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Association of Sinonasal Inflammation With Functional Brain Connectivity

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IMPORTANCE In recent years, there have been several meaningful advances in the understanding of the cognitive effects of chronic rhinosinusitis. However, an investigation exploring the potential link between the underlying inflammatory disease and higher-order neural processing has not yet been performed.

OBJECTIVE To describe the association of sinonasal inflammation with functional brain connectivity (Fc), which may underlie chronic rhinosinusitis–related cognitive changes.

DESIGN, SETTING, AND PARTICIPANTS This is a case-control study using the Human Connectome Project (Washington University–University of Minnesota Consortium of the Human Connectome Project 1200 release), an open-access and publicly available data set that includes demographic, imaging, and behavioral data for 1206 healthy adults aged 22 to 35 years. Twenty-two participants demonstrated sinonasal inflammation (Lund-Mackay score [LMS] $\geq$ 10) and were compared with age-matched and sex-matched healthy controls (LMS = 0). These participants were further stratified into moderate (LMS < 14, n = 13) and severe (LMS $\geq$ 14, n = 9) inflammation groups. Participants were screened and excluded if they had a history of psychiatric disorder and/or neurological or genetic diseases. Participants with diabetes or cardiovascular disease were also excluded, as these conditions may affect neuroimaging quality. The data were accessed between October 2019 and August 2020. Data analysis was performed between May 2020 and August 2020.

MAIN OUTCOMES AND MEASURES The primary outcome was the difference in resting state Fc within and between the default mode, frontoparietal, salience, and dorsal attention brain networks. Secondary outcomes included assessments of cognitive function using the National Institutes of Health Toolbox Cognition Battery.

RESULTS A total of 22 patients with chronic rhinosinusitis and 22 healthy controls (2 [5%] were aged 22-25 years, 26 [59%] were aged 26-30 years, and 16 [36%] were aged 31-35 years; 30 [68%] were men) were included in the analysis. Participants with sinonasal inflammation showed decreased Fc within the frontoparietal network, in a region involving bilateral frontal medial cortices. This region demonstrated increased Fc to 2 nodes within the default-mode network and decreased Fc to 1 node within the salience network. The magnitude of these differences increased with inflammation severity (dose dependent). There were no significant associations seen on cognitive testing.

CONCLUSIONS AND RELEVANCE In this case-control study, participants with sinonasal inflammation showed decreased brain connectivity within a major functional hub with a central role in modulating cognition. This region also shows increased connectivity to areas that are activated during introspective and self-referential processing and decreased connectivity to areas involved in detection and response to stimuli. Future prospective studies are warranted to determine the applicability of these findings to a clinical chronic rhinosinusitis population.

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In recent years, there have been several meaningful advances in the understanding of the cognitive effects of chronic rhinosinusitis (CRS). Specifically, researchers have shown that patients with CRS report poorer overall cognitive function and exhibit worse performance on tests of reaction time,[1] processing speed,[2] and selective attention.[2,3] In addition, this dysfunction has been found to be associated with rhinosinusitis-specific quality of life[4] and responsive to medical or surgical intervention.[2,3] Collectively, these data indicate that there may be a relatively unexplored putative link between the underlying inflammatory disease and higher-order neural processing.

The human brain is indisputably complex and composed of interconnected networks that function together to process information and execute behavior.[5] In disease states, these dynamic interactions may be disrupted and manifest as cognitive dysfunction. Resting-state functional magnetic resonance imaging is a powerful technique that measures spontaneous brain activity through detection of blood-oxygen level-dependent signal.[6] Functional connectivity (Fc) analysis of these data allows for the study of brain networks that may be anatomically distinct yet functionally linked based on synchronous fluctuations of low-frequency signal.[7] Several contemporary studies of chronic inflammatory and immune conditions, including Sjögren syndrome[8] and inflammatory bowel disease,[9-11] have identified alterations in Fc within networks associated with cognitive control and stimulus detection. Despite the increasing attention to the cognitive dysfunction seen in CRS, to our knowledge, an investigation of functional brain connectivity exploring this phenomenon has not yet been performed.

In this study, we used resting-state functional magnetic resonance imaging data from a publicly available data set, the Human Connectome Project (HCP), to examine the Fc profile of brain networks involved in cognitive processing in participants with sinonasal inflammation compared with healthy controls. We hypothesized that, when comparing these groups, there would be differences in Fc within and between brain networks. The goal of this investigation is to suggest potential neural correlates for the cognitive dysfunction seen in CRS, with the understanding that the study cohort is defined only by radiographic findings and not clinical criteria, as a proof of concept and direct future research to this relatively unexplored area.

Key Points

Question Is sinonasal inflammation associated with functional brain connectivity?

Findings In this case-control study of 22 patients with chronic rhinosinusitis and 22 healthy controls, participants with sinonasal inflammation showed decreased brain connectivity within the frontoparietal network, a major functional hub. This region also showed increased connectivity to areas that activate during introspective processing and decreased connectivity to areas that are involved in detection and response to stimuli.

Meaning This study provides initial evidence for alterations in functional brain connectivity as a potential basis for cognitive dysfunction seen in patients with chronic rhinosinusitis.

Methods

Participants

The participants for the current study were selected from the Human Connectome Project (Washington University-University of Minnesota Consortium of the Human Connectome Project [WU-Minn HCP] 1200 release), an open-access and publicly available data set that includes demographic, imaging, and behavioral data for 1206 healthy adults aged 22 to 35 years (https://www.humanconnectome.org/).[12] Participants within this data set were screened to exclude a history of psychiatric disorders (eg, depression or schizophrenia), neurological diseases, and genetic disease (eg, cystic fibrosis or primary ciliary dyskinesia). Participants were also excluded if they had a history of diabetes or cardiovascular disease, as these conditions may affect neuroimaging quality. Participants were administered the Mini-Mental State Exam (MMSE)[13] to assess overall cognitive function and included if their score was normal (≥27).[14] Additional details are available in the HCP S1200 release reference manual.[15] The data were accessed between October 2019 and August 2020. Data analysis was performed between May 2020 and August 2020. Use of these data complies with the WU-Minn HCP Consortium Open Access Data Use agreement. Informed consent was not obtained, as the data used in this study were a part of an open access data set.

Image Acquisition

Structural Imaging

As part of the HCP database, high-resolution T1-weighted and T2-weighted brain images, inclusive of the paranasal sinuses, were acquired using a 3-T Siemens Connectome Skyra magnetic resonance imaging scanner (Siemens Medical Systems) with a 32-channel head coil at an isotropic resolution of 0.7 mm^3. The T1-weighted scan was acquired using a 3-dimensional magnetization-prepared rapid acquisition with gradient echo sequence. All structural scans were defaced by the HCP using the algorithm outlined in Milchenko and Marcus.[16]

Functional Imaging

All functional images were acquired on the same scanner as above using a multiband gradient-echo planar imaging sequence, and 1200 images were obtained per run across 2 runs. Each scan had a duration of 14 minutes and 33 seconds, during which participants were instructed to keep their eyes open and fixated on a crosshair.[17] Additional details are available in the HCP S1200 release reference manual and related imaging publications.[15,17,18]

Group Selection

All 1113 available T2-weighted structural images were reviewed for evidence of sinonasal inflammation by an otolaryngologist (A.J. or J.D.B.). Previous literature has demonstrated strong correlation (r = 0.837; P < .001) between computed tomography and magnetic resonance imaging in the

radiographic assessment of sinonasal inflammation.[19,20] In accordance with the Lund-Mackay scoring (LMS) system,[21] the maxillary, frontal, anterior, and posterior ethmoid and sphenoid sinuses on each side were assessed, and a score of 0 (no abnormality), 1 (partial opacification), or 2 points (complete opacification) was assigned. The ostiomeatal complex was scored either 0 (not obstructed) or 2 points (obstructed). Based on the understanding that likelihood of clinical CRS increases with increasing LMS,[22] and a previously reported mean LMS of 9.8 in patients with clinical CRS,[22] we selected an LMS cutoff of 10 or greater (n = 22) to define the sinonasal inflammation group. These participants were further stratified into groups based on inflammation severity; moderate (LMS < 14; n = 13) and severe (LMS ≥ 14; n = 9). A total of 22 age group-matched and sex-matched participants without evidence of sinonasal inflammation (LMS = 0) were selected from the same data set as healthy controls. The size of the study population was sufficiently large (n ≥ 20) and consistent with recommendations from previous literature to ensure adequate sensitivity and reliability of the results.[23]

Cognitive and Sensory Analysis

To assess general cognitive functioning, MMSE and Cognitive Function Composite scores were calculated and reported in the HCP data set. The Cognitive Function Composite is a component of the NIH Toolbox Cognition Battery and is an age-adjusted composite score reflecting crystallized (dependent on past learning experiences) and fluid (capacity for new learning and information processing in novel situations) cognitive abilities.[24] Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).[25] Summary scores, PSQI component scores, and individual question responses were reported.

Participants completed cognitive tasks from the NIH Toolbox Cognition Battery designed to measure specific cognitive domains: attention and executive function, episodic memory, working memory, language, and processing speed. In addition to cognitive measures, participants also completed sensory tasks from the NIH Toolbox Sensation Measures (ie, the Odor Identification Test, Regional Taste Intensity Test, and Pain Interference Survey). A full description of the tests is included at the NIH Toolbox website: https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox.

Data analysis was performed using R (version 3.6.3) within the RStudio platform (R Foundation for Statistical Computing, version 1.2.1335). Shapiro-Wilk tests were used to assess for normality of distribution. A 1-way multivariate analysis of variance (ANOVA) was performed to investigate the effect of group (severe inflammation, moderate inflammation, and control) for each of the 19 behavioral variables. Significance was set at a Bonferroni-adjusted $P < .0026$ (0.05/19 tests).

Functional Connectivity Analysis

Preprocessing

Standardized preprocessing pipelines of functional and anatomical volumes were applied using CONN toolbox, version 18.b (https://www.nitrc.org/projects/conn). In brief, preprocessing included functional data realignment to the first scan of the first session using B-spline interpolation; unwarping and susceptibility distortion correction along each phase-encoded direction (right-left and left-right); outlier detection and motion correction where acquisitions with displacements above 0.9 mm or global blood-oxygen level-dependent signal changes above 5 SDs were flagged, and framewise displacement at each time point was estimated to be used in the future for outlier regression; functional and anatomical data normalization into standard MNI space and segmentation into gray matter, white matter, and cerebrospinal fluid; and functional data smoothing using spatial convolution with a Gaussian kernel of 8-mm full-width half maximum. Additional denoising steps included band-pass filtering at 0.008 to 0.09 Hz and removal of signal associated with the motion parameters, white matter, cerebrospinal fluid, and outlying functional volumes using ordinary least squares regression.

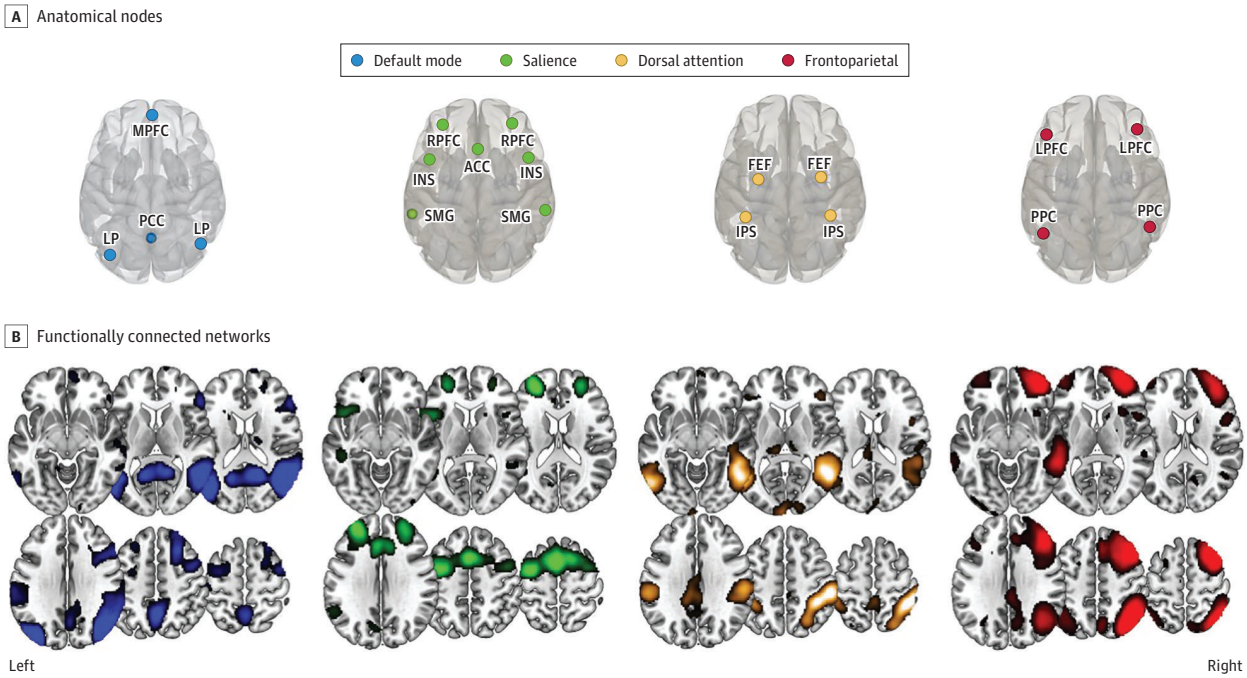
Independent Component (Intranetwork Connectivity) Analysis

Using the CONN toolbox software, an independent component analysis was first applied using all 44 participants (sinonasal inflammation = 22; healthy controls = 22) to identify statistically generated independent components. Using correlational spatial match-to-template approach, the components that most closely matched the networks of interest—the default-mode network (DMN), frontoparietal network (FPN), salience network (SN), and dorsal attention network—were selected (**Figure 1**). These networks were selected a priori based on previous studies.[1-4] Next, a participant-specific version of the spatial map and associated time series for each network using back-projection was generated. Finally, the resulting individual Z-score maps derived from the back-projection were submitted to a 2-way ANOVA with the participant as a random factor and the group and network as a fixed factor. Statistical analyses were performed to identify differences within each network (intranetwork) between the entire sinonasal inflammation group and healthy controls. Significance was set at a voxel-wise $P < .001$ and cluster size family-wise error-corrected $P \leq .05$ at a minimal cluster size of 237 mm^3.

ROI–ROI (Internetwork Connectivity) Analysis

Region of interest (ROI) seed-based analysis was used to characterize cross-network (internetwork) connectivity of the region demonstrating altered connectivity in participants with sinonasal inflammation in the independent component analysis. The seed ROI was set to the FPN region that showed decreased connectivity in the sinonasal inflammation group, and 19 predefined anatomical nodes within CONN toolbox corresponding to the networks of interest were set as the target ROIs, including DMN: medial prefrontal cortex (MPFC), precuneus cortex, bilateral lateral parietal region; SN: anterior cingulate cortex, bilateral anterior insula, rostral prefrontal cortex (RPFC), and supramarginal gyrus; dorsal attention network: bilateral frontal eye field and intraparietal sulcus; FPN: bilateral lateral prefrontal cortex and posterior parietal cortex (Figure 1). As with the independent component analysis, differences in intensity of seed-to-target connections between groups were investigated using a 2-way ANOVA. Significant differences were set to a 2-sided family-wise error-corrected $P \leq .05$.

Figure 1. Spatial Representation of Selected Networks and Regions of Interest



A, Anatomical nodes used for internetwork connectivity analysis predefined within CONN toolbox corresponding to the networks of interest are overlaid over the 3-dimensional standard Montreal Neurologic Institute (MNI) brain template for default mode (blue spheres), salience (green spheres), dorsal-attention (yellow spheres), and frontoparietal (red spheres) networks. B, Functionally connected networks extracted by independent component analysis for intranetwork connectivity analysis are overlaid over axial slices of the standard MNI brain template. Colors represent correlations threshold at $t > 3.5$. ACC indicates anterior cingulate cortex; FEF, frontal eye field; INS, insular sulcus; IPS, intraparietal sulcus; LP, lateral parietal; LPFC, lateral prefrontal cortex; MPFC, medial prefrontal cortex; PCC, precuneus cortex; PPC, posterior parietal cortex; RPFC, rostral prefrontal cortex; SMG, supramarginal gyrus.

Results

Participants

A total of 22 patients with chronic rhinosinusitis and 22 healthy controls (2 [5%] were aged 22-25 years, 26 [59%] were aged 26-30 years, and 16 [36%] were aged 31-35 years; 30 [68%] were men) were included in the analysis. Of the 22 participants with sinonasal inflammation included in the study, 13 were categorized as having moderate inflammation (LMS < 14), and 9 as having severe inflammation (LMS ≥ 14). There was no difference in distribution of age or sex between these groups (**Table 1**).

Cognitive and Sensory Analysis

Overall cognitive status, as assessed by both MMSE and Cognitive Function Composite, was similar between groups. Self-reported sleep quality overall score and domains (ie, subjective quality, latency, duration, habitual efficiency, disturbances, use of sleep medications, and daytime dysfunction) as assessed by the PSQI were also not different between groups (Table 1).

Additionally, statistical analysis did not suggest any differences in cognitive assessment using the NIH Toolbox Cognition Battery between groups. Similarly, analysis did not indicate any differences in olfaction, taste, and pain between groups as measured by the NIH Toolbox Sensation Measures testing component. For a complete list of tests and results, see Table 1.

Functional Connectivity Analysis

Independent Component (Intranetwork Connectivity) Analysis

Results from the independent component analysis (**Figure 2**) showed that Fc was decreased in participants with sinonasal inflammation within a region of the FPN, involving the bilateral frontal medial cortex and left frontal pole (peak Montreal Neurologic Institute [MNI] coordinates: −4, 60, −18; mean [95% CI] connectivity: sinonasal inflammation, −1.45 [−1.02 to −1.88]; control, 0.06 [0.41 to −0.29]). When observing comparisons from the 2-way ANOVA between severe and mild inflammation individually against healthy controls, the magnitude of this finding increased with increasing level of inflammation: moderate, −1.12 (−0.64 to −1.61); severe, −1.91 (−1.10 to −2.72) (Figure 2). This area was used as a ROI seed for subsequent analyses.

ROI-ROI (Internetwork Connectivity) Analysis

Using the seed ROI identified above within the FPN, there was increased connectivity in the sinonasal inflammation group compared with controls with 2 target ROIs in the DMN: the MPFC (sinonasal inflammation, 0.43 [0.53 to 0.34]; control, 0.23 [0.31 to 0.14]) and left lateral parietal (sinonasal inflam-

Table 1. Demographic Characteristics and Cognitive and Sensory Measures

Characteristic/measure	Mean (95% CI)			P value[a]
	Inflammation group			
	Severe (n = 9)	Moderate (n = 13)	Control group (n = 22)	
Age, y, No. (%)				
22-25	1 (11)	0	1 (5)	NA
26-30	5 (56)	8 (62)	13 (59)	
31-35	3 (33)	5 (39)	8 (36)	
Male sex, No. (%)	7 (78)	8 (62)	15 (68)	.72
Overall cognitive status				
MMSE	29.3 (29.8 to 28.7)	28.8 (29.5 to 28.1)	28.9 (29.3 to 28.3)	.48
Cognitive function composite score	129.1 (139.8 to 118.4)	106.9 (123.2 to 90.5)	110.8 (121.5 to 100.1)	.08
Pittsburgh Sleep Quality Index				
Global score				
Subjective sleep quality (1)	1.1 (1.3 to 0.8)	0.9 (1.2 to 0.6)	0.8 (1.1 to 0.8)	.52
Sleep latency (2)	0.8 (1.4 to 0.1)	1.0 (1.4 to 0.5)	1.2 (1.5 to 0.8)	.42
Sleep duration (3)	0.3 (0.8 to −0.2)	0.8 (1.4 to 0.3)	0.9 (1.4 to 0.3)	.38
Habitual sleep efficiency (4)	0.3 (0.8 to −0.2)	0.7 (1.2 to 0.1)	0.5 (0.9 to 0.07)	.66
Sleep disturbances (5)	1.2 (1.7 to 0.7)	1.2 (1.4 to 0.9)	0.9 (1.1 to 0.5)	.14
Use of sleep medication (6)	0.3 (1.1 to −0.4)	0.5 (1.1 to −0.04)	0.1 (0.2 to −0.03)	.21
Daytime dysfunction (7)	0.7 (1.0 to 0.2)	0.8 (1.1 to 0.2)	0.7 (0.9 to 0.3)	.91
NIH Toolbox Cognition Battery				
Attention and executive functioning				
Dimensional Card Sort Test	104.9 (111.4 to 98.2)	95.4 (104.5 to 86.2)	98.7 (102.5 to 94.7)	.15
Flanker Inhibitory Control and Attention Test	104.6 (113.3 to 95.7)	100.5 (107.1 to 93.7)	97.9 (102.5 to 93.1)	.31
Episodic memory				
Picture Sequence Memory Test	111.8 (122.6 to 101.0)	105.4 (118.5 to 92.3)	105.4 (113.9 to 96.7)	.67
Working memory				
List sorting working memory	110.6 (118.5 to 102.7)	101.4 (107.8 to 94.9)	108.4 (115.4 to 101.2)	.23
Language				
Picture vocabulary	120.8 (129.0 to 112.6)	104.9 (116.5 to 93.2)	111.0 (118.1 to 103.9)	.09
Oral Reading Recognition Test	110.9 (120.0 to 101.8)	103.8 (115.8 to 91.8)	106.9 (113.5 to 100.1)	.60
Processing speed				
Pattern Comparison Processing Speed Test	118.6 (127.9 to 109.2)	96.0 (107.9 to 84.0)	93.6 (103.9 to 83.2)	.01
NIH Toolbox Sensation Measures				
Olfaction (Odor Identification Test)	100.0 (109.4 to 90.6)	91.8 (101.4 to 82.2)	96.6 (102.7 to 90.3)	.40
Taste (Regional Taste Intensity Test)	96.8 (110.2 to 83.4)	100.2 (111 to 89.2)	100.1 (106.9 to 93.1)	.87
Pain (Pain Interference Survey)	46.2 (51.8 to 40.4)	53.1 (59.6 to 46.6)	46.6 (49.7 to 43.3)	.07

Abbreviations: MMSE, Mini-Mental State Exam; NIH, National Institutes of Health.

[a] Level of significance set to .0026 (Bonferroni corrected).

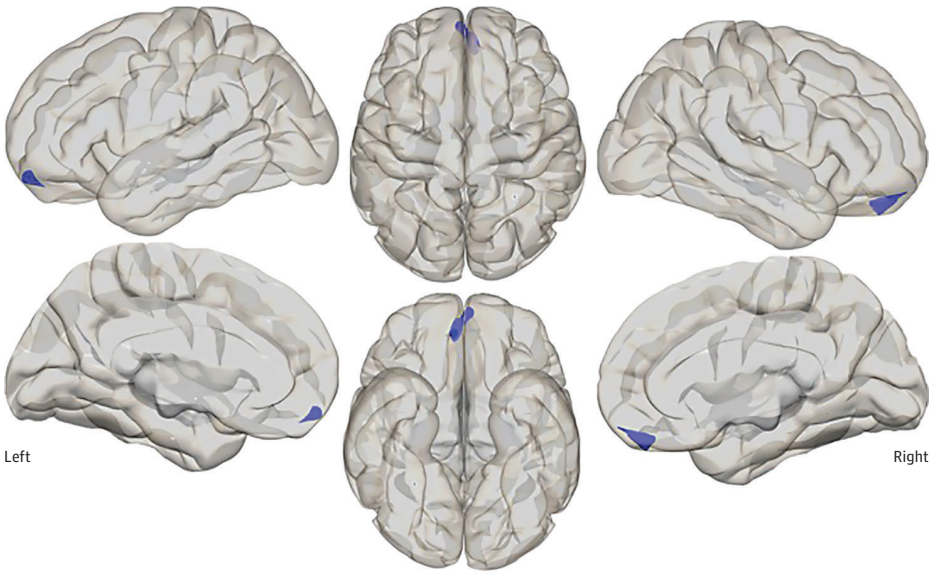
mation, 0.26 [0.37 to 0.16]; control, 0.14 [0.22 to 0.06]) and decreased connectivity with the right RPFC SN node (sinonasal inflammation, −0.25 [−0.18 to −0.32]; control, −0.05 [0.03 to −0.150]).

When stratifying the inflammation groups for separate analysis (ie, moderate vs severe), several additional target ROIs reached significance. Specifically, when considering the severe sinonasal inflammation group vs healthy controls, the MPFC (severe inflammation, 0.48 [0.62 to 0.35]; control, 0.23 [0.31 to 0.14]) and bilateral lateral parietals (left: severe inflammation, 0.36 [0.54 to 0.17]; control, 0.14 [0.22 to 0.06]; right: severe inflammation, 0.33 [0.47 to 0.19]; control, 0.09 [0.14 to 0.04]) showed increased connectivity and bilateral RPFCs (left: severe inflammation, 0.23 [−0.11 to −0.35]; control, −0.09 [−0.03 to −0.15]; right: severe inflammation, −0.33 [−0.22 to −0.44]; control, −0.05 [0.03 to −0.15]), the left supramarginal gyrus (severe inflammation, −0.17 [−0.03 to −0.32]; control, −0.02 [0.02 to −0.07]) and the right anterior insula (severe inflammation, −0.23 [−0.10 to −0.35]; control, −0.09 [−0.04 to −0.14]) showed decreased connectivity (**Table 2**, **Figure 3**). Thus, the magnitude of the effect increased commensurate with increased inflammation severity.

Discussion

In this proof-of-concept study, we found that compared with controls, participants with sinonasal inflammation demon-

Figure 2. Differences Between Participants With Inflammation vs Healthy Controls Within the Frontoparietal Network



Network	Region	Size, mm^3	Peak MNI (x, y, z)	*t*	*P* value
Inflammation < control					
Frontoparietal	Frontal medial cortex	2.630	(-4, 60, -18)	-3.54	.021

Color scale represents *t* value over an inflated Montreal Neurologic Institute (MNI) brain template. Table includes cluster size in mm^3, MNI coordinates of the peak intensity voxel, family-wise error–corrected peak *P* and *t*-score values.

Table 2. Significant Differences in Intensity of Seed-to-Node Connections Between Severe Inflammation and Controls Using a 2-Way ANOVA[a]

Target	Location (x, y, z)	*t*	*P* value[b]	Mean (95% CI)[c] Inflammation group: Severe (n = 9)	Moderate (n = 13)	Control group (n = 22)
Severe inflammation > control						
Default mode						
LP (R)	(47, −67, 29)	4.38	.003	0.33 (0.47 to 0.19)	0.20 (0.23 to 0.08)	0.09 (0.14 to 0.04)
MPFC	(1, 55, −3)	3.35	.01	0.48 (0.62 to 0.35)	0.40 (0.54 to 0.26)	0.23 (0.31 to 0.14)
LP (L)	(−39, −77, 33)	2.83	.03	0.36 (0.54 to 0.17)	0.20 (0.33 to 0.06)	0.14 (0.22 to 0.06)
Severe inflammation < control						
Salience						
RPFC (R)	(32, 46, 27)	−3.63	.01	−0.33 (−0.22 to −0.44)	−0.21 (−0.11 to −0.29)	−0.05 (0.03 to −0.15)
SMG (L)	(−60, −39, 31)	−2.78	.03	−0.17 (−0.03 to −0.32)	−0.08 (0.005 to −0.15)	−0.02 (0.02 to −0.07)
Anterior insula (R)	(47, 14, 0)	−2.76	.03	−0.23 (−0.10 to −0.35)	−0.13 (−0.01 to −0.22)	−0.09 (−0.04 to −0.14)
RPFC (L)	(−32, 45, 27)	−2.56	.04	−0.23 (−0.11 to −0.35)	−0.16 (−0.07 to −0.23)	−0.09 (−0.03 to −0.15)

Abbreviations: ANOVA, analysis of variance; L, left; LP, lateral parietal; MPFC, medial prefrontal cortex; R, right; RPFC, rostral prefrontal cortex; SMG, supramarginal gyrus.

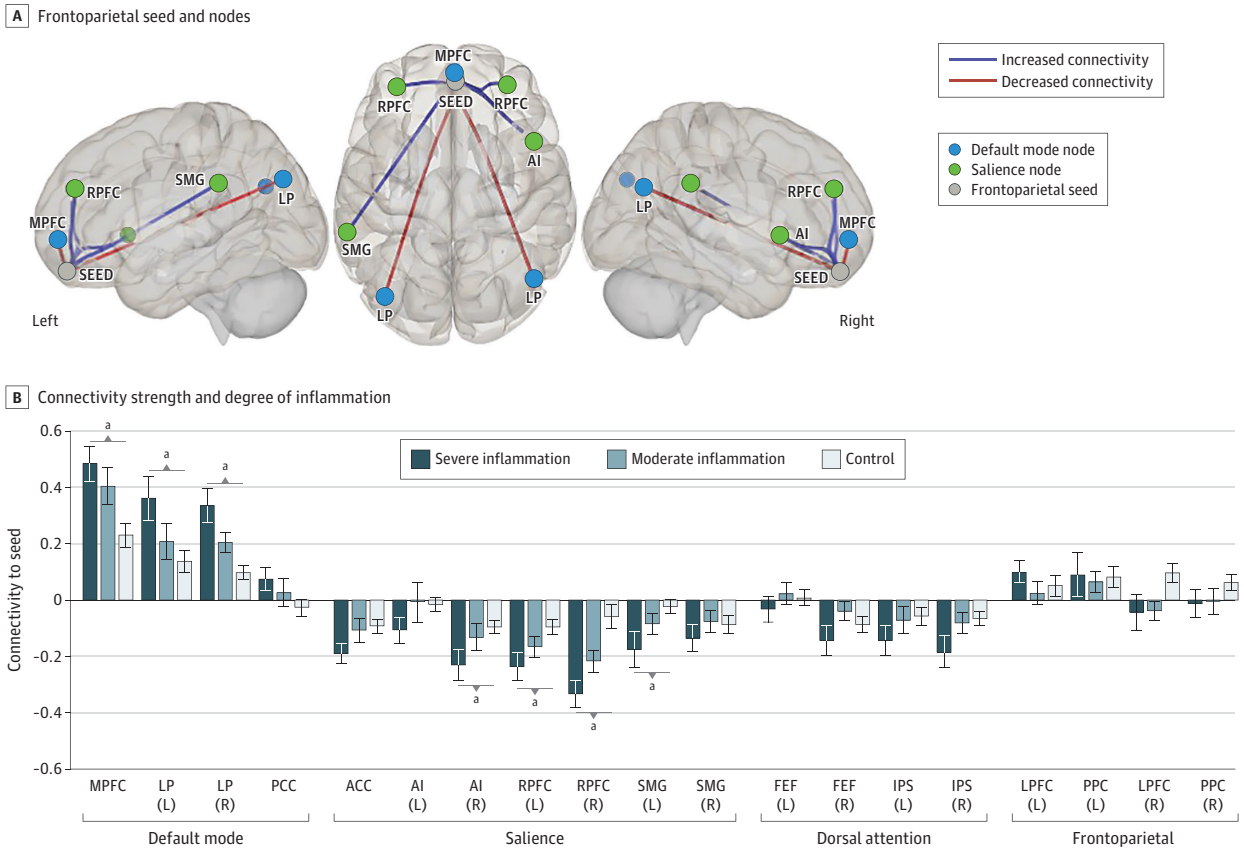
[a] Significant differences in intensity of seed-to-node connections between severe inflammation and controls using a 2-way ANOVA. Connectivity strength between moderate inflammation and controls included to illustrate dose-dependent changes in connectivity strength.

[b] False discovery rate $P < .05$ of participants with severe inflammation vs controls.

[c] Mean, Fisher *r* transformed strength of correlation coefficient and 95% CI.

strated decreased Fc within the FPN, a major network that has a central role in modulating cognition through extensive connections to other brain areas.[26] Furthermore, this region demonstrated increased Fc to areas within the DMN, which is activated in introspective and self-referential processing, and decreased connectivity to nodes within the SN, which is involved in detection and response to relevant stimuli.[27,28] Although definitive conclusions are not possible given the limi-

Figure 3. Connectivity Between the Frontoparietal Seed and Nodes of High-Order Cognitive Networks



A, Participants with severe inflammation showed significant increased connectivity (red lines) with default mode nodes (blue spheres) and decreased connectivity (blue lines) with nodes of the salience network (green spheres) at a family-wise error–corrected $P < .05$. B, Histogram shows a dose-dependent association between connectivity strength showed and degree of inflammation. ACC indicates anterior cingulate cortex; AI, anterior insula; FEF, frontal eye field; IPS, intraparietal sulcus; L, left; LP, lateral parietal; LPFC, lateral prefrontal cortex; MPFC, medial prefrontal cortex; PCC, precuneus cortex; PPC, posterior parietal cortex; R, right; RPFC, rostral prefrontal cortex; SMG, supramarginal gyrus.

[a] Family-wise error–corrected $P < .05$.

tations inherent in the data set, including lack of rhinosinusitis-specific clinical information, our results present initial evidence for Fc alterations as a potential basis for cognitive impairments seen in patients affected by CRS and may help direct future research.[1-3]

We found a dose-dependent decrease in Fc within the FPN in participants with sinonasal inflammation in the regions of the bilateral frontal medial cortices and left frontal pole (Figure 2). The FPN is of particular significance for its critical role in cognitive performance and control. Indeed, this network is an important control hub for higher-order neural processing and exhibits increased activity during complex cognitive tasks.[26,29] In addition, intrinsic Fc of the FPN and connectivity to other brain regions has been shown to reflect fluid intelligence and predict overall cognitive performance.[30-32] However, in our study of relatively young participants who were extensively screened for comorbid cognitive and psychiatric impairment, we did not find a statistical difference between groups in objective measures of cognitive performance. Similarly, in a functional magnetic resonance imaging study of patients with smell loss after an upper respiratory tract infection, reorganization of higher-order brain network connectivity was observed after olfactory training; however, no interval differences were found in the threshold, discrimination, and identification composite score.[33] Therefore, given the brain's ability to adapt and compensate, particularly in young and cognitively healthy individuals, our findings may represent early and subclinical functional brain alterations that may precede or be more sensitive than anticipated behavioral responses. It is possible that a clinical CRS cohort with broader age distribution and more significant symptoms may have even greater changes in functional brain connectivity in the regions identified in this study.

The FPN's dynamic interaction with other brain areas is also essential for cognitive homeostasis.[28] Dysfunction within this network may result in psychopathology, including schizophrenia, anxiety, and major depression.[25,29,30] The finding of functional alteration within the FPN among participants with sinonasal inflammation and without clinical psychiatric disease presents the possibility for interactive and overlapping effects of these otherwise distinct diseases. It is well known that

comorbid depression is highly prevalent in CRS (seen in 20%-30% of patients)[3,34,35] and significantly contributes to the burden of disease.[36,37] In a prospective study by Litvack et al,[38] the authors found comparable CRS-specific quality-of-life improvements between depressed and nondepressed patients and, interestingly, that depression severity also improved following endoscopic sinus surgery. These results, in conjunction with the similar pattern of disruption in the FPN, suggest that the basis of the cognitive effects of CRS and depression may be interrelated. Further investigation, particularly in light of the findings in this study, would be helpful to better understand this important neuropsychological relationship.

The ability to switch cognitive states and direct attention away from internally focused thoughts and rumination to externally focused tasks involves tightly coordinated activation of the SN and deactivation of the DMN.[39] Notably, we found opposite effects of sinonasal inflammation in the resting state in these important networks, which effectively increases their dissonance and disrupts this otherwise tightly coupled relationship. Although we did not find any differences in measures of attention and executive function or working memory on cognitive assessments, previous work by Rowan et al[2] has demonstrated significant impairment on the Stroop interference test in patients with CRS. The Stroop test is a widely used measure of selective attention and cognitive interference involving the naming of colors in the presence of color-word mismatches (eg, blue ink color used to print the word *red*).[40] Several regions within the SN, including the anterior cingulate and insula, have been associated with performance of this task,[41] which are also reflected in our Fc findings. Therefore, prior behavioral studies as well as this investigation suggest that alterations in the SN related to sinonasal inflammation as well as the relative uncoupling of the SN and DMN may be associated with impairment in efficient switching between cognitive states.

Previously proposed mechanisms for cognitive dysfunction in CRS include contributions from prevalent comorbid psychiatric illness and sleep dysfunction, as well as a more direct cause implicating the effect of inflammatory cytokines on the brain.[38,42] However, the results of our study were derived from cognitively and psychiatrically healthy participants with similar PSQI sleep scores between groups. Therefore, our results, as interpreted in this context, are supportive of a more direct association of immune molecules, including cytokines and antibodies, with brain function. Furthermore, the dose-dependent association of our findings, seen both within and between networks, further supports the biological plausibility of our results. Interestingly, other inflammatory and autoimmune conditions, such as Crohn disease and type 2 diabetes mellitus, have also demonstrated similar large-scale brain dysfunction, although the precise causes remain a topic of active investigation.[9,11] For example, treatment with anti-tumor necrosis factor-α medications have been shown to improve cognition in patients with sarcoidosis, and cytokines involved in the T-helper type 2 response (ie, IL-4, IL-5, IL-8, and IL-13) correlate with cognitive function in sickle cell disease.[43,44] Additionally, there is growing evidence that inflammatory cytokines may play a role in synaptic plasticity, neurogenesis, and neuromodulation on a molecular level.[42] Therefore, adjunctive therapeutics to address the downstream inflammatory sequelae (eg, immunomodulator therapy) and psychotherapy may help cope with CRS effects and improve quality of life beyond standard CRS treatment. Further research in the potential link between inflammation and brain function would be helpful to further elucidate the possible neuroimmunological sequelae associated with sinonasal inflammation and help direct research and treatments.

Limitations

There are several limitations to our study. First, the results are based on a cohort of young, cognitively normal participants identified radiographically from a large database, rather than by clinical examination and history. While this provides some benefits in minimizing confounding comorbid cognitive impairment and psychiatric disease, it certainly does not represent a clinical CRS population. Thus, the generalizability of the results is limited, and further prospective investigation using a clinical CRS cohort is warranted to draw more definitive conclusions. In addition, the number of participants in the cohort was relatively modest, which may reduce statistical power, particularly with assessment of behavioral performance. This might also preclude replicable individual difference analysis. Furthermore, this pilot study was retrospective and did not involve follow-up assessments, which could be powerful in determining the resiliency after treatment and potential long-term effects of network disruption.

Conclusions

This study provides several important insights into potential neural correlates of cognitive dysfunction seen in sinonasal inflammation. Participants with sinonasal inflammation showed increased functional brain connectivity within a major functional hub with a central role in modulating cognition. This region demonstrated increased connectivity to areas that are activated during introspective and self-referential processing and decreased connectivity to areas that are involved in detection and response to stimuli. The magnitude of these differences increased with inflammation severity (dose dependent). Future studies are warranted to determine the possible immunological associations of sinonasal inflammation and cognition, as well as to extend the applicability of these findings to a clinical CRS population.

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