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Role of amygdala in stress-induced upregulation of airway IL-1 signaling in asthma

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ABSTRACT

Psychological stress, an important contributor to asthma morbidity, potentiates the immune response to allergen, but the brain mechanisms mediating this response are not fully understood. The amygdala is likely to play an important role, given its sensitivity to threat and connectivity with descending immune modulatory pathways. In this study, we recruited thirty asthmatic participants and examined glucose metabolism in the amygdala, using [F-18]fluorodeoxyglucose positron emission tomography, during a laboratory stressor. Stress hormone and airway inflammatory measurements were also acquired. Results showed that activity in the amygdala was significantly increased during the stressor, compared to a matched control task ($p < .05$ corrected). Moreover, the increase in amygdala activity was associated with a greater increase in sputum IL-1R1 mRNA and alpha amylase response ($p < .05$ corrected), which were also positively correlated ($p = .01$). These findings suggest that heightened amygdala reactivity may contribute to asthma morbidity via descending proinflammatory sympathetic signaling pathways.

1. Introduction

Overwhelming empirical evidence demonstrates that the contents of the mind – thoughts, emotions, beliefs – influence the physiological function of the body. Increases in symptoms and even exacerbations occur in association with psychological distress across many chronic inflammatory diseases including asthma (Chen & Miller, 2007; Loerbroks, Bosch, Douwes, Angerer, & Li, 2014; Trueba & Ritz, 2013), inflammatory bowel disease (Brzozowski et al., 2016), psoriasis (Hall et al., 2012; Yang & Zheng, 2020), rheumatoid arthritis (de Brouwer et al., 2014; Yilmaz, Umay, Gundogdu, Ozgur Karaahmet, & Ozturk, 2017), and cardiovascular disease (Albus, 2010). Despite the recognition that an integration of emotional, immune, and physiological responses takes place in the central nervous system (CNS) and affects disease severity, we know little about the efferent neural mechanisms that impact peripheral pathology in humans. In asthma, evidence suggests that stress and emotion prime underlying inflammation and enhance symptom expression (Liu et al., 2002; Marin, Chen, Munch, & Miller, 2009; Rosenkranz et al., 2016), yet research aimed at understanding the physiological underpinnings to develop new strategies in the management of asthma has focused almost exclusively on the lung and airways.

Asthma is highly prevalent – affecting approximately 10% of the population – and is often associated with poor psychological wellbeing (Katon et al., 2007; Stanescu, Kirby, Thomas, Yardley, & Ainsworth, 2019; Yan Zhang et al., 2019). Asthma is characterized by airway obstruction and inflammation that is heterogeneous, with a variety of phenotypes (Wenzel, 2012). Indeed, in previous work, we have proposed that a heightened CNS response to stress and emotion may constitute a *neurophenotype* for asthma, that is vulnerable to stress- and emotion-induced exacerbations (Rosenkranz, Busse, Sheridan, Crisafi, & Davidson, 2012). In our prior work, components of the salience network, the insula and anterior cingulate cortex in particular, have shown differential engagement by disease-related emotional cues (e.g. wheeze,

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constrict) following allergen exposure, which predicted the magnitude of the fall in lung function and development of airway inflammation (Rosenkranz et al., 2005; Rosenkranz, Busse, Sheridan, Crisafi, & Davidson, 2012). This network has also shown increased engagement during a laboratory stressor that predicts increased priming of airway inflammation in asthma (Rosenkranz et al., 2018, 2016).

The amygdala, another component of the salience network, is known to be engaged during the experience of social threat, particularly when the threat is uncertain (Bas-Hoogendam, van Steenbergen, van der Wee, & Westenberg, 2020; Fox, Oler, Tromp, Fudge, & Kalin, 2015; Williams et al., 2015), and greater amygdala engagement during exposure to socially threatening stimuli is associated with elevated peripheral inflammation (Leschak et al., 2020). Further, greater metabolism in the amygdala confers risk for development of anxiety disorders and depression (Fox, Oler, Shackman, et al., 2015). Thus, in the current study, we sought to examine the involvement of the amygdala in a circuit through which the experience of psychological distress contributes to perturbations in allergic asthma, in the context of uncertain social threat – the Trier Social Stress Test. Our analyses focused on the right amygdala a priori, based on several studies showing right-sided dominance of the salience network (Yaodan Zhang et al., 2019), greater right amygdala control over sympathetic outflow (Sturm et al., 2018), greater right amygdala involvement during social threat (Fox, Oler, Shackman, et al., 2015; Kalin et al., 2016; Shackman et al., n.d.; Williams et al., 2015), and a stronger association of right amygdala activation in response to socially threatening stimuli during inflammation with increased psychological sequelae (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012). Here, we report on brain-periphery pathways through which priming of inflammation in asthma may occur.

2. Materials and methods

2.1. Participants

Thirty participants with allergic asthma (average age 26.23 ± 6.04 years, 12 female) were recruited for study. Half the participants had well-controlled asthma, defined as a score on the Asthma Control Questionnaire (6-item version; ACQ) ≤ 0.75 (Juniper, Bousquet, Abetz, & Bateman, 2006; Juniper, Buist, Cox, Ferrie, & King, 1999). Only one participant was not under asthma control, defined as ACQ6 ≥ 1.5. Asthma control for the remainder of the participants was good with ACQ6 ranging from 0.75 to 1.5. Baseline lung function, measured by percent predicted forced expiratory volume in 1 s (FEV_1), ranged from 59% to 112%, with a normal average value ($M = 87.9\%$, $SD = 12.5\%$). Based upon baseline FEV_1 values only, asthma severity ranged from mild-to-severe; however, only one participant was not under asthma control at the time of recruitment with the as-needed use of a beta-agonist alone. In addition to their asthma characteristics, participants were selected according to the degree of chronic stress present in their lives over the previous 6 months, as determined by the UCLA chronic life stress interview (LSI), where 15 individuals had high and 15 had low levels of chronic stress (see criteria below).

Participants were recruited within Madison, WI and the surrounding community using an established database of asthmatic individuals, flyers, and online advertisements. All participants had a physician's diagnosis of asthma for at least 6 months prior to study entry and a positive skin test to at least one common aeroallergen. Participants were excluded if they used medication for anxiety or depression or if they required asthma medication beyond an inhaled β-agonist on an as-needed basis, due to the potential impact of these medications on the function of the brain circuits of interest in this study. Participants were also excluded if they were a current smoker, a former smoker with a history exceeding 5 pack years, pregnant, breastfeeding, or had any history of bipolar or schizophrenic disorders, traumatic brain injury or seizures. UW-Madison's Health Sciences Institutional Review Board approved the protocol, and all participants provided written informed consent and were given monetary compensation for their participation.

2.2. Chronic stress

High and low chronic stress assessments were made using the UCLA-LSI for Adults (Hammen, 1991). This semi-structured interview covers 9 domains: intimate relationships, close friendships, social life, family of origin relationships, relationships with one's children (if applicable), work, finances, health of self, and health of family members. Presence of stressors and overall function, over the previous six months in each of these domains, was rated on a 1 (high function/low stress) to 5 (low function/high stress) point scale, in half-point increments. Interviews were conducted by experienced clinical interviewers and were scored by an independent team. High chronic stress was defined as an average score above 2.5, coupled with no domain score less than 2 and at least 1 domain score of 3.5 or above. Low chronic stress was defined as an average score below 2 and all single domain scores below 3. Effects of background chronic stressors were described in a previous report (Rosenkranz et al., 2016) and, thus the current report focuses only on effects of the acute laboratory stressor.

2.3. Study design and procedures

Data were collected during three consecutive lab visits (Fig. 1). This set of visits occurred twice, once for each condition (stress and control). Condition order was randomly assigned. On the first day of each set of visits, sputum samples were collected for baseline assessment of inflammatory biomarkers and a physical exam was performed to rule out respiratory infection and recent asthma exacerbation. On the second day, the experimental manipulation (stress or control) was performed. All study visits began at approximately 8 a.m. To prepare for the [F-18] fluorodeoxyglucose (FDG) positron emission tomography (PET) scans and stress hormone measures, participants were asked to fast and abstain from caffeine for at least 4 h prior to arrival, and a negative pregnancy test was confirmed for women of childbearing potential. Blood glucose levels were tested to confirm a fasting state. Fraction of exhaled nitric oxide (FeNO; parts per billion) was measured to establish baseline airway inflammation. After insertion of an IV catheter for the administration of FDG, participants rested quietly for 1 h, while watching a video with neutral content. After the 1 h rest and immediately before injection of FDG, a saliva sample was collected for measurement of baseline cortisol and alpha amylase. Immediately following FDG injection, participants were escorted to a nearby room where they performed the Trier Social Stress Task (TSST) or control task for about 30 min, corresponding to the FDG uptake period. One saliva sample was collected 15 min into the task, and an additional sample was collected immediately after task completion. Participants were then positioned in the PET scanner. PET scans measuring FDG uptake into the brain were collected for 30 min.[1] During PET scanning, saliva samples were collected every 10 min for 50 min post-task, for a total of 8 samples. After completion of PET scanning, FeNO was measured hourly for 4 h. On the third day, participants returned to provide samples of sputum and measurements of FeNO. A structural magnetic resonance imaging (MRI) scan, for co-registration purposes, was also collected during one of the study visits. In most cases, the MRI scan was acquired on the baseline day (the day before the PET scan), but in a few cases this scan was acquired on a different day due to schedule constraints or scanner availability.

2.4. Experimental conditions

An extended version of the TSST was used in the stress condition

[1] The FDG brain scan was only 30 min in duration. FDG lung scans were also acquired for an additional 25 min, but not reported on here.

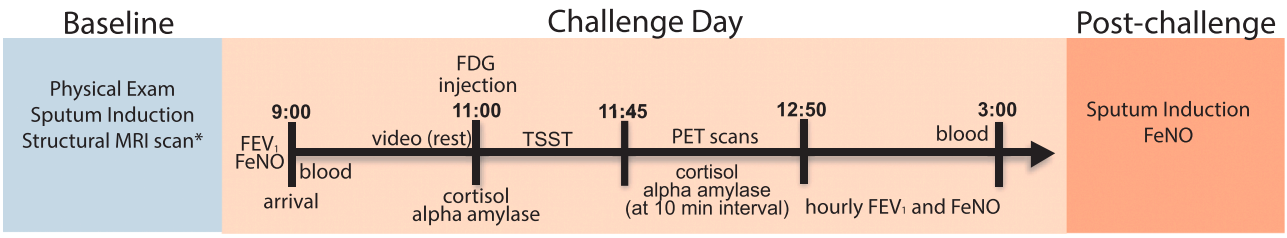

Fig. 1. Timing of study visits and measures. This 3 consecutive-day set of visits occurred twice, once for each challenge, with challenge order randomized across participants. *The structural MRI scan typically occurred on the baseline day (day 1), but occasionally was collected on a different day, due to scheduling constraints.

(Kirschbaum, Pirke, & Hellhammer, 1993), and referred to here as the modified TSST (mTSST). This is a well-validated and standardized social stressor with proven consistency in evoking a physiological stress response. The version used here extends the duration of the original task from 15 to 30 min by adding an additional verbal performance and mental arithmetic task, in order to accommodate the bulk of the radiotracer uptake into the brain. The second verbal task involved defining difficult words. This extended version has been validated for evocation of a robust stress response, assessed by both self-report and salivary cortisol (Kern et al., 2008). As in the original version, the mTSST is performed standing in front of a microphone, before a panel of two stern and unresponsive judges and a video camera. Participants were given 5 min to prepare a speech after the topic was revealed but were not allowed to use their notes during the speech.

The control task was designed to match the mTSST in structure, duration, cognitive function (e.g., performing mental arithmetic, accessing working memory), and physical activity (standing, speaking, etc.), with the stress-provoking aspects removed. The panel of judges and microphone were absent, and participants were told explicitly that no one could hear them speaking and that their performance would not be recorded or evaluated. A sound pressure meter was used to confirm that participants spoke during the entire task. Otherwise, the conceptual framework and environment were identical to that of the stress task. Participants prepared for 5 min and then spoke for 5 min about a recent book they read, movie they had seen, or trip they had taken. For the specific instructions given, see Supplemental materials. After each 5 min segment, the experimenter entered the room and gave instructions for the next segment. The second verbal task and both mental arithmetic tasks were identical to that of the stress condition but were far less difficult (e.g., serial subtraction in increments of 2, rather than 17).

2.5. Brain imaging

Anatomical MRI data were acquired, for localization of the PET signal, on a 3.0-T MR750 scanner (GE Healthcare, Waukesha, WI, USA) with an 8-channel head coil. A three-dimensional magnetization-prepared rapid gradient echo (3D MPRAGE) image was acquired using the following parameters: inversion time/echo time/repetition time, 450/3.2/8.2 ms; flip angle, 12°; 1 mm slice thickness, field of view, 256 mm; and acquisition matrix size, 256 × 256, 160 × 1 mm slices. The T1-weighted anatomical images were skull stripped using the Brain Extraction Tool (BET), part of Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's Software Library (FSL; Smith et al., 2004). Participants were familiarized with both PET and MRI scanning environments prior to data acquisition.

Regional cerebral glucose metabolism was measured using FDG PET with a Siemens ECAT EXACT HR+ PET scanner in three-dimensional mode (Brix et al., 1997). Because arterial plasma samples were not acquired and plasma glucose was not used in the derived outcome, we assume glucose metabolism is represented by cerebral FDG metabolism. A certified PET technician injected a bolus of 5–7 mCi of FDG via an indwelling catheter in the antecubital vein, just prior to the mTSST and control task. Approximately thirty-five minutes after injection and following task performance, participants were positioned in the PET scanner such that the canthomeatal line was parallel to the in-plane field of view (FOV). A dynamic time series sequence of six 5-min FDG emission frames was acquired. A 6-min 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 128 × 128 × 63, corresponding to voxel dimensions of 2.57 × 2.57 × 2.43 mm^3.

Advanced Normalization Tools (ANTs; Avants & Gee, 2004) software package and FSL were used for the pre-processing of PET data. Control and stress task PET images were independently motion corrected using FSL's MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson et al., 2002) tool and the 5-minute frames were summed across the 30-minute FDG acquisition. All PET images were skull-stripped using the BET tool in FSL. For the purposes of image co-registration, the T1-weighted structural image was segmented into grey and white matter using the FAST tool in FSL and a 3-mm smoothing kernel was applied to the grey matter mask. PET images were bias corrected using ANTS N4BiasFieldCorrection tool to remove variations in intensity across the image to improve image registration. Individual bias-corrected PET images were then co-registered to the corresponding smoothed grey matter mask using FMRIB's Linear Image Registration Tool (FLIRT) in FSL. Raw PET data were scaled by dividing by the mean grey matter voxel intensity. ANTS was used to create and spatially normalize (to Montreal Neurological Institute (MNI) space) a study-specific template from T1-weighted images. Concatenated transforms from individual space all the way to MNI space were applied to the individual scaled PET images. Finally, an 8-mm smoothing kernel was applied to the spatially normalized PET data.

2.6. Assessment of stress hormones

Levels of two salivary stress hormones, cortisol and alpha amylase (AA), provided measures of stress response magnitude to the mTSST and control task. These hormones served as markers of hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system activity, respectively. Participants used salivettes (Sarstedt, Inc.; Nümbrecht, Germany) to collect saliva samples at baseline, 15 min into each task, immediately after the end of each task, and every 10 min for the next 50 min, for a total of 8 saliva samples/task. Cortisol and AA levels were quantified by Dr. Nicolas Rohleder at Brandeis University, using standard assay techniques. Cortisol was measured using a commercially available luminescence immunoassay (CLIA; IBL-Hamburg, Hamburg, Germany), and AA was measured using an enzyme-kinetic assay using reagents provided by Roche Diagnostics (Indianapolis, IN, USA) as previously described (Rohleder & Nater, 2009). Intra- and inter-assay coefficients of variation for cortisol were 4.51 and 6.08, respectively, and 4.39 and .67 for AA.

2.7. Inflammatory measures

FeNO is used clinically to measure Type 2 airway inflammation in

asthma (Hoffmeyer, Raulf-Heimsoth, & Brüning, 2009). FeNO was measured according to American Thoracic Society guidelines (Silkoff et al., 2004, 1997; NIOX System; Aerocrine, Solna, Sweden). Measurements were performed at baseline, prior to each stress and control task, as well as hourly after PET scanning to evaluate task-related changes in airway inflammation.

Induced sputum was obtained following an inhalation of nebulized 3% saline solution (Evans, Esnault, Denlinger, & Jarjour, 2018). The sputum was diluted 1:1 with a 10% dithiothreitol solution. Cytospin slides were prepared for cell counts of the sputum samples. Samples (up to 1×10^6 cells/aliquot) were stored in 1 mL of Trizol Reagent (Invitrogen, Carlsbad, CA) for RNA purification. Gene expression of cytokines in the IL-1ß/IL-17 pathway (IL-1R1, IL-17A, IL-23) was examined in cells from sputum, due to their involvement in both asthma pathogenesis (Esnault et al., 2012; Evans et al., 2018; Vazquez-Tello, Halwani, Hamid, & Al-Muhsen, 2013) and depressive- and anxiety-like behavior (Beurel, Harrington, & Jope, 2013; Chen, Yang, Li, & Kijlstra, 2011; Rossi et al., 2012), as well as their implication in corticosteroid insensitivity. Total RNA was extracted according to the Trizol Reagent manufacturer's recommendations. The reference genes, ß-glucuronidase (GUSB) and ribosomal protein S26 were used to normalize the samples. Data are expressed as average -ΔCt for GUSB and S26 using the comparative cycle threshold (ΔCT) method as described previously (Esnault et al., 2012). Difference scores were computed using these -ΔCt values, to reflect differences, relative to the reference genes, in stress and control conditions.

2.8. Data analysis

2.8.1. Regional cerebral glucose metabolism with FDG-PET

We used the Randomize tool in FSL (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) for analysis of PET data. Voxel-wise analyses were carried out in an anatomical region of interest (ROI) mask of the right amygdala. The right amygdala mask was defined based on the probabilistic map from the Harvard-Oxford Subcortical Structural Atlas available for FSL, including only voxels with a probability of 50% or greater of being labeled as amygdala.

A linear mixed effects model was used to test the main effect of challenge within the right amygdala ROI. Linear regression was used to test the association between the difference in amygdala regional glucose metabolism in the stress and control conditions (stress-control) with peripheral inflammatory biomarkers and stress hormones. Nonparametric permutation tests using the threshold-free cluster enhancement (TFCE) approach (Smith & Nichols, 2009), within the Randomize tool, were used to correct for multiple comparisons. Whole-brain analyses were performed as part of a separate set of hypotheses and are reported elsewhere (Rosenkranz et al., 2018; Rosenkranz et al., 2016).

2.8.2. Stress Hormones and Inflammatory biomarkers

Effects related to the presence of high vs. low levels of chronic stress were reported previously (Rosenkranz et al., 2016). Therefore, all models described here collapse across group to examine the within-subject effects of the acute laboratory stressor, relative to the control condition. For all peripheral physiological measures, mixed models were used to examine the effects of challenge condition, time, and their interactions. A random intercept was used to adjust for repeated measures within-subject and models were estimated using the lmer function (Bates, Machler, Bolker, & Walker, 2015) of the lme4 library of the R software package (www.r-project.org). P-values were computed according to the calculation of Satterthwaite's approximation, as implemented in the lmer Test library in R (SAS Technical Report R-101: Tests of Hypotheses in Fixed-Effects Linear Models, 1978). A random effect for time was also considered but was not found to be significant and thus was omitted. Likewise, to identify the most parsimonious model, we started with full models, including a Challenge × Time interaction (and higher order polynomial terms when necessary), and omitted insignificant interaction terms through a backwards model selection. Other parameter estimates remained stable during model selection. Because a quadratic trend over time was present in cortisol data, we included quadratic terms, as well as their interactions, in these models. In the AA data, both quadratic and cubic trends over time were present and were included in the model.

Paired samples *t*-tests, as implemented in R, were used to compare mRNA expression of each cytokine assessed in the IL-1ß/IL-17 pathway in response to stress vs. control challenges. Relationships between stress hormone change and cytokine mRNA expression were tested using Pearson's correlation. Change in stress hormones in these analyses, as well as in analyses examining relations with amygdala glucose metabolism, was indexed by the difference (stress-control) in area under the curve (AUC) with respect to ground across samples for each challenge condition, calculated as described by Pruessner and colleagues (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The threshold for statistical significance in all analyses was set at $p < .05$.

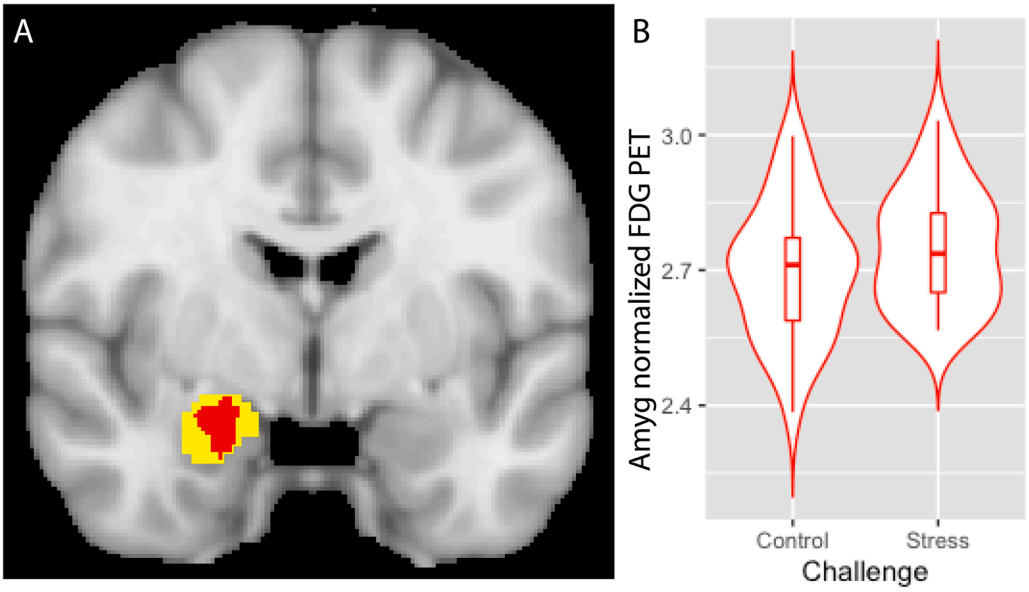

Fig. 2. Psychological stress increases amygdala metabolism. Glucose metabolism in the right amygdala is significantly greater during stress relative to control condition. A) Voxels showing a significant main effect of stress (stress > control; red) in a small-volume corrected analysis of a Harvard-Oxford amygdala defined region of interest (yellow; image thresholded at corrected $p < .05$). B) Distribution of mean values of normalized amygdala glucose metabolism in voxels (red) showing a significant main effect of challenge during stress and control conditions.

3. Results

3.1. FDG-PET

The results of the linear mixed-effects model showed a main effect of challenge condition at a small-volume corrected threshold of $p < .05$ (peak voxel: 31, − 3, − 27; 208 mm^3), such that glucose metabolism in the right amygdala was significantly greater during the mTSST compared to the control condition (Fig. 2). The results of the linear regression analyses revealed a positive relationship between amygdala glucose metabolism during the mTSST (mTSST – control) and increase from baseline to post-mTSST (mTSST(post-pre) – control(post-pre)) in sputum IL-1R1 mRNA (peak voxel: 26, 2, − 16, 123 mm^3; Fig. 3a). mTSST-evoked change in amygdala glucose metabolism was unrelated to mTSST-induced changes in sputum cell IL-23A or IL-17A mRNA expression. A positive relationship was observed between amygdala glucose metabolism (mTSST-control) and baseline FeNO (average of stress and control; peak voxel: 30, − 2, − 26; 59 mm^3; Fig. 3b), but not with the relative increase in FeNO 4 h post-mTSST. The mTSST-induced increase in salivary stress hormones, cortisol and alpha amylase AUC, relative to control showed a positive relationship with the increase in amygdala activation that did not survive correction for multiple comparisons.

3.2. Peripheral physiological measures

The results of mixed models testing the effects of challenge condition on cortisol release showed a significant main effect of challenge (B = 10.01, t(441) = 11.72, p < .001) and a significant challenge × quadratic trend in time interaction (B = 0.005, t(439) = − 5.49, p < .001), such that the quadratic trend over time was larger in response to the mTSST than the control condition and overall, cortisol levels were increased in response to the mTSST relative to the control condition (Fig. 4a). A similar effect was observed for the effects of challenge condition on release of AA, with main effects of challenge condition (B = 31.96, t(449) = 5.13, p < .001) and time (B = − 3.22, t(448) = − 12.02, p < .001), indicating that AA release was greater in response to the mTSST compared to the control condition, but in both conditions, AA levels increased over time of measurement (Fig. 4b). In addition, a significant cubic trend over time was present for AA (B = 0.002, t(448) = 9.19, p < .001).

In analyses addressing airway inflammation, the results of mixed

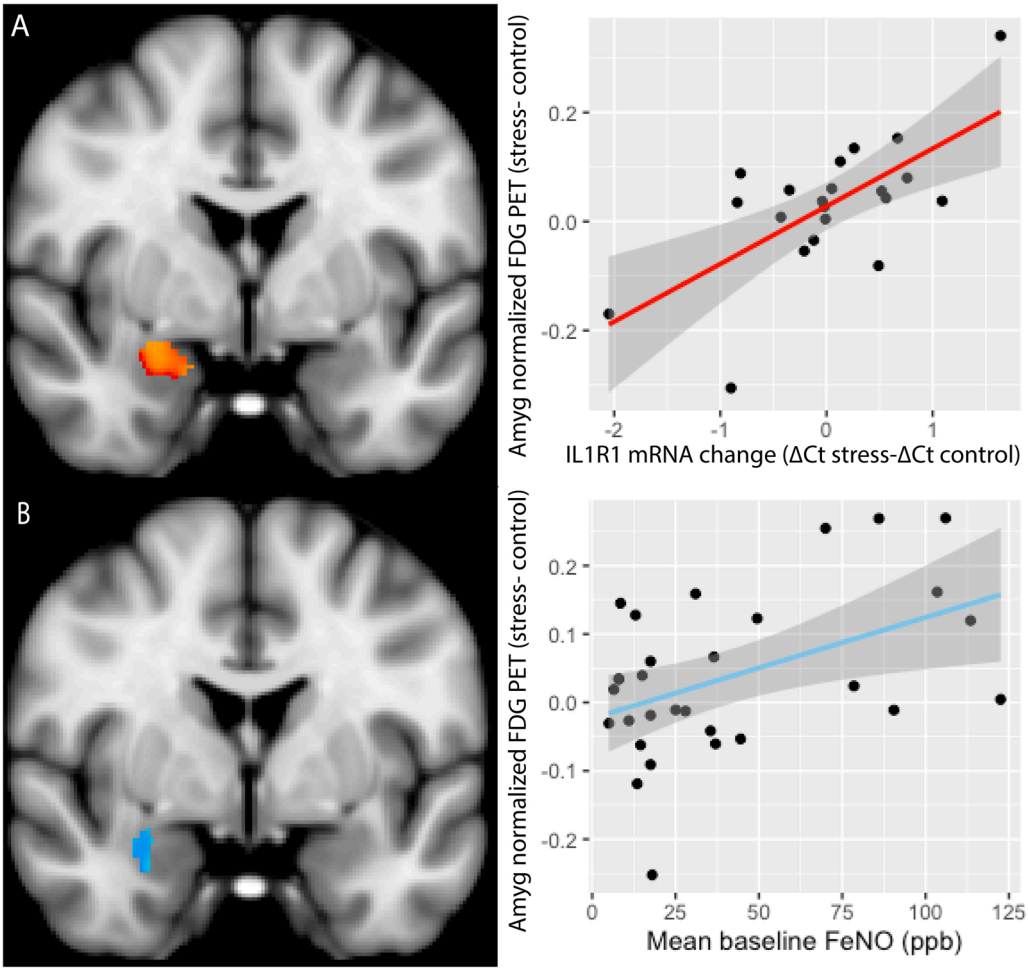

Fig. 3. Relationship between stress-induced amygdala metabolism and airway inflammation. Increase in glucose metabolism in the amygdala during stress relative to the control condition is significantly associated with (A) increase in sputum IL-1R1 mRNA expression level (average -ΔCt using both GUSB and S26 as housekeeping genes) and (B) mean (across challenge conditions) baseline exhaled nitric oxide (FeNO). Images thresholded at p < .05, corrected. Scatter plots are circular and provided for illustrative purposes only.

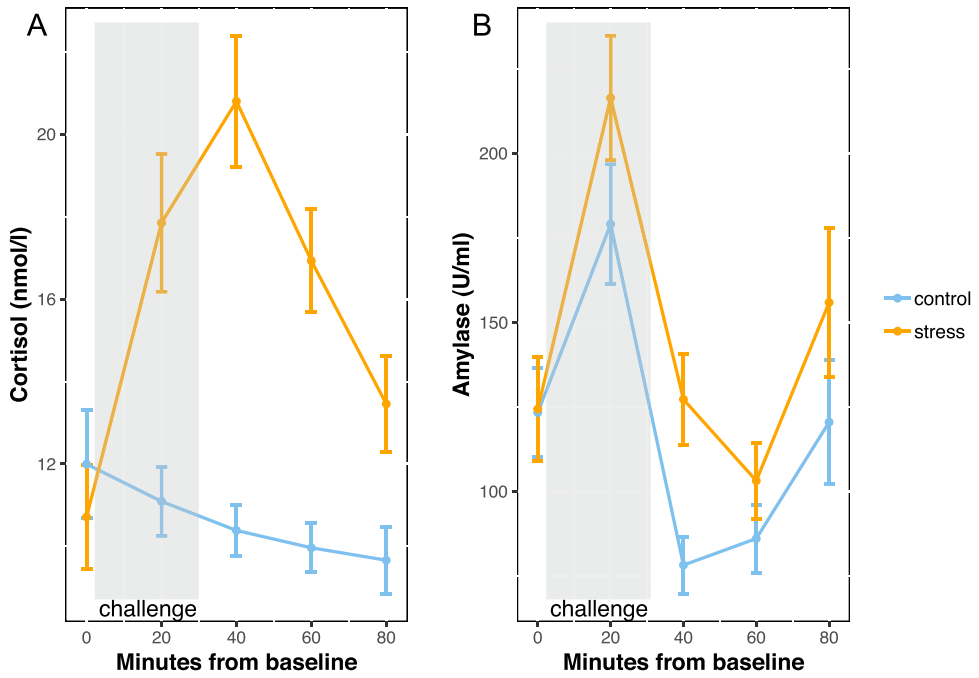

Fig. 4. Stress hormone responses to stress and control laboratory challenges. Means displayed by challenge for (A) salivary cortisol and (B) salivary alpha amylase. Error bars represent standard error of the mean.

model analyses showed a significant linear effect of time (B = 0.02, t (198) = 3.14, p < .01), such that FeNO levels increased across the 4 post-challenge measurements (See Table 1). However, this increase in FeNO did not differ significantly between stress and control conditions. Results of paired *t*-tests revealed significantly greater IL-17A mRNA expression in sputum cells in response to control compared to the stress challenge (t(19) = 2.10, p < .05). IL-1R1 and IL-23A mRNA expression did not differ in response to stress vs. control conditions.

Finally, in analyses examining the relationship between change in stress hormones and inflammatory biomarkers, results showed a significant relationship between stress-induced increase in alpha amylase AUC, relative to the control challenge, and increase in sputum IL-1R1 mRNA expression ($r = 0.54$, $p = .012$, n = 20; Fig. 5a). The analogous relationship with the relative increase in cortisol AUC was marginal ($r = 0.43$, $p = .061$, n = 19). Associations between relative increases in stress hormones and increases in IL-17A and IL-23 mRNA were not significant (all *ps* > 0.1). As a post hoc analysis, we examined whether the relative increase in alpha amylase AUC mediated the relationship between the increase in amygdala glucose metabolism and increase in sputum IL-1R1 mRNA expression using the method described by Baron and Kenny (1986). This method requires a significant correlation between each pairwise comparison. Thus, we extracted the mean glucose metabolic rate for the cluster in the amygdala that showed a significant relationship with increase in IL-1R1 mRNA (shown in Fig. 3a) and computed the Pearson correlation between mean glucose metabolic rate in this cluster and the relative increase in alpha amylase AUC, the result of which was significant ($r = 0.45$, $p = .040$, n = 20; Fig. 5b). In order to test for causal mediation, we used the mediate function implemented in R software (mediation package in R; Imai, Keele, Tingley, & Yamamoto, 2010). Results showed that, while the average direct effect (B = 3.39, $p = .020$) of differential amygdala glucose metabolism on change in IL-1R1 mRNA expression, and the total effect (B = 4.22, $p = .010$) of both differential amygdala glucose metabolism and increase in alpha amylase AUC on change in IL-1R1 mRNA expression were significant, the indirect effect (i.e. the average causal mediation effect) of the increase in alpha amylase on change in IL-1R1 mRNA expression was not significant (B = 0.84, $p = .220$).

Table 1
Participant characteristics and peripheral physiological measures. Mean and standard deviation of participant characteristics and physiological measures by challenge condition and time point, where appropriate.

Time	Condition	Baseline	1 h	2 h	3 h	4 h
Age (years)		26.23 (6.04)				
ACQ		.78 (1.09)				
Cortisol (nmol/L)	Stress	10.71 (7.03)				
	Control	11.84 (8.02)				
Alpha Amylase (U/mL)	Stress	124.34 (85.91)				
	Control	115.35 (76.18)				
FEV1 (% predicted)	Stress	88.00 (12.48)	92.42 (12.66)	92.23 (13.52)	91.48 (12.85)	90.60 (12.57)
	Control	87.73 (12.70)	92.83 (12.69)	92.67 (12.39)	92.33 (12.37)	91.20 (12.16)
FeNO (ppb)	Stress	42.03 (37.19)	40.65 (40.06)	42.58 (39.97)	44.57 (39.51)	45.1 (38.14)
	Control	39.86 (35.87)	37.52 (33.73)	35.79 (31.92)	37.81 (33.38)	39.86 (31.96)

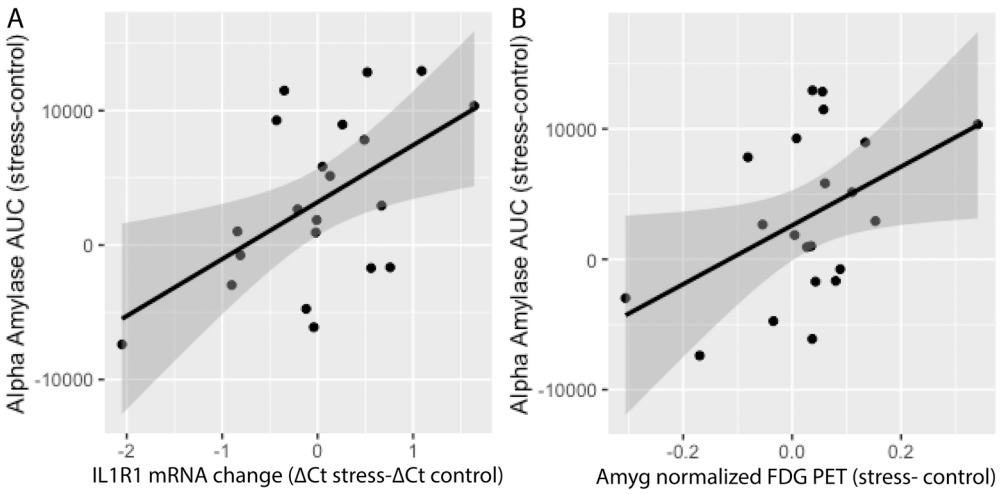

Fig. 5. Relationships among changes in stress hormones, airway inflammatory biomarkers, and amygdala glucose metabolism. (A) A greater increase in sputum IL-1R1 mRNA expression during the stress relative to control condition is associated with a greater increase in salivary alpha amylase. (B) Amygdala voxels where glucose metabolic rate during stress, relative to control, was significantly associated with a larger increase in IL-1R1 mRNA (Fig. 2a), also showed a significant positive correlation with the stress (relative to control) induced increase in alpha amylase.

4. Discussion

This study showed that glucose metabolic rate in the amygdala measured by FDG PET is increased during an acute laboratory stressor in patients with asthma; and the magnitude of this increase is associated with an increase in IL-1R1 gene expression in airway cells. Moreover, the stress-related increase in amygdala glucose metabolism was potentiated in those with increased airway inflammation at baseline, suggesting a possible priming of the CNS stress response and a potential mechanism through which dysfunction is perpetuated in these reciprocal brain-immune pathways. These results corroborate and extend our prior analyses (Rosenkranz et al., 2018) implicating other salience network components, the insula and anterior cingulate cortex, in the bi-directional brain-immune response to psychological stress. As nodes in the salience work, the insula, anterior cingulate cortex, and amygdala are connected both functionally (Seeley et al., 2007) and structurally (Mufson, Mesulam, & Pandya, 1981; Vogt, 2016). The addition of the amygdala to this circuit contributes a critical piece of the puzzle, linking activities of the salience network to descending peripheral sympathetic and immune regulation.

IL-1R1 is a receptor that triggers intracellular signals following binding with IL-1α and IL-1β. Though IL-1 signaling is not part of the classical type-2 immune response implicated in allergic inflammation, recognition of its importance in asthma pathophysiology and our understanding of its synergy with more canonical allergic inflammatory pathways has grown in recent years. IL-1β is associated with asthma symptoms and nocturnal asthma (Baines, Simpson, Wood, Scott, & Gibson, 2011; Borish et al., 1992; Jarjour & Busse, 1995), and both IL-1α and IL-1β proteins are increased in bronchoalveolar lavage (BAL) fluid following segmental bronchoprovocation with an allergen, in asthma patients with a robust allergic response (Bernau et al., 2021). We recently reported that sputum expression of both type-2 and type-17 immune response markers correlate with IL-1R1 in asthma participants, although IL-1/IL-17 molecular markers most strongly correlated with loss of lung function and neutrophilia, a phenotype that is resistant to corticosteroids (Evans et al., 2018). These observations are consistent with a reported increase in IL-1β production in a group of asthma patients with high sputum neutrophilia (Hastie et al., 2010). In addition to airway inflammation, the expression of the IL-1R1 on fibroblasts and epithelial and airway smooth muscle cells (Bellehumeur, Blanchet, Fontaine, Bourcier, & Akoum, 2009; Suwara et al., 2014; Whelan et al., 2004) suggests that IL-1 may play a crucial role in lung tissue remodeling and thus loss of pulmonary function in asthma (Al-Muhsen, Johnson, & Hamid, 2011). Therefore, the IL-1 pathway plays a prominent role in asthma pathophysiology and, as such, its dysregulation is a potential therapeutic target (Lee et al., 2010).

In this study, we measured IL-1R1 rather than IL-1β directly. Unlike most cytokines, IL-1β requires activation of the inflammasome to transform the pro-IL-1β into the secreted, mature, biologically active form. Therefore, the level of IL-1β transcript measured by PCR may not reflect the amount of active IL-1β that is released from cells in sputum samples. IL-1R1 expression, on the other hand, reflects the strength of IL-1 signaling capacity, and it is the receptor on lymphocytes that drives them into a type-17 phenotype, producing IL-17 (Esnault et al., 2012). Nonetheless, IL-1R1 and mature IL-1β are concomitantly regulated (Wu et al., 2018) and IL-1β upregulates IL-1R1 (Bellehumeur et al., 2009). Furthermore, in a prior study, we observed a strong correlation between IL-1R1 expression level and NLRP3[2], an inflammasome marker, in sputum samples from individuals participating in the Severe Asthma Research Program (SARP), supporting the association of IL-1R1 expression with the maturation of the IL-1β bioactive protein. Thus, our observation of upregulation of IL-1 signaling capacity, in association with greater amygdala activation and in the absence of allergen exposure, suggests that an amplified airway inflammatory response would ensue in the event of allergen exposure. Importantly, since the airway response to stress in this study was pro-inflammatory (IL-1), rather than a Type-2 response, it may shed light on why stress on top of underlying inflammation (i.e. a two-hit scenario), is not responsive to usual anti-inflammatory treatment (Haczku & Panettieri, 2010) since a IL-1/type-17 response is not responsive to regulation by corticosteroids (Panettieri, 2018).

Though we cannot ascribe a causal role for the amygdala in increasing sputum levels of IL-1R1 mRNA, its potential descending regulatory impact on airway inflammation via the sympathetic nervous system (SNS) is a plausible and parsimonious possibility. During psychological stress, the amygdala responds by, among other things, stimulating release of epinephrine and norepinephrine (NE) from the adrenal medulla and peripheral sympathetic terminals via the paraventricular nucleus of the hypothalamus and brain stem nuclei (Rodrigues, LeDoux, & Sapolsky, 2009). These sympathetic nerves innervate tissues throughout the body, including bone marrow. In both stressed humans and animal models of stress, noradrenergic signaling in bone marrow upregulates myelopoiesis, with a bias toward production of immature, proinflammatory monocytes and granulocytes (Powell et al., 2013). These animal models revealed that these immature, proinflammatory cells are recruited to the lung in a primed state, and are accompanied by

[2] Measured using RT-PCR; Spearman, $r = 0.825$, $p < .0001$, $n = 41$; unpublished d ata from the investigation described in Evans et al. (2018).

increased levels of IL-1β mRNA (Curry et al., 2010). Though evidence for formal mediation was lacking, our data do show limited support for amygdala influence of IL-1R1 mRNA expression through sympathetic signaling. The region of the amygdala where increased glucose metabolism during the mTSST was associated with increased expression of IL-1R1 mRNA was also positively associated with stress-induced increases in salivary alpha amylase, a marker of sympathetic activation. In turn, those with a larger salivary alpha amylase response had a larger increase in sputum IL-1R1 mRNA. Thus, it is possible that in our study, the stress-induced elevations in IL-1 signaling capacity arise from immature, proinflammatory cells recruited to the airway, rather than from resident cells.

The prominent role of the IL-1 signaling cascade in asthma may also be important in perpetuating the relationship between psychological stress, airway inflammation and psychopathology (Iwata et al., 2016). Increased IL-1 signaling is reported in individuals with depression (Ellul, Boyer, Groc, Leboyer, & Fond, 2016; Goldsmith, Rapaport, & Miller, 2016), and its peripheral administration evokes depressive- and anxiety-like behavior in animal models (Bluthé, Beaudu, Kelley, & Dantzer, 1995; Bluthé, Michaud, Kelley, & Dantzer, 1996). Moreover, elevated IL-1β is associated with increased glucocorticoid insensitivity and treatment resistance in depression (Maes, Song, & Yirmiya, 2012). On the other hand, knockdown of IL-1R1 to reduce receptor expression in animal models, or IL-1 antagonism decreases anxiety- and depressive-like behavior (Maes et al., 2012; Wohleb et al., 2014). In addition to the lung, bone marrow derived IL-1β-producing monocytes are recruited to the brain in response to stress, where they are essential in establishing stress-induced anxiety-like behavior; an effect that is blocked with propranolol (McKim et al., 2018; Wohleb et al., 2011; Wohleb, Powell, Godbout, & Sheridan, 2013). In our study, the temporal precedence of the amygdala activation, relative to the change in IL-1R1 mRNA measured in sputum suggests that we are tapping into the descending limb of this bi-directional pathway. However, it is also clear from the literature that this is a cycle that can be self-perpetuating, when the increases in IL-1 signaling prime the amygdala and impact other brain regions whose dysfunction contributes to stress sensitivity, depression, and anxiety (Maes et al., 2012).

Although our experimental design emphasizes the descending, brain to lung direction of communication, the brain-lung relationship is truly bidirectional. Here, FeNO level at baseline, averaged across stress and control conditions, was associated with greater glucose metabolism in the amygdala during the stress, relative to the control challenge, suggesting that airway inflammation primes amygdala responsivity to stress. FeNO is a biomarker of Type 2 inflammation and though it has not been associated with altered sensitivity of stress-related brain circuits, we have previously shown that allergen-induced provocation of airway inflammation in asthma does lead to heightened responsivity of the salience network (Rosenkranz et al., 2005; Rosenkranz, Busse, Sheridan, Crisafi, & Davidson, 2012), of which the amygdala is a constituent (Seeley et al., 2007). Greater amygdala reactivity has also been demonstrated in the context of other models of peripheral inflammation (Swartz, Prather, & Hariri, 2017), and has been associated with enhanced feelings of social disconnection (Inagaki et al., 2012) and perceived stress (Leschak et al., 2020). Moreover, higher levels of FeNO are associated with greater experience of negative affect and perceived stress (Kullowatz et al., 2008; Ritz, Trueba, Simon, & Auchus, 2014; Trueba, Smith, Auchus, & Ritz, 2013), which has been shown to involve amygdala responsivity in other contexts (Barrett, Bliss-Moreau, Duncan, Rauch, & Wright, 2007; Leschak et al., 2020; Silvers, Wager, Weber, & Ochsner, 2015). Thus, our data supports the concept that stress contributes to increased airway inflammation, and when chronic, dysregulated affect. Ongoing elevations in airway inflammation, indicated by FeNO, may prime the amygdala for an amplified response to stress, leading to increased sympathetic signaling and release of primed monocytes and granulocytes from bone marrow that are recruited to the lungs and brain, where they perpetuate asthma pathophysiology and mood and anxiety disorders. It is important to point out, nonetheless, that IL-1R1 mRNA was not increased overall in response to stress, but its greater expression during stress relative to the control challenge was associated with increased amygdala response to stress. Indeed, IL-17A mRNA expression was greater overall during the control challenge relative to stress. Further, this proposed model is based on animal studies, where experimental stress exposure is prolonged and more severe than the acute stressor applied in our study. It is unclear how much time is necessary, following sympathetic signaling, to observe an increase in release of primed monocytes and granulocytes from bone marrow. These animal studies have not yet been directly translated to human studies, but supporting evidence has been reported in individuals with chronic stress (e.g. low socioeconomic status; Powell et al., 2013). Future research should test this model directly in individuals with asthma, compared to a non-asthma control group, to further determine the specificity of these results to asthma.

There are important limitations to our study that warrant consideration. First, a healthy, non-asthma comparison group was not part of the experimental design, limiting the conclusions that we can draw about the specificity of these findings to asthma. Indeed, we would expect an increase in amygdala glucose metabolism during the mTSST, regardless of asthma status. Further, previous studies have reported increased systemic expression of inflammatory biomarkers, in response to the TSST, in normal healthy volunteers (Boyle, Stanton, Eisenberger, Seeman, & Bower, 2020). Nonetheless, what is unique about this study is that, due to asthma, participants had some degree of airway inflammation at baseline and baseline FeNO levels predicted the increase in the amygdala response to the mTSST, suggesting that relative to those without asthma or other source of ongoing inflammation, individuals with asthma would be expected to show greater amygdala reactivity. Although, this pattern has been observed in other inflammatory contexts (Inagaki et al., 2012; Tawakol et al., 2017), the results described here inform the importance and the specific mechanisms of the interrelationship between psychological stress and asthma.

Second, this study was limited to participants with allergic asthma and was designed to test the interrelationships between stress and airway inflammation. Inflammation, however, is not the only contributor to airway pathophysiology in asthma. Bronchoconstriction, for example, can be modulated by stress and emotion (Ritz, 2012) as well, though this response was not observed in our study using spirometry (Rosenkranz et al., 2016). Thus, the results reported here may not generalize to individuals with non-allergic forms of asthma (e.g., exercise-induced) and other brain circuits may underlie relationships between asthma and psychological factors in these individuals.

Finally, although salivary alpha amylase is considered a valid and reliable indicator of autonomic activity in stress research (Ali & Nater, 2020) and has been shown to reflect central noradrenergic signaling, it is not without its critics (Bosch, Veerman, de Geus, & Proctor, 2011). In particular, alpha amylase level measured in saliva is regulated by both sympathetic and parasympathetic activity and is impacted by collection method and salivary flow rate. Though we followed collection, storage, and analytic recommendations advanced by experts in the field (Rohleder & Nater, 2009), variance in the levels reported here is reflective of both SNS activity and these other factors.

In summary, we have demonstrated that the amygdala is a crucial nexus for bi-directional communication between the brain and lung and may be key for addressing both psychological comorbidities in asthma and preventing future loss of disease control. An implication of the data presented here is that reduction in amygdala reactivity directly, or improvement in amygdala regulation, may present a novel treatment target. Pharmacological interventions, such as antidepressant medications, have been shown to improve asthma control (Brown et al., 2018; Brown, Vornik, Khan, & Rush, 2007; Shoair, Cook, Shipman, & Dunn, 2020), but the neural mechanisms that underlie this improvement are unknown. Similarly, our findings imply that achievement of asthma control pharmacologically may improve psychological function through

pathways that have yet to be delineated (Sastre et al., 2018). The data presented here may begin to elucidate these pathways. This question could be addressed with behavioral interventions, such as mindfulness training, which has been shown to strengthen the connectivity of brain networks that regulate the amygdala (Kral et al., 2018) and reduce amygdala reactivity (Goldin & Gross, 2010), as well as to buffer the effects of stress on inflammation (Rosenkranz et al., 2013). Few studies have empirically examined the utility of behavioral interventions directed at stress reduction in asthma, and among those that have, most have tested only participant-reported psychological outcomes (López-Lois, González-Barcala, & Facal, 2020; Paudyal, Jones, Grindey, Dawood, & Smith, 2017) such as quality of life or perceived stress, rather than physiological outcomes such as airway inflammation, or clinician-reported outcomes such as disease control. Further investigation of the model proposed here, including its modifiability with pharmacological and behavioral interventions, should be the focus of future research).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2021.108226.

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