Brain, Behavior, and Immunity 115 (2024) 480–493

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Resting state functional connectivity changes following mindfulness-based stress reduction predict improvements in disease control for patients with asthma

Claire Laubacher [a], Tammi R.A. Kral [a,b], Ted Imhoff-Smith [e], Danika R. Klaus [b], Robin I. Goldman [a], Jane Sachs [a], Richard J. Davidson [a,b,d], William W. Busse [c], Melissa A. Rosenkranz [a,d,*]

[a] Center for Healthy Minds, University of Wisconsin-Madison, 625 W. Washington Ave, Madison, WI 53703, USA
[b] Healthy Minds Innovations, University of Wisconsin-Madison, 625 W. Washington Ave, Madison, WI 53703, USA
[c] Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, 600 Highland Ave, Madison, WI 53792, USA
[d] Department of Psychiatry, University of Wisconsin-Madison, 6001 Research Park Blvd, Madison, WI 53719, USA
[e] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, 600 Highland Ave, Madison, WI 53792, USA

A B S T R A C T

Background: The staggering morbidity associated with chronic inflammatory diseases can be reduced by psychological interventions, including Mindfulness-Based Stress Reduction (MBSR). Proposed mechanisms for MBSR's beneficial effects include changes in salience network function. Salience network perturbations are also associated with chronic inflammation, including airway inflammation in asthma, a chronic inflammatory disease affecting approximately 10% of the population. However, no studies have examined whether MBSR-related improvements in disease control are related to changes in salience network function.

Methods: Adults with asthma were randomized to 8 weeks of MBSR or a waitlist control group. Resting state functional connectivity was measured using fMRI before randomization, immediately post-intervention, and 4 months post-intervention. Using key salience network regions as seeds, we calculated group differences in change in functional connectivity over time and examined whether functional connectivity changes were associated with increased mindfulness, improved asthma control, and decreased inflammatory biomarkers.

Results: The MBSR group showed greater increases in functional connectivity between salience network regions relative to the waitlist group. Improvements in asthma control correlated with increased functional connectivity between the salience network and regions important for attention control and emotion regulation. Improvements in inflammatory biomarkers were related to decreased functional connectivity between the salience network and other networks.

Conclusions: Increased resting salience network coherence and connectivity with networks that subserve attention and emotion regulation may contribute to the benefits of MBSR for patients with asthma. Understanding the neural underpinnings of MBSR-related benefits in patients is a critical step towards optimizing brain-targeted interventions for chronic inflammatory disease management.

1. Introduction

Ninety percent of the $4.1 trillion in annual U.S. healthcare spending is used to care for people with chronic health conditions (Health and Economic Costs of Chronic Diseases | CDC, 2022). Chronic inflammation is an important component of the pathophysiology in the ten most prevalent of these chronic health conditions (Furman et al., 2019; Slavich, 2015). Unfortunately, chronic inflammation often remains poorly controlled despite access and adherence to existing treatments. Further, disease management is often complicated by comorbid psychiatric disorders and stress-related exacerbations. This is particularly apparent in asthma, a highly prevalent chronic inflammatory disease of the airways (Most Recent National Asthma Data | CDC, 2021). Patients with asthma are twice as likely as other individuals to suffer from anxiety and depressive disorders (Jiang et al., 2014; Lu et al., 2012; Lu et al., 2018). Patients with asthma and comorbid psychopathology or high levels of psychosocial stress are more likely to experience poor disease control and to endure more frequent, more severe asthma exacerbations (Chen & Miller, 2007; Zhang et al., 2016). Unfortunately, when asthma symptoms are exacerbated by stress, they are also less responsive to common treatments (Brehm et al., 2015; Ippoliti et al., 2006). Over the next 20 years, suboptimal asthma control is projected to cost American adolescents and adults 15 million quality adjusted life years and $963.5 billion (Yaghoubi et al., 2019). Thus, additional management strategies

* Corresponding author at: Center for Healthy Minds, University of Wisconsin-Madison, 625 W. Washington Ave, Madison, WI 53703, USA.
E-mail address: marosenk@wisc.edu (M.A. Rosenkranz).

https://doi.org/10.1016/j.bbi.2023.10.026
Received 30 March 2023; Received in revised form 23 October 2023; Accepted 28 October 2023
Available online 2 November 2023

are urgently needed to target and address deleterious mind–body relationships in asthma (Marshall, 2019).

Meditation-based interventions that reduce stress and promote overall wellbeing are well-suited to address this gap (Ainsworth et al., 2022; Paudyal et al., 2018). Specifically, mindfulness training, which cultivates non-judgmental awareness of sensations and thoughts in the present moment (Kabat-Zinn, 1990), can alter multiple biopsychosocial processes that contribute to asthma (Dantzer, 2018; Rosenkranz & Davidson, 2009). For instance, mindfulness programs can reduce distress (Galante et al., 2021), depressive and anxiety symptoms (Wielgosz et al., 2019), and peripheral markers of chronic stress (Pascoe et al., 2017) and inflammation (Black & Slavich, 2016). Recently, our group demonstrated, in a randomized control trial, that patients with asthma who received 8 weeks of Mindfulness Based Stress Reduction (MBSR; (Kabat-Zinn, 1990) training had improved disease control, reduced distress, and reduced markers of airway inflammation up to 4 months after completing the intervention (Higgins et al., 2022). The current study builds on these findings by examining the neural changes associated with the benefits of MBSR for patients with asthma, an important next step towards a biological, mechanistic understanding that can guide intervention optimization and appropriate integration of mindfulness training into clinical asthma management protocols.

Multiple lines of evidence suggest that changes in the function of a group of brain regions known as the "salience network" (SN) may be integral to the improvements in asthma brought about by MBSR. These regions, including the anterior cingulate cortex (ACC), the anterior insula, and the amygdalae, modulate cognitive, affective, and autonomic functions to shift attention towards important information in the body or in the environment (Menon & D'Esposito, 2022; Seeley, 2019). In individuals with asthma, acute increases in SN activity in response to social stress and unpleasant emotional stimuli have been associated with greater increases in airway inflammation (Ritz et al., 2019; Rosenkranz et al., 2005, 2018, 2022). After mindfulness training in healthy individuals, the insula and the ACC show greater activation during meditation states and while attending to both positive and negative emotions (Fox et al., 2016; Gotink et al., 2016; Kral et al., 2018; Young et al., 2018).

The apparent contradiction that emerges from these observations, that SN activity is aberrantly increased in asthma and that beneficial interventions like mindfulness increase SN activation, highlights the complexity of SN function. Regions that comprise the SN participate both in the afferent sensory and affective appraisal of peripheral inflammation and emotion, as well as descending regulatory responses to those stimuli. Therefore, studies measuring SN activation from different populations and under different task demands may recruit these afferent and efferent functions to different degrees. One way around this complexity is to use a neuroimaging modality that probes trait-like organization of brain architecture under no task-specific demands, such as resting state functional connectivity (Kieliba et al., 2019; Pezzulo et al., 2021). Unlike activation in response to a task, resting state functional connectivity (rsFC) does not inform under what circumstances SN regions will be recruited. Instead, it relates to the synchrony between regions, reflecting how efficiently they communicate and how well they function together as a unit. High within-network rsFC indicates a group of regions that will more strongly activate (or deactivate) together when recruited but not under which circumstances they will be recruited. Although there is more limited work focused on within-SN rsFC in patients with asthma and in longitudinal studies of MBSR (Kilpatrick et al., 2011; Su et al., 2016; Yang et al., 2016) the direction of findings in these two bodies of literature converge. Within-SN rsFC is disrupted in the context of acute and chronic inflammation (Aruldass et al., 2021; Labrenz et al., 2019), is decreased in anxiety and depressive disorders (Kolesar et al., 2019; Xu et al., 2019; Young et al., 2023), and increased within-SN rsFC has been associated with increased trait mindfulness (Bilevicius et al., 2018; Parkinson et al., 2019; Sezer et al., 2022).

Taken together, these findings led to the hypothesis that meditation training will increase within-SN rsFC in patients with asthma. To test this, we examined changes in rsFC in participants with asthma randomized to 8 weeks of MBSR training or a waitlist control (WLC) group. We hypothesized that rsFC among key SN nodes (ACC, insula, amygdalae) would increase from baseline to post-intervention to a greater extent after MBSR than in WLC. We also hypothesized that increases in within-SN rsFC would correlate with the asthma-specific benefits associated with MBSR training, including improved asthma control and decreased inflammatory biomarkers. Further, we tested whether more general benefits of mindfulness, such as increased self-reported mindfulness and decreased distress, were also related to increased within-SN rsFC in people with asthma.

2. Methods

2.1. Participants

Seventy-three meditation-naïve adults with asthma participated between 2014 and 2018 as part of a larger Randomized Controlled Trial (ClinicalTrials.gov NCT02157766). During screening, previous training and current practice of meditation and other mind–body techniques was assessed. Participants were excluded if they previously completed an MBSR course, had a history of attending meditation retreats, had a meditation practice within the past year, or had a regular practice of mind–body techniques such as yoga or Tai Chi. Participants were between 18 and 65 years old, had at least a 6 month history of physician-diagnosed asthma, and displayed at least one indicator of elevated Type 2 airway inflammation: fraction of exhaled nitric oxide (FeNO) $\geq$ 30 ppb, blood eosinophil count $\geq$ 150 cells/μL, or percent sputum eosinophils $\geq$ 2 % of total leukocytes (Dweik et al., 2011; Global Strategy for Asthma Management and Prevention, 2019). Individuals were excluded if they had a current or past diagnosis of a neurological disorder, traumatic brain injury, bipolar disorder, schizophrenia, or schizoaffective disorder; if they had severe airway obstruction (pre-albuterol FEV1 $<$ 60 % while holding all medication); if they were currently using high-dose inhaled corticosteroid therapy (>1000 mcg daily Fluticasone or the equivalent), oral corticosteroids, or monoclonal antibodies targeting eosinophils; if they were a current smoker or had a smoking history exceeding 5 pack-years within the last 10 years; if they were pregnant; or if they were otherwise unable to safely complete a magnetic resonance imaging (MRI) scan.

The study protocol was approved by the Health Sciences Institutional Review Board at the University of Wisconsin–Madison. Written informed consent was obtained from all participants according to the Declaration of Helsinki (World Medical Association, 2013). Participants were given monetary compensation for their participation.

2.2. Study design

After completing a baseline assessment (T1), participants were randomized to 8-weeks of MBSR or a WLC group. Experimenters were blind to group assignment. MBSR included a standard course of eight weekly 2.5-hour sessions and one 6-hour intensive retreat led by two experienced, certified MBSR instructors. Both the MBSR and WLC groups were assessed after completing the intervention (T2, 8 weeks post-baseline) and four months after intervention completion (T3). Assessments were rescheduled if participants had a viral or respiratory infection in the previous 2 weeks. Participants were asked to hold medications before the assessments, including Zyrtec (5 days), Allegra/Claritin (4 days), antihistamines (2 days), leukotriene inhibitors (2 days), nasal steroids (24 h), inhaled corticosteroids (12 h), and albuterol (6 h). The current study examines data from the subset of participants with useable rsFC data (N = 52; MBSR = 26, WLC = 26; see Statistical Analyses; Fig. 1).

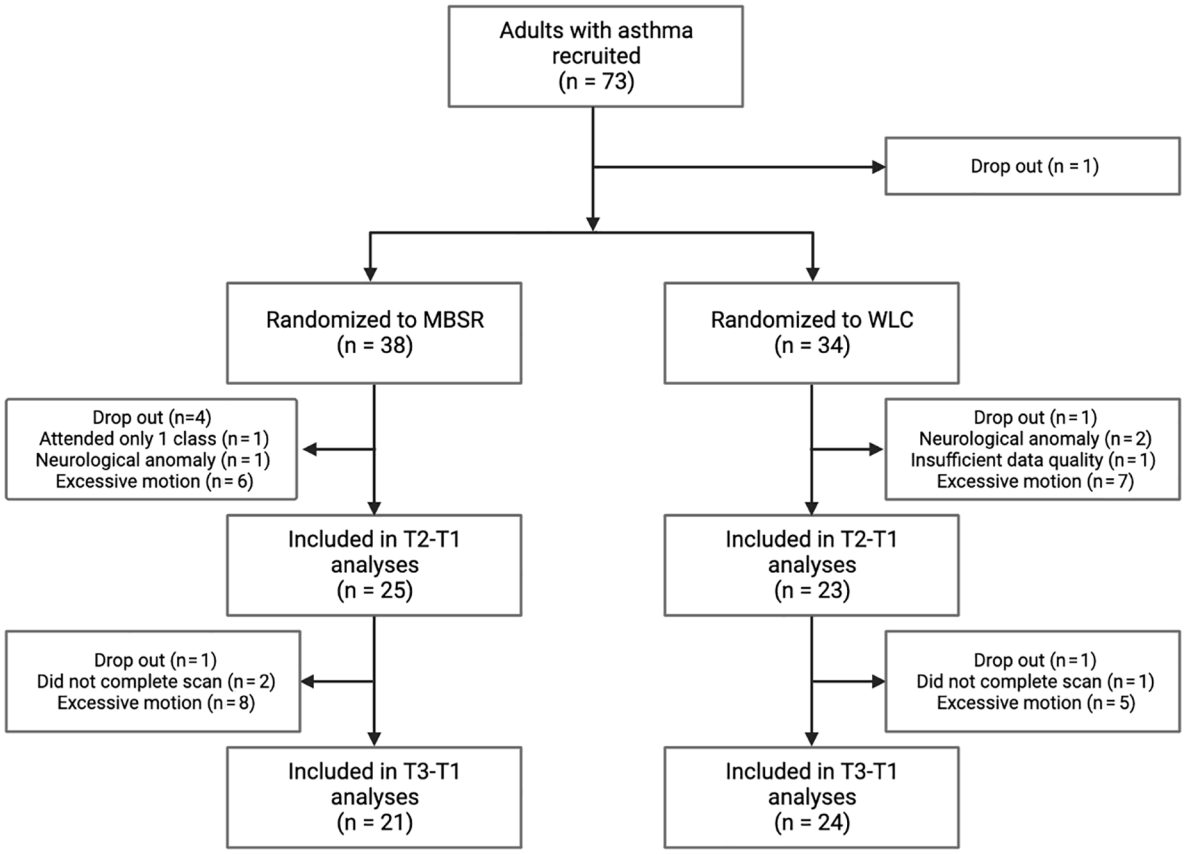

Fig. 1. Adults with asthma in a randomized trial of MBSR that were included in resting state functional connectivity analyses; Of the 73 adults with asthma recruited for the study, 72 were randomized at T1 (38 MBSR, 34 WLC), 67 completed T2 assessments (34 MBSR, 33 WLC), and 48 were included in the T2-T1 analyses (25 MBSR, 23 WLC). Two were excluded for failure to attend more than 1 MBSR class, 3 were excluded for neurological abnormalities (1 MBSR, 2 WLC), 1 did not pass resting state data quality control (1 WLC), and 13 had > 50 % of resting state data censored for excessive motion (6 MBSR, 7 WLC). Forty-five participants were included in the T3-T1 analyses (21 MBSR, 24 WLC). Two additional participants dropped out of the study between T2 and T3 (1 MBSR, 1 WLC), 3 did not complete the resting state scan (2 MBSR, 1 WLC), and 13 had > 50 % of resting state data censored for excessive motion (8 MBSR, 5 WLC). MBSR = Mindfulness Based Stress Reduction, WLC = waitlist control.

2.3. Self-report measures

Participants completed self-report measures of mindfulness, asthma symptom burden, and psychological symptoms. Mindfulness was evaluated with the Five Facet Mindfulness Questionnaire (FFMQ). Participants rated how often each of 39 statements generally applies to them [1 = never or rarely true, 5 = very often or always true]. Total score reflects the sum of 5 subscales: Observing (α = 0.79, 0.84, 0.82), Describing (α = 0.93, 0.94, 0.93), Acting with Awareness (α = 0.82, 0.87, 0.87), Non-judging of Inner Experience (α = 0.88, 0.94, 0.94), and Non-reactivity to Inner Experience (α = 0.86, 0.90, 0.90) (Baer et al., 2006). Four subscale scores range from 8 to 40 and Non-reactivity to Inner Experience ranges from 7 to 35. The FFMQ has satisfactory test–retest reliability over 6-months (ICCs ≥ 0.74 for all facets; Jensen et al., 2016) and is sensitive to intervention-related change (Baer et al., 2019). For the FFMQ total score, Cronbach's alpha was excellent at all three time points (0.93, 0.96, 0.95). However, it is important to note that this measure of trait mindfulness was developed using healthy volunteers and has not been validated in patients with asthma.

The degree of clinical impairment caused by asthma symptoms was assessed with the Asthma Control Questionnaire. The ACQ-6 evaluates symptom burden during the previous week, including night awakenings, symptom frequency and severity, and disease-related activity limitations for a total score between 0 (no impairment) and 6 (maximum impairment). The measure has good test–retest reliability (ICC 0.82) and is sensitive to intervention-related change (Juniper et al., 1999, 2005). Cronbach's alpha was acceptable (0.76, 0.82, 0.79) across all 3 time points.

Psychological distress was evaluated with the Symptom Checklist-90 Revised (SCL-90-R; Derogatis & Cleary, 1977). Participants rated the degree to which they were bothered by 90 symptoms in the past week [0 = Not at all, 4 = Extremely]. These ratings generate a Global Severity Index (GSI; mean of all items), which quantifies overall psychological distress, and a Positive Symptom Distress Index (PSDI; mean of items with non-zero responses), which quantifies the intensity of distress. The SCL-90-R is a well validated measure of general psychological distress with high internal consistency and test–retest reliability in both clinical and nonclinical populations (Hildenbrand et al., 2015). Cronbach's alpha was excellent at all three time points (0.96, 0.95, 0.96). Levels of depression and anxiety symptoms were measured with the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI; Beck et al., 1961, 1988). Cronbach's alpha was acceptable at all three time points for both measures (BDI 0.86, 0.90, 0.90; BAI 0.80, 0.81, 0.79). In both measures, participants chose which statement on a 4-point scale best described their symptoms over the past two weeks. Scores range from 0 to 63 with higher scores indicating more severe symptoms.

Participants randomized to the MBSR group also reported the number of minutes they practiced mindfulness meditation over the course of the study, which was summarized as total minutes of practice during the 8 weeks of training (T1 to T2) and minutes practiced from the beginning of training until the 4 month post-intervention follow-up (T1 to T3).

2.4. Inflammatory biomarkers

In the predominant asthma endotype (Fahy, 2015), activation of Type 2 inflammatory pathways leads to asthma symptoms through production of nitric oxide, recruitment of eosinophils into the airway, and bronchoconstriction (Busse et al., 2021). Type 2 inflammation was assessed both in the airway (percentage of eosinophils in sputum and fraction of exhaled nitric oxide (FeNO)) and systemically (percentage of eosinophils in circulation). Sputum and venous blood were collected and processed as described previously to determine cell distributions and leukocyte differentials; See supplemental methods). FeNO in exhaled breath was measured according to American Thoracic Society guidelines (NIOX System; Aerocrine, Solna, Sweden; Silkoff et al., 2004).

2.5. Image acquisition and processing

Images were acquired using a GE MR750 3.0 Tesla MRI scanner and a 32-channel head coil. High-resolution T1-weighted anatomical images were acquired with an inversion recovery fast gradient echo sequence (450 ms inversion time; 256 × 256 in-plane resolution; 256 mm field of view (FOV); 192 × 1.0 mm axial slices). Functional resting state scans were acquired with a 12-minute gradient echo-planar imaging (EPI) sequence (360 volumes; repetition time (TR)/echo time (TE)/Flip, 2000/20 ms/75∘; 224 mm FOV; 96 × 64 matrix; 2.33 × 3.5 mm in-plane resolution; 44 interleaved sagittal slices; 3 mm slice thickness with 0.5 mm gap).

Resting state functional images were processed using a combination of AFNI (versions 17.3) and FMRI Expert Analysis Tool Version 6.00, part of FMRIB's Software Library (FSL), including the following steps: removal of the first four volumes, motion correction with MCFLIRT (Jenkinson et al., 2002), BET (Smith, 2002) brain extraction and boundary-based registration of the participant's functional data with their anatomical image (Greve & Fischl, 2009), and registration of each participant's functional data to Montreal Neurological Institute (MNI) space using a 12-degrees of freedom affine transformation (FLIRT), followed by a nonlinear transformation (FNIRT). White matter and cerebrospinal fluid nuisance regressors (average time series from FAST image segmentation eroded with a 3 × 3 × 3 voxel kernel), their derivatives, and the six motion regressors from MCFLIRT were added to AFNI's 3dDeconvolve, where high motion time points were censored (>0.2 mm framewise displacement; Power et al., 2014). Participants were excluded if ≥ 50 % of data points were censored for excessive motion, leaving less than 6 min of quality resting state data. Images were subsequently smoothed with a 5-mm full-width half-maximum Gaussian kernel.

2.6. Statistical analyses

Behavioral data: Data from fifty-two participants (MBSR = 26, WLC = 26) were used in analyses, as detailed in Fig. 1. Baseline group differences in demographics and the outcome variables of interest were calculated using the lm and chisq.test packages in R (version 4.0.3; R Core Team, 2020). To determine whether the sample with available rsFC data showed intervention effects consistent with those observed in the full sample (N = 72; Higgins et al., 2022), linear mixed modeling was performed using the "lmer" function (Bates et al., 2015) from the lme4 and lmerTest packages in R (R Core Team, 2020) with further details in Supplemental Methods.

Resting State Functional Connectivity Analysis: To investigate rsFC changes among core SN nodes, five seeds were selected from the bilateral anterior insula, dorsal anterior cingulate cortex (dACC), and bilateral amygdalae. Anterior insula and ACC seeds were generated by drawing 5-mm spheres around the peak MNI152 coordinates identified by applying FSL's cluster command to the results of a Neurosynth automated *meta*-analysis (Yarkoni et al., 2011) of the term "salience network" (dACC 10, 26, 28; left insula −38, 14, −6; right insula 36, 14, 6). Right and left amygdala seeds were generated from the Harvard-Oxford Structural Atlas with a 50 % probability threshold (Craddock et al., 2011).

Because the current investigation focuses on within-SN rsFC changes, an a-priori specified mask of SN regions was generated to restrict the analytic search space. This mask included the previously described bilateral amygdalae seeds, bilateral anterior insulae defined by the functional resting state parcellation from Deen et al. (2011), and the dorsal anterior cingulate, defined by Shackman et al. (2011), with the anterior portion of the anterior cingulate defined with the Harvard-Oxford Structural atlas.

To compute rsFC within this mask, a Fisher-Z transformed correlation was calculated between the average time series of a seed region and each voxel in the mask excluding the seed. To examine rsFC changes over time, two difference score maps were generated by subtracting the T1 correlation map from the T2 correlation map or the T3 correlation map. An analogous procedure was performed for whole brain analyses.

Group differences in voxel-wise change score maps (T2-T1 and T3-T1) were estimated to identify intervention effects. Therefore, the group comparisons were [MBSR (T2 - T1)] > [WL (T2 - T1)] and [MBSR (T3 - T1)] > [WL (T3 - T1)]. To further interpret group differences, average voxel-wise change score maps from each group alone were examined. Threshold-free cluster enhancement (TFCE) with familywise error (FWE) correction was applied to control inflation of Type I error during statistical analysis with FSL's randomize (Winkler et al., 2014) and the resulting statistical maps were thresholded at $p < 0.05$. In all analyses, age and sex were included as covariates of no interest. Analyses were repeated controlling for anti-inflammatory medication use. Subjects were coded as using inhaled corticosteroids during the study (MBSR = 7, WLC = 11) or not using inhaled corticosteroids during the study (MBSR = 19, WLC = 15; Table S1).

To examine brain-behavior and brain-biomarker relationships, mean-centered self-report or mean-centered biomarker difference scores (T2-T1 or T3-T1) were regressed on rsFC change score maps within the *a priori* specified SN mask. These analyses were repeated for the whole brain. All analyses controlled for average group differences in rsFC change, age and sex. For FeNO analyses, BDI and BAI scores were included as additional covariates of no interest to control for the complex and opposing effects these symptoms can have on FeNO (Ritz & Trueba, 2014; Higgins et al., 2022). While we hypothesized that brain-behavior and brain-biomarker relationships would remain similar over time in both groups, we followed up regression analyses with models testing the interaction between group and self-report difference scores, as well as the interaction between group and biomarker difference scores to ensure that our interpretations were not confounded by intervention-related changes in brain-behavior or brain-biomarker relationships. Analyses with asthma indicators (ACQ-6, FeNO, eosinophils) were repeated controlling for inhaled corticosteroid use during the study (Table S2).

3. Results

3.1. Behavioral effects of the intervention

Briefly, group differences in change in self-report and inflammatory outcomes for the rsFC sample (N = 52) largely replicated effects observed in the full sample (N = 72; Higgins et al., 2022). The MBSR group showed greater increases in total self-reported mindfulness (FFMQ: $b = 1.21$, $F(1, 47.49) = 5.04$, $p = 0.029$), greater improvements in asthma control (ACQ-6: $b = -0.05$, $F(1, 267.71) = 5.93$, $p = 0.016$), marginally greater decreases in FeNO ($b = -1.83$, $F(1, 46.12) = 4.01$, $p = 0.051$), and marginally greater decreases in distress (PSDI; $b = -0.02$, $F(1, 47.73) = 3.93$, $p = 0.053$) relative to the WLC group. Descriptive statistics for each group at each time point are presented in Table 1 and additional behavioral analyses are detailed in the supplement. ACQ-6 and FeNO results were unchanged when controlling for inhaled

Table 1
Descriptive statistics. Mean and standard deviation for outcome measures from individuals with usable resting state functional connectivity data at each data collection time point: baseline (T1), post-intervention (T2), and 4-month post-intervention follow-up (T3). FMQ = Five Facet Mindfulness Questionnaire; SCL90-R = Symptom Checklist-90 Revised.

	MBSR			Wait-List Control		
Age at T1	39.98 ± 14.64			36.76 ± 11.96		
Sex (F, M)	12, 14			11, 15		
Duration of asthma (years)	19.61 ± 13.60			19.19 ± 11.74		
	T1 (N = 26)	T2 (N = 25)	T3 (N = 21)	Time 1 (N = 26)	Time 2 (N = 23)	Time 3 (N = 24)
FEV1 % predicted	91.88 ± 9.80%	93.32 ± 10.47%	91.47 ± 10.70%	93.61 ± 11.50%	93.17 ± 12.30%	91.75 ± 11.23%
> 80 %	N = 21	N = 23	N = 18	N = 21	N = 18	N= 19
65%-80%	N = 5	N = 2	N = 3	N = 5	N = 5	N = 5
Asthma Control Questionnaire-6	0.80 ± 0.54	0.59 ± 0.46	0.56 ± 0.51	0.63 ± 0.55	0.74 ± 0.64	0.70 ± 0.61
FFMQ Total Score	132.27 ± 22.18	134.97 ± 23.97	136.29 ± 27.41	130.12 ± 20.03[a]	123.59 ± 24.64[a]	129.56 ± 24.83[a]
FFMQ Observe Score	26.85 ± 6.06	28.44 ± 5.04	28.05 ± 5.57	28.08 ± 4.96	27.36 ± 6.92[a]	28.17 ± 5.77[a]
FFMQ Describe Score	28.04 ± 7.65	28.44 ± 7.84	27.43 ± 8.06	27.08 ± 6.96	25.82 ± 7.48[a]	27.00 ± 7.52[a]
FFMQ Act with Awareness Score	25.54 ± 4.49	25.56 ± 5.03	26.29 ± 6.24	24.19 ± 5.14	23.55 ± 6.08[a]	24.48 ± 6.12[a]
FFMQ Nonjudgement of Inner Experience Score	29.15 ± 5.90	29.32 ± 7.55	30.76 ± 7.66	27.92 ± 7.02[a]	25.91 ± 7.35[a]	28.00 ± 8.12[a]
FFMQ Nonreactivity to Inner Experience Score	22.69 ± 5.56	23.04 ± 5.95	23.76 ± 6.05	22.04 ± 4.14[a]	20.95 ± 4.48[a]	21.91 ± 5.18[a]
SCL90-R Global Severity Index	0.45 ± 0.35	0.38 ± 0.29	0.39 ± 0.36	0.38 ± 0.29	0.39 ± 0.28	0.34 ± 0.28
SCL90-R Positive Symptom Distress Index	1.40 ± 0.37	1.29 ± 0.24	1.31 ± 0.35	1.22 ± 0.26	1.27 ± 0.23	1.27 ± 0.25[a]
Fraction of Exhaled Nitric Oxide (FeNO)	40.81 ± 26.13	36.68 ± 21.70	32.23 ± 17.23	33.15 ± 24.70	36.09 ± 35.32	35.67 ± 33.81
Sputum eosinophils	1.43 ± 2.39 %	1.10 ± 0.20 %[c]	1.81 ± 4.29 %[d]	1.23 ± 2.57 %[a]	3.10 ± 3.59[e]	2.05 ± 3.50 %
Blood eosinophils	3.35 ± 2.63 %	4.8 ± 3. 70 %	2.81 ± 1.87 %	3.48 ± 1.16 %[b]	3.59 ± 2.07 %[a]	3.36 ± 2.09 %

[a] One missing value
[b] Two missing values
[c] N = 22
[d] N = 18
[e] N = 18

corticosteroid use.

3.2. Intervention effects on resting state functional connectivity change

Between T1 and T2, there were significant group differences in change in rsFC between the left insula seed and the ACC in voxel-wise analyses within the pre-specified SN mask. Consistent with our hypothesis, rsFC between the left insula seed and the dACC increased more in the MBSR group than in the WLC group (Fig. 2, Figure S1). No other seeds tested showed group differences in change in rsFC within the SN mask between T1 and T2 (Table 2). In the whole-brain analysis, no additional group differences were detected in change in rsFC over time with the five seeds tested and no association between change in rsFC and practice time were observed.

Analyses of change in rsFC between T1 and T3 within the SN mask also showed greater increases between SN nodes in the MBSR relative to the WLC group. In the MBSR group, rsFC increased between the left amygdala seed and a region in dACC, and with a second region in the pregenual anterior cingulate, extending into ventromedial prefrontal cortex (vmPFC; Fig. 2, Table 2). No rsFC changes were detected in the WLC group. In whole-brain analyses, no significant group differences in change in rsFC over time were detected with the five seeds tested.

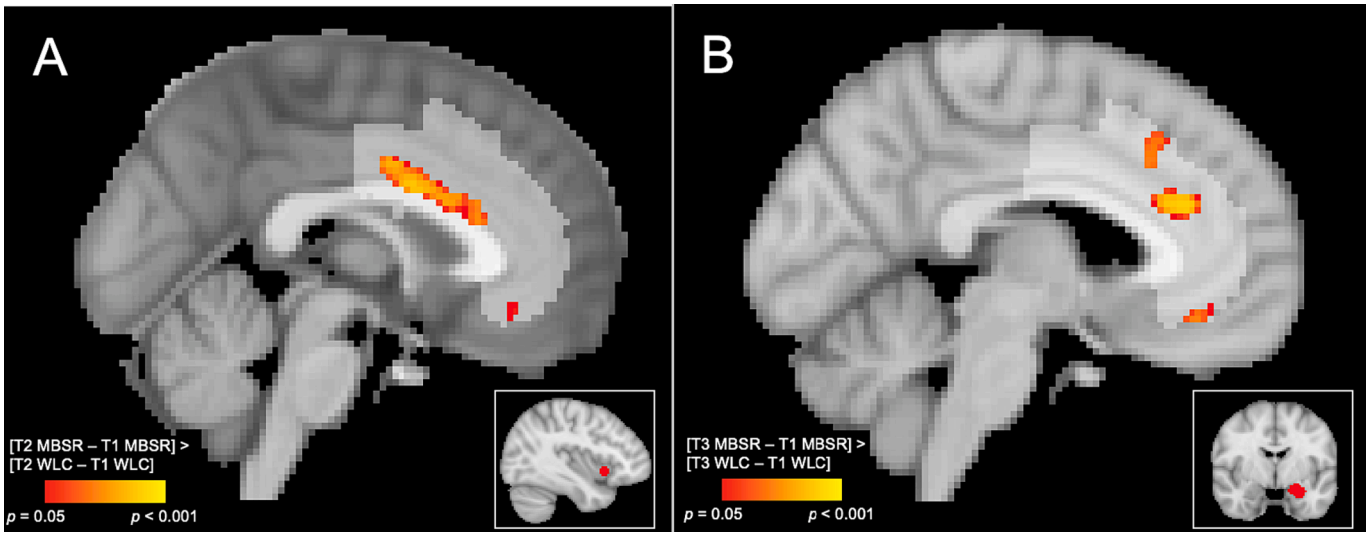

Fig. 2. The MBSR group had greater increases in within-salience network functional connectivity from before to after intervention. Resting state functional connectivity (rsFC) was calculated between salience network (SN) seeds and an *a priori* specified SN mask (highlighted in grey) at baseline (T1), post-intervention (T2), and 4 months post-intervention (T3). A. Voxels where the T2-T1 increase in rsFC with the anterior insula seed was greater in MBSR than the waitlist control group, displayed in standard MNI space at x = 0. Location of the insula seed (5 mm sphere around MNI −38, 14, −6) is displayed in the box in the lower right of the panel. B. Voxels where the T3-T1 increase in rsFC with left amygdala seed (lower right box; defined anatomically by the Harvard Oxford atlas) was greater in the MBSR than waitlist control group, displayed in MNI space at x = -4. Models controlled for age and sex and results were family-wise error corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$). See Figure S1 for a visualization of rsFC change for individual subjects.

Table 2
Intervention effects. Group difference in T2-T1 and T3-T1 changes in functional connectivity were calculated for 4 salience network (SN) seeds within an *a-priori* specified SN mask and whole brain. Changes over time were also examined within each intervention group. Results were FWE corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$). Clusters with fewer than 10 voxels were not reported. ACC = anterior cingulate cortex, mOFC = medial orbital frontal cortex, PCC = posterior cingulate cortex, PRG = precentral gyrus, POG = postcentral gyrus, SFG = superior frontal gyrus, sgACC = subgenual anterior cingulate cortex).

Masked analyses

Seed	Contrast	Size (voxels)	Peak voxel t-stat	Peak p-value	Peak coordinates MNI (x, y, z)	Location of cluster
T2 – T1 Left insula	MBSR > WLC	200	4.04	0.015	2, 4, 28	R ACC
		15	4.30	0.034	−2, 36, −12	L paracingulate gyrus
	MBSR > 0	221	4.80	0.007	6, 14, 26	R ACC
	WLC > 0	44	4.09	0.027	−10, 10, 46	L paracingulate gyrus
		33	4.92	0.008	12, 8, 34	R ACC
		15	4.57	0.021	4, −10, 46	R ACC
T3 – T1 Left amygdala	MBSR > WLC	229	4.82	0.006	−4, 34, 22	L ACC
		38	4.53	0.021	−8, 34, −14	L sgACC/mOFC
	MBSR > 0	217	4.48	0.010	−12, 34, 20	L ACC
T3 – T1 Right amygdala	MBSR > 0	18	4.40	0.030	6, 14, 46	R paracingulate gyrus
		17	4.97	0.020	−12, 20, 32	L ACC
		14	4.12	0.035	−10, 36, 20	L ACC

Whole brain analyses

Seed	Contrast	Size (voxels)	Peak voxel t-stat	Peak p-value	MNI (x, y, z)	Location of cluster
T2 – T1 Left insula	MBSR > 0	47	4.80	0.039	6, 14, 26	R ACC
	WLC > 0	1859	5.95	0.010	−16, −28, 42	L PRG, PCC, precuneus
		1814	5.97	0.006	−60, −22, 20	L POG, supramarginal gyrus, PRG, central/ parietal opercular cortex
		73	4.53	0.040	−20, −6, 70	L SFG
		67	4.83	0.036	16, −40, 50	R precuneus
		26	4.68	0.042	2, −4, 72	R premotor cortex
T3 – T1 Left amygdala	MBSR > 0	18	4.45	0.040	−16, −54, −8	L lingual gyrus
		14	4.54	0.042	−8, −54, 0	L lingual gyrus
T3 – T1 Right amygdala	Minutes of practice time in MBSR group	2569	6.25	0.012	–22, −78, 16	L occipital cortex
		535	4.8	0.035	34, −66, 24	R occipital cortex
		42	4.52	0.046	46, −40, −16	R inferior temporal gyrus
		39	5.74	0.037	26, −60, 66	R inferior temporal gyrus
		26	5.99	0.035	42, −42, −8	R temporo-occipital white matter

However, increased practice time was associated with decreased functional connectivity between the left amygdala seed and left occipital regions (Table 2). When controlling for corticosteroid use, the findings within the mask were unchanged (Table S1), although whole brain findings were diminished.

3.3. Whole-brain correlations

Correlations with change in mindfulness, asthma control, inflammatory biomarkers, and psychological distress were performed within the SN mask and whole brain. Results in the mask largely mirrored results from whole brain analyses and are reported in Supplemental Table 3.

3.3.1. Mindfulness

Across all participants, the only significant correlations between change in total mindfulness scores and changes in rsFC was an increase in rsFC between the right insula seed and cerebellum from T1 to T2. However, patterns of associations were found between rsFC changes and changes in specific mindfulness subscales (Table 3). In the T1 to T2 analyses, for the dACC and left insula seeds, increases in Acting with Awareness scores were associated with reduced rsFC with somatomotor regions, bilateral middle frontal gyrus, and additional regions listed in Table 3. In T1 to T3 analyses, increasing Nonreactivity to Inner Experience scores were correlated with increases in rsFC between bilateral amygdala seeds and other SN nodes, specifically, the dACC and the contralateral insula into adjacent opercular cortex (Fig. 3). For the left amygdala seed, this association extended beyond right opercular cortex into the inferior frontal gyrus and right putamen. Changes in other subscales were associated with connectivity changes between SN seeds and regions outside the SN. There were no significant group differences in the relationship between change in FFMQ subscales and change in rsFC other than a few relationships with T2-T1 right insula rsFC, which were primarily driven by changes in the control group, as detailed in Table 3.

3.3.2. Asthma control

Because improvements in asthma control in the MBSR group were most pronounced at T3, we were interested in the predictive value of rsFC changes immediately after the intervention (T2) for ACQ-6 improvement from T1 to T3. Increased rsFC from T1 to T2 between the dACC seed and left dorsal lateral prefrontal cortex (dlPFC), extending into the inferior frontal gyrus, predicted improvements in asthma control (decreases in ACQ-6 scores) from T1 to T3 across all participants (Fig. 4). This pattern was not found when comparing changes in asthma control to changes in rsFC when both measures spanned the same time interval (Table 4). There were no significant group differences in the relationship between change in asthma control and change in rsFC. Follow-up analyses show that this relationship was driven by the MBSR group, with no significant relationship observed between change in rsFC and change in ACQ in the WLC group. These patterns were unchanged when controlling for inhaled corticosteroid use (Table S2).

3.3.3. Inflammatory biomarkers

Expected relationships between increased rsFC among SN regions and decreased inflammatory biomarkers were not observed. Instead, decreases in rsFC between SN seeds and regions *outside* the SN — primarily occipital and cerebellar regions — were associated with decreases in inflammatory biomarkers between T1 and T2, including

Table 3
Correlations between changes in functional connectivity and changes in Five Facet Mindfulness Questionnaire Subscales. Positive (+) and negative (-) relationships between changes in FFMQ subscales and changes in whole-brain resting state functional connectivity were calculated from baseline to post-intervention (T2-T1) and baseline to 4-month post-intervention follow-up (T3-T1). Results controlled for age and sex and were FWE corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$). Clusters with fewer than 10 voxels were not reported. CO = central opercular cortex, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, mPFC = medial prefrontal crotex, MTG = middle temporal gyrus, PO = parietal opercular cortex, POG = postcentral gryus, PRG = precentral gyrus, SFG = superior frontal gyrus, SMA = supplementary motor area.

Whole brain analyses							
Seed	Correlation direction	Contrast	Cluster size (voxels)	Peak voxel t-stat	Peak p value	Peak coordinates MNI (x, y, z)	Location of cluster
T2-T1 Left amygdala	–	T2-T1 FFMQ Describe change	34	5.74	0.027	10, −78, −16	R lingual gyrus
T2-T1 dACC	–	T2-T1 FFMQ Act with Awareness change	790	4.69	0.027	−62, −38, 16	L planum temporale, Heschel's gyrus, angular gyrus
			281	4.47	0.029	−46, 26, −10	L IFG
			254	4.62	0.031	−52, 14, 42	L MFG
			188	4.64	0.035	54, 18, 42	R MFG
			188	4.43	0.037	12, 68, 18	R frontal pole
			155	4.61	0.039	62, −20, −18	R MTG
			97	4.39	0.038	64, −54, 0	R MTG
			60	4.53	0.040	52, 30, 28	R MFG
			45	3.86	0.045	−54, −20, −14	L MTG
			43	4.73	0.039	48, −48, 26	R angular gyrus
			40	5.43	0.032	60, −64, 18	L occipital cortex
			21	4.95	0.041	−28, 26, 50	L MFG
			18	4.65	0.045	−26, 56, 32	L frontal pole
			18	4.76	0.042	−54, −40, 54	R supramarginal gyrus
			15	4.36	0.045	−42, 48, 10	L frontal pole
T2-T1 Right insula	–	T2-T1 FFMQ total change	296	5.08	0.025	26, −84, −30	Cerebellum
			41	5.49	0.030	68, −26, −12	Cerebellum
			32	4.39	0.043	34, −70, −52	Cerebellum
			18	4.17	0.046	32, −68, −34	Cerebellum
			18	5.40	0.035	50, 44, −14	Cerebellum
			14	5.21	0.038	26, −56, −52	Cerebellum
		T2-T1 FFMQ total change WLC > MBSR	14	4.87	0.041	22, −58, −18	R cerebellum
			11	4.61	0.045	12, −68, −8	R lingual gyrus
		T2-T1 FFMQ total change WLC < 0	1431	4.85	0.021	30, −66, −52	R cerebellum, lingual gyrus, posterior temporal cortex
			85	5.96	0.022	−18, −38, −24	L cerebellum
			30	3.97	0.046	0, −26, −34	Brainstem
	–	T2-T1 FFMQ Act with Awareness change	1491	6.22	0.007	20, 54, −18	R frontal pole, mPFC
			1012	4.70	0.022	−44, 18, 44	L MFG, PRG
			672	5.05	0.021	54, 38, 20	R MFG
			180	4.64	0.026	12, 40, 44	R SFG
			112	4.20	0.038	38, 14, 46	R MFG
			83	5.29	0.026	−16, 60, 24	L frontal pole
			66	3.81	0.045	−10, 32, 52	L SFG
			43	3.52	0.046	20, 30, 58	R SFG
		T2-T1 FFMQ Observe change	351	5.56	0.021	8, 18, 64	R SFG, SMA
			249	5.09	0.027	58, 6, 32	R PRG
		WLC > MBSR	36	4.18	0.043	−24, −8, 72	L SFG
		T2-T1 FFMQ Observe change WLC > 0	73	4.52	0.037	−10, −86, 12	L cerebellum
T2-T1 Left Insula	–	T2-T1 FFMQ Act with Awareness change	129	5.11	0.029	40, −30, 12	R planum temporale, posterior insula
			13	5.14	0.040	58, −44, 6	R MTG
			11	4.61	0.042	4, −16, 74	R PRG
T2-T1 Right Insula		T3- T1 FFMQ Observe change	175	4.81	0.032	20, −70, −8	R lingual gyrus
			91	4.46	0.038	−14, −84, 14	L intracalcarine cortex
		MBSR > WLC	79	4.28	0.039	−16, −68, −8	L lingual gyrus
			79	5.09	0.030	–22, −72, 18	L cuneal cortex
			69	3.85	0.044	12, −66, 6	R intracalcarine cortex
		T3- T1 FFMQ Observe change MBSR > 0	5842	5.57	0.007	–23, −74, 20	Bilateral lingual gyrus, cuneal cortex, intracalcarine cortex, lateral occipital cortex, occipital pole
T3-T1 Left amygdala	+	T3-T1 FFMQ Non-React change	4583	6.26	0.001	54, −2, 6	R CO, insula, IFG, putamen, amygdala, temporal pole
			343	5.21	0.016	10, −10, 42	R ACC
			165	3.77	0.043	48, −4, 34	R PRG
			155	4.26	0.034	−58, 2, 12	L PRG, COp
			74	4.05	0.042	2, 2, 68	R SMA
			48	4.27	0.040	18, −28, 58	R PRG
			16	4.04	0.047	−56, −8, 24	L POG
T3-T1 Right amygdala	+	T3-T1 FFMQ Non-React change	27	6.14	0.028	−40, 2, 10	L dorsal anterior insula/opercular cortex
			17	4.64	0.040	−4, 6, 42	L ACC

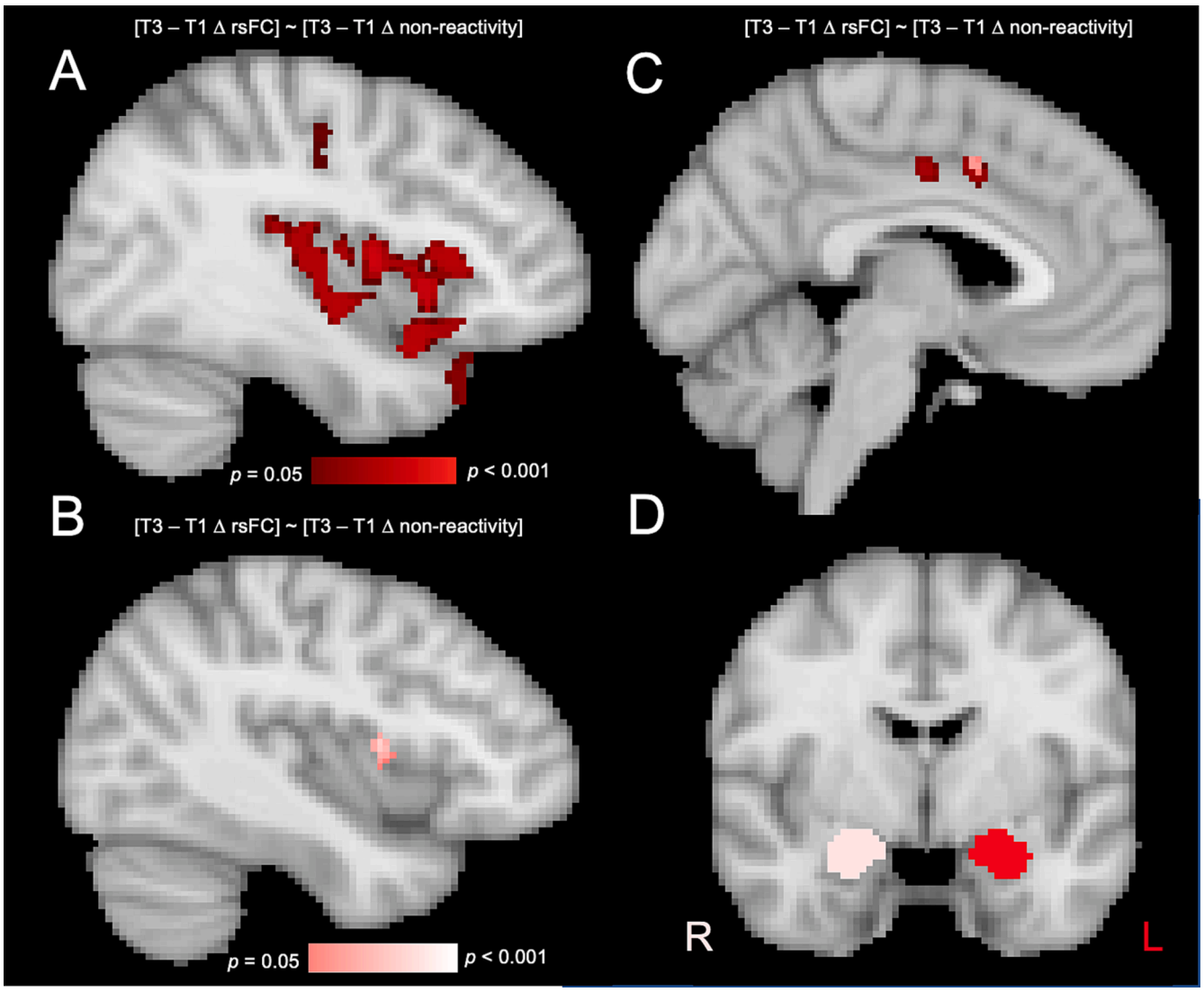

Fig. 3. Increase in mindful non-reactivity was associated with increased functional connectivity between key nodes of the salience network (SN) from baseline to 4-month post-intervention follow-up (T1 to T3). For each node of the SN, change in FFMQ Non-Reactivity to Inner Experience scores (T3-T1) was regressed on whole-brain voxel-wise change in functional connectivity (T3-T1), controlling for age and sex. Increased rsFC between bilateral amygdale seeds (Left = red, Right = pink) and key nodes of the SN (bilateral insula and dACC) was associated with increased Non-Reactivity to Inner Experience scores from T1 to T3. Specifically, increased Non-Reactivity to Inner Experience was positively correlated with: A. Increased rsFC between the left amygdala seed and a large cluster including the right central opercular cortex, right insula, right inferior frontal gyrus, and right amygdala, displayed at MNI x = 40, B. Increased rsFC between the right amygdala seed and left operculum (adjacent to insula), displayed at MNI x = -40, C. Increased rsFC between the bilateral amygdala seeds and dACC, displayed at MNI x = -4.. All results were corrected for family-wise error (TFCE; $p < 0.05$). D. Amygdala seeds were generated using a > 50 % probability from the Harvard-Oxford anatomical atlas displayed at MNI y = -2. FFMQ = Five Facet Mindfulness Questionnaire.

decreased percentage of blood eosinophils (left amygdala seed), decreased FeNO (dACC seed), and decreased percentage of sputum eosinophils (dACC seed; Table 4). In this third finding, the area where decreased T1 to T2 sputum eosinophils was related to decreased dACC rsFC extended from occipital and cerebellar regions further into adjacent temporo-parietal regions. Notably, the biomarker with the greatest intervention-related effect, decreased FeNO between T1 and T3, was associated with decreased rsFC between the dACC seed and multiple regions that included somatomotor areas, as well as decreased rsFC between the right amygdala and a small region of the left putamen. This effect did not differ between groups. In the MBSR group alone, decreased FeNO from T1 to T3 was associated with reduced rsFC among the bilateral amygdalae and somatomotor and striatal regions (Figure S4). Results were comparable when controlling for inhaled corticosteroid use (Table S2).

3.3.4. *Psychological distress*

No correlations between change in Positive Symptom Distress Index or Global Severity Index and change in rsFC were observed for any of the five seeds tested between T1 and T2 or between T1 and T3. One interaction was detected between T2-T1 GSI change and rsFC change from the right insula seed, but the relationship between change in rsFC and change in GSI was not significant in either group (Table 4).

4. Discussion

This study is the first to examine functional brain changes related to improvements in asthma outcomes following a mindfulness-based intervention. As reported previously (Higgins et al., 2022), participants randomized to MBSR training had greater improvements in asthma control and greater increases in self-reported mindfulness compared to the WLC group. While not significantly different from WLC

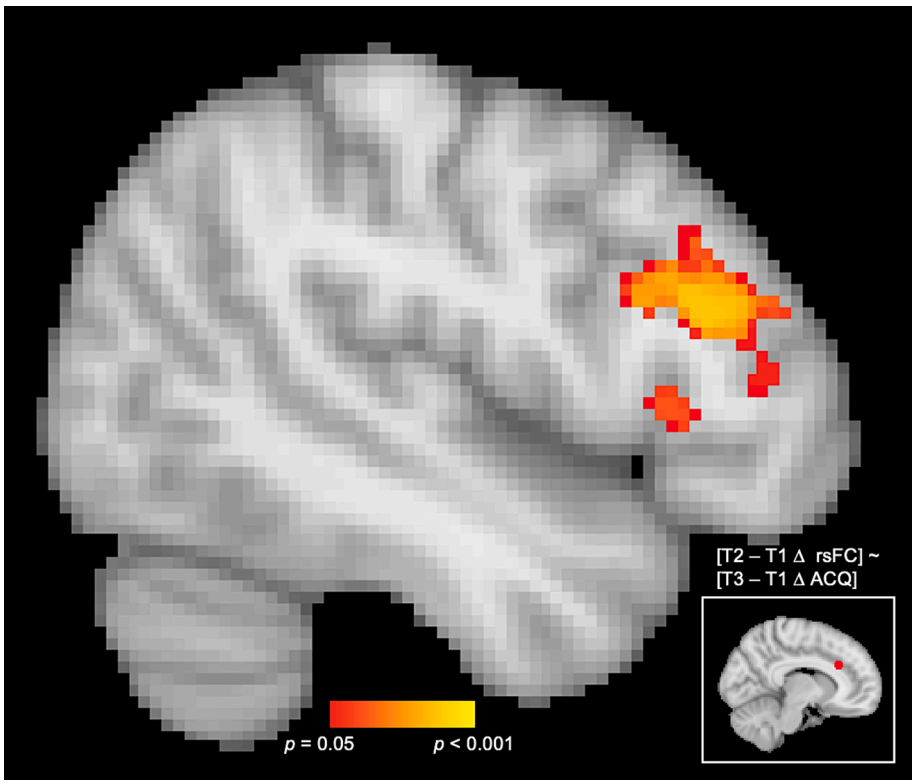

Fig. 4. Increased functional connectivity between dACC and left dorsal lateral prefrontal cortex over the intervention period (T2-T1) was associated with improved asthma control (ACQ; T3-T1). To determine whether changes in rsFC temporally precede changes in asthma control (ACQ), for each node of the salience network (SN), change in ACQ from baseline to the four months post-intervention (T3-T1) was regressed on whole-brain voxel-wise change in rsFC from baseline to immediately post-intervention (T2-T1), controlling for age and sex. Across groups (N = 46), increased rsFC between the dACC seed (5 mm sphere centered at MNI: 10, 26, 28) and the left dorsal lateral prefrontal cortex, extending into inferior frontal gyrus, from baseline to post-intervention (T1 to T2), was associated with improved asthma control, quantified with the Asthma Control Questionnaire (ACQ-6), from baseline to four months post-intervention (T1 to T3). Results were FWE corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$) and displayed in MNI space at x = -46. See Figure S3 for visualization of rsFC change for individual subjects.

in this smaller sample, reductions in a biomarker of airway inflammation, FeNO, mirrored significant effects observed in the full sample (Higgins et al., 2022). Overall, our fMRI results support our hypothesis that meditation training is associated with increased within-SN rsFC in patients with asthma. In addition, our findings suggest that the interactions between SN and other brain networks are predictive of improvements in asthma-related outcomes.

Consistent with our hypothesis, we found that rsFC increased more between the left anterior insula and the dACC and between the left amygdala and dACC for individuals in the MBSR group than those in the WLC group. Further, increasing rsFC among several SN nodes was associated with increasing Non-reactivity to Inner Experience scores from baseline to 4 months post-intervention. Increasing non-reactivity requires maintaining awareness of thoughts and sensations while disengaging from automatic appraisals of those thoughts and sensations (Wielgosz et al., 2019). This is related to two important SN functions: sustained attention (Menon & D'Esposito, 2022) and assigning affective meaning to interoceptive signals (Seeley, 2019). Perceived changes in these two functions have been described by patients with asthma as helpful components of mindfulness training in qualitative studies. Specifically, increased present-focused attention and greater differentiation between the sensory experience of breathing and the emotions associated with breathlessness were important facets of how mindfulness training led to less rumination and worry, fewer activity limitations, and a greater sense of symptom control (Malpass et al., 2015, 2018). This parallels the reductions in chronic pain-related disability associated with increased within-SN rsFC observed following mindfulness training (Su et al., 2016). Therefore, in our study, within-SN rsFC may correspond with a greater ability to modulate the subjective emotional intensity and attention capture associated with disease-related cues like breathlessness.

However, not all of the asthma-related benefits associated with mindfulness training were related to within-SN rsFC increases. Improvements in asthma control were related to changes in rsFC between SN nodes and attention control-related regions outside of SN. Increased rsFC between the ACC seed and the left dorsal lateral prefrontal cortex (dlPFC) immediately after the intervention (T2) predicted improved asthma control 4 months after the intervention was completed (T3). Due to the critical role of left dlPFC activity in the executive control of attention (Gbadeyan et al., 2016), neural models of mindfulness training posit that increased connectivity between the dlPFC and SN nodes is related to the increased moment-to-moment awareness needed to detect distraction and return mental focus to the intended target during meditation (Lutz et al., 2015). Increased coupling between dlPFC and ACC may link improved attention control to improvements in emotion regulation (Wielgosz et al., 2019). Specifically, the dlPFC coactivates with dACC when shifting attention is strategically used to alter emotional states through, for instance, distraction or cognitive reappraisal (Buhle et al., 2014; Lantrip et al., 2017). Increasing left dlPFC activity is thought to be a key mechanism by which cognitive therapies and neuromodulation techniques improve symptoms for psychiatric conditions characterized by emotion regulation difficulties (Lefaucheur et al., 2020; Marwood et al., 2018). There is preliminary evidence that neuromodulation targeting left dlPFC can increase rsFC both between dlPFC and dACC and between dACC and bilateral insula (Tik et al., 2017), mirroring the pattern of changes observed in the MBSR group.

Table 4
Correlations between changes in resting state functional connectivity and changes in asthma severity indicators and distress. Positive (+) and negative (-) relationships between changes in asthma severity indicators and changes in whole-brain resting state functional connectivity were calculated from baseline to post-intervention (T2-T1) and baseline to 4-month post-intervention follow-up (T3-T1). Asthma severity indicators included self-reported asthma control (ACQ-6), fraction exhaled nitric oxide (FENO), circulating (blood) eosinophils, and airway (sputum) eosinophils. Distress indicators included SCL-90 Global Symptom Distress Index (GSI) and Positive Symtpom Distres Index (PSDI). Results controlled for age and sex and were FWE corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$). Clusters with fewer than 10 voxels were not reported. IFG = inferior frontal gyrus, dlPFC = dorsal lateral prefrontal cortex, mPFC = medial prefrontal cortex, MFG = middle frontal gyrus, PCC = posterior cingulate cortex, SFG = superior frontal gyrus, SMA = supplementary motor area, ITG = inferior temporal gyrus.

Whole brain analyses							
Seed	Correlation direction	Contrast	Size (voxels)	Peak voxel t-stat	Peak p value	Peak coordinates MNI(x, y, z)	Location of cluster
T2-T1 dACC	–	T3-T1 ACQ-6 change[a]	669	5.09	0.016	−46, 28, 20	L IFG, dlPFC
	+	T2-T1 FeNO change[b]	15	5.32	0.043	12, −46, 12	R cerebellum
	+	T2-T1 sputum eosinophil change	19,983	5.81	0.004	−18, −74, 32	Extensive occipito-parietal span (local peaks in bilateral cuneal cortex, intracalcarine cortex, precuneus, lingual gyrus, lateral occipital cortex), which extend into cerebellum, temporal cortex (R hippocampus/amygdala), and midbrain (thalamus, putamen)
			138	6.31	0.016	38, 58, 8	R frontal pole
			29	3.01	0.048	−4, −22, 76	L PRG
			15	5.09	0.047	4, 52, 20	R mPFC
T2-T1 Right insula	+	T2-T1 sputum eosinophil change	317	5.18	0.025	−42, −30, 22	R central/parietal opercular cortex, R Heschls's gyrus
		T2- T1 GSI change MBSR < WLC	91	4.03	0.044	−2, −90, 8	Bilateral occipital pole
			55	4.69	0.041	14, −94, 30	R occipital pole
T2-T1 Left amygdala	+	T2-T1 blood eosinophil change	16	5.07	0.045	−68, −16, 17	L cerebellum
T2-T1 Right amygdala		WLC > MBSR	2445	5.06	0.010	−40, −80, −8	L inferior lateral occipital cortex
		T2-T1 blood eosinophil change	907	4.91	0.022	24, −52, −12	R temporal occipital fusiform cortex
			18	4.85	0.037	−12, −88, 42	L superior lateral occipital cortex
			13	5.95	0.034	8, −72, −44	R cerebellum
T3-T1 dACC	+	T3-T1 FeNO change[b]	584	5.15	0.024	−10, −8, 76	L SFG, PRG
			113	5.24	0.033	−22, −2, 52	L SFG, MFG
			66	4.33	0.039	14, −10, 76	R PRG, SMA
			40	4.24	0.042	6, −22, 50	R PRG, PCC
T3-T1 Right amygdala	–	T3-T1 blood eosinophil change	7024	5.49	0.007	−10, −90, 24	L occipital pole
	+	T3-T1 FeNO change[b]	8	5.54	0.044	−26, 8, 0	L putamen

[a] In Asthma Control Questionnaire, higher scores indicate more severe symptoms.
[b] FeNO change analyses controlled for changes in Beck Depression Inventory and Beck Anxiety Inventory scores.

Thus, improvements in asthma control and SN function in response to mindfulness training may depend on increasing connectivity between SN and executive areas like dlPFC, and observed increases in dlPFC-dACC rsFC may reflect improvements in attention control and emotion regulation.

The observed increase in dACC-dlPFC rsFC also highlights how the current study's focus on key SN nodes both complements and builds upon previous investigations of the effects of mindfulness training (Bilevicius et al., 2018; Parkinson et al., 2019; Sezer et al., 2022). A recent *meta*-analysis examining pre-to-post intervention rsFC changes illustrates that most studies to date have focused on a seed in the posterior cingulate cortex (PCC) as a node in the default mode network, a group of regions related to self-referential thinking. The key meta-analytic finding was that mindfulness training is associated with increased rsFC between the PCC and a dACC region that overlaps with the dACC seed used in the current investigation (Rahrig et al., 2022). There was insufficient evidence in this meta-analysis to conclude that mindfulness-training is associated with increases in connectivity between the PCC and dlPFC, despite several studies showing associations between increased connectivity between these regions and clinically relevant responses to training, including reductions in circulating IL-6 (Creswell et al., 2016), increases in attention (Kral et al., 2019), and reductions in PTSD symptoms (King et al., 2016). Our data support a model where mindfulness meditation increases both PCC-dACC rsFC and dACC-dlPFC rsFC, rather than or in addition to direct increases in PCC to dlPFC rsFC increases, although our findings may not generalize beyond populations with asthma or other chronic inflammatory diseases. Future work may benefit from integrating a triple-network framework, that explores how training in mindfulness impacts interactions among the default mode network, central executive network, and salience networks (Wielgosz et al., 2019).

Changes in inflammatory biomarkers were also not related to increases in within-SN rsFC. Instead, we observed that reductions in inflammation were consistently associated with reductions in rsFC between SN seeds and regions outside the SN. Interestingly, reduced FeNO over time was associated with reduced rsFC between the right amygdala and left putamen (a component of the dorsal striatum) and between the dACC and regions of the somatomotor network (Thomas Yeo et al., 2011), including the supplementary motor area (SMA). In the context of elevated peripheral inflammation, there are coordinated changes in circuits that support learning from behavioral outcomes (Gilbertson et al., 2021; Rolls, 2019; Zorrilla & Koob, 2013), including changes in SN activity related to increased sensitivity to negative outcomes, changes in dorsal striatal activity related to reduced sensitivity to reward (Harrison et al., 2016), and changes in dorsal striatal communication with SMA to induce psychomotor slowing (Felger, 2018). The reductions in rsFC

within these circuits that were related to the decreases in FeNO may reflect normalization of motivated behavior when inflammation is reduced. We also observed that decreases in rsFC between SN seeds and occipital and cerebellar regions was associated with reductions in eosinophils. It is possible that this pattern reflects decreased sensory-motor reactivity, but we are hesitant to speculate since there are limited data to engender confidence in specific interpretations. Because the SN tends to simultaneously couple with both primary somatosensory and visual areas (Snyder et al., 2021), the changing rsFC between SN nodes and somatosensory areas related to FeNO, and the changing rsFC between SN nodes and visual occipital areas related to eosinophils, may reflect an underlying shared process related to levels of peripheral Type 2 inflammatory markers. However, different neural correlates associated with changes in FeNO compared to eosinophilic biomarkers may also reflect that, although they are both involved in the Type 2 inflammatory response, their relationship with the clinical manifestations of asthma differs (Couillard et al., 2022). For instance, FeNO more closely indexes ongoing inflammation, while eosinophil counts are more indicative of exacerbation risk (Price et al., 2015). Importantly, the patterns of increased within-SN rsFC associated with MBSR training can occur alongside patterns associated with reduced inflammation - reductions in rsFC between SN nodes and somatomotor or primary sensory nodes.

This study has important limitations to consider. Because the study spanned multiple seasons, levels of environmental allergen burden varied considerably between assessments for each individual and between individuals. While this approach reflects a more ecologically valid evaluation of the intervention, it introduces substantial noise to intervention-related changes. Thus, it is likely that weaker intervention-related changes were present in our data that we lacked power to detect. Our relatively small sample size and focus on mild asthma also limits our power to detect small effects. Specifically, we did not have sufficient power to explore potential individual differences in clinical characteristics that may moderate the strength of the effect of MBSR on asthma control, such as asthma severity or medication usage. Further, comparing the effects of MBSR to a waitlist control group rather than an active control group limits our ability to determine if the intervention-related changes are specific to mindfulness or if other behavioral interventions with a similar structure would be associated with comparable changes. Now that we have established that measurable intervention-related changes are present, further study with more stringent controls (e.g., MacCoon et al., 2012) is warranted. Additionally, there are limitations inherent in our seed-based analytic approach. It assumes that each of our seeds is equally indexing the same resting network fluctuations, and that the location of SN hubs are uniform across participants. Our focus on within-SN rsFC may have missed MBSR-related changes in rsFC found exclusively between nodes of other networks (such as PCC-dlPFC). Similarly, we did not measure inflammatory signaling outside of the Type 2 pathway that can also influence asthma control (Allgire et al., 2021).

Overall, our findings point to important next steps for optimizing and integrating mindfulness training into clinical practice. There is a great need for additional treatment approaches for the 30 to 50 % of patients with moderate or severe asthma who experience poor disease control, despite using daily anti-inflammatory medications (Czira et al., 2022). While we hypothesized a simple, parsimonious model where increased within-SN rsFC explained the beneficial effects of MBSR on asthma control, our data suggest increased within-SN rsFC, increased dACC-dlPFC rsFC, and decreased SN-somatomotor rsFC are related to beneficial outcomes in patients with asthma. Our data implicate attentional and emotion regulation processes as factors that may modulate asthma control. Thus, emphasizing these skills in the context of MBSR training may be especially beneficial. Further, the patients who may benefit most from mindfulness interventions could be those who struggle with these skills, which can manifest as high psychological distress or comorbid psychiatric symptoms. Indeed, while we did not find any intervention-related within-SN rsFC alterations associated with changes in psychological distress in the current investigation, in the larger clinical trial, patients with asthma who had the highest depressive symptoms at baseline were also those who experienced the largest reduction in asthma symptom burden 4 months post-intervention (Higgins et al., 2022). We can speculate that variations in within-SN rsFC may correspond with changes in how, or whether, pro-inflammatory processes are upregulated in the context of emotional distress. However, future studies should investigate the intermediate physiological and psychological processes by which changes in SN function lead to improved asthma control given that improved emotion regulation is known to modulate multiple psychological, autonomic, and immune pathways proposed to underlie the relationship between negative emotion and worsening asthma symptoms (Dantzer, 2018; Rosenkranz & Davidson, 2009).

The autonomic nervous system is a particularly intriguing candidate for mediating brain-lung interactions given the role of SN in regulating the autonomic nervous system (Gianaros et al., 2014; Kimmerly, 2017). Indeed, changes in parasympathetic function, indexed by improvements in vagally-mediated heart rate variability (HRV), have been proposed as a candidate mechanism both for the benefits of mindfulness training and for other mind–body interventions for asthma. For instance, both HRV biofeedback and paced breathing, which increase HRV, have resulted in improved asthma symptoms, improved lung function, and reductions in asthma exacerbation frequency (Lehrer, 2022; Lehrer et al., 2018). However, it has also been argued that breath-focused interventions like biofeedback or paced breathing may unintentionally cultivate mindful awareness or acceptance of breathing sensations without explicit instructions (Bailey et al., 2016), and meta-analytic evidence shows that mindfulness training does not consistently result in improvements in HRV compared to control conditions (Brown et al., 2021). The ambiguity in the literature is further complicated by unresolved methodological difficulties, as any changes in resting heart rate or respiration resulting from breath-focused interventions will influence the calculation of HRV, making it difficult to isolate the hypothesized component of vagal tone from this proxy metric. Thus, the complex relationship between breath awareness, mindfulness, and asthma medications that target the autonomic nervous system will be important to consider in future studies focused on the role of parasympathetic function in mind–body interventions for patients with asthma. Further elucidating the dynamics of this complex system may also provide insight into how the brain can be leveraged in treatments for other chronic inflammatory diseases characterized by stress-related exacerbations, high rates of psychiatric comorbidity, and prevalent residual symptoms with standard of care treatment.

5. Conclusion

Given the contribution of stress and emotion to asthma symptom expression, the brain is an underexplored target for improving disease management. Our results suggest that changes in within-SN rsFC contribute to the benefits experienced by patients with asthma in response to MBSR; however, changes in rsFC between the SN and other regions, such as the left dorsal lateral prefrontal cortex, warrant further exploration for their role in the benefits of MBSR to those with asthma. Mindfulness and other contemplative-based mental exercises could be a powerful addition to treatment as usual for many patients with poorly controlled asthma, given its distinct mechanisms of action, targeting the brain and its relationship with the lung.

Funding Statement: This work was supported by the National Center for Complementary and Integrative Health [P01AT004952] and National Institutes of Health [Medical Scientist Training Program grant, T32 GM140935].

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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.

Data availability

Data will be made available on request.

Acknowledgements

The authors wish to gratefully acknowledge Lori Wollet, Julia Bach, Holly Eversol, Hailey Imhoff, Evelyn Falibene, Michele Wolff, Ashlee Lindsay, Ted Imhoff-Smith, Jeanne Harris, Elizabeth Nord, Kaley Ellis, Kara Chung, and Pema Lhamo for their indispensable work in participant recruitment, data collection, and data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.10.026.

References

Ainsworth, B., Stanescu, S., Stuart, B., Russell, D., Liddiard, M., Djukanovic, R., Thomas, M., 2022. A feasibility trial of a digital mindfulness-based intervention to improve asthma-related quality of life for primary care patients with asthma. J. Behav. Med. 45 (1), 133–147. https://doi.org/10.1007/s10865-021-00249-3.

Allgire, E., McAlees, J.W., Lewkowich, I.P., Sah, R., 2021. Asthma and posttraumatic stress disorder (PTSD): Emerging links, potential models and mechanisms. Brain Behav. Immun. 97, 275–285. https://doi.org/10.1016/j.bbi.2021.06.001.

Aruldass, A.R., Kitzbichler, M.G., Morgan, S.E., Lim, S., Lynall, M.-E., Turner, L., Vertes, P., Wellcome Trust Consortium for Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA), Cavanagh, J., Cowen, P., Pariante, C.M., Harrison, N. A., Bullmore, E.T., 2021. Dysconnectivity of a brain functional network was associated with blood inflammatory markers in depression. Brain Behav. Immun. 98, 299–309. https://doi.org/10.1016/j.bbi.2021.08.226.

Baer, R., Gu, J., Cavanagh, K., Strauss, C., 2019. Differential sensitivity of mindfulness questionnaires to change with treatment: A systematic review and meta-analysis. Psychol. Assess. 31 (10), 1247–1263. https://doi.org/10.1037/pas0000744.

Baer, R.A., Smith, G.T., Hopkins, J., Krietemeyer, J., Toney, L., 2006. Using self-report assessment methods to explore facets of mindfulness. Assessment 13 (1), 27–45. https://doi.org/10.1177/1073191105283504.

Bailey, N.W., Bridgman, T.K., Marx, W., Fitzgerald, P.B., 2016. Asthma and mindfulness: An increase in mindfulness as the mechanism of action behind breathing retraining techniques? Mindfulness 7 (6), 1249–1255. https://doi.org/10.1007/s12671-016-0551-7.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), Article 1. doi: 10.18637/jss.v067.i01.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: Psychometric properties. J. Consult. Clin. Psychol. 56 (6), 893–897. https://doi.org/10.1037/0022-006X.56.6.893.

Bilevicius, E., Smith, S.D., Kornelsen, J., 2018. Resting-State Network Functional Connectivity Patterns Associated with the Mindful Attention Awareness Scale. Brain Connect. 8 (1), 40–48. https://doi.org/10.1089/brain.2017.0520.

Black, D.S., Slavich, G.M., 2016. Mindfulness meditation and the immune system: A systematic review of randomized controlled trials. Ann. N. Y. Acad. Sci. 1373 (1), 13–24. https://doi.org/10.1111/nyas.12998.

Brehm, J.M., Ramratnam, S.K., Tse, S.M., Croteau-Chonka, D.C., Pino-Yanes, M., Rosas-Salazar, C., Litonjua, A.A., Raby, B.A., Boutaoui, N., Han, Y.-Y., Chen, W., Forno, E., Marsland, A.L., Nugent, N.R., Eng, C., Colón-Semidey, A., Alvarez, M., Acosta-Pérez, E., Spear, M.L., Celedón, J.C., 2015. Stress and Bronchodilator Response in Children with Asthma. American Journal of Respiratory and Critical Care Medicine 192 (1), 47–56. https://doi.org/10.1164/rccm.201501-0037OC.

Buhle, J.T., Silvers, J.A., Wager, T.D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., Ochsner, K.N., 2014. Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. Cereb. Cortex 24 (11), 2981–2990. https://doi.org/10.1093/cercor/bht154.

Busse, W.W., Kraft, M., Rabe, K.F., Deniz, Y., Rowe, P.J., Ruddy, M., Castro, M., 2021. Understanding the key issues in the treatment of uncontrolled persistent asthma with type 2 inflammation. Eur. Respir. J. 58 (2) https://doi.org/10.1183/13993003.03393-2020.

Most Recent National Asthma Data | CDC. (2021, April 7). https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm.

Chen, E., Miller, G.E., 2007. Stress and inflammation in exacerbations of asthma. Brain Behav. Immun. 21 (8), 993–999. https://doi.org/10.1016/j.bbi.2007.03.009.

Couillard, S., Pavord, I.D., Heaney, L.G., Petousi, N., Hinks, T.S.C., 2022. Sub-stratification of type-2 high airway disease for therapeutic decision-making: A "bomb" (blood eosinophils) meets "magnet" (FeNO) framework. Respirology (Carlton, Vic.) 27 (8), 573–577. https://doi.org/10.1111/resp.14294.

Craddock, R.C., James, G.A., Holtzheimer, P.E., Hu, X.P., Mayberg, H.S., 2011. A whole brain fMRI atlas generated via spatially constrained spectral clustering. Hum. Brain Mapp. 33 (8), 1914–1928. https://doi.org/10.1002/hbm.21333.

Creswell, J.D., Taren, A.A., Lindsay, E.K., Greco, C.M., Gianaros, P.J., Fairgrieve, A., Marsland, A.L., Brown, K.W., Way, B.M., Rosen, R.K., Ferris, J.L., 2016. Alterations in Resting-State Functional Connectivity Link Mindfulness Meditation With Reduced Interleukin-6: A Randomized Controlled Trial. Biol. Psychiatry 80 (1), 53–61. https://doi.org/10.1016/j.biopsych.2016.01.008.

Czira, A., Turner, M., Martin, A., Hinds, D., Birch, H., Gardiner, F., Zhang, S., 2022. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. Respir. Med. 191, 106670 https://doi.org/10.1016/j.rmed.2021.106670.

Dantzer, R., 2018. Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. Physiol. Rev. 98 (1), 477–504. https://doi.org/10.1152/physrev.00039.2016.

Deen, B., Pitskel, N. B., & Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. *Cerebral Cortex (New York, N.Y.: 1991)*, *21*(7), 1498–1506. doi: 10.1093/cercor/bhq186.

Derogatis, L.R., Cleary, P.A., 1977. Confirmation of the dimensional structure of the scl-90: A study in construct validation. J. Clin. Psychol. 33 (4), 981–989. https://doi.org/10.1002/1097-4679(197710)33:4<981::AID-JCLP2270330412>3.0.CO;2-0.

Dweik, R.A., Boggs, P.B., Erzurum, S.C., Irvin, C.G., Leigh, M.W., Lundberg, J.O., Olin, A.-C., Plummer, A.L., Taylor, D.R., American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications, 2011. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am. J. Respir. Crit. Care Med. 184 (5), 602–615. https://doi.org/10.1164/rccm.9120-11ST.

Fahy, J.V., 2015. Type 2 inflammation in asthma—Present in most, absent in many. Nat. Rev. Immunol. 15 (1), 57–65. https://doi.org/10.1038/nri3786.

Felger, J.C., 2018. Imaging the Role of Inflammation in Mood and Anxiety-related Disorders. Curr. Neuropharmacol. 16 (5), 533–558. https://doi.org/10.2174/1570159X15666171123201142.

Fox, K.C.R., Dixon, M.L., Nijeboer, S., Girn, M., Floman, J.L., Lifshitz, M., Ellamil, M., Sedlmeier, P., Christoff, K., 2016. Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. Neurosci. Biobehav. Rev. 65, 208–228. https://doi.org/10.1016/j.neubiorev.2016.03.021.

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D.W., Fasano, A., Miller, G.W., Miller, A.H., Mantovani, A., Weyand, C.M., Barzilai, N., Goronzy, J.J., Rando, T.A., Effros, R.B., Lucia, A., Kleinstreuer, N., Slavich, G.M., 2019. Chronic inflammation in the etiology of disease across the life span. Nat. Med. 25 (12), 1822–1832. https://doi.org/10.1038/s41591-019-0675-0.

Galante, J., Friedrich, C., Dawson, A.F., Modrego-Alarcón, M., Gebbing, P., Delgado-Suárez, I., Gupta, R., Dean, L., Dalgleish, T., White, I.R., Jones, P.B., 2021. Mindfulness-based programmes for mental health promotion in adults in nonclinical settings: A systematic review and meta-analysis of randomised controlled trials. PLoS Med. 18 (1), e1003481.

Gbadeyan, O., McMahon, K., Steinhauser, M., Meinzer, M., 2016. Stimulation of Dorsolateral Prefrontal Cortex Enhances Adaptive Cognitive Control: A High-Definition Transcranial Direct Current Stimulation Study. J. Neurosci. 36 (50), 12530–12536. https://doi.org/10.1523/JNEUROSCI.2450-16.2016.

Gianaros, P.J., Marsland, A.L., Kuan, D.-C.-H., Schirda, B.L., Jennings, J.R., Sheu, L.K., Hariri, A.R., Gross, J.J., Manuck, S.B., 2014. An inflammatory pathway links atherosclerotic cardiovascular disease risk to neural activity evoked by the cognitive regulation of emotion. Biol. Psychiatry 75 (9), 738–745. https://doi.org/10.1016/j.biopsych.2013.10.012.

Gilbertson, H., Fang, L., Andrzejewski, J.A., Carlson, J.M., 2021. Dorsal anterior cingulate cortex intrinsic functional connectivity linked to electrocortical measures of error monitoring. Psychophysiology 58 (5), e13794.

Gotink, R.A., Meijboom, R., Vernooij, M.W., Smits, M., Hunink, M.G.M., 2016. 8-week Mindfulness Based Stress Reduction induces brain changes similar to traditional long-term meditation practice—A systematic review. Brain Cogn. 108, 32–41. https://doi.org/10.1016/j.bandc.2016.07.001.

Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 48 (1), 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060.

Harrison, N.A., Voon, V., Cercignani, M., Cooper, E.A., Pessiglione, M., Critchley, H.D., 2016. A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. Biol. Psychiatry 80 (1), 73–81. https://doi.org/10.1016/j.biopsych.2015.07.018.

Health and Economic Costs of Chronic Diseases | CDC. (2022, October 14). https://www.cdc.gov/chronicdisease/about/costs/index.htm.

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

Hildenbrand, A.K., Nicholls, E.G., Aggarwal, R., Brody-Bizar, E., Daly, B.P., 2015. Symptom Checklist-90-Revised (SCL-90-R). In: The Encyclopedia of Clinical Psychology. John Wiley & Sons, Ltd., pp. 1–5. https://doi.org/10.1002/9781118625392.wbecp495

Ippoliti, F., Santis, W.D., Volterrani, A., Canitano, N., Frattolillo, D., Lucarelli, S., Frediani, S., Frediani, T., 2006. Psychological stress affects response to sublingual immunotherapy in asthmatic children allergic to house dust mite. Pediatr. Allergy Immunol. 17 (5), 337–345. https://doi.org/10.1111/j.1399-3038.2006.00417.x.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17 (2), 825–841. https://doi.org/10.1016/s1053-8119(02)91132-8.

Jensen, C.G., Niclasen, J., Vangkilde, S.A., Petersen, A., Hasselbalch, S.G., 2016. General inattentiveness is a long-term reliable trait independently predictive of psychological health: Danish validation studies of the Mindful Attention Awareness Scale. Psychol. Assess. 28, e70–e87. https://doi.org/10.1037/pas0000196.

Jiang, M., Qin, P., Yang, X., 2014. Comorbidity between depression and asthma via immune-inflammatory pathways: A meta-analysis. J. Affect. Disord. 166, 22–29. https://doi.org/10.1016/j.jad.2014.04.027.

Juniper, E.F., O'Byrne, P.M., Guyatt, G.H., Ferrie, P.J., King, D.R., 1999. Development and validation of a questionnaire to measure asthma control. Eur. Respir. J. 14 (4), 902–907. https://doi.org/10.1034/j.1399-3003.1999.14d29.x.

Juniper, E.F., Svensson, K., Mörk, A.-C., Ståhl, E., 2005. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir. Med. 99 (5), 553–558. https://doi.org/10.1016/j.rmed.2004.10.008.

Kabat-Zinn, J. (1990). *Full catastrophe living: Using the wisdom of your body and mind to face stress, pain and illness*.

Kieliba, P., Madugula, S., Filippini, N., Duff, E.P., Makin, T.R., 2019. Large-scale intrinsic connectivity is consistent across varying task demands. PLoS One 14 (4), e0213861.

Kilpatrick, L.A., Suyenobu, B.Y., Smith, S.R., Bueller, J.A., Goodman, T., Creswell, J.D., Tillisch, K., Mayer, E.A., Naliboff, B.D., 2011. Impact of Mindfulness-Based Stress Reduction training on intrinsic brain connectivity. Neuroimage 56 (1), 290–298. https://doi.org/10.1016/j.neuroimage.2011.02.034.

Kimmerly, D.S., 2017. A review of human neuroimaging investigations involved with central autonomic regulation of baroreflex-mediated cardiovascular control. Auton. Neurosci. 207, 10–21. https://doi.org/10.1016/j.autneu.2017.05.008.

King, A.P., Block, S.R., Sripada, R.K., Rauch, S., Giardino, N., Favorite, T., Angstadt, M., Kessler, D., Welsh, R., Liberzon, I., 2016. Altered Default Mode Network (dmn) Resting State Functional Connectivity Following a Mindfulness-Based Exposure Therapy for Posttraumatic Stress Disorder (ptsd) in Combat Veterans of Afghanistan and Iraq. Depress. Anxiety 33 (4), 289–299. https://doi.org/10.1002/da.22481.

Kolesar, T.A., Bilevicius, E., Wilson, A.D., Kornelsen, J., 2019. Systematic review and meta-analyses of neural structural and functional differences in generalized anxiety disorder and healthy controls using magnetic resonance imaging. NeuroImage: Clinical 24, 102016. https://doi.org/10.1016/j.nicl.2019.102016.

Kral, T.R.A., Schuyler, B.S., Mumford, J.A., Rosenkranz, M.A., Lutz, A., Davidson, R.J., 2018. Impact of short- and long-term mindfulness meditation training on amygdala reactivity to emotional stimuli. Neuroimage 181, 301–313. https://doi.org/10.1016/j.neuroimage.2018.07.013.

Kral, T.R.A., Imhoff-Smith, T., Dean, D.C., Grupe, D., Adluru, N., Patsenko, E., Mumford, J.A., Goldman, R., Rosenkranz, M.A., Davidson, R.J., 2019. Mindfulness-Based Stress Reduction-related changes in posterior cingulate resting brain connectivity. Soc. Cogn. Affect. Neurosci. 14 (7), 777–787. https://doi.org/10.1093/scan/nsz050.

Labrenz, F., Ferri, F., Wrede, K., Forsting, M., Schedlowski, M., Engler, H., Elsenbruch, S., Benson, S., Costantini, M., 2019. Altered temporal variance and functional connectivity of BOLD signal is associated with state anxiety during acute systemic inflammation. Neuroimage 184, 916–924. https://doi.org/10.1016/j.neuroimage.2018.09.056.

Lantrip, C., Gunning, F.M., Flashman, L., Roth, R.M., Holtzheimer, P.E., 2017. Effects of Transcranial Magnetic Stimulation on the Cognitive Control of Emotion: Potential Antidepressant Mechanisms. J. ECT 33 (2), 73–80. https://doi.org/10.1097/YCT.0000000000000386.

Lefaucheur, J.-P., Aleman, A., Baeken, C., Benninger, D.H., Brunelin, J., Di Lazzaro, V., Filipovic, S.R., Grefkes, C., Hasan, A., Hummel, F.C., Jaaskelainen, S.K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J.-P., Nyffeler, T., Oliveira-Maia, A.J., Oliviero, A., Ziemann, U., 2020. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). Clin. Neurophysiol. 131 (2), 474–528. https://doi.org/10.1016/j.clinph.2019.11.002.

Lehrer, P., 2022. My Life in HRV Biofeedback Research. Appl. Psychophysiol. Biofeedback 47 (4), 289–298. https://doi.org/10.1007/s10484-022-09535-5.

Lehrer, P.M., Irvin, C.G., Lu, S.-E., Scardella, A., Roehmheld-Hamm, B., Aviles-Velez, M., Graves, J., Vaschillo, E.G., Vaschillo, B., Hoyte, F., Nelson, H., Wamboldt, F.S., 2018. HRV biofeedback not a substitute for steroid controller medication for ASTHMA. Appl. Psychophysiol. Biofeedback 43 (1), 57–73. https://doi.org/10.1007/s10484-017-9382-0.

Lu, Z., Chen, L., Xu, S., Bao, Q., Ma, Y., Guo, L., Zhang, S., Huang, X., Cao, C., Ruan, L., 2018. Allergic disorders and risk of depression: A systematic review and meta-analysis of 51 large-scale studies. Ann. Allergy Asthma Immunol. 120 (3), 310–317. e2. https://doi.org/10.1016/j.anai.2017.12.011.

Lu, Y., Mak, K.-K., van Bever, H.P.S., Ng, T.P., Mak, A., Ho, R.-C.-M., 2012. Prevalence of anxiety and depressive symptoms in adolescents with asthma: A meta-analysis and meta-regression. Pediatr. Allergy Immunol. 23 (8), 707–715. https://doi.org/10.1111/pai.12000.

Lutz, A., Jha, A.P., Dunne, J.D., Saron, C.D., 2015. Investigating the phenomenological matrix of mindfulness-related practices from a neurocognitive perspective. Am. Psychol. 70 (7), 632–658. https://doi.org/10.1037/a0039585.

MacCoon, D.G., Imel, Z.E., Rosenkranz, M.A., Sheftel, J.G., Weng, H.Y., Sullivan, J.C., Bonus, K.A., Stoney, C.M., Salomons, T.V., Davidson, R.J., Lutz, A., 2012. The validation of an active control intervention for Mindfulness Based Stress Reduction (MBSR). Behav. Res. Ther. 50 (1), 3–12. https://doi.org/10.1016/j.brat.2011.10.011.

Malpass, A., Kessler, D., Sharp, D., Shaw, A., 2015. MBCT for Patients with Respiratory Conditions Who Experience Anxiety and Depression: A Qualitative Study. Mindfulness 6 (5), 1181–1191. https://doi.org/10.1007/s12671-014-0370-7.

Malpass, A., Feder, G., Dodd, J.W., 2018. Understanding changes in dyspnoea perception in obstructive lung disease after mindfulness training. BMJ Open Respir. Res. 5 (1), e000309.

Marshall, G.D., 2019. Psychological stress, immunity, and asthma: Developing a paradigm for effective therapy and prevention. Curr. Opin. Behav. Sci. 28, 14–19. https://doi.org/10.1016/j.cobeha.2019.01.006.

Marwood, L., Wise, T., Perkins, A.M., Cleare, A.J., 2018. Meta-analyses of the neural mechanisms and predictors of response to psychotherapy in depression and anxiety. Neurosci. Biobehav. Rev. 95, 61–72. https://doi.org/10.1016/j.neubiorev.2018.09.022.

Menon, V., & D'Esposito, M. (2022). The role of PFC networks in cognitive control and executive function. *Neuropsychopharmacology*, *47*(1), Article 1. doi: 10.1038/s41386-021-01152-w.

Parkinson, T.D., Kornelsen, J., Smith, S.D., 2019. Trait Mindfulness and Functional Connectivity in Cognitive and Attentional Resting State Networks. Front. Hum. Neurosci. 13, 112. https://doi.org/10.3389/fnhum.2019.00112.

Pascoe, M.C., Thompson, D.R., Jenkins, Z.M., Ski, C.F., 2017. Mindfulness mediates the physiological markers of stress: Systematic review and meta-analysis. J. Psychiatr. Res. 95, 156–178. https://doi.org/10.1016/j.jpsychires.2017.08.004.

Paudyal, P., Jones, C., Grindey, C., Dawood, R., Smith, H., 2018. Meditation for asthma: Systematic review and meta-analysis. The Journal of Asthma: Official Journal of the Association for the Care of Asthma 55 (7), 771–778. https://doi.org/10.1080/02770903.2017.1365887.

Pezzulo, G., Zorzi, M., Corbetta, M., 2021. The secret life of predictive brains: What's spontaneous activity for? Trends Cogn. Sci. 25 (9), 730–743. https://doi.org/10.1016/j.tics.2021.05.007.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048.

Price, D.B., Rigazio, A., Campbell, J.D., Bleecker, E.R., Corrigan, C.J., Thomas, M., Wenzel, S.E., Wilson, A.M., Small, M.B., Gopalan, G., Ashton, V.L., Burden, A., Hillyer, E.V., Kerkhof, M., Pavord, I.D., 2015. Blood eosinophil count and prospective annual asthma disease burden: A UK cohort study. Lancet Respir. Med. 3 (11), 849–858. https://doi.org/10.1016/S2213-2600(15)00367-7.

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.R-project.org/.

Rahrig, H., Vago, D.R., Passarelli, M.A., Auten, A., Lynn, N.A., Brown, K.W., 2022. Meta-analytic evidence that mindfulness training alters resting state default mode network connectivity. Sci. Rep. 12(1), Article 1 https://doi.org/10.1038/s41598-022-15195-6.

Ritz, T., Kroll, J. L., Patel, S. V., Chen, J. R., Yezhuvath, U. S., Aslan, S., Khan, D. A., Pinkham, A. E., Rosenfield, D., & Brown, E. S. (2019). Central nervous system signatures of affect in asthma: Associations with emotion-induced bronchoconstriction, airway inflammation, and asthma control. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *126*(6), 1725–1736. doi: 10.1152/japplphysiol.01018.2018.

Ritz, T., Trueba, A.F., 2014. Airway nitric oxide and psychological processes in asthma and health: A review. Ann. Allergy Asthma Immunol. 112 (4), 302–308. https://doi.org/10.1016/j.anai.2013.11.022.

Rolls, E.T., 2019. The cingulate cortex and limbic systems for emotion, action, and memory. Brain Struct. Funct. 224 (9), 3001–3018. https://doi.org/10.1007/s00429-019-01945-2.

Rosenkranz, M.A., Busse, W.W., Johnstone, T., Swenson, C.A., Crisafi, G.M., Jackson, M. M., Bosch, J.A., Sheridan, J.F., Davidson, R.J., 2005. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc. Natl. Acad. Sci. 102 (37), 13319–13324. https://doi.org/10.1073/pnas.0504365102.

Rosenkranz, M.A., Davidson, R.J., 2009. Affective neural circuitry and mind-body influences in asthma. Neuroimage 47 (3), 972–980. https://doi.org/10.1016/j.neuroimage.2009.05.042.

Rosenkranz, M.A., Esnault, S., Christian, B.T., Crisafi, G., Gresham, L.K., Higgins, A.T., Moore, M.N., Moore, S.M., Weng, H.Y., Salk, R.H., Busse, W.W., Davidson, R.J., 2018. Corrigendum to "Mind-body interactions in the regulation of airway inflammation in asthma: A PET study of acute and chronic stress" [Brain Behav. Immun. 58 (2016) 18–30]. Brain Behav. Immun. 67, 398–401. https://doi.org/10.1016/j.bbi.2017.08.009.

Rosenkranz, M.A., Esnault, S., Gresham, L., Davidson, R.J., Christian, B.T., Jarjour, N.N., Busse, W.W., 2022. Role of amygdala in stress-induced upregulation of airway IL-1 signaling in asthma. Biol. Psychol. 167, 108226 https://doi.org/10.1016/j.biopsycho.2021.108226.

Seeley, W.W., 2019. The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. J. Neurosci. 39 (50), 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019.

Sezer, I., Pizzagalli, D.A., Sacchet, M.D., 2022. Resting-state fMRI functional connectivity and mindfulness in clinical and non-clinical contexts: A review and synthesis. Neurosci. Biobehav. Rev. 135, 104583 https://doi.org/10.1016/j.neubiorev.2022.104583.

Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12 (3), 154–167. https://doi.org/10.1038/nrn2994.

Silkoff, P.E., Carlson, M., Bourke, T., Katial, R., Ögren, E., Szefler, S.J., 2004. The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food

and Drug Administration for monitoring therapy in asthma. J. Allergy Clin. Immunol. 114 (5), 1241–1256. https://doi.org/10.1016/j.jaci.2004.08.042.
Slavich, G.M., 2015. Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority. Brain Behav. Immun. 45, 13–14. https://doi.org/10.1016/j.bbi.2014.10.012.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155. https://doi.org/10.1002/hbm.10062.
Snyder, W., Uddin, L.Q., Nomi, J.S., 2021. Dynamic functional connectivity profile of the salience network across the life span. Hum. Brain Mapp. 42 (14), 4740–4749. https://doi.org/10.1002/hbm.25581.
Global Strategy for Asthma Management and Prevention. (2019). Global Initiative for Asthma. www.ginasthma.org.
Su, I.-W., Wu, F.-W., Liang, K.-C., Cheng, K.-Y., Hsieh, S.-T., Sun, W.-Z., Chou, T.-L., 2016. Pain Perception Can Be Modulated by Mindfulness Training: A Resting-State fMRI Study. Front. Hum. Neurosci. 10, 570. https://doi.org/10.3389/fnhum.2016.00570.
Thomas Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (3), 1125–1165. https://doi.org/10.1152/jn.00338.2011.
Tik, M., Hoffmann, A., Sladky, R., Tomova, L., Hummer, A., Navarro de Lara, L., Bukowski, H., Pripfl, J., Biswal, B., Lamm, C., Windischberger, C., 2017. Towards understanding rTMS mechanism of action: Stimulation of the DLPFC causes network-specific increase in functional connectivity. Neuroimage 162, 289–296. https://doi.org/10.1016/j.neuroimage.2017.09.022.
Wielgosz, J., Goldberg, S.B., Kral, T.R.A., Dunne, J.D., Davidson, R.J., 2019. Mindfulness Meditation and Psychopathology. Annu. Rev. Clin. Psychol. 15, 285–316. https://doi.org/10.1146/annurev-clinpsy-021815-093423.
Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage 92, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060.
World Medical Association, 2013. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 310 (20), 2191–2194. https://doi.org/10.1001/jama.2013.281053.
Xu, J., Van Dam, N.T., Feng, C., Luo, Y., Ai, H., Gu, R., Xu, P., 2019. Anxious brain networks: A coordinate-based activation likelihood estimation meta-analysis of resting-state functional connectivity studies in anxiety. Neurosci. Biobehav. Rev. 96, 21–30. https://doi.org/10.1016/j.neubiorev.2018.11.005.
Yaghoubi, M., Adibi, A., Safari, A., FitzGerald, J.M., 2019. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. Am. J. Respir. Crit. Care Med. 200 (9), 1102–1112. https://doi.org/10.1164/rccm.201901-0016OC.
Yang, C.-C., Barrós-Loscertales, A., Pinazo, D., Ventura-Campos, N., Borchardt, V., Bustamante, J.-C., Rodríguez-Pujadas, A., Fuentes-Claramonte, P., Balaguer, R., Ávila, C., Walter, M., 2016. State and Training Effects of Mindfulness Meditation on Brain Networks Reflect Neuronal Mechanisms of Its Antidepressant Effect. Neural Plast. 2016, 9504642. https://doi.org/10.1155/2016/9504642.
Yarkoni, T., Poldrack, R.A., Nichols, T.E., Van Essen, D.C., Wager, T.D., 2011. Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods 8 (8), 665–670. https://doi.org/10.1038/nmeth.1635.
Young, I.M., Dadario, N.B., Tanglay, O., Chen, E., Cook, B., Taylor, H.M., Crawford, L., Yeung, J.T., Nicholas, P.J., Doyen, S., Sughrue, M.E., 2023. Connectivity model of the anatomic substrates and network abnormalities in major depressive disorder: A coordinate meta-analysis of resting-state functional connectivity. Journal of Affective Disorders Reports 11, 100478. https://doi.org/10.1016/j.jadr.2023.100478.
Young, K.S., van der Velden, A.M., Craske, M.G., Pallesen, K.J., Fjorback, L., Roepstorff, A., Parsons, C.E., 2018. The impact of mindfulness-based interventions on brain activity: A systematic review of functional magnetic resonance imaging studies. Neurosci. Biobehav. Rev. 84, 424–433. https://doi.org/10.1016/j.neubiorev.2017.08.003.
Zhang, L., Zhang, X., Zheng, J., Wang, L., Zhang, H.-P., Wang, L., Wang, G., 2016. Co-morbid psychological dysfunction is associated with a higher risk of asthma exacerbations: A systematic review and meta-analysis. J. Thorac. Dis. 8 (6), 1257–1268. https://doi.org/10.21037/jtd.2016.04.68.
Zorrilla, E.P., Koob, G.F., 2013. Amygdalostriatal projections in the neurocircuitry for motivation: A neuroanatomical thread through the career of Ann Kelley. Neurosci. Biobehav. Rev. 37 (9, Part A), 1932–1945. https://doi.org/10.1016/j.neubiorev.2012.11.019.
Brown, L., Rando, A. A., Eichel, K., Van Dam, N. T., Celano, C. M., Huffman, J. C., & Morris, M. E. (2021). The Effects of Mindfulness and Meditation on Vagally Mediated Heart Rate Variability: A Meta-Analysis. Psychosomatic medicine, 83(6), 631–640. https://doi.org/10.1097/PSY.0000000000000900.