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Original Research

Impact of Endovascular Revascularization on Functional Connectivity and Cognition in Symptomatic Chronic Internal Carotid Artery Occlusion Patients: A Preliminary Exploratory Study

Renjie Ji[1,†], Shixin Zhang[2,†], Hanfeng Chen[1], Chunlan Deng[1], Ziqi Xu[1], Jie Zhang[3,*], Benyan Luo[1,*]

[1]Department of Neurology, The First Affiliated Hospital, School of Medicine, Zhejiang University, 310003 Hangzhou, Zhejiang, China
[2]Zhejiang Provincial Center for Disease Control and Prevention, 310051 Hangzhou, Zhejiang, China
[3]Department of Rehabilitation Medicine, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, 310014 Hangzhou, Zhejiang, China
*Correspondence: zhangjie91@zju.edu.cn (Jie Zhang); luobenyan@zju.edu.cn (Benyan Luo)
†These authors contributed equally.
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Abstract

Background: Symptomatic chronic internal carotid artery occlusion (CICAO) may lead to stroke and cognitive decline. Although endovascular recanalization has been proven to reduce the risk of future strokes, the effect on cognition remains controversial and requires further exploration. We explored alterations in functional connectivity (FC) and their associations with cognition in patients with symptomatic CICAO before and after carotid revascularization. **Methods**: Eighteen patients with unilateral CICAO and fifteen healthy controls (HCs) were enrolled. Resting-state functional magnetic resonance imaging (rs-fMRI) and neuropsychological assessment were performed on all participants, before and after 6 months post-recanalization in the patient group. FC alterations in multiple brain networks and their correlations with cognitive scores were analyzed. **Results**: The FC of the CICAO group were markedly lower relative to the HC group for the following: the dorsal attention network (DAN) with the ipsilateral (occlusion side, right) middle frontal gyrus and frontal pole; the default mode network (DMN) with the ipsilateral angular gyrus; the visual network (VN) with the ipsilateral fusiform gyrus; and the frontoparietal network (FPN) with middle temporal gyrus on the side contralateral to the occlusion. The decreased FC of the DAN exhibited a positive association with the total score of the Mini-Mental State Examination (MMSE, r = 0.499, p = 0.049), Montreal Cognitive Assessment (MoCA, r = 0.515, p = 0.041), and Backward Digit Span Test (BDST, r = 0.594, p = 0.015), and negatively correlated with the score of Trail Making Test (TMT)-A (r = –0.563, p = 0.023) and TMT-B (r = –0.602, p = 0.014). The CICAO group exhibited significantly increased FC of the DMN seed region with the middle occipital gyrus ipsilateral to the occlusion. Additionally, the VN seed region demonstrated increased FC with the fusiform gyrus ipsilateral to the occlusion following endovascular recanalization. The preoperative FC values of the DMN exhibited a strong positive association with the improvement in TMT-A score (r = 0.629, p = 0.021). **Conclusion**: Our exploratory study found that FC disruption may induce cognitive decline in symptomatic CICAO patients. Endovascular recanalization may improve FC within key brain networks, supporting cognitive improvement. The baseline DMN FC was significantly associated with the postoperative improvement in TMT-A scores, suggesting that preoperative DMN FC could serve as a potential predictor of cognitive recovery. **Clinical Trial registration**: NCT05292729. Registered 1 December 2021, https://clinicaltrials.gov/study/NCT05292729?intr=NCT05292729&rank=1.

Keywords: cognitive dysfunction; neuropsychological tests; functional magnetic resonance imaging; carotid artery, internal; vascular occlusion

1. Introduction

Chronic internal carotid artery occlusion (CICAO) is a prevalent cerebrovascular condition. It is mainly characterized with a high risk of ischemic stroke [1–3], and cognitive dysfunction [4]. The latter is a common neurological deficit in patients with CICAO affecting multiple cognitive domains, which requires significant attention. The prevalence of cognitive decline in CICAO patients ranges between 50% to 67% [5]. The pathogenesis of cognitive decline in CICAO patients is still poorly understood. Cerebral hypoperfusion is considered to be a key contributing factor [2], with long-term hemodynamic disturbances can lead to neuronal damage or disruption of brain microstructures [6]. In patients with symptomatic CICAO, cognitive impairment is closely linked to stroke etiology, pathogenesis, and lesion location, given the heterogeneous nature of stroke [7–9]. Neuroinflammation, a key consequence of ischemic brain injury, is also a significant contributor to post-stroke cognitive decline [10]. Supporting this, Glumac *et al*. [11] demonstrated that corticosteroids, by mitigating the perioperative inflammatory response, can reduce the incidence and severity of cognitive decline, further emphasizing the crucial role of inflammatory pathways in the development of post-stroke cognitive impairment.

The current guidelines do not recommend endovascular revascularization for symptomatic CICAO due to lack of high quality evidence [12,13]. However, for patients with hemodynamic impairment, endovascular therapy may be considered as an alternative treatment option [14]. Previous studies have demonstrated the applicability and safety of endovascular revascularization in this patient population [15–17]. Successful recanalization not only reduces ischemic events, but prevents continuous brain function impairment by improving cerebral perfusion as well. Notably, the cognitive improvement of symptomatic CICAO patients following carotid revascularization has been successfully demonstrated [18,19]. The underlying neuro-mechanism is however not well understood and requires further investigation.

The resting-state functional magnetic resonance imaging (rs-fMRI) is increasingly being utilized to assess brain functional connectivity (FC) and its association with cognitive functions. Several investigations have uncovered brain functional alterations in patients with carotid stenosis and showed disruption in brain connectivity [20–22]. Increased FC following revascularization have been associated with cognitive benefits [6,23–25]. Given that CICAO patients are more vulnerable to compromised hemodynamics than those with carotid stenosis [26], the manifestation of FC disruptions in CICAO may differ. Nevertheless, the changes in brain connectivity in symptomatic CICAO patients following carotid revascularization remain unexplored.

This preliminary exploratory study employed rs-fMRI to investigate alterations in FC within the neural networks of symptomatic CICAO patients before and after endovascular revascularization. We further examined the correlation between these FC alterations and cognitive function. Our primary hypothesis was that changes in brain connectivity mediate cognitive decline in patients with symptomatic CICAO. We also hypothesized that improvements in cognitive function following endovascular therapy would be associated with increased FC within specific brain networks.

2. Materials and Methods

2.1 Patients and Healthy Controls (HCs)

Our study has a small-sample exploratory design. Between January 2022 to May 2023, 18 patients with symptomatic unilateral CICAO and who were candidates for endovascular recanalization were enrolled into the study. Confirmed symptomatic CICAO due to a diagnosis of transient ischemic attack (TIA) or infarction within the distribution territory of the affected carotid artery during 6 months preceding enrolment in the study. The following inclusion criteria were applied: (1) age $\geq$45 years; (2) completely occluded internal carotid artery (ICA) confirmed by digital subtraction angiography (DSA) and the presence of a stump with proximal ICA lumen patency. Additionally, the cavernous and/or petrous segments needed to exhibit reconstitution via collateral filling from branches of ipsilateral external carotid artery, anterior communicating artery (AcomA), and/or posterior communicating artery (PcomA). This corresponds to the Type A and Type B classifications of CICAO patients as defined by Hasan *et al*. [27]; (3) A modified Rankin score (mRS) of $\leq$2. (4) education level ($\geq$6 years). The exclusion criteria included: (1) ipsilateral middle cerebral artery stenosis $\geq$50% or contralateral carotid artery or middle cerebral artery stenosis $\geq$50%; (2) non-atherosclerotic carotid artery occlusion, such as that caused by arteritis or dissection; (3) Language comprehension or expression disorders that prevent or hinder cooperation with neuropsychological assessment; (4) concurrent neurodegenerative or psychiatric diseases; (5) congestive heart failure [left ventricular ejection fraction (LVEF) $<$40%]; or severe renal failure [estimated glomerular filtration rate (eGFR) of $<$ 30 mL/min/1.73 m^2]; or severe liver failure (Child-Pugh Class C); or malignancy; (6) contraindications for an MRI scan (metal implants); (7) acute carotid artery occlusion. In addition, 15 HCs without cerebral large artery stenosis or occlusion (confirmed by ultrasound) were recruited. Our study was conducted in compliance with the Declaration of Helsinki. Patients or their families/legal guardians provided written informed consent. The study protocol was approval by the Institutional Review Board of the First Affiliated Hospital of Zhejiang university.

2.2 Carotid Artery Recanalization Procedure

Patients were administered two antiplatelet agents (aspirin and clopidogrel) for a minimum of 5 days prior to undergoing endovascular revascularization. The procedure was performed via the femoral artery access under local anaesthesia and general heparinization, utilizing embolic-protection devices. Technical success was characterised by the successful implantation of stents following the recanalization of the occluded carotid artery, achieving a final residual diameter stenosis of 20% or less and modified Thrombolysis in Cerebral Infarction (mTICI) grade 3 antegrade flow [28]. Post-recanalization systolic blood pressure was maintained between 100 and 140 mmHg. Patients were prescribed with antiplatelet agents (aspirin and clopidogrel) for a duration of three months post-intervention and followed by lifelong monoclonal antiplatelet therapy. The occurrence of neurological sequelae, intracranial haemorrhages, and mortality was documented in the postoperative period. Additionally, computer tomography (CT) angiography (CTA) was scheduled at the 6-month follow-up.

2.3 Cognitive Performance Assessment

In our study, neuropsychological evaluations were conducted by a neurologist who had undergone specialized training. Mini-Mental State Examination (MMSE)

(Chinese version) [29] and Montreal Cognitive Assessment (MoCA) (Beijing Version) [30] were used to assess the global cognition. Trail Making Test (TMT)-A and -B were used to examine visuospatial and executive function [31]. Symbol Digit Test (SDT) [32] was employed to examine visual search, perception, and graphomotor speed. Digit Span Test (DST), including Forward DST (FDST) and Backward DST (BDST) [32], was used to evaluate working memory. Neuropsychological assessments were conducted within 7 days before surgery for patients and at baseline for healthy controls. Identical assessments were repeated for patients at the 6-month follow-up after carotid artery recanalization.

2.4 MRI Examination

Patients received brain MRI sessions at two time points: 1 week prior to carotid recanalization and 6 months following the procedure. Imaging data were obtained using 3.0-Tesla MR system (SIGNA Architect, General Electric (GE) Medical systems, Waukesha, WI, USA and DISCOVERY MR750, GE). A standard 19-channel head coil was used to receive the signal (GE Healthcare, serial number, SN: H01511, Aurora, OH, USA). The subjects were placed on supine, with their heads supported with foam pads and a belt. They were required to close their eyes, avoid thinking about anything and falling asleep during the MRI.

In the SIGNA Architect System (SN: PG75A1900119SC, GE Medical systems), T1 parameters were as follows: repetition time (TR) of 7.7 ms; echo time (TE) of 3.1 ms; field-of-view (FOV) of 256 mm; voxel size of 1.0 × 1.0 × 1.0 mm; slice thickness of 1.0 mm; 176 slices; and a total scanning time of 4 min and 39 s. The parameters of rs-fMRI sequence included: TR of 2000 ms; TE of 30.0 ms; voxel size of 3.4 × 3.4 × 3.6 mm; FOV of 220 mm; slice thickness of 3.6 mm; 36 slices (6 patients and 3 HCs); and total scanning time of 6 min and 40 s. In the DISCOVERY MR750 System (SN:PG75E1900019SC, GE Medical systems), T1 parameters included: TR of 8.2 ms; TE of 3.2 ms; voxel size of 1.0 × 1.0 × 1.0 mm; FOV of 256 mm; slice thickness of 1.0 mm; 180 slices; and total scanning time of 4 min and 52 s. The parameters of rs-fMRI scanning included: TR of 2000 ms; TE of 30.0 ms; voxel size of 3.4 × 3.4 × 3.2 mm; FOV of 220 mm; slice thickness of 3.2 mm; 45 slices (12 patients and 12 HCs); and total scanning time of 6 min and 40 s.

2.5 Imaging Processing and Analysis

The initial pre-processing step included flipping the images of patients with left-sided carotid occlusion, standardizing the affected hemisphere to the right-hand side across all participants. Pre-processing of rs-fMRI and T1 data was conducted using the data processing & analysis for brain imaging (DPABI) package (Version 7.0, The R-fMRI Lab, Institute of Psychology, Chinese Academy of Sciences, Beijing, China) [33]. The first 10 time points were excluded to stabilize the magnetic field and allow participants to adapt. Slice timing was corrected by matching the centre slice, while head motion was corrected by spatial realignment to the mean volume of a series of images. The T1 images were co-registered to the fMRI image, segmented and normalized to a group specific template in Montreal Neurological Institute (MNI) space via the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolkit [34] within DPABI package (http://rfmri.org/DPABI). Detrending was applied to fMRI images to remove signal intensity drift. Nuisance regression was carried out to remove physiological noise from cerebrospinal fluid, white matter, and motion (Friston 24 method). The last pre-processing step included applying band-pass filtering between 0.01 and 0.10 Hz, followed by image smoothening using a 4-mm full-width half-maximum (FWHM) Gaussian kernel to reduce the registration error between subjects and improve signal-to-noise ratio.

After the pre-processing, seed-based voxel-wise functional connection analysis was conducted using DPABI. The following 6 networks were evaluated based on a previous study in patients with carotid artery stenosis [15]: salience network (SN), at the seed of dorsal anterior cingulate cortex (–1, 10, 46); visual network (VN), at the seed of left primary visual cortex (–4, –81, –10); default mode network (DMN), at the seed of posterior cingulate cortex (0, –50, 22); sensorimotor network (SMN), at the seed of left primary motor cortex (–41, –20, 62); frontoparietal network (FPN), at the seed of left middle frontal gyrus (–45, 29, 32); and dorsal attention network (DAN), at the seed of left frontal eye field (–26, 6, 48). All spherical seeds with a 4 mm radius were positioned contralateral to the occlusion side.

2.6 Statistical Analysis

R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) was utilized to analyse data in the two groups. Data normality distribution was tested by the Shapiro-Wilks normality test. Those that followed a normal distribution were presented as the mean ± standard deviation (SD), and a *t*-test was used to analyse inter-group comparison. Non-normally distributed data was expressed as a median (interquartile range (IQR)), and Mann-Whitney U test was used for inter-group comparison. Fisher's exact test was used to compare categorical variables between the two groups. A two-tailed significance level of $p < 0.05$ was applied in all comparisons.

At the image level, one-sample *t*-test were performed for both the control and the patient groups before and after endovascular recanalization, with a minimum cluster size of 40 voxels and a threshold of $p < 0.001$. A two-sample *t*-test was performed to compare FC values within each of the six networks between patients and healthy controls, with the gender, age, instrument model and Mean framewise displacement (FD) Jenkinson as covariates [35]. A paired *t*-

test was assessed the pre- and post-operation FC strengths in the patient group with the mean FD Jenkinson as covariates. The Gaussian random field (GRF) correction was applied with the voxel level $p < 0.005$ and cluster level two-sided $p < 0.05$.

To explore the relationship between FC alterations and baseline cognitive performance, the average of the FC strengths for each patient (N = 18) were extracted from voxels in each distinct cluster. Pearson correlation analysis was conducted to associate these FC values with their respective cognitive scores. The relationship between FC alterations in distinct clusters and the changes in cognitive assessment pre- and post-operation was analysed using partial correlation analysis, with education years and age included as covariates. All Pearson correlation analysis were two-sided, and a $p < 0.05$ was set as a cut-off for significance.

3. Results

3.1 Patient Features and Results of Cognitive Testing

Prior to rs-fMRI analysis, we established the head movement threshold (3.0 mm and 3.0 degree in max head motion) [33] to exclude subjects with excessive head motion. Ultimately, no patients were excluded based on this criterion. Among the 18 patients, infarct lesions were predominantly located in watershed areas, with 15 cases in the internal watershed, 2 cases involving both anterior and posterior watershed regions, and 1 case in the anterior watershed region. The Circle of Willis was evaluated via DSA. The AcomA was observed in eight patients, the PcomA in six patients, with AcomA and PcomA observed in four patients. All patients with symptomatic CICAO underwent endovascular recanalization procedures. Due to the inability of a micro-guidewire to enter the true lumen, there were two failed cases of endovascular recanalization. Another patient who was successfully recanalized suffered a transient exacerbation of neurological symptoms due to new ischemic infarcts in the hemisphere ipsilateral to occlusion which confirmed by MRI scan. No other patients suffered any perioperative complications. Therefore, after excluding the aforementioned three cases, 15 patients completed the follow-up.

The baseline characteristics and cognitive function evaluations are presented in Table 1. Comparative analysis confirmed that the two groups did not markedly differ in age, sex, education, and vascular risk factors. Marked differences were observed in cognitive performance, with patients with symptomatic CICAO exhibiting lower MMSE, MoCA, SDT, FDST, and BDST scores. Conversely, patients presented with significantly higher TMT-A and -B scores. These findings suggested a decline in general cognition and several specific cognitive domains, including attention, working memory, visual-spatial function and executive function in the symptomatic CICAO patients compared to the HCs.

Table 1. Demographic characteristics and cognitive scores of HCs and patients with symptomatic CICAO.

	HCs (N = 15)	Patients (N = 18)	*p* values
Sex-male	12 (80%)	15 (83.3%)	1.000
Age	57.7 ± 8.1	62.7 ± 7.4	0.078
Education	6 (6, 9)	6 (6, 9)	0.817
Smoking	6 (40%)	11 (61.1%)	0.303
Drinking	2 (13.3%)	6 (33.3%)	0.242
Hypertension	10 (66.7%)	14 (77.8%)	0.697
Diabetes	3 (20%)	6 (33.3%)	0.458
MMSE	29 (28.5, 30)	25 (24, 26)	<0.001*
MoCA	28 (27, 28)	23 (20, 23)	<0.001*
SDT	30 (28, 33.5)	14.5 (10, 22)	<0.001*
TMT-A	50 (48, 51)	109.5 (98, 135)	<0.001*
TMT-B	87.6 ± 8.75	178.8 ± 64.5	<0.001*
Forward DST	8 (8, 8)	6 (6, 7)	<0.001*
Backward DST	7 (7, 7)	5 (5, 5)	<0.001*

*: denotes statistical significance. MMSE, Minimum Mental State Examination; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; SDT, Symbol Digit Test; DST, Digit Span Test; HC, healthy control; CICAO, chronic internal carotid artery occlusion.

The CTA performed at 6 months in 15 patients and confirmed no restenosis or occlusion. During the 6-month follow-up period, patients who achieved successful recanalization had no recurrent stroke or TIA. The MMSE, MoCA, and FDST scores were higher in the patient group after carotid recanalization (Table 2).

Table 2. Cognitive scores pre- and post-operation within the patient group.

Cognitive score	Pre-operation	Post-operation	*p* values
MMSE	25 (24, 26)	26 (25, 27)	0.009*
MoCA	23 (20, 23)	26 (21.5, 26)	0.019*
SDT	15.4 ± 7.3	17.7 ± 8.4	0.424
TMT-A	114.8 ± 23.3	104.6 ± 24.9	0.257
TMT-B	182.2 ± 54.1	172.9 ± 58.5	0.653
Forward DST	6 (6, 7)	7 (7, 8)	0.009*
Backward DST	5 (5, 5)	5 (5, 6)	0.217

*: denotes statistical significance.

3.2 Alterations of FC Between Symptomatic CICAO Healthy Controls and Patients at Baseline

In the patient group before endovascular recanalization, the side with ipsilateral to the occlusion (right) exhibited asymmetrical hypo-connectivity within the 6 selected networks, with seeding performed at the occlusion contralateral side (left; Fig. 1). Hypo-connectivity of a specific network in patients with symptomatic CICAO was defined by abnormally lower connectivity strengths compared to those observed in HCs. At baseline, for the DAN seed, the patients group showed disrupted FC particularly within

Table 3. Functional connectivity differences in neural networks between patients and healthy controls.

Networks	Coordinates (MNI)			Cluster size	T score
	X	Y	Z		
Dorsal attention network					
Frontal pole (R)	42	39	9	55	4.22
Middle frontal gyrus (R)	33	27	51	43	4.43
Frontoparietal network					
Middle temporal gyrus (L)	–57	–42	0	86	5.69
Default mode network					
Angular gyrus (R)	45	–57	33	43	3.83
Visual network					
Occipital fusiform gyrus (R)	27	–87	–18	96	4.53

Patients with left-sided carotid occlusion were flipped to the right side. MNI, Montreal Neurological Institute; R, right; L, left.

the ipsilateral (occlusion side, right) frontal pole and middle frontal gyrus compared to the HCs. The DMN seed region revealed reduced FC with the ipsilateral angular gyrus, while the VN seed region showed reduced FC with the ipsilateral fusiform gyrus (Fig. 2, Table 3). Additionally, the FPN seed region displayed reduced FC with the middle temporal gyrus on the side contralateral to the occlusion (Fig. 2, Table 3). Notably, the between-group differences in the SMN and SN were not significant.

3.3 Association Between Baseline FC Alterations and Cognitive Function

We further assessed the correlation between FC changes and cognitive function, revealed: a positively correlation between a reduction in DAN with frontal pole (ipsilateral to occlusion) and the total score of MMSE (r = 0.499, $p = 0.049$), MoCA (r = 0.515, $p = 0.041$), BDST (r = 0.594, $p = 0.015$); and a negative association with TMT-A (r = –0.563, $p = 0.023$) and TMT-B scores (r = –0.602, $p = 0.014$) (Fig. 3).

3.4 Recovery of FC After Carotid Artery Recanalization

Six months after endovascular recanalization, the inter-hemispheric FC exhibited a symmetrical shape, particularly in the DMN, similar to manifestations observed in HCs (Fig. 4). The two-sample paired *t*-test, adjusted for mean FD of head motion, revealed significant FC increases. Specifically, the DMN seed region exhibited enhanced FC with the middle occipital gyrus ipsilateral to occlusion, and the VN seed region showed increased FC with the fusiform gyrus ipsilateral to occlusion following endovascular recanalization (voxel-level $p < 0.005$ and cluster-level $p < 0.05$, corrected by GRF) (Fig. 5).

3.5 Association Between Increased FC and Enhanced Cognitive Performance

The improvement scores for the patient group were calculated by subtracting the post-operative MMSE, MoCA, SDT, TMT-A, TMT-B, FDST and BDST, from preoperative the scores, and then taking the absolute values. The mean FC values for preoperative and postoperative FC were extracted for two distinct cluster, DMN and VN, and partial correlation analysis revealed a positive association of the preoperative FC values of the DMN with the improvement in TMT-A score (r = 0.629, $p = 0.021$) (Fig. 6).

4. Discussion

The impact of carotid recanalization on symptomatic CICAO patients was explored, focusing on the possibility of enhancing cognition and brain connectivity. There were two main findings in this study. First, at baseline, FC showed significantly decreased networks of DAN, FPN, DMN and VN in the patient group compared to HCs. Furthermore, decreased FC in the DAN between frontal pole ipsilateral to occlusion was significantly correlated with cognitive decline in the patient group. Second, both cognitive scores and brain FC were significantly improved after carotid recanalization in symptomatic CICAO patients. The baseline FC strengths of DMN exhibited a positive relationship with TMT-A score improvement after carotid recanalization. However, increased FC of the DMN with ipsilateral middle occipital gyrus to occlusion and VN with ipsilateral fusiform gyrus to occlusion did not correlate with improvements in cognitive scores. These findings suggested that cognitive decline in symptomatic CICAO patients may attributed to the disruptions of FC. Furthermore, carotid revascularization can increase the FC and improve cognitive function in symptomatic CICAO patients.

Park and Friston [36] revealed that neural activity can be understood as a complex interplay of distinct brain networks [37]. Brain networks exhibit intricate interconnectivity, influencing and modulating each other's activity. Through coordinated function, these networks contribute to various aspects of brain function, including cognition [36]. Before carotid revascularization, the patients showed diffuse disruption of multiple brain networks, including in the DAN (at the frontal pole ipsilateral to occlusion and ipsilateral middle frontal gyrus), DMN (at the ipsilateral an-

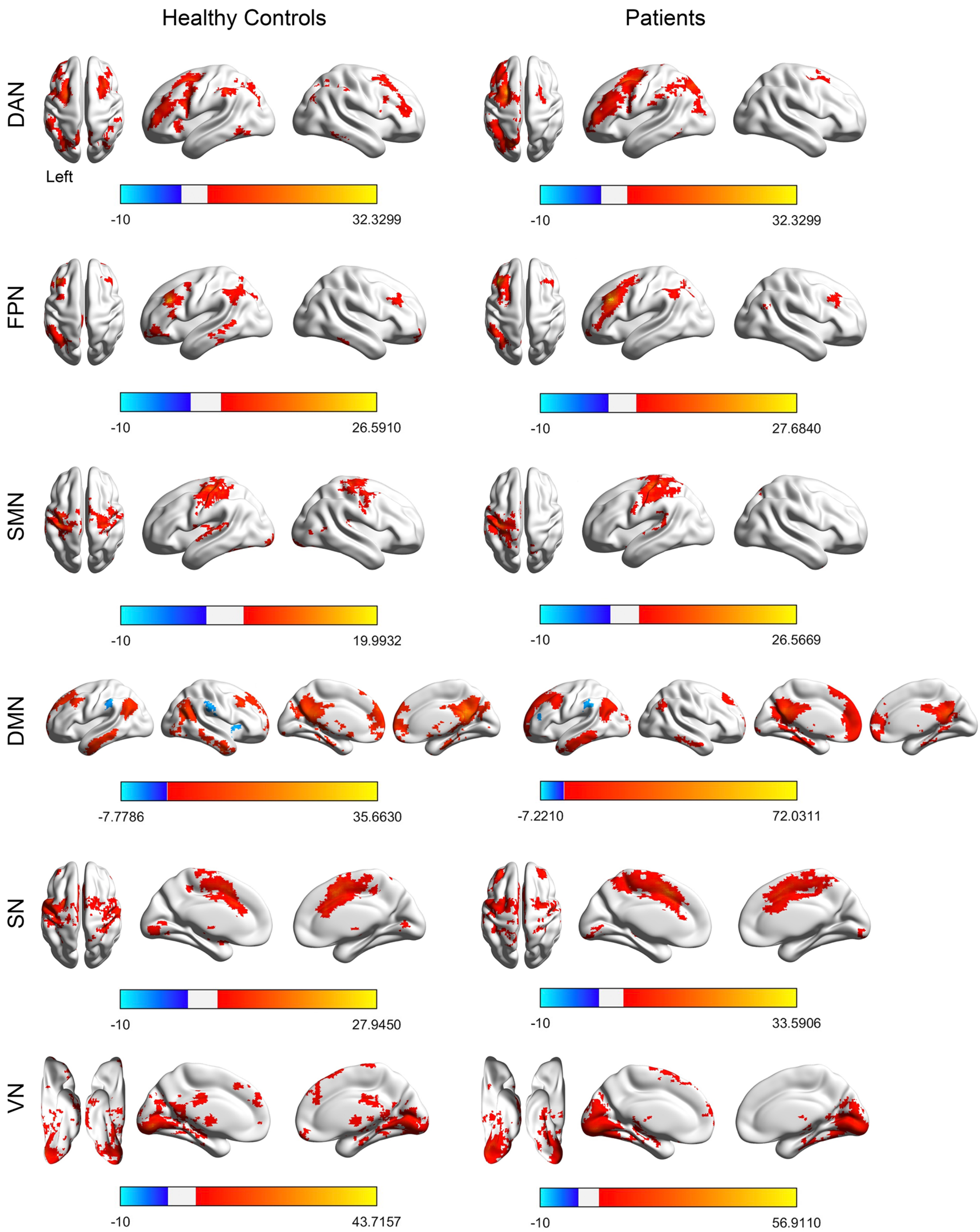

Fig. 1. A within-group examination of six brain networks in patients and healthy controls. The predefined regions of interest (ROIs) for specific networks are indicated by hollow circles. Patients with left-sided of carotid occlusion were flipped to the right side. Color bars indicate T scores. DAN, dorsal attention network; SMN, sensorimotor network; FPN, frontoparietal network; DMN, default mode network; VN, visual network; SN, salience network.

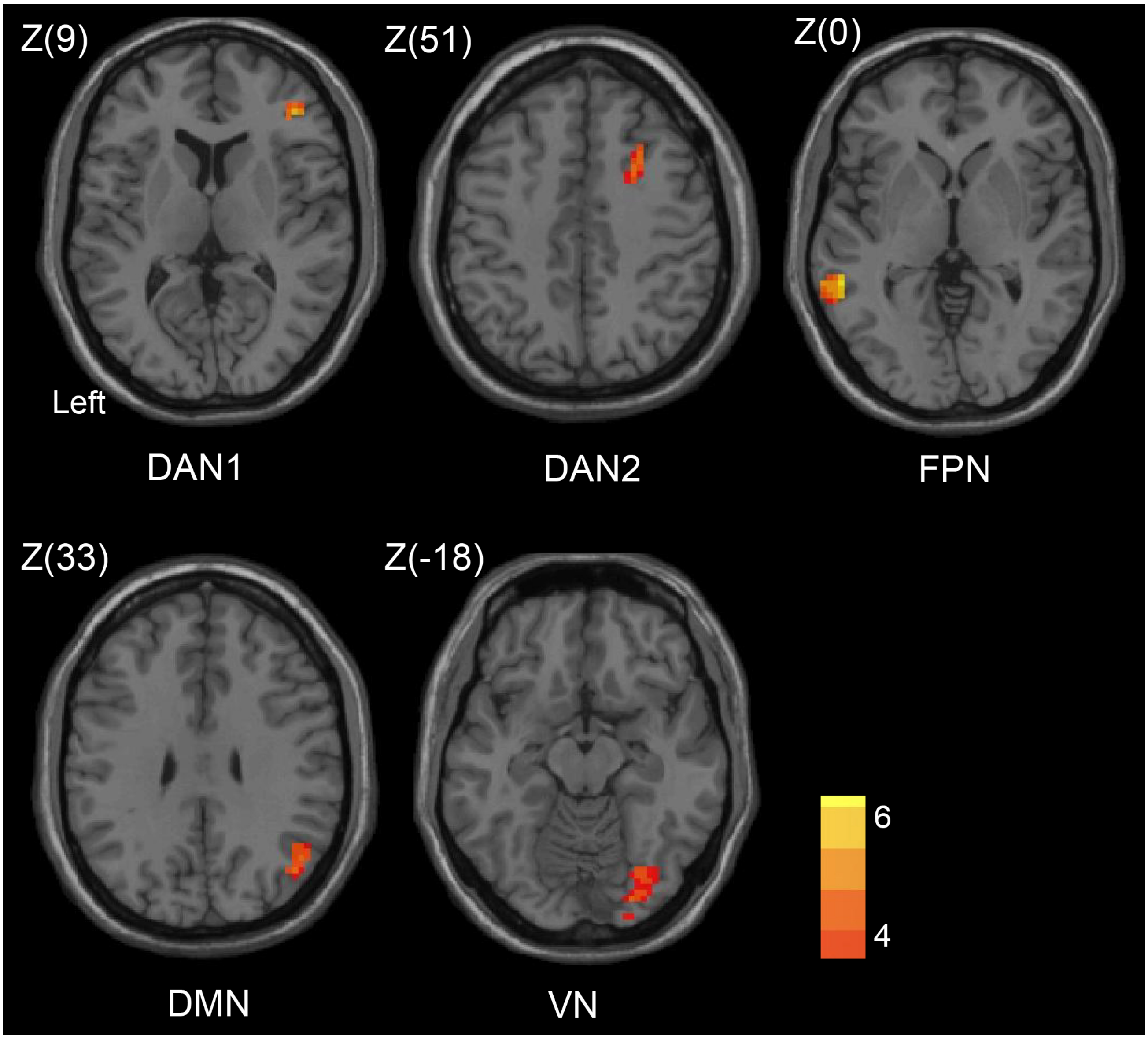

Fig. 2. Group comparisons of six brain networks between patients and HCs. Clusters with significant increments of functional connectivity are shown in red. Patients with left-sided of carotid occlusion were flipped to the right side. Color bars indicate T scores (voxel-level $p < 0.005$, cluster-level $p < 0.05$).

gular gyrus), VN (at the ipsilateral fusiform gyrus), FPN (at the contralateral middle temporal gyrus) and none in the SN or SMN. The DAN, crucial for orienting and maintaining attention, encompasses the intraparietal sulcus and frontal eye fields bilaterally [38,39]. Disruptions in DAN FC have been implicated in cognitive decline observed in mild cognitive impairment (MCI) and Alzheimer's disease (AD) [40–42]. The FPN, comprising the posterior parietal cortex and lateral prefrontal cortex, serves as a critical hub for cognitive regulation, particularly fluid intelligence [43]. Furthermore, frontoparietal regions controls in various cognitive functions, such as mental imagery, episodic memory retrieval and working memory [44]. In our study, the FPN seed region showed reduced FC with the middle temporal gyrus contralateral to occlusion, indicating that the unilateral internal carotid artery occlusion not only affects the brain connectivity of the affected hemisphere but also impacts the contralateral hemisphere. The DMN has been extensively studied [45] and with evidence suggesting its role, including reviewing past knowledge and processing memory [46]. Zhang *et al*. [47] reported disruption FC in the DMN influenced the disease severity in AD patients. In addition, the DMN is closely related to processes associated with episodic memory [48]. The VN interacts with other brain networks, enabling the integration of complex cognitive processes involving visuospatial functions [49]. Reduced VN FC has been linked to cognitive decline, particularly affecting object recognition and visuospatial orien-

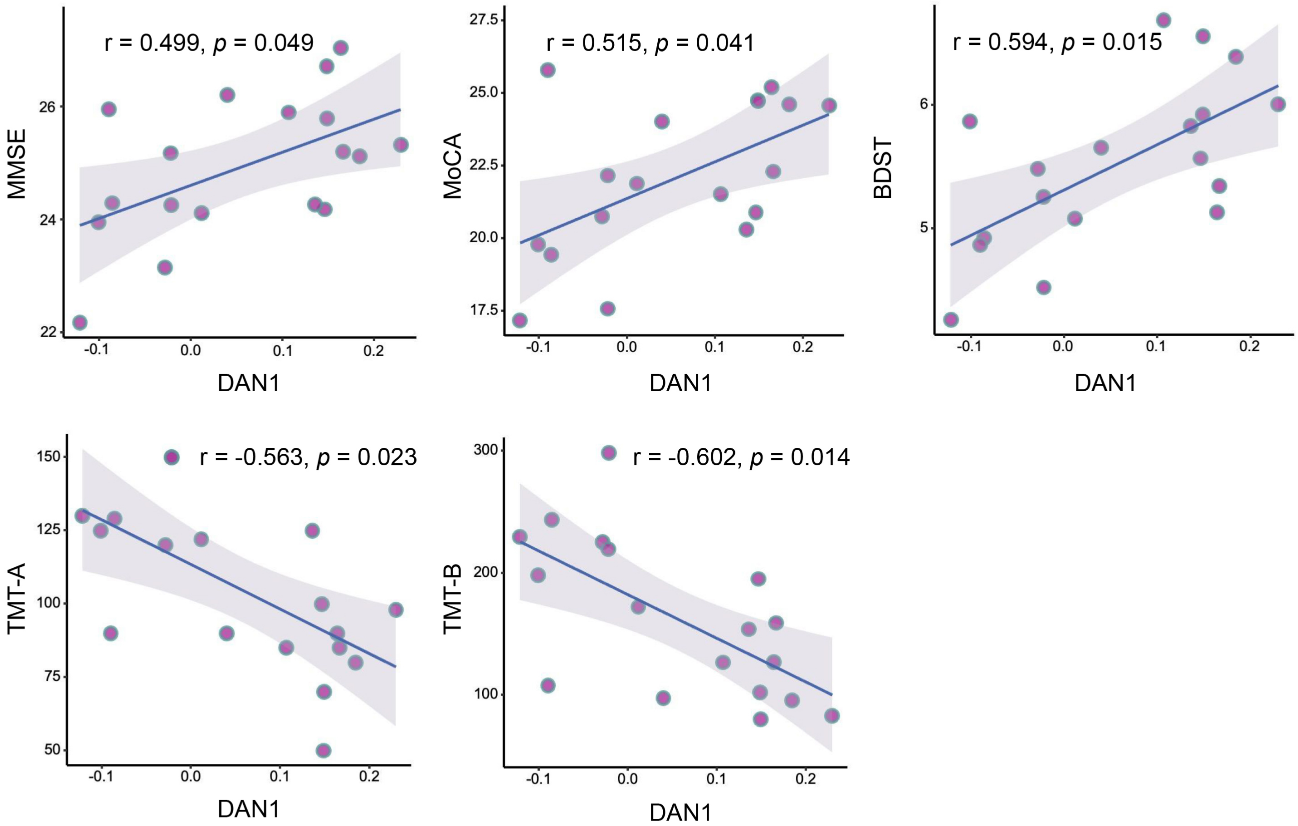

Fig. 3. Pearson correlation analysis between FC strength and neurocognitive performance at baseline. DAN1, dorsal attention network (at the frontal pole ipsilateral to occlusion); BDST, backward Digit Span Test.

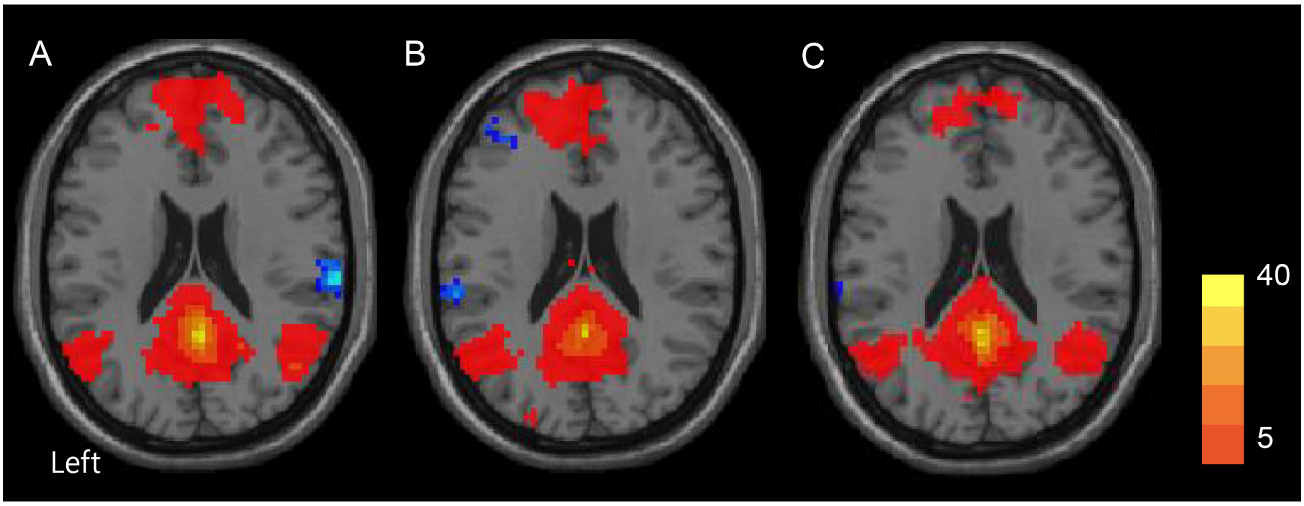

Fig. 4. FC maps at the group-level in the DMN. From left to right: healthy controls (A), CICAO patients before carotid recanalization (B), 6 months after carotid recanalization (C). Color bars indicate T scores (voxel-level $p < 0.001$; cluster >40 voxels). FC, functional connectivity.

tation [50]. In our study, the observed widespread disruptions of FC within these cognitive-related brain networks likely contribute to cognitive impairment in CICAO patients. While comparing the FC of asymptomatic carotid stenosis patients (CAS) and HCs, Lin *et al*. [22] observed disruptions of FC in the FPN, SN, DMN and DAN. A comparing the rs-FC data in patients with asymptomatic unilateral carotid stenosis or occlusion with age-matched HCs, reported a decrease in connectivity strength in DAN, FPN and DMN [51]. Our results are congruent with the aforementioned reports. In addition, we found that the regions in the DMN, FPN and DAN predominantly in the territory

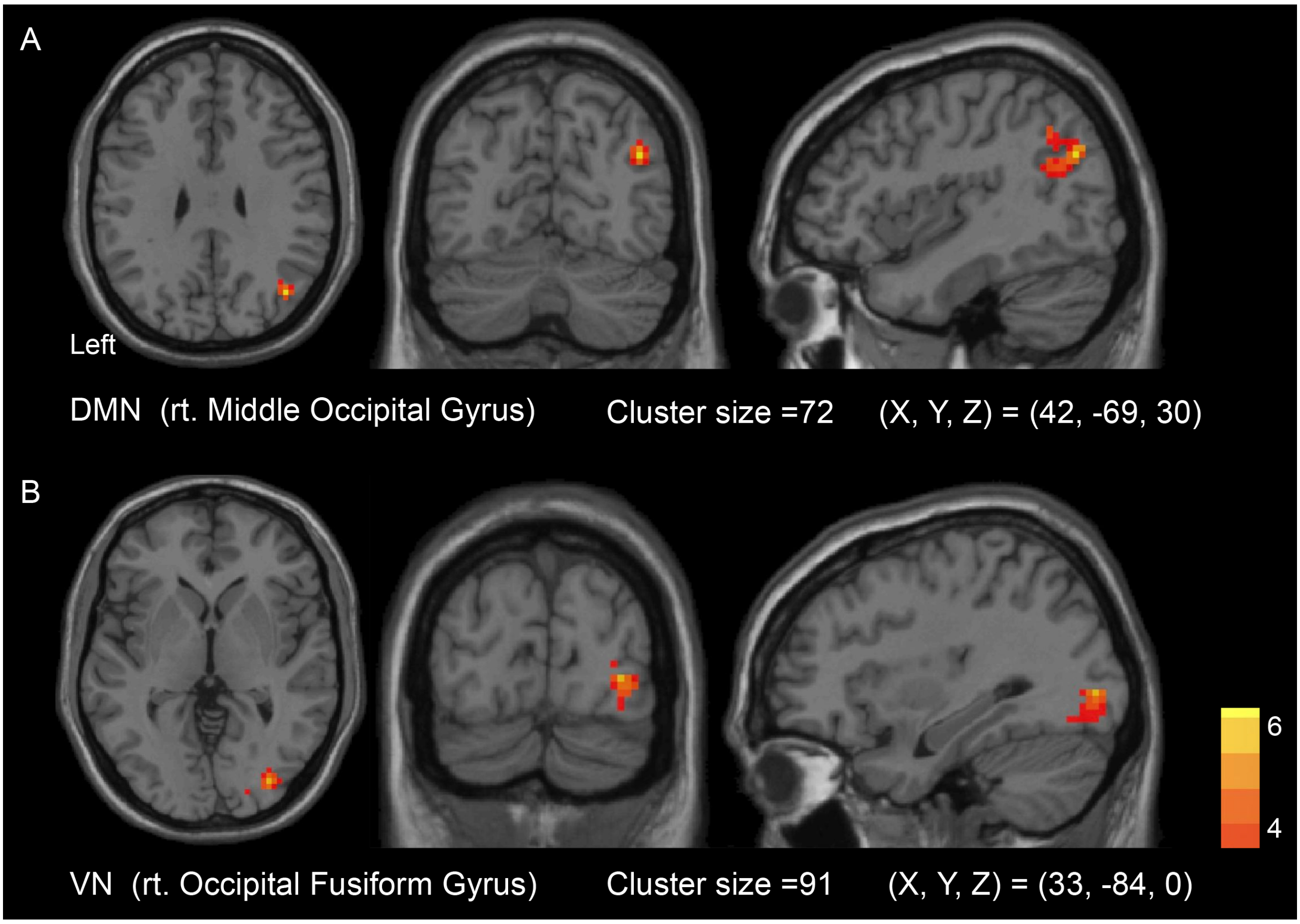

Fig. 5. Seed-to-voxel contrast between post-operation and pre-operation of carotid recanalization showed significantly increased FC strengths in DMN with right Middle Occipital Gyrus (A) and VN with right Occipital Fusiform Gyrus (B). Patients with left-sided carotid occlusion were flipped to the right side. Color bars indicate T scores (voxel-level $p < 0.005$).

supplied by the internal carotid artery (ICA) were significantly impacted, suggesting that FC disruption in symptomatic CICAO patients may be related to hypoperfusion and region-specific.

Furthermore, the decreased FC in the DAN (at the frontal pole ipsilateral to occlusion) was related to cognitive decline in the patients. The frontal pole, referred to as the Brodmann area 10, plays a vital role in the higher-order cognitive domains [52]. This, in combination with the above results, suggests that disruptions in FC between the DAN and the frontal pole, play a crucial role which lead to cognitive decline in symptomatic CICAO patients.

This study, observed a marked increase in FC in DMN (at the middle occipital gyrus ipsilateral to occlusion) in patients after carotid recanalization. Cheng *et al.* [23] observed a modest increase of FC in the DMN ipsilateral to stenosis in asymptomatic CAS patients following stenting. Similarly, Kohta *et al.* [53] reported an increased FC of the DMN after carotid stenting. To the best of our knowledge, this is the first rs-fMRI study performed in patients with symptomatic CICAO, showing differences in rs-FC after carotid recanalization. This is consistent with the aforementioned studies. The increased FC of the DMN, may attribute to the improvement in cerebral perfusion following successful recanalization of the carotid artery [54]. Considering the strong association between the DMN and cognitive function, the observed cognitive improvements in our patients may be partially explained by enhanced FC of the DMN. Furthermore, partial correlation analysis uncovered a positive correlation between the preoperative FC of DMN and the improvements in TMT-A score. This means that the baseline FC strength of the DMN could serve as a significant predictor for cognitive improvement following carotid artery recanalization.

A marked elevation in FC in the VN was also uncovered in patients following endovascular revascularization. The VN, which includes both the primary visual cortex and several higher-order visual areas distributed across the occipital, parietal, and temporal lobes, interacts with other cognitive networks to support higher-level cognitive functions that rely on visuospatial information processing [49]. The fusiform gyrus is an integral part of the ventral visual stream involved in the modulation of visual cognitive functions [55]. Decreased FC in VN (at the fusiform

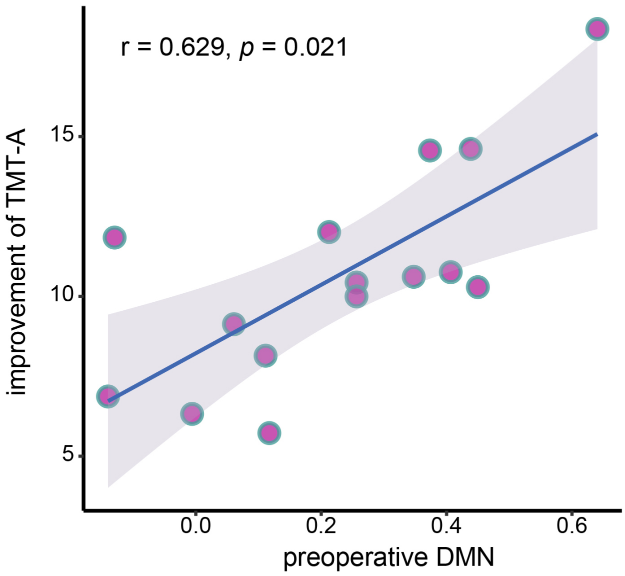

Fig. 6. Partial correlation analysis uncovered a positive association between the preoperative FC of DMN and improvements in TMT-A score.

gyrus ipsilateral to occlusion) suggests a reduced transmission of visuospatial information from the primary to the higher cortex. This may be exhibited with the dysfunction of visual cognitive functions. Though VN is mainly supplied by the vertebrobasilar circulation, the patients in this study presented with decreased FC of VN at baseline probably due to the posterior communicating artery and posterior leptomeningeal branch of the brain providing compensatory blood supply to the carotid artery system. Once the carotid artery is recanalized, this compensatory mechanism is reduced or eliminated, resulting in enhanced perfusion of the VN, which may increase the FC of the VN. However, no significant correlation was observed between the increase FC of VN with the improvement of cognition scores.

The following limitations need to be highlighted. Firstly, due to the exploratory design, a power analysis was not conducted. Besides, owing to the limited sample size, multiple comparison corrections were not applied during the Pearson correlation analysis, potentially increasing the likelihood of Type I errors. Moreover, the small sample size also precluded FC analyses stratified by the side of occlusion and sex differences. Recent research has uncovered sex differences in stroke prognosis [56] and vascular cognitive impairment [57]. Secondly, routine postoperative brain MRI scans to detect silent micro-embolism, which may affect cognitive decline, were not performed in the patient group. However, a comparison of the T1 structural imaging before and 6 months after the surgery, revealed that patients who underwent successful recanalization did not exhibit increased lesions postoperatively. Thirdly, the potential impact of learning effects on the assessment of patients' cognitive functions during follow-up cannot be ruled out. However, given that the reassessment interval was six months, any learning effects, if present, were likely to be minimal. Fourthly, pinpointing the exact timing of occlusion was a significant challenge. The duration of the occlusion could potentially influence the reversibility of cognitive impairments. Fifth, the follow-up period of our study was relatively short, meaning the long-term outcomes of carotid revascularization on cognition are yet to be determined. Finally, data were acquired from two MRI systems, which could potentially introduce bias. To mitigate this potential impact, data from the two systems were processed separately, and instrument model was incorporated as a covariate in the statistical analysis. Therefore, these findings should be interpreted carefully and deserve validation in larger cohorts.

5. Conclusion

Disruptions in FC within brain networks may induce cognitive decline in symptomatic CICAO patients. Endovascular recanalization improves FC within brain networks, thereby promoting cognitive improvement. The baseline DMN FC may serve as a potential predictor of cognitive recovery. However, as this was a small-scale exploratory study, these findings should be interpreted with caution. Further investigations enrolling more patients and adopting a longer follow-up are advocated to confirm our findings.

Availability of Data and Materials

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

RJJ, JZ and BYL contributed to the study conception and design. Material preparation, data collection and analysis were performed by RJJ, SXZ, CLD, HFC and ZQX. The first draft of the manuscript was written by RJJ, SXZ and revised by BYL, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by Institutional Review Board of the First Affiliated Hospital of Zhejiang university (Reference number: 2021IIT No.772). Written informed consent was obtained from patients or their families/legal guardians. This study has been performed in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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