Journal of Inflammation Research

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ORIGINAL RESEARCH

Graph Theory Further Revealed Visual Spatial Working Memory Impairment in Patients with Inflammatory Bowel Disease

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Background: Inflammatory Bowel Disease (IBD) patients may experience cognitive impairments in Visuospatial Working Memory (VSWM), significantly impacting their quality of life. However, the mechanisms underlying these impairments remain poorly understood.

Methods: We studied functional MRI and graph theory analysis to investigate changes in functional connectivity networks during the Mental Rotation Task (MRT) in IBD patients. Twenty IBD patients (13 males, 7 females; mean age = 34.95 ± 13.80 years; mean disease duration = 2.43 ± 2.37 years) participated in the study. Exclusion criteria encompassed recent use of analgesics, 5-Aminosalicylate, corticosteroids, or immunosuppressants within the past three months. Additionally, we recruited 20 age-, gender-, and education-matched healthy controls for comparison.

Results: Compared to a control group, IBD patients exhibited significantly longer reaction times and reduced accuracy during the MRT. Our analysis revealed abnormalities in multiple nodal attributes within the functional connectivity network, particularly in regions such as the bilateral orbitofrontal cortex, right supplementary motor area, bilateral parahippocampal gyrus, and bilateral anterior temporal lobe. We observed that the nodal efficiency in the left temporal pole is negatively correlated with Red Blood Cell Distribution Width (RDW) and positively correlated with response time of MRT.

Conclusion: Our findings revealed notable abnormalities in multiple node attributes among IBD patients during MRT, providing evidence of cognitive impairments in VSWM in IBD patients. This study found RDW maybe can serve as a clinical indicator for predicting early VSWM impairment in patients with IBD.

Keywords: inflammatory bowel disease, graph theory, visuospatial working memory, cognitive impairment, mental rotation task

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and recurrent inflammatory condition characterized by symptoms such as fever, diarrhea, abdominal pain, and weight loss. Its global incidence is steadily increasing.[1] IBD affects the physical and mental health of patients, while the precise mechanisms underlying the development of IBD remain incompletely elucidated. Recent research suggests that IBD may affect cognitive function through the brain-gut axis, which connects the enteric and central nervous systems.[2] Multiple studies have linked IBD with anxiety and depression, which can significantly impact disease progression and overall well-being, including cognitive impairment.[3,4] Therefore, there is a clear need for in-depth research to thoroughly explore the intricate relationship between IBD and cognition.

Neuropsychological research suggests that individuals with IBD may experience cognitive impairment due to psychological stress and negative affect.[5] Recent research had posited a correlation between gastrointestinal symptoms and mental disorders, specifically depression and anxiety, which is facilitated by the gut-brain axis.[6] Psychological stress has the potential to induce an elevated stress system response, exacerbate intestinal inflammatory reactions, and even

Received: 6 March 2024
Accepted: 25 April 2024
Published: 8 May 2024

elicit abdominal pain in the absence of peripheral abnormalities. Heightened anxiety frequently precedes the onset of a painful abdominal syndrome.[7] Recent studies suggest that negative mood in IBD patients can elicit aberrant alterations in both brain structure and function. Patients with CD exhibited cortical thickness abnormalities in the bilateral temporal poles and insular gyrus, which are associated with social emotional processing.[8] The investigation into the emotional visual stimulation task among patients with UC determined the cognitive impairment is associated with alterations in the signals of brain regions involved in emotion processing.[9] Furthermore, emotions can impact the impairment of visuospatial working memory.[10] The long-term gastrointestinal symptoms experienced by individuals with IBD may induce anxiety, depression, and other mental disorders, consequently resulting in visuospatial memory impairment.[11]

Visuospatial working memory (VSWM) involves the retention and manipulation of spatial information within a brief timeframe, requiring intricate cooperation among various brain regions.[12,13] The mental rotation task (MRT) is commonly used in psychology to assess visuospatial working memory function, widely used to test visuospatial cognitive impairment.[10] Despite abnormal cognitive performance in IBD patients and compromised visual networks,[14,15] our understanding of VSWM deficits in IBD remains incomplete. Based on the MRT, we employed it as the task during Functional Magnetic Resonance Imaging (fMRI) scanning to evaluate VSWM in patients with IBD. And then, to enhance our understanding, we employed graph theory analysis to assess task-state fMRI, a powerful tool that quantitatively examines functional brain networks' nodes and edges.[16] While graph theory analysis has primarily been applied to resting-state fMRI data,[17] its utility in task-fMRI is promising and reliable. Deuker et al demonstrated the high reliability of graph theory during working memory tasks using magnetoencephalography data.[18] This approach has been increasingly adopted to investigate cognitive processes and the neurophysiological underpinnings of various disorders.[19]

In this study, we applied graph theory analysis for the first time in the task-fMRI analysis of MRT to investigate changes in brain connectivity patterns among IBD patients. We hope that graph theory analysis can provide new insights in the field of neuroimaging for IBD patients, thereby contributing to a deeper understanding of the underlying mechanisms of cognitive impairment and facilitating early diagnosis of cognitive deficits in IBD patients.

Materials and Methods

Participants

Twenty patients with IBD (13 males and 7 females; age = 34.95 ± 13.80 years old; disease duration = 2.43 ± 2.37 years) were recruited from the First Affiliated Hospital of Shantou University Medical College. 17 patients are currently undergoing treatment with biologics. The patients were included if they had (1) a diagnosis of UC and CD as determined by clinical, radiological, endoscopic, and histological criteria by an experienced gastroenterologist from the First Affiliated Hospital of Shantou University Medical College; (2) normal vision or corrected visual acuity; (3) right-handed; (4) more than 6 years of formal schooling (Completed primary school education and above). The exclusion criteria were as follows: (1) intracranial organic abnormalities, (2) a history of craniocerebral trauma or cerebrovascular accident, (3) severe liver, kidney, or heart insufficiency, (4) chronic wasting diseases, (5) mental illness, (6) psychoactive substance abuse and the use of antipsychotics and antidepressants, (7) Use of analgesics within the past three months, (8) Use of 5-Aminosalicylate, corticosteroids or immunosuppressants within the past three months, (9) patients with a history of IBD-related abdominal surgery, and (10) MRI contraindications. The control group consisted of 20 healthy volunteers who were matched with IBD patients in terms of age, gender, and education level.

All participants' mental status was evaluated by specialized psychiatric physicians at the First Affiliated Hospital of Shantou University Medical College, and patients with psychiatric disorders other than anxiety and depression were excluded. The experiment was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (approval NO. B-2021-246). All participants signed the written informed consent.

Neuropsychological Evaluation and Disease Severity Evaluation

All participants were evaluated using a set of neuropsychological scales, which included the Montreal Cognitive Assessment (MoCA),[20] Center for Epidemiologic Studies Depression Scale (CES-D) 20,[21] Self-Rating Anxiety Scale (SAS),[22] and Fatigue Symptom Inventory (FSI).[23] The MoCA was employed to assess the cognitive function of

participants. The CES-D and SAS were used to assess the mental status of participants. Higher scores indicated more severe symptoms of anxiety and depression. FSI assesses the level of fatigue in participants, including severity, frequency of fatigue, and perceived interference related to fatigue.

Crohn's disease activity index (CDAI) is used to assess the severity of the patient's condition. A total score of <150 indicates remission; a total score of ≥150 indicates disease activity, with 150–220 points indicating mild activity, 221–450 points indicating moderate activity, and >450 points indicating severe activity.

Experimental Procedure of Task-fMRI

E-Prime 3.0 software (Psychology Software Tools Inc., Pittsburgh, PA, USA) was used for programming and presenting the MRT. The stimuli were presented continuously in a block design, with alternating blocks of fixation, comparison, and rotation. This alternation occurred four times throughout the entire experiment. At the beginning of each fixation block (30 seconds), a fixation cross was displayed on the screen. Rotation and comparison blocks each comprised 12 trials. Each trial included a 0.5-second baseline condition (center fixation) followed by a 6.5-second task-related stimulus presentation. During the task-related stimulus presentation, participants were shown two three-dimensional (3D) images on the left and right sides of the screen. In the rotation block, the 3D objects on the right side underwent a 50° vertical axis rotation compared to those on the left side. In the comparison block, the 3D object on the right side remained unchanged. Subsequently, Participants were required to determine whether the left and right 3D images were identical or mirrored within a designated trial duration and provide their judgment promptly. The entire experimental session lasted 13 minutes and 12 seconds. Before the fMRI scan, all participants received comprehensive instructions and underwent a training session for the MRT. E-Prime software and stimulus presentation goggles were used to facilitate stimulus presentation. The software E-Prime was used to record the accuracy and response times of the MRT.

MRI Image and Data Acquisition

MRI data were acquired using a 1.5T MR scanner (GE Medical Systems, Milwaukee, WI, USA) equipped with a standard GE head coil. fMRI data were obtained employing an echo-planar imaging (EPI) sequence with the following acquisition parameters: repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, imaging matrix = 64 × 64, field of view (FoV) = 230 mm, and a slice thickness of 6.0 mm. A total of 20 axial slices were acquired in an interleaved manner. For anatomical T1-weighted imaging, this study utilized a fast spoiled gradient recalled (FSPGR) sequence with the following parameters: TR = 30 ms, TE = 3.0 ms, FA = 30°, matrix size = 256 × 256, FoV = 250 mm, slice thickness = 1.3 mm, and acquisition of 244 slices in an interleaved fashion.

The Task-fMRI Processing

The task-fMRI data were processed using Data Processing and Analysis of Brain Imaging (DPABI) V7.0 (http://rfmri.org/dpabi). The preprocessing steps involved: (1) transformation from DICOM into NIFTI; (2) deletion of the first 2 time points; (3) slice timing correction; (4) head motion correction; (5) spatial normalization (transformed into the Montreal Neurological Institute space); (6) spatially smoothing (FWHM = 6 mm); (7) linearly detrending; (8) regression of the Friston 24 head motion parameters, white matter signal, cerebrospinal fluid signal and other noise signals; (9) bandpass filter (0.01–0.1 Hz).

Dynamic functional connectivity analysis was conducted using the graph theoretical network analysis toolbox (GRETNA, http://www.nitrc.org/projects/gretna/). This study computed correlation coefficients for time series data between regions of interest (ROIs) defined by the AAL90 atlas in each dataset. This study conducted a sliding-window analysis with a window size of 18 TRs and a step size of 1 TR. A total of 241 sliding windows were generated.

Each task block lasts for 84 seconds (28 TRs). To ensure that the sliding window remains within the time range of the task block, we select the first 11 sliding window points that fall within the same task block duration. It is important to note that the final TR of each task block includes the remaining time for that block. This study labels a set of 44 FC matrices for each task as task stimulus correlation matrices.

The Graph Theory Analysis

This study utilized the undirected matrix to create a total of 241 sliding windows and extracted 44 sliding window matrices for comparison tasks and rotation tasks respectively. This study employed the cost thresholding method to binarize all the FC matrices. The threshold range was set from 0.1 to 0.4 with a step size of 0.02. Subsequently, this study computed the nodal level topological properties for both comparison tasks and rotation tasks.

This study calculated four topological properties, including nodal efficiency, nodal local efficiency, degree centrality, and nodal clustering coefficient, using the generated temporal mask. Degree centrality is the most straightforward graph-theoretical metric for characterizing hubs, as it reflects the number of edges directly linked to a node.[24] Nodes with higher degree centrality are more significant within the network. Nodal efficiency measures information transmission and resource allocation within a network.[25] The nodal local efficiency, which quantifies the network's information processing capacity among neighboring nodes after the removal of a specific node,[26] revealing its fault tolerance within the network. Additionally, the nodal clustering coefficient, which represents the degree of interconnectedness between a node and its neighboring nodes, reflects the functional connectivity and information transmission efficiency within the local network.[27] Subsequently, this study extracted the Area Under Curve (AUC) within a specified range of sparse thresholds for each topological property. This study computed the mean and variance for each topology attribute of every subject. This study performed a two-sample *t*-test to compare the AUC values of the topological attributes between the IBD group and control group using GRETNA.

To identify the critical nodes in the whole-brain network, commonly referred to as network hubs, this study utilized a single topological attribute measurement method known as degree centrality. This study used nodal degree centrality to assess the spatial distribution of nodes with the highest connectivity in both the comparison and rotation task scenarios. Nodes were ranked according to their average AUC values, and the top 10% with the highest degree centrality for each task condition were designated as hubs.

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS, Windows version, version: 26). Clinical and neuropsychological data, as well as MRT data, were subjected to comparative analysis between the IBD and control groups using the Mann–Whitney *U*-test. Gender distribution was assessed using the Chi-square test. Descriptive statistics for measurement data were presented as means ± SD. The statistical significance threshold was set at $P < 0.05$. Additionally, this study employed independent sample t-tests utilizing variance values of various graph-theoretical topological properties to identify differences in network nodes between the two tasks and between the two participant groups. The statistical significance threshold was set at $P < 0.05$.

This study conducted Spearman correlation analyses between the abnormal attributes of brain network nodes and white blood cell count, neutrophil count, monocyte count, lymphocyte count, red blood cell distribution width (RDW), platelets, mean platelet volume, erythrocyte sedimentation rate, C-reactive protein, albumin, CDAI, MRT response time, and accuracy. Based on the obtained correlation results, this study used age, gender, and years of education as covariates to construct a partial correlation network for conducting partial correlation analyses.

Result Visualization

This study utilized the chart script in GRETNA to create the hub figure of two tasks, employed BrainNetViewer (https://www.nitrc.org/projects/bnv/) for visualizing the results, and utilized the ICBM152 (The international consortium for brain mapping 152) brain template to display the network results.

Result

Result of Clinical Characteristics and MRT Performance

There were no differences in the age, gender, and educational level between IBD patients and health controls ($P > 0.05$). Compared to control group, IBD patients showed lower accuracy ($Z = 2.199$, $P = 0.030$) and longer response time ($Z = -4.490$, $P < 0.001$) under the rotation task. As shown in Table 1.

Table 1 Demographic, Clinical Characteristics and Mental Rotation Task Performance Score of Inflammatory Bowel Disease Group and Control Group

	Group		Normal Range	Z	P
	IBD Group	Control Group			
Age (years)	34.95 ± 13.80	34.35 ± 11.78	–	0.081	0.947[b]
Gender (male/female)	13/7	9/11	–		0.204[a]
Education (years)	11.60 ± 4.13	13.05 ± 4.52	–	1.188	0.242[b]
Disease duration (years)	2.43 ± 2.37	–	–	–	–
Accuracy	0.93 ± 0.26	0.95 ± 0.03	–	2.199	0.030[b]
Response Time (ms)	3057.18 ± 243.83	2648.38 ± 203.21	–	−4.490	0.000[b]
White blood cell count (×10^9/L)	5.47 ± 1.68	5.67 ± 0.92	3.50–9.50	0.866	0.398
Neutrophil count (×10^9/L)	3.49 ± 1.44	3.43 ± 0.97	1.80–6.30	0.460	0.659
Monocyte count (× 10^9/L)	0.42 ± 0.27	0.35 ± 0.13	0.10–0.60	−0.488	0.640
Lymphocyte count (× 10^9/L)	1.39 ± 0.54	1.69 ± 0.30	1.10–3.20	1.921	0.056
Red blood cell volume distribution width (%)	14.20 ± 2.24	12.92 ± 0.73	11.50–14.50	−0.1787	0.076
Hemoglobin (g/L)	124.60 ± 20.88	137.15 ± 9.47	130.00–175.00	1.638	0.102
Platelet count (× 10^9/L)	254.15 ± 85.57	238.30 ± 61.63	125.00–350.00	−0.487	0.640
Mean platelet volume (fl)	9.16 ± 1.27	8.55 ± 1.24	6.00–12.00	−1.394	0.165
Erythrocyte sedimentation rate (mm/h)	19.00 ± 18.02	5.95 ± 4.16	0.00–15.00	−2.062	0.040
C-reactive protein (mg/L)	8.83 ± 12.14	4.47 ± 3.23	0.00–8.00	−0.162	0.883
Albumin (g/L)	39.47 ± 5.81	42.09 ± 2.54	40.00–55.00	1.515	0.134
Clinical disease activity index	103.07 ± 104.68		–		–
Biologics use	17				

Note: a. Chi-square test; b. Mann–Whitney *U*-test; Values are mean ± SD.
Abbreviation: IBD, inflammatory bowel disease.

There were no differences in the MoCA, CES-D, and SAS scores between IBD patients and health controls ($P > 0.05$). The perceived interference score related to fatigue in IBD group was higher than that of control group ($Z = -2.913$, $P = 0.003$). As shown in Table 2.

Table 2 Psychological Characteristics of Inflammatory Bowel Disease Group and Control Group

	Group		Z	P
	IBD Group	Control Group		
Montreal cognitive assessment	26.00 ± 3.06	26.95 ± 2.91	1.415	0.165[a]
Visuospatial/ Executive Functioning	4.30 ± 1.34	4.70 ± 0.65	0.555	0.659[a]
Naming	2.95 ± 0.22	2.95 ± 0.22	0.000	1.000[a]
Delayed recall	3.30 ± 1.75	3.6 ± 1.27	0.308	0.779[a]
Attention	5.75 ± 0.55	5.70 ± 0.65	−0.078	0.938[a]
Language	1.70 ± 0.80	1.90 ± 0.85	1.004	0.369[a]
Abstraction	1.70 ± 0.57	1.60 ± 0.75	−0.179	0.904[a]
Orientation	5.80 ± 0.52	5.85 ± 0.49	0.448	0.799[a]
Center for epidemiologic studies depression scale	17.45 ± 10.37	11.60 ± 6.541	−1.897	0.060[a]
Self-rating anxiety scale	38.51 ± 10.19	33.90 ± 6.14	−1.397	0.165[a]
Fatigue symptom inventory Severity				
Most fatigue	5.40 ± 2.33	5.30 ± 1.38	−0.881	0.398[a]
Least fatigue	1.95 ± 1.57	1.95 ± 1.23	0.056	0.968[a]
Average fatigue	3.60 ± 1.27	3.10 ± 0.97	−1.384	0.192[a]
Current fatigue	2.25 ± 1.59	2.00 ± 1.89	−0.702	0.482[a]
Frequency fatigue				
No. day	3.25 ± 1.86	2.50 ± 1.10	−1.367	0.183[a]
Extent of the day	3.70 ± 1.92	2.50 ± 1.50	−1.977	0.052[a]
Interference	2.93 ± 1.50	1.74 ± 0.69	−2.913	0.003[a]

Note: a. Mann–Whitney *U*-test; Values are mean ± SD.

Result of Tasks in Degree Centrality

The top 10% degree centrality in each condition was selected as the hubs. (Figure 1A) showed that network hubs for the comparison task were the right lingual gyrus, right calcarine fissure and surrounding cortex, left orbital part of inferior frontal gyrus, right superior frontal gyrus (dorsolateral), left lingual gyrus, right middle frontal gyrus, right inferior temporal gyrus, left middle temporal gyrus and right orbital part of inferior frontal gyrus. Network hubs for the rotation task included right middle frontal gyrus, right middle temporal gyrus, left middle frontal gyrus, right superior frontal gyrus (dorsolateral), right orbital part of inferior frontal gyrus, right lingual gyrus, left superior frontal gyrus (dorsolateral), right inferior temporal gyrus and left middle temporal gyrus, as shown in (Figure 1B).

In the rotation task, the right superior parietal lobule, right medial superior frontal gyrus, left olfactory cortex, and right middle temporal gyrus demonstrated significantly lower degree centrality variance values compared to those in the comparison task ($P < 0.05$), as presented in Table 3.

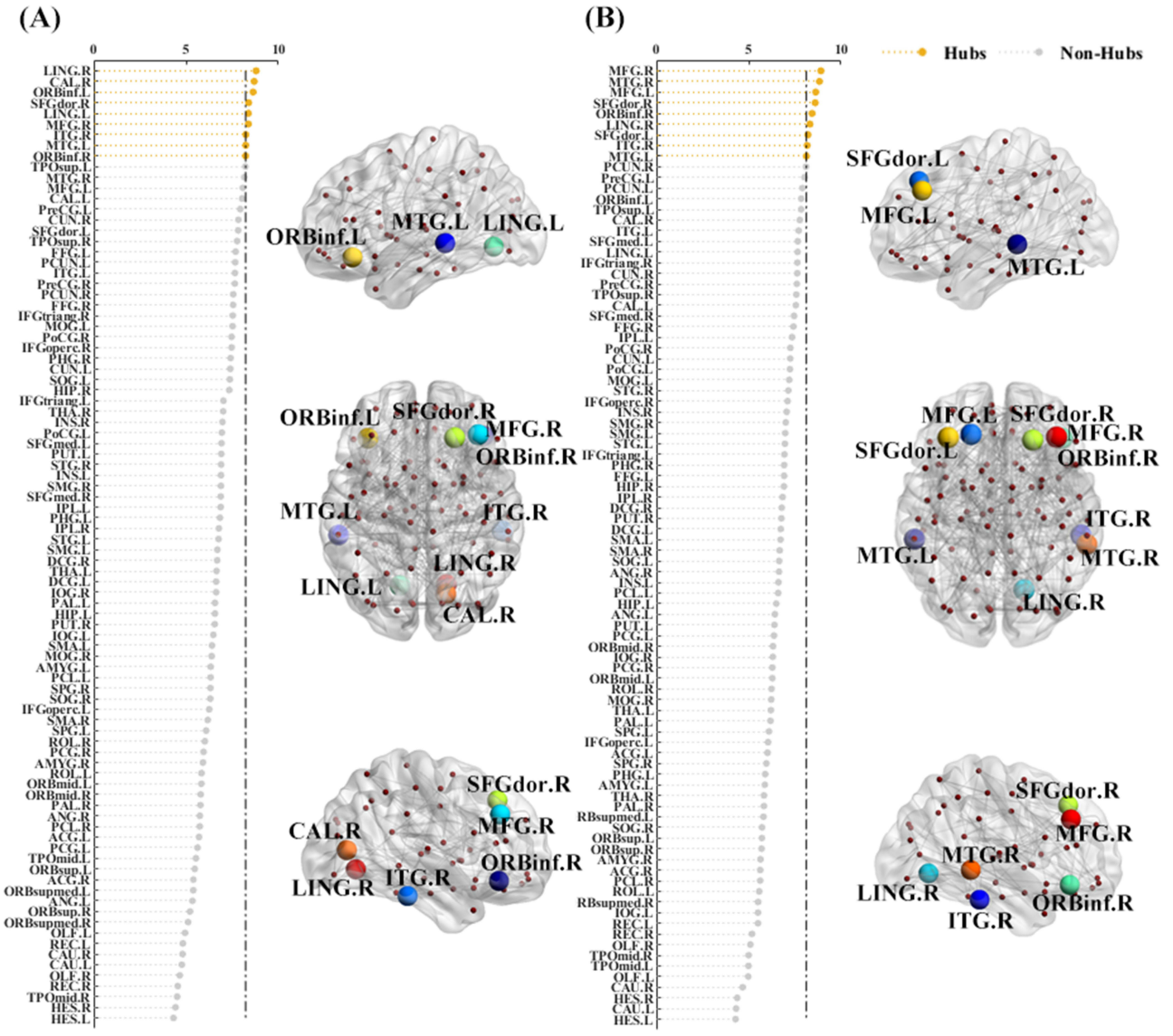

Figure 1 Network hubs of comparison task and rotation task in degree centrality ((**A**) Comparison task; (**B**) Rotation task.).
Abbreviations: ORBinf, the orbital part of Inferior frontal gyrus; MTG, middle temporal gyrus; LING, Lingual gyrus; SFGdor, the dorsolateral of superior frontal gyrus; MFG, middle frontal gyrus; ITG, inferior temporal gyrus; CAL, Calcarine fissure and surrounding cortex; L, left; R, right.

Table 3 Degree Centrality of Comparison Task and Rotation Task

Brain region	Comparison task	Rotation task	T_{var}	P_{var}
Left olfactory cortex	4.948 ± 1.373	5.571 ± 2.515	−2.191	0.036[a]
Right medial superior frontal gyrus	5.393 ± 2.123	4.957 ± 4.224	−2.218	0.034[a]
Right superior parietal lobule gyrus	6.324 ± 1.954	5.182 ± 3.560	−2.084	0.046[a]
Right middle temporal gyrus	8.154 ± 1.597	3.214 ± 2.009	−2.930	0.006[a]

Note: a. *T*-test; Values are mean ± SD.

Results of Graph Theory Analysis Between IBD Group and Control Group

As shown in (Table 4 and Figure 2) there are significant differences in the variance values of topology attributes between control group and IBD group ($P < 0.05$). Compared to the control group, the degree centrality variance of the right supplementary motor area (SMA), left olfactory cortex, and right parahippocampal gyrus (PHG) was significantly higher in the IBD group. The nodal clustering coefficient variance of left hippocampus (HIP) and left PHG was higher in the IBD group. The nodal efficiency variance of right SMA, bilateral gyrus rectus, right PHG, left amygdala, right temporal pole (superior temporal gyrus), and left temporal pole (middle temporal gyrus) was higher in the IBD patients. The nodal local efficiency variance of the left PHG was higher in the IBD group compared to the control group.

Results of Correlation Analysis

Using correlation analysis, this study identified a significant positive correlation between MRT response time and the local efficiency of the left PHG (rs = 0.699, $P < 0.001$), as well as the nodal efficiency of the left temporal pole (middle temporal gyrus) (rs = 0.495, $P = 0.027$), as depicted in (Figure 3C and D). Simultaneously, RDW demonstrated a significant negative correlation with the nodal local efficiency of the left PHG (rs = −0.475, $P = 0.034$), as well as the nodal efficiency of the left temporal pole (middle temporal gyrus) (rs = −0.511, $P = 0.021$), as shown in (Figure 3A and B). Using age, gender, and years of education as covariates, this study constructed a partial correlation network including MRT response time, RDW,

Table 4 The Differences of Nodal Attributes Between the Control Group and Inflammatory Bowel Disease Group

Brain region	Control group	IBD group	T_{var}	P_{var}
Degree Centrality				
Right supplementary motor area	6.546 ± 2.116	6.807 ± 1.608	2.234	0.042[a]
Left olfactory cortex	5.322 ± 1.900	4.631 ± 1.618	2.201	0.045[a]
Right parahippocampal gyrus	7.417 ± 1.860	6.427 ± 1.810	2.654	0.019[a]
Nodal ClustCoeff				
Left hippocampus	0.174 ± 0.014	0.169 ± 0.023	2.376	0.032[a]
Left parahippocampal gyrus	0.173 ± 0.019	0.169 ± 0.010	2.632	0.020[a]
Nodal Efficiency				
Right supplementary motor area	0.170 ± 0.016	0.0171 ± 0.012	2.520	0.024[a]
Left gyrus rectus	0.167 ± 0.019	0.146 ± 0.016	2.235	0.042[a]
Right gyrus rectus	0.164 ± 0.016	0.142 ± 0.019	2.602	0.021[a]
Right parahippocampal gyrus	0.177 ± 0.015	0.162 ± 0.016	2.209	0.044[a]
Left amygdala	0.168 ± 0.013	0.160 ± 0.009	2.900	0.012[a]
Right temporal pole (Superior temporal gyrus)	0.184 ± 0.009	0.169 ± 0.012	2.204	0.045[a]
Left temporal pole (Middle temporal gyrus)	0.158 ± 0.022	0.140 ± 0.021	2.476	0.027[a]
Nodal Local Efficiency				
Left parahippocampal gyrus	0.226 ± 0.019	0.215 ± 0.009	2.218	0.044[a]

Note: a. *T*-test; Values are mean ± SD. Abbreviations: IBD: inflammatory bowel disease.

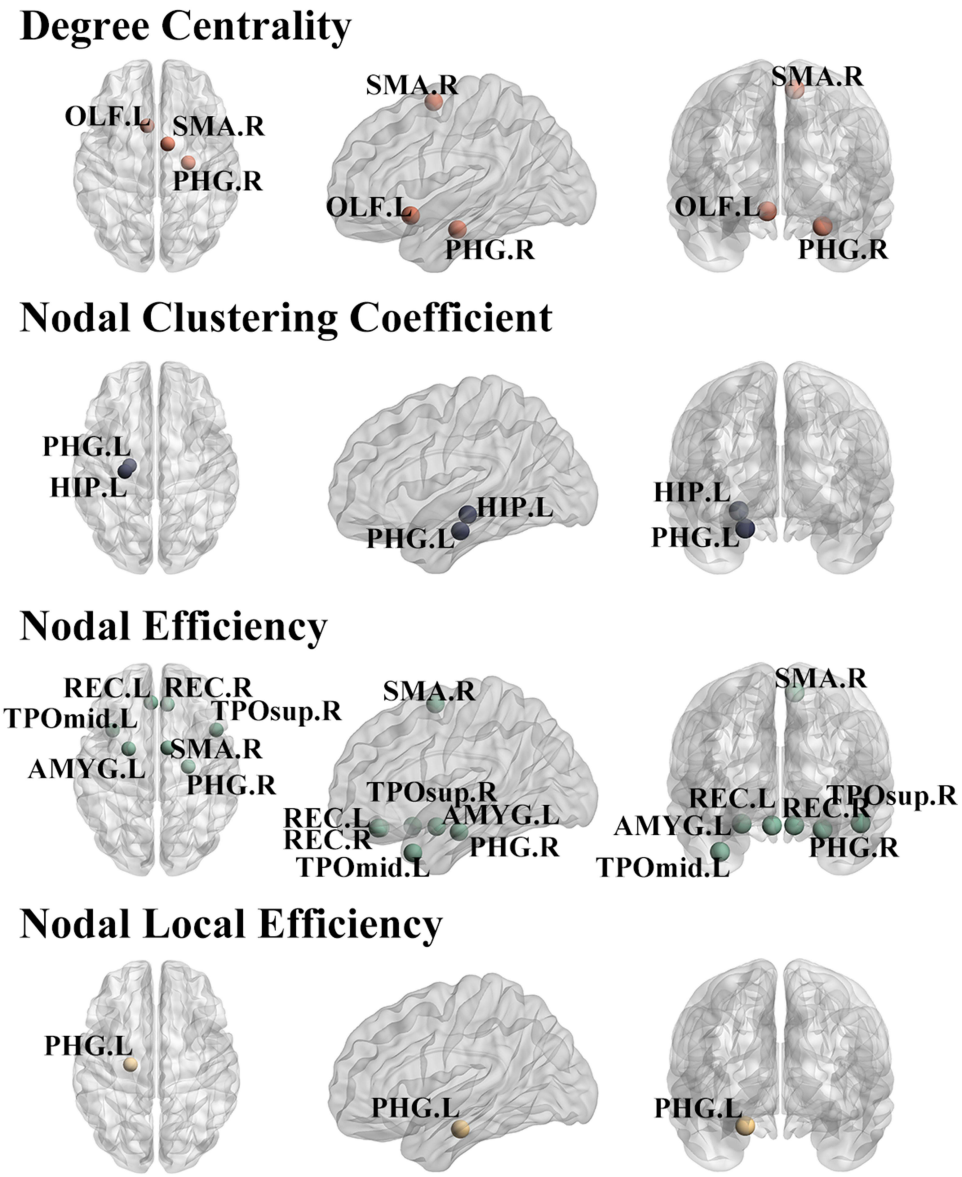

Figure 2 The differences of nodal attributes between the control group and inflammatory bowel disease group.
Abbreviations: OLF, olfactory cortex; SMA, supplementary motor area; PHG, parahippocampal gyrus; HIP, hippocampus; REC, gyrus rectus; TPOmid, temporal pole: middle temporal gyrus; TPOsup, temporal pole: superior temporal gyrus; AMYG, amygdala; L, left; R, right.

local efficiency of the left PHG, and nodal efficiency of the left temporal pole (middle temporal gyrus), as displayed in (Figure 3E). RDW is negatively correlated with the nodal efficiency in the left temporal pole (r = −0.514, $P = 0.029$). The response time of MRT is positively correlated with the nodal efficiency in the left temporal pole (r = 0.554, $P = 0.017$) and the nodal local efficiency in the left PHG (r = 0.616, $P = 0.006$).

Discussion

In this study, we applied graph theory analysis for the first time to explore network changes during the MRT and to assess their application in evaluating VSWM impairments in IBD patients. First, this study employed degree centrality to assess network structural changes during the MRT and verified the reliability of our study. Second, our findings revealed decreased robustness in key brain regions of VSWM, including the bilateral orbitofrontal cortex (OFC), right SMA, bilateral PHG, and bilateral anterior temporal lobe. Significantly, we observed a negative correlation between nodal

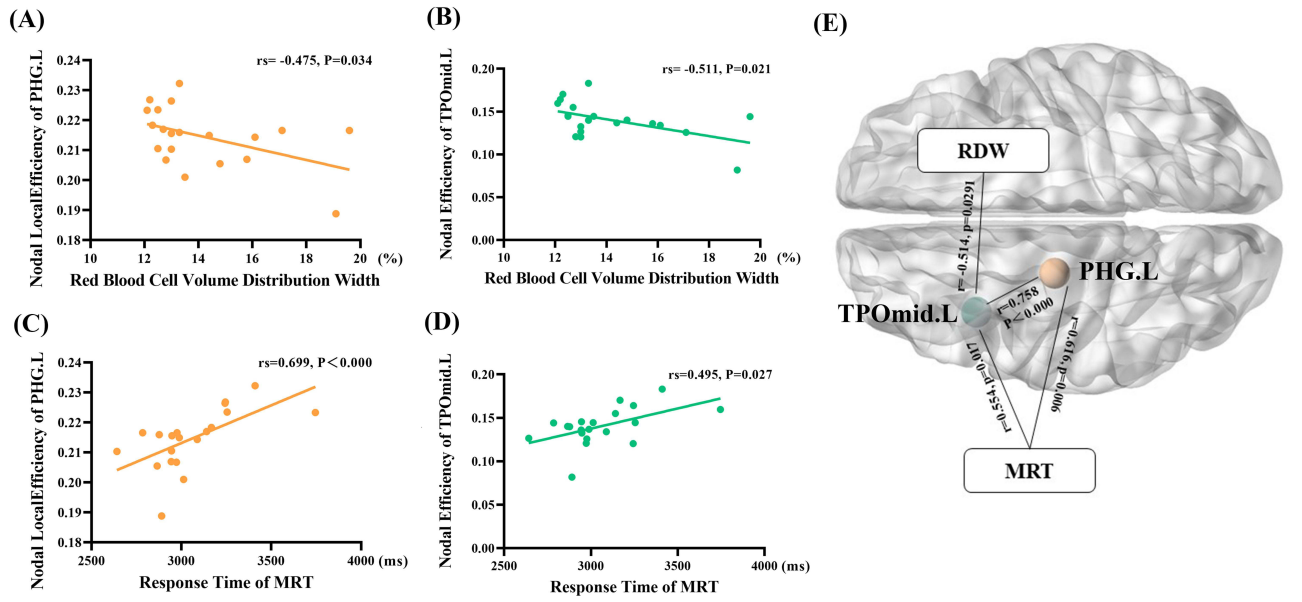

Figure 3 Results of correlation analysis ((**A** and **B**) The correlation between topology attribute and red blood cell volume distribution width in inflammatory bowel disease patients; (**C** and **D**) The correlation between topology attribute and mental rotation task response time in inflammatory bowel disease patients; (**E**) Partial Correlation Network.).
Abbreviations: MRT, mental rotation task; RDW, red blood cell volume distribution width; TPOmid, temporal pole: middle temporal gyrus; L, left.

efficiency in the left temporal pole and RDW, suggesting RDW as a potential biomarker for early identification of VSWM impairments in IBD patients.

The Reliability of Graph Theory in Task-State fMRI

In agreement with findings from other studies,[28,29] we observed key network hubs during the rotation tasks similar to key brain regions of VSWM process. During both tasks, we noted a marked concentration of network hubs within the right hemisphere. The result is consistent with previous studies[30,31] supporting the theoretical concept of the lateralization of VSWM processing to the right hemisphere. Additionally, we observed the dorsolateral prefrontal cortex and posterior parietal lobe (specifically, the precuneus) are crucially involved in the mental rotation processes, which aligns with findings from other studies.[28,32,33] The above finding verifies the reliability and efficacy of our study, indicating that we can reveal the neural mechanisms underlying cognitive processes by applying graph theory.[34]

Mechanisms of VSWM Impairments in IBD Patients

Our findings provide more evidence into mechanisms of VSWM impairments in IBD patients, revealing potential compensatory mechanisms and vulnerabilities within their brain networks. During the MRT, we observed decreased nodal efficiency and robustness in several brain regions among IBD patients, including bilateral OFC, medial temporal lobe (comprising hippocampus, PHG, and olfactory cortex) and temporal pole. The OFC is crucial for integrating and responding to various sensory information,[35,36] particularly visual inputs from the temporal lobe.[37,38] Meanwhile, the medial temporal lobe is responsible for visual scene encoding and spatial scene memory, collaborating with the OFC during the VSWM process.[39,40] The temporal pole, receiving inputs from the occipitotemporal pathway, OFC, and medial temporal lobe, is involved in various aspects of visual cognitive functions.[41] Moreover, SMA activation is closely associated with the difficulty of MRT and plays a role in accumulating spatial directional information and providing linear measurements of space.[42–44] Damage to the above brain regions in the IBD patients may lead to visual discrimination disorders, short-term and long-term visual memory impairments,[41] resulting in reduced efficiency in learning, living, and working,[45] and even delayed response to danger,[46] significantly impacting the quality of life of IBD patients.

Consistent with previous studies,[20,47,48] we observed reduced information transmission between brain regions in IBD patients, and decreased organization and coordination ability of the overall brain network. Additionally, our results also

suggest a potential nodal reorganization within the brain functional network of IBD patients. In contrast to previous studies,[49,50] we did not find a correlation between emotional disorders and limbic system damage. The relatively low level of depression and anxiety in IBD patients in this study may limit the exploration of their correlation.

Role of RDW Indicators in IBD Patients

RDW is an easily accessible and cost-effective novel predictive biomarker that may serve for the early identification and prevention of VSWM impairment in IBD patients. Intestinal inflammation is a characteristic of IBD patients. RDW, as a blood parameter, may reflect features like microvascular lesions, inflammatory cytokines, and blood oxygen levels,[51] which have been used to predict disease activity in IBD. Additionally, RDW has been applied in predicting cognitive impairment[52] and dementia.[53] The correlation between peripheral inflammation and cognitive impairment has been confirmed.[54] Importantly, previous studies suggest that intestinal inflammation can induce spatial object recognition and spatial memory impairments through the activation of inflammatory factors.[55] We speculate that VSWM impairments in IBD patients are associated with their intestinal inflammation. However, the limitation to our speculation is that this study did not find evidence of a correlation between RDW and intestinal inflammation symptoms in IBD patients. Further large-sample analyses could provide further insights into the connection between RDW and inflammation-related cognition impairments.

Limitation and Future Directions

The main limitation was the relatively small sample size (N = 20) employed in our research, which will impact the generalizability of our results to a broader population. However, the good effect sizes of the task-state fMRI research with small sample sizes (N = 16–32) have been confirmed.[56] The voxel-wise effect sizes in fMRI studies using classical task paradigms can reach up to 95%, particularly with block-design paradigms.[57,58] Further expansion of the sample size in research will better validate the conclusions of this study.

Conclusion

In this study, we applied graph theory analysis for the first time to task-state fMRI research on the MRT. We successfully identified significant impairments in VSWM function among IBD patients and to investigate the underlying mechanisms. Analysis of brain network node topological attributes revealed significant abnormalities in multiple nodes, including the bilateral OFC, right SMA, bilateral PHG, and bilateral anterior temporal lobe. Notably, this study observed the nodal efficiency in the left temporal pole was negatively correlated with RDW and positively correlated with response time of MRT. These findings suggest that RDW can be used as an indicator to predict cognitive impairment in IBD patients in clinical practice, thus guiding early intervention to improve the quality of life of IBD patients. Future research can validate the applicability and guidance of RDW as a clinical indicator through large-sample psychometric scale surveys.

Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research involving human subjects, and approved by the Ethics Committee of The First Affiliated Hospital of Shantou University Medical College, Shantou, China (protocol code NO. B-2021-246).

Informed Consent Statement

All participants signed the written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article

has been submitted; and agree to be accountable for all aspects of the work. All authors have read and approved the final submitted manuscript.

Funding

This study was supported by the grants from the National Natural Science Foundation of China (GrantsNos.82004468, 82274657, and 81774395); the China Postdoctoral Science Foundation (Grants Nos. 2019M663021); the Natural Science Foundation of Guangdong Province (Grants No. 2019A1515011744); the Science and Technology Planning Project of Guangdong Province (Grants No.2017A020215060); the Medical Science and Technology Research Foundation of Guangdong Province of China (Grants No. B2020138); the Shantou Technology Bureau Science Foundation of China (Grants No. [2019] 106); and the Grant for Key Disciplinary Project of Clinical Medicine under the Guangdong High-level University Development Program (Grant No. 002-18120302).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Windsor JW, Kaplan GG. Evolving epidemiology of IBD. *Curr Gastroenterol Rep*. 2019;21:40. doi:10.1007/s11894-019-0705-6
2. Novotný M, Klimova B, Valis M. Microbiome and cognitive impairment: Can any diets influence learning processes in a positive way? *Front Aging Neurosci*. 2019;11:170. doi:10.3389/fnagi.2019.00170
3. Yamamoto-Furusho JK, Bozada Gutiérrez KE, Sarmiento-Aguilar A, Fresán-Orellana A, Arguelles-Castro P, García-Alanis M. Depression and Anxiety disorders impact in the quality of life of patients with inflammatory bowel disease. *Psychiatry J*. 2021;2021:5540786. doi:10.1155/2021/5540786
4. Li J, Li GX, Guo Y, Lu XQ, Li L, Ding JP. Regional homogeneity in the patients of irritable bowel syndrome complicated with depression: a resting-state functional magnetic resonance imaging study. *Zhonghua Yi Xue Za Zhi*. 2018;98:196–201. doi:10.3760/cma.j.issn.0376-2491.2018.03.008
5. Thomann AK, Schmitgen MM, Kmuche D, et al. Exploring joint patterns of brain structure and function in inflammatory bowel diseases using multimodal data fusion. *Neurogastroenterol Motil*. 2021;33:e14078. doi:10.1111/nmo.14078
6. Gracie DJ, Hamlin PJ, Ford AC. The influence of the brain-gut axis in inflammatory bowel disease and possible implications for treatment. *Lancet Gastroenterol Hepatol*. 2019;4:632–642. doi:10.1016/s2468-1253(19)30089-5
7. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med*. 2011;62:381–396. doi:10.1146/annurev-med-012309-103958
8. Nair VA, Beniwal-Patel P, Mbah I, Young BM, Prabhakaran V, Saha S. Structural Imaging Changes and Behavioral Correlates in Patients with Crohn's Disease in Remission. *Front Hum Neurosci*. 2016;10:460. doi:10.3389/fnhum.2016.00460
9. Agostini A, Filippini N, Cevolani D, et al. Brain functional changes in patients with ulcerative colitis: a functional magnetic resonance imaging study on emotional processing. *Inflamm Bowel Dis*. 2011;17:1769–1777. doi:10.1002/ibd.21549
10. Wang L, Ke J, Zhang H. A functional near-infrared spectroscopy examination of the neural correlates of mental rotation for individuals with different depressive tendencies. *Front Hum Neurosci*. 2022;16:760738. doi:10.3389/fnhum.2022.760738
11. Schoultz M, Atherton I, Hubbard G, Watson AJ. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a protocol for systematic review of prospective cohort studies. *Syst Rev*. 2013;2:8. doi:10.1186/2046-4053-2-8
12. Chu NCW, Sturnieks DL, Lord SR, Menant JC. Visuospatial working memory and obstacle crossing in young and older people. *Exp Brain Res*. 2022;240:2871–2883. doi:10.1007/s00221-022-06458-9
13. Wang L, Bolin J, Lu Z, Carr M. Visuospatial working memory mediates the relationship between executive functioning and spatial ability. *Front Psychol*. 2018;9:2302. doi:10.3389/fpsyg.2018.02302
14. Kornelsen J, Witges K, Labus J, Mayer EA, Bernstein CN. Brain structure and function changes in inflammatory bowel disease. *Neuroimage: Rep*. 2022;2:100097. doi:10.1016/j.ynirp.2022.100097
15. Kornelsen J, Wilson A, Labus JS, Witges K, Mayer EA, Bernstein CN. Brain resting-state network alterations associated with Crohn's disease. *Front Neurol*. 2020;11:48. doi:10.3389/fneur.2020.00048
16. He Y, Evans A. Graph theoretical modeling of brain connectivity. *Curr Opin Neurol*. 2010;23:341–350. doi:10.1097/WCO.0b013e32833aa567
17. Ma K, Zhang X, Song C, et al. Altered topological properties and their relationship to cognitive functions in unilateral temporal lobe epilepsy. *Epilepsy Behav*. 2023;144:109247. doi:10.1016/j.yebeh.2023.109247
18. Welton T, Kent DA, Auer DP, Dineen RA. Reproducibility of graph-theoretic brain network metrics: a systematic review. *Brain Connect*. 2015;5:193–202. doi:10.1089/brain.2014.0313
19. Liu P, Li R, Bao C, et al. Altered topological patterns of brain functional networks in Crohn's disease. *Brain Imaging Behav*. 2018;12:1466–1478. doi:10.1007/s11682-017-9814-8
20. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x
21. Chin WY, Choi EP, Chan KT, Wong CK, Chilcot J. The psychometric properties of the center for epidemiologic studies depression scale in Chinese primary care patients: factor structure, construct validity, reliability, sensitivity and responsiveness. *PLoS One*. 2015;10(8):e0135131. doi:10.1371/journal.pone.0135131
22. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics*. 1971;12(6):371–379. doi:10.1016/S0033-3182(71)71479-0
23. Donovan KA, Jacobsen PB. The fatigue symptom inventory: a systematic review of its psychometric properties. *Support Care Cancer*. 2010;19(2):169–185. doi:10.1007/s00520-010-0989-4

24. van den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cognit Sci*. 2013;17:683–696. doi:10.1016/j.tics.2013.09.012
25. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*. 2010;52:1059–1069. doi:10.1016/j.neuroimage.2009.10.003
26. Latora V, Marchiori M. Efficient behavior of small-world networks. *Phys Rev Lett*. 2001;87(198701). doi:10.1103/PhysRevLett.87.198701
27. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature*. 1998;393:440–442. doi:10.1038/30918
28. Jackson MC, Morgan HM, Shapiro KL, Mohr H, Linden DE. Strategic resource allocation in the human brain supports cognitive coordination of object and spatial working memory. *Hum Brain Mapp*. 2011;32:1330–1348. doi:10.1002/hbm.21112
29. Schendan HE, Stern CE. Mental rotation and object categorization share a common network of prefrontal and dorsal and ventral regions of posterior cortex. *Neuroimage*. 2007;35(3):1264–1277. doi:10.1016/j.neuroimage.2007.01.012
30. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. *Cogn Affect Behav Neurosci*. 2003;3:255–274. doi:10.3758/cabn.3.4.255
31. Skagerlund K, Karlsson T, Träff U. Magnitude Processing in the Brain: an fMRI Study of Time, Space, and Numerosity as a Shared Cortical System. *Front Hum Neurosci*. 2016;10:500. doi:10.3389/fnhum.2016.00500
32. Wen T, Mitchell DJ, Duncan J. Response of the multiple-demand network during simple stimulus discriminations. *Neuroimage*. 2018;177:79–87. doi:10.1016/j.neuroimage.2018.05.019
33. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*. 2002;3:201–215. doi:10.1038/nrn755
34. Bolt T, Laurienti PJ, Lyday R, Morgan A, Dagenbach D. Graph-theoretical study of functional changes associated with the Iowa gambling task. *Front Hum Neurosci*. 2016;10:314. doi:10.3389/fnhum.2016.00314
35. Sharma S, Bandyopadhyay S. Differential rapid plasticity in auditory and visual responses in the primarily multisensory orbitofrontal cortex. *eNeuro*. 2020;7(3):ENEURO.0061–20.2020. doi:10.1523/ENEURO.0061-20.2020
36. Alsiö J, Lehmann O, McKenzie C, Theobald DE, Searle L, Xia J. Serotonergic innervations of the orbitofrontal and medial-prefrontal cortices are differentially involved in visual discrimination and reversal learning in rats. *Cereb Cortex*. 2021;31(2):1090–1105. doi:10.1093/cercor/bhaa277
37. Saleemm KS, Kondom H, Pricem JL. Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey. *J Comp Neurol*. 2008;506(4):659–693. doi:10.1002/cne.21577
38. Saleemm KS, Millerm B, Pricem JL. Subdivisions and connectional networks of the lateral prefrontal cortex in the macaque monkey. *J Comp Neurol*. 2014;522(7):1641–1690. doi:10.1002/cne.23498
39. Lee AC, Bussey TJ, Murray EA, et al. Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia*. 2005;43:1–11. doi:10.1016/j.neuropsychologia.2004.07.017
40. Epstein RA, Ward EJ. How reliable are visual context effects in the parahippocampal place area? *Cereb Cortex*. 2010;20:294–303. doi:10.1093/cercor/bhp099
41. Herlin B, Navarro V, Dupont S. The temporal pole: from anatomy to function-A literature appraisal. *J Chem Neuroanat*. 2021;113:101925. doi:10.1016/j.jchemneu.2021.101925
42. Richter W, Somorjai R, Summers R, et al. Motor area activity during mental rotation studied by time-resolved single-trial fMRI. *J Cogn Neurosci*. 2000;12:310–320. doi:10.1162/089892900562129
43. Milivojevic B, Hamm JP, Corballis MC. Functional neuroanatomy of mental rotation. *J Cogn Neurosci*. 2009;21:945–959. doi:10.1162/jocn.2009.21085
44. Cona G, Marino G, Semenza C. TMS of supplementary motor area (SMA) facilitates mental rotation performance: evidence for sequence processing in SMA. *Neuroimage*. 2017;146:770–777. doi:10.1016/j.neuroimage.2016.10.032
45. Zhu Q, Deng J, Yao M, et al. Effects of physical activity on visuospatial working memory in healthy individuals: a systematic review and meta-analysis. *Front Psychol*. 2023;(14):1103003. doi:10.3389/fpsyg.2023.1103003
46. Anstey KJ, Horswill MS, Wood JM, Hatherly C. The role of cognitive and visual abilities as predictors in the multifactorial model of driving safety. *Accid Anal Prev*. 2012;45:766–774. doi:10.1016/j.aap.2011.10.006
47. Thomann AK, Reindl W, Wüstenberg T, Kmuche D, Ebert MP, Szabo K. Aberrant brain structural large-scale connectome in Crohn's disease. *Neurogastroenterol Motil*. 2019;31(6):e13593. doi:10.1111/nmo.13593
48. Bao C, Liu P, Liu H, Jin X, Shi Y, Wu L. Difference in regional neural fluctuations and functional connectivity in Crohn's disease: a resting-state functional MRI study. *Brain Imaging Behav*. 2018;12(6):1795–1803. doi:10.1007/s11682-018-9850-z
49. Bao CH, Liu P, Liu HR, et al. Alterations in brain grey matter structures in patients with crohn's disease and their correlation with psychological distress. *J Crohns Colitis*. 2015;9(7):532–540. doi:10.1093/ecco-jcc/jjv057
50. Bao CH, Liu P, Liu HR, et al. Differences in regional homogeneity between patients with Crohn's disease with and without abdominal pain revealed by resting-state functional magnetic resonance imaging. *Pain*. 2016;157:1037–1044. doi:10.1097/j.pain.0000000000000479
51. Li N, Zhou H, Tang Q. Red blood cell distribution width: a novel predictive indicator for cardiovascular and cerebrovascular diseases. *Dis Markers*. 2017;2017:7089493. doi:10.1155/2017/7089493
52. Du Y, Jin M, Liu Q, et al. Association of red blood cell indices with mild cognitive impairment in Chinese elderly individuals: a matched case-control study. *Curr Alzheimer Res*. 2020;17:1161–1166. doi:10.2174/1567205018666210218144856
53. Qiang YX, Deng YT, Zhang YR, et al. Associations of blood cell indices and anemia with risk of incident dementia: a prospective cohort study of 313,448 participants. *Alzheimers Dement*. 2023;19:3965–3976. doi:10.1002/alz.13088
54. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA*. 2004;292(18):2237–2242. doi:10.1001/jama.292.18.2237
55. He XF, Li LL, Xian WB, et al. Chronic colitis exacerbates NLRP3-dependent neuroinflammation and cognitive impairment in middle-aged brain. *J Neuroinflammation*. 2021;18(1):153. doi:10.1186/s12974-021-02199-8
56. Friston K. Ten ironic rules for non-statistical reviewers. *Neuroimage*. 2012;61:1300–1310. doi:10.1016/j.neuroimage.2012.04.018
57. Baker DH, Vilidaite G, Lygo FA, et al. Power contours: optimising sample size and precision in experimental psychology and human neuroscience. *Psychol Methods*. 2021;26:295–314. doi:10.1037/met0000337
58. Geuter S, Qi G, Welsh RC, Wager TD, Lindquist MA. Effect size and power in fMRI group analysis. *bioRxiv*. 2018;295048. doi:10.1101/295048