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Full-length Article

Salience network resting state functional connectivity during airway inflammation in asthma: A feature of mental health resilience?

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ABSTRACT

Background: Inflammation is an established contributor to the pathophysiology of depression and the prevalence of depression in those with chronic inflammatory disease is two- to four-fold higher than the general population. Yet little is known about the neurobiological changes that confer depression or resilience to depression, that occur when episodes of heightened inflammation are frequent or span many years.
Methods: We used an innovative combination of longitudinal resting state functional magnetic resonance imaging coupled to segmental bronchial provocation with allergen (SBP-Ag) to assess changes in resting state functional connectivity (rsFC) of the salience network (SN) caused by an acute inflammatory exacerbation in twenty-six adults (15 female) with asthma and varying levels of depressive symptoms. Eosinophils measured in bronchoalveolar lavage fluid and blood provided an index of allergic inflammation and the Beck Depression Inventory provided an index of depressive symptoms.
Results: We found that in those with the highest symptoms of depression at baseline, SN rsFC declined most from pre- to post-SBP-Ag in the context of a robust eosinophilic response to challenge, but in those with low depressive symptoms SN rsFC was maintained or increased, even in those with the most pronounced SBP-Ag response.
Conclusions: Thus, the maintenance of SN rsFC during inflammation may be a biomarker of resilience to depression, perhaps via more effective orchestration of large-scale brain network dynamics by the SN. These findings advance our understanding of the functional role of the SN during inflammation and inform treatment recommendations for those with comorbid inflammatory disease and depression.

1. Introduction

Inflammation is now recognized as an important contributing factor to Major Depressive Disorder (MDD), in at least a subset of individuals (Beurel et al., 2020; Kiecolt-Glaser et al., 2015; Miller and Raison, 2016), and is associated with a more severe and treatment resistant depressive phenotype (Felger, 2023; Lynall et al., 2020). Inflammation that is chronic or severe has a particularly pernicious impact on depressive symptoms, evident in the two to four-fold increase in prevalence of mood disorders in those with chronic inflammatory diseases in the U.S (Barberio et al., 2021; Matcham et al., 2013; Strine et al., 2008). This growing body of evidence has spurred interest in the neural basis of the relationship between depressive symptoms and systemic inflammation, resulting in an increase in research in this domain. Yet, few studies have examined the neural basis of this relationship in populations with chronic inflammatory disease, an approach that may offer some unique insights.

Though the most common approaches to investigating the neural mechanisms that connect systemic inflammation and depressive symptoms have led to important advances in our understanding, they have

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notable limitations. Observational studies have typically examined the function of brain networks implicated in depression, comparing depressed individuals with and without elevations in biomarkers of systemic inflammation, such as C-reactive protein (CRP; (Aruldass et al., 2021; Felger et al., 2016; Yin et al., 2019)). These studies are responsible for important progress but are also inherently agnostic with respect to causality. Experimental approaches have investigated changes in engagement of these brain networks in healthy adults following acute inflammatory provocation (e.g., endotoxin administration) and relationships between these functional brain changes and changes in mood symptoms (Eisenberger et al., 2010; Harrison et al., 2015; Kullmann et al., 2013). While these experimental approaches have also moved the field forward and do enable some causal inference, they cannot account for potential differences in immune responsivity and regulation between healthy and depressed individuals (Blume et al., 2011). An elegant approach represents a combination of these designs and involves examination of brain function and mood changes that follow interferon therapy in individuals undergoing treatment for cancer or Hepatitis C infection (Dipasquale et al., 2016; Felger et al., 2013; Musselman et al., 2001; Raison et al., 2009). Nonetheless, none of these designs accommodate the long-term, cumulative exposures and physiological adaptations to these exposures that occur in the context of chronic inflammatory diseases; nor can they inform the biology of those with chronic inflammation who are not yet depressed or what factors might promote resilience to depression in this context. Here, the application of an experimental design (i.e., inflammatory provocation) in individuals with chronic inflammation may shed new light on underlying neural mechanisms, with greater ecological validity.

Asthma, a disease characterized by chronic inflammation of the airways and variable airflow obstruction, provides a particularly useful model. Like other chronic inflammatory diseases, prevalence of mood disorders is elevated in asthma (Stanescu et al., 2019). Unlike other chronic inflammatory diseases, however, symptom provocation with allergen in asthma is safe, tolerable, and recapitulates the response to natural exposures to a large extent. Importantly, asthma impacts a large and growing segment of society – approximately 10 % of U.S. adults – with notable health disparities, where Black and low-income Americans are disproportionately affected (Centers for Disease Control and Prevention, n.d.). Moreover, like depression, asthma is also more prevalent in females (Centers for Disease Control and Prevention, n.d.).

As the evidence base grows, the literature is largely converging on the salience, reward, and motor networks as primary neural mediators between systemic inflammation and depression-related symptoms (Felger, 2018; Goldsmith et al., 2022; Han and Ham, 2021; Harrison, 2017). Burrows et al. (2021), for example, demonstrated reduced salience and reward network sensitivity to reward anticipation in depressed patients with high compared to low CRP in blood. Similarly, Harrison et al. (2009) showed that deterioration in mood, consequent to typhoid vaccination-induced systemic inflammation, was associated with increased sensitivity of the salience network (SN) to emotional faces and reduced resting state functional connectivity (rsFC) within salience and reward networks. Amygdala reactivity to emotional faces was also significantly potentiated and attenuated, respectively, in response to initiation of interferon or anti-tumor necrosis factor alpha (TNF-α) treatment, in a report by Davies et al. (2021).

In our prior work in patients with asthma, the SN has also featured prominently in investigations of the neural circuits functionally impacted in response to allergen-provoked airway inflammation. In three separate studies, the insula and anterior cingulate cortex (ACC) were differentially responsive to emotional cues under inflammatory conditions (Dill-McFarland et al., 2023; Rosenkranz et al., 2012, 2005). Nonetheless, we were unable to evaluate the relationship between depressive symptoms and inflammation-related change in SN function in these previous studies. Thus, in the current study, we used a novel combination of segmental bronchial provocation with allergen (SBP-Ag) and fMRI BOLD measures of resting state functional connectivity (rsFC), to evaluate the impact of airway inflammation on network level brain function, in a sample of patients with asthma that varied in symptoms of depression. SBP-Ag is an innovative approach to initiating airway inflammation that uses bronchoscopy to insert allergen into a single airway segment, provoking a robust inflammatory response in that segment without reducing lung function (Denlinger et al., 2013; Kelly et al., 2017). We examined changes in connectivity within the SN at rest, during this heightened inflammatory state compared to a stable baseline state, and whether changes in rsFC were related to depressive symptoms.

There is a small but growing body of work reporting the impact of inflammation on rsFC (Goldsmith et al., 2022). This literature tends to focus on depressed individuals who vary in presence or magnitude of inflammation and is generally consistent in showing a decrease in rsFC, across a range of functional brain networks. Theoretically consistent, a parallel literature addressing changes in rsFC following psychological interventions, when efficacious, generally shows increases in post-treatment rsFC, across a variety of brain networks and interventions (Dunlop et al., 2023; Laubacher et al., 2024; Sezer et al., 2022). It is noteworthy, however, that not all individuals with elevations in inflammation are depressed. Comparatively little is known about the impact of inflammation on rsFC across a range of depressive symptoms. Moreover, few studies have examined the impact of inflammation on rsFC within the SN, a network centrally implicated in both immune and emotional dysregulation, as well as their interaction. A better understanding of the dynamics of the SN at rest, in response to inflammatory challenge in a sample of patients with long-standing inflammation, may clarify its functional role during inflammation and the relevance of this role to depression. Therefore, in the current study our analyses were focused on the dynamics of rsFC in the SN.

2. Materials and methods

2.1. Participants

Twenty-six participants (age 19–41 years; 15 F; 22 White, 2 Black, 2 multi-racial) with physician-diagnosed asthma and no other major health problems were recruited. Participants had had an asthma diagnosis for 16.8 years on average (range 3–33 years). Eligible participants had no more than mild reductions in baseline lung function (forced expiratory volume in 1 sec. (FEV_1) $\geq$ 70 %), evidence of clinically significant reversibility in airway obstruction (12 % reversibility or PC_{20} response to methacholine $\leq$16.0 mg/ml), used no corticosteroids for $\geq$one month prior to enrollment, and showed clinically significant reductions in lung function ($\geq$20 % decrease in FEV_1) in response to allergen during a screening whole-lung challenge. For participants taking psychotropic medication, dose of medication was stable for at least a month prior to study visits.

2.2. Study design

Each participant was assessed immediately before and 48 h after airway inflammation was induced with segmental bronchoprovocation with allergen (SBP-Ag); timed to capture the peak airway inflammatory response. Pre- and post-SBP-Ag assessments included participant reported psychological symptoms, resting state functional magnetic resonance imaging (rsfMRI), and bronchoalveolar lavage (BAL) fluid and blood collection to assess inflammation. Participants did not use bronchodilator medication for at least 6 h before assessments. All study activities were approved by the University of Wisconsin-Madison Institutional Review Board and all participants provided written informed consent.

2.3. Procedures

2.3.1. Segmental bronchoprovocation with allergen (SBP-Ag)

Bronchoscopies were performed under conscious sedation using

intramuscular glycopyrolate (0.2 mg) and midazolam (0.5–2.0 mg). Nasopharyngeal anesthesia was achieved with topical lidocaine (1 % solution, lidocaine gel, lidocaine spray). Prior to bronchoscope insertion, participants received 180 mcg of albuterol to prevent bronchospasm and Afrin nasal spray to reduce nasal congestion. A fiberoptic bronchoscope was passed into a pulmonary segment, where 1 % lidocaine solution (<600 mg or <9 mg/kg) was instilled to prevent cough. The target bronchopulmonary segment underwent lavage with 4 × 40 ml of 0.9 % NaCl immediately before introducing allergen extract. The concentration and type of extract (house dust mite, cat dander, or ragweed) was determined for each participant to match 1 % of the dose required for a 20 % reduction in FEV_1 during the screening whole-lung allergen challenge.

2.3.2. Inflammatory markers

The population of inflammatory cells in the airway was assessed using BAL fluid collected at baseline and 48 h post-SBP-Ag. Cell differentials from BAL fluid were determined by counting 1000 cells on two cytospin preparations stained with Wright-Giemsa-based Hema-3 (ThermoFisher, Pittsburgh, PA). Changes in absolute blood eosinophil count and serum IL-6 concentration were used to characterize the systemic inflammatory response. Blood eosinophils were enumerated by hemacytometer using phyloxin staining. Serum IL-6 was measured using a high-sensitivity IL-6 ELISA kit (R&D Systems, Minneapolis, MN, USA). Post-SBP-Ag minus pre-SBP-Ag difference scores in the % eosinophils of total cells counted in BAL fluid, absolute number of eosinophils, and serum-IL-6 concentration were used to index the airway and systemic inflammatory responses, respectively.

2.3.3. Psychological symptoms

Depressive symptoms were assessed using the Beck Depression Inventory (BDI; (Beck and Ward, 1961)), a 21-item self-report inventory shown to have strong split-half reliability (Pearson r = 0.86, Spearman-Brown = 0.93). Item 9, assessing suicidality, was removed, resulting in a 20-item measure. Participants chose which statement best described their symptoms over the past two weeks on a scale of 0 to 3 (none, mild, moderate, severe). A total score of 0–13 indicates minimal depression, 14–19 mild depression, 20–28 moderate depression, and a score over 29 indicates severe depression.

The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was used to assess positive and negative dimensions of affect, where participants rated 20 mood states on a 1–5 scale (1 = none, 5 = extremely) and items loading on positive and negative affect scores (10 items each), respectively, are summed for a total score of each valence ranging from 10 to 50. These scales are reliable, have good internal consistency and strong convergent and discriminative validity.

2.3.4. MRI acquisition

Structural and functional MRI data were collected prior to each bronchoscopy on a GE 750 3.0 Tesla MRI scanner with a 32-channel head coil. Anatomical scans consisted of a high-resolution 3D T1-weighted inversion recovery fast gradient echo image (450 ms inversion time; 256 × 256 in-plane resolution; 256 mm field of view (FOV); 192 × 1.0 mm axial slices). 12-minute rsfMRI scans were acquired using a gradient echo-planar imaging (EPI) sequence (360 volumes; repetition time (TR)/echo time (TE)/Flip, 2000/20 ms/75°; 224 mm FOV; 64 × 64 matrix; 3.5 × 3.5 mm in-plane resolution; 44 interleaved sagittal slices; 3 mm slice thickness with 0.5 mm gap).

2.3.5. MRI preprocessing

Structural MRI scans were reviewed by a neuroradiologist for neurological abnormalities; none were found. Functional images were processed using a combination of AFNI (Cox, 1996;version 17.3) and FMRI Expert Analysis Tool Version 6.00, part of FMRIB's Software Library (FSL; Smith et al., 2004), including the following steps: removal of the first four volumes, motion correction using MCFLIRT (Jenkinson et al., 2002), BET brain extraction (Smith, 2002), and co-registration of the participant's functional data with their anatomical image using the boundary-based registration approach (Greve and Fischl, 2009). A 12 degrees-of-freedom affine transformation using FLIRT (Jenkinson et al., 2002) was followed by FNIRT (Andersson et al., 2007) nonlinear transformation to register each participant's functional data to a standard template in Montreal Neurological Institute (MNI) 152 space. Images were segmented into white matter, gray matter, and cerebrospinal fluid with FAST (Zhang et al., 2001) to generate masks that were subsequently eroded using a 3x3x3 voxel kernel. The average time series from white matter and cerebrospinal fluid masks, their derivatives, and six motion regressors were included as nuisance regressors in AFNI's 3dDeconvolve and high-motion time points were censored (>0.2 mm framewise displacement; Power et al., 2014). Participants were excluded from analysis if they had >50 % of TRs censored for motion, resulting in <6 min of quality data. Images were smoothed using a 5-mm full-width half-maximum Gaussian kernel.

2.3.6. Resting state functional connectivity (rsFC) analysis

To investigate rsFC changes among core nodes of the SN, five regions of interest (ROIs) were selected as seeds and targets: the bilateral amygdalae (amyg), bilateral anterior insulae (AIC), and the dorsal anterior cingulate (dACC). Amyg ROIs were defined using a 50 % probability threshold from the Harvard-Oxford Structural Atlas (Craddock et al., 2012). AIC ROIs were defined as the combined dorsal and ventral anterior insula subregions reported by Deen et al. (2011). A dACC ROI was defined using the dorsal cingulate region identified by Shackman et al. (2011).

For each ROI, four types of analyses were conducted: 1) examining the pre-challenge relationship between rsFC and either baseline inflammatory biomarkers or baseline depression scores; 2) examining average change in rsFC from pre-to-post SBP-Ag, 3) examining the relationship between change in rsFC and change in psychological measures that were responsive to SBP-Ag challenge, 4) examining the relationship between change in rsFC and change in inflammatory biomarkers, baseline depression scores, and their interaction. For change analyses, pre-to-post SBP-Ag change score maps were computed by subtracting the pre-challenge rsFC map from the post-challenge rsFC map. All variables modeled were on a continuous scale. Analyses were performed using FSL's Randomise (Winkler et al., 2014) and thresholded at $p < 0.05$, controlling for inflation of type I error using threshold-free cluster enhancement (TFCE) with familywise error correction (Winkler et al., 2014).

2.3.7. Statistical methods

Two participants were excluded from neuroimaging analyses for excessive motion or poor registration during fMRI preprocessing and two participants were excluded from analyses involving BAL fluid due to poor quality of the BAL fluid sample. Thus, the final sample for each analysis ranged from 22 to 26 participants (59 % female).

Descriptive statistics and relationships among inflammatory biomarkers and baseline depression scores were evaluated using the stats package in R (Chambers, 1992; R Core Team, 2021). To visualize results and to assess for model outliers, the average Fisher-Z transformed timeseries correlation between the seed ROI and the cluster of voxels in the target regions with significant group-level effects was extracted for each participant. Linear regression model outliers were identified using Cook's D and excluded with a cutoff threshold of 20 % of the F distribution. Results with and without outliers were consistent unless otherwise specified.

3. Results

3.1. Descriptive statistics of psychological measures and inflammatory biomarkers at baseline

Participants had mean scores at baseline on the psychological assessments as follows: BDI: 8.84 ± 5.37, PANAS Positive Affect: 26.96 ± 7.80; PANAS Negative Affect: 14.48 ± 4.95. Mean % BAL EOS and number of blood EOS at baseline were 0.71 ± 0.72 and 11.31 ± 6.14, respectively, and mean baseline serum IL-6 concentration was 1.20 ± 0.88 pg/ml (Table 1).

3.2. Pre-challenge relationship between SN rsFC, inflammatory biomarkers, and depression scores

At baseline, BDI scores were not correlated with % BAL eosinophils, number of blood eosinophils or serum IL-6 concentration ($r(24) = -0.06$, $p = 0.79$; $r(26) = -0.19$, $p = 0.36$; $r(24) = 0.13$, $p = 0.55$). Higher % of BAL eosinophils was associated with lower baseline rsFC between the right amyg and left AIC. Similarly, a greater number of blood EOS was associated with lower rsFC between the left amyg and left AIC, as well as between the left amgy and dACC (Table 2). No relationships between pre-challenge serum IL-6 concentration and rsFC were detected. No relationships between baseline BDI scores and rsFC among the SN ROIs were detected.

3.3. Inflammatory response to SBP-Ag

Consistent with a robust induction of inflammation in the airway, the % eosinophils in BAL fluid significantly increased from before to 48-hours post-SBP-Ag ($t(23) = -5.29$, $p < 0.001$). At 48-hours post-SBP-Ag, there was also an increase in the number of blood eosinophils ($t(25) = -3.86$, $p < 0.001$) and in the concentration of serum IL-6 ($t(23) = -2.24$, $p = 0.034$), indicating induction of systemic inflammation. However, challenge-related changes in BAL and blood inflammatory markers were unrelated to one another. In contrast to measures of inflammation, there was no overall change in lung function at either 4 h post-SBP-Ag ($t(25) = 0.14$, $p = 0.889$) or at 48 h post-SBP-Ag ($t(25) = 0.30$, $p = 0.770$).

Table 1
Airway inflammation was induced in 26 adults with asthma with segmental bronchoprovocation (SBP-Ag) challenge using individualized allergen extract. Bronchoalveolar lavage fluid (BAL) and blood were collected to assess inflammation at baseline and 48 h post-challenge. The Beck Depression Inventory (BDI) and Positive and Negative Affect Schedule (PANAS) were used to assess baseline and challenge-related changes in depression, positive (PA) and negative (NA) affect. EOS = Eosinophils; IL = interleukin.

		Pre-challenge			Post-challenge		
	N	Sample mean	Min	Max	Sample mean	Min	Max
Age	26	26.11 ± 6.40 years	19	41			
Asthma duration	26	16.8 years	3	33			
BDI	25	8.84 ± 5.37	2	21	9.16 ± 5.57	2	24
PANAS PA	25	26.96 ± 7.80	15	46	24.64 ± 8.43	12	49
PANAS NA	25	14.48 ± 4.95	10	27	15.48 ± 4.85	10	29
% EOS in BAL fluid	24	0.71 ± 0.72 %	0 %	2 %	31.24 ± 28.45 %	0.3 %	84 %
Blood eosinophil count	26	11.31 ± 6.14	1	24	16.08 ± 6.22	4	31
Blood IL-6 (pg/ml)	24	1.20 ± 0.88	0.21	4.07	1.61 ± 0.93	0.30	3.81

3.4. SBP-Ag challenge-induced changes in brain and behavior

BDI scores did not change in response to SBP-Ag (BDI: $t(24) = -0.55$, $p = 0.60$). There was likewise no change in negative affect ($t(24) = 1.07$, $p = 0.295$), whereas positive affect scores significantly decreased ($t(24) = -2.34$, $p = 0.028$).

BDI score before SBP-Ag was not correlated with the change in percentage of BAL eosinophils from pre- to post-challenge ($r(24) = -0.07$, $p = 0.77$), nor with the change in blood eosinophil number ($r(26) = -0.13$, $p = 0.52$) or serum IL-6 concentration ($r(24) = 0.13$, $p = 0.54$). Likewise, the challenge-related decrease in positive affect was not correlated with change in percentage of BAL eosinophils ($r(23) = 0.12$, $p = 0.58$), change in blood eosinophil number ($r(25) = 0.04$, $p = 0.85$), or with change in serum IL-6 ($r(23) = 0.05$, $p = 0.82$). No overall change in SN rsFC was detected from pre- to post-SBP-Ag between *a priori*-specified seeds-target pairs.

3.5. Depression scores moderate the relationship between SN rsFC and inflammatory response to SBP-Ag

We examined the relationship between change in SN rsFC and change in percentage of BAL eosinophils in response to SBP-Ag, as well as how that relationship was moderated by depression scores (Table 3). The magnitude of increase in BAL eosinophils was correlated with the magnitude of decrease in rsFC between the right amyg and the right AIC. Moreover, this effect was moderated by baseline BDI score, such that the negative relationship between BAL eosinophils and rsFC was strongest in participants with the highest depression scores (Fig. 1, Table 3). When two model outliers were removed, the interaction persisted, although the main effect was no longer significant.

Baseline depression score also predicted the pre- to post-challenge change in rsFC between the right AIC seed and a cluster in dACC, such that people with the highest BDI scores showed the largest decrease in connectivity following challenge (Table 3). When one model outlier was removed, this instead became an interaction, where a challenge-related decrease in SN rsFC, in those with a robust eosinophil response, was most pronounced in those with the highest baseline depression symptoms (Fig. 2). No other relationships between change in rsFC, change in BAL eosinophils, and baseline depression scores were detected in the seed-target pairs tested.

We further examined the relationship between change in SN rsFC and change in blood eosinophil count in response to SBP-Ag, as well as how that relationship was moderated by baseline BDI scores (Table 3). While there was no zero-order relationship between change in blood eosinophils and change in rsFC in these analyses, an interaction with baseline depression score was found, analogous to that observed for BAL EOS. In individuals with high baseline BDI scores, magnitude of increase in blood eosinophils was associated with the magnitude of decrease in rsFC between the left and right insula (Fig. 3), as well as between the left insula and the dACC (Fig. 4). Those with low BDI scores who responded to the allergen challenge did not show a reduction in connectivity between these regions. In both analyses, the interaction remained when one model outlier was removed.

We ran analogous tests examining the relationship between change in SN rsFC and change in serum IL-6 in response to SBP-Ag, as well as the moderating effect of baseline depressive symptoms on this relationship. No significant correlations or interactions were found.

4. Discussion

In the present study, the magnitude of the airway inflammatory response to segmental allergen challenge in patients with asthma was associated with the magnitude of decrease in the connectivity between the right amygdala and right anterior insula – components of the SN – at rest. This relationship was moderated by baseline symptoms of depression, such that individuals reporting more depressive symptoms showed

Table 2
Pre-challenge relationships between inflammation and SN rsFC. Voxel-wise analysis between SN regions of interest and target ROIs was used to identify associations between rsFC and inflammatory biomarkers in bronchoalveolar lavage (BAL) fluid and blood. Results were family-wise error corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$).

Seed	Target	Regressor	Correlation direction	Cluster size (voxels)	Peak voxel t-stat	Peak coordinates MNI (x, y, z)
R amygdala	L AIC	BAL EOS	Negative	18	4.30	−40, 2, −10
L amygdala	L AIC	Blood EOS	Negative	5	4.48	−34, 22, −2
L amygdala	dACC	Blood EOS	Negative	3	4.76	−2, 10, 32

Table 3
Depression scores moderate the relationship between SN rsFC change and inflammatory response to segmental bronchoprovocation with allergen (SBP-Ag). Change in rsFC from pre- to post- SBP-Ag was calculated among 5 regions of interest from the salience network (SN). Voxel-wise analysis within the target ROI was used to identify regions where change in rsFC was related to change in inflammatory biomarkers, baseline Beck Depression Inventory (BDI) scores, and their interaction. Results were family-wise error corrected with threshold-free cluster enhancement (TFCE; $p < 0.05$). BAL = bronchoalveolar lavage; EOS = Eosinophils; R AIC = right anterior insula; dACC = dorsal anterior cingulate cortex. *This analysis dropped one model outlier from analysis above.

Seed	Target	Regressor	Correlation direction	Cluster size (voxels)	Peak voxel t-stat	Peak coordinates MNI (x, y, z)
R amygdala	R AIC	BAL EOS	Negative	9	3.87	40, 14, −12
				5	4.19	44, 0, −4
		BDI	Negative	31	4.52	42, 4, 4
				18	5.17	38, 8, −12
		BAL EOS*BDI	Negative	40	3.61	40, 16, −6
R AIC	dACC	BDI	Negative	15	5.22	2, 22, 40
R AIC*	dACC	BAL EOS*BDI	Negative	9	5.75	10, 14, 40
L AIC	R AIC	Blood EOS*BDI	Negative	60	4.76	38, 22, −2
		BDI	Negative	70	3.85	40,4,-12
				28	4.39	34, 20, −6
				5	2.92	44, 6, 2
L AIC	dACC	Blood EOS*BDI	Negative	17	4.99	0, −14, 28
				17	3.86	4, −2, 44
				8	4.56	−4, 12, 24

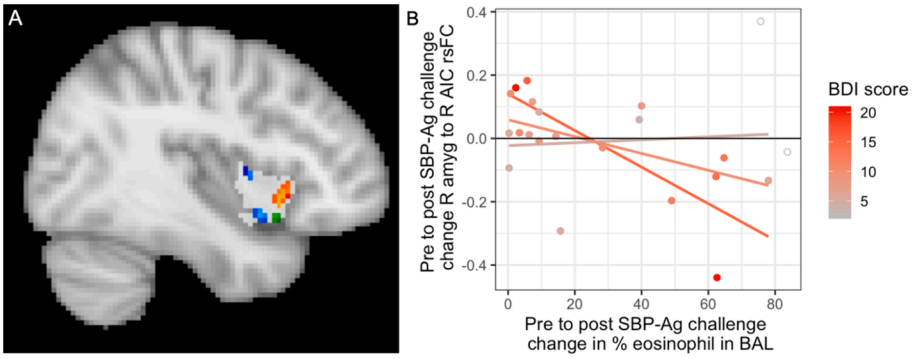

Fig. 1. Baseline depression scores moderate the relationship between BAL eosinophil change and right amygdala to right anterior insula (R AIC) rsFc in response to SBP-Ag challenge. A) Voxels where there was a significant relationship between change in rsFC between the right amygdala seed and the R AIC target region of interest pre- to post-segmental bronchoprovocation with allergen (SBP-Ag) and 1) change in percentage of eosinophil (EOS) in bronchoalveolar lavage (green), 2) baseline Beck Depression Inventory (BDI) scores (blue), and their interaction (red). R AIC target search space is highlighted in gray. Displayed at MNI x = 40. B) Average rsFC was extracted for each subject between the right amygdala seed and the cluster where group-level BDI × EOS interaction was found (red A, 40 voxels, Table 1). While baseline BDI score in the analysis testing the interaction between change in BAL eosinophils and baseline depressive symptoms on change in SN rsFC was statistically modeled as a continuous variable, for visualization purposes, this relationship is displayed at three levels of BDI score: BDI = 3.8 (1 SD below mean), BDI = 9.7 (mean BDI), and BDI = 14.2 (1 SD above the mean). Two model outliers are depicted in open circles and were included in the analysis to generate the cluster in A but not the estimation of change score relationships in B. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a greater reduction in connectivity following challenge, whereas those with no or minimal depressive symptoms did not show this decrease in connectivity. Analogous interaction effects were observed between the magnitude of the eosinophilic response to challenge, both in blood and in the lungs, and depressive symptoms on resting state connectivity between the AIC and dACC and between the right and left AIC. These results corroborate and clarify those of previous studies and extend them by contextualizing these relationships in a sample of patients with persistently dysregulated inflammation spanning 3.4–33.0 years, during an acute inflammatory exacerbation.

Reduced connectivity within the SN predicts more severe psychological symptoms *trans*-diagnostically and is associated with anhedonia, negative bias, threat dysregulation, difficulties with attention/cognitive control, and poor satisfaction with life (Goldstein-Piekarski et al., 2022). In depression specifically, the SN also tends to show reduced connectivity among its own nodes (Peng et al., 2020; Young et al., 2023) and with nodes of other networks (Ambrosi et al., 2017; Kaiser et al., 2015; Yu et al., 2020). Only a few studies have investigated changes in rsFC in response to acute inflammatory provocation, the results of which are similar to those found in depressed individuals. States of acute inflammation, in otherwise healthy volunteers, are associated with directionally mixed patterns of change in rsFC across

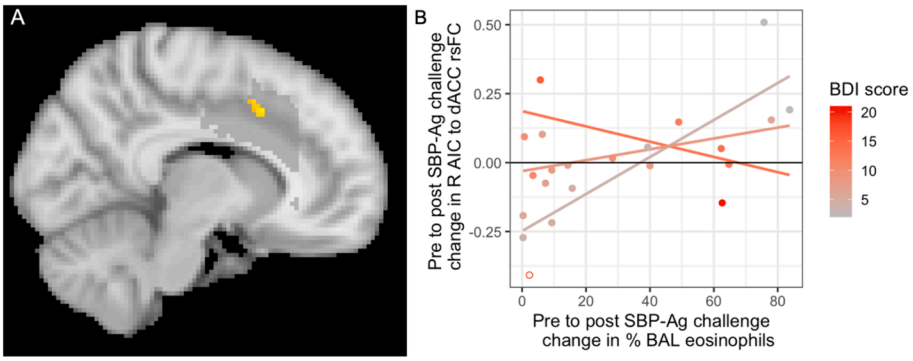

Fig. 2. Baseline depression scores moderate the relationship between BAL eosinophil change and R AIC to right dACC rsFC in response to SBP-Ag challenge. A) Voxels within the dACC target region of interest (darkened gray) where pre- to post-segmental bronchoprovocation with allergen (SBP-Ag) change in rsFC with the right anterior insula (R AI) seed showed a relationship with change in the percentage of BAL eosinophils that was moderated by pre-challenge BDI scores. Displayed at MNI x = 10. B) Average rsFC between R AIC seed and dACC cluster (A) was extracted for each subject. The interaction between change in BAL eosinophils and depression scores was statistically modeled with BDI as a continuous variable. For visualization purposes only, the strength of the relationship between change in BAL eosinophils and change in rsFC between these two regions was estimated at three levels of BDI score: BDI = 3.8 (1 SD below mean), BDI = 9.7 (mean BDI), and BDI = 14.2 (1 SD above the mean). One model outlier was not included in Fig. 2 analyses, depicted as an open circle.

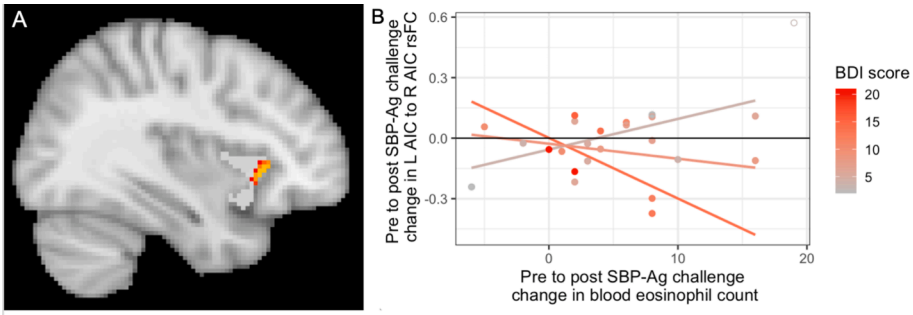

Fig. 3. Baseline depression scores moderate the relationship between blood eosinophil change and left anterior insula (L AIC) to right anterior insula (R AIC) rsFC in response to SBP-Ag challenge. A) Voxels in red indicate a significant interaction between change in blood eosinophil count and baseline Beck Depression Inventory (BDI) scores on change in rsFC between the right and left AIC. R AIC search space is highlighted in gray. Displayed at MNI x = 35. B) Average rsFC was extracted for each subject between the left AIC seed and the cluster depicted in A. The interaction between change in blood eosinophils and depression scores was statistically modeled with BDI as a continuous variable. For visualization purposes only, the strength of the relationship between change in blood eosinophils and change in rsFC between these two regions was estimated at three levels of BDI score: BDI = 3.38 (1 SD below mean), BDI = 8.91 (mean BDI), and BDI = 13.94 (1 SD above the mean). The exclusion of one model outlier, depicted in an open circle, did not change the pattern of results. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

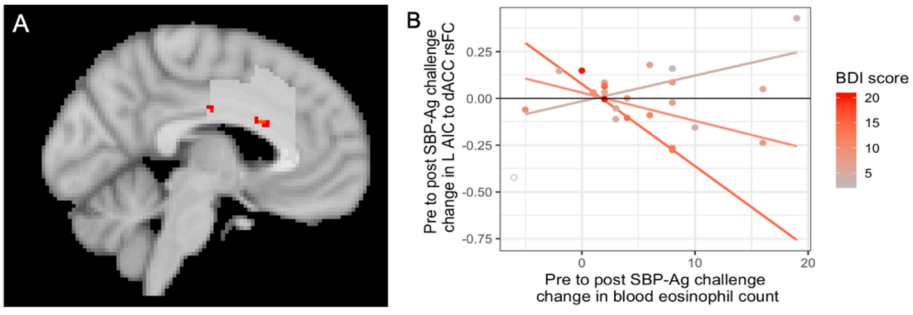

Fig. 4. Baseline depression scores moderate the relationship between blood eosinophil change and left anterior insula (L AIC) to dACC rsFC in response to SBP-Ag challenge. A) Voxels in red indicate a significant interaction between change in blood eosinophil count and baseline Beck Depression Inventory (BDI) scores on change in rsFC between the left AIC and dACC. dACC search space is highlighted in gray. Displayed at MNI x = −4. B) Average rsFC was extracted for each subject between the right amygdala seed and the clusters depicted in A. The interaction between change in blood eosinophils and depression scores was statistically modeled with BDI as a continuous variable. For visualization purposes only, the strength of the relationship between change in blood eosinophils and change in rsFC between these two regions was estimated at three levels of BDI score: BDI = 3.38 (1 SD below mean), BDI = 8.91 (mean BDI), and BDI = 13.9 (1 SD above the mean). The exclusion of one model outlier, depicted in an open circle, did not change the pattern of results. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

networks, relative to baseline or placebo control, but generally show reductions in connectivity both within the SN and between SN nodes and other brain networks (Labrenz et al., 2019, 2016), though not universally (see Lekander et al., 2016). When both depression and inflammation are considered together, the literature is highly consistent. As a recent review by Goldsmith and colleagues (2022) details, systemic inflammation is associated with an overall reduction in functional connectivity in depressed individuals, including among SN nodes, that is mirrored by reduced structural connectivity, and typically correlates with severity of depressive symptoms (see also Aruldass et al., 2021; Mehta et al., 2018; Nusslock et al., 2019; Yin et al., 2019).The study that is perhaps most conceptually relevant in design to that reported here was published by Dispasquale *et al* (2016). MRI data were acquired from patients undergoing treatment with IFN-α for Hepatitis C virus infection at baseline and 4 h post-infusion. Using graph theory methods, they showed that IFN-α induced global as well as local reductions in functional connectivity (including nodes of the SN), reflecting a reduction in both the absolute number of nodal connections, as well as the efficiency of information processing. Further, the acute changes in efficiency of global and network connectivity were strongly correlated with sickness and mood symptoms. Nonetheless, a stated limitation of this study was its inability to address the neurobiological changes, adaptive and otherwise, associated with chronically elevated inflammation.

Investigation of rsFC in individuals with chronic inflammatory disease can shed light on inflammation-related changes in the functional organization and strength of brain networks that may develop over longer periods of time. Few studies have rigorously addressed this question. Results from our analyses contrasting SN rsFC measured at baseline with that following an acute airway inflammatory provocation in asthmatic participants, are consistent with changes reported in response to acute inflammatory provocations in healthy samples. Further, the dynamics of SN rsFC in asthma patients with more pronounced symptoms of depression and a robust inflammatory response to challenge resembles that of depressed patients with heighted inflammation at baseline. However, asthma patients with low levels of depressive symptoms and a *similarly robust response to challenge* appear to be resilient to the effects of acute inflammatory provocation on SN connectivity. Importantly, it was not the case that those low in depressive symptoms had greater SN connectivity at baseline, but rather that they maintained or increased connectivity in the face of an acute challenge. Estimates of the percentage of individuals with asthma who have a diagnosis of MDD vary, ranging from 16 to 54 % (Bardach et al., 2020; Stanescu et al., 2019; Zielinski et al., 2000), which is elevated relative to the general population. However, based on these estimates, 46 to 84 % of those with asthma are not depressed and identifying the features of those resilient to depression despite long-standing inflammation is an important step in reducing the cost, in terms of both human suffering and public health, of asthma and other chronic inflammatory diseases. Our data suggest a potential protective effect of SN connectivity, in the context of inflammation, on mental health.

Greater relative SN rsFC has been a marker of better mental health in multiple contexts. Individuals with greater trait mindfulness, for example, exhibited greater SN connectivity at rest (Sezer et al., 2022) and training in mindfulness in previously untrained individuals resulted in increased SN connectivity in both patients with asthma (Laubacher et al., 2024) and those with chronic pain (Su et al., 2016), which was associated with functional improvements. In patients with depression, SN rsFC increased following cognitive behavior therapy (CBT) in those who achieved remission (Zhang et al., 2017), which is consistent with work showing that hypometabolism in the insula at baseline was predictive of those who remit from depression in response to CBT (McGrath et al., 2013).

A central role of the SN is to mediate activity between several large-scale networks involved in attention and cognitive control. The AIC, in particular, is thought to orchestrate switching between default mode (DMN) and central executive (CEN) networks, based on relative homeostatic advantage (Goulden et al., 2014; Molnar-Szakacs and Uddin, 2022; Uddin, 2015) and some have argued that the AIC functions to gate executive control (Molnar-Szakacs and Uddin, 2022). Further, Goldstein-Piekarski *et al.* corroborate a role for insula disconnectivity in negative bias and "inattentive-cognitive dyscontrol symptoms" in depression and anxiety, highlighting the importance of interactions between the SN and CEN (Goldstein-Piekarski et al., 2022). Therefore, in the context of inflammation, an increase in SN connectivity may reflect more efficient integration of information and function of this network, enabling more effective engagement of attentional control and emotion regulation to promote resilience. Indeed, preliminary evidence does exist showing a relationship between connectivity within the SN and network dynamics between the DMN and CEN, which was related to severity of depressive symptoms (Manoliu et al., 2014). This hypothesis is also consistent with neurobiological accounts of both CBT and mindfulness training. Dunlop and colleagues report that reduced SN rsFC prior to treatment initiation predicts differential response to CBT vs. anti-depressant medication and an increase in SN rsFC was seen selectively in those who remitted in response to CBT (Dunlop et al., 2023). Cognitive control and the ability to shift attention are core aspects of CBT and the findings reported by Dunlop *et al*. suggest that, in response to salient or interoceptive information, effectively engaging attentional control processes is foundational to CBT treatment efficacy; or in other words, effective switching between DMN and CEN. Similarly, training in mindfulness strengthens attentional control and the ability to disengage from reflexive and ruminative thought patterns. In accordance with these skills, we and others have shown that mindfulness training increased connectivity within the SN (Laubacher et al., 2024), as well as connectivity between SN and both DMN and CEN (Bremer et al., 2022; Laubacher et al., 2024). Moreover, increased SN-CEN connectivity predicted improvements in asthma control (Laubacher et al., 2024). Thus, the findings of our current study suggest that, in those with chronic inflammatory disease, maintenance of strong SN rsFC during inflammatory episodes may represent a phenotype resilient to depression, and further, that for those who suffer from chronic inflammatory diseases, interventions that strengthen attention and cognitive control may be most efficacious in preventing or ameliorating symptoms of depression.

There are several limitations that should be acknowledged when considering the results reported here. First, the participants in our sample reported a level of depressive symptoms that ranged from low (BDI score of 2) to moderate (BDI score of 21), but overall, this was not a depressed sample. This pattern may not generalize to those with severe depression. In addition, we employed an innovative, but complex method for initiating airway inflammation– SBP-Ag – which enabled evaluation of airway inflammatory effects on brain network function, that were uncompromised by concomitant effects of reduced lung function but constrained the size of our sample. This modest sample size likely limited our ability to detect smaller effects and constrained our ability to explore important individual differences, such as effects of sex on the relationships reported. Relatedly, we do not know if the effects reported here are specific to the SN or if other networks show similar patterns. To balance risk for type I error with power, given our small sample size, we limited *a priori* analyses to seeds within the SN. Future research should expand on this work to evaluate effects of acute inflammatory challenge in a chronically inflamed clinical sample, on connectivity within other brain networks and on the connectivity dynamics between networks. Despite these limitations, we report effects that largely corroborate the existing literature related to SN rsFC alterations in depression, and its inflammatory sub-type in particular, and advance our understanding in this regard by identifying a potential biomarker of resilience to depression in those with chronic inflammation. This knowledge is an integral piece of the puzzle in moving toward a personalized medicine approach to treating depression.

CRediT authorship contribution statement

Claire Laubacher: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Theodore P. Imhoff-Smith:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Danika R. Klaus:** Writing – review & editing, Investigation, Data curation. **Corrina J. Frye:** Writing – review & editing, Investigation, Data curation. **Stephane Esnault:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **William W. Busse:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Melissa A. Rosenkranz:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Disclosures

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