RESEARCH ARTICLE

Toward neuroimaging-based network biomarkers for transient ischemic attack

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Abstract

Stroke is associated with topological disruptions of large-scale functional brain networks. However, whether these disruptions occur in transient ischemic attack (TIA), an important risk factor for stroke, remains largely unknown. Combining multimodal MRI techniques, we systematically examined TIA-related topological alterations of functional brain networks, and tested their reproducibility, structural, and metabolic substrates, associations with clinical risk factors and abilities as diagnostic and prognostic biomarkers. We found that functional networks in patients with TIA exhibited decreased whole-brain network efficiency, reduced nodal centralities in the bilateral insula and basal ganglia, and impaired connectivity of inter-hemispheric communication. These alterations remained largely unchanged when using different brain parcellation schemes or correcting for micro head motion or for regional gray matter volume, cerebral blood flow or hemodynamic lag of BOLD signals in the patients. Moreover, some alterations correlated with the levels of high-density lipoprotein cholesterol (an index related to ischemic attacks via modulation of atherosclerosis) in the patients, distinguished the patients from healthy individuals, and predicted future ischemic attacks in the patients. Collectively, these findings highlight the emergence of characteristic network dysfunctions in TIA, which may aid in elucidating pathological mechanisms and establishing diagnostic and prognostic biomarkers for the disease.

KEYWORDS

brain networks, graph theory, inter-hemispheric connectivity, multimodal MRI, transient ischemic attack

1 | INTRODUCTION

Transient ischemic attack (TIA) is a transient episode of neurologic deficits caused by brain ischemia. It induces various transient symptoms but leads to persistent cognitive deficits in multiple domains (Bakker et al., 2003b; Sachdev et al., 2004). Further, TIA is an important risk factor for

eventual stroke or silent stroke (Giles & Rothwell, 2007), and thus represents a key time window for early diagnosis and intervention. However, the identification of TIA is currently challenging, as it is mainly based on symptoms, due to the lack of objective and reliable biomarkers.

Advanced noninvasive MRI technique provide promising avenues to identify and establish such biomarkers by detecting structural and

functional brain alterations in TIA, including gray matter (GM) atrophy (Li et al., 2015), cerebral blood flow (CBF) reduction (Kleinman et al., 2012), and disturbances in the amplitude and connectivity of spontaneous brain activity (Guo et al., 2014; Li et al., 2013). However, these studies mainly focused on local features of specific regions and connections. There is a growing body of evidence supporting that the human brain operates essentially as a network to integrate various information inputs across multiple distributed systems (Barch, 2013; Bullmore & Sporns, 2009; Cole, Bassett, Power, Braver, & Petersen, 2014; Sporns, 2014). This feature makes the human brain particularly amenable to study with network approaches, such as seed-based functional connectivity and independent component analysis. However, these two methods can only provide information about how regions are related to each other within neural circuits; they cannot reveal connectivity patterns between different circuits. In contrast, complex network analysis is a powerful tool to map and characterize both within- and between-circuit connectivity patterns of the entire assembly of brain regions. Thus, complex network analysis of TIA can provide a more complete holistic view of how the disease affects patients' brain.

Human brain networks can be constructed from multimodal neuroimaging data and further topologically characterized with graph-based approaches (Bullmore & Sporns, 2009; He & Evans, 2010). To date, several nontrivial organizational principles have been convergently observed in the human brain networks, including small-worldness (Liao, Vasilakos, & He, 2017), modularity (Sporns & Betzel, 2016) and hubs (van den Heuvel & Sporns, 2013). Moreover, these properties have been frequently reported to be altered in ischemic stroke (Adhikari et al., 2017; Wang et al., 2010; Yin et al., 2014; Zhu et al., 2017). To the best of our knowledge, however, there are no studies examining whether these topological alterations emerge in TIA.

In this study, we employed resting-state blood oxygen level-dependent functional MRI (R-BOLD-fMRI) to investigate the topological alterations of functional brain network in patients with TIA. R-BOLD-fMRI measures spontaneous neuronal activity of the brain (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007) and has been widely used to investigate intrinsic functional brain networks (Wang, Zuo, & He, 2010). Specifically, we sought to determine whether and how TIA disrupts the topological organization of the whole-brain functional network and whether these topological abnormalities (if observed) are associated with risk factors for TIA. Further, we examined whether these abnormalities could differentiate patients with TIA from healthy elderly individuals and predict ischemic attacks of the patients during the one-year follow-up. Finally, given structural and metabolic substrates of functional brain networks (Alexander-Bloch, Giedd, & Bullmore, 2013; Liang, Zou, He, & Yang, 2013), we also utilized structural MRI and resting-state arterial spin labeling functional MRI (R-ASL-fMRI) to explore the extent to which these functional network abnormalities are attributable to regional alterations in GM volume and CBF.

2 | MATERIALS AND METHODS

2.1 | Participants

According to the WHO guidelines, transient ischemic attack is defined as a sudden onset of neurological symptoms that are of vascular etiology and resolve within 24 hr. Following the guidelines, we recruited 51 patients with TIA who had transient (i.e., less than 24 hr) neurologic symptoms due to a possible vascular etiology as evaluated by experienced clinical neurologists. The patients were from the Department of Neurology, Anshan Changda Hospital from April 2015 to June 2016. Patients with hemorrhage, leukoaraiosis, epilepsy, migraine, or a history of psychiatric disease were excluded from this study. For each patient, we recorded the following information: (a) history of TIA and stroke; (b) risk factors including hypertension, diabetes mellitus, coronary artery disease, current smoking, and drinking; (c) medications used before the MR scanning; (d) in-hospital evaluation of arterial stenosis (carotid duplex ultrasound and MR angiography), atrial fibrillation (electrocardiogram) and brain infarcts (diffusion-weighted imaging and T2-FLAIR); (e) 1-year telephone follow-up of stroke and/or TIA. Based on the methods described by Johnston et al. (2007) an ABCD2 score, which considers age, blood pressure, clinical features, duration of symptoms, and history of diabetes, was obtained for each patient to evaluate the risk for subsequent stroke. In addition, 41 age- and sex-matched healthy controls (HCs) were recruited from the local community via advertisements. The HCs had no physical diseases or history of psychiatric or neurologic diseases. Four participants (three patients and one control) were excluded due to inadequate image quality of multimodal MRI data, leaving 48 TIA patients (age = 30–79 years; 37 males) and 40 HCs (age = 40–77 years; 29 males) in the final analysis. Of the 48 patients, 4 (8.3%) experienced a history of stroke and 25 (52.1%) had a history of TIA before they were recruited in the current study, 6 (12.5%) had white matter hyperintensity in diffusion-weighted images, and 9 (18.8%) had intracranial large-vessel stenosis or carotid artery stenosis. This study was approved by the Ethics Committee of the Center for Cognition and Brain Disorders, Hangzhou Normal University. Written informed consent was obtained from each participant.

2.2 | Physiological and biochemical tests

All participants completed a series of physiological and biochemical tests within 24 hr before the MR scanning, including blood systolic pressure, blood diastolic pressure, blood sugar level, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Additionally, all participants underwent the mini-mental state examination (MMSE) to evaluate global cognition (Schultz-Larsen, Lomholt, & Kreiner, 2007).

2.3 | Multimodal MRI data acquisition

All MRI data were acquired using a GE MR-750 3.0 T scanner (GE Medical Systems, Waukesha, WI) at Anshan Changda Hospital.

The time intervals between the last TIA and MR scanning were from 6 hr to 16 days (2.673 ± 2.978 days) for all patients. During the data acquisition, the participants were instructed to keep awake, relax with their eyes closed, and remain motionless as much as possible.

2.3.1 | R-BOLD-fMRI data

The R-BOLD-fMRI data were acquired using an echo-planar imaging sequence: 43 axial slices, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, matrix = 64×64 , field of view (FOV) = 220×220 mm², thickness/gap = 3.2/0 mm and flip angle = 60°. This session consisted of 240 contiguous volumes and lasted for 8 min.

2.3.2 | R-ASL fMRI data

The R-ASL-fMRI data were acquired using a pseudo continuous ASL 3D fast-spin echo encoded spiral readout imaging sequence: 45 axial slices, TR = 4,781 ms, TE = 11.12 ms, matrix size = 128×128 , FOV = 220×220 mm², thickness/gap = 3/0 mm, points = 512, arms = 12, labeling duration = 1,500 ms and postlabel delay = 1,525 ms. The session lasted for about 7 min.

2.3.3 | Structural MRI data

The structural MRI data were acquired using a 3D-MPRAGE sequence: 176 sagittal slices, TR = 8,100 ms, TE = 3.1 ms, matrix = 256×256 , FOV = 256×256 mm², and thickness/gap = 1.0/0 mm. This session lasted for about 5 min.

After careful visual inspection, three patients were excluded from further analysis due to incomplete coverage of the whole brain in the R-BOLD-fMRI scan (two) or loss of the structural image (one).

2.4 | Multimodal MRI data preprocessing

The multimodal MRI data underwent modality-specific preprocessing as follows.

2.4.1 | R-BOLD-fMRI data

The R-BOLD-fMRI data were preprocessed using the GREYNA package (Wang et al., 2015) based on SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) and included (a) removal of the first five volumes; (b) correction for intra-volume time delays between slices (Sinc interpolation); (c) correction for inter-volume head motion (rigid-body transformation); (d) spatial normalization to the Montreal Neurological Institute (MNI) space via deformation fields derived from tissue segmentation of structural images; (e) removal of linear trends; (f) band-pass filtering (0.01–0.08 Hz); and (g) regressing out nuisance signals including 24-parameter head motion profiles (Friston, Williams, Howard, Frackowiak, & Turner, 1996), WM signals and cerebrospinal fluid signals. We did not regress out the global signals as this step is controversial for R-BOLD-fMRI data (Murphy & Fox, 2017). Notably, all nuisance signals were also band-pass filtered (0.01–0.08 Hz) (Hallquist,

Hwang, & Luna, 2013). One HC was excluded based on the head movement criterion of maximal displacement >2 mm, rotation >2° or mean framewise displacement >0.5.

2.4.2 | R-ASL-fMRI data

For the R-ASL-fMRI data, individual CBF maps were created using an automated script on the scanner workstation and were subsequently normalized to the MNI space via the deformation fields derived from tissue segmentation of structural images using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). The normalized CBF maps were further spatially smoothed with a Gaussian kernel with a 6-mm full width at half maximum.

2.4.3 | Structural MRI data

For the structural MRI data, individual images were first segmented into GM, WM, and cerebrospinal fluid on the basis of an adaptive maximum A posteriori technique. The resultant GM maps were then normalized to the MNI space and nonlinearly modulated to compensate for spatial normalization effects. The modulated GM maps were further spatially smoothed using a Gaussian kernel with a 6-mm full width at half maximum.

2.5 | Network construction

In the jargon of graph theory, a network is composed of a set of nodes linked by edges. In this study, we constructed functional brain networks at the macroscale with nodes representing brain regions and edges representing interregional functional connectivity.

2.5.1 | Node definition

To define network nodes, we divided the brain into 90 regions of interest (ROIs) based on the anatomical automatic labeling atlas (Tzourio-Mazoyer et al., 2002), with each ROI representing a node (Table S1).

2.5.2 | Edge definition

To measure interregional functional connectivity, we calculated Pearson correlation coefficients of regional representative time series between any pair of ROIs. For each ROI, the representative time series was calculated as the weighted average of BOLD signals over all voxels within the ROI, with the weights denoting GM probabilities in terms of the probability map in the SPM toolbox. This resulted in a 90×90 correlation matrix for each participant.

2.5.3 | Threshold selection

To de-noise spurious interregional connectivity, only significant correlations ($p < .05$, Bonferroni-corrected across connections) were retained and set to one, whereas others were set to zero. Such a significance level-based thresholding procedure effectively avoids

erroneous evaluations of network topology (Toppi et al., 2012) and has been frequently used in previous brain network studies (Bassett et al., 2011; Wang et al., 2013; Wang et al., 2015). Of note, the significance level-based thresholding procedure is identical to setting an absolute correlation threshold when the degree of freedom is fixed across edges. Finally, negative correlations were excluded in this study because of their ambiguous interpretation (Fox, Zhang, Snyder, & Raichle, 2009; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Weissenbacher et al., 2009) and detrimental effects on test-retest reliability (Wang et al., 2011).

2.6 | Network analysis

For the brain networks constructed above, we calculated four global metrics (clustering coefficient, characteristic path length, local efficiency and global efficiency) and three nodal centrality metrics (degree, efficiency and betweenness) to characterize their topological organization. These metrics are briefly explained below in the context of a network G with N nodes and K edges.

2.6.1 | Global network metrics

The clustering coefficient of the network G is the average of all nodal clustering coefficients, where the nodal clustering coefficient for a given node i is defined as the number of existing connections between the node's neighbors divided by all their possible connections (Watts & Strogatz, 1998). The clustering coefficient quantifies the extent of local interconnectivity or cliquishness of a network. The characteristic path length of the network G is defined as the shortest path length (i.e., the smallest number of connections) required to travel from one node to another, averaged over all possible pairs of nodes (Watts & Strogatz, 1998). The characteristic path length reflects the mean distance or overall routing efficiency between any pair of nodes in a network. Of note, the harmonic mean is used for the calculation of characteristic path length to deal with the possible dilemma of isolated nodes.

Compared with the clustering coefficient and characteristic path length, efficiency is a more biologically relevant metric to describe brain networks from the perspective of parallel information propagation and exchange (Achard & Bullmore, 2007; Latora & Marchiori, 2001). Mathematically, the global efficiency of the network G is computed as the reciprocal of the shortest path length required to travel from one node to another, averaged over all possible pairs of nodes. Global efficiency reflects the ability of parallel information transmission over the network. The local efficiency of the network G is the average of all nodal local efficiencies, where the nodal local efficiency for a given node i is defined as the global efficiency of the subgraph G_i that is composed of nodes directly linking to the node i . Local efficiency measures the fault tolerance of the network, indicating the capacity for information exchange for each subgraph when the index node is eliminated.

To determine whether brain networks were topologically organized into small-world organizations, we calculated normalized

versions of the aforementioned global network metrics by dividing them by the corresponding mean derived from 100 random networks that preserved the same number of nodes and edges and the same degree distributions as the real brain networks (Maslov & Sneppen, 2002; Milo et al., 2002). Typically, a network is said to be small world if it has a normalized clustering coefficient and local efficiency larger than one and a normalized characteristic path length and global efficiency approximately equal to one (Watts & Strogatz, 1998).

2.6.2 | Nodal network metrics

The nodal degree for a given node i is defined as the number of edges linked to the node. The nodal degree reflects the overall connectivity of a node with other nodes in a network. The nodal efficiency for a given node i is computed as an average of the reciprocal of the shortest path length between the node and other nodes in the network G (Achard & Bullmore, 2007). Nodal efficiency measures the ability of an index node to propagate and exchange information with other nodes in a network. The nodal betweenness for a given node i is computed as the number of shortest paths between pairs of other nodes that pass through the node (Freeman, 1977). Nodal betweenness captures the influence of an index node over information flow between other nodes in a network. Of note, although the three nodal metrics are typically interrelated and resemble each other with respect to their spatial distributions in the brain, they capture roles of individual nodes within a network from different viewpoints (Wang, Wang, He, et al., 2015), and thus reveal TIA-related alterations in complementary ways.

2.7 | Statistical analysis

We tested between-group differences in global organization, nodal centrality and interregional functional connectivity of whole-brain functional networks, and further examined their associations with clinical, physiological and biochemical variables of the patients. Additionally, between-group differences in regional GM volume and CBF were determined.

2.7.1 | Between-group differences in global and nodal network metrics

Between-group differences in global and nodal network measures were inferred using nonparametric permutation tests. Briefly, for each metric, we initially calculated the between-group difference of the mean values. An empirical distribution of the difference was then obtained by randomly reallocating all the values into two groups and recomputing the mean differences between the two randomized groups (10,000 permutations). The 95th percentile point of the empirical distribution was used as a critical value in a one-tailed test of whether the observed group difference could occur by chance. For nodal results, a false discovery rate (FDR) procedure was employed to correct for multiple comparisons. The nonparametric permutation

approach was also used to infer between-group differences in regional GM volume and CBF followed by an FDR procedure.

2.7.2 | Between-group differences in interregional functional connectivity

To locate region pairs showing altered functional connectivity in the patients, we used a network-based-statistic (NBS) approach (Zalesky, Fornito, & Bullmore, 2010). First, we performed two-sample one-tailed *t*-tests on the significantly positive connections that were present in at the least 80% of all participants. A primary threshold (i.e., $p < .01$) was then applied to define suprathreshold links within which any connected component and its size (defined as the number of edges included in the component) were determined. To estimate the significance of each component, a null distribution of connected component size was derived empirically using a nonparametric permutation approach (10,000 permutations). For each permutation, connectivity matrices of all subjects were reallocated randomly into two groups, and two-sample one-tailed *t*-tests were conducted for the same set of connections mentioned above. The same primary threshold (i.e., $p < .01$) was then used to generate suprathreshold links within which the maximal connected component size was recorded. Finally, for a connected component of size *M* found in the right grouping of controls and patients, the corrected *p*-value was determined by calculating the proportion of the 10,000 permutations for which the maximal connected component was larger than *M*.

2.7.3 | Relationship between network metrics and clinical variables in TIA

For any network metric showing TIA-related alterations, a Pearson correlation analysis was used to assess its associations with clinical, physiological, and biochemical characteristics of the patients, including the ABCD2 scores, blood systolic pressure, blood diastolic pressure, blood sugar level, cholesterol, triglycerides, HDL-C, and LDL-C. Again, the FDR procedure was used to correct for multiple comparisons.

2.7.4 | Receiver operating characteristic analysis for classification and prediction

To examine whether the network alterations could serve as potential biomarkers for TIA, we performed a preliminary discriminatory analysis by plotting the receiver operating characteristic (ROC) curve for each network metric showing significant between-group differences. For network metrics showing significant between-group differences, ROC analyses were also performed to examine their potential for predicting follow-up ischemic attacks in the patients.

2.8 | Validation of reproducibility

We performed a series of analyses to validate the reproducibility of our main findings.

2.8.1 | Effects of regional brain parcellation

Previous studies have demonstrated that different brain parcellation schemes significantly affect topological organization of functional brain networks (Wang et al., 2009) and confound between-group comparisons (Lord et al., 2016). Thus, we repeated our analyses by constructing individual functional brain networks based on two other commonly used atlases (246 and 264 ROIs, respectively) (Fan et al., 2016; Power et al., 2011). Due to the lack of direct correspondence of brain regions among different atlases, these analyses were used to test the reproducibility of global rather than nodal alterations.

2.8.2 | Effects of regional GM atrophy

Previous studies have shown that TIA is associated with GM atrophy in specific regions (Li et al., 2015). To determine whether and to what extent GM atrophy contributes to nodal alterations in this study, we re-analyzed between-group differences in nodal metrics (degree, efficiency, and betweenness) with regional mean GM volume as a covariate of no interest.

2.8.3 | Effects of regional perfusion deficits

Previous studies have found that functional brain networks have a physiological basis, as evidenced by the fact that highly connected regions are related to high rates of metabolism and CBF (Liang et al., 2013; Tomasi, Wang, & Volkow, 2013). Given that patients experiencing TIA are frequently reported to show hypoperfusion (Kleinman et al., 2012; MacIntosh et al., 2010; Qiao et al., 2013; Zaharchuk et al., 2012) and that the patients included in this study also showed decreased CBF (Lv et al., 2018), we further examined whether and to what extent TIA-related nodal alterations in this study resulted from regional CBF decreases. This was achieved by recomputing between-group differences in nodal metrics (degree, efficiency, and betweenness) with regional mean CBF as a covariate of no interest.

2.8.4 | Effects of head motion

In this study, we regressed out 24-parameter head motion profiles at the individual level, which was an efficient strategy to control for residual head motion (Yan et al., 2013). To further consolidate our findings, we also reanalyzed between-group differences and correlation results by treating micro head motion (i.e., mean framewise displacement) as a covariate of no interest (Fair et al., 2012).

2.8.5 | Effects of gender

Although the between-group difference was not significant, the gender distribution was not exactly the same in the controls as that in the patients. To test the possible effects of this factor, we reanalyzed between-group differences and correlation results with gender as a covariate of no interest.

2.8.6 | Effects of hemodynamic lags

Previous studies have found that hemodynamic lags could affect estimation of functional connectivity in patients with perfusion deficits (Chi et al., 2018; Christen et al., 2015; Jahanian, Christen, Moseley, & Zaharchuk, 2018; Siegel, Snyder, Ramsey, Shulman, & Corbetta, 2016). Given that the hemodynamic lags were present in some patients in this study (Lv et al., 2018), we evaluated their effects on our findings by recomputing regional representative time series after correcting for the hemodynamic lags. Specifically, we shifted the time series of each voxel of each patient according to their hemodynamic lags as determined in our previous study (Lv et al., 2018). The shifted time series were then used to compute regional representative time course as the weighted average over all voxels within each region. Finally, the previously used procedures were repeated with respect to network construction, property calculation and statistical analysis.

2.8.7 | Effects of thresholding procedure

In this study, we utilized a significance level-based thresholding method, which enabled the examination of absolute network organization (He et al., 2009). However, this method resulted in different network densities across participants, which may confound subsequent between-group comparisons (van Wijk, Stam, & Daffertshofer, 2010). Thus, we also employed a sparsity-based thresholding procedure to examine relative network organization by ensuring the same network density across participants (sparsity was defined as the ratio of the number of actual edges divided by the maximum possible number of edges in a network). Specifically, due to the lack of a conclusive method to select a single sparsity threshold, we repeatedly thresholded all correlation matrices (with negative correlations excluded) over a consecutive sparsity range of [0.05 0.4] with an interval = 0.02. This range ensures that the resultant networks have sparse properties (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Wang et al., 2009) and are estimable for the small-world attributes (Watts & Strogatz, 1998). Finally, we calculated the area under curve (i.e., integral over the sparsity range) for each global and nodal network metric of each participant, on which statistical analyses were performed (Zhang et al., 2011).

2.9 | Brain visualization

The brain results were visualized in surface space using the BrainNet viewer (Xia, Wang, & He, 2013).

3 | RESULTS

3.1 | Demographics, clinical characteristics and head motion

Demographic, clinical, physiological and biochemical information for the final 48 patients with TIA and 40 HCs is summarized in Table 1. There were no significant differences in age ($p = .188$), sex ($p = .621$) or MMSE scores ($p = .222$) between the TIA patients and HCs. Compared with the

HCs, the TIA patients exhibited significantly higher blood systolic pressure ($p < .001$), diastolic pressure ($p = .008$), blood sugar level ($p < .001$), total cholesterol ($p = .037$) and LDL-C ($p = .004$). In addition, there were no significant differences in the maximum (mean $\pm$ standard deviation: HCs = 0.959 ± 0.445 , TIA = 0.903 ± 0.395 ; $p = .270$), root-mean-square (mean $\pm$ standard deviation: HCs = 0.263 ± 0.140 , TIA = 0.256 ± 0.108 ; $p = .380$) or mean framewise displacement (mean $\pm$ standard deviation: HCs = 0.110 ± 0.075 , TIA = 0.120 ± 0.062 ; $p = .226$) of head motion profiles between the two groups. No significant correlations were observed for the mean framewise displacement with any clinical, physiological or biochemical variable in the patients ($p > .05$).

3.2 | Disrupted global organization in TIA

After applying a significance-based threshold to individual functional connectivity matrices, the TIA patients had fewer surviving connections than the HCs ($p = .017$). Further graph-based network analysis revealed that relative to matched random networks, the functional brain networks showed efficient small-world organization as characterized by larger-than-1 normalized clustering coefficient (mean $\pm$ standard deviation: HCs = 1.462 ± 0.265 , TIA = 1.544 ± 0.313) and local efficiency (mean $\pm$ standard deviation: HCs = 1.143 ± 0.070 , TIA = 1.173 ± 0.097) and approximately-equal-to-1 normalized characteristic path length (mean $\pm$ standard deviation: HCs = 1.021 ± 0.018 , TIA = 1.031 ± 0.022) and global efficiency (mean $\pm$ standard deviation: HCs = 0.980 ± 0.017 , TIA = 0.970 ± 0.020). Nevertheless, significant between-group differences were observed in the quantitative network parameters, as characterized by significantly increased characteristic path length ($p = .007$, Cohen's $d = 0.531$) and normalized characteristic path length ($p = .010$, Cohen's $d = 0.507$) and decreased clustering coefficient ($p = .041$, Cohen's $d = 0.385$), local efficiency ($p = .028$, Cohen's $d = 0.422$), global efficiency ($p = .008$, Cohen's $d = 0.508$) and normalized global efficiency ($p = .011$, Cohen's $d = 0.510$) in the patients (Figure 1).

3.3 | Decreased nodal centrality in TIA

Compared with the HCs, the TIA patients showed significantly decreased nodal degree in the bilateral insula, left caudate and pallidum and right putamen and decreased nodal efficiency in the bilateral insula and putamen, left amygdala, caudate, pallidum and middle occipital gyrus and right rolandic operculum and middle temporal gyrus of the temporal pole ($p < .05$, FDR corrected, Cohen's $d = 0.554\text{--}0.765$) (Table 2). No regions exhibited increased nodal degree or efficiency in the patients ($p > .05$, FDR corrected). No regions showed significant between-group differences in nodal betweenness ($p > .05$, FDR corrected).

3.4 | Impaired interregional functional connectivity in TIA

With a cluster-defining threshold of $p < .01$, we identified a single connected component that exhibited decreased functional connectivity in the patients with TIA compared with the HCs ($p < .001$, corrected)

TABLE 1 Demographics and clinical characteristics of all participants

	TIA (n = 48)	HCs (n = 40)	p-value
Age (years)	57.604 ± 9.778	55.025 ± 8.135	.188 ^a
Sex, no. (M/F)	37/11	29/11	.621 ^b
MMSE	29.208 ± 2.609	28.615 ± 1.664	.222 ^a
Blood systolic pressure (mmHg)	145.542 ± 20.753	127.469 ± 19.835 ^c	<.001 ^a
Blood diastolic pressure (mmHg)	86.667 ± 10.383	80.031 ± 11.070 ^c	.008 ^a
Blood sugar level (mmol/L)	6.299 ± 2.113	5.200 ± 0.740 ^c	<.001 ^a
Total cholesterol (mmol/L)	5.275 ± 1.173	4.753 ± 1.011 ^c	.037 ^a
Triglycerides (mmol/L)	1.603 ± 0.940	1.917 ± 1.345 ^c	.234 ^a
HDL-C (mmol/L)	1.111 ± 0.238	1.051 ± 0.290 ^c	.311 ^a
LDL-C (mmol/L)	3.314 ± 0.974	2.691 ± 0.904 ^c	.004 ^a
ABCD2 scores, median (min–max)	4 (2–6)		
Smoking, no	31 (64.6%)	19 (47.5%)	.107 ^b
Drinking, no	20 (41.7%)	21 (52.5%)	.310 ^b
Hypertension, no	22 (45.8%)	6 (15%)	.002 ^b
Diabetes, no	8 (16.7%)	0 (0%)	<.001 ^b
Coronary artery disease, no	2 (4.2%)	0 (0%)	<.001 ^b
Atrial fibrillation, no	1 (2.1%)		
Medication			
Antiplatelets, no	48 (100%)		
Statins, no	2 (4.2%)		
White matter hyperintensity, no	6 (12.5%)		
Vessel stenosis, no. (%)	9 (18.8%)		
TIA/stroke attack in one-year follow-up, no. (%)	12 (27.3%) ^d		

Note: Data are presented as mean ± standard deviation unless stated otherwise. TIA, transient ischemic attack; HCs, healthy controls; M, male; F, female; MMSE, mini-mental state examination; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

^aData were obtained using two-sample two-side t-tests.

^bData were obtained using Pearson Chi-square tests.

^cData were missing for five controls.

^dFour patients dropped out in the one-year follow-up.

(Figure 2). The component included 181 edges linking 74 nodes that involved frontal, occipital, temporal and subcortical regions, and the insula. Using a more rigorous threshold of $p < .001$, three smaller components were found to show decreased functional connectivity in the patients that included 23 nodes and 22 edges ($p < .001$, corrected), 8 nodes and 9 edges ($p = .008$, corrected) and 4 nodes and 3 edges ($p = .046$, corrected), respectively. Interestingly, the edges included in the connected components were mainly inter-hemispheric connections (124/181, 68.5%, 20/22, 90.9%; 6/9, 66.7%; and 3/3, 100%). No components were found to show significantly increased functional connectivity in the patients.

3.5 | Brain-clinical relationships in TIA

No significant correlations were observed in the patients after multiple comparison correction ($p > .05$, FDR). Using an uncorrected lenient threshold of $p < .05$, characteristic path length negatively ($r = -0.309$,

$p = .033$), global efficiency positively ($r = 0.308$, $p = .033$), and nodal degree ($r = 0.420$, $p = .003$) and efficiency ($r = 0.429$, $p = .002$) of the left insula positively correlated with the HDL-C in the patients (Figure 3).

3.6 | Sensitivity and specificity of network metrics in classification and prediction of TIA

Among the network metrics showing significant between-group differences, the mean functional connectivity strength of the identified NBS-based component exhibited the highest accuracy (area under curve = 0.891, $p < .001$) for distinguishing the TIA patients from HCs. Specifically, using the cut-off value of 0.381, 45 of the 48 patients with TIA and 32 of the 40 HCs were classified correctly, yielding a sensitivity of 93.8% and a specificity of 80.0% (Figure 4). All other network metrics exhibited poor discriminant performance (area under curve <0.7).

FIGURE 1 Altered global network metrics in TIA. Compared with the HCs, patients with TIA exhibited significantly increased characteristic path length L_p and normalized characteristic path length $\hat{L}_p$, and decreased clustering coefficient C_p , local efficiency E_{loce} , global efficiency E_{glob} and normalized global efficiency $\hat{E}_{glob}$. TIA, transient ischemic attack; HCs, healthy controls [Color figure can be viewed at wileyonlinelibrary.com]

Compared with the patients without follow-up ischemic attacks, those suffering from ischemic attacks in 1 year after the MR scanning showed significantly lower nodal degree and efficiency in the right insula (permutation test; $p < .05$, FDR corrected). Moreover, the nodal degree of the right insula showed high performance (area under curve = 0.809, $p < .001$, sensitivity = 0.844 and specificity = 0.833) for distinguishing the patients with from patients without follow-up ischemic attacks.

3.7 | Reproducibility of the main results

Our validation analyses indicated that the reported TIA-related alterations in global network metrics remained largely unchanged when using two other atlases or after correcting for micro head motion, gender, or hemodynamic lag of BOLD signals (Table 3). However, no significant between-group differences were found in any global metric when the sparsity-based thresholding procedure was used to examine relative network organization ($p > .05$). For nodal metrics, the reported TIA-related alterations were also largely reproducible after correcting for micro head motion, gender or regional GM volume, CBF or hemodynamic lag of BOLD signals (Table 2). Interestingly, we noted that the TIA-related alterations in nodal degree were primarily accounted for by regional GM volume and CBF (Table 2). Regarding the sparsity-based thresholding procedure, no regions exhibited significant TIA-related alterations ($p > .05$, FDR corrected). Nevertheless, similar regions survived when a liberal threshold of $p < .05$ (uncorrected) was used. Finally, the observed correlation results were largely preserved after correcting for micro head motion and gender. These validation analyses indicate that our main findings are generally reproducible after taking multiple potential confounding factors into account.

4 | DISCUSSION

In this study, we investigated the topological organization of intrinsic functional brain networks in patients with TIA. We found that TIA was associated with disrupted network organization at multiple levels. Moreover, the network disruptions were largely reproducible when using different brain parcellation schemes or correcting for micro head motion and regional gray matter volume, cerebral blood flow and hemodynamic lag of BOLD signals, correlated with the patients' biochemical indicators, and distinguished the patients from HCs and predicted future ischemic attacks in the patients with clinically relevant accuracy. Overall, these findings provide evidence for the network disconnection nature of TIA, which may help to elucidate the pathophysiological underpinnings and to establish objective and reliable biomarkers for TIA.

The human brain has highly specific cellular and circuit architecture to support specialized information processing on the one hand and can effectively integrate information across distributed systems via long-range shortcut on the other hand. This powerful functionality can be quantitatively characterized by small-world organization, an attractive model to support efficient information transfer of both specialized or modular and integrated or distributed processing (Bassett & Bullmore, 2017; Liao et al., 2017). In this study, we found that functional brain networks of the TIA patients followed the small-world organization, suggesting the preservation of an optimal wiring layout in TIA.

Despite the optimal wiring layout, quantitative comparisons revealed a longer characteristic path length and lower clustering coefficient of functional brain networks in the patients with TIA. Analogously, network efficiency analysis revealed decreased local and

TABLE 2 Decreased nodal centrality in TIA

Brain regions	Nodal efficiency			Nodal degree			Nodal betweenness		
	TIA	HCs	p-value	TIA	HCs	p-value	TIA	HCs	p-value
INS.L	0.655 ± 0.094	0.714 ± 0.081	.002^{a-d}	31.896 ± 12.181	39.700 ± 14.419	.002^b	43.728 ± 36.130	43.033 ± 30.841	.452
INS.R	0.637 ± 0.090	0.698 ± 0.088	.001^{a-e}	28.396 ± 12.649	37.225 ± 13.968	.001^{b-d}	36.039 ± 29.312	33.017 ± 19.812	.249
CAU.L	0.562 ± 0.108	0.643 ± 0.110	<.001^{a-e}	19.396 ± 10.843	29.125 ± 16.012	<.001^{b-d}	28.371 ± 34.358	27.465 ± 23.829	.355
PALL	0.581 ± 0.084	0.662 ± 0.104	<.001^{a-e}	20.563 ± 14.985	31.875 ± 16.106	<.001^{b-d}	20.815 ± 23.401	20.713 ± 17.604	.484
PUT.L	0.621 ± 0.101	0.678 ± 0.096	.004^{a-e}	26.229 ± 14.103	34.125 ± 14.905	.007	41.343 ± 34.298	34.232 ± 22.772	.121
PUT.R	0.616 ± 0.094	0.675 ± 0.102	.002^{a-e}	25.083 ± 13.568	33.900 ± 15.203	.002^b	38.853 ± 34.708	32.256 ± 25.615	.152
AMYG.L	0.619 ± 0.105	0.683 ± 0.097	.002^{a-e}	25.833 ± 15.568	34.825 ± 15.568	.005	23.808 ± 20.030	36.296 ± 23.127	.101
MOG.L	0.663 ± 0.101	0.722 ± 0.095	.003^{a-d}	32.250 ± 15.812	40.825 ± 15.674	.006	44.816 ± 43.478	61.720 ± 66.051	.008
ROL.R	0.651 ± 0.084	0.700 ± 0.092	.004^{a,b,d}	31.000 ± 12.181	38.000 ± 14.419	.010	37.385 ± 28.360	30.460 ± 19.836	.097
TPOmid.R	0.631 ± 0.099	0.687 ± 0.082	.002^{b-d}	27.292 ± 14.320	35.475 ± 13.082	.003	36.361 ± 32.239	34.501 ± 25.375	.273

Note: Regions were considered abnormal in patients with TIA if they significantly ($p < .05$, FDR corrected) differed from the healthy controls in at least one of the three nodal centralities (bold font). Data of nodal centrality are presented as mean ± standard deviation. TIA, transient ischemic attack; HCs, healthy controls; INS, insula; CAU, caudate; PAL, pallidum; PUT, putamen; AMYG, amygdala; MOG, middle occipital gyrus; ROL, rolandic operculum; TPOmid, temporal pole: middle temporal gyrus; L, left; R, right.

^aRegions that remained significant decreases after correcting for regional GM volume ($p < .05$, FDR corrected).

^bRegions that remained significant decreases after correcting for mean framewise displacement of head motion ($p < .05$, FDR corrected).

^cRegions that remained centrality decreases after correcting for gender ($p < .05$, FDR corrected).

^dRegions that remained significant decreases after correcting for hemodynamic lags of BOLD signals ($p < .05$, FDR corrected).

^eRegions that remained significant decreases after correcting for regional CBF ($p < .05$, FDR corrected).

global efficiency in the patients. The clustering coefficient and local efficiency reflect functional segregation to support modular information processing and are predominantly associated with short-range connections between nearby brain regions, whereas the characteristic path length and global efficiency reflect functional integration in favor of distributed information processing and are mainly associated with long-range connections between and across remote brain regions. Accordingly, the observed alterations suggest a reduced ability to support modular and distributed information processing in the TIA patients. In particular, the TIA-related increase in characteristic path length and decrease in global efficiency remained after normalization by benchmark random networks and were consistently detected when different brain parcellation schemes were used. These findings suggest that the impaired global integration might be an intrinsic alteration in TIA and could serve as a reliable indicator for the condition. The integrated deficits may be consequences of TIA-related damage to interregional coordination, especially inter-hemispheric communication, as revealed by our functional connectivity analysis. It is worth noting that lower global efficiency was also observed for functional brain networks in patients with stroke (Fallani et al., 2009; Yin et al., 2014). Given that a considerable proportion of TIA patients experience a complete ischemic stroke in the near future (Johnston et al., 2007; Johnston, Gress, Browner, & Sidney, 2000), it would be interesting for future studies to explore whether the TIA-induced integrated impairments continue to worsen in TIA converters and recover in non-converters.

At a nodal level, TIA-related centrality decreased mainly in the bilateral insula and subcortical basal ganglia. The insula receives numerous inputs directly from cortical areas and indirectly via the

thalamus for sensory, somatic and interoceptive processing; moreover, it is also related to high-order processing by interconnecting with cognition- and emotion-related regions such as the medial temporal lobe and amygdala (Craig, 2009; Mesulam & Mufson, 1982). Similarly, despite historically being considered a motor structure, the basal ganglia receives projections from all lobes of the cerebral cortex and is implicated in cognitive and emotional processing (Mink, 1996). With regard to TIA, it not only causes motor-related symptoms such as paralysis, weakness, or numbness but also is accompanied by cognitive impairments in multiple domains, including executive function, information processing speed and abstraction (Bakker et al., 2003a; Sachdev et al., 2004). Thus, we propose that these alterations may at least partly contribute to the sensory, motor, cognitive, and emotional problems in TIA, a speculation that could be tested in the future. Interestingly, the centrality alterations appear to be independent of GM atrophy and cerebral hypoperfusion, implying that they are essentially functional rather than derivatives of structural or metabolic abnormalities. Future studies are required to uncover additional mechanisms related to the centrality alterations of the insula and basal ganglia.

In addition, three cortical regions were found to show decreased nodal centrality in TIA, including the left middle occipital gyrus, right rolandic operculum, and middle temporal gyrus of the temporal pole. The left middle occipital gyrus is considered a part of the visual dorsal stream, and is involved in object localization (Wandell, Dumoulin, & Brewer, 2007). Activation of the rolandic operculum is related to the structuring of individual words into phrases and sentences during the perception of spoken sentences (Indefrey et al., 2001). The middle temporal gyrus is involved in semantic memory and language

FIGURE 2 Impaired interregional functional connectivity in TIA. (a) A single connected component was identified to exhibit decreased functional connectivity in the patients with TIA when using a cluster defining threshold of $p < .01$. (b) Using a more rigorous cluster-defining threshold of $p < .001$, three smaller components were detected to show decreased functional connectivity in the patients with TIA. Notably, the components were mainly composed of inter-hemispheric connections. Nodal size denotes nodal degree (i.e., the number of connections) in the connected component (bigger for more) and edge width denotes the significance level of between-group differences (thicker for more significant). See Table S1 for regional abbreviations. TIA, transient ischemic attack [Color figure can be viewed at wileyonlinelibrary.com]

processes (Kiehl et al., 2004). Thus, we speculate that the decreased nodal centrality in these cortical regions may be related to the difficulties in visual, acoustic and language processing in patients with TIA. However, the cortical alterations became nonsignificant after correcting for potential GM atrophy and cerebral hypoperfusion, suggesting a structural and metabolic substrate. Future studies are needed to clarify the differentiation and related origin of function-structure and function-perfusion relationships between cortical and subcortical regions.

Our NBS analysis revealed widespread functional connectivity decreases in the patients with TIA, which included all regions showing decreased centrality in the patients. Thus, these two sets of results mutually support each other. Intriguingly, the TIA-related functional connectivity decreases mainly involved interhemispheric connections. This is consistent with previous studies in stroke, which consistently reported reductions in interhemispheric functional connectivity of multiple brain systems, including the somatomotor network (Carter et al., 2010; Carter et al., 2012; Park et al., 2011; Wang, Yu, et al., 2010) attention network (Nomura et al., 2010) and language network (Warren, Crinion, Lambon Ralph, & Wise, 2009). Our results imply that impaired interhemispheric connectivity is already detectable in TIA, an important risk factor for stroke, and thus may be a reliable marker of

ischemic attacks. However, this finding was from network analysis at a regional level, which is unable to reveal subtle focal alterations. Future studies utilizing a voxel-mirrored homotopic connectivity method (Zuo et al., 2010), which allows for an examination of inter-hemispheric functional connectivity between homotopic regions of two hemispheres at a voxel level, may provide more details on disruptions of inter-hemispheric communication in TIA.

We found that the increased characteristic path length was negatively, while the decreased global efficiency and nodal centrality of the left insula were positively correlated with HDL-C in the TIA patients. That is, the higher the HDL-C in the patients (i.e., the closer they approached the HC values), the closer to normal were the relevant network metrics. HDL-C is associated with the incidence of cardiovascular events. Specifically, a lower level of HDL-C is associated with accumulation of atherosclerosis within the walls of arteries, which elevates the risk of ischemic attacks (Parhofer, 2015). Therefore, the network alterations may serve as an index to monitor the risk of ischemic attacks. A deeper understanding of the relationships could be obtained by systematically elucidating sequential or causal relationships among upstream pathophysiological and molecular pathology, midstream brain alterations, and downstream clinical phenotypes in the disease. Notably, our correlation results did not pass multiple

FIGURE 3 Relationship between network measures and clinical/physiological/biochemical variables in TIA. In the TIA patients, significant correlations were observed for the high-density lipoprotein cholesterol (HDL-C) with characteristic path length L_p , global efficiency E_{glob} , and nodal degree k_i and nodal efficiency e_i of the left insula. HDL-C, high-density lipoprotein cholesterol; TIA, transient ischemic attack [Color figure can be viewed at wileyonlinelibrary.com]

comparison correction and thus the relevant findings should be interpreted with caution.

Currently, the diagnosis of TIA is mainly based on subjective knowledge and experience, and thus inevitably suffers from bias. Because it is an important risk factor for ischemic stroke (Johnston et al., 2000; Johnston et al., 2007), an accurate and objective diagnosis of TIA would be of great clinical value for early intervention to prevent or delay possible progression. Using the ROC method, our preliminary analysis showed that functional network alterations could not only differentiate TIA patients from HCs but could also predict

follow-up ischemic attacks in the patients with clinically relevant sensitivity and specificity. These findings highlight the potential of functional brain analysis in establishing diagnostic and prognostic biomarkers for TIA. Notably, the insula was related to the HDL-C and could predict follow-up ischemic attacks in the patients simultaneously. Interestingly, previous studies found that insular ischemic stroke was associated with an increased risk of poststroke mortality (Hanne et al., 2017; Sposato et al., 2016). These findings together suggest the insula as a key structure in the vascular etiology of brain ischemia and as a promising treatment target on which influence can

FIGURE 4 TIA-control classification and prediction of follow-up ischemic attacks. (a) The mean functional connectivity strength of the identified NBS component (cluster defining threshold of $p < .01$) distinguished TIA patients from HCs with a high sensitivity and specificity. (b) Nodal degree of the right insula predicted follow-up ischemic attacks with a high sensitivity and specificity. ROC, receiver operating characteristic; AUC, area under curve; TIA, transient ischemic attack; HCs, healthy controls [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Reproducibility of our main findings

		C_p	L_p	E_{loc}	E_{glob}	$\hat{C}_p$	$\hat{L}_p$	$\hat{E}_{loc}$	$\hat{E}_{glob}$
Main results	p-value	.041 (↓)	.007 (↑)	.028 (↓)	.008 (↓)	.095	.010 (↑)	.061	.011 (↓)
	cohen's d	0.385	0.531	0.422	0.508	0.284	0.507	0.348	0.510
Brain parcellation									
Fan	p-value	.072	.018 (↑)	.062	.017 (↓)	.069	.008 (↑)	.060	.007 (↓)
	cohen's d	0.318	0.472	0.336	0.463	0.321	0.521	0.343	0.528
Power	p-value	.157	.028 (↑)	.076	.031 (↓)	.110	.014 (↑)	.028 ↑	.014 (↓)
	cohen's d	0.216	0.415	0.306	0.403	0.268	0.481	0.396	0.481
Head motion	p-value	.031 (↓)	.006 (↑)	.023 (↓)	.007 (↓)	.090	.011 (↑)	.049 ↑	.009 (↓)
	cohen's d	0.407	0.554	0.442	0.532	0.295	0.509	0.354	0.513
Gender	p-value	.044 (↓)	.009 (↑)	.027 (↓)	.012 (↓)	.112	.009 (↑)	.066	.012 (↓)
	cohen's d	0.378	0.525	0.416	0.502	0.270	0.496	0.332	0.499
Hemodynamic lags	p-value	.042 (↓)	.009 (↑)	.024 (↓)	.011 (↓)	.115	.017 (↑)	.070	.015 (↓)
	cohen's d	0.386	0.514	0.426	0.492	0.260	0.465	0.323	0.468

Note: Significant between-group differences and related effect sizes are highlighted in bold. C_p , clustering coefficient; L_p , characteristic path length; E_{loc} , local efficiency; E_{glob} , global efficiency; $\hat{C}_p$, normalized clustering coefficient; $\hat{L}_p$, normalized characteristic path length; $\hat{E}_{loc}$, normalized local efficiency; $\hat{E}_{glob}$, normalized global efficiency; ↓, TIA < HCs; ↑, TIA > HCs; Fan, brain parcellation from Fan et al. (2016); Power, brain parcellation from Power et al. (2011).

be exerted to improve prognosis of the disease. Future follow-up studies are of great importance to elucidate the roles played by the insula when TIA progress to stroke.

The present study has several limitations. First, we did not collect MRI data during the follow-up period, and thus cannot examine how functional brain networks reorganize as TIA continues to advance. Future longitudinal studies are warranted to examine whether the current approach could be used to monitor progression of TIA. Second, this study lacked cognitive data for the patients. It would be interesting to investigate the relationships between large-scale network alterations and cognitive dysfunction associated with TIA. Third, based on one-dimensional features, our preliminary ROC analyses indicated that functional brain network alterations are promising as diagnostic and prognostic biomarkers for TIA. The generalization ability of these results should be cross-validated in the future by utilizing more sophisticated discriminant methods based on multivariable techniques. Fourth, all patients included in this study took medication previously. However, we did not collect a detailed medication history, and thus cannot rule out the possible effects of medication on our findings. Future studies enrolling drug-naïve patients could help clarify this issue. Fifth, although our findings from the correlation, classification, and prediction analyses strongly suggest the potential of the observed network alterations as diagnostic and prognostic biomarkers for TIA, they are not yet sufficient to become biomarkers in clinical practice because little is known regarding the specificity of these alterations to TIA. Exploring such specificity is an important direction for future research. Finally, recent evidence highlights poor correspondence among different modalities of brain networks (Reid et al., 2016). Accordingly, it is important to examine similarities and differences in TIA-induced topological alterations among different MRI modalities to provide a more complete view of network disorganization in the disease.

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SUPPORTING INFORMATION

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