IL-6 which decreased, replicating prior studies and validating the allergen challenge as a provocation of airway inflammation in individuals with asthma (Fig. 3a and Sup. Table S2). FeNO increased from pre- to 24hr post-challenge ($B = 25.3$, $t(28.06) = 4.79$, $p < 0.001$; corrected $p = 0.001$). Piecewise linear mixed models were used to model a linear trend in FeNO immediately pre- and post-challenge followed by a quadratic trend in FeNO levels in the four hours

Table 1

Baseline participant characteristics. ACQ6, FEV₁, and FeNO values were averaged within participants across stress and control visits, before taking the average across all participants. ACQ6: Asthma Control Questionnaire 6-item version. LSI: UCLA Life Stress Interview. FEV₁: Forced Expiratory Volume in one second. FeNO: Fraction of Exhaled Nitric Oxide parts per billion (ppb).

Variable	Mean (Range)
Age (years)	26.03 (19.13 – 45.31)
Duration (years since self-reported asthma onset)	15.25 (2.95 – 32.97)
Sex	18F, 10 M
Chronic Stress (LSI)	2.27 (1.69 – 2.94)
Asthma Control (ACQ6)	0.62 (0 – 2.08)
Baseline FEV ₁ % Predicted	93.11 (72.5 – 112.5)
Post-Drop FEV ₁ % Predicted	64.17 (50 – 88.5)
Fraction of Exhaled Nitric Oxide (ppb)	41.63 (10–106)

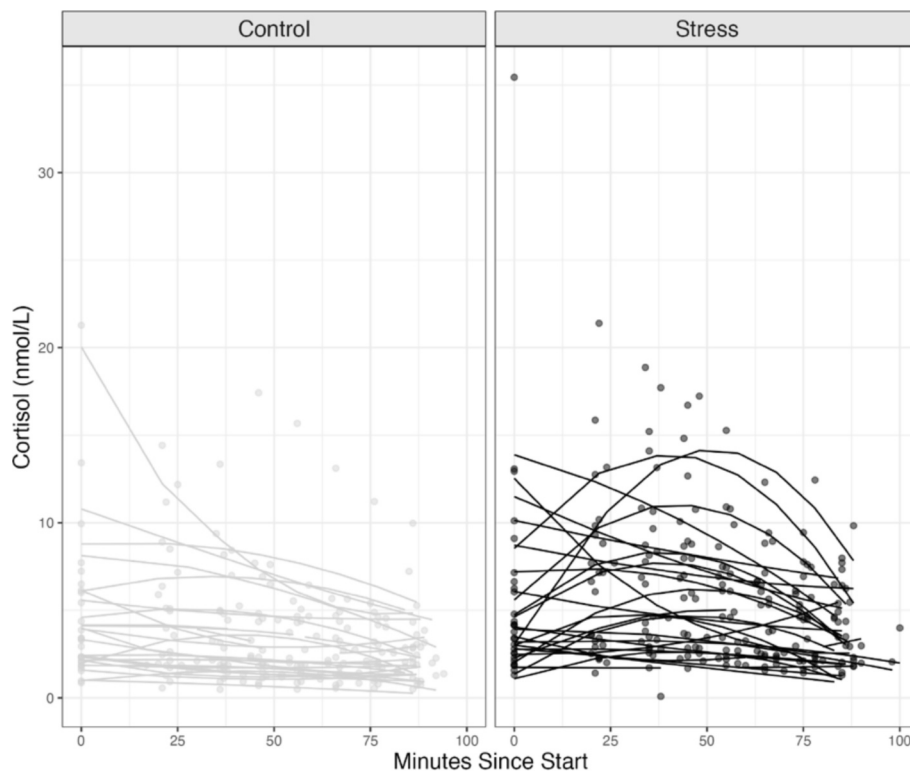


Fig. 2. Stress increases cortisol response, which follows a quadratic trend, relative to control condition. Cortisol was greater during stress, compared to control ($B = 2.79$, $t(27.5) = 3.5$, $p = 0.0016$) and showed a quadratic trend ($B = -0.097$, $t(27.3) = -2.78$, $p = 0.0097$). Predicted trajectories plotted, with raw data points; influential outlier trajectories not shown. Statistics for full sample.

following WL-AG, based on prior data showing this trend (Rosenkranz et al., 2016). Results showed that FeNO decreased from before to after both tasks ($B = -0.04$, $t(26.4) = -3.3$, $p = 0.003$; corrected $p = 0.004$), then followed a quadratic trend between 1 and 4hr post-WL-AG ($B = -0.04$, $t(36) = -2.88$, $p = 0.007$; corrected $p = 0.007$), with one outlier excluded. Similarly, sputum EOS ($B = 10.37$, $t(22.6) = 6.7$, $p < 0.001$; corrected $p = 0.001$) and expression of mRNA transcripts IL-17A ($B = 1.27$, $t(25) = 5.8$, $p < 0.001$; corrected $p = 0.001$), IL-23A ($B = 0.78$, $t(25) = 3.8$, $p = 0.0009$; corrected $p = 0.001$), and IL-1R1 ($B = 1.39$, $t(25) = 5.3$, $p < 0.001$; corrected $p = 0.001$) increased following WL-AG. See Supplement for results of the effects of WL-AG on exploratory cytokine transcripts. Note, in our extensive experience with allergen challenges in humans with asthma, spanning decades, we have found no significant differences in the asthma characteristics or airway cell differential response among participants challenged with these three different allergens (e.g. Denlinger et al., 2013). Changes in percent lymphocytes in sputum did not differ between allergens in this sample.

3.3. Impact of stress on inflammatory response to allergen challenge

Contrary to predictions, the TSST did not significantly impact the effect of WL-AG on airway inflammation, overall, for any biomarker. Instead, individual differences in the cortisol response to stress were associated with overall levels of FeNO and IL-23A mRNA expression in the stress condition (Fig. 3b). Partially supporting our hypothesis that the magnitude of cortisol stress response would be positively associated with the magnitude of airway inflammation following WL-AG, cortisol AUCg was positively associated with FeNO ($B = 14.1$, $t(21.5) = 2.17$, $p = 0.041$; corrected $p = 0.103$) and IL-23A mRNA expression in sputum cells ($B = 1.16$, $t(22.14) = 2.38$, $p = 0.026$; corrected $p = 0.103$). There were no significant time x cortisol interactions, indicating that it was the combination of baseline and post-stress measures of airway inflammation that was predicted by stress reactivity, rather than the increase in

inflammation in response to challenge. FeNO results were significant only after the removal of four influential outliers. No significant associations were found between changes in mRNA expression or FeNO AUCg and perceived stress ratings.

3.4. Brain response to stress

Consistent with our previous findings, glucose metabolism in the cerebellum increased during the stress relative to the control condition (Fig. 4a-b). Glucose metabolism in the pre and postcentral gyri was significantly lower in the stress relative to the control condition (Fig. 4c-d). See Table 2 for cluster details.

3.5. Brain and cortisol responses to stress are positively correlated

Increased glucose metabolism in response to stress in widespread regions, including the amygdala, insula, dACC, and prefrontal cortex, was associated with a larger salivary cortisol response to stress, compared to the control condition, in whole-brain analyses (Fig. 5a-b; Table 2). The effect of the TSST on perceived stress ratings was not associated with brain glucose metabolism.

Table 2. Regions where glucose metabolism was correlated with peripheral outcome. + indicates a positive correlation between glucose metabolism and peripheral outcome in the stress condition, relative to the control. – indicates a negative correlation between glucose metabolism and peripheral outcome in the stress condition, relative to the control. Main effects indicate regions where glucose metabolism in the stress condition was greater (stress > control) or less (stress < control) than that in the control condition. AUC area under the curve. dACC dorsal Anterior Cingulate Cortex.

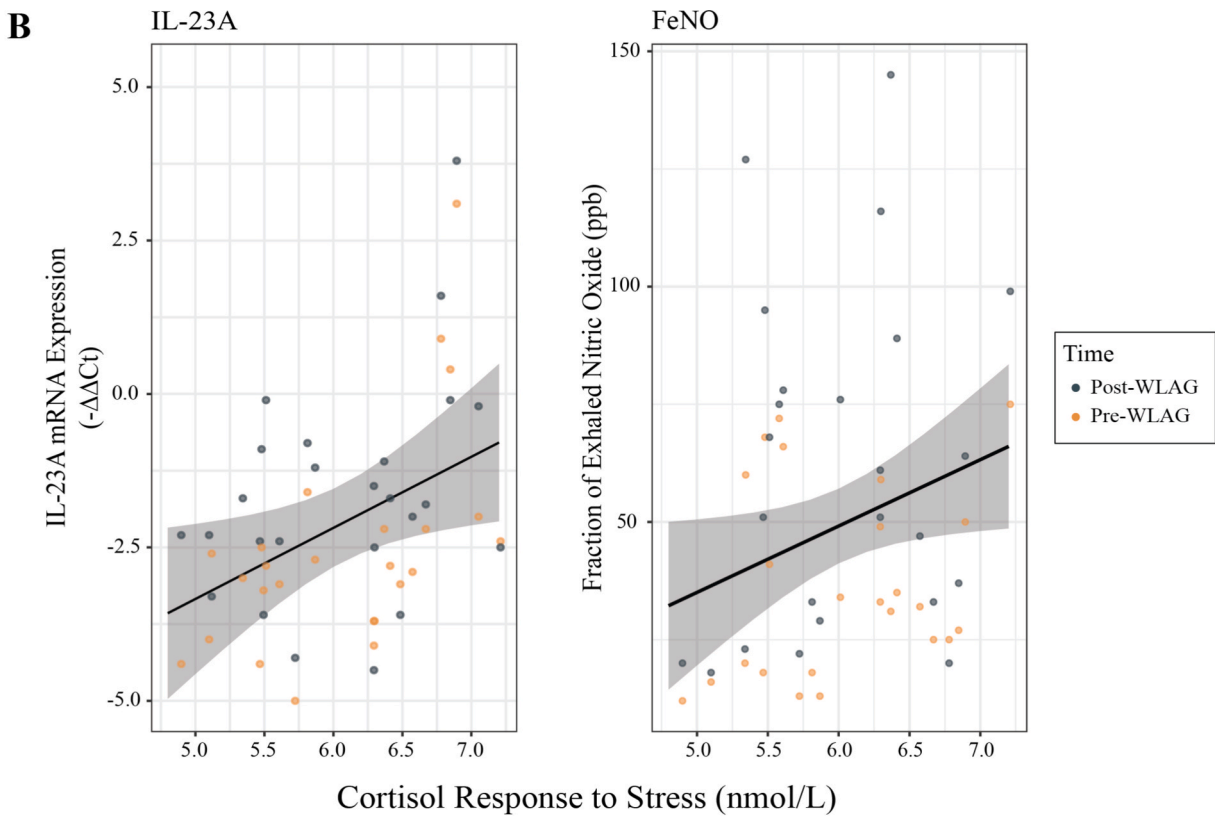
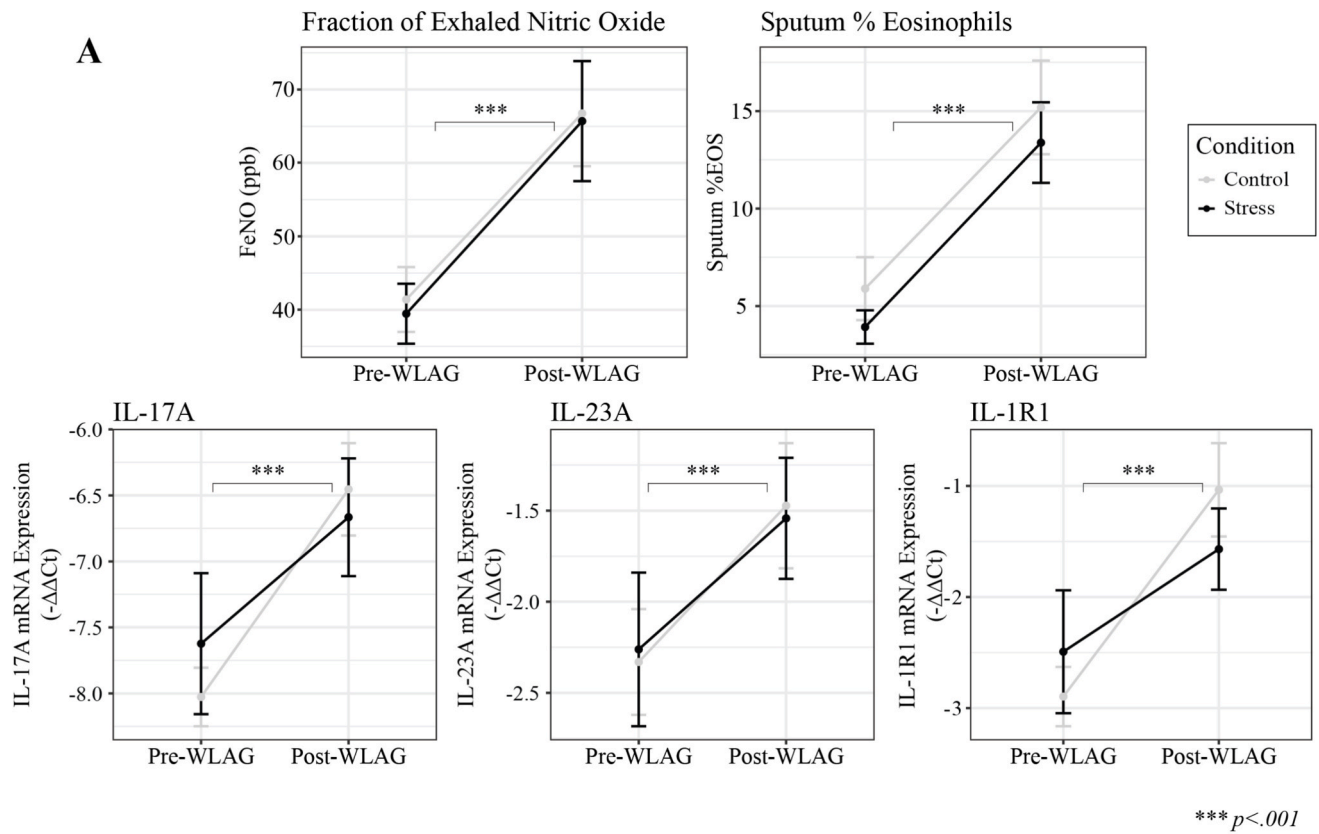


Fig. 3. (A) Allergen challenge induced airway inflammation. FeNO, Sputum %EOS, and expression of mRNA transcripts IL-17A, IL-23A, and IL-1R1 increased following whole-lung allergen challenge. (B) Cortisol area under the curve was associated with IL-23A and FeNO, collapsed across pre- and post-WLAC measures, in the stress condition. $-\Delta\Delta Ct$ represents the difference in cycle threshold (Ct) values between control and stress conditions, normalized to the housekeeping gene GUSB. Pre-WLAG: before whole-lung allergen challenge. Post-WLAG: 24 h after whole-lung allergen challenge.

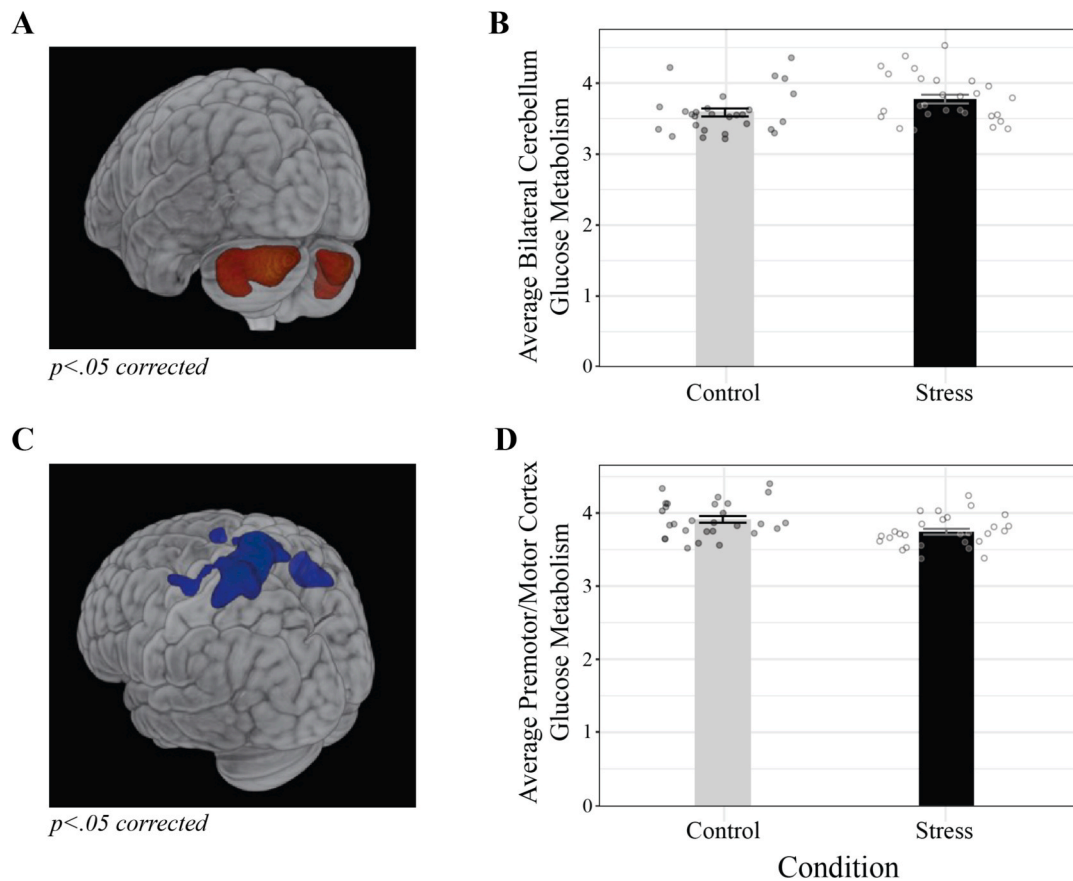


Fig. 4. Glucose metabolism in stress condition compared to control condition. **A)** Cluster of voxels that showed greater glucose metabolism during stress, relative to the control condition (bilateral cerebellum). **B)** Average glucose metabolism in significant voxels in the cerebellum, by condition. **C)** Clusters of voxels that showed less glucose metabolism during stress, relative to control condition (premotor/motor gyri, superior frontal gyrus). **D)** Average glucose metabolism in significant voxels in the premotor/motor cortex, by condition. Plots displaying glucose metabolism, averaged across the clusters, are intended for visualization only and not statistical inference, which would be a case of circular analysis (Kriegeskorte et al., 2009).

3.6. Stress-induced increases in brain glucose metabolism predict increases in airway TH17 response to challenge

Supporting our hypothesis, greater glucose metabolism (stress vs. control) in amygdala (Fig. 6a) and dACC (Fig. 6b) ROIs was associated with a greater increase in sputum IL-23A mRNA expression following stress, relative to control conditions. The same pattern was found in the IFOC, at an uncorrected threshold of $p < 0.01$. See Table 3 for ROI cluster details. There were no other associations between differential glucose metabolism and change in mRNA expression, sputum % EOS, or FeNO AUCg in whole-brain or ROI analyses.

Table 3. Region of interest (ROI) correlations with biomarkers. Regions where glucose metabolism was correlated with biomarkers. + indicates a positive correlation between glucose metabolism and biomarker outcome in the stress condition, relative to the control.

3.7. Moderation by chronic stress

Models examining the moderating effect of chronic stress on the relationship between acute stress and airway inflammation were analogous to those described above, with a condition \times time \times chronic stress (LSI) interaction. There was a significant interaction between condition, time, and LSI score on sputum EOS ($B = -13.81$, $t(16.92) = -2.81$, $p = 0.012$; corrected $p = 0.031$, Fig. 7a) and IL-17A ($B = 4.52$, $t(24) = 2.933$, $p = 0.007$, corrected $p = 0.031$, Fig. 7b). The impact of acute stress on the increase in IL-17A was more pronounced for those with higher LSI, such that they demonstrated a greater increase in IL-17A following the TSST, whereas the IL-17A response in those with lower LSI appeared to

be blunted by the TSST, compared to the control condition. Conversely, there was no difference between conditions on the increase in sputum EOS for those with higher LSI, but the slope of increase in sputum EOS for those with lower LSI was slightly steeper in response to WL-AG following the TSST, relative to the control task. LSI did not significantly affect any other inflammatory outcomes.

3.8. Discussion

Here, we built upon our prior work showing salience network engagement during psychological stress and its association with the priming of Th2 and Th17 immunity in the airway in patients with asthma (Rosenkranz et al., 2016, 2022), with the addition of an immune challenge. We combined PET neuroimaging with a laboratory psychosocial stress induction and allergen challenge, in a full cross-over design, to rigorously examine the neural mechanisms and immune signaling pathways through which acute stress influences airway inflammatory responses to allergen exposure in asthma. We showed that responsiveness to the TSST, as indexed by salivary cortisol, predicted increased glucose metabolism in the amygdala and dACC, which in turn predicted amplification of sputum IL-23A mRNA when allergen challenge followed stress, compared to the control task. Individuals more responsive to the TSST also had higher FeNO and IL-23A mRNA expression levels, irrespective of changes in brain glucose metabolism. These results corroborate and extend our previous findings, and highlight the importance of threat-sensitive neural circuits and the predominance of Th17 pathways in stress-related potentiation of airway inflammation. This work emphasizes the need to focus translational research on

Table 2
Whole-brain analyses.

Contrast/ Correlation and direction	Cluster size (voxels)	Peak voxel p value	Peak coordinates MNI (x, y, z)	Location of cluster
+ Log cortisol area under the curve (AUC)	66,744	0.001	30, -50, -56	R Cerebellum
	350	0.046	58, -4, 40	R Precentral gyrus
	34	0.05	66, -26, 2	R Superior temporal gyrus
	7	0.05	52, -32, -4	R Middle temporal gyrus
+ Log cortisol area under the curve (AUC): IFOC local peaks	1022	0.013	-32, 22, 8	L Frontal operculum
	547	0.017	38, 30, 0	R Frontal orbital cortex
	35	0.03	34, -16, 8	R Posterior insula
	5	0.042	-42, -2, -10	L Dorsal anterior insula
	2	0.042	32, -22, 8	R Posterior insula
	2	0.046	34, -8, 12	R Posterior insula
+ Log cortisol area under the curve (AUC): amygdala local peaks	107	0.022	-24, -6, -22	L Basolateral amygdala
	46	0.01	14, -4, -20	R Amygdala
	4	0.035	28, -10, -14	R Amygdala
	386	0.041	8, 30, 38	R dACC
+ Log cortisol area under the curve (AUC): dACC local peaks	8	0.021	-8, 30, -4	L Subgenual anterior cingulate cortex
	2	0.042	4, 30, 0	R Subgenual anterior cingulate cortex
Main effect: stress > control	1785	0.009	-26, -80, -38	L Cerebellum (Crus II)
	1415	0.019	30, -80, -36	R Cerebellum (Crus II)
	74	0.049	2, -66, -34	R Cerebellum (Vermis)
Main effect: stress < control	2801	0.011	-10, -34, 64	L Precentral gyrus
	414	0.041	34, -52, 46	R Superior parietal lobule
	61	0.046	26, 8, 52	R Superior/ middle frontal gyrus
	28	0.048	28, -10, 54	R Precentral gyrus
- CCL2	3724	0.032	42, -64, -52	R Cerebellum
	3313	0.033	-36, -44, -48	L Cerebellum
- IL-10	2489	0.031	-36, -44, -48	L Cerebellum
	2473	0.032	24, -76, -32	R Cerebellum (Crus I)
	337	0.047	-58, -38, -6	L Middle temporal gyrus
	216	0.046	4, -56, -38	R/Central Cerebellum
	112	0.047	-48, 6, -28	L Temporal pole
	109	0.047	-46, -66, -16	L Lateral occipital cortex
	27	0.047	-30, 24, -36	L Temporal pole

interventions that improve the regulation of these neural circuits and target Th17 pathways.

Our central hypothesis posited that engagement of the salience network—a coordinated set of brain regions responsive to threat and involved in descending physiological regulation (Kraynak et al., 2018)—during psychosocial stress would predict a more potent airway inflammatory response when participants were later challenged with inhaled allergen. We found support for this hypothesis, with greater stress-induced glucose metabolism in the amygdala and dACC, and to a lesser extent the IFOC, predicting greater allergen-induced upregulation

of IL-23A mRNA expression in the lung following stress compared to control conditions. A robust literature implicates these regions in immune regulation, in affective and stress-provoking contexts, to support allostasis (Critchley et al., 2003; Leschak et al., 2020; Rodrigues et al., 2009; Swartz et al., 2017). In asthma, these regions consistently connect emotion with airway inflammation, in both animal models and human studies (e.g., Ritz et al., 2019; Rosenkranz et al., 2005, 2012, 2018, 2022). For instance, in rodent models of asthma, animals show anxiety-like behavior, that scales with activity in the PFC, amygdala, and ACC (Dehdar et al., 2019; Lewkowich et al., 2020; Gholami-Mahtaj et al., 2022), as well as increases in brain Th17-related mediators and mixed evidence for increases in Th2 cytokines (Lewkowich et al., 2020; Tonelli et al., 2009).

IL-23 is critical to the maintenance and expansion of Th17 cells and facilitates the release of their effector cytokines, including IL-17A (Khader et al., 2009; McKenzie et al., 2006). In asthma, IL-23 enhances the production and recruitment to the lungs of both Th17 cells and Th2 inflammatory mediators (Wakashin et al., 2008; Wu & Peebles, 2023). During acute airway inflammatory challenge, IL-23 expression and Th17 cell numbers increase (Hellings et al., 2003; Lee & Park, 2022), whereas anti-IL-23 therapies decrease both Th17 and Th2 cell responses to allergen (Lee & Park, 2022). In airway disease, IL-17A (Christenson et al., 2019) and mixed Th2/Th17 phenotypes (Irvin et al., 2014) are associated with heightened airway hyper-reactivity, airway obstruction, and reduced corticosteroid responsiveness. In the current study, allergen challenge illuminated the importance of the Th17 pathway, relative to Th2, in airway responses to provocation in a context of stress. Moreover, in this same cohort, the Th17 response to segmental bronchial provocation with allergen was associated with increased salience network reactivity to emotional cues, more so than the Th2 response (Dill-McFarland et al., 2024). The present findings extend our previous work examining the airway response to psychological stress alone, to suggest that the sensitivity of the Th17 pathway to acute stress emerges in the context of response to allergen exposure.

Salience network modulation of airway inflammation in response to psychosocial stress is likely carried out in part through modulation of HPA axis and sympathetic nervous system (SNS) function (Dedovic et al., 2009; Sapolsky et al., 2000). Here, cortisol responses to the TSST correlated with increases in brain glucose metabolism in a wide swath of the brain, with local peaks in the amygdala, dACC, and PFC, as well as with biomarkers of both Th17 and Th2 signaling in the lung. While we did not measure SNS activity in the current study, our prior work showed that increased SNS activity in response to the TSST correlated positively with both amygdala activation and Th17-promoting immune activity in the lung, in response to stress provocation alone (Rosenkranz et al., 2016, 2022).

Despite the well-known anti-inflammatory effects of stress hormones, stress can facilitate airway inflammation in asthma, demonstrated both here and in our prior work (Liu et al., 2002; Rosenkranz et al., 2016, 2022). Preclinical studies that combine stress and allergen challenge paradigms similarly show that psychosocial stress increases corticosterone concurrently with allergen-induced lung inflammation (Bei et al., 2013). This is likely driven, at least in part, by reduced glucocorticoid sensitivity. Specifically, IL-17A and IL-23 increase glucocorticoid receptor- β expression on peripheral blood mononuclear cells, rendering airway immune cells less sensitive to the anti-inflammatory effects of steroids and contributing to steroid resistance in asthmatic adults (Vazquez-Tello et al., 2013). At the same time, SNS activity upregulates IL-23A via substance P (Cunin et al., 2011), which could additionally potentiate Th17-related airway responses.

Chronic stress also contributes to glucocorticoid insensitivity, diminishing the immunosuppressive effects of stress hormones (Chen et al., 2006; Steptoe et al., 2007). Indeed, in our data, acute stress potentiated the increase in airway IL-17A mRNA expression for those with higher chronic stress but blunted the IL-17A response in those with low chronic stress. This parallels our observations with a stress

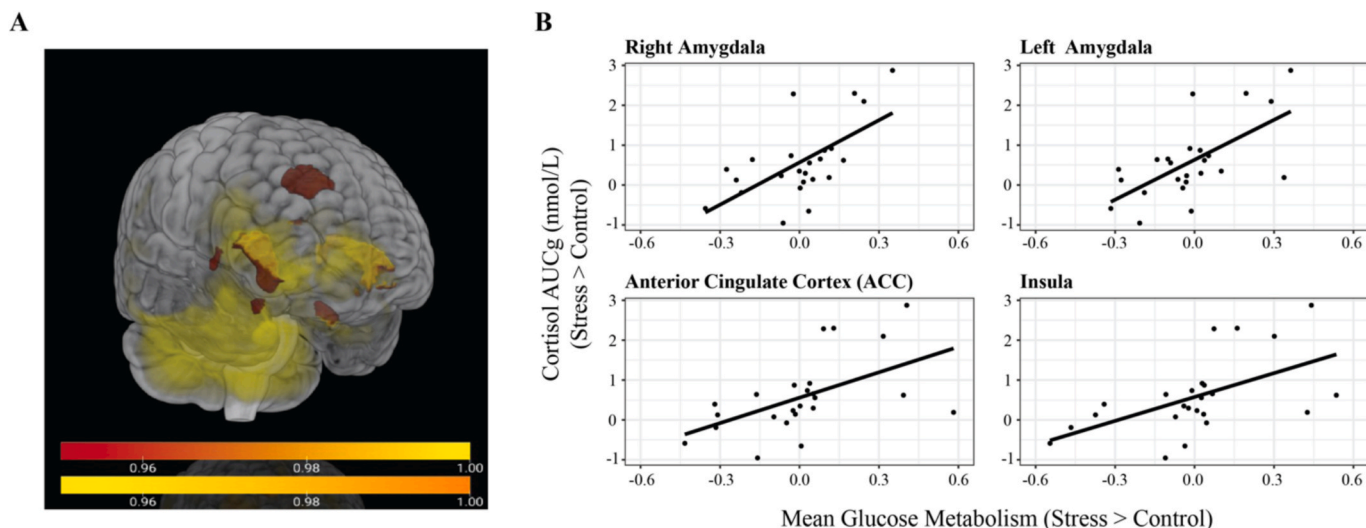


Fig. 5. Cortisol is associated with glucose metabolism in a widespread pattern following stress, relative to the control condition. **A)** Glucose metabolism was associated with greater salivary cortisol response to stress, compared to control, in regions that include local peaks in the amygdala, insula, and dACC. Yellow = all voxels showing a significant positive correlation with the magnitude of stress-evoked cortisol; Red = local peaks. **B)** Relationship between difference in cortisol area under the curve (stress minus control) and difference in glucose metabolism (stress minus control) averaged across Harvard-Oxford cortical atlas-defined right and left amygdalae, ACC, and bilateral insula. Plots displaying glucose metabolism, averaged across the clusters, in relationship to other variables, are intended for visualization only and not statistical inference, which would be a case of circular analysis (Kriegeskorte et al., 2009). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

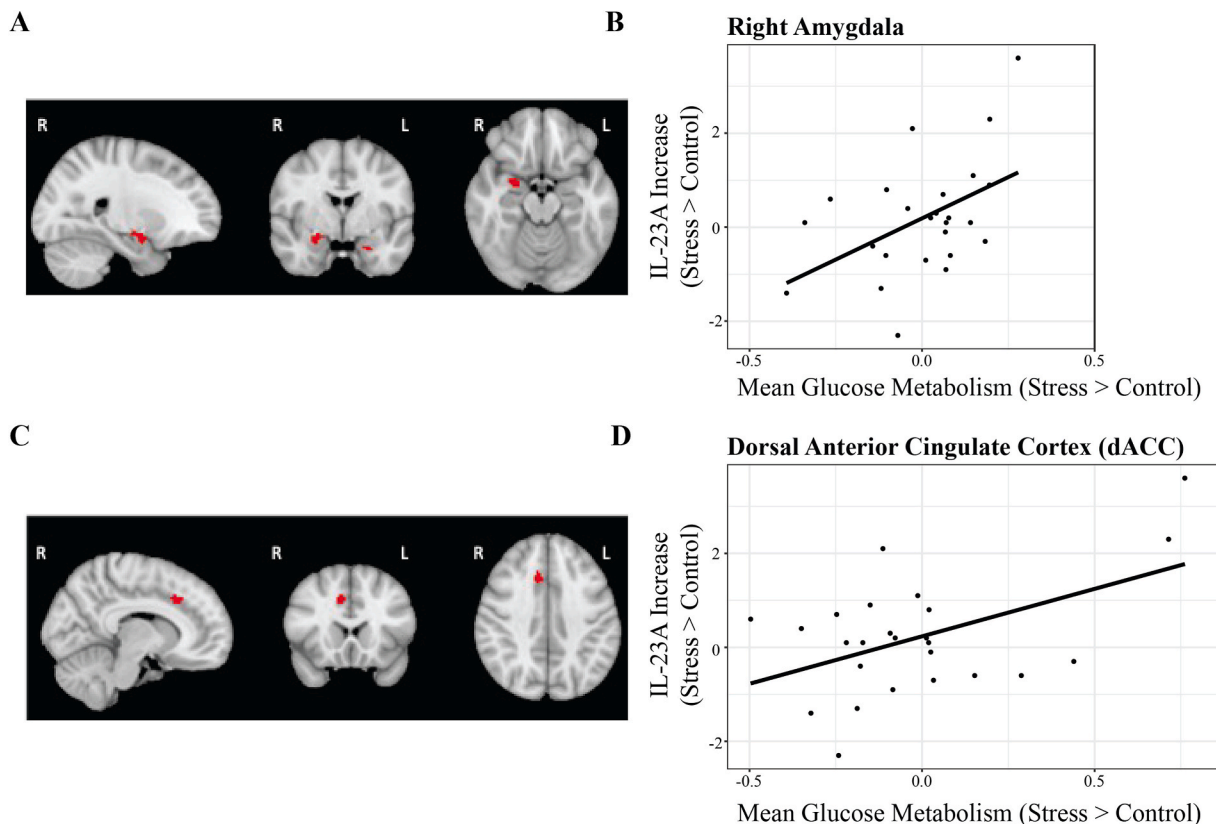


Fig. 6. Differential glucose metabolism (stress-control) in the amygdala and dACC predicts IL-23A mRNA expression following stress, relative to the control condition. Clusters in the right and left amygdala (**A**) and dACC (**C**) where glucose metabolism correlated with IL-23A mRNA expression, in the stress condition compared to the control condition. Relationship between the difference in IL-23A mRNA expression (stress minus control) and the average difference in amygdala (**B**) and dACC (**D**) glucose metabolism (stress minus control). Plots displaying glucose metabolism, averaged across the clusters, in relationship to other variables, are intended for visualization only and not statistical inference, which would be a case of circular analysis (Kriegeskorte et al., 2009).

Table 3
Small volume-corrected region of interest (ROI) analyses.

Region search space	Correlation and direction	Cluster size (voxels)	Peak voxel p value	Peak MNI coordinates (x, y, z)	Location of cluster
Amygdala	+ IL-23A	85	0.031	18, -6, -12	R Amygdala
		17	0.039	-22, -2, -26	L Amygdala
Dorsal Anterior Cingulate Cortex (dACC)	+ IL-23A	45	0.048	10, 20, 36	R Paracingulate gyrus/Anterior cingulate gyrus
Insula/Frontal Opercular Cortex (IFOC)	+ IL-23A	1935	0.012*	-36, 2, -10	L Posterior insula
		24	0.035*	36, 10, -18	R Ventral anterior insula
		1	0.049*	60, 4, 4	R Central opercular cortex

*uncorrected threshold.

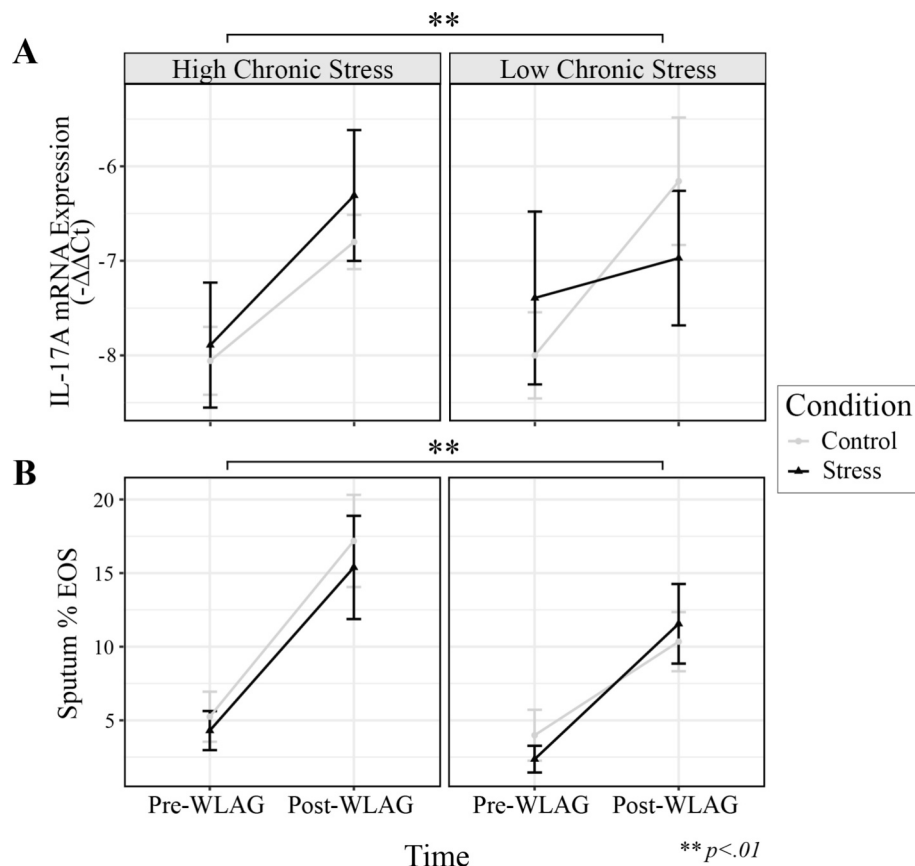


Fig. 7. Chronic stress moderates the effect of acute stress on IL-17A mRNA expression and sputum EOS. **A)** Participants with higher levels of chronic stress showed a greater increase in IL-17A following the TSST compared to the control condition. **B)** Those with higher levels of chronic stress showed no difference in sputum EOS during the control condition compared to the TSST. $-\Delta\Delta Ct$ represents the difference in cycle threshold (Ct) values between control and stress conditions, normalized to the housekeeping gene GUSB. Analyses used continuous values of chronic stress; dichotomization into high and low chronic stress is to aid in visual representation only. Pre-WLAG: before whole-lung allergen challenge. Post-WLAG: 24 h after whole-lung allergen challenge.

provocation alone, which showed that acute stress potentiated eosinophilic inflammation only for those reporting high chronic stress (Rosenkranz et al., 2016). Importantly, in the current study, only Th17-related inflammation following allergen challenge was potentiated by the TSST in those with chronic stress; Th2 responses were not differentially affected. However, the allergen challenge may have swamped more subtle effects of stress hormones on the eosinophilic response in this experimental design.

Outside the salience network, stress-related processing was evident in increased cerebellar glucose metabolism. The cerebellum has been implicated in cognitive and affective processing (for meta-analysis, Pierce et al., 2023), alongside its better-recognized roles in motor learning and coordination. Reciprocal connections with affective and autonomic centers (Dietrichs, 1984; Katsumi et al., 2023) position the cerebellum to anticipate and regulate energy demands during stress,

participating in allostatic processes. This does not appear to be a spurious observation, as we previously observed a robust increase in cerebellar glucose metabolism during the TSST in adults with asthma (Rosenkranz et al., unpublished data). Additionally, our group has reported altered cerebellar structure in those with asthma, relative to controls (Carrol et al., under review; Nair et al., 2023), suggesting asthma's pathological impacts on the brain may extend to the cerebellum. This work underscores the need for future asthma research to probe cerebellar involvement in mind–body interactions.

In addition to increases in brain glucose metabolism during stress, glucose metabolism decreased in the motor cortex, consistent with a freezing response characterized by less efficient motor planning and execution. Though not assessed here, freezing behavior has been associated with reduced motor cortex activity during acute stress in non-human primates (Kalin et al., 2005) and increased ACC and amygdala

activity in rodents (Jhang et al., 2018). This neural response pattern suggests a more comprehensive stress responsivity profile in the current participants.

3.9. Limitations

Despite the power gained with a within-subjects repeated-measures design, a modest sample size limited our power to detect small effects. We fell short of reaching our target sample size of $N = 50$ due to the COVID-19 pandemic. Power analyses indicated that for 80 % power with 28 participants and $\alpha = 0.05$, we could detect a medium-size effect (Cohen's $d = 0.56$). Consequently, small effects or those in regions with more noise may not have surpassed the threshold for significance. Additionally, although females had higher cortisol AUC_g and levels of IL23A, IL17A, and IL1R1 mRNA at baseline, we did not have sufficient power to examine the effects of sex on full models. This should be considered in future work, given previously reported sex differences in these outcomes.

This sample was relatively homogenous in race and ethnicity, with nearly 90 % of participants identifying as White Non-Hispanic (NH), so the generalizability of our results to minoritized populations requires further investigation. Future work must include greater racial diversity, since asthma prevalence and severity are greater in Black, Indigenous, and Multiracial NH individuals (CDC, 2023), who also are disproportionately impacted by stress associated with structural racism.

Our sample was also restricted to those with mild asthma, who did not use inhaled corticosteroids, due to safety concerns with performing inhaled allergen challenge in patients with more severe disease. This likely limited the magnitude of the potentiating effects of stress on airway responses to allergen challenge, reflected in the paucity of differences between stress and control conditions. We anticipate that these effects would be more pronounced in those with more severe disease but could not test this hypothesis with this paradigm.

Similarly, low variability in chronic stress levels may have limited our ability to detect stress-related effects on airway inflammation. While our prior study recruited individuals with more extreme levels of chronic stress (Rosenkranz et al., 2016), most participants here reported chronic stress levels within one standard deviation of the mean. This narrower range may have been insufficient to reveal interactions with acute stress. Attenuated physiological responses to the TSST might also explain the absence of significant group differences in stress-potentiating inflammatory responses to allergen. The mean peak cortisol response to the TSST was 7.1 nmol/L in this cohort, compared to a more robust ~ 18 nmol/L for those with low chronic stress in our prior study (Rosenkranz et al., 2016). This discrepancy highlights that participants with comparably low chronic stress showed substantially lower physiological stress reactivity to the TSST here, which may have limited the stress-related modulation of inflammatory responses following allergen. Nonetheless, even in this relatively low stress reactive sample, we were able to discern effects of stress reactivity on the airway immune response to allergen challenge.

3.10. Conclusions

Individual differences in brain and cortisol responses to psychosocial stress predicted Th17-related airway responses, despite no significant stress-related potentiation of airway inflammation in the group overall. These results contribute to our growing body of evidence highlighting the crucial role of threat-sensitive brain activity in exacerbating Th17-related airway inflammation in asthma. Critically, the addition of an asthma provocation enabled examination of the efferent arm of the lung-brain axis and the molecular pathways differentially mobilized in response.

Reducing psychological stress may help prevent asthma exacerbations, yet the current standard of care often overlooks extrapulmonary factors. This work sheds light on the role of stress-related brain activity

in inflammatory processes in asthma. Our findings linking airway Th17 activity with stress, alongside documented relationships between Th17 immunity with depression and anxiety (Beurel et al., 2013; Y. Chen et al., 2011; Davami et al., 2016; Lewkowich et al., 2020), underscore the potential relevance of behavioral interventions in asthma, and support the possibility that reducing distress promotes more salubrious inflammatory regulation. Indeed, behavioral interventions like Mindfulness-Based Stress Reduction have shown promise in reducing airway inflammation and improving asthma control (Higgins et al., 2022). This work motivates and provides a foundation for future research to develop personalized interventions targeting both pulmonary (e.g., Th17) and extrapulmonary (e.g., stress-related) factors in airway diseases.

CRedit authorship contribution statement

Estelle T. Higgins: Writing – review & editing, Writing – original draft, Formal analysis. **William W. Busse:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Stephane Esnault:** Writing – review & editing, Methodology, Formal analysis. **Bradley T. Christian:** Writing – review & editing, Resources, Methodology. **Danika R. Klaus:** Writing – review & editing, Project administration, Investigation. **Julia C. Bach:** Writing – review & editing, Project administration, Investigation. **Corrina J. Frye:** Writing – review & editing, Investigation. **Melissa A. Rosenkranz:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2025.04.004>.

Data availability

Data will be made available on request.

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