Neural mechanisms of mindfulness-based stress reduction in asthma

Short title: Mindfulness-related brain changes in asthma

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Abstract

Mindfulness-based stress reduction (MBSR) can improve symptoms of chronic inflammation; in asthma, improving asthma control and reducing airway inflammation. Understanding the neural mechanisms underlying these salubrious outcomes could help identify neuroimmune phenotypes and personalize interventions. Adults with asthma were randomized to 8 weeks of MBSR (n=38) or a wait-list group (n=34). Clinically relevant asthma-related and psychological outcomes were measured, and task-based fMRI data were acquired during exposure to emotional cues at baseline, post-intervention, and 6mo follow-up. Whole-brain group x time interactions and voxelwise regressions were used to evaluate changes in neural responses to emotion cues from baseline and their relationship to psychological and biological outcomes. Post-intervention, MBSR participants showed decreased lateral prefrontal/orbitofrontal cortex responses to aversive cues relative to controls, which was associated with increased mindfulness. Across participants, decreased salience network reactivity at post-intervention was associated with reduced psychological distress and airway inflammation. At 6 months, some relationships persisted while others did not. Results suggest that mindfulness training reduced effortful regulation of cognitive and affective responses to emotional cues, instead promoting more efficient processing strategies and reduced affective reactivity. Our findings clarify neural mechanisms underlying MBSR's clinical benefits for asthma, underscoring mind-brain-immune relationships as a critical target for asthma treatment.

Keywords: asthma, mindfulness, neuroimaging

Introduction

The mind and the neural processes that subserve it are underutilized targets for intervention in asthma and other chronic inflammatory diseases in which psychological factors substantively contribute to disease expression and treatment responsiveness [1,2]. Asthma affects approximately 8% of the U.S. population [3], and is characterized by airway inflammation, hyperresponsiveness, and bronchoconstriction [4]. Stress and emotion impact asthma at many levels, leading to poorer asthma control, risk for exacerbations, and increased need for emergency treatment [5]. Furthermore, the prevalence of depression and anxiety in asthma is nearly double that of the general population [6] and comorbid psychopathology is associated with increased asthma burden and worse outcomes [1,7].

Since cognitive and emotional states are products of the brain, mind-body interactions in asthma implicate a critical role of the brain in asthma outcomes. Psychological stress worsens asthma, in part by promoting a proinflammatory milieu in the airways via descending neural signaling [2,8–10]. However, central nervous system contributions to asthma pathophysiology remain underexplored. Moreover, despite the availability of multiple pharmaceutical treatment classes, asthma remains uncontrolled in 30-50% of patients, imposing significant economic, healthcare, and quality of life burden [11]. This reality, combined with evidence of psychological contributions to asthma, has prompted the inclusion of psychological factors in clinical asthma management guidelines [12]. Understanding the mechanisms through which psychological processes contribute to asthma would inform novel intervention development and increase treatment precision.

Mindfulness-based interventions have the potential to improve clinical care in asthma. Mindfulness-based stress reduction (MBSR), the predominant mindfulness intervention in

63 secular Western settings, consists of sustained focused attention, cultivating nonjudgmental
64 awareness, and non-reactivity [13]. In asthma, MBSR improves disease control [14] and asthma-
65 related quality of life [15]. Though several studies have investigated the efficacy of MBSR in
66 ameliorating disease-related outcomes, and others have examined the neural changes associated
67 with MBSR training, studies examining the neural underpinnings of improvement in disease-
68 related outcomes are limited to pain (e.g., [16]) and psychological symptoms (e.g., [17]). A
69 greater understanding of the neural basis of improved asthma symptoms following MBSR
70 training would contribute not only to intervention optimization, but also to our understanding of
71 the biological pathways through which mental content shapes peripheral biology.
72 Neural networks involved in processing salient information and regulating emotion
73 overlap with those implicated in immune modulation, including in asthma (e.g., [9-10,18-21]) .
74 In particular, the salience network—comprising the lateral prefrontal cortex (PFC), amygdala,
75 anterior cingulate cortex (ACC), and insula—participates in processing, responding to, and
76 modulating emotion [22,23]. Meta-analytic studies have implicated these same regions in
77 responding to and regulating peripheral inflammation [24,25]. In rodent models of asthma,
78 inflammation modulates similar circuits, which impact anxiety-like behaviors [26–28]. In
79 humans with asthma, ACC and insula responses to emotionally-evocative stimuli predict
80 subsequent airway inflammatory responses to allergen challenge and increased airways
81 obstruction [18-20]. This neurocircuitry overlap suggests that how the brain monitors, interprets,
82 and responds to salient internal and external cues may interact with immune regulation.
83 Importantly, meditation-based interventions such as MBSR have been shown to impact
84 function and structure in neural circuits implicated in the regulation of inflammation. Notably,
85 the dorsolateral PFC, ACC, insula, and amygdala consistently show alterations following

meditation training [29–31]. These neural changes are thought to reflect emotional, cognitive, and behavioral shifts related to mindfulness training, including altered sensory and emotional awareness, reactivity, and regulation [30,32]. Thus, MBSR-related neural changes may benefit mind-body relationships in asthma.

To better understand the neural shifts following MBSR training that foster improvements in asthma outcomes, we used task-based functional magnetic resonance imaging (fMRI) to measure changes in neural responsivity following participation in an 8-week MBSR intervention, relative to a wait-list control group, in adults with asthma. During fMRI acquisition, participants responded to an asthma-specific variant of the Stroop Task [33]. We hypothesized that MBSR would alter neural responses in the insula, ACC, lateral PFC, and amygdala, and that these changes would be correlated with improvements in disease-related outcomes.

Results

Effects of MBSR on self-report and neural reactivity

Self-report and inflammatory outcomes following the 8-week MBSR intervention were reported previously [14]. Briefly, the MBSR group showed greater increases in self-reported mindfulness, greater improvements in asthma control, greater decreases in airway inflammation, and greater decreases in psychological symptom-related distress, relative to the control group. Neither performance nor accuracy on the Asthma Stroop task differed over time between MBSR and wait-list groups for any word category (asthma, negative, neutral).

To investigate neural correlates of these changes, we examined fMRI BOLD responses to emotionally salient cues using an Asthma Stroop task. Because effects were largely consistent, we report only results from the contrast of emotion words (averaged across asthma-related and negative categories) relative to valence-neutral words in the main text. See Supplementary Materials for asthma relative to neutral word contrast results. Participants who received MBSR training showed decreased activation in right ventrolateral prefrontal cortex (vlPFC)/lateral orbitofrontal cortex (OFC) and left medial temporal gyrus (MTG) in response to emotion relative to neutral words from baseline (T1) to immediately post-intervention (T2), compared to wait-list controls (Fig 1). We found no significant changes in activation from baseline to 6mo follow-up (T3) that differed by group. This suggests that MBSR decreased attention- and emotion-related neural reactivity immediately following the intervention, though the effects were not enduring.

Voxelwise neural activity regressions with self-report and peripheral measures

Mindfulness

We next assessed the relationship between changes in self-reported mindfulness (Five Facet Mindfulness Questionnaire; FFMQ) and neural reactivity. An interaction between mindfulness score and group on BOLD response covered a large segment of the cortex, including regions of the left dorsolateral prefrontal cortex (dlPFC), bilateral insulae, left anterior cingulate cortex (ACC), bilateral precentral gyri, and right precuneus and posterior cingulate cortex (PCC; Fig 2). Post-hoc analyses showed that this was driven by a significant association between increased mindfulness and decreased BOLD response in the MBSR group over time, whereas this relationship was absent in the wait-list group. Additional clusters in the dlPFC and right insula, that were discontiguous with this large multi-region cluster, also showed significant group x time interactions (Fig 2), with an analogous pattern to that described above.

There were no additional between-group differences in relationships between change in mindfulness scores and BOLD response within *a priori* small-volume-corrected regions of interest (ROI). However, across groups, an increase in mindfulness score from baseline to post-intervention was associated with decreased dACC activation, in response to emotion vs neutral words which persisted at 6mo (Fig 3).

To clarify effects that are dependent on persistent engagement with the intervention, we assessed whether self-reported mindfulness practice predicted changes in neural reactivity. Although there were no significant relationships between self-reported practice time and change in neural response overall, small-volume-corrected analyses showed that greater time spent in formal practice was associated with decreased left central amygdala activation to emotion versus neutral words from baseline to 6mo follow-up, suggesting reduced emotional reactivity for those who practiced more. However, this cluster was very small (see Supplementary Table S4),

potentially due to insufficient power since only ~50% of participants continued to practice post-intervention.

Distress

As reported previously, MBSR participants experienced greater decreases in psychological symptom intensity (SCL90 Positive Symptom Distress Index; PSDI) over time [14]. Moreover, greater decreases in psychological symptoms (GSI) were associated with greater intervention-related improvements in asthma control (ACQ-6), relative to wait-list controls [14]. In the brain, a decrease in psychological symptoms was associated with widespread decreases in activation to emotion words, from baseline to post-intervention across groups (Fig 4). Specifically, a decrease in symptoms was associated with decreased right insula-frontal opercular cortex (IFOC), PCC, postcentral gyrus, lateral occipital cortex, ACC, left vlPFC, precuneus, right caudate, and bilateral precentral and medial temporal gyri activation. There were no interactions between group and change in symptoms, and no significant associations between change in BOLD responses to emotion words and change in symptom intensity.

In contrast to our predictions, at 6mo follow-up, a decrease in depressive symptoms was associated with an increased bilateral ventral PFC response to emotion compared to neutral words, relative to baseline. However, this cluster was largely nonoverlapping with the cluster showing an association between decreased psychological symptoms and decreased neural response from baseline to post-intervention, described above.

In analyses restricted to small-volume-corrected regions of interest, a decrease in psychological symptoms was differentially associated with changes in dACC response to emotion relative to neutral words from baseline to 6mo follow-up in the MBSR group relative to

controls (Fig 5). This was driven by a significant association between decreased psychological symptoms and increased dACC activation in the MBSR group, a relationship that was opposite in controls. No significant associations with psychological distress across groups were observed in any small-volume-corrected analyses. Overall, improvements in distress following the mindfulness intervention were associated with reduced cognitive-affective and salience network neural reactivity.

Asthma outcomes

MBSR-related improvements in asthma control (Asthma Control Questionnaire 6-item version; ACQ-6) were significantly associated with increased dACC activation to emotion vs neutral words from baseline to 6mo follow-up, whereas no association was observed in controls (Fig 6). Similarly, reductions in asthma severity (Composite Asthma Severity Index; CASI) were associated with increased right IFOC responses to emotion vs neutral words from baseline to 6mo follow-up, in MBSR relative to control participants. We found no significant relationships between neural responses to emotion words and asthma-related outcomes in analyses collapsing across groups.

Asthma-related inflammation was indexed by the number of eosinophils (EOS) in blood, the percentage of EOS in sputum, and fraction of exhaled nitric oxide (FeNO), all biomarkers of the TH2 immune response that characterizes allergic diseases and the predominant asthma endotype. In small-volume-corrected analyses, decreases in blood EOS from baseline to post-intervention were associated with decreased right IFOC activation to emotion words across groups (Fig 7a). Similarly, decreases in sputum EOS were associated with decreased left dorsal anterior insula response from baseline to post-intervention (Fig 7c), suggesting that reductions in

salience network responsivity predict improved inflammatory outcomes. Contrary to hypotheses, decreased FeNO was associated with increased amygdala activity from baseline to post-intervention.

Discussion

Understanding the role of the mind in asthma is essential to optimal disease control, given its impact on symptoms and treatment response. This study is the first to examine how mindfulness training impacts neural responses to emotional information and how these effects relate to disease-relevant outcomes in adults with asthma. MBSR training was associated with decreased frontolateral and medial temporal neural reactivity to emotional cues, which scaled with increases in mindfulness. Participants with the largest decreases in neural reactivity in these regions, among others, also experienced the greatest reductions in psychological distress and inflammation, which may reflect a shift toward less effortful, more efficient regulatory responses to emotional information. At the 6-month follow-up, some of these patterns persisted, while others were consistent with a return to more effortful regulation. Our results advance our understanding of mind-body interactions in asthma and shed light on the neural mechanisms associated with previously reported clinical benefits of MBSR for this population [14]. The relevance of these findings is high, as they translate to improved disease control and fill an unmet need in asthma management based on a neurobehavioral treatable trait approach.

MBSR may boost regulatory efficiency

MBSR-related decreases in prefrontal responses to emotional cues suggest that participants resolved the Stroop conflict using fewer neural resources, perhaps reflecting reduced reliance on effortful cognitive control and increased efficiency in cognitive-affective regulation—both supporting decreased emotional reactivity. Cognition and emotion are mutually influential and subserved by overlapping neural circuits [34–37]. For instance, heightened emotional reactivity can bias attention toward threat, and executive function processes are invoked to modulate affective responses [35,36]. Thus, *cognitive-affective regulation* refers to

the cognitive processes engaged while experiencing and responding to emotional information. Through initially effortful engagement, this form of regulation can become automatic with practice [38].

Consistent with this possibility, widespread decreases in frontal and parietal responsivity were associated with increased self-reported mindfulness in MBSR participants relative to controls, as well as with decreased distress for all participants at post-intervention. Cultivating core mindfulness skills such as non-reactivity, equanimity, and acceptance [13]—i.e., "non-appraisal"—is consistent with a reduced need to effortfully resolve emotion-related interference with cognitive processing. In contrast, other behavioral interventions emphasize effortful top-down cognitive control strategies like reappraisal [39,40]. While both skill sets can improve outcomes, non-appraisal strategies require fewer cognitive, neural, and autonomic resources [40], contributing to increased efficiency [41] and a shift in participants' relationship to their experiences [39].

Mindfulness training could also lead to changes in neural reactivity consistent with increased regulatory efficiency by reducing attentional bias from salient distractors [32,42]. In asthma, disease-relevant cues capture attention and cause cognitive interference [43], reflected in increased BOLD responses in cognitive control and affective neural circuits, including lateral/medial PFC and dACC, during asthma Stroop tasks [19,20]. Here, the reduced ACC and IFOC reactivity associated with increased mindfulness, alongside MBSR-related decreases in prefrontal activation, aligns with evidence that mindfulness training may increase processing efficiency by altering attention allocation, reducing the extent to which salient distractors capture attention and engage emotion [39,42]. Less attention capture may also facilitate less reliance on effortful regulatory processing of aversive distractors. Though speculative, the absence of

changes in Stroop performance despite decreased neural engagement is consistent with greater regulatory efficiency. However, our study was not powered to detect behavioral Stroop effects (i.e. valence-related reaction time differences) so neural-behavioral dissociation should be interpreted with appropriate caution.

Though our experimental paradigm cannot disentangle neural activity involved in regulation from that involved in reactivity, it is plausible that increases in non-appraisal and reduced attentional bias following MBSR training contribute to decreased emotional reactivity to affective stimuli. The lateral PFC/OFC, together with its roles in both cognitive *control* and emotion *regulation*, is involved in *processing* aversive stimuli [44]. MBSR training has been associated with widespread decreases in cortical and prefrontal activation during emotional Stroop tasks [45,46] and in association with reduced physical and psychological symptoms [16,47,48]. Thus, in the context of emotional conflict tasks, decreased prefrontal activation following MBSR may also reflect reduced emotional reactivity (e.g., [65,69]). The interplay between non-appraisal, reduced attentional bias, and emotional reactivity likely converges to give rise to the observed mindfulness-related improvements in distress [14].

Mind-brain-immune interactions

As core components of the salience network, the ACC and IFOC integrate cognition, emotion, and immune function. Functionally, the ACC couples affective evaluations with cognitive control to coordinate physiological and behavioral adjustments in response to internal or external sensory feedback [36,49]. Similarly, the IFOC directs attention toward salient emotional and homeostatic cues to adaptively guide behavior [50–52]. Like prefrontal regions discussed earlier, the ACC and IFOC contribute to emotion-related cognition and have shown decreased reactivity to emotional [53,54] and physiological [55] stimuli with mindfulness

training. Here, reduced ACC and IFOC reactivity was associated with increased mindfulness in the MBSR group. Further, decreases in distress and inflammation, regardless of the reason for these improvements, were associated with reductions in ACC and IFOC reactivity in both groups, but those in the MBSR group showed larger decreases in distress and inflammation (see [14]). Notably, asthma medication use did not differ over time or by group, suggesting that the observed reductions in inflammation were not driven by changes in medication adherence (see Supplement for details). IFOC reactivity also showed a modest decrease from pre- to post-training in MBSR participants, relative to wait-list controls (uncorrected $Z>3.1$). The association between decreased IFOC reactivity and decreased inflammation may implicate the IFOC in connecting emotion regulatory processes with peripheral immune function in asthma. This interpretation aligns with prior studies showing that IFOC and ACC reactivity, following psychosocial stress [8,9] or in response to emotion stimuli [19], correlates with increases in airway inflammation and asthma symptoms [20].

Proposed Mechanisms

Mechanistically, MBSR may impact inflammatory responses through autonomic and endocrine pathways that are modulated by the ACC and IFOC. The IFOC and ACC coordinate communications among the central nervous system, autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (HPA) axis, and immune system [50,56]. Mindfulness training enhances one's capacity to manage stress through skills like non-appraisal, which can lead to reduced negative emotional reactivity and alter one's perception of stimuli as stressful. These psychological changes may be reflected in the decreased ACC and IFOC reactivity we observed. In turn, mindfulness-related alterations in ACC and IFOC activity may be associated with reduced ANS and HPA-axis mobilization and downstream proinflammatory activity. In asthma,

where dysregulated ANS and HPA responses can exacerbate inflammation, reduced IFOC reactivity may be one pathway through which mindfulness relates to improved immune regulation (for review, see [81]). However, since ANS or HPA responses were not directly assessed here, this remains speculative.

It is important to note that reduced IFOC activity may *follow*, rather than *precede* reduced peripheral inflammation in the biological change of events. In other words,, reduced airway inflammation may *contribute to* a decrease in IFOC reactivity. In addition to efferent regulation, the IFOC responds to afferent signals, integrating bottom-up bodily information with top-down processes. Given the IFOC's involvement in guiding behavior based on predictive models [58], decreased reactivity may reflect a shift toward monitoring and responding to physiological symptoms with less elaboration from contextual emotional or cognitive cues. Since brain-immune communication is bidirectional, it is not possible to resolve the direction of causality with this study design. Nonetheless, the observed IFOC and ACC changes likely reflect a combination of altered reactivity, regulation, and their integration.

Together, the observed decreased PFC, IFOC, and ACC activity, correlated with improved symptoms, support the hypotheses that 1) emotion and inflammation modulation involves shared circuity, and 2) an intervention shown to benefit regulation of both emotion and inflammation impacts this shared circuitry. These patterns elucidate mechanisms (e.g., reduced prefrontal reactivity) through which mindfulness training may reinforce adaptive attention to, evaluation of, and response to salient disease-relevant cues in asthma. Still, these interpretations should be taken with appropriate caution, given the correlational nature of the analyses.

Maintenance of neural response patterns

Our findings suggest that decreased engagement of emotion-relevant neural regions immediately post-intervention (T2) supports psychological and immune benefits in asthma, possibly through more efficient and less effortful processing of affective information. Most of these effects persisted at 6-month follow-up (T3). However, other observations are consistent with a shift from non-appraisal-like attention at T2 to explicit regulation, such as active attentional-shifting, at T3. In whole-brain analyses, *increased* engagement of cognitive control circuitry was associated with improvements in psychological symptoms, asthma control, and asthma severity from baseline to T3. This may reflect a transition in how participants maintained the previously-reported clinical benefits of MBSR [14]. For example, participants may invoke skills like non-judgmental awareness less readily in the months after the intervention, instead using effortful regulation strategies. Accordingly, while nearly all participants reported practicing mindfulness during the intervention period (T1-T2), almost half reported no practice in the period after the intervention (T2-T3), with no significant relationships between practice and brain changes.

Some evidence suggests that mechanisms linking cognitive processes with emotion responses change with mindfulness practice. For instance, both novice meditators after intensive meditation retreats and experienced practitioners [38,39] have shown reduced emotional reactivity without recruiting prefrontal regulatory regions, proposed to reflect an automatic non-judgmental attentional stance that reduces the coupling between sensory experiences and their affective interpretation [30,59]. Consistent with this proposed mechanism of change, participants in our study appeared to recruit fewer cognitive resources immediately after the intervention, when practice was frequent, but appeared to invoke more resources over time as regular practice decreased. Nonetheless, a few clusters (in ROI-focused analyses only) did show this pattern of

increased engagement associated with improved mindfulness and distress at both T2 and T3. Crucially, neural signatures thought to indicate increased emotion regulation–whether automatic or effortful–were associated with beneficial outcomes at both post-intervention time points. Prior work has similarly shown that MBSR-related benefits for mental distress persist at four years post-intervention even when formal practice declines [60]. These changes were less consistent and robust in our data, warranting cautious interpretation.

Limitations

A few important limitations of our study should be acknowledged. First, the modest sample size likely limited statistical power to detect small effects. Though the final sample size (n = 72) was near the target sample size (n = 80) expected to provide high power to detect large effects, power to detect smaller effects is questionable, and replication is necessary. Our sample also lacked racial and ethnic diversity, which is important given the disproportionate burden of asthma in historically marginalized communities [3]. Additionally, the absence of an active control group limits the attribution of changes specifically to mindfulness training, since some effects may have been driven by nonspecific intervention factors, such as expectancy effects or supportive group and instructor interactions. Though this design was selected for reasons of feasibility, future studies that include an active control group would allow disambiguation of intervention-specific effects and mechanisms from common factors.

Our ability to detect intervention effects was also likely hindered by variability in inflammatory measures due to the several-month span of study participation. For example, allergen burden and viral infections, both drivers of asthma symptoms and airway inflammation, fluctuate substantially across seasons. Since data collection spanned seasons, this variability was present both within and between participants. Subsequent studies could reduce these sources of

noise by adjusting for environmental allergen burden fluctuations or enrolling asthma patients sensitive only to seasonally consistent triggers. Despite this variability, our design reflects a real-world implementation of MBSR, enhancing ecological validity.

Conclusion

Mindfulness training altered neural responses to aversive cues, which correlated with improved outcomes in adults with asthma. Changes in neural reactivity in overlapping networks were associated with both psychological and inflammatory improvements, suggesting that how the brain processes emotion may have real-world implications for the regulation of inflammation and disease control in asthma.

Clinical Implications

In clinical populations like asthma, these patterns may reflect reduced worry about, anticipation of, identification with, or elaboration of symptoms (e.g., catastrophizing) alongside more accurate perception, evaluation, and response to triggers and symptoms. By fostering present-moment awareness, mindfulness supports more effective disease management. Our results underscore the importance of targeting psychological factors in comprehensive asthma care, for example, implementing mindfulness-based interventions in tandem with pharmacological treatment. Understanding the neural mechanisms underlying these relationships can help tailor interventions to different patient profiles, such as those characterized by psychological comorbidities, cognitive styles, or inflammatory phenotypes (e.g. corticosteroid-resistant). This will ultimately guide future research and treatments to more precisely address both emotional and physiological aspects of asthma to reduce disease burden, morbidity, and mortality.

Materials & Methods

Experimental design

Seventy-three adults with asthma aged 18-65 years (*M*=38.1, 43 female), recruited from Madison, WI and surrounding areas, were enrolled (for more information, see clinicaltrials.gov NCT02157766; posted 06-06-2014). All participants had an asthma diagnosis for ≥ 6 months with evidence of elevated Type 2 inflammation at enrollment, based on at least one of the following criteria: fraction of exhaled nitric oxide (FeNO) ≥ 30 ppb, blood eosinophil count ≥ 150 cells/μL, or percent sputum eosinophils ≥ 2% of total leukocytes [61,62]. FeNO of 30 ppb is a mid-point between the threshold for Type 2 inflammation (FeNO ≥ 20 ppb) and high FeNO (≥ 50 ppb) [62,63]. Exclusion criteria included taking >1000mcp Fluticasone or the equivalent, incompatibility with the magnetic resonance imaging (MRI) environment, and previous MBSR participation or current meditation/mind-body practice. Further exclusion criteria included current smoker status or a smoking history exceeding five pack-years within the last 10 years, pregnancy, history of neurological disorder, current bipolar or psychotic disorder, and traumatic brain injury. Psychotropic medications were allowed, provided the dose was stable for ≥ 6 months. All participants provided written informed consent and were compensated monetarily. 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. The University of Wisconsin-Madison's Health Sciences Institutional Review Board approved the protocol.

Participants completed a baseline visit (T1) before randomization to MBSR (n = 38) or wait-list (n = 34) groups. Participants completed a second visit immediately following the intervention (T2; n = 67). The average duration between the end of the intervention and the T2

visit was 19.25 days (range:18-72). A final visit took place approximately 4 months post-intervention (T3; n = 64). Two participants were excluded from analyses due to insufficient (< 2) MBSR class attendance. See Supplementary Fig S1A for participant discontinuation and withdrawal details. At each visit, MRI data were acquired and biomarkers of asthma-relevant inflammation, self-reported asthma control, asthma severity, and psychological symptoms were collected (Supplementary Fig S1B). Participants randomized to the wait-list control group were offered MBSR, at no cost, after study completion.

Intervention

The intervention consisted of a standard Mindfulness-Based Stress Reduction (MBSR) intervention, developed by Jon Kabat-Zinn. MBSR involves focused attention on the breath, bodily sensations, and mental content and takes place sitting, walking, and in yoga postures [64]. The intervention took place over eight weekly 2.5-hr sessions, one 6-hr intensive retreat, and daily at-home practice. Two certified and experienced MBSR instructors led the intervention, in classes also offered to and attended by community members. Participants recorded daily at-home practice each week.

Data acquisition

Self-report

Mindfulness. The Five Facet Mindfulness Questionnaire (FFMQ) consists of 39 Likert-scale questions that comprise five facets: Observing, Describing, Acting with Awareness, Non-judging of Inner Experience, and Non-reactivity to Inner Experience [65]. Ratings are made on a 5-point scale and summed for a total score out of 195.

Psychological Assessments. The Symptom Checklist-90 Revised (SCL-90R), used to assess psychological symptoms, contains 90 Likert-scale questions in nine symptom areas, each rated on a scale of 0-4 [66]. We assessed two global indices derived from this instrument: the Global Severity Index (GSI) reflects the number of symptoms and level of distress, and the Positive Symptom Distress Index (PSDI) reflects the intensity of distress. To assess symptoms of depression and anxiety, we used the Beck Depression Inventory [67] and Beck Anxiety Inventory [68]. The BDI and BAI each comprise 21 psychometrically validated Likert-scale questions measuring symptoms, each endorsed from 0-3 based on severity.

Type 2 inflammation, asthma control & severity

Type 2 inflammation, characterizing the most common asthma endophenotype, was measured using fraction of exhaled nitric oxide (FeNO), measured in breath condensate according to American Thoracic Society guidelines [42], and eosinophil (EOS) populations in blood and sputum. Sputum collection and processing were performed as previously described [14]. To quantify blood EOS, venous blood samples were collected into EDTA-coated tubes and slides were prepared to determine cell differentials. Percent of sputum EOS and total blood EOS count were used in analyses.

Asthma control refers to the successful management of symptoms and disease-related impairments [62], whereas asthma severity is based on the treatment required to attain control, current impairment, and future exacerbation risk [70]. We assessed asthma control using the Asthma Control Questionnaire 6-item version (ACQ-6) [44] and asthma severity using the Composite Asthma Severity Index (CASI) [43]. The ACQ-6 comprises six Likert-scale questions assessing symptoms and medication use during the previous week [71]. Participants rate each

item on a 7-point scale, and item scores are averaged for a final score out of six. The CASI includes four symptom-related and three medication-related items about the previous two weeks, which are summed for a total score ranging from 0-20 [70].

Neuroimaging

Image Acquisition. Anatomical and functional MRI images were acquired on a GE MR750 3.0 Tesla MRI scanner with a 32-channel head coil. Anatomical scans were high-resolution 3D T1-weighted inversion recovery fast gradient echo images (450ms inversion time, 1 x 1mm in-plane resolution, 256x256 matrix size, 256 mm field of view, 192 x 1.0mm axial slices). Two runs of functional task-based data were acquired using a gradient echo EPI sequence (1.75 x 1.75mm in-plane resolution, 128x128 matrix size, 224mm field of view, TR/TE/Flip = 2000ms/20ms/75º, 44 x 3.5mm interleaved sagittal slices, and 196 volumes per run).

Imaging Task. During acquisition of fMRI data, participants performed the Asthma Stroop Task, a modified version of the classic Stroop task [33], in which they responded to the color of asthma-relevant (e.g., wheeze), negative (e.g., loneliness), or valence-neutral (e.g., curtain) words. Asthma-relevant words were associated with the experience of asthma, generated by individuals with asthma. Negative and neutral words were selected from the ANEW dataset [72]. Each set was matched on word length, usage frequency, and part of speech. In each run, 10 stimuli per category were presented for 2s in random order, with a pseudo-randomized interstimulus interval of 4-8s. Reaction time and accuracy were recorded on an MRI-compatible button box.

Image Processing. Functional images were processed using FMRI Expert Analysis Tool (FEAT) Version 6.00 from the FMRIB Software Library (FSL) [46]. Preprocessing included

467 removal of the first four volumes, a high-pass temporal filter of 60s, FILM pre-whitening,
468 motion correction using MCFLIRT [74], BET brain extraction [75], and 5mm full-width-at-half-
469 maximum (FWHM) spatial smoothing. Transformations for image co-registration were
470 computed at the first level and applied during second-level analysis in a two-stage process.
471 Boundary-Based Registration [76] was used to register each participant's functional data to their
472 anatomical image, and a 12-degree-of-freedom affine transformation was used to register each
473 participant's anatomical scan to MNI space using linear (FLIRT) and nonlinear (FNIRT)
474 registration [74,77].

475 **Data Analysis.** Functional data were analyzed using a General Linear Model in three
476 levels [78]. Level-one analyses modeled stimulus presentation with a double-gamma
477 hemodynamic response function including stimulus valence, reaction time, and 6 directions of
478 motion with their derivatives. High-motion time points with a framewise displacement greater
479 than .5mm were censored [79], and individual scans were excluded from analysis if ≥ 25% of
480 data points were censored. Resulting contrast maps including Asthma vs Neutral (As-Nu),
481 Asthma vs Negative (As-Ng), Negative vs Neutral (Ng-Nu), and averaged Asthma and Negative
482 vs Neutral (Emo-Nu) were used in second-level fixed effects models. To examine changes over
483 time, baseline (T1) statistical maps were subtracted from T2 or T3 statistical maps to generate
484 difference images (T2-T1 and T3-T1) for each participant. To assess group differences over
485 time, mixed effects analyses using FLAME 1 were performed across the whole brain and within
486 *a priori*-specified regions of interest (ROIs). A cluster-forming threshold of $Z > 3.1$ was applied
487 to resulting statistical maps, with a significance threshold of $p < .05$ [80]. Two participants were
488 excluded due to excessive motion, two were excluded for neurological abnormalities, and one
489 did not complete neuroimaging due to claustrophobia (T2-T1 N = 62; T3-T1 N = 59).

To assess the relationship between changes in peripheral measures and neural activity, whole-brain and ROI regressions were performed. Inflammatory and self-report difference scores (pre-training minus post-training) were regressed on difference images (post-training minus pre-training) for each participant. Resulting statistical maps were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) and familywise error correction as implemented in FSL [81,82], and thresholded at $p < .05$. Regression analyses examined interactions between group and regressor changes over time, as well as changes over time across groups. Analyses of practice time aggregated total in-class and at-home practice minutes from the beginning of the intervention through study completion.

ROIs included salience network regions: bilateral amygdalae, dorsal anterior cingulate cortex (dACC), and the insula-frontal opercular cortex (IFOC). A bilateral amygdala mask was defined anatomically based on the Harvard-Oxford Atlas [83] with a 50% probability threshold (505 voxels). The dACC mask was defined by Shackman et al. [36] based on the Harvard-Oxford Atlas (4355 voxels). A mask including the insula, central and frontal operculum, and lateral orbitofrontal cortex with medial boundaries at the lateral-most insula coordinates was created using the Harvard-Oxford Atlas with a 25% probability threshold (6719 voxels). This IFOC ROI was defined based on co-activation of these regions in our previous work [8,19,20] and cytoarchitectonic evidence of functional continuity in this region [52,84].

For voxelwise regressions, outliers were defined as regressor change scores >3 standard deviations from the mean, whose inclusion skewed the distribution of change scores ($n = 7$ total). Reported results were consistent with and without outliers unless otherwise noted. Post-hoc analyses were performed on extracted clusters to characterize associations and create scatterplots for visualization purposes only.

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Data and materials availability: All data needed to evaluate conclusions in the paper can be found in the paper and/or Supplementary Materials. Data will be made available upon request.

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Competing interests: Dr. Richard J. Davidson is the founder, president, and serves on the board of directors for the non-profit organization, Healthy Minds Innovations, Inc. No donors, either anonymous or identified, have participated in the design, conduct, or reporting of research results in this manuscript. All other authors have nothing to disclose.

Figures

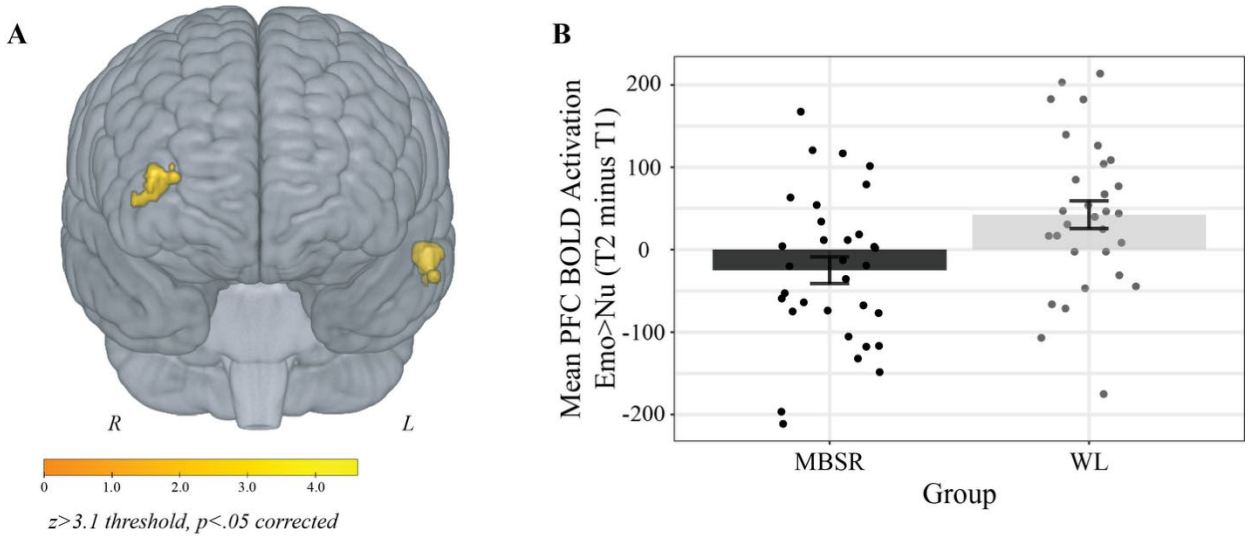

Figure 1. MBSR training decreased right vlPFC/OFC and left MTG BOLD response to emotionally-salient cues (Emo > Nu) from baseline (T1) to post-intervention (T2), relative to wait-list controls. A. Brain shows cluster of voxels where activation to emotion (vs neutral) words decreased more in MBSR participants compared to controls, from T1 to T2 (right vlPFC/OFC, left MTG). **B.** Bar plot shows average change in vlPFC/OFC activation (Emo > Nu) from T1 to T2 for each participant, by group. Bar plot is for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009), vlPFC: ventrolateral prefrontal cortex. OFC: orbitofrontal cortex. MTG: medial temporal gyrus. MBSR: mindfulness-based stress reduction

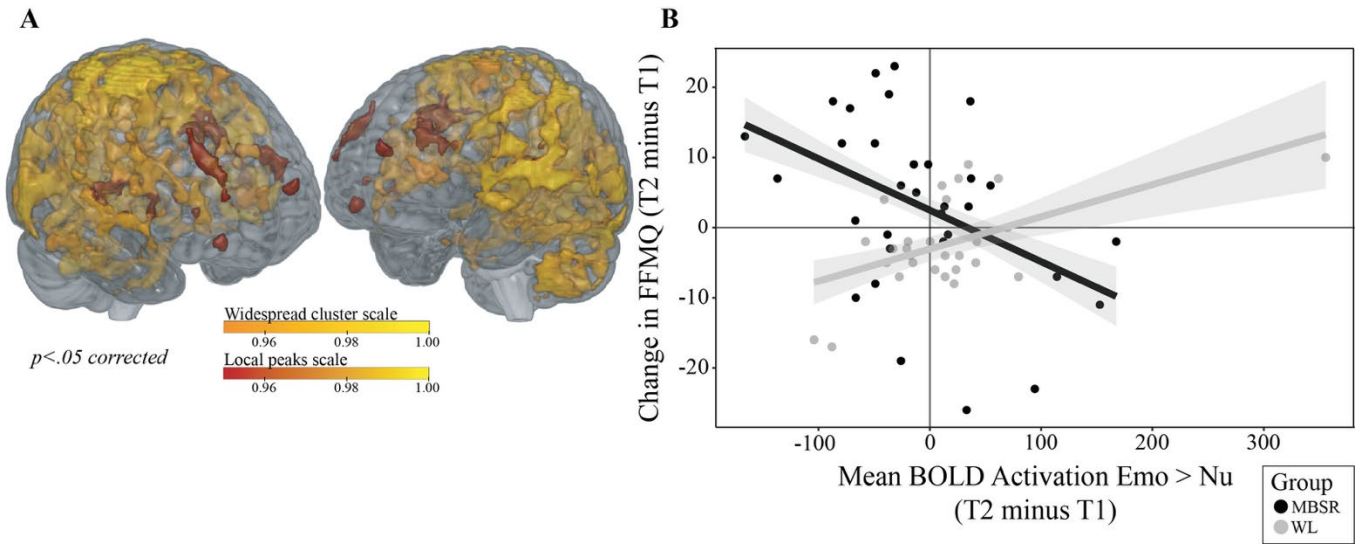

Figure 2. MBSR-related increases in mindfulness (FFMQ) were associated with decreased BOLD response to emotionally-salient words in MBSR, relative to wait-list control, participants from baseline (T1) to post-intervention (T2). A. Brain shows clusters of voxels where the change in BOLD response to emotionally-salient words (Emo > Nu) from T1 to T2 was associated with increased FFMQ scores in the MBSR, relative to wait-list control, group (one outlier excluded). Yellow = widespread cluster including regions of left dlPFC, bilateral insula, left ACC, bilateral precentral gyrus, right precuneus/PCC. Red = local dACC, dlPFC, and left insula peaks. **B.** Scatterplot shows group x time interaction between average change in BOLD response (widespread cluster) and change in FFMQ scores. Results were unchanged with removal of extreme value. Scatterplot is for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009). FFMQ: five facet mindfulness questionnaire. dlPFC: dorsolateral prefrontal cortex. ACC: anterior cingulate cortex. PCC: posterior cingulate cortex.

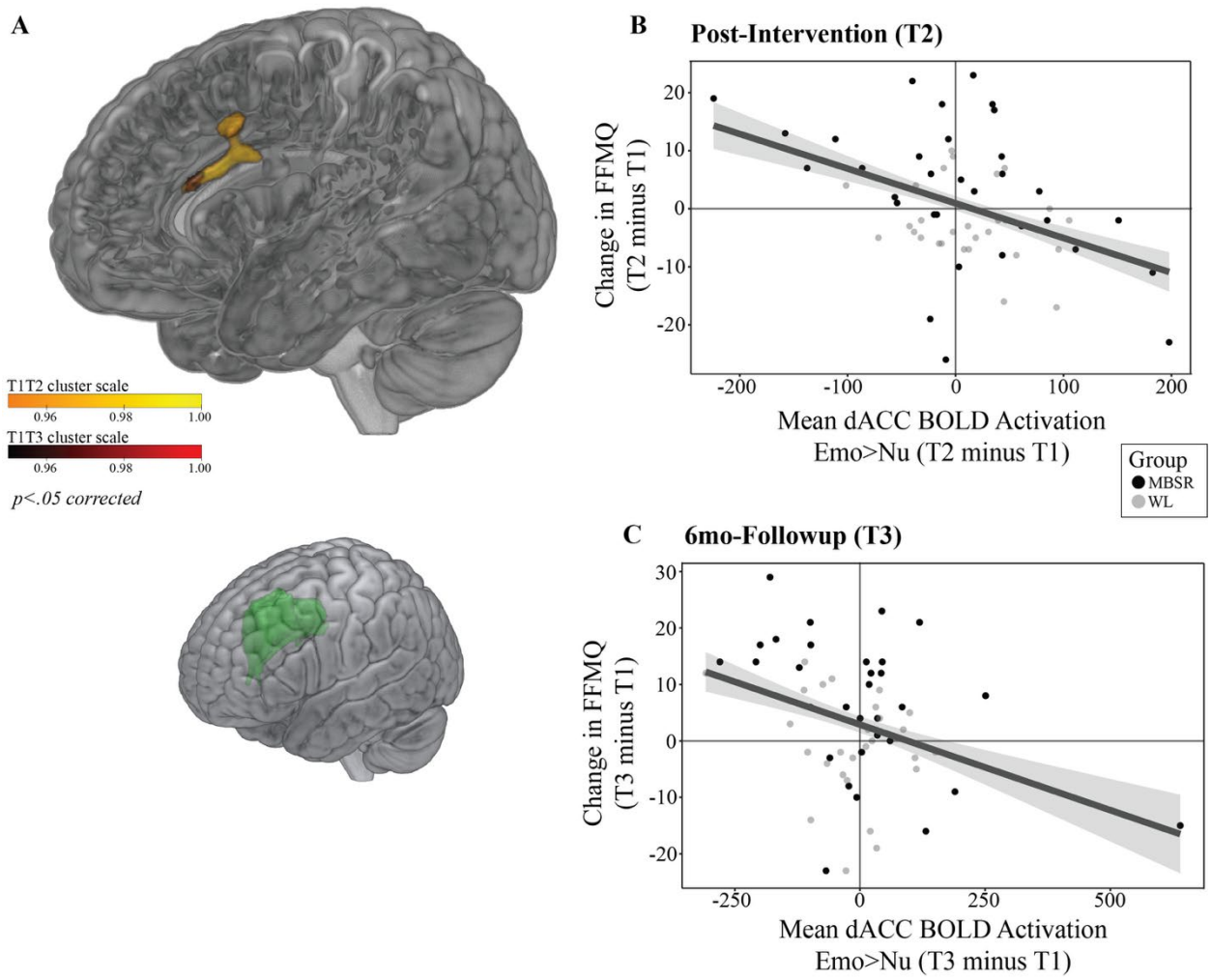

Figure 3. Increases in mindfulness (FFMQ) were associated with decreased BOLD response to emotionally-salient words in dACC region of interest analyses across MBSR and WL groups from baseline (T1) to post-intervention (T2) and 6mo followup (T3). A. Brain shows cluster of voxels where the change in BOLD response to emotionally-salient words (Emo > Nu) from baseline to follow-up was associated with increased FFMQ scores in dACC region of interest analyses. Yellow = post-intervention (T1T2). Red = 6mo follow-up (T1T3). Green = dACC region of interest search space. **B.** Scatterplot shows relationship between average change in dACC BOLD response and change in FFMQ scores across groups from baseline to post-intervention (T1T2). **C.** Scatterplot shows relationship between average change in dACC BOLD

response and change in FFMQ scores across groups from baseline to 6mo followup (T1T3). Results were unchanged with removal of extreme value. Scatterplots are for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009). FFMQ: five facet mindfulness questionnaire. dACC: dorsal anterior cingulate cortex

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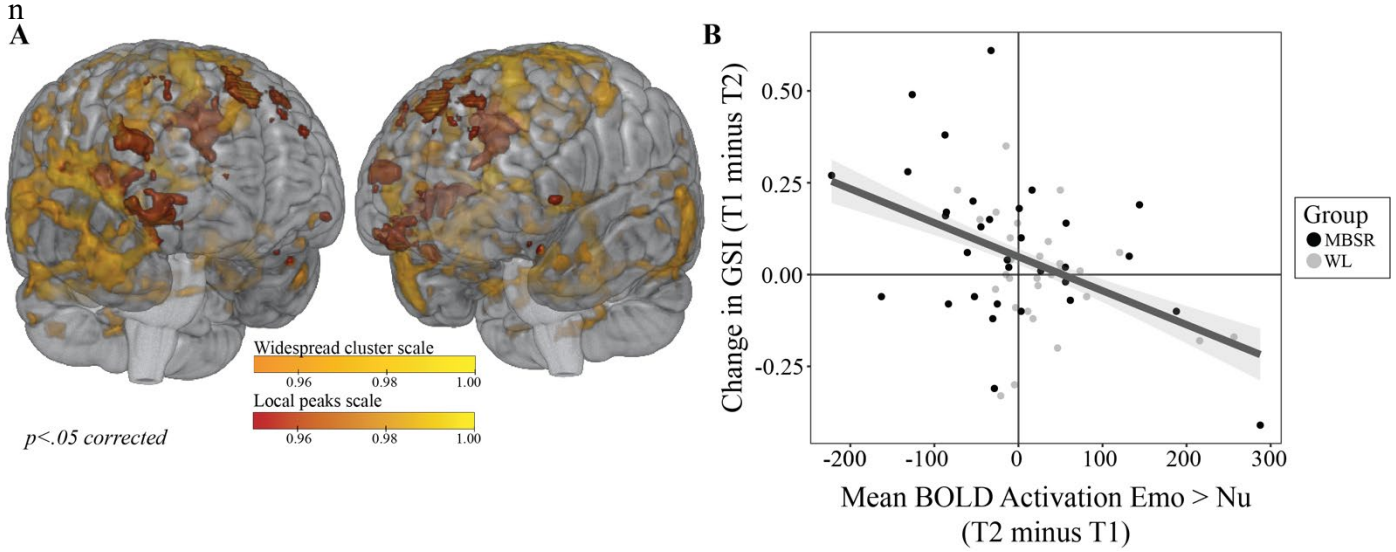

Figure 4. Decreased distress (GSI) was associated with decreased BOLD response to emotionally-salient words across MBSR and WL groups, from baseline (T1) to post-intervention (T2) in whole-brain analyses. A. Brain shows clusters of voxels where the change in BOLD response to emotionally-salient words (Emo > Nu) from baseline to follow-up was associated with decreased distress (GSI) at post-intervention (T2). Orange-yellow = widespread cluster including right IFOC, ACC, left lateral PFC, precuneus, R caudate, bilateral precentral and medial temporal gyri, PCC, postcentral gyrus, and lateral occipital cortex. Red = extracted local peaks in IFOC, frontal pole, and dACC. **B.** Scatterplot shows relationship between average change in widespread activation and change in GSI from baseline to post-intervention (T1T2). Scatterplot is for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009). GSI: global severity index. IFOC: insula-frontal-opercular cortex. ACC: anterior cingulate cortex. PFC: prefrontal cortex. PCC: posterior cingulate cortex

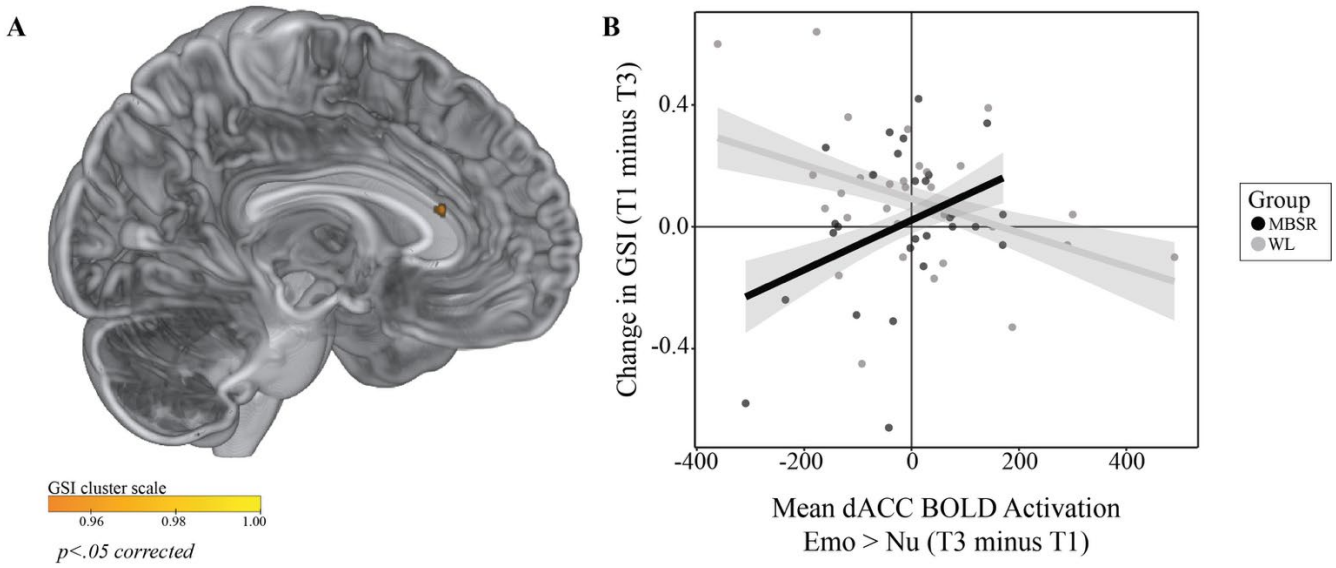

Figure 5. Decreased distress (GSI) was associated with decreased BOLD response to emotionally-salient words from baseline (T1) to 6mo followup (T3) in dACC region of interest analyses, in MBSR relative to wait-list groups. A. Brain shows cluster of voxels where the change in dACC response to emotionally-salient words (Emo > Nu) from baseline to 6mo followup was associated with decreased global symptoms (GSI) at 6mo followup (T3). **B.** Scatterplot shows group x time interaction between average change in dACC activation and change in GSI from baseline to 6mo followup (T1T3). Scatterplot is for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009). dACC: dorsal anterior cingulate cortex. GSI: global severity index

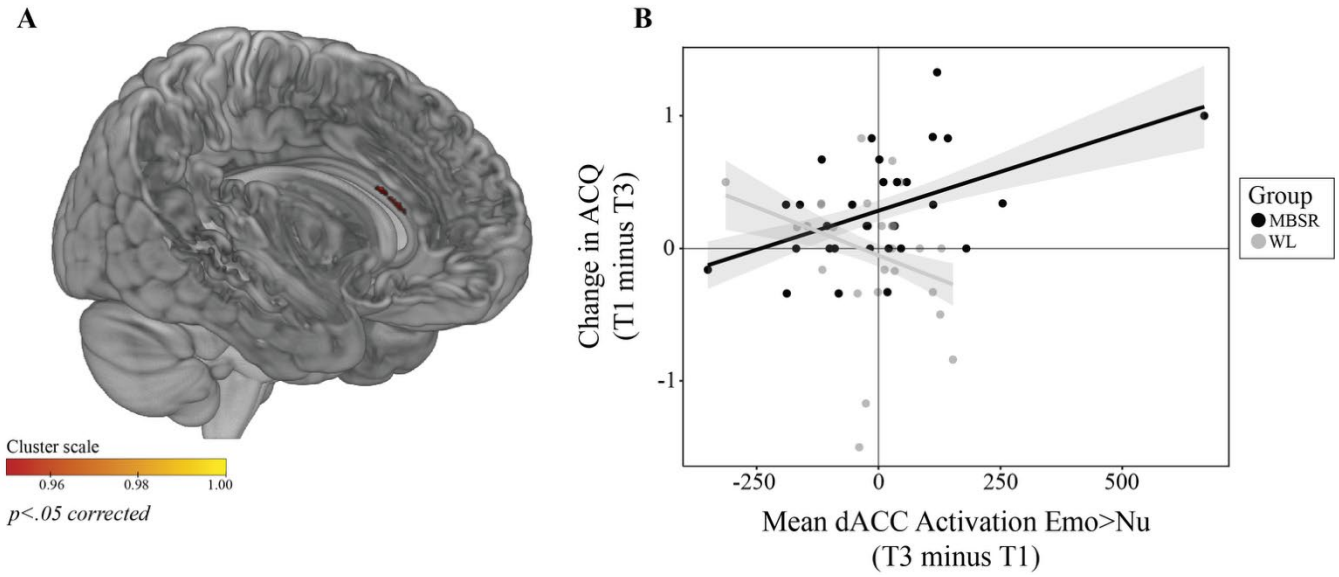

Figure 6. **MBSR-related improvements in asthma control (ACQ-6) were associated with increased BOLD response to emotionally-salient words in MBSR, relative to wait-list control, participants from baseline (T1) to 6mo followup (T3). A.** Brain shows cluster of voxels in the dACC where the change in BOLD response to emotionally-salient words (Emo > Nu) from T1 to T3 was associated with improved ACQ-6 scores in the MBSR, relative to wait-list control, group (one outlier excluded). **B.** Scatterplot shows this group x time interaction between average change in BOLD response and change in ACQ-6 scores from baseline to 6mo followup (T1T3). Results were unchanged with removal of extreme value. Scatterplot is for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009). ACQ-6: asthma control questionnaire 6-item version. dACC: dorsal anterior cingulate cortex. MBSR: mindfulness-based stress reduction

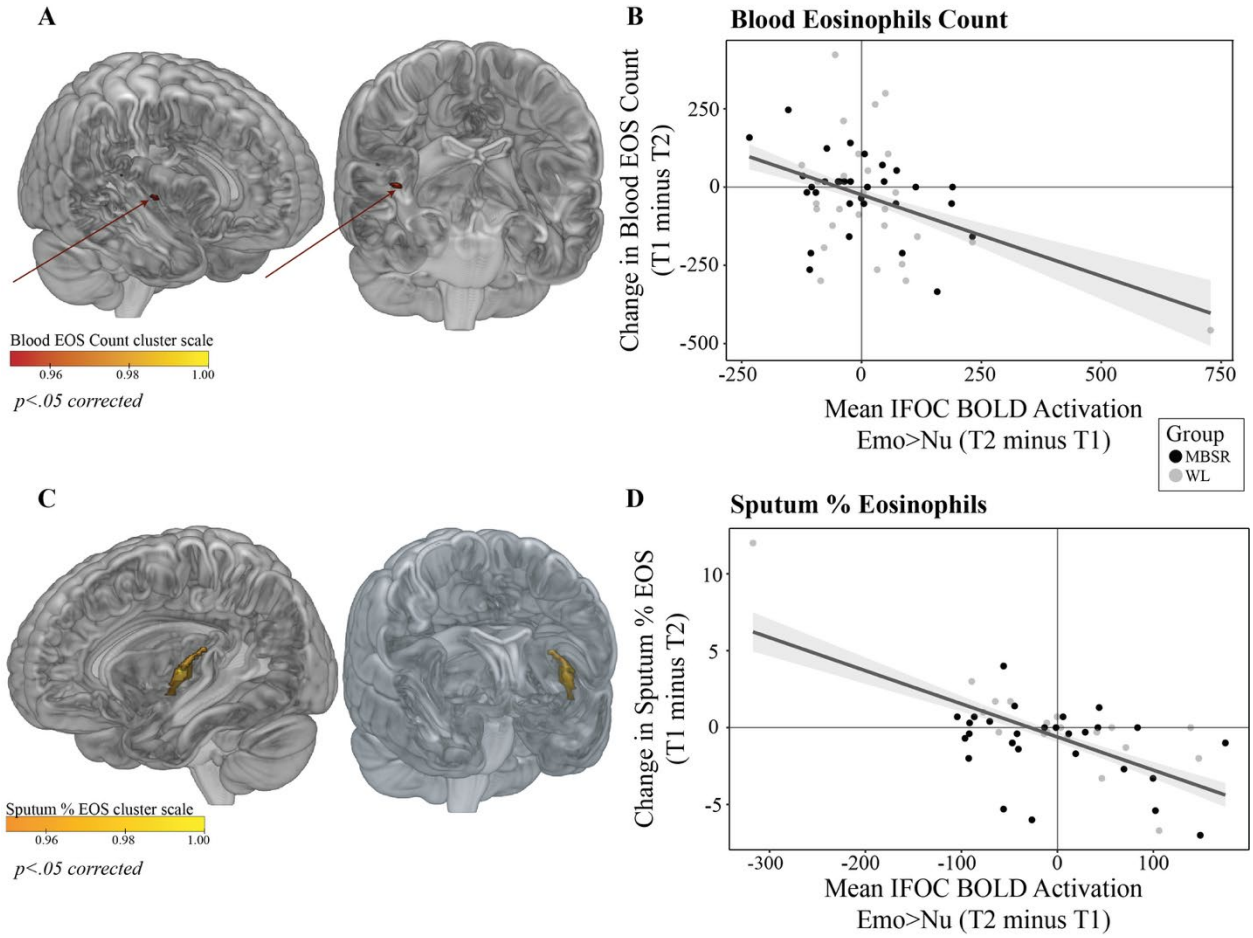

Figure 7. Decreased inflammation (blood and sputum EOS) was associated with decreased BOLD response to emotionally-salient words across both groups from baseline (T1) to post-intervention (T2) in IFOC region of interest analyses. A., C. Brains show clusters of voxels where the change in IFOC response to emotionally-salient words (Emo > Nu) from baseline to post-intervention (T2) was associated with decreased blood EOS (**A**) or decreased sputum EOS (**C**) at post-intervention (one outlier removed from each analysis). **B., D.** Scatterplots show relationship between average change in IFOC activation and change in blood EOS (**B**) or sputum EOS (**D**) from baseline to post-intervention (T1T2). Results were unchanged with removal of extreme values. Scatterplots are for visualization only; inferential statistics based on extracted cluster values would provide inflated effect sizes (Kriegeskorte et al., 2009). IFOC: insula-frontal-opercular cortex. EOS: eosinophils