Archival Report

Biological Psychiatry: GOS

# Resting-State Network Dynamics in Asthma: Interplay Between Depressive Symptoms and Airway Inflammation

Maxie Liebscher, Claire Laubacher, Theodore P. Imhoff-Smith, Rasmus M. Birn, Danika R. Klaus, Corrina J. Frye, William W. Busse, and Melissa A. Rosenkranz

## ABSTRACT

**BACKGROUND:** Asthma and depression frequently co-occur, potentially worsening each other's symptoms. The salience network (SN) may play a key role in this link, but the roles of the default mode network (DMN) and frontoparietal network (FPN), as outlined in the triple network theory, remain unclear in the asthma-depression connection. This longitudinal study investigated pre-post changes in graph-theory metrics within and between the 3 networks in individuals with asthma and how these relate to depressive symptoms.

**METHODS:** Twenty-four individuals with asthma underwent functional magnetic resonance imaging scans pre- and postsegmental allergen challenge. Depressive symptoms were assessed at baseline using the Beck Depression Inventory. Changes in graph-theory metrics were analyzed using region-of-interest (ROI)-to-ROI analyses, controlling for sex.

**RESULTS:** Allergen challenge led to changes in network properties. Within-network analyses showed decreased degree centrality ($\beta$ = 0.50, false discovery rate–corrected $p$ [$p_{FDR}$] = .004) and betweenness centrality ($\beta$ = 0.10, $p_{FDR}$ = .025) of the posterior cingulate cortex (DMN) and reduced degree centrality of the anterior cingulate cortex (SN), which correlated with depressive symptoms ($\beta$ = 0.05, $p_{FDR}$ = .017). Between-network analyses showed reduced closeness centrality in the bilateral lateral parietal during SN-DMN interactions (right: $\beta$ = 0.23, $p_{FDR}$ = .010; left: $\beta$ = 0.23, $p_{FDR}$ = .013) and increased degree centrality in the left posterior parietal cortex during SN-FPN interactions ($\beta$ = −0.10, $p_{FDR}$ = .038), which correlated with depressive symptoms.

**CONCLUSIONS:** Allergen challenge alters graph-theory metrics within and between resting-state networks, with changes linked to depression symptoms. Findings highlight the SN's critical role in network switching and its vulnerability to inflammation in asthma-depression connection.

https://doi.org/10.1016/j.bpsgos.2025.100527

Chronic systemic inflammation, often accompanied by fatigue, pain, and mood disorders, is an important component in the most prevalent chronic health conditions [for review, see (1,2)] that account for 90% of U.S. health care expenditures (3). Among these, asthma stands out as a common chronic inflammatory disease, affecting 8% of the U.S. population (4). Characterized by inflammation, hyperreactivity of the airway, and variable airflow obstruction, asthma is frequently comorbid with other conditions, particularly depression (5). This comorbidity with depression can worsen disease control and increase the risk of asthma exacerbations (6) [for review, see (7)]. Understanding the mechanisms connecting asthma and depression is therefore crucial to identifying factors driving these diseases.

## Asthma, Depression, and Triple Network Theory

Given that depression can negatively influence asthma control (8) and lead to altered pulmonary function (9), it is important to understand the underlying mechanisms. Previous research links depression, systemic inflammation, and altered salience network (SN) function (10–13), particularly in the insula and anterior cingulate cortex (ACC). These regions show exaggerated responses to emotional cues under inflammatory conditions, such as allergen exposure in asthma (10,12,13). In our previous study, Laubacher *et al.* (11), we examined changes in resting-state functional connectivity (rsFC) within the SN in relation to depression in patients with asthma after an allergen exposure. We found that patients with higher baseline depression scores experienced greater decreases in SN rsFC, whereas those with lower depression scores maintained SN rsFC, suggesting resilience to inflammation-related neural disruptions.

Building on these findings, the triple network theory (14) suggests that the SN, default mode network (DMN), and frontoparietal network (FPN) form a dynamic system, with the SN facilitating switching between the DMN and FPN depending on the context (15). Typically, the DMN and FPN show anticorrelated activity. Harrison *et al.* (16) found that





ISSN: 2667-1743

inflammation-induced mood deterioration was linked to reduced rsFC within salience and reward networks. Similarly, Goldsmith *et al.* (17) reported inflammation-related dysconnectivity in cortical and subcortical regions. Despite these insights, interactions between these 3 resting-state networks (RSNs), particularly between SN-DMN and SN-FPN, remain poorly understood in the context of asthma, with and without depression.

To further explore this, a recent study by Zheng *et al.* (18) using graph theory found increased connectivity degree in the right anterior insula (part of the SN) in individuals with depression, suggesting dysfunctional switching between the DMN and FPN. This highlights the SN's critical role in regulating DMN and FPN interactions, which may be relevant in asthma. Moreover, findings from Manoliu *et al.* (19) showed that the right anterior insula modulates DMN and FPN connectivity, and disruptions in this region are linked to greater depression severity. While some studies have begun exploring relationships between the 3 RSNs in asthma, the role of depressive symptoms remains underexplored.

Research on asthma within the framework of the triple network theory is growing. Li *et al.* (20) reported network-specific alterations in DMN- and FPN-related brain regions in individuals with asthma. Similarly, Zhang *et al.* (21) found increased SN connections with both DMN and FPN and decreased connections between the DMN and FPN in individuals with asthma. These findings suggest that the SN may play an important role in the neural mechanisms linking asthma and mood. However, more research, particularly using graph-theory metrics, is needed to better understand how depressive symptoms and asthma interact within the framework of the triple network theory.

## Graph Theory Versus Other Neuroimaging Metrics

Graph theory is a valuable approach to understand neural mechanisms linking asthma and depressive symptoms. It quantifies complex brain network dynamics by offering insights into network structure, including small-worldness and centralized hubs [for review, see (22,23)]. Unlike other neuroimaging methods such as rsFC or diffusion tensor imaging, graph theory not only identifies networks but also investigates their structure and function. It reveals how brain regions communicate and function as integrated systems [for review, see (23)]. Identifying central nodes and their connectivity is key to understanding how network disruptions may underlie depressive symptoms or responses to inflammation. Graph-theory metrics also help explain how asthma may worsen depression and vice versa by impairing communication in regions involved in emotion regulation and cognitive control, particularly within the SN (11).

Key graph-theory metrics include betweenness centrality, closeness centrality, and degree centrality, as well as clustering coefficient, local efficiency, and global efficiency. Betweenness centrality reflects a node's role in connecting other nodes [for review, see (23,24)], indicating its importance in maintaining connections and simplifying communication. In depression, altered activity in central nodes with high betweenness centrality may impair the ability to facilitate communication between brain regions involved in mood regulation (25) [for review, see (26)].

Closeness centrality reflects how close a node is to all others in a network [for review, see (23,24)], reflecting its ability to quickly interact with other nodes. In depression, reduced closeness centrality may underlie slower cognitive processing (27) and emotional dysregulation (28). Similar disruptions in asthma could increase emotional reactivity [for review, see (29)]. Degree centrality, which measures a node's total connections [for review, see (23,24)], provides additional insights. Reduced degree centrality in regions such as the insula and ACC may signal asthma-related changes that impair mood regulation [for review, see (30)], contributing to the high comorbidity with depression.

Local efficiency and global efficiency reflect how effectively information is exchanged within a node's neighborhood and across the entire network, respectively [for review, see (24)]. In depression, altered local efficiency is linked to impaired integration of cognitive and emotional brain regions (31), affecting emotional regulation. The clustering coefficient indicates how interconnected a node's neighbors are, thereby reflecting network resilience [for review, see (24)]. While network resilience is key to emotional and cognitive functions in both depression and asthma, the role of the clustering coefficient in asthma-related network alterations remains underexplored. Together, these graph-theory metrics may help clarify the neural mechanisms linking asthma and depression.

## Research Gaps and Objectives

Previous studies suggest that altered rsFC, particularly in the SN, may link asthma and depression. However, the roles of the DMN and FPN [key components of the triple network theory (14)] remain underexplored. Because the SN is thought to regulate dynamics between the DMN and FPN (15), understanding these interactions is crucial. To date, no studies have used graph theory to examine how asthma and depressive symptoms interact across these networks. This method could offer deeper insights than rsFC alone. The present study addresses these gaps by applying graph-theory analyses to explore network dynamics in asthma and depression.

## The Present Study

This longitudinal exploratory study aimed to investigate changes in graph-theory metrics in response to allergen challenge in patients with asthma, examining how depressive symptoms relate to these changes within and between the SN, DMN, and FPN.

We hypothesized that 1) graph-theory metrics will decrease within the SN after allergen provocation, with similar changes in the DMN and FPN due to inflammation, and 2) between-network analyses (SN-DMN, SN-FPN) will show altered graph-theory metrics in response to allergen exposure, suggesting that allergen exposure affects SN's role in switching between the DMN and FPN. In addition, 3) within and 4) between networks, changes in graph-theory metrics will vary by baseline depression scores, with

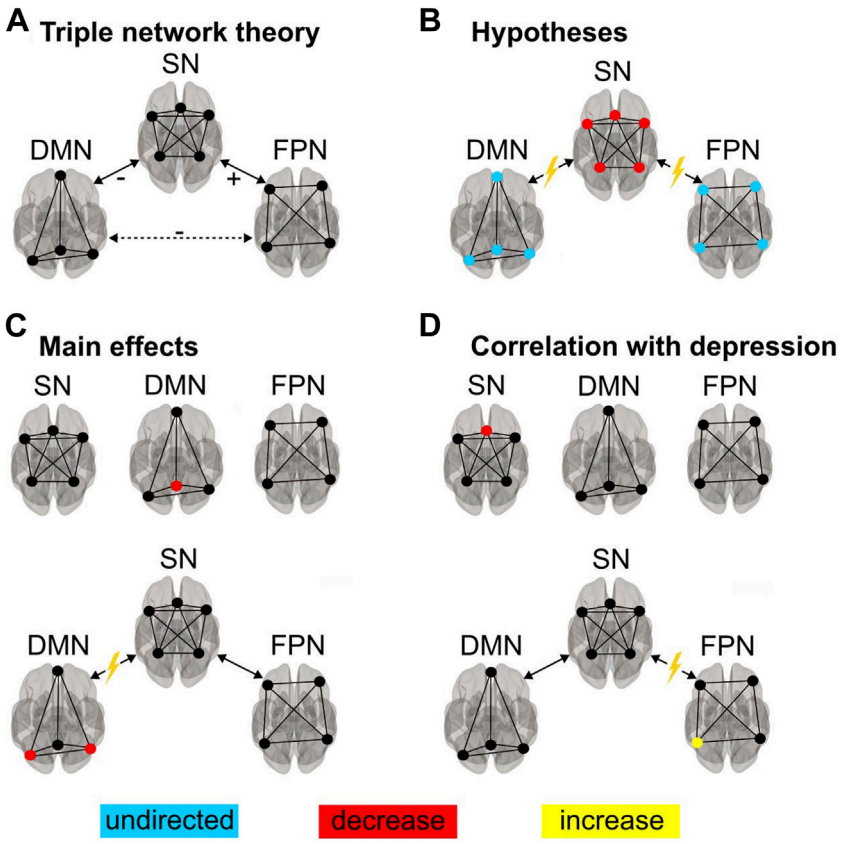


**Figure 1.** Visualization of the triple network theory, proposed hypotheses, and key within- and between-network graph-theory results, showing pre-post changes after the allergen challenge (main effects, models without depression scores) and their correlation with baseline depression symptoms (models with depression scores) in individuals with asthma. Summarized visualization of the proposed dynamic interactions among the 3 resting-state networks (salience network [SN], default mode network [DMN], and frontoparietal network [FPN]) based on the triple network theory **(A)**, hypotheses **(B)**, and significant findings from the main effects **(C)** and correlational analyses **(D)** within and between the networks. **(A)** According to the triple network theory, DMN and SN, as well as DMN and FPN, exhibit an anticorrelated interaction, while SN and FPN show a correlated interaction. The SN plays a crucial role in switching between the DMN and FPN. **(B)** We hypothesized that the interactions between the SN-DMN and SN-FPN would be altered, along with a decrease in within-SN graph-theory metrics (shown in red) in response to the allergen challenge. Additionally, we expect changes in graph-theory metrics within the DMN and FPN (without a specific direction; shown in blue). **(C)** Main effect analyses revealed that, within the DMN, the posterior cingulate cortex exhibited decreases in graph-theory metrics in response to the allergen challenge. Between the SN and DMN, the bilateral lateral parietal also showed decreases in graph-theory metrics after the allergen challenge. **(D)** Correlational analyses between baseline depression scores and changes in graph-theory metrics showed that the anterior cingulate cortex within the SN exhibited decreases in graph-theory metrics. Between the SN and FPN, the left posterior parietal cortex showed increases in graph-theory metrics (shown in yellow) in correlation with baseline depression scores. Altered connections between network nodes, based on our hypotheses and findings, are represented by dotted lines.

higher depression correlating with more disrupted network dynamics.

## METHODS AND MATERIALS

### Participants

A total of 26 participants diagnosed with asthma and no other serious health problems were included in this study. They had mild impairment of lung function (forced expiratory volume in 1 second [$FEV_1$] $\geq$ 70%), showed clinically significant reversibility of airway obstruction (12% reversibility or provocative concentration 20 response to methacholine $\leq$16.0 mg/mL), had not used corticosteroids for over a month, and showed clinically significant impairment of lung function ($\geq$20% decrease in $FEV_1$) in response to allergens. Participants who were treated for depression and anxiety ($n$ = 4) were on a stable dose for at least one month. The University of Wisconsin-Madison Institutional Review Board approved all study procedures, and participants provided a written informed consent. During functional magnetic resonance imaging (fMRI) preprocessing, 2 participants were excluded due to excessive movement or poor coregistration, leaving a final sample of 24 participants.

### Study Design

Participants were examined immediately before and 48 hours after airway inflammation induced by segmental bronchoprovocation with an allergen (SBP-Ag). Both pre- and postchallenge examinations included assessments of depressive symptoms and resting-state fMRI (rs-fMRI). Participants did not use bronchodilator medication for at least 6 hours before assessments.

### Procedures

**Segmental Bronchoprovocation With an Allergen.** All participants underwent SBP-Ag. Details are provided in the Supplement.

**Depressive Symptoms.** Depressive symptoms were assessed immediately before and 48 hours after SBP-Ag using the Beck Depression Inventory (BDI) (32). Only the BDI total score before SBP-Ag (baseline) was included in the analyses. Details are provided in the Supplement.

**Neuroimaging Acquisition and Preprocessing.** Structural and functional MRI data were collected before each bronchoscopy on a GE Discovery MR750 3T MRI scanner with a 32-channel head coil. Details on neuroimaging acquisition

and preprocessing procedures are provided in the Supplement.

**Graph-Theory Resting-State Analyses.** Graph-theory metrics within and between networks were calculated using the CONN Toolbox (version 22.a) (33), with implemented regions of interest (ROIs) from an independent component analysis of 497 participants in the Human Connectome Project (33,34). For each network, corresponding ROIs were selected: SN (ACC, anterior insula [bilateral], amygdala [bilateral]), DMN (medial prefrontal cortex, posterior cingulate cortex [PCC], lateral parietal [LP] [bilateral]), and FPN (lateral prefrontal cortex [bilateral], posterior parietal cortex [PPC] [bilateral]). Detailed information, including Montreal Neurological Institute coordinates of all ROIs, is provided in the Supplement. For within-network analyses, all ROIs of each network were included. For between-network analyses, all ROIs of the respective network combinations (SN-DMN, SN-FPN) were included.

To test the main effect of airway inflammatory challenge within and between networks, changes in graph-theory metrics in response to SBP-Ag were calculated, covarying for sex. To further examine correlations with depression, the pre-post changes in each graph-theory metric were correlated with baseline depression scores, also controlled for sex. A one-sided (positive) cost threshold of 0.36 was applied for within-network analyses and 0.26 for between-network analyses, based on an exploratory approach to select cost thresholds that maximized the difference between local efficiency and global efficiency scores compared with lattices, as suggested by CONN's developer (35). An analysis threshold of $p < .05$, false discovery rate (FDR) corrected, was applied. Within-network analyses focused on betweenness centrality, closeness centrality, degree centrality, and local efficiency. Between-network analyses examined global efficiency and the clustering coefficient. Detailed information on the mathematical calculation of graph-theory metrics in CONN can be found elsewhere (36).

**Post Hoc and Exploratory Analyses.** We conducted a series of follow-up analyses that included investigations of the relationship between cognitive symptoms and changes in graph-theory metrics, correlations between inflammatory response and depression severity on changes in graph-theory metrics, and the main effect and correlation analyses between the DMN and FPN. Details are provided in the Supplement.

### Statistical Analyses

Statistical analyses were conducted in CONN or R (version 4.4.0) (37) with RStudio (version 2024.04.0) (38). Statistical analyses performed in CONN are described above. R was used to calculate descriptive statistics.

## RESULTS

### Sample Characteristics

The sample for this study included 24 participants with asthma. Sample characteristics are presented in Table 1.

**Table 1. Sample Characteristics**

| | Mean (SD) or *n* | Minimum | Maximum |
|---|---|---|---|
| Sex, Female/Male | 15/9 | – | – |
| Age, Years | 26.54 (6.48) | 19 | 41 |
| Baseline Depression Score[a] | 8.67 (5.31) | 2 | 21 |
| Treated for Depression and/or Anxiety, Yes/No | 4/20 | – | – |

[a]Measured with the Beck Depression Inventory (minimum = 0, maximum = 63) (32). Higher scores indicate more severe depression symptoms.

### Within-Network Analyses

**Main Effect Analyses.** Significant graph-theory results are presented in Table 2 and Figure 1. Within DMN, the PCC showed significant decreases in degree centrality ($\beta = 0.50$, $p_{uncorrected} = .001$, $p_{FDR} = .004$) and betweenness centrality ($\beta = 0.10$, $p_{uncorrected} = .008$, $p_{FDR} = .025$) in response to the allergen challenge. There were no significant graph-theory results within SN and FPN.

**Correlational Analyses.** Significant within-SN graph-theory results are presented in Table 2 and Figure 1. Within SN, the ACC showed a significant correlation between baseline depression score and decreases in degree centrality ($\beta = 0.05$, $p_{uncorrected} = .003$, $p_{FDR} = .017$) in response to the allergen challenge. There were no significant graph-theory results within DMN and FPN.

### Between-Network Analyses

**Main Effect Analyses.** Significant graph-theory results are presented in Table 3 and Figure 1. Between the SN and DMN, a significant decrease in closeness centrality was observed in response to the allergen challenge in the right LP ($\beta = 0.23$, $p_{uncorrected} = .001$, $p_{FDR} = .010$) and left LP ($\beta = 0.23$, $p_{uncorrected} = .003$, $p_{FDR} = .013$). There were no significant graph-theory results between the SN and FPN.

**Correlational Analyses.** Significant graph-theory results are presented in Table 3 and Figure 1. Between the SN and FPN, there was a significant correlation between baseline depression scores and increased degree centrality ($\beta = -0.10$, $p_{uncorrected} = .004$, $p_{FDR} = .038$) of the left PPC in response to the allergen challenge. There were no significant graph-theory results between the SN and DMN.

### Post Hoc Analyses

Within SN, the ACC showed a significant correlation between higher baseline cognitive symptoms of depression and decreases in closeness centrality ($\beta = 0.02$, $p_{uncorrected} = .010$, $p_{FDR} = .041$) in response to the allergen challenge. No other significant correlations were found within the DMN (all $ps \geq .496$ [uncorrected]) and the FPN (all $ps \geq .399$ [uncorrected]). Additionally, no significant correlations with between-network change were observed for SN-DMN (all $ps \geq .285$ [uncorrected]), SN-FPN (all $ps \geq .381$ [uncorrected]), and DMN-FPN (all $ps \geq .283$ [uncorrected]).

**Table 2. Significant Within-Network Graph-Theory Results Showing Pre-Post Change After Allergen Challenge (Main Effects, Models Without Depression Scores) and in Relation to Baseline Depression Symptoms (Correlation, Models With Depression Scores) in Individuals With Asthma**

| Network | ROI | Graph-Theory Metric | Condition | Beta | *t* | $p_{uncorrected}$ | $p_{FDR}$ |
|---|---|---|---|---|---|---|---|
| Main Effect | | | | | | | |
| DMN | PCC | Degree centrality | Two sided[a] | 0.50 | 3.47 | .002* | .009*,** |
| | | | Pre > post | 0.50 | 3.47 | .001* | .004*,** |
| | | Betweenness centrality | Pre > post | 0.10 | 2.59 | .008* | .025*,** |
| Correlation | | | | | | | |
| SN | ACC | Degree centrality | Two sided[a] | 0.05 | 2.99 | .007* | .035*,** |
| | | | Pre > post | 0.05 | 2.99 | .003* | .017*,** |

*$p < .05$, uncorrected; **$p < .05$, FDR corrected.

ACC, anterior cingulate cortex; DMN, default mode network; FDR, false discovery rate; PCC, posterior cingulate cortex; ROI, region of interest; SN, salience network.

[a]Refers to a general comparison between pre- and postmeasurements, indicating whether there is a difference without specifying the direction (pre > post or pre < post). This analysis is included for completeness. More specific directional results are reported and discussed in the text.

## DISCUSSION

This longitudinal study investigated changes in graph-theory metrics in response to an inflammatory challenge, focusing on varying levels of depressive symptoms, within and between the SN, DMN, and FPN in patients with asthma. The findings partially support our hypotheses. Significant decreases were observed in DMN metrics (PCC) and SN-DMN metrics (bilateral LP) after the inflammatory challenge, indicating altered network dynamics. However, no significant main effects were found within SN, FPN, or SN-FPN.

Depression-related differences were consistent with our hypothesis, showing greater disruption in network dynamics for individuals with higher depressive symptoms. In particular, ACC metrics in SN decreased more in those with higher baseline depression scores, while left PPC metrics (SN-FPN) increased in those with more depressive symptoms. SN-FPN interactions showed increased left PPC metrics in those with more symptoms of depression. No differences were observed within the DMN or FPN or between the SN and DMN.

### Within Network

**Main Effects.** We observed that the airway inflammatory provocation (SBP-Ag) affected the PCC (DMN node), with decreases in degree centrality and betweenness centrality after the allergen challenge. Degree centrality reflects the number of direct connections a node has, indicating a reduction in PCC's integration within the DMN [for review, see (23,24)]. The decrease in betweenness centrality suggests that the PCC played a less critical role in network communication, acting as a bridge between regions, after the challenge. We did not observe similar findings within the SN and FPN.

The PCC, a key node of the DMN, plays a crucial role in self-referential thought [for review, see (39,40)]. The observed reduction in its connections and communication suggests diminished function in response to inflammation, reflecting impaired DMN activity in the context of acute inflammation, consistent with previous studies on DMN alterations in inflammatory conditions (20). Impairments in the DMN, particularly in the PCC, could disrupt cognitive and emotional

**Table 3. Significant Between-Network Graph-Theory Results Showing Pre-Post Change After Allergen Challenge (Main Effects, Models Without Depression Scores) and in Relation to Baseline Depression Symptoms (Correlation, Models With Depression Scores) in Individuals With Asthma**

| Network | ROI | Graph-Theory Metric | Condition | Beta | *t* | $p_{uncorrected}$ | $p_{FDR}$ |
|---|---|---|---|---|---|---|---|
| Main Effect | | | | | | | |
| SN-DMN | Network | Global efficiency | Two sided[a] | −0.06 | −2.61 | .016* | – |
| | LP, right | Closeness centrality | Two sided[a] | 0.23 | 3.44 | .002* | .021*,** |
| | | | Pre > post | 0.23 | 3.44 | .001* | .010*,** |
| | LP, left | Closeness centrality | Undirected | 0.23 | 3.07 | .006* | .025*,** |
| | | | Pre > post | 0.23 | 3.07 | .003* | .013*,** |
| Correlation | | | | | | | |
| SN-FPN | PPC, left | Degree centrality | Pre < post | −0.10 | −2.90 | .004* | .038*,** |

*$p < .05$, uncorrected; **$p < .05$, FDR corrected.

DMN, default mode network; FDR, false discovery rate; FPN, frontoparietal network; LP, lateral parietal; PPC, posterior parietal cortex; ROI, region of interest; SN, salience network.

[a]Refers to a general comparison between pre- and postmeasurements, indicating whether there is a difference without specifying the direction (pre > post or pre < post). This analysis is included for completeness. More specific directional results are reported and discussed in the text.

functions, including emotion regulation, attentional control, and self-referential processing [for review, see (39,40)]. A reduction in PCC connections may limit the flow of information needed for these functions, affecting emotional control and attention. While changes in PCC metrics were not significantly associated with baseline cognitive symptoms of depression, their impact after the allergen challenge would provide more insight. The effect of these changes on emotion-cognition interactions could be more apparent, although our current measure of cognitive symptoms may not fully capture this. These alterations in DMN connections and communication may influence how patients with asthma perceive their symptoms, potentially heightening symptom severity and discomfort. In summary, allergen provocation alters not only the SN function but also the DMN, emphasizing inflammation's broad impact on brain networks, although further research is needed to confirm these findings.

**Correlations With Symptoms of Depression.** Our correlational analyses revealed that the impact of the airway inflammatory provocation (SBP-Ag) on the ACC (SN node) was correlated with depressive symptoms. The ACC exhibited decreases in degree centrality in response to inflammation, with greater loss of connections in individuals with higher depression scores. This aligns with our previous study (11), in which those with the highest depression symptoms showed the most significant rsFC decline within the SN. We did not observe similar findings within the DMN and FPN.

As discussed in Laubacher *et al.* (11), the reduction in ACC connectivity within the SN aligns with research linking reduced SN connectivity to anhedonia, negative emotional bias, and poor life satisfaction (41)—common features of depression (42). Literature also shows that systemic inflammation, as in asthma, is associated with reduced structural and functional connectivity in the SN, particularly in individuals at risk of depression [for review, see (17)]. Similar to our findings, another graph-theory study reported reductions in nodal connections due to inflammation, correlated with mood disturbances (43).

## Between Networks

**Main Effects.** In response to an inflammatory challenge, the bilateral LP (DMN nodes) showed decreased closeness centrality in SN-DMN analyses, indicating impaired interaction with other nodes. Closeness centrality reflects the efficiency of node interaction [for review, see (23,24)], and the observed reduction suggests slower or less efficient communication. We did not observe similar findings between the SN and FPN.

The results of these analyses suggest that inflammation may reorganize network interactions, impairing communication within the DMN and between the DMN and SN. The reduction in closeness centrality of the LP, a node important in self-reflection and emotional regulation [for review, see (39,40)], could contribute to cognitive disruptions and emotional reactivity (12,13) in patients with asthma during inflammatory episodes. However, these changes in LP metrics were not significantly associated with baseline cognitive symptoms of depression, indicating that such symptoms may not fully reflect the impact of network changes on cognition. This underscores the importance of internetwork interactions in the neural response to inflammation in asthma. Further research is needed to better understand these processes and their effects on symptom regulation.

**Correlations With Symptoms of Depression.** Analyses of the SN-FPN revealed that the impact of inflammatory provocation on the left PPC (FPN node) depended on symptoms of depression at baseline. Greater increases in degree centrality of the left PPC were observed in individuals with higher baseline depressive symptoms after the challenge. We did not observe similar findings between the SN and DMN.

This pattern suggests that inflammation can affect neuronal networks involved in cognitive processes [for review, see (44–46)]. In particular, the left PPC, which is important for attention and sensory information integration (47) [for review, see (48)], seems to undergo reorganization in individuals with asthma, especially those with higher baseline depression symptoms. This reorganization might be an adaptive attempt to compensate for impaired function in regions involved in emotional regulation and self-referential thinking. However, such compensatory mechanisms could have both positive and negative implications: While they may help maintain certain cognitive functions, they could also contribute to maladaptive cognitive overload. Post hoc analyses revealed a correlation between changes in graph-theory metrics and baseline cognitive symptoms of depression within the SN, specifically in the ACC. No such associations were found within the FPN, suggesting that baseline cognitive symptoms may not fully capture inflammation-related changes in the FPN. However, the ACC's role in switching between the DMN and FPN indicates that alterations here may still contribute to cognitive dysfunction. Further research is needed to explore the consequences of these network changes and potential interventions.

## Post Hoc: Correlations With Cognitive Symptoms of Depression

Post hoc analyses revealed that airway inflammatory provocation was associated with baseline cognitive symptoms of depression in the ACC, a node of the SN. In individuals with higher depression-related cognitive symptoms, the ACC exhibited decreased closeness centrality, indicating slower communication within the SN. We did not observe similar findings within the DMN and FPN and between the networks.

The network dynamics of the ACC, involved in emotional processing and cognition-related functions such as integration of interoceptive information (49,50), rumination (51), and the cognitive processing of stress (52), may be disrupted in individuals with asthma and higher depression-related cognitive symptoms. This disruption could exacerbate symptoms, such as shortness of breath, through impaired interoception, heightened rumination, and less effective stress regulation. Further research is needed to explore the relationship between RSN dynamics, cognitive function, depression, and asthma.

## Null Findings

We observed several null findings in our main effect and correlational analyses within and between the networks, with

no significant changes after the inflammatory challenge. A possible explanation could be the small sample size, limiting the detection of small effects. Despite this, alterations in graph-theory metrics of the SN may account for some of these null findings. SN's role in coordinating the DMN and FPN, as postulated by Menon and Uddin (15), suggests that disruptions in this coordination could impair communication within and between the networks. Furthermore, post hoc analyses revealed no significant correlations between baseline cognitive symptoms of depression and changes in graph-theory metrics within the DMN or FPN or between networks. These null findings may, in part, also be explained by the observed alterations in SN function.

### Strengths and Limitations

The present study shows alterations within and between the SN, DMN, and FPN in response to an inflammatory challenge, which are partially linked to variability in depressive symptoms. The main strength of this study is that 1) we used the CONN Toolbox, which increases the replicability of our results, due to its user-friendly pipelines, and that 2) the longitudinal experimental design of this study allows for inference of causality.

There are several limitations to consider. 1) The sample size of only 24 participants limits our ability to detect small-to-moderate sized effects. However, given the nature of our participant group and the complexity of the experimental design, this sample size is defensible. 2) The sample's depressive symptoms ranged from none (BDI score = 2) to moderate (BDI score = 21), indicating that results may not generalize to populations with more severe symptoms. However, individuals with major depression often do not participate in complex studies [for review, see (53)], making future studies with severely depressed populations difficult. Additionally, because we did not expect symptoms of depression to change in a meaningful way as a consequence of allergen challenge, no other assessment tools were used to evaluate depression symptoms/severity after the allergen challenge. Nonetheless, it is important to confirm that this is the case, and future studies should consider acquiring measures appropriate for capturing acute change in depressive symptoms after the challenge. 3) No control group was included, which is necessary to confirm the specificity of the observed changes. Nonetheless, the acquisition of fMRI data occurred before each bronchoscopy procedure, with a full 48 hours in between the first bronchoscopy and the second fMRI scan. Therefore, it is unlikely that the stress of this procedure gave rise to the observations reported here. 4) Repeated fMRI scans could introduce confounding factors like habituation or re-exposure effects.

### Future Research

Our study shows inflammation-induced alterations in graph-theory metrics within and between the RSNs SN, DMN, and FPN, influenced by depressive symptoms. Future research should replicate these findings with a larger sample size and a control group to confirm their robustness. Additionally, studies including individuals with more severe depression symptoms and exploring sex differences would be valuable, given the higher risk of depression (54,55) and chronic inflammation in women [for review, see (56)].

## Conclusions

Our study demonstrates that allergen exposure alters key RSNs, including the SN, DMN, and FPN, with some changes influenced by depressive symptoms. Inflammatory processes may disrupt the balance between SN-DMN and SN-FPN, highlighting SN's role in network switching. These findings offer insights into the neural mechanisms underlying depression and resilience in asthma, warranting further research to assess their clinical significance.

## ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Heart, Lung, and Blood Institute (Grant No. R01HL123284-04 [to WWB]) and the National Institute on Aging (Grant No. 1RF1AG082215 [to MAR]).

This work was conducted as part of an internship by Maxie Liebscher, which was partially funded through an Erasmus+ Student Mobility grant provided by Leonardo-Büro Sachsen. However, the scholarship had no influence on the content or direction of this work.

MAR and WWB were responsible for the concept and design. ML, CL, MAR, TPI-S, CJF, and DRK acquired, analyzed, or interpreted data. ML and MAR drafted the article. All authors were responsible for the critical revision of the article for important intellectual content. ML, CL, and MAR were responsible for statistical analysis. WWB and MAR obtained funding. RMB was responsible for administrative, technical, or material support. MAR was responsible for supervision.

We are very grateful for the methodological advice provided by Tammi Kral, Ph.D. (Center for Healthy Minds, University of Wisconsin-Madison, Madison, Wisconsin), and Olusola Ajilore, M.D., Ph.D. (University of Illinois at Chicago, Chicago).

Data will be made available on request.

WWB received consulting fees; payment or honoraria for lectures, presentations, speakers' bureaus, article writing, or educational events; and financial support and/or travel support for attending meetings from GlaxoSmithKline, Sanofi, and Regeneron. WWB has also received royalties or licenses from Elsevier. RMB is a consultant for Turing Medical Technologies, Inc. All other authors report no biomedical financial interests or potential conflicts of interest.

## ARTICLE INFORMATION

From the Center for Healthy Minds, University of Wisconsin-Madison, Madison, Wisconsin (ML, CL, MAR); German Center for Neurodegenerative Diseases, Dresden, Germany (ML); Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (TPI-S); Department of Psychiatry, University of Wisconsin-Madison, Madison, Wisconsin (RMB, MAR); Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (DRK, WWB); and Waisman Center, University of Wisconsin-Madison, Madison, Wisconsin (CJF).

Address correspondence to Melissa A. Rosenkranz, Ph.D., at melissa.rosenkranz@wisc.edu.

Received Dec 9, 2024; revised Apr 15, 2025; accepted Apr 27, 2025.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsgos.2025.100527.

## REFERENCES

1. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, *et al.* (2019): Chronic inflammation in the etiology of disease across the life span. Nat Med 25:1822–1832.
2. Slavich GM (2015): Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority. Brain Behav Immun 45:13–14.
3. US Centers for Disease Control and Prevention (2024): Health and economic costs of chronic diseases. Available at: https://www.cdc.gov/chronicdisease/about/costs/index.htm. Accessed June 26, 2024.

4. US Centers for Disease Control and Prevention (2024): Most Recent National Asthma Data. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed June 26, 2024.
5. Katon W, Lozano P, Russo J, McCauley E, Richardson L, Bush T (2007): The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls. J Adolesc Health 41:455–463.
6. Zhang L, Zhang X, Zheng J, Wang L, Zhang HP, Wang L, Wang G (2016): Co-morbid psychological dysfunction is associated with a higher risk of asthma exacerbations: A systematic review and meta-analysis. J Thorac Dis 8:1257–1268.
7. Chen E, Miller GE (2007): Stress and inflammation in exacerbations of asthma. Brain Behav Immun 21:993–999.
8. Urrutia I, Aguirre U, Pascual S, Esteban C, Ballaz A, Arrizubieta I, Larrea I (2012): Impact of anxiety and depression on disease control and quality of life in asthma patients. J Asthma 49:201–208.
9. Krommydas GC, Gourgoulianis KI, Angelopoulos NV, Kotrotsiou E, Raftopoulos V, Molyvdas PA (2004): Depression and pulmonary function in outpatients with asthma. Respir Med 98:220–224.
10. Dill-McFarland KA, Altman MC, Esnault S, Jarjour NN, Busse WW, Rosenkranz MA (2024): Molecular pathways underlying lung-brain axis signaling in asthma: Relevance for psychopathology and neuro-inflammation. J Allergy Clin Immunol 153:111–121.
11. Laubacher C, Imhoff-Smith TP, Klaus DR, Frye CJ, Esnault S, Busse WW, Rosenkranz MA (2024): Salience network resting state functional connectivity during airway inflammation in asthma: A feature of mental health resilience? Brain Behav Immun 122:9–17.
12. Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, *et al.* (2005): Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci U S A 102:13319–13324.
13. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ (2012): Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS One 7:e40921.
14. Menon V (2011): Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci 15:483–506.
15. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: A network model of insula function. Brain Struct Funct 214:655–667.
16. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD (2009): Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry 66:407–414.
17. Goldsmith DR, Bekhbat M, Mehta ND, Felger JC (2023): Inflammation-related functional and structural dysconnectivity as a pathway to psychopathology. Biol Psychiatry 93:405–418.
18. Zheng H, Xu L, Xie F, Guo X, Zhang J, Yao L, Wu X (2015): The altered triple networks interaction in depression under resting state based on graph theory. Biomed Res Int 2015:386326.
19. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, *et al.* (2013): Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. Front Hum Neurosci 7:930.
20. Li QG, Zhou FQ, Huang X, Zhou X, Liu C, Zhang T, *et al.* (2018): Alterations of resting-state functional network centrality in patients with asthma: Evidence from a voxel-wise degree centrality analysis. Neuroreport 29:1151–1156.
21. Zhang Y, Yang Y, Xu X, Yuan Y (2022): Coupling of spatial and directional functional network connectivity reveals a physiological basis for salience network hubs in asthma. Brain Imaging Behav 16:176–185.
22. Bullmore E, Sporns O (2009): Complex brain networks: Graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198.
23. Farahani FV, Karwowski W, Lighthall NR (2019): Application of graph theory for identifying connectivity patterns in human brain networks: A systematic review. Front Neurosci 13:585.
24. Wang J, Zuo X, He Y (2010): Graph-based network analysis of resting-state functional MRI. Front Syst Neurosci 4:16.
25. Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, *et al.* (2005): Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. Biol Psychiatry 57:1079–1088.
26. Drevets WC, Price JL, Furey ML (2008): Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. Brain Struct Funct 213:93–118.
27. Den Hartog HM, Derix MM, Van Bemmel AL, Kremer B, Jolles J (2003): Cognitive functioning in young and middle-aged unmedicated outpatients with major depression: Testing the effort and cognitive speed hypotheses. Psychol Med 33:1443–1451.
28. Brockmeyer T, Bents H, Holtforth MG, Pfeiffer N, Herzog W, Friederich HC (2012): Specific emotion regulation impairments in major depression and anorexia nervosa. Psychiatry Res 200:550–553.
29. Lehrer PM, Isenberg S, Hochron SM (1993): Asthma and emotion: A review. J Asthma 30:5–21.
30. Rosenkranz MA, Davidson RJ (2009): Affective neural circuitry and mind-body influences in asthma. Neuroimage 47:972–980.
31. Ye M, Qing P, Zhang K, Liu G (2016): Altered network efficiency in major depressive disorder. BMC Psychiatry 16:450.
32. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961): An inventory for measuring depression. Arch Gen Psychiatry 4:561–571.
33. Whitfield-Gabrieli S, Nieto-Castanon A (2012): Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2:125–141.
34. Neuroimaging tools & resources Collaboratory (2024): Conn: Functional connectivity toolbox. Available at: https://www.nitrc.org/projects/conn/. Accessed October 3, 2024.
35. Nieto-Castanon A (2018): Small-world network properties & Network edges options. Available at: https://www.nitrc.org/forum/forum.php?thread_id=9338&forum_id=1144. Accessed October 3, 2024.
36. Nieto-Castanon A (2020): Graph measures (ROI-level). Available at: https://web.conn-toolbox.org/fmri-methods/connectivity-measures/graphs-roi-level. Accessed October 3, 2024.
37. R Core Team (2021): R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing.
38. RStudio Team (2024): Integrated Development Environment for R. Boston, MA: RStudio, PBC.
39. Andrews-Hanna JR (2012): The brain's default network and its adaptive role in internal mentation. Neuroscientist 18:251–270.
40. Buckner RL, Andrews-Hanna JR, Schacter DL (2008): The brain's default network: Anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1–38.
41. Goldstein-Piekarski AN, Ball TM, Samara Z, Staveland BR, Keller AS, Fleming SL, *et al.* (2022): Mapping neural circuit biotypes to symptoms and behavioral dimensions of depression and anxiety. Biol Psychiatry 91:561–571.
42. Mayo Foundation for Medical Education and Research (2024): Depression (major depressive disorder). Available at: https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007. Accessed October 3, 2024.
43. Dipasquale O, Cooper EA, Tibble J, Voon V, Baglio F, Baselli G, *et al.* (2016): Interferon-$\alpha$ acutely impairs whole-brain functional connectivity network architecture – A preliminary study. Brain Behav Immun 58:31–39.
44. Lindquist KA, Barrett LF (2012): A functional architecture of the human brain: Emerging insights from the science of emotion. Trends Cogn Sci 16:533–540.
45. Menon V (2015): Large-scale functional brain organization. In: Toga AW, editor. Brain Mapping: An Encyclopedic Reference. New York, NY: Elsevier, 449–459.
46. Schimmelpfennig J, Topczewski J, Zajkowski W, Jankowiak-Siuda K (2023): The role of the salience network in cognitive and affective deficits. Front Hum Neurosci 17:1133367.
47. Andersen RA, Essick GK, Siegel RM (1987): Neurons of area 7 activated by both visual stimuli and oculomotor behavior. Exp Brain Res 67:316–322.
48. Freedman DJ, Ibos G (2018): An integrative framework for sensory, motor, and cognitive functions of the posterior parietal cortex. Neuron 97:1219–1234.

49. Farb NAS, Zuo Z, Price CJ (2023): Interoceptive awareness of the breath preserves attention and language networks amidst widespread cortical deactivation: A within-participant neuroimaging study. eNeuro 10:ENEURO.0088-23.2023.
50. Sugawara A, Katsunuma R, Terasawa Y, Sekiguchi A (2024): Interoceptive training impacts the neural circuit of the anterior insula cortex. Transl Psychiatry 14:206.
51. Sheena MK, Jimmy J, Burkhouse KL, Klumpp H (2021): Anterior cingulate cortex activity during attentional control corresponds with rumination in depression and social anxiety. Psychiatry Res Neuroimaging 317:111385.
52. Brown VM, Morey RA (2012): Neural systems for cognitive and emotional processing in posttraumatic stress disorder. Front Psychol 3:449.
53. Ferguson MC, McNicol E, Kleykamp BA, Sandoval K, Haroutounian S, Holzer KJ, *et al.* (2023): Perspectives on participation in clinical trials among individuals with pain, depression, and/or anxiety: An ACTTION scoping review. J Pain 24:24–37.
54. Li S, Zhang X, Cai Y, Zheng L, Pang H, Lou L (2023): Sex difference in incidence of major depressive disorder: An analysis from the Global Burden of Disease Study 2019. Ann Gen Psychiatry 22:53.
55. Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU (1993): Sex differences in rates of depression: Cross-national perspectives. J Affect Disord 29:77–84.
56. Ngo ST, Steyn FJ, McCombe PA (2014): Gender differences in autoimmune disease. Front Neuroendocrinol 35:347–369.