Central Nervous System Signatures of Affect in Asthma: Associations with Emotion-Induced Bronchoconstriction, Airway Inflammation, and Asthma Control

Thomas Ritz\textsuperscript{1*}, Juliet L. Kroll\textsuperscript{1}, Sheenal V. Patel\textsuperscript{2}, Justin R. Chen\textsuperscript{2}, Uma S. Yezhuvath\textsuperscript{3}, Sina Aslan\textsuperscript{2,3,4}, David A. Khan\textsuperscript{2}, Amy E. Pinkham\textsuperscript{4}, David Rosenfield\textsuperscript{1} & E. Sherwood Brown\textsuperscript{2}

\textsuperscript{1}Southern Methodist University, Dallas, Texas, USA

\textsuperscript{2}The University of Texas Southwestern Medical Center, Dallas, Texas, USA

\textsuperscript{3}Advance MRI LLC, Frisco, Texas, USA

\textsuperscript{4}University of Texas at Dallas, Richardson, Texas, USA

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* Address for correspondence: Thomas Ritz, Department of Psychology, Southern Methodist University, P.O. Box 750442, Dallas, TX 75275-0442; phone: +1 214 768 3724, fax: +1 214 768 0821;

Email:tritz@smu.edu
Abstract

Background: Effects of asthma on affect have been noted for some time but little is known about associated brain processes. We therefore examined whether emotion-induced bronchoconstriction, airway inflammation, and asthma control are related to specific patterns of brain activity during processing negative affective stimuli.

Methods: Fifteen adults with asthma viewed alternating blocks of distressing film clips (negative condition), affectively neutral film clips (neutral condition) and a crosshair image (baseline condition) while undergoing blood oxygenation level dependent (BOLD) functional MRI (fMRI). Block-design fMRI analysis evaluated the BOLD response to ‘negative – baseline’ and ‘neutral – baseline’ contrasts. Airway response to these film clips was also assessed with impulse oscillometry in a separate session. Measures of airway inflammation (fractional exhaled nitric oxide, $FE_{NO}$) and asthma control (Asthma Control Questionnaire, ACQ) were additionally obtained. A whole brain voxel-based regression analysis of contrast maps was performed against respiratory resistance increase during negative and neutral films, $FE_{NO}$ and ACQ.

Results: Peak airway obstruction to negative affective stimulation was associated with stronger activation of the anterior and middle cingulate gyrus, including the dorsal anterior cingulate cortex (dACC). Stronger airway inflammation and lower asthma control were associated with reduced activation to negative stimuli in the superior frontal gyrus, middle cingulate gyrus, and supplementary motor area.

Conclusion: Activation of the dACC in negative-affect induced airway obstruction could be part of an integrated defensive response to critical environmental change. In addition, reduced frontal and limbic activation during processing of negative affect may reflect consequences of pathophysiological processes for CNS functioning.
Keywords: Asthma; affect-induced bronchoconstriction affect; functional magnetic resonance imaging; cingulate cortex; airway inflammation; respiratory resistance; asthma control

New & Noteworthy:

This functional magnetic resonance imaging study shows, for the first time, that the degree of airway constriction due to negative affective stimuli in asthma is associated with stronger response to these stimuli in the dorsal anterior and middle cingulate cortex. Asthma patients with stronger airway inflammation and reduced asthma control also show reduced activation in a number of cortical and subcortical areas relevant for affective processing and breathing control.
Affective behavior has long been an object of the scientific study of asthma. Emotions and stress are frequently identified as triggers of bronchoconstriction by patients and clinicians. Evidence from observational and laboratory manipulation studies suggests that affective processes are associated with worsening of lung function or airway inflammation. Studies using laboratory emotion-induction have shown clinically relevant bronchoconstriction in 20-40% of patients. Previously, we demonstrated that the airway response to emotional stimuli can be eliminated by cholinergic blockade and is not associated with airway inflammation or hyperreactivity, indicating that central nervous system (CNS) mediated vagal excitation as the most plausible pathway of affective influence on the airways.

A wide range of cortical and subcortical regions are instrumental in coordinating autonomic functions, such as ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex, middle frontal gyrus, anterior cingulate cortex (ACC), insula, amygdala, hippocampus, nuclei of the hypothalamus, periaqueductal gray, locus coeruleus, nucleus tractus solitarius, nucleus ambiguus and dorsal motor nucleus of the vagus. Human imaging studies have shown that activation or deactivation of many of these areas are associated with cardiac function, across behaviorally challenging situations. Vagal preganglionic neurons, mostly located in the rostral nucleus ambiguus, provide the final common pathway for vagal control of airway constriction. Retrograde transneuronal labeling studies in rats have shown that vagal preganglionic neurons receive rich descending innervation from regions involved in central control of autonomic functions in stress, including central nucleus of the amygdala, nuclei of the hypothalamus, periaqueductal gray, and nucleus tractus solitarius. However, little is known about central nervous system (CNS) processes associated with emotion-elicited airway constriction. Studies have identified discrete CNS activity associated with dyspnea or airway immune responses to cognitive processes and allergen challenge in asthma. Only one study has recently examined CNS activity during an extended psychosocial stress task using positron emission tomography and...
intermittent spirometry\(^6\)\(^7\), but the association of bronchoconstriction during distress with CNS processes was not examined.

Knowledge about affect-related neural processes in asthma could help improve disease control and management by identifying targets for behavioral or pharmacological interventions. Psychological triggers have been linked to asthma control impairments and exacerbations beyond other major trigger factors such as infections or air pollution\(^6\)\(^3\). At the same time, studies have observed that some individuals with asthma demonstrate a reduced responsiveness to emotions or stress, either in self-report\(^6\)\(^1\), facial expressiveness\(^2\)\(^8\), endocrine\(^6\), or respiratory parameters\(^2\)\(^4\). It is possible that inflammatory processes in asthma impact the CNS and thereby alter affective responsiveness. Systemic inflammation and pro-inflammatory cytokine levels are associated with anhedonia, depression, and stress\(^1\)\(^1\), although it is not known whether the same processes are at work in allergic inflammation. Alternatively, it has been speculated that patients may voluntarily reduce their emotional expression in order to avoid affect-induced symptoms\(^5\)\(^4\).

We therefore sought to study CNS signatures of affect in asthma. More specifically, we aimed to identify CNS regions associated with emotion-induced airway constriction. We expected that stronger constriction would be associated with greater activation of in limbic areas related to affective processing\(^4\)\(^3\)،\(^8\)\(^2\). Due to a lack of studies examining brain activity in emotion-induced asthma and airway constriction, we elected to cast a wider net and utilized whole brain analysis. Moreover, we hypothesized that the fraction of exhaled nitric oxide (\(\text{FENO}\)), a surrogate measure of eosinophilic airway inflammation\(^4\)\(^,5\)\(^5\),\(^7\)\(^3\), would be related to distinct alterations in CNS processing of affective stimuli, with impairments in self-reported asthma control at least partially reflecting such differences.

**Method**

_Design Overview_
Participants with asthma were scheduled for two sessions of emotion-induction with films (Figure 1). During the first impulse oscillometry (IOS) session ("IOS session"), respiratory resistance (Rrs) was measured continuously with the IOS technique during film presentation. During the second session ("fMRI Session"), identical stimulus material was presented while blood oxygen level-dependent (BOLD) fMRI was used to measure task-based signal changes.

Participants

Twenty study participants between the ages of 18-55 were recruited on a university campus and from the community. They were required to have a physician-documented diagnosis of asthma and attend two assessment sessions, approximately one week apart. Exclusion criteria for patients were treatment with oral corticosteroids in the previous 2 months, forced expiratory volume in the 1st second (FEV1) below 70% of predicted, presence or history of medical or neurological disorder that may affect brain function and the physiological systems of interest, such as angina, myocardial infarction, congestive heart failure, transient ischemic attacks, cerebrovascular accidents, uncontrolled diabetes mellitus, emphysema, or chronic obstructive pulmonary disease, history of seizures or head trauma, endocrine disorders or renal disease; presence or history of schizophrenia, bipolar disorder, or dementia; current presence of major depressive disorder or blood-injury-injection phobia; current or recent history (within 1 year) of substance-related disorders, current recreational drug use or consuming more than 20 alcoholic drinks per week; current smoking or recent history (within 6 months) of smoking (ex-smokers were not allowed to have more than 6 pack-years of smoking history); treatment with drugs having sympathetic and parasympathetic effects, anxiolytics or other psychoactive drugs; previous electroconvulsive therapy; presence of history of orthopaedic circumstances and metallic inserts contraindicated for MR scanning; pregnancy determined by urine test; and no proficiency in English.

Asthma severity was determined by NHLBI/NAEPP guidelines.\(^{50}\)
All procedures were approved by local institutional review boards and all participants provided written informed consent at the beginning of the first session. Participants were reimbursed with a total of $100 for taking part in both sessions and students could alternatively elect to receive course credit.

**Measures**

**Physiological assessments** FeNO assessments (Niox mino, Aerocrine, Sweden)\(^1\) and spirometry (Jaeger/Toennies AM2, Höchberg, Germany) for forced expiratory volume in the first second (FEV\(_1\)), expressed as percentage of the predicted norm value) were conducted at both sessions. The IOS technique (CareFusion/Jaeger, Höchberg, Germany) was used to measure airway diameter (Rrs) directly and continuously during the emotion-induction task\(^{58,75}\). Rrs at 5Hz (Rrs\(_{5Hz}\)) was extracted as an index of total respiratory resistance of the respiratory tract.

**Questionnaires.** At the beginning of the IOS session, participants completed a questionnaire battery that included an ad-hoc questionnaire on demographics, asthma history, manifestation and past treatment, the Asthma Control Test\(^{49}\), the Asthma Trigger Inventory (ATI)\(^{60}\), the Hospital Depression and Anxiety Scale (HADS)\(^{84}\), and the Medical Fears Survey (MFS)\(^{37}\). At the beginning of both sessions, the Asthma Control Questionnaire (ACQ)\(^{35}\) was also administered to characterize asthma control impairment in the past week before the session, which included six self-report items and FEV\(_1\) scored as the seventh item.

At baseline and after each stimulus block, participants indicated how they felt while viewing the films displayed during the experimental paradigm. An 11-point rating scale ranging from 0 (“not at all”) to 10 (“extremely”) were used for the measurement. These ratings included both mood (anxious, disgusted) and physical symptoms (shortness of breath, chest tightness).

**Procedures**

Questionnaire measures, FeNO, and FEV\(_1\) were captured at the beginning of each session. The emotion-induction task (details in fMRI and IOS Task sections below) was identical for both sessions.
Participants were asked to passively view the series of emotional and neutral films clips. During the first session, $R_{rs_{5Hz}}$ was measured continuously during each clip and the first 85 seconds of recovery. During the second imaging session, stimulus videos were rear-projected onto a screen and viewed by participants via a mirror mounted on the head coil. Following the neuroimaging session (runs 1 and 2: negative films, run 3: neutral films, details in fMRI and IOS Task) patients provided additional self-report on symptoms and spirometry was repeated to ensure patient safety.

**MRI Acquisition**

All images were collected using a high-field 3-Tesla (3T) Philips Achieva scanner equipped with a 32-channel head coil. Functional images were acquired using an Echo Planar Imaging (EPI) sequence with these parameters: repetition time (TR)=2000 ms, echo time (TE)=30 ms, voxel size=3.4 x 3.4 x 4.0 mm, flip angle=70°, field of view (FOV)=220 x 220 mm, matrix size=64 x 64, 39 axial slices and 266 volumes per run. A total of three runs were acquired per participant (scan time/run: 9min 5s). Five dummy volumes were discarded at the beginning of each run to allow for T1 stabilization. For anatomical reference, a high resolution anatomical (T1) images were acquired using magnetization-prepared rapid gradient-echo (MPRAGE) sequence: TR/TE/TI=8.2/3.8/873 ms, voxel size=1.0 × 1.0 × 1.0 mm, flip angle=12°; FOV=256 × 256 mm, 160 sagittal slices.

**fMRI and IOS Task**

A total of nine video clips (44s each) were shown in three blocks in both IOS and fMRI sessions. Each stimulus block had 20s of baseline condition at the beginning and at the end, where a fixation crosshair was presented. The first six films (i.e. blocks 1 and 2) were considered negative films, which contained scenes of surgery, injection and injury adopted from prior studies. This type of film stimulus was chosen because it is particularly powerful in eliciting significant distress and bronchoconstriction$^{[58,62]}$, with the average response over 5 minutes showing a medium effect size ($g=0.61-0.64$)$^{[59]}$. Consistent with the most pronounced bronchoconstriction typically occurring in the
first minute of this type of film (with a large effect size, $g=1.62$)\(^{(59)}\), the short film clips utilized in the present study were demonstrated to elicit significant airway responses in a prior study\(^{(34)}\). The last three clips (block 3, neutral films) were extracts from a geology lecture on sedimentary rock formation. Each film clip was followed by a 120s of recovery period during which a fixation crosshair was presented. Self-report symptom measures were captured at baseline and between each stimulus block.

Stimulus delivery and timing was controlled using Presentation software (Neurobehavioral Systems Inc., Albany, CA). The order of films was intentionally kept constant as the focus of the study was on individual differences in asthma control, airway inflammation and emotion-induced airway reactivity in their association with BOLD activation, rather than a general characterization of negative versus neutral film effects. Random film ordering would have potentially created unwanted variance via differential contamination from carry-over effects across participants\(^{(76)}\).

Data Analysis

Two-way repeated measures mixed model repeated measures ANOVAs compared anxiety, disgust, and dyspnea (mean of shortness of breath and chest tightness) ratings from baseline (mean of pre- and post-stimulation baseline ratings) to negative (mean of block 1 and 2 ratings) and neutral (block 3 rating) for both sessions (IOS, fMRI). A one-way model was used to analyze Rrs_{5Hz} levels during the first session, which compared means of negative films, negative film recoveries, neutral films, and neutral film recoveries, in addition to pre-and post-stimulation baselines.

Functional images were analyzed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). Initial motion correction was implemented by spatially realigning all images to the first image in the time series. Each participant’s T1 image was coregistered to their functional data, following which it was segmented into different tissue classes. These segments were used to create a custom study-specific template using the Diffeomorphic
Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) Toolbox\(^{(2)}\). DARTEL flow fields were computed for each participant: these contained the nonlinear deformation for warping individual images to the custom template. Next, an affine transformation from the custom template space to standard Montreal Neurologic Institute (MNI) space was computed. A combination of the flow fields and affine transformation parameters was used to spatially normalize the functional images (isotropic voxel size 2 x 2 x 2 mm). The resultant time series was smoothed with an isotropic Gaussian kernel having full-width at half-maximum (FWHM) 4 x 4 x 4 mm. Five of the 20 participants were excluded from further analysis either due to excessive head motion (> 2.5 mm and > 2.5 degrees, \(n=3\)) or image quality issues (\(n=2\)). For one participant, imaging data acquisition was incomplete for the first negative film block due to a processing error during the assessment. The imaging data from the remaining blocks were included for further analysis. Thus, the imaging data were analyzed for 15 subjects.

At the single subject level, statistical analysis was performed using a voxel-by-voxel general linear model (GLM)\(^{(17)}\). Task-related regressors (presentation of films) were modeled as a boxcar function convolved with a canonical hemodynamic response function (HRF). All stimulus blocks (runs) \emph{per} participant were modeled within a single design matrix. Intrinsic temporal autocorrelations in the fMRI signal were accounted for by using a first degree autoregressive AR(1) model. Low frequency MR signal drifts was removed via high-pass filtering (filter frequency 1/128.0 Hz). Following statistical analysis, beta maps were generated for the modeled conditions. Contrasts generated for each participant included (a) negative films > baseline as primary comparison, and (b) neutral films > baseline as secondary control comparisons. Additionally, for exploratory analysis we generated the contrast negative > neutral films \emph{per} participant. In our primary analyses, negative and neutral films were not directly contrasted because the film order was intentionally fixed across participants to avoid differential influences of carry-over effects across participants\(^{(76)}\).
At the group level, random effects analysis performed included one sample t-tests to establish significant BOLD activation during negative or neutral films over baseline. Further voxel-by-voxel multiple regression analyses were performed against Rs5Hz change (peak of negative films, at the group and individual level, minus baseline; measured at the IOS session), FeNO, and the ACQ (measured before the fMRI session) as predictors of the (negative films > baseline) contrast. To increase sensitivity and clinical relevance of this analysis, we focused on the negative film with the strongest bronchoconstriction, both per person and averaged over all participants. Further regression analyses were performed against affective (anxiety, disgust) and symptoms (dyspnea: mean of shortness of breath and chest tightness) ratings, ATI psychological trigger subscale, HADS anxiety and depression, and MFS subscales for blood and mutilation. For the (neutral films > baseline) control contrast, regression analysis was similarly performed against Rs5Hz change (peak neutral films minus baseline), affective and symptoms ratings. Demographic variables (age, gender) and corticosteroid usage were added to each model as covariates to control for residual variance. As the standard criterion for statistical analysis, statistical maps were generated with activations identified within a whole brain binary mask (excluding cerebellum) at a voxel-level threshold of $p<0.005$ and $k>236-356$ depending on the analysis, which corresponded to family-wise error (FWE) correction of $p$[FWE]<0.05. The FWE correction (using –ACF option) was computed by the AFNI toolbox’s 3dClustSim routine (http://afni.nimh.nih.gov).

Results

Sample characterization

Final analysis was based on $N=15$ participants who were young to middle aged, had a high level of education, and had mostly well-controlled asthma (66.7% had ACT values >19), using SABA as needed in most cases and/or inhaled corticosteroids with or without LABA (Table 1). FeNO was high on average, with values >30ppb in 53.8% of the sample.

Affective response to film stimulation
Negative films elicited a strong increase in disgust over baseline, \( t(106)=6.55, p<.001 \). Anxiety and dyspnea were also elevated, \( t(14)=2.60 \) and \( 2.51, ps=.021 \) and \( .025 \) (Figure 2 a-c). Although ratings were somewhat lower in the fMRI session as to be expected from a second administration, differences were not significant \( (ps>.103) \). No significant affective response was found for neutral films over baseline \( (ps>.816) \).

**Effect of affective stimulation on respiratory resistance**

\( R_{5Hz} \) increased from baseline to negative film stimulation, \( t(13)=3.09, p=.009 \), but not from baseline to neutral films \( (p>.120) \) (Figure 2d). Recovery periods following negative and neutral films showed markedly lower values than during films.

Across subjects, the change in \( R_{5Hz} \) to negative films was not significantly correlated with change in anxiety, disgust, or dyspnea ratings \( (p<.500) \), but \( R_{5Hz} \) change was positively correlated in tendency with the ATI psychological trigger subscale, \( r(14)=.49, p=.077 \).

**Effects of negative and neutral films on BOLD activity**

For negative films (compared to baseline), significantly increased BOLD activations were observed in multiple regions including superior frontal gyrus, precentral gyrus, thalamus, lateral geniculum body, fusiform gyrus, lingual gyrus, cuneus and occipital gyrus (Figure 3a, Table 2a). Significant deactivations were observed in the cingulate gyrus and calcarine gyrus along with bilateral clusters in the precuneus and cuneus (Table 2a).

During neutral film presentation (compared to baseline), significant BOLD activation increases were observed bilaterally within lingual gyrus along with right inferior frontal gyrus (pars opercularis), while deactivations were observed in the precuneus (Figure 3b, Table 2b). [Footnote 1]

**Association between airway responses and BOLD activation to negative films**

\( R_{5Hz} \) peak increase due to negative films in the IOS session was positively correlated with increased BOLD activation within the anterior and middle cingulate gyri - in the fMRI session. This was
found for the strongest of the six negative films at the group level (Figure 4a, Table 3a) and at the
individual level, with identical activation peak coordinates (which was not surprising, given the \( r=.96 \)
between Rrs5Hz peak increase at group and individual levels; data for individual maxima are therefore
not shown). Exploratory analysis revealed significant positive correlation between the BOLD change
within dorsal ACC against both group (cluster volume 1,072mm\(^3\); cluster peak \( x=-2, y=28, z=32 \); peak
\( t=7.4 \)) and individual level Rrs5Hz peak changes (cluster volume 992mm\(^3\); peak \( t=8 \)). This analysis was
performed at uncorrected \( p<0.005, k>160 \) mm\(^3\).

**Association of affective and symptom ratings with BOLD activation during negative films**

The anxiety response to negative film (rating change for negative films minus baseline) was not
associated with any substantial significant changes in BOLD activation across individuals. A stronger
disgust response was associated with reduced left insular activation (cluster volume 3,088 mm\(^3\); cluster
peak \( x=-26, y=20, z=-6 \); peak \( t=6.7 \)).

Stronger dyspnea responses corresponded with weaker activation in the right inferior frontal
gyrus (pars triangularis and pars opercularis) with cluster volume 2,648 mm\(^3\) (cluster peak
\( x=32, y=18, z=28 \); peak \( t=6.19 \)).

**BOLD activation during neutral films: Association with airway response and ratings of affect and
dyspnea to neutral films**

The airway response to neutral films (peak rating change during neutral films minus baseline) in
the IOS session was not significantly associated with any changes in BOLD activation to neutral films in
the fMRI session. Similarly, the regression analysis of anxiety (and dyspnea responses) during neutral
film viewing was not significantly correlated to BOLD change. There were no non-zero ratings for the
disgust response: so, this analysis could not be performed.

**Association of FE\(_{200}\) and ACQ with BOLD activation during negative films**
FENO levels at the fMRI session were associated with reduced BOLD activation in the bilateral superior frontal gyrus, anterior, posterior and middle cingulate gyri and supplementary motor area along with left precuneus (Figure 4b, Table 3b). [Footnote 2]

Lower asthma control (higher ACQ scores) was associated with reduced activation to negative affective stimulation bilaterally in the superior frontal gyrus, middle and posterior cingulate gyri, precuneus and supplementary motor area (Figure 4c, Table 3c). The experiential responses to negative films (ratings of anxiety, disgust, or dyspnea) were not significantly related to the ACQ (p>.459). [Footnote 3]

In the fMRI session, higher FENO was associated with stronger increases in anxiety, \( r(13)=.59, p=.035 \), and dyspnea, \( r(13)=.69, p=.009 \), but not disgust, \( p=.954 \).

Association of BOLD activation during negative films with psychological asthma triggers and habitual affect

An additional cluster of BOLD activation during negative films (compared to baseline) correlated positively with the ATI psychological asthma triggers subscale in the right frontal lobe with a cluster volume of 2,384 mm\(^3\); cluster peak \( x=24, y=-18, z=38 \); peak \( t=6.9 \). No significant dACC activation clusters were found for this scale. The MFS mutilation subscale also correlated positively with BOLD activation cluster in the left posterior cingulate cortex, cuneus, and precuneus (cluster volume 2,384 mm\(^3\); cluster peak \( x=0, y=-52, z=28 \); peak \( t=8.7 \), but fears related to blood were not significantly associated with the BOLD response, nor were anxious and depressed mood subscales of the HADS.

Discussion

The present study demonstrates that bronchoconstriction in response to negative affective stimuli is associated with stronger activation of cingulate cortex areas, in particular the anterior (ACC) and midcingulate cortex (MCC) regions, during viewing of the same material. Prior research has provided evidence that emotion-induced asthma is associated with exaggerated airway response to
affective challenges\textsuperscript{(64)} and that emotion-induced bronchoconstriction is most likely mediated by central vagal excitation\textsuperscript{(58)}. The present study went one step further by demonstrating, for the first time, distinct CNS correlates of emotion-induced airway reactivity. Interestingly, limbic and cortical regions had reduced BOLD activation in exposure to affective stimuli in those with elevated \( F_{E\text{NO}} \). Most strikingly, superior medial PFC, cingulate cortex, and supplementary motor cortex regions revealed a reduced activation with both higher \( F_{E\text{NO}} \) and self-report of low asthma control. This convergence of findings lends credit to the interpretation that CNS processing of affect is altered as asthma pathophysiology and control deteriorate.

In contrast to the association of asthma control and \( F_{E\text{NO}} \) with reduced BOLD activation, the airway constrictive response to emotional stimuli was found to be associated with stronger neural activation in dorsal ACC (dACC) or anterior MCC (aMCC) regions. The dACC and aMCC have been linked to a variety of affective, cognitive, and motivational processes relevant to the detection of, and response to, changes in the environment, such as error detection, conflict monitoring, cognitive control, salience, processing of discrepancies between expectancies and outcomes, pain, negative affect, and awareness of emotion\textsuperscript{(10,36,38,52,56,71,72,74)}. Most recently, the role of the dACC in top-down control of cardiovascular activity during exercise has been demonstrated by invasive recordings during deep brain stimulation surgery\textsuperscript{(21)}. Our findings of reduced BOLD activation to both airway inflammation and asthma control deficits were not in conflict with the elevated BOLD activation with stronger airway constriction, as regions associated with the respective regressors were not overlapping. This is in line with a lack of association between emotion-induced bronchoconstriction and \( F_{E\text{NO}} \) or asthma-relevant characteristics such as age of onset, severity, or medication intake\textsuperscript{(58)}. These findings converge with the observed association of dACC/MCC glucose metabolism increase during a psychosocial stressor with elevated blood eosinophils 24 h after stress\textsuperscript{(67)}. Additional findings from that study at uncorrected thresholds have also linked MCC and ventral ACC regions with IL-23A and IL-1R1 mRNA changes in sputum,
respectively, which could link psychological stress effects to an endotype of neutrophilic infiltration of the airways. These emerging findings emphasize a potential role of dACC and MCC areas for a future understanding of psychologically induced asthma.

In a recent model of adaptive control, this area mediates between reward/punishment-value and goal-directed action in response to pain and negative affect. It is therefore possible that the airway constriction to emotional stimuli is part of an integrated peripheral and CNS activation pattern in response to critical changes in the environment that are potentially threatening and therefore command a change in activity and mobilization of coping behavior. The functional significance of the, most likely vagally mediated, narrowing of the airway passages in this context is unclear. It could be speculated that it is an evolutionary vestige of an airway protective response that was aimed at reducing the exposure to penetrating objects or substances, or an adaptive adjustment that stabilizes the airway walls in anticipation of elevated airflow linked to behavioral mobilization. The area of the dACC/aMCC has also been linked to facial muscle displays of affect. In primates, the caudal ACC region has facial representations and projects to the facial nucleus that controls muscles for the expression of negative affect and cognitive effort in humans. Together with our findings these insights may add a new level of interpretation to the previously observed associations between facial muscle activation, emotion, and the airways in asthma, although such inferences from prior research remain speculative, awaiting scrutiny by mechanistic studies.

During processing of the affective material, individuals with stronger airway inflammation and poorer asthma control showed a reduced activation in brain areas relevant to voluntary drive to breathe, emotional processing, and control over affective processes. There is relatively consistent evidence that the supplementary motor area, which was among those showing reduced BOLD activation, is associated with volitional control of breathing. Various areas of the PFC have typically been associated with affective control and inhibition of fear. The reduced activation of PFC areas...
could either indicate deficiencies in affective control processes or a lack of perceived importance or salience of the affective material in the first place, thus necessitating a reduced need to cope. Our findings that regions of the ACC linked to processing stimulus salience were also less activated with higher FENO and poorer asthma control make the latter possibility more likely. The broader interference of inflammation and lower asthma control with affective processes could be due to distraction by disease-related cues, resources recruited for disease management, and/or through pathways linking airway pathophysiology, such as peripheral airway and/or systemic inflammatory processes impacting susceptible CNS regions. Our finding that FENO was also associated with these reductions in CNS activity makes it more likely that peripheral airway pathophysiology impacts susceptible CNS regions. A growing number of studies have documented associations between peripheral systemic inflammation and CNS activity, but evidence of such effects of asthma-relevant inflammatory activity is scarce. In one recent study, FENO was found to be associated with greater glucose metabolism in the MCC during psychological stress, however, this was only shown for average FENO collapsed across baseline and stress measurements.

However, it should be noted that nitric oxide (NO) has multiple peripheral and CNS functions, complicating the traditional interpretation of FENO as a pure indicator of allergic airway inflammation. In the CNS, NO acts as a neurotransmitter and also has both neuroprotective and neurotoxic functions. CNS NO modulates the action of transmitter substances such as dopamine action in the basal ganglia, thus affecting motor activity and reward processing, NMDA receptor function in the hippocampus and thus long-term potentiation in learning and memory, or in the dorsal periaqueductal gray, modulating anxiety-like behaviors. Whereas CNS modulatory and protective activity of NO is usually limited to changes at low NO concentrations, at high levels, NO is neurotoxic. High levels of airway NO typical for uncontrolled allergic asthma could thus also have neurotoxic consequences in the CNS. It is also possible that the association of FENO, which is linked to eosinophilic
infiltration of the airways, with reduced brain activity is not direct but driven by underlying third
variables. Eotaxin-1, an eosinophil chemoattractant, can cross the blood brain barrier and has been
associated with neurodegeneration\(^{(30)}\). Further research is needed detailing such potential pathways of
influence.

It could be speculated that personality, temperament, or psychological disorders such as anxiety
and depression were the cause of a reduced recruitment of affect-relevant CNS regions. Anxiety has
been linked to reduced activation of the PFC and ACC regions\(^{(47)}\) and depression has been shown to be
associated with reduced cingulate and associated salience network functioning\(^{(52)}\). In addition, anxiety
and depression are associated with deficits in asthma control\(^{(15,63)}\). However, since anxious and
depressive mood were not associated with differences in BOLD activity, the possibility that the observed
BOLD activity reductions are consequences of habitual negative mood appears less likely.

Our study was limited in that our assessments for airway constriction, inflammation, and CNS
activity only provided surrogate measures of physiological processes. More direct measures of bronchial
smooth muscle tone, eosinophil counts from bronchial lavage, or neuronal activity would have been too
invasive or intrusive for human emotion studies, or were economically not feasible. Drawing on prior
fMRI findings on brain regions linked to behavior also requires great caution\(^{(78)}\). Without further
evidence from direct recordings of neuronal activity or neural stimulation techniques (such as
transcranial magnetic stimulation), interpretations remain speculative, especially given the wide range
of behavioral states and functions that have been associated with areas like the ACC. Further limitations
were sample size and focus on a younger age group of individuals with mostly mild to moderate
persistent asthma. More severe cases of asthma or depression were excluded because of institutional
concerns over potential adverse effects of our stimulation protocol in the imaging environment. Because
the major focus of the study was on between-individual associations of emotion-induced airway
reactivity inflammation, and asthma control with BOLD activation, we also did not counterbalance
between films, thus not allowing for a direct comparison of negative versus neutral films. Our focus on differential responding within individuals with asthma also led us to omit a healthy participants group at this stage of our research. The small sample size of the group with asthma may also have affected power to detect some associations, such as those between BOLD activity and ratings of affect.

Maximizing sensitivity for detection of associations was important because our study also had to overcome potentially larger sources of error variance due to assessment of airway obstruction and BOLD activity in separate sessions. This separate assessment was a limitation in itself, necessitated through the lack of availability of fMRI-compatible technology measuring airway diameter changes continuously throughout stimulation. Pre-post stimulation spirometry would have been likely insensitive to vagally mediated acute airway obstruction by emotional stimuli. Unwanted variance added through this limitation may have reduced our sensitivity to detect BOLD activity in other CNS regions that control autonomic function and affective processing, such as PFC, insula, or periaqueductal gray. Other peripheral stress reactivity indices, such as blood pressure, also have suggested multiple associations with a large network of regions. To increase sensitivity in studying the association of Rrs and BOLD response measured in different sessions we focused on the strongest activation amongst the six negative film stimuli (at both group and individual levels), while average response to all negative films did not show an association with the dACC/aMCC region in the corrected whole-brain analysis.

Technological progress will eventually allow for combined assessment of BOLD activity and Rrs in future research.

Another limitation of our study was the lack of ventilation measurements. Changing levels of PCO₂ are known to influence BOLD signal intensity and studies of emotional stimulation, in particular those involving anxiety and fear induction, would need to control for the possibility of hyperventilation induced by stimulation procedures. Due to more frequent equipment failures we elected to omit this variable. However, we are cautiously optimistic that PCO₂ was not altered during film stimulation, as
prior studies with asthma patients did not show any effect of this type of film material on PCO$_2$\textsuperscript{(58,62)}.

Furthermore, those with blood-injection-injury phobia, who are likely to demonstrate hyperventilation during exposure to relevant stimuli\textsuperscript{(3)}, were excluded from this study.

In conclusion, our study highlights for the first time that stronger affect-induced airway constriction is linked to more activation of the dACC/aMCC region, possibly constituting part of an integrated defensive response pattern. In addition, airway inflammation and poor asthma control are associated with reduced cortical and limbic activation during processing of negative affect, which could be due to pathophysiological influences on the CNS. These findings can provide novel insights into CNS affective processing in asthma and may eventually improve our understanding of elicitors and mechanisms of emotion-induced asthma exacerbations.
Acknowledgements

This study was supported by seed funds from Dedman College at Southern Methodist University and a University Research Council Project Grant. We thank Ashton Steele, Steve Dorman, Maryam Saifi, Sharon Deol, and Julie Kim for their help in data collection, Alexandra Kulikova and Brittany Mason for their administrative help, and Karleyton Evans for advice in early stages of planning the study.
References


1. BOLD activation for negative relative to neutral films (contrast: negative > neutral) was observed in the left superior and middle frontal gyrus (cluster volume 2,664 mm³; cluster peak $x=-26,y=50,z=20$; peak $t=6.3$), while activation for the contrast negative < neutral was observed in the right lingual/parahippocampal gyrus and right fusiform/parahippocampal gyrus (4,512 mm³; $x=28,y=-46,z=-6$; peak $t=6.1$). (All activations have been thresholded at FWE $p<0.05$, cluster-corrected). Because the order of tasks was intentionally held constant for between-subjects analyses of responses to negative films (rather than comparison of within-subject change across film qualities), any interpretation of these findings would need to consider systematic carry-over effects.

2. Activation maxima for regions that showed significant negative correlation between BOLD change during negative film viewing (compared to neutral) and FENO were found in the left middle cingulate gyrus and left superior temporal gyrus (24,056 mm³; $x=-8,y=30,z=46$; peak $t=12.0$), the left inferior frontal gyrus (pars triangularis), left insula, and left parahippocampal gyrus, (5,600 mm³; $x=-38,y=24,z=2$; peak $t=11.5$), right superior and middle temporal gyrus (5,224 mm³; $x=46,y=-20,z=8$; peak $t=11.4$), left lingual gyrus (2,608 mm³; $x=-14,y=-90,z=-14$; peak $t=10.2$), left supplementary motor area, left superior medial frontal gyrus, and left superior frontal gyrus (2,608 mm³; $x=-4,y=20,z=54$; peak $t=9.5$), left superior and middle temporal gyrus (3,528 mm³; $x=6,y=28,z=40$; peak $t=8.6$), right and left superior medial frontal gyrus and right ACC (3,528 mm³; $x=6,y=28,z=40$; peak $t=8.4$), right superior temporal pole, right insula, and right inferior frontal gyrus (pars orbitalis) (4,256 mm³; $x=34,y=12,z=-24$; peak $t=7.9$), middle occipital gyrus and right lingual gyrus (2,184 mm³; $x=32,y=-82,z=2$; peak $t=7.5$), and left paracentral lobule and left inferior parietal lobule (2,184 mm³; $x=-14,y=-26,z=74$; peak $t=6.3$).
3. Activation maxima for regions that showed significant negative correlation between BOLD change during negative film viewing (compared to neutral) and ACQ score were found in left precentral gyrus and left frontal lobe (4,008 mm³; x=-32, y=-12, z=44; peak t=10.3), left superior medial frontal gyrus (8,984 mm³; x=-2, y=58, z=16; peak t=9.9), and left precuneus (2,704 mm³; x=-6, y=-52, z=50; peak t=7.6).
**Table 1. Demographic, anthropometric, and asthma-relevant variables for study participants (N=15)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (M, SD)</td>
<td>25.8 (9.7)</td>
</tr>
<tr>
<td>Sex, women (%)</td>
<td>53.3</td>
</tr>
<tr>
<td>Race, White (%)</td>
<td>73.3</td>
</tr>
<tr>
<td>Ethnicity, Hispanic (%)</td>
<td>13.3</td>
</tr>
<tr>
<td>Education, years (M, SD)</td>
<td>14.9 (2.8)</td>
</tr>
<tr>
<td>BMI (M, SD)</td>
<td>23.7 (4.2)</td>
</tr>
<tr>
<td>Asthma onset, years (M, SD)</td>
<td>8.5 (6.7)</td>
</tr>
<tr>
<td>Family history of asthma, %</td>
<td>66.7</td>
</tr>
<tr>
<td>Asthma severity, intermittent, %</td>
<td>26.7</td>
</tr>
<tr>
<td>mild persistent, %</td>
<td>46.7</td>
</tr>
<tr>
<td>moderate persistent, %</td>
<td>13.3</td>
</tr>
<tr>
<td>severe persistent, %</td>
<td>6.7</td>
</tr>
<tr>
<td>Asthma control*, well controlled, %</td>
<td>66.7</td>
</tr>
<tr>
<td>not well controlled, %</td>
<td>20.0</td>
</tr>
<tr>
<td>very poorly controlled, %</td>
<td>13.3</td>
</tr>
<tr>
<td>Medication: SABA, %</td>
<td>80.0</td>
</tr>
<tr>
<td>LABA, %</td>
<td>13.3</td>
</tr>
<tr>
<td>Inhaled corticosteroids, %</td>
<td>26.7</td>
</tr>
<tr>
<td>FEV₁ % of predicted (M, SD)</td>
<td>96.0 (10.0)</td>
</tr>
<tr>
<td>FE_NO, ppb (M, SD)</td>
<td>62.5 (61.7)</td>
</tr>
</tbody>
</table>
Severity determined for those not on maintenance medication and/or well-controlled

Abbreviations: SABA, short-acting beta-adrenergic bronchodilators; LABA, long-acting beta-adrenergic bronchodilators; FEV₁, forced expiratory volume in the 1st s; FENO, fraction of exhaled nitric oxide
### Table 2a

Regions of significant BOLD activations and deactivations for negative films (contrast: negative vs. baseline)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Cluster Size (mm³)</th>
<th>Peak T</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Fusiform gyrus</td>
<td>117,952</td>
<td>15.7</td>
<td>26</td>
<td>-74</td>
<td>-4</td>
</tr>
<tr>
<td>R. Cuneus</td>
<td>14.7</td>
<td>18</td>
<td>-94</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>L. Middle occipital gyrus</td>
<td>14.4</td>
<td>-18</td>
<td>-96</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Lateral Geniculum Body</td>
<td>3,472</td>
<td>13.2</td>
<td>24</td>
<td>-26</td>
<td>-4</td>
</tr>
<tr>
<td>R. Lingual gyrus</td>
<td>7.1</td>
<td>8</td>
<td>-34</td>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>R. Thalamus</td>
<td>6.1</td>
<td>18</td>
<td>-26</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>L. Lingual gyrus</td>
<td>7,032</td>
<td>9.0</td>
<td>-10</td>
<td>-32</td>
<td>-6</td>
</tr>
<tr>
<td>L. Thalamus</td>
<td>7.1</td>
<td>-20</td>
<td>-22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>L. Superior frontal gyrus</td>
<td>6.1</td>
<td>-16</td>
<td>12</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>L. Precentral gyrus</td>
<td>3,872</td>
<td>5.4</td>
<td>-36</td>
<td>-2</td>
<td>58</td>
</tr>
<tr>
<td>L. Precentral gyrus</td>
<td>5.4</td>
<td>-34</td>
<td>0</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td><strong>Deactivations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulate Gyrus (WM)</td>
<td>4,736</td>
<td>11.1</td>
<td>-18</td>
<td>-48</td>
<td>26</td>
</tr>
<tr>
<td>L. Precuneus</td>
<td>9.2</td>
<td>-22</td>
<td>-52</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>R. Precuneus (WM)</td>
<td>3,912</td>
<td>8.1</td>
<td>22</td>
<td>-46</td>
<td>20</td>
</tr>
<tr>
<td>L. Calcarine gyrus</td>
<td>4,072</td>
<td>5.6</td>
<td>-8</td>
<td>-76</td>
<td>16</td>
</tr>
<tr>
<td>R. Cuneus</td>
<td>5.3</td>
<td>8</td>
<td>-78</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>L. Cuneus</td>
<td>5.0</td>
<td>-8</td>
<td>-84</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Maps have been thresholded at FWE \( p < 0.05 \) (cluster-corrected). R = right; L = left, WM: White matter.
Table 2b. Regions of significant BOLD activations and deactivations for neutral films (contrast: neutral vs. baseline)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Cluster Size (mm³)</th>
<th>Peak T</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. Lingual gyrus</td>
<td>69,312</td>
<td>14.7</td>
<td>14</td>
<td>-74</td>
<td>-12</td>
</tr>
<tr>
<td>R. Lingual gyrus</td>
<td>11.8</td>
<td>8</td>
<td>-82</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>L. Lingual gyrus</td>
<td>9.8</td>
<td>-10</td>
<td>-82</td>
<td>-12</td>
<td></td>
</tr>
<tr>
<td>R. Inferior frontal gyrus (WM)</td>
<td>3,496</td>
<td>5.7</td>
<td>44</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>R. Inferior frontal gyrus (Pars Opercularis)</td>
<td>5.5</td>
<td>56</td>
<td>20</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>R. Inferior frontal gyrus (Pars Opercularis)</td>
<td>5.5</td>
<td>38</td>
<td>6</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>Deactivations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. Precuneus</td>
<td>7,752</td>
<td>8.3</td>
<td>-20</td>
<td>-48</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.3</td>
<td>20</td>
<td>-40</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Maps have been thresholded at FWE p<0.05 (cluster-corrected). R = right; L = left, WM: White matter.
Table 3a. Activation maxima for regions that showed significant positive correlation between BOLD change during negative film viewing (compared to baseline) and Rrs$_{5Hz}$ peak increase due to negative films (compared to baseline) in the IOS session ($n$=14).

<table>
<thead>
<tr>
<th>Regions of Activation</th>
<th>Cluster Size (mm$^3$)</th>
<th>Peak T</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Middle/Dorsal anterior cingulate gyrus</td>
<td>5,072</td>
<td>7.4</td>
<td>-2</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>R. Anterior cingulate gyrus</td>
<td>6.4</td>
<td>6</td>
<td>52</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>R. Anterior cingulate gyrus</td>
<td>6.3</td>
<td>8</td>
<td>40</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Note: Activations have been thresholded at FWE $p<0.05$ (cluster-corrected). R = right; L = left.
Table 3b: Activation maxima for regions that showed significant negative correlation between BOLD change during negative film viewing (compared to baseline) and $F_{ENO}$ score ($n=13$).

<table>
<thead>
<tr>
<th>Regions of Activation</th>
<th>Size (mm$^3$)</th>
<th>Peak T</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Posterior cingulate gyrus</td>
<td>2,672</td>
<td>15.8</td>
<td>6</td>
<td>-42</td>
<td>26</td>
</tr>
<tr>
<td>R. Middle cingulate gyrus</td>
<td>8.8</td>
<td>8</td>
<td>-42</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>L. Middle cingulate gyrus</td>
<td>7.2</td>
<td>-2</td>
<td>-42</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>L. Medial superior frontal gyrus</td>
<td>6,280</td>
<td>12.5</td>
<td>-2</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>L. Medial superior frontal gyrus</td>
<td>8.2</td>
<td>-8</td>
<td>32</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>R. Medial superior frontal gyrus</td>
<td>7.1</td>
<td>8</td>
<td>32</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>R. Supplementary motor area</td>
<td>2,296</td>
<td>7.3</td>
<td>8</td>
<td>-8</td>
<td>50</td>
</tr>
<tr>
<td>R. Middle cingulate gyrus</td>
<td>6.1</td>
<td>2</td>
<td>-6</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>L. Supplementary motor area</td>
<td>6.0</td>
<td>-10</td>
<td>-2</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

Note: Activations have been thresholded at FWE $p<0.05$ (cluster-corrected). R = right; L = left.
Table 3c. Activation maxima for regions that showed significant negative correlation between BOLD change during negative film viewing (compared to baseline) and ACQ score.

<table>
<thead>
<tr>
<th>Regions of Activation</th>
<th>Cluster Size (mm³)</th>
<th>Peak T</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Superior frontal gyrus</td>
<td>18,000</td>
<td>12.2</td>
<td>18</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>R. Superior frontal gyrus</td>
<td>10.1</td>
<td>22</td>
<td>36</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>L. Superior frontal gyrus</td>
<td>8.3</td>
<td>-26</td>
<td>52</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>L. Precuneus</td>
<td>7,384</td>
<td>10.4</td>
<td>-6</td>
<td>-48</td>
<td>48</td>
</tr>
<tr>
<td>R. Precuneus</td>
<td>7.3</td>
<td>4</td>
<td>-42</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>L. Middle cingulate gyrus</td>
<td>4,360</td>
<td>7.1</td>
<td>0</td>
<td>-2</td>
<td>40</td>
</tr>
<tr>
<td>R. Supplementary motor area</td>
<td>5.6</td>
<td>4</td>
<td>4</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Note: Activations have been thresholded at FWE $p < 0.05$ (cluster-corrected). R = right; L = left.
Figure Captions

**Figure 1.** Overview of the analytical sequences

**Figure 2.** Ratings of a) anxiety, b) disgust, and c) dyspnea in response to negative and neutral films in Session 1 and 2, and d) airway response (change in $R_{5Hz}$) in Session 1.

**Figure 3a,b.** Results of the main effects analysis have been overlaid on the averaged T1 template provided within SPM. Regions of significant activation are indicated in hot colors and deactivation are indicated in cool colors. (a) For the negative film (vs. baseline) contrast, regions of activation included middle and superior frontal gyri, thalamus, superior and inferior parietal lobule, middle and superior occipital gyri. Regions of significant deactivation included the calcarine gyrus. (b) For the neutral film (vs. baseline) contrast, clusters of activation included inferior frontal gyrus, middle temporal gyrus, cuneus, middle and superior occipital gyri.

**Figure 4a-c.** Selected brain areas activated in response to negative affective stimulation and associated with airway response to stimulation, airway inflammation, and asthma control. Results of the voxel based regression analysis have been overlaid on the averaged T1 template provided within SPM. (a) Regions of significant positive correlation between the airway response (increase in $R_{5Hz}$ during Session 1) and the negative (vs. baseline) contrast were within the anterior and middle cingulate gyri; (b) Regions of significant negative correlation between the negative (vs. baseline) contrast and $F_{ENO}$ were localized to the bilateral supplementary motor area (among other areas, see Table 2b) (c) Regions of significant negative correlation between the negative film (vs. baseline) contrast and Asthma Control Questionnaire scores (high score indicate lower control) were seen within the bilateral superior frontal gyrus (among other areas, see Table 2c). All results have been thresholded at FWE cluster corrected at $p<0.05$. Image orientations are in neurologic convention (L=Left).
Figure 1

Session 1: Impulse Oscillometry

Baseline 20 s +

Negative 1

44 s 120 s
film recovery film recovery

Negative 2

44 s 120 s
film recovery film recovery

Negative 3

44 s 120 s
film recovery film recovery

Negative 4

44 s 120 s
film recovery film recovery

Negative 5

44 s 120 s
film recovery film recovery

Negative 6

44 s 120 s
film recovery film recovery

Neutral 1

44 s 120 s
film recovery film recovery

Neutral 2

44 s 120 s
film recovery film recovery

Neutral 3

44 s 120 s
film recovery film recovery

Baseline 20 s +

Ratings

Session 2: Functional Magnetic Resonance Imaging

Baseline 20 s +

Negative 1

44 s 120 s
film recovery film recovery

Negative 2

44 s 120 s
film recovery film recovery

Negative 3

44 s 120 s
film recovery film recovery

Negative 4

44 s 120 s
film recovery film recovery

Negative 5

44 s 120 s
film recovery film recovery

Negative 6

44 s 120 s
film recovery film recovery

Neutral 1

44 s 120 s
film recovery film recovery

Neutral 2

44 s 120 s
film recovery film recovery

Neutral 3

44 s 120 s
film recovery film recovery

Baseline 20 s +

Ratings

Ratings

Ratings