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Resting-State Network Dynamics in Asthma: Interplay between depressive symptoms and airway inflammation

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Asthma and depression often occur together and may influence each other. This study investigated how brain networks—the salience network, default mode network, and fronto-parietal network—respond to allergen exposure in 24 people with asthma. Graph-theory metrics were measured before and after exposure using resting-state fMRI. Results showed that individuals with more depressive symptoms had greater changes in these graph-theory metrics, particularly in the salience network. The findings suggest that altered communication within and between the three networks may be linked to asthma-related inflammation and vulnerability to depression.

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

Running title (short): Resting-State Network Dynamics in Asthma

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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 fronto-parietal network (FPN), as outlined in the triple network theory, remain unclear in the asthma-depression connection.

Objective: This longitudinal study investigated pre-to-post changes in graph-theory metrics within and between the three networks in individuals with asthma, and how these relate to depressive symptoms.

Methods: Twenty-four individuals with asthma underwent fMRI scans pre- and post-segmental allergen challenge. Depressive symptoms were assessed at baseline using the Beck Depression Inventory. Changes in graph-theory metrics were analyzed using regions-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 (β = 0.50, *p*-FDR = .004) and betweenness centrality (β = 0.10, *p*-FDR = .025) of the PCC (DMN), and reduced degree centrality of the ACC (SN), which correlated with depressive symptoms (β = 0.05, *p*-FDR = .017). Between-network analyses showed reduced closeness centrality in the bilateral LP during SN-DMN interaction (right: β = 0.23, *p*-FDR = .010; left: β = 0.23, *p*-FDR = .013), and increased degree centrality in the left PPC during SN-FPN interactions (β = -0.10, *p*-FDR = .038), which correlated with depressive symptoms.

Conclusion: 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.

Keywords (around 7): Resting-state, fMRI, graph theory, inflammation, asthma, depression, salience network, default mode network, fronto-parietal network, triple network theory

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1 INTRODUCTION

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. healthcare spending (3). Among these, asthma stands out as a common chronic inflammatory disease, affecting 8% of the U.S. population (4). Characterized by inflammation and hyperreactivity of the airway, and variable airflow obstruction, asthma is frequently comorbid with other conditions, particularly depression (5). This comorbidity can worsen disease control and increase the risk of asthma exacerbations (6) [for review, see (7)]. Understanding the mechanisms connecting asthma and depression is crucial to identifying factors driving these diseases.

1.1 Asthma, Depression, and Triple Network Theory

As 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 by Laubacher et al.(11), we examined changes in resting-state functional connectivity (rsFC) within the SN in asthma patients after an allergen exposure in relation to depression. 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 fronto-parietal 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 anti-correlated activity. Harrison et al.[16] found that 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 three resting state networks (RSNs), particularly between SN-DMN and SN-FPN, remain poorly understood in the context of asthma, with and without depression.

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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 depressed individuals, 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 three 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.

1.2 Graph Theory vs. Other Neuroimaging Metrics

Graph theory is a valuable approach for understanding neural mechanisms linking asthma and depressive symptoms. It quantifies complex brain network dynamics, offering insights into network structure, including small-worldness and centralized hubs [for review, see (22,23)]. Unlike other neuroimaging methods like 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 the clustering coefficient, local 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

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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 like 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 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, reflecting network resilience [for review, see (24)]. While network resilience is key to emotional and cognitive function 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.

1.3 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. Since 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.

1.4 The Present Study

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

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We hypothesize that: 1a) graph-theory metrics will decrease within the SN following allergen provocation, with similar changes in the DMN and FPN due to inflammation; 1b) between-network analyses (SN-DMN, SN-FPN) will show altered graph-theory metrics in response to allergen exposure, suggesting allergen exposure impacts the SN's role in switching between the DMN and FPN (Figure 1B). Additionally, 2a) within and 2b) between networks, changes in graph-theory metrics will vary by baseline depression scores, with higher depression correlating with more disrupted network dynamics.

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2 MATERIAL AND METHODS

2.1 Participants

Twenty-six participants with diagnosed asthma and no other serious health problems were included in this study. They had mild impairment of lung function (forced expiratory volume in one second [FEV_1] $\geq$ 70 %), showed clinically significant reversibility of airway obstruction (12 % reversibility or PC_{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 written informed consent. During functional magnetic resonance imaging (fMRI) preprocessing, two participants were excluded due to excessive movement or poor co-registration, leaving a final sample of twenty-four participants.

2.2 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 post-challenge examinations included assessments of depressive symptoms and resting-state fMRI (rsfMRI). Participants did not use bronchodilator medication for at least 6 hours before assessments.

2.3 Procedures

2.3.1 Segmental Bronchoprovocation with Allergen (SBP-Ag)

All participants underwent segmental bronchoprovocation with an allergen. Details are provided in the **Supplementary Material**.

2.3.2 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 **Supplementary Material**.

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2.3.3 Neuroimaging Acquisition and Preprocessing

Structural and functional magnetic resonance imaging (MRI) data were collected prior to 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 **Supplementary Material**.

2.3.4 Graph-Theory Resting-State Analyses

Graph-theory metrics within and between networks were calculated using the CONN Toolbox (version 22.a) (33), with the 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 [MPFC], posterior cingulate cortex [PCC], lateral parietal [LP; bilateral]), FPN (lateral prefrontal cortex [LPFC; bilateral], posterior parietal cortex [PPC; bilateral]). Detailed information, including MNI coordinates of all ROIs, is provided in the **Supplementary Material**. 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 maximize the difference between local and global efficiency scores compared to 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).

2.3.5 Post-Hoc and Exploratory Analyses

We conducted a series of follow-up analyses that include 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, as well as

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the main effect and correlation analyses between the DMN-FPN. Details are provided in the **Supplementary Material**.

2.4 Statistical Analyses

Statistical analyses were conducted in CONN or in 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.

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3 RESULTS

3.1 Sample Characteristics

The sample for this study included *n* = 24 participants with asthma. Sample characteristics can be found in **Table 1**.

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Table 1. *Sample characteristics*

	Sample ***M* (*SD*)**	**Minimum**	**Maximum**
Sex: Female/Male (*n*)	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 (*n*)	4/20	-	-

M = mean, SD = standard deviation.

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

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3.2 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 (β = 0.50, *p*-uncorrected = .001, *p*-FDR = .004) and betweenness centrality (β = 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 can be found in **Table 2 and Figure 1**. Within SN, the ACC showed a significant correlation between baseline depression score and decreases in degree centrality (β = 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.

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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*

Analysis	Network	ROIs	Graph theory metric	Condition	Beta	*T*	*p*-uncorrected	*p*-FDR corrected
Main effect	DMN	PCC	Degree centrality	Two-sided[a]	0.50	3.47	.002*	.009*[+]
				Pre > post	0.50	3.47	.001*	.004*[+]
			Between-ness 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*

[a]Refers to a general comparison between pre- and post-measurements, 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.

ACC = Anterior cingulate cortex, DMN = Default mode network, PCC = Posterior cingulate cortex, ROIs = Regions-of-interest, SN = Salience network, T = t-test statistic.

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3.3 Between-Network Analyses

Main effect analyses: Significant graph-theory results are presented in **Table 3 and Figure 1**. Between SN-DMN, a significant decrease in closeness centrality was observed in response to the allergen challenge in the right LP (β = 0.23, *p*-uncorrected = .001, *p*-FDR = .010) and left LP (β = 0.23, *p*-uncorrected = .003, *p*-FDR = .013). There were no significant graph-theory results between SN-FPN.

Correlational analyses: Significant graph-theory results are presented in **Table 3 and Figure 1**. Between SN-FPN, there was a significant correlation between baseline depression scores and increased degree centrality (β = -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 SN-DMN.

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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*

Analysis	Network	ROIs	Graph theory metric	Condition	Beta	*T*	*p*-uncorrected	*p*-FDR corrected
Main effect	SN-DMN	Network	Gobal 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*

[a]Refers to a general comparison between pre- and post-measurements, 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.

DMN = Default mode network, FPN = Fronto-parietal network, LP = Lateral parietal, PPC = Posterior parietal cortex, ROIs = Regions-of-interest, SN = Salience network, T = t-test statistic.

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3.4 Post-Hoc Analyses

Within SN, the ACC showed a significant correlation between higher baseline cognitive symptoms of depression and decreases in closeness centrality (β = 0.02, *T* = 2.52**,** *p*-uncorrected = .010, *p*-FDR = .041) in response to the allergen challenge. No other significant correlations were found within the DMN (all *p*'s ≥ .496 [uncorrected]) and the FPN (all *p*'s ≥ .399 [uncorrected]). Additionally, no significant correlations with between-network change were observed for SN-DMN (all *p*'s ≥ .285 [uncorrected]), SN-FPN (all *p*'s ≥ .381 [uncorrected]), and DMN-FPN (all *p*'s ≥ .283 [uncorrected]).

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Figure 1. *Visualization of the triple network theory, proposed hypotheses, and key within- and between-network graph-theory results, showing pre-post changes after allergen challenge (main effects, models without depression scores) and their correlation with baseline depression symptoms (models with depression scores) in individuals with asthma*

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Summarized visualization of the proposed dynamic interactions between the three RSNs (SN, DMN, and 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 expected changes in graph-theory metrics within the DMN and FPN (without a specific direction; shown in blue).* ***C:*** *The main effects analyses revealed that within DMN, the PCC exhibited decreases in graph-theory metrics in response to the allergen challenge. Between SN-DMN, the bilateral LP also showed decreases in graph-theory metrics following the allergen challenge.* ***D:*** *Correlational analyses between baseline depression scores and changes in graph-theory metrics showed that the ACC within the SN exhibited decreases in graph-theory metrics. Between SN-FPN, the left PPC 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. ACC = Anterior cingulate cortex, DMN = Default mode network, FPN = Fronto-parietal network, LP = Lateral parietal, PCC = Posterior cingulate cortex, PPC = Posterior parietal cortex, RSNs = Resting-state networks, SN = Salience network.*

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4 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 asthma patients. The findings partially support our hypotheses. Significant decreases were observed in DMN metrics (PCC) and in 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. Specifically, 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 DMN or FPN or between SN-DMN.

4.1 Within-Network

4.1.1 Main Effects

We observed that the airway inflammatory provocation (SBP-Ag) affected the PCC (DMN node), with decreases in degree centrality and betweenness centrality following the allergen challenge. Degree centrality reflects the number of direct connections a node has, indicating a reduction in the 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, following 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 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,

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affecting emotional control and attention. While changes in PCC metrics were not significantly associated with baseline cognitive symptoms of depression, their impact following allergen challenge would provide more insight. The effect of these changes on emotion-cognition interactions could be more apparent, though our current measure of cognitive symptoms may not fully capture this. These alterations in DMN connections and communication may influence how asthma patients perceive their symptoms, potentially heightening symptom severity and discomfort. In summary, allergen provocation alters not only SN function but also the DMN, emphasizing inflammation's broad impact on brain networks, though further research is needed to confirm these findings.

4.1.2 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 by Laubacher et al.[11], where those with the highest depression symptoms showed the most significant rsFC decline within the SN. We did not observe similar findings within 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).

4.2 Between-Networks

4.2.1 Main Effects

In response to 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 SN-FPN.

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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 asthma patients 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 inter-network interactions in the neural response to inflammation in asthma. Further research is needed to better understand these processes and their effects on symptom regulation.

4.2.2 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 following challenge. We did not observe similar findings between SN-DMN.

This pattern suggests that inflammation can impact neuronal networks involved in cognitive processes [for review, see (44–46)]. Specifically, the left PPC, important for attention and sensory information integration (47) [for review, see (48)], appears 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.

4.3 Post-Hoc: Correlations with Cognitive Symptoms of Depression

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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 as well as between the networks.

The network dynamics of the ACC, involved in emotional processing and cognition-related functions like integration of interoceptive information (50,51), rumination (52), and the cognitive processing of stress (53), 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 resting-state network dynamics, cognitive function, depression, and asthma.

4.4 Null Findings

We observed several null findings in our main effect and correlational analyses within and between the networks, with no significant changes following 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. The SN's role in coordinating the DMN and FPN, as postulated by Menon & 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.

4.5 Strengths and Limitations

The present study shows alterations within and between 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. 2.) The longitudinal experimental design of this study allows for inference of causality.

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There are several limitations to consider. 1.) The sample size of only twenty-four 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 (54)], making future studies with more severely depressed populations difficult. Additionally, as 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 following 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 48h in between the 1st bronchoscopy and the 2nd 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.

4.6 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 (55,56) and chronic inflammation in women [for review, see (57)].

4.7 Conclusions

In conclusion, 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 the 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.

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6 DECLARATIONS (IF APPLICABLE)

6.1 Data availability

Data will be made available on request.

6.2 Authors' contributions

Concept and design: MAR, WWB. Acquisition, analysis, or interpretation of data: ML, CL, MAR, TIS, CF, and DRK. Drafting of the manuscript: ML, MAR. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: ML, CL, MAR. Obtained funding: WWB, MAR. Administrative, technical, or material support: RB. Supervision: MAR.

Declaration of competing interest

6.3 Disclosures and funding

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Supplement Description:

Supplement Methods, Results, Figure S1, Table S1

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7 REFERENCES

1. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25:1822–32.

2. Slavich GM. Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority. Brain Behav Immun. 2015;45:13–4.

3. U.S. Centers for Disease Control and Prevention. Health and Economic Costs of Chronic Diseases [internet]. 2024 May 15; Available from: https://www.cdc.gov/chronicdisease/about/costs/index.htm

4. U.S. Centers for Disease Control and Prevention. Most Recent National Asthma Data [internet|. 2024 Jun 21; Available from: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

5. Katon W, Lozano P, Russo J, McCauley E, Richardson L, Bush T. The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls. J Adolesc Health. 2007;41(5):455–63.

6. Zhang L, Zhang X, Zheng J, Wang L, Zhang HP, Wang L, et al. Co-morbid psychological dysfunction is associated with a higher risk of asthma exacerbations: a systematic review and meta-analysis. J Thorac Dis. 2016;8(6):1257–68.

7. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun. 2007;21(8):993–9.

8. Urrutia I, Aguirre U, Pascual S, Esteban C, Ballaz A, Arrizubieta I, et al. Impact of Anxiety and Depression on Disease Control and Quality of Life in Asthma Patients. J Asthma. 2012;49(2):201–8.

9. Krommydas GC, Gourgoulianis KI, Angelopoulos NV, Kotrotsiou E, Raftopoulos V, Molyvdas PA. Depression and pulmonary function in outpatients with asthma. Respir Med. 2004;98(3):220–4.

10. Dill-McFarland KA, Altman MC, Esnault S, Jarjour NN, Busse WW, Rosenkranz MA. Molecular pathways underlying lung-brain axis signaling in asthma: Relevance for psychopathology and neuroinflammation. J Allergy Clin Immunol. 2024;153(1):111–21.

11. Laubacher C, Imhoff-Smith TP, Klaus DR, Frye CJ, Esnault S, Busse WW, et al. Salience network resting state functional connectivity during airway inflammation in asthma: A feature of mental health resilience? Brain Behav Immun. 2024;2(122):9–17.

12. Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci USA. 2005;102(37):13319–24.

13. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS One. 2012;7(8):e40921.

14. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483–506.

15. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010;214(5–6):655–67.

16. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry. 2009;66(5):407–14.

17. Goldsmith DR, Bekhbat M, Mehta ND, Felger JC. Inflammation-Related Functional and Structural Dysconnectivity as a Pathway to Psychopathology. Biol Psychiatry. 2023;93(5):405–18.

18. Zheng H, Xu L, Xie F, Guo X, Zhang J, Yao L, et al. The Altered Triple Networks Interaction in Depression under Resting State Based on Graph Theory. Biomed Res Int. 2015;2015:386326.

19. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. Front Hum Neurosci. 2014;7:930.

Journal Pre-proof

20. Li QG, Zhou FQ, Huang X, Zhou X, Liu C, Zhang T, et al. Alterations of resting-state functional network centrality in patients with asthma: evidence from a voxel-wise degree centrality analysis. Neuroreport. 2018;29(14):1151–6.

21. Zhang Y, Yang Y, Xu X, Yuan Y. Coupling of spatial and directional functional network connectivity reveals a physiological basis for salience network hubs in asthma. Brain Imaging Behav. 2022;16(1):176–85.

22. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009;10(3):186–98.

23. Farahani FV, Karwowski W, Lighthall NR. Application of Graph Theory for Identifying Connectivity Patterns in Human Brain Networks: A Systematic Review. Front Neurosci. 2019;6(13):585.

24. Wang J, Zuo X, He Y. Graph-based network analysis of resting-state functional MRI. Front Syst Neurosci. 2010;4(16).

25. Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol Psychiatry. 2005;57(10):1079–88.

26. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008;213(1–2):93–118.

27. Den Hartog HM, Derix MM, Van Bemmel AL, Kremer B, Jolles J. Cognitive functioning in young and middle-aged unmedicated out-patients with major depression: testing the effort and cognitive speed hypotheses. Psychol Med. 2003;33(8):1443–51.

28. Brockmeyer T, Bents H, Holtforth MG, Pfeiffer N, Herzog W, Friederich HC. Specific emotion regulation impairments in major depression and anorexia nervosa. Psychiatry Res. 2012;200(2–3):550–3.

29. Lehrer PM, Isenberg S, Hochron SM. Asthma and emotion: a review. J Asthma. 1993;30(1):5–21.

30. Rosenkranz MA, Davidson RJ. Affective neural circuitry and mind-body influences in asthma. Neuroimage. 2009;47(3):972–80.

31. Ye M, Qing P, Zhang K, Liu G. Altered network efficiency in major depressive disorder. BMC Psychiatry. 2016;16(1):450.

32. Beck AT, Ward CH. An inventory for measuring depression. Arch Gen Psychiatry. 1961;561–71.

33. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3).

34. NeuroImaging Tools & Resources Collaboratoy. Conn: functional connectivity toolbox [Internet]. 2024; Available from: https://www. nitrc.org/projects/conn/

35. Nieto-Castanon A. Small-world network properties & Network edges options [internet] [Internet]. 2018. Available from: https://www.nitrc.org/forum/forum.php?thread_id=9338&forum_id=1144

36. Nieto-Castanon A. Graph measures (ROI-level) [internet]. 2020; Available from: https://web.conn-toolbox.org/fmri-methods/connectivity-measures/graphs-roi-level

37. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021.

38. RStudio Team. Integrated development environment for R. Boston, MA: RStudio, PBC; 2024.

39. Andrews-Hanna JR. The brain's default network and its adaptive role in internal mentation. Neuroscientist. 2012;18(3):251–70.

40. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Acad Sci. 2008;1124:1–38.

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41. Goldstein-Piekarski AN, Ball TM, Samara Z, Staveland BR, Keller AS, Fleming SL, et al. Mapping Neural Circuit Biotypes to Symptoms and Behavioral Dimensions of Depression and Anxiety. Biol Psychiatry. 2022;91(6):561–71.

42. Mayo Foundation for Medical Education and Research. Depression (major depressive disorder) [internet|. 2024 Sep 6; Available from: https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007

43. Dipasquale O, Cooper EA, Tibble J, Voon V, Baglio F, Baselli G, et al. Interferon-α acutely impairs whole-brain functional connectivity network architecture - A preliminary study. Brain Behav Immun. 2016;58:31–9.

44. Lindquist KA, Barrett LF. A functional architecture of the human brain: emerging insights from the science of emotion. Trends Cogn Sci. 2012;16(11):533–40.

45. Menon V. Large-scale functional brain organization. In: Brain Mapping: An Encyclopedic Reference. New York, NY: Elsevier; 2015. p. 449–59.

46. Schimmelpfennig J, Topczewski J, Zajkowski W, Jankowiak-Siuda K. The role of the salience network in cognitive and affective deficits. Front Hum Neurosci. 2023;20(17):1133367.

47. Andersen RA, Essick GK, Siegel RM. Neurons of area 7 activated by both visual stimuli and oculomotor behavior. Exp Brain Res. 1987;67(2):316–22.

48. Freedman DJ, Ibos G. An Integrative Framework for Sensory, Motor, and Cognitive Functions of the Posterior Parietal Cortex. Neuron. 2018;97(6):1219–34.

49. Nejad AB, Fossati P, Lemogne C. Self-referential processing, rumination, and cortical midline structures in major depression. Front Hum Neurosci. 2013;10(7):666.

50. Farb NAS, Zuo Z, Price CJ. Interoceptive Awareness of the Breath Preserves Attention and Language Networks amidst Widespread Cortical Deactivation: A Within-Participant Neuroimaging Study. eNeuro. 2023;10(6).

51. Sugawara A, Katsunuma R, Terasawa Y, Sekiguchi A. Interoceptive training impacts the neural circuit of the anterior insula cortex. Transl Psychiatry. 2024;14(206).

52. Sheena MK, Jimmy J, Burkhouse KL, Klumpp H. Anterior cingulate cortex activity during attentional control corresponds with rumination in depression and social anxiety. Psychiatry Res Neuroimaging. 2021;317:111385.

53. Brown VM, Morey RA. Neural systems for cognitive and emotional processing in posttraumatic stress disorder. Front Psychol. 2012;3(449).

54. Ferguson MC, McNicol E, Kleykamp BA, Sandoval K, Haroutounian S, Holzer KJ, et al. Perspectives on Participation in Clinical Trials Among Individuals With Pain, Depression, and/or Anxiety: An ACTTION Scoping Review. J Pain. 2023;24(1):24–37.

55. Li S, Zhang X, Cai Y, Zheng L, Pang H, Lou L. Sex difference in incidence of major depressive disorder: an analysis from the Global Burden of Disease Study 2019. Ann Gen Psychiatry. 2023;22(1):53.

56. Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU. Sex differences in rates of depression: cross-national perspectives. J Affect Disord. 1993;29(2–3):77–84.

57. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocr. 2014;35(3):347–69.

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KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Biological Sample	Human participants (with diagnosed asthma; male and female)	University of Wisconsin-Madison (DOI: 10.1016/j.bbi.2024.07.042)	-	
Chemical Compound or Drug	Lidocaine (1% solution, gel, spray)	-	-	
Chemical Compound or Drug	Glycopyrrolate (0.2 mg)	-	-	
Chemical Compound or Drug	Midazolam (0.5–2.0 mg)	-	-	
Chemical Compound or Drug	Albuterol (180 mcg)	-	-	
Chemical Compound or Drug	Afrin nasal spray	-	-	
Chemical Compound or Drug	Allergen extracts (house dust mite, cat dander, ragweed)	Greer Labs, Lenoir, NC	-	
Software; Algorithm	CONN functional connectivity toolbox (version 22.a)	DOI: 10.1089/brain.2012.0073	RRID:SCR_009550	
Software; Algorithm	RStudio (version 2024.04.0)	Rstudio, Inc.	RRID:SCR_000432	
Software; Algorithm	AFNI (version 17.3)	NIH / NIMH	RRID:SCR_005927	
Software; Algorithm	FSL (version 6.00)	FMRIB, University of Oxford	RRID:SCR_002823	
Other	Beck Depression Inventory (BDI), 21-item self-report questionnaire	Beck, A. T., & Ward, C. H. (1961). An inventory for measuring depression. *Arch Gen Psychiatry*, 561–571.	-	
Other	Segmental Bronchoprovocation Provocation with Allergen (SBP-Ag)	University of Wisconsin-Madison (DOI: 10.1016/j.bbi.2024.07.042)	-	
Other	GE Discovery MR750 3T MRI scanner with 32-channel head coil	GE Healthcare	-	

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Key Resource Table

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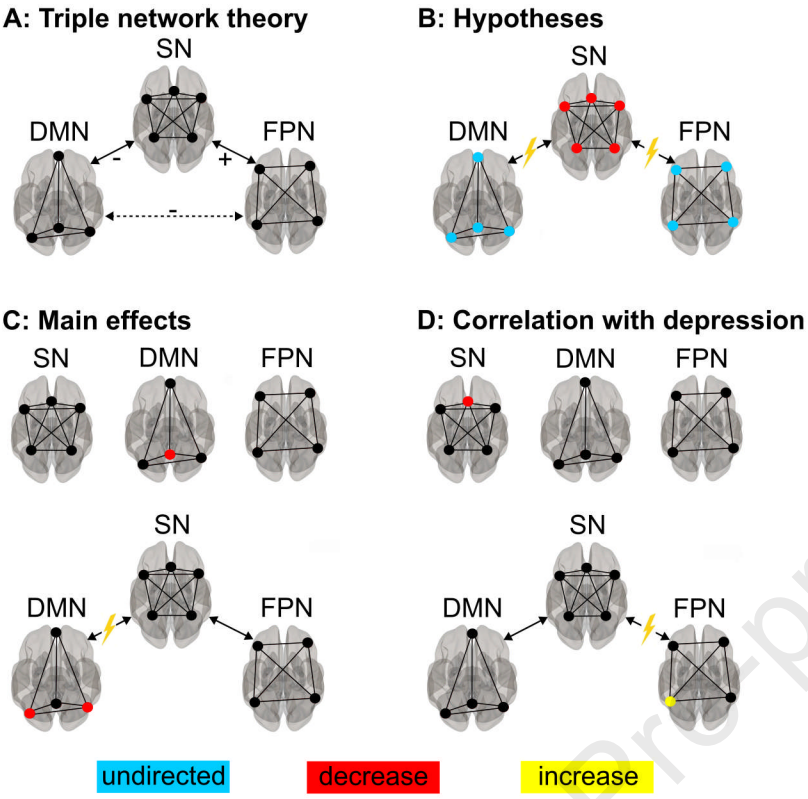

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