ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Application of the concept of neural networks surgery in cerebrovascular disease treatment

Qifeng Yu[1,2], Yuming Jiao[1,2], Ran Huo[1,2], Hongyuan Xu[1,2], Jie Wang[1,2], Shaozhi Zhao[1,2], Qiheng He[1,2], Junze Zhang[1,2], Yingfan Sun[1,2], Shuo Wang[1,2], Jizong Zhao[1,2], and Yong Cao[1,2,3,4]*

[1]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

[2]China National Clinical Research Center for Neurological Diseases, Beijing, China

[3]Beijing Neurosurgical Institute, Capital Medical University, Beijing, China

[4]Beijing Institute of Brain Disorders, Laboratory of Brain Disorders, Ministry of Science and Technology, Collaborative Innovation Center for Brain Disorders, Capital Medical University, Beijing, China

Abstract

Based on advanced techniques, both the brain structural network and functional network can be reflected, giving rise to a new field: neural networks. Entering the 21st century, along with the extensive research on neural networks and the digital brain imaging field of neuromodulation, the neurosurgical field has entered into a novel stage: neural networks surgery. Neural networks surgery was developed to devote to protecting the cognitive function of patients with central nervous system diseases. By lucubrate, multiple new views of cerebrovascular disease have emerged. In this paper, we review the applications of this novel concept in treating cerebrovascular diseases, primarily through three aspects: disease mechanism, progression, and treatment strategy. Based on recent research, the development of a novel treatment system for cerebrovascular diseases might help clarify the course of these diseases, provide optimal treatment strategies, and protect the cognitive function of patients to the greatest extent.

Keywords: Cerebrovascular disease; Neural networks surgery; Neural networks; Neurosurgery; Cognitive function

***Corresponding author:**
Yong Cao
(caoyong@bjtth.org)

Citation: Yu Q, Jiao Y, Huo R, *et al*., 2023, Application of the concept of neural networks surgery in cerebrovascular disease treatment. *Brain & Heart*, 1(1): 223. https://doi.org/10.36922/bh.v1i1.223

Received: October 14, 2022

Accepted: December 16, 2022

Published Online: December 30, 2022

1. Introduction

The concept of neural networks surgery has been extensively discussed in the field of neurosurgery. Neural networks surgery is defined as locating neural networks and their relay stations by utilizing current advances in neural networks research and advanced imaging technologies to regulate neural signal transmission in the field of operative neuromodulation. This concept emphasizes the transition from traditional neurosurgery based on excision or ablation to "surgery of networks" and highly specific surgical treatments to restore neural function[1].

In the 21st century, this field is commonly described as the developmental consequence of three dimensions (anatomy and cognitive discovery of the brain, medical imaging innovations, and medical devices). The history of neurosurgery can be divided into three stages: classical neurosurgery, microsurgery, and minimally invasive neurosurgery. Research on neural networks and advances in digital stereometric brain imaging today have led to the emergence of the field of neural networks surgery[1].

In the last decades, with the development and application of advanced imaging equipment, multiple imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI), digital subtraction angiography (DSA), single photon emission computed tomography (SPECT), and positron emission tomography (PET), have made great contributions to both clinical and fundamental research. Meanwhile, a combination of techniques that reflects the cerebral anatomical structure and the brain function has been introduced; this new concept is known as brain networks[2]. Unlike the localizationist theory, which proposes that one cortical area executes a specific function discretely and separately, such as the Broca's area for motor images of speech and the Wernicke's area for sensory images of words, the brain network model is related to functional segregation and integration. It implies that a significant part of human behavior is determined by global communication (Figure 1)[3,4]. Following extensive research on brain networks, this complex network has gained recognition as the physiological basis of cerebral information management and cognitive expression. As the potential of brain networks in maintaining cognitive function becomes more apparent, scientists have put forward the concept of human connectome (Table 1). For now, advanced medical techniques are used in human connectome research to construct individual structural and functional connectivity (FC), and the brain, as a complex functional system with topological feature, has been modeled based on the network analysis method and the graph theory[5]. The topological feature of brain networks is another theoretical basis for raising the concept of neural networks surgery; the investigation of other deuterogenic discoveries, including hubs, module, and default mode network (DMN), helps in the exploration of network connective rules (Figure 2). Understanding the mechanism of lesion and plasticity plays a critical role in condition assessment, prognosis prediction, and even cerebral function protection in surgery[3,6,7]. Patients with cerebrovascular disease often presents with stroke, of which 85% of stroke cases are ischemic stroke, while 15% are hemorrhagic[8]. The occurrence of stroke is affected by various factors[9]. Data from the Global Burden of Disease study have indicated an increase in stroke-related mortality and other worldwide epidemiological metrics from 1990 to 2019; in China, the incidence, prevalence rate, and mortality of stroke increased by 86%, 106%, and 32.3%, respectively; more importantly, the age-standardized rates decreased during this period[10]. Related studies have listed ten modifiable risk factors that have over 90% population-attributable stroke risk globally[11]. Due to the

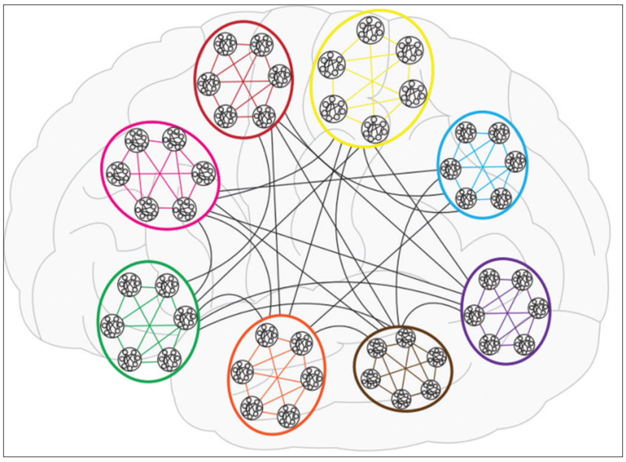

Figure 1. A general map of brain networks. Human behavior requires the interaction of multiple networks.

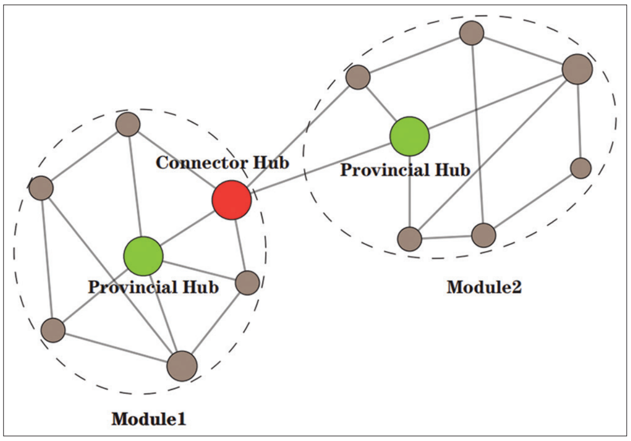

Figure 2. General structure of modules and hubs in a network. The internal module connections are identified in dashed circles. The degree of nodes is reflected by their size (the number of connections that are maintained by a node). Provincial hubs mainly connect nodes within their own module, and connector hubs are important in the interconnection of modules.

Table 1. Difference between human connectome and brain networks

Human connectome	Brain networks
The functional and structural connections of the brain.	The working pattern of the brain is abstracted into a connection of nodes by edges.

complexity and high incidence of cerebrovascular disease, innovations to traditional interventions and new programs are necessary.

Neurosurgery aims to preserve brain function, while managing lesions effectively. In the process of vascular malformation resection, aneurysm clipping, and nerve interventional therapy, the brain function should be preserved as much as possible to ensure a satisfactory quality of life[12]. Nowadays, with the application of novel neural imaging equipment and microsurgery techniques, the prognosis of patients has considerably improved[13]. With the advancements in treatment methods, cognitive protection has gained widespread attention in the field of neurosurgery, especially in cerebrovascular diseases. With the explosion of human connectome and neural networks surgery, combining cerebrovascular disease treatment with brain networks has been a subject of interest. Neural networks surgery aims to improve the efficiency of neural function and cognitive protection by stabilizing the complex network. This new insight has been applied to numerous studies, contributing to preoperative planning, intraoperative brain function protection, and post-operative prognosis assessment in the neurosurgical field. However, the application of this concept in cerebrovascular disease is in the early stage. Therefore, it is imperative to continue to explore and improve the application of cognitive-related brain networks analysis technology, protection methods, and intervening measures. We aim to review the application of the neural networks surgery concept in the treatment of cerebrovascular disease from three aspects (disease mechanism, progression, and the new strategies in neurosurgery for cerebrovascular disease) and describe its effect on prognosis and plasticity maintenance.

2. A deeper understanding of disease pathogenesis and improvement in diagnosis

As the concept of brain networks emerges in the field of neurology, we gain a deeper understanding of the pathogenesis of certain cerebrovascular diseases, thus filling in the gaps of prior ones, including some classical diseases, such as moyamoya disease (MMD), intracranial aneurysm (IA), and even the accompanying symptoms after stroke. Along with advanced medical techniques, this new concept has brought about a great deal of disease diagnosis methods. In this section, we discuss some novel achievements in disease mechanism following advanced diagnosis methods.

Over centuries, the answer to how certain cognitive operations are affected by local structural damage to different parts of the brain is often centered on Broca's approach[14]. Ever since diaschisis was first described by von Monakov, many studies have focused on the possibility that stroke does not only affect the function of focal areas, but also the region far from the local damage[15]. Resting-state FC can be used to prove network topography. Recently, the application of resting-state FC measurement has made great progress in discovering the effects of stroke on brain networks and the causal effect of linkage deficits on behavioral abnormalities[16,17].

In a study, after measuring the attention and motor deficits in right hemisphere-damaged patients, Baldassarre *et al.* found that the most common and robust disruption are a decrement of interhemispheric connectivity in brain networks, thereby concluding that attention deficits are significantly more correlated with abnormal interhemispheric FC within the dorsal attention network, while motor deficits are significantly correlated with abnormal motor networks. This study further deepens our understanding of stroke-related behavioral deficits[14].

Cerebral microbleeds (CMBs) are small foci of chronic brain hemorrhages that are caused by the structural malformation of small blood vessels and the deposits of blood products. They are often related to stroke[18] and are always accompanied by dysfunction, dementia, and cognitive impairment[19]. Therefore, pre-symptomatic detection of CMBs may help relieve the enormous burdens on hospitals and patients. Al-Masni *et al.* have proposed a fully automated two-stage integrated deep learning approach for efficient CMB detection, a regional-based You Only Look Once network for potential CMB candidate detection, and a three-dimensional convolutional neural network for reducing false positives[20]. Conventionally, in the study of CMB formation, Perls' Prussian blue stain is often used in the histological analysis of fixed tissue sections[21]. This deep learning approach significantly increases the accuracy of CMB detection and decreases the false positive rate. In their research, Crouzet *et al.*, aiming at the advances in digital pathology, developed and compared three digital pathology approaches to identify and quantify CMBs from sections stained with Prussian blue; they concluded that the deep learning approach is more precise than the ratiometric approach, but the latter has higher accuracy and versatility[22]. The deep learning approach can certainly be referred to as another CMB diagnosis improvement.

IA rupture often leads to a dismal prognosis or even death. Several studies have reported that in the general population, the morbidity of IAs has increased to more than 5%. However, IAs that are small in size or with low-intensity contrast to normal vessels in medical imaging scans are hard to distinguish; as a result, undetected IAs could cause severe consequences[23,24]. Since 2017, deep neural networks have been used to detect cerebral aneurysms[25] by combining them with traditional IA detection techniques, such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), and DSA[26,27]. Bo *et al*. have put forward the Global Localization-based IA Network, which is an automatic deep-learning model for IA segmentation and can be applied to CTA images. Based on the new recognition, it has been discovered that IAs are related to the vascular network distributed in the brain, indicating that the position information is significant. This model has truly enhanced the detection precision of IAs, thus making a progress in IA detection[28]. Meanwhile, Chen *et al*. have developed a computer-assisted detection (CAD) system for cerebral aneurysms in contrast-unenhanced time-of-flight MRA images using a fully convolutional network. When validating the internal and external test sets, the presented system achieved a sensitivity of 94.4% and 82.9%, respectively, proving that this CAD system can improve the accuracy of IA diagnosis[29]. As is known to neurosurgeons, symptomatic cerebral vasospasm (SCV) is a common complication following IA rupture, causing severe cerebral ischemia and increased mortality[30]. Dumont has validated an artificial neural network model of SCV; this tool allows clinicians to identify those patients who have a high risk for SCV and thus should be prophylactically treated. According to the result, this tool has excellent negative predictive value and acceptable positive predictive value[31].

Cerebral amyloid angiopathy (CAA) has been recognized as one of the accompanying lesions of Alzheimer's disease (AD). Its pathogenesis is related to the cerebrovascular deposition of amyloid-β, which may cause spontaneous intracerebral hemorrhage (ICH) and age-related cognitive decline[32]. Recent studies have indicated that CAA is not only a specific cerebrovascular pathological feature, but also a clinical syndrome and a set of clinical imaging diagnostic criteria (the Boston criteria)[33]. Arvanitakis *et al*. and Boyle *et al*. have discovered that CAA appears to cause cognitive deficit and is independent of AD or other accompanying pathologies, including ICH. In a subsequent community-based cohort study, individuals harboring CAA not only had an increased risk of dementia, but also a decline in both global and domain-specific cognition[34,35]. Scientists have proposed that CAA-related cognitive impairment is associated with CMBs and altered structural connectivity. In order to verify this hypothesis, Reijmer *et al*., in their study, examined brain networks as a surrogate measure of global small-vessel pathology in CAA; the result showed that lower global network efficiency leads to a dismal performance of processing speed and executive functioning independently; the study also showed direct evidence linking CAA with impairments in white matter connectivity under PET[36]. In another study, after researching Dutch CAA mutation carriers and control subjects, Drenth *et al*. found that both pre-symptomatic and symptomatic groups had decreased connectivity in medial and lateral visual networks, DMN, executive control, and bilateral frontoparietal networks; the symptomatic group, however, showed diminished connectivity in all but one network, whereas the pre-symptomatic group had decreased connectivity solely in the frontoparietal left network; based on the data, they concluded that although CAA affects network connectivity, it has no association with aging or other neurodegenerative processes[37]. This novel recognition of CAA may have significant clinical implications.

Significant carotid stenosis often causes severe clinical or subclinical complications due to decompensated hemodynamics, and it may lead to impairment of cognitive function[38]. In a previous study, asymptomatic carotid stenosis patients showed decreased or asymmetrical FC of the frontoparietal network, DMN, dorsal attention network, and sensorimotor network[39]. However, the impact of unilateral carotid stenosis on the overall functional networks has not been investigated. In order to study the whole-brain influence of carotid stenosis, Chang *et al*. recruited 27 patients with unilateral carotid stenosis (≥60%) and 20 controls. The study showed that FC was indeed disrupted in patients with carotid stenosis but not in a global pattern, affecting only hemodynamically impaired regions. The indicators in the study, including global efficiency, characteristic path length, and modularity, have been found to be highly associated with neuropsychological performance, and thus could be potential predictors of cognitive deficit in patients with carotid stenosis so as to improve the accuracy of diagnosis[40].

In the context of MMD, several case reports have concluded that this disease not just disrupts the blood vessels that supply brain regions, but also affects the brain networks interaction of specific brain regions; therefore, the reorganization of brain networks interaction may have a role in the recovery of patients with MMD[41,42].

3. New strategies in cerebrovascular disease treatment

3.1. Protection of hubs in brain networks

Ever since it has been discovered that the brain performs its functions based on a complex network, a plethora of relative concepts have progressively come into view[5]. With advanced medical imaging technologies, functional MRI (fMRI) or diffusion-weighted imaging has been used to investigate the interaction of different brain regions functionally or structurally[43]. With the help of the graph theory to analyze data from medical imaging, brain networks can be described as a combination of nodes (*i.e.*, brain regions) connected by edges (*i.e.*, white matter tracts)[5]. In brain networks, the majority of nodes have few connections, while the remaining nodes, which are known as hubs, have many connections[44]. Through the analysis of both structural and FC data, studies have revealed that these brain hubs are mainly located at the posterior cingulate cortex/precuneus, medial prefrontal cortex, and lateral temporal and parietal cortices, among which most of these regions are considered as parts of the DMN, which plays a significant role in the resting state[45-47]. The previous studies have shown compelling evidence to validate the aforementioned theory. Based on resting-state FC MRI defined hubs, Power *et al.* used two methods (identifying network nodes that participate in multiple sub-networks of the brain, and identifying the spatial locations where several systems are represented within a small volume) to confirm the previously accepted hubs in brain networks and considered novel brain regions in both methods. Their research supports the earlier finding and identifies putative hubs in brain networks[48]. According to another study, network hubs play a critical role in information transfer during resting and task states by combining with regional cerebral blood flow (rCBF) and functional connectivity strength (FCS). During resting state, FCS has high spatial correlation with rCBF; this correlation is stronger in the DMN and executive control network than in the visual and sensorimotor networks, having a connection-distance dependent relationship. However, during task state, the indices are related to task load. Meanwhile, rCBF and metabolism are positively associated with either structural or functional hubs. From the studies above, it can be concluded that there is a tight association between blood supply and brain functional topology during both rest and task states, and the studies also indicate the importance of functional hubs in brain networks[49,50].

Since we know that hubs are vital in maintaining whole-brain network stability, the primary task now is to identify specific hubs in certain behavior. By combing with meta-analyses and the graph-theoretic approach, a tri-network model in human semantic processing has been proposed by Xu *et al.*, who have found that the semantic system is topologically segregated into three brain modules: DMN, left perisylvian network, and left frontoparietal network. These three modules serve as the multimodal experiential system, the non-experiential system, and the semantic control system, respectively, with five hubs (posterior middle temporal gyrus [pMTG], anterior temporal lobe, posterior intraparietal sulcus, angular gyrus, and superior and middle frontal gyrus) involved in the integration of information in semantic processing (Figure 3)[6]. This model directs the focus onto hub protection to achieve cognitive maintenance following neurosurgical intervention. Through further investigations, the influence of brain lesions on brain network topology has been identified. Yuan *et al.* have contributed a lesion model to explore this issue and found that the damage to brain network hubs causes two different directions of change in network topology, one being more integrated (global) and the other being more segregated (local). The result further confirms the significant role of hubs in brain networks[51].

Previous studies have shown that neurosurgery has been the primary focus in the treatment of nervous system diseases. Based on three data sets of fMRI and 127 participants, Buckner *et al.* gained a consensus estimate of cortical hubs; PET amyloid imaging in AD patients compared with older controls showed high amyloid-β deposition in the locations of cortical hubs, consistent with the accepted hubs[52]. This finding suggests that brain network hubs may have an association with cognitive deficits. Aben *et al.* have developed a lesion impact score that integrates information on infarct size with healthy brain network topology to estimate the damage to network hubs; the research has verified that this scoring system can predict the cognitive recovery of patients based on the damage of hubs in brain networks[43]. This evidence opens a new insight into the treatment of cerebrovascular disease; during surgery, the hubs need to be protected to achieve the purpose of cognitive function protection; after surgery, the focal hemorrhage needs to be estimated accurately; and pre-symptomatic intervention must be confirmed. Based on the topological feature of brain networks, there is a huge possibility for neural function recovery if the network hubs are not damaged in surgery.

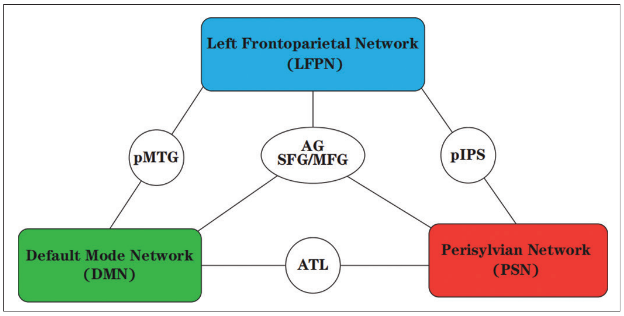

Figure 3. Three modules of semantic system. LFPN, DMN, and PSN serve as semantic control system, multimodal experiential system, and language-supported system, respectively. AG, angular gyrus; ATL, anterior temporal lobe; pMTG, posterior middle temporal gyrus; pIPS, posterior intraparietal sulcus; SFG/MFG, superior and middle frontal gyrus; LFN, left frontoparietal network; DMN, default mode network; PSN, perisylvian network.

In that way, patients may have a better prognosis as a result of the protection of hubs.

3.2. Protection of brain networks connectivity

Along with the extensive exploration of brain networks, computational analyses have revealed abundant characteristics of brain networks[4], such as clusters of brain regions[53], hierarchical organization[54], small-world attributes[55], distinct functional streams, motifs[56], and so on. The physiological basis of these features is the connectivity of brain networks. The development of noninvasive diffusion tractography imaging (DTI) has revealed the histological basis of brain networks connectivity, of which the structure involved is the white matter tract. By analyzing the data collected from DIT, a number of reviews have divided brain networks connectivity into three types: association bundles interconnecting ipsilateral cortical sites; projection fibers connecting cortical areas with subcortical structures; and commissural bundles connecting contralateral hemispheres[3]. As previous studies have provided some insights into the structural basis of brain networks connectivity, combing with clinical trials, several relative indicators have been developed to estimate the connective characteristic, including path length and global efficiency[57]. Furthermore, it has been concluded that a change from short-range connection to long-range connectivity, along with increasing age, and a change in interregional connectivity patterns to form stronger cortico-cortical but weaker subcortical-cortical connections indicate that the completeness of brain networks connectivity is related to their plasticity. Meanwhile, a reduction in lesions-induced FC affects not only the ipsilateral hemisphere, but also extends to the contralateral side[2]. All the above evidence emphasizes the significance of either structural or FC in brain networks.

Further clinical studies have opened a novel insight for us. A total of 26 depressed MCI patients with amyloid accumulation and 27 depressed MCI patients without amyloid accumulation were recruited in a study conducted by Lee *et al*. to prove that cerebral amyloidopathy can truly affect the brain network topology and may be associated with cognitive symptoms. The result showed a significant correlation between disrupted network connectivity and patients with amyloid accumulation in brain vessels, which certainly relate to depressed elderly[58]. Another review has concluded that the disruption of network connectivity is directly associated with depressive symptoms in cerebral small vessel disease patients[59]. Based on 10 stroke patients and 18 healthy controls (HC), Bosnell *et al*. have found that apart from cognitive function, motor function disruption is related to the interruption of brain structural connectivity[60]. With the development of imaging techniques, the variation in the definition of diaschisis has been summarized in a review; in contrast to traditional focal diaschisis, connectional diaschisis is highly related to clinical stroke-induced motor and attentional network disruption, which causes motor and cognitive abnormalities; furthermore, the normalization of remote connectivity changes relates to a better recovery[61].

Multiple studies have shown that interregional connections, similar to hubs, play a key role in maintaining cognitive function and improving patients' prognosis. Maintaining the integrity of brain networks connectivity has yet to become an additional focus in neurosurgical intervention for cerebrovascular diseases.

3.3. Cognitive protection

With the development of treatment means for cerebrovascular diseases beyond neural function protection to satisfy the basic requirements of life, cognitive protection has been emphasized in surgery. According to the localizationist theory, a structural correspondence exists between the cognitive function of the human brain and the cortical regions, indicating that human character, thoughts, and emotions are located in specific parts of the brain. For example, the third frontal circumvolution is related to speech articulation, while the posterior part of the left temporal gyrus is associated with word comprehension. However, recent studies have proven that human cognitive function is achieved through the interaction of multiple networks in global regions, thus providing a theoretical basis for cognitive protection in neurosurgery[3]. Correspondingly, the deuterogenic neural networks surgery idea that aims at achieving neural and cognitive function protection by maintaining the stability of brain networks in neurosurgery has been applied in many clinical trials. Boukrina and Barret have reviewed studies of post-stroke delirium and spatial neglect, concluding that right hemisphere strokes may impair the ascending arousal system and cortical attention networks, which are composed of ascending projections from the midbrain nuclei and integrating dorsal and ventral cortical and limbic components, causing spatial neglect and thus lowering the threshold for developing delirium[62]. In a study of chronic stroke patients, Bonilha *et al*. observed that patients with non-fluent aphasia, who had lesions in superior longitudinal fasciculus and precentral, inferior frontal, supramarginal, and insular cortices after stroke, achieved better assisted speech from preserving the pMTG, inferior fronto-occipital fasciculus, and uncinate fasciculus; this indicates that the interaction of brain networks plays a vital role in cognitive function maintenance[63]. In a study conducted by Altinbas *et al*., the cognitive difference in patients who underwent carotid artery stenting and carotid endarterectomy (CEA) was not statistically significant, but a higher rate of new ischemic lesions was observed in carotid artery stenting-treated patients compared with CEA-treated ones[64]. Another research on neuropsychological sequelae prediction following treatment with microsurgical clipping or endovascular embolization in patients with anterior communicating artery aneurysm has indicated that microsurgical clipping-treated patient had significantly more severe cognitive deficits[12]. All the above studies are evidence showing that cognitive protection in cerebrovascular diseases has received its due attention and further research and clinical trials must follow their lead.

By reviewing neurological research and clinical trials, we put forward three new strategies for the surgical treatment of cerebrovascular disease. As hubs and connectivity are critical components of brain networks, they play an irreplaceable role in maintaining the stability of the global network to preserve human cognitive function (Table 2). As the preservation of human cognitive function has gained widespread attention clinically, the concept of neural networks surgery provides us an immense insight into the treatment of cerebrovascular disease. As discussed above, the protection of network hubs and connectivity relates to better cognitive recovery and preserves the human central nervous system up to a point of plasticity. There is an urgent need for new strategies in neurosurgery to be developed and applied in clinical settings.

4. Impact on the course of the disease

As aforementioned, brain network stability is vital for maintaining cognitive function and is also the basis for the plasticity of the central nervous system. Brain network hubs and interregional connections are the key factors in maintaining the stability of brain networks and ensuring their plasticity. Studies have described several critical indicators that can be applied in the prediction of cognitive situation, prognosis, and even the cognitive recovery of patients with the central nervous system diseases.

Table 2. New strategies in cerebrovascular disease treatment (examples in this review)

Treatment strategy	First author	Disease
Hub protection	Buckner[52]	AD
Hub protection	Aben[43]	Ischemic stroke
Connectivity protection	Lee[58]	AD
Connectivity protection	Cuadrado-Godia[59]	Cerebral small vessel disease
Connectivity protection	Bosnell[60]	Stroke
Connectivity protection	Carrera[61]	Diaschisis
Cognitive protection	Boukrina[62]	Stroke
Cognitive protection	Altinbas[64]	CAS
Cognitive protection	Chan[12]	Anterior communicating artery aneurysm

AD, Alzheimer's disease; CAS, carotid artery stenosis.

The prediction of cognitive decline in multiple sclerosis (MS) patients is usually considered difficult. In their clinical study, Nauta *et al*. investigated the role of magnetoencephalography (MEG) in measuring functional brain network organization to predict cognitive decline in MS patients; using resting-state MEG recordings, structural MRI, and neuropsychological assessments, they found that the level of functional brain network integration is an independent predictive marker of cognitive decline and suggested that MEG may be a great prediction tool for disease progression in MS[65]. In a study of AD patients with MCI, Zhang *et al*. used a proposed highly-available nodes approach to develop a brain network model based on rest-state fMRI data; they successfully constructed a reliable brain network model and also identified 18 significant regions as hubs. This model can be used to predict cognitive impairment in AD patients and analyze the topological feature of brain networks[66]. Moreover, in a study comprising Parkinson's disease (PD) patients with MCI (PD-MCI), PD patients without MCI (PD-nMCI), and HC, Chen *et al*. found that all three groups exhibited small-world architecture in their functional brain networks, and early-stage PD-MCI patients had decreased clustering coefficient, increased characteristic path length, and changed nodal centrality in multiple brain functional networks, including the DMN, control network, somatomotor network, and visual network. The research has not only found the cause of MCI in PD patients, but also suggested that these key indicators can be applied for cognitive situation prediction, even for reflecting prognosis and network plasticity in the central nervous system diseases[7].

Most cerebrovascular diseases often begin with cognitive impairment or are accompanied by symptoms of cognitive dysfunction. In a deeper study of brain networks, many scientists focus on the evaluation of cognitive impairment and long-term prognosis of patients with cerebrovascular disease.

Temporo-occipital junction arteriovenous malformations (TOJ-AVMs) certainly do not affect the eloquent brain cortex; instead, they form beside functional fiber tracts. Jiao *et al*. have found that lesion-to-eloquent fiber distance is a significant risk factor related to a dismal prognosis in patients with TOJ-AVMs; this indicator could be a significant reminder for surgical performance[67]. In

Table 3. Prediction of the disease course

First author	Disease	Symptoms	Indicator	Predictive Tools
Nauta[65]	MS	Cognitive decline	Functional brain network integration level	MEG
Zhang[66]	AD	Mild cognitive impairment	Characteristic of brain network	A highly-available nodes approach
Chen[7]	PD	Mild cognitive impairment	Characteristic of brain network	MRI
Jiao[67]	AVM	Postoperative neurological deficits	Lesion-to-eloquent fiber distance	DSA, CT, fMRI, and DTI
Kazumata[68]	MMD	Cognitive function impairment	Gray matter density	DTI
Lei[69]	MMD	Progressive cognitive decline	ALFF of BOLD fMRI	BOLD fMRI
Lei[70]	MMD	Vascular cognitive impairment	CNE	fMRI
He[71]	CAS and CAO	Cognitive function impairment	Global attributes	rs-fMRI

AD, Alzheimer's disease; ALFF, amplitude of low-frequency fluctuations; AVM, arteriovenous malformations; BOLD fMRI, blood oxygen level-dependent functional magnetic resonance imaging; CAO, carotid artery occlusion; CAS, carotid artery stenosis; CNE, connectivity number entropy; CT, computed tomography; DSA, digital subtraction angiography; MEG, magnetoencephalography; MMD, moyamoya disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; PD, Parkinson's disease; rs-fMRI, resting-state functional magnetic resonance imaging.

terms of MMD, Kazumata *et al*. have observed a decrease in gray matter density and fractional anisotropy but an increase in radial diffusivity using DTI in 23 adult patients with MMD; moreover, the impaired regions have been found to be associated with basic cognitive functions, including processing speed, attention, working memory, and so on[68]. In another study, Lei *et al*. investigated the relationship between MMD patients with vascular cognitive impairment (VCI) and the amplitude of low-frequency fluctuations (ALFF) of blood oxygen level-dependent fMRI at rest; significant differences in ALFF were observed between VCI/non-VCI and normal control groups in multiple brain regions, with some changes associated with progressive cognitive decline[69]. The dynamic measurement of connectivity number entropy (CNE), which characterizes both spatial and temporal dimensions of network interactions, was also used in an MMD study; significant differences in CNE were observed between VCI/non-VCI and normal control groups[70]. Their studies indicate that both ALFF and CNE can be regarded as indicators, which may play important roles in predicting the cognitive function and prognosis of patients with MMD. On the other hand, in a study of patients with asymptomatic carotid artery stenosis and occlusion (CAO), distinct differences in the global attributes (including assortativity, hierarchy, network efficiency, and small-worldness) of brain networks were observed among all three groups. Compared with HC, the carotid artery stenosis and CAO groups showed decreased nodal efficiency of hubs in multiple brain regions; furthermore, a compensatory functional connection in the contralateral cerebral hemisphere of patients with carotid artery stenosis and CAO was observed, suggesting that the network has a degree of plasticity[71].

All the above studies are evidence showing the application of the concept of brain networks in cerebrovascular disease for disease progression prediction. Clearly, this application is vital for predicting patients' cognitive function and recovery after surgery (Table 3). By utilizing these indicators and approaches in further studies, it is possible to prevent a dismal prognosis and improve the cognitive recovery of patients with cerebrovascular diseases.

5. Conclusions

In this paper, we mainly review the application of the concept of neural networks surgery in cerebrovascular disease treatment. With the advancements in medical technologies, neurosurgery has transitioned from the traditional protection of neural function to a more systematic and sophisticated comprehensive protection of brain neural function and cognitive function. This review first renews the mechanism of several types of common cerebrovascular diseases following the application of the neural networks surgery concept. Subsequently, new strategies in neurosurgery are proposed for the treatment of cerebrovascular diseases, including the protection of hubs, network connectivity, and cognitive function. Finally, we relate that some indicators or features of brain networks may play certain roles in predicting the prognosis and cognitive recovery of patients with cerebrovascular disease. From this perspective, we may develop a novel treatment system for cerebrovascular diseases. This system entails identifying diseases, predicting possible cognitive function disruption and degree of recovery, designing surgical strategies, choosing reasonable surgical methods, and executing according to priority. Combining the concept of neural networks surgery and advanced medical techniques, we hope that this system can improve the prognosis and cognitive function of patients with cerebrovascular diseases following treatment.

Acknowledgments

None.

Funding

This work was funded by Beijing Advanced Innovation Center for Big Data-Based Precision Medicine (PXM2020_014226_000066) and the National Natural Science Foundation of China (81901175).

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Yuming Jiao, Ran Huo
Visualization: Hongyuan Xu, Jie Wang, Shaozhi Zhao, Qiheng He, Junze Zhang, Yingfan Sun
Supervision: Yong Cao
Writing – original draft: Qifeng Yu
Writing – review & editing: Yong Cao, Shuo Wang, Jizong Zhao

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Sakas DE, Panourias IG, Simpson BA, 2007, An introduction to neural networks surgery, a field of neuromodulation which is based on advances in neural networks science and digitised brain imaging. *Acta Neurochir Suppl*, 97: 3–13.

   https://doi.org/10.1007/978-3-211-33081-4_1

2. Hart MG, Ypma RJ, Romero-Garcia R, *et al.*, 2016, Graph theory analysis of complex brain networks: New concepts in brain mapping applied to neurosurgery. *J Neurosurg*, 124: 1665–1678.

   https://doi.org/10.3171/2015.4.jns142683

3. Herbet G, Duffau H, 2020, Revisiting the functional anatomy of the human brain: Toward a meta-networking theory of cerebral functions. *Physiol Rev*, 100: 1181–1228.

   https://doi.org/10.1152/physrev.00033.2019

4. Sporns O, Tononi G, Kötter R, 2005, The human connectome: A structural description of the human brain. *PLoS Comput Biol*, 1: e42.

   https://doi.org/10.1371/journal.pcbi.0010042

5. Bullmore E, Sporns O, 2009, Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*, 10: 186–198.

   https://doi.org/10.1038/nrn2575

6. Xu Y, He Y, Bi Y, 2017, A tri-network model of human semantic processing. *Front Psychol*, 8: 1538.

   https://doi.org/10.3389/fpsyg.2017.01538

7. Chen X, Liu M, Wu Z, *et al.*, 2020, Topological abnormalities of functional brain network in early-stage Parkinson's disease patients with mild cognitive impairment. *Front Neurosci*, 14: 616872.

   https://doi.org/10.3389/fnins.2020.616872

8. Thom T, Haase N, Rosamond W, *et al.*, 2006, Heart disease and stroke statistics--2006 update: A report from the American heart association statistics committee and stroke statistics subcommittee. *Circulation*, 113: e85–e151.

   https://doi.org/10.1161/circulationaha.105.171600

9. Caplan LR, Searls DE, Hon FK, 2009, Cerebrovascular disease. *Med Clin North Am*, 93: 353–369.

10. Ma Q, Li R, Wang L, *et al.*, 2021, Temporal trend and attributable risk factors of stroke burden in China, 1990-2019: An analysis for the global burden of disease study 2019. *Lancet Public Health*, 6: e897–e906.

    https://doi.org/10.1016/S2468-2667(21)00228-0

11. O'Donnell MJ, Chin SL, Rangarajan S, *et al.*, 2016, Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. *Lancet*, 388: 761–775.

    https://doi.org/10.1016/S0140-6736(16)30506-2

12. Chan A, Ho S, Poon WS, 2002, Neuropsychological sequelae of patients treated with microsurgical clipping or endovascular embolization for anterior communicating artery aneurysm. *Eur Neurol*, 47: 37–44.

    https://doi.org/10.1159/000047945

13. Li C, Zhu H, Zong X, *et al.*, 2018, History, current situation, and future development of endoscopic neurosurgery in China. *World Neurosurg*, 110: 270–275.

    https://doi.org/10.1016/j.wneu.2017.11.103

14. Baldassarre A, Ramsey L, Rengachary J, *et al.*, 2016, Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. *Brain*, 139: 2024–2038.

    https://doi.org/10.1093/brain/aww107

15. Baldassarre A, Ramsey L, Hacker CL, *et al.*, 2014, Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain*, 137: 3267–3283.

    https://doi.org/10.1093/brain/awu297

16. Gordon EM, Laumann TO, Adeyemo B, *et al.*, 2016. Generation and evaluation of a cortical area parcellation from resting-state correlations. *Cereb Cortex*, 26: 288–303.

https://doi.org/10.1093/cercor/bhu239

17. Varsou O, Macleod MJ, Schwarzbauer C, 2014, Functional connectivity magnetic resonance imaging in stroke: An evidence-based clinical review. *Int J Stroke*, 9: 191–198.

https://doi.org/10.1111/ijs.12033

18. Martinez-Ramirez S, Greenberg SM, Viswanathan A, 2014, Cerebral microbleeds: Overview and implications in cognitive impairment. *Alzheimers Res Ther*, 6: 33.

https://doi.org/10.1186/alzrt263

19. Charidimou A, Krishnan A, Werring DJ, *et al.*, 2013, Cerebral microbleeds: A guide to detection and clinical relevance in different disease settings. *Neuroradiology*, 55: 655–674.

https://doi.org/10.1007/s00234-013-1175-4

20. Al-Masni MA, Kim WR, Kim EY, *et al.*, 2020, A two cascaded network integrating regional-based YOLO and 3D-CNN for cerebral microbleeds detection. *Annu Int Conf IEEE Eng Med Biol Soc*, 2020: 1055–1058.

https://doi.org/10.1109/EMBC44109.2020.9176073

21. Wadi LC, Grigoryan MM, Kim RC, *et al.*, 2020, Mechanisms of cerebral microbleeds. *J Neuropathol Exp Neurol*, 42: 1093–1099.

https://doi.org/10.1093/jnen/nlaa082

22. Crouzet C, Jeong G, Chae RH, *et al.*, 2021, Spectroscopic and deep learning–based approaches to identify and quantify cerebral microhemorrhages. *Sci Rep*, 11: 10725.

https://doi.org/10.1038/s41598-021-88236-1

23. Jayaraman MV, Mayo-Smith WW, Tung GA, *et al.*, 2004, Detection of intracranial aneurysms: Multi-detector row CT angiography compared with DSA. *Radiology*, 230: 510–518.

https://doi.org/10.1148/radiol.2302021465

24. Brown RD Jr., Broderick JP, 2014, Unruptured intracranial aneurysms: Epidemiology, natural history, management options, and familial screening. *Lancet Neurol*, 13: 393–404.

https://doi.org/1016/S1474-4422(14)70015-8

25. Nemoto M, Hayashi N, Hanaoka S, *et al.*, 2017, Feasibility study of a generalized framework for developing computer-aided detection systems-a new paradigm. *J Digit Imaging*, 30: 629–639.

https://doi.org/0.1007/s10278-017-9968-3

26. Ueda D, Yamamoto A, Nishimori M, *et al.*, 2019, Deep learning for MR angiography: Automated detection of cerebral aneurysms. *Radiology*, 290: 187–194.

https://doi.org/10.1148/radiol.2018180901

27. Westerlaan HE, van Dijk JM, der Weide MC, *et al.*, 2011, Intracranial aneurysms in patients with subarachnoid hemorrhage: CT angiography as a primary examination tool for diagnosis--systematic review and meta-analysis. *Radiology*, 258: 134–145.

https://doi.org/10.1148/radiol.10092373

28. Bo ZH, Qiao H, Tian C, *et al.*, 2021, Toward human intervention-free clinical diagnosis of intracranial aneurysm via deep neural network. *Patterns* (*N Y*), 2: 100197.

https://doi.org/10.1016/j.patter.2020.100197

29. Chen G, Wei X, Lei H, *et al.*, 2020, Automated computer-assisted detection system for cerebral aneurysms in time-of-flight magnetic resonance angiography using fully convolutional network. *Biomed Eng Online,* 19: 38.

https://doi.org/10.1186/s12938-020-00770-7

30. Findlay JM, Nisar J, Darsaut T, 2016, Cerebral vasospasm: A review. *Can J Neurol Sci*, 43: 15–32.

https://doi.org/10.1017/cjn.2015.288

31. Dumont TM, 2016, Prospective assessment of a symptomatic cerebral vasospasm predictive neural network model. *World Neurosurg*, 94: 126–130.

https://doi.org/10.1016/j.wneu.2016.06.110

32. Boulouis G, Charidimou A, Greenberg SM, 2016, Sporadic cerebral amyloid angiopathy: Pathophysiology, neuroimaging features, and clinical implications. *Semin Neurol*, 36: 233–243.

https://doi.org/10.1055/s-0036-1581993

33. Charidimou A, Gang Q, Werring DJ, 2012, Sporadic cerebral amyloid angiopathy revisited: Recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry*, 83, 124–137.

https://doi.org/10.1136/jnnp-2011-301308

34. Arvanitakis Z, Leurgans SE, Wang Z, *et al.*, 2011, Cerebral amyloid angiopathy pathology and cognitive domains in older persons. *Ann Neurol*, 69: 320–327.

https://doi.org/10.1002/ana.22112

35. Boyle PA, Yu L, Nag S, *et al.*, 2015, Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons. *Neurology*, 85: 1930–1936.

https://doi.org/10.1212/wnl.0000000000002175

36. Reijmer YD, Fotiadis P, Martinez-Ramirez S, *et al.*, 2015, Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. *Brain*, 138: 179–188.

https://doi.org/10.1093/brain/awu316

37. Drenth N, van der Grond J, Rombouts SA, *et al.*, 2021, Cerebral amyloid angiopathy is associated with decreased functional brain connectivity. *Neuroimage Clin*, 29: 102546.

https://doi.org/10.1016/j.nicl.2020.102546

38. Yonas H, Smith HA, Durham SR, *et al*., 1993, Increased stroke risk predicted by compromised cerebral blood flow reactivity. *J Neurosurg*, 79: 483–489.

https://doi.org/10.3171/jns.1993.79.4.0483

39. Lin CJ, Tu PC, Chern CM, *et al*., 2014, Connectivity features for identifying cognitive impairment in presymptomatic carotid stenosis. *PLoS One*, 9: e85441.

https://doi.org/10.1371/journal.pone.0085441

40. Chang TY, Huang KL, Ho MY, *et al*., 2016, Graph theoretical analysis of functional networks and its relationship to cognitive decline in patients with carotid stenosis. *J Cereb Blood Flow Metab*, 36: 808–818.

https://doi.org/10.1177/0271678X15608390

41. Calabrò RS, Bramanti P, Baglieri A, *et al*., 2015, Functional cortical and cerebellar reorganization in a case of moyamoya disease. *Innov Clin Neurosci*, 12: 24–28.

42. Jefferson AL, Glosser G, Detre JA, *et al*., 2006, Neuropsychological and perfusion MR imaging correlates of revascularization in a case of moyamoya syndrome. *AJNR Am J Neuroradiol*, 27: 98–100.

43. Aben HP, Biessels GJ, Weaver NA, *et al*., 2019, Extent to which network hubs are affected by ischemic stroke predicts cognitive recovery. *Stroke*, 50: 2768–2774.

\ https://doi.org/10.1161/STROKEAHA.119.025637

44. Gong G, He Y, Concha L, *et al*., 2009, Mapping anatomical connectivity patterns of human cerebral cortex using *in vivo* diffusion tensor imaging tractography. *Cereb Cortex*, 19: 524–536.

https://doi.org/10.1093/cercor/bhn102

45. Hagmann P, Cammoun L, Gigandet X, *et al*., 2008, Mapping the structural core of human cerebral cortex. *PLoS Biol*, 6: e159.

https://doi.org/10.1371/journal.pbio.0060159

46. Tomasi D,Volkow ND, 2010, Functional connectivity density mapping. *Proc Natl Acad Sci U S A*, 107: 9885–9890.

https://doi.org/10.1073/pnas.1001414107

47. Raichle ME, Macleod AM, Snyder AZ, *et al*., 2001, A default mode of brain function. *Proc Natl Acad Sci U S A*, 98: 676–682.

https://doi.org/10.1073/pnas.98.2.676

48. Power JD, Schlaggar BL, Lessov-Schlaggar CN, *et al*., 2013, Evidence for hubs in human functional brain networks. *Neuron*, 79: 798–813.

https://doi.org/10.1016/j.neuron.2013.07.035

49. Várkuti B, Cavusoglu M, Kullik A, *et al*., 2011, Quantifying the link between anatomical connectivity, gray matter volume and regional cerebral blood flow: An integrative MRI study. *PLoS One*, 6: e14801.

https://doi.org/10.1371/journal.pone.0014801

50. Liang X, Zou Q, He Y, *et al*., 2013, Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. *Proc Natl Acad Sci U S A*, 110: 1929–1934.

https://doi.org/10.1073/pnas.1214900110

51. Yuan B, Fang Y, Han Z, *et al*., 2017, Brain hubs in lesion models: Predicting functional network topology with lesion patterns in patients. *Sci Rep*, 7: 17908.

https://doi.org/10.1038/s41598-017-17886-x

52. Buckner RL, Sepulcre J, Talukdar T, *et al*., 2009, Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci*, 29: 1860–1873.

https://doi.org/10.1523/JNEUROSCI.5062-08.2009

53. Hilgetag CC, Burns GA, O'Neill MA, *et al*., 2000, Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. *Philos Trans R Soc Lond B Biol Sci*, 355: 91–110.

https://doi.org/10.1098/rstb.2000.0551

54. Hilgetag CC, O'Neill MA, Young MP, 2000, Hierarchical organization of macaque and cat cortical sensory systems explored with a novel network processor. *Philos Trans R Soc Lond B Biol Sci*, 355: 71–89.

https://doi.org/10.1098/rstb.2000.0550

55. Sporns O, Zwi JD, 2004, The small world of the cerebral cortex. *Neuroinformatics*, 2: 145–162.

https://doi.org/10.1385/NI:2:2:145

56. Sporns O, Kötter R, 2004, Motifs in brain networks. *PLoS Biol*, 2: e369.

https://doi.org/10.1371/journal.pbio.0020369

57. Li Y, Liu Y, Li J, *et al*., 2009, Brain anatomical network and intelligence. *PLoS Comput Biol*, 5: e1000395.

https://doi.org/10.1371/journal.pcbi.1000395

58. Lee S, Kim D, Youn H, *et al*., 2021, Brain network analysis reveals that amyloidopathy affects comorbid cognitive dysfunction in older adults with depression. *Sci Rep*, 11: 4299.

https://doi.org/10.1038/s41598-021-83739-3

59. Cuadrado-Godia E, Dwivedi P, Sharma S, *et al*., 2018, Cerebral small vessel disease: A review focusing on pathophysiology, biomarkers, and machine learning strategies. *J Stroke*, 20: 302–320.

https://doi.org/10.5853/jos.2017.02922

60. Bosnell RA, Kincses T, Stagg CJ, *et al*., 2011, Motor practice promotes increased activity in brain regions structurally disconnected after subcortical stroke. *Neurorehabil Neural Repair*, 25: 607–616.

https://doi.org/10.1177/1545968311405675

61. Carrera E, Tononi G, 2014, Diaschisis: Past, present, future. *Brain*, 137l: 2408–2422.

https://doi.org/10.1093/brain/awu101

62. Boukrina O, Barrett AM, 2017, Disruption of the ascending arousal system and cortical attention networks in post-stroke delirium and spatial neglect. *Neurosci Biobehav Rev*, 83: 1–10.

https://doi.org/10.1016/j.neubiorev.2017.09.024

63. Bonilha L, Hillis AE, Wilmskoetter J, *et al*., 2019, Neural structures supporting spontaneous and assisted (entrained) speech fluency. *Brain*, 142: 3951–3962.

https://doi.org/10.1093/brain/awz309

64. Altinbas A, Van Zandvoort MJ, van den Berg E, *et al*., 2011, Cognition after carotid endarterectomy or stenting: A randomized comparison. *Neurology*, 77: 1084–1090.

https://doi.org/10.1212/wnl.0b013e31822e55b9

65. Nauta IM, Kulik SD, Breedt LC, *et al*., 2021, Functional brain network organization measured with magnetoencephalography predicts cognitive decline in multiple sclerosis. *Mult Scler*, 27: 1727–1737.

https://doi.org/10.1177/1352458520977160

66. Zhang X, Liu J, Chen Y, *et al*., 2021, Brain network construction and analysis for patients with mild cognitive impairment and Alzheimer's disease based on a highly-available nodes approach. *Brain Behav*, 11: e02027.

https://doi.org/10.1002/brb3.2027

67. Jiao Y, Lin F, Wu J, *et al*., 2016, Lesion-to-eloquent fiber distance is a crucial risk factor in presurgical evaluation of arteriovenous malformations in the temporo–occipital junction. *World Neurosurg*, 93: 355–364.

https://doi.org/10.1016/j.wneu.2016.06.059

68. Kazumata K, Tha KK, Narita H, *et al*., 2015, Chronic ischemia alters brain microstructural integrity and cognitive performance in adult moyamoya disease. *Stroke*, 46: 354–360.

https://doi.org/10.1161/strokeaha.114.007407

69. Lei Y, Li Y, Ni W, *et al*., 2014, Spontaneous brain activity in adult patients with moyamoya disease: A resting-state fMRI study. *Brain Res*, 1546: 27–33.

https://doi.org/10.1016/j.brainres.2013.12.022

70. Lei Y, Song B, Chen L, *et al*., 2020, Reconfigured functional network dynamics in adult moyamoya disease: A resting-state fMRI study. *Brain Imaging Behav*, 14: 715–727.

https://doi.org/10.1007/s11682-018-0009-8

71. He S, Liu Z, Xu Z, *et al*., 2020, Brain functional network in chronic asymptomatic carotid artery stenosis and occlusion: Changes and compensation. *Neural Plast*, 2020: 9345602.

https://doi.org/10.1155/2020/9345602