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Mapping Resting State Networks: Insights into motor impairment of Acute Post Stroke Patients

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Research Article

Keywords: Stroke, National Institutes of Health Stroke Scale (NIHSS), Resting-state functional brain networks, Default Mode Network

Posted Date: March 30th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9236395/v1

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Additional Declarations: The authors declare no competing interests.

Mapping Resting State Networks: Insights into Motor Impairment in Acute Post Stroke Patients

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3/15/2026

Statements and Declarations:

Ethical declaration: This study was approved by Ethics committee of Istanbul Medipol University
Funding declaration: " We declare that there were no funding sources for this research"
Conflict of Interest declaration: "The authors declare that there are no conflicts of interest related to this study"

Abstract: Stroke is the most common neurological condition that causes disability or in more severe cases death. The course of recovery after a stroke and the most appropriate rehabilitation and treatment methods in this context remain uncertain. Although the structural damage caused by a stroke may be localized in a specific brain area, dysfunction may occur remotely in areas of the brain that are far from the area of damage. Areas that are directly damaged or indirectly affected are organized into a larger functional network that is in dynamic balance with other networks in the brain. Therefore, measurement of resting state functional brain networks can predict the clinical picture and prognosis of stroke. The aim of this research is to investigate the relationship between resting state functional brain networks and motor Decadency in acute stroke patients.

Twenty right-handed patients, 17 of whom were men and 3 of whom were women, with an average age of 58.8+7.3 and their first stroke, were included in the study. In the acute period, fMRI was also applied to patients to evaluate the resting state brain networks. Patients were also evaluated with the MoCa and NIHSS scales. Resting status of the patient-The correlation between the obtained resting status network components and the NIHSS scores was evaluated to analyze the fMRI records.

The patients' NIHSS scores were 2.65 (+1.47) and their MoCa scores were 20.89 (+4.01). In the resting state brain networks analysis, the Default Mode Network (DMN) and Sensorimotor Network (SMN) emerged as the most significant networks. The functional connectivity of the Default Mode Network with the left Cerebellum and Precuneus cortex decreased as NIHSS scores increased, while the functional connectivity of the SMN with the Frontal Operculum, Inferior Frontal Gyrus and Insular Cortex showed high activity as NIHSS scores increased.

Our findings reveal that there is a correlation between the neurological symptoms that occur in the acute phase of stroke and the functional brain networks in the resting state. This finding reveals that there is a basis for predicting post-stroke prognosis and even planning rehabilitation in a specific way through resting state functional brain networks.

Keywords: Stroke, National Institutes of Health Stroke Scale (NIHSS), Resting-state functional brain networks, Default Mode Network

INTRODUCTION

Stroke causes sudden disruption of physiological brain functions, and this process can lead to impairments in the motor networks involved in the execution of voluntary movements. Stroke causes sudden disruption of physiological brain functions, and this process can lead to impairments in the motor networks involved in the execution of voluntary movements. Research has shown that the absolute number of stroke cases increased by 70% between 1999 and 2019 (7). Every year, 12.2 million strokes occur worldwide, meaning that one in four people over the age of 25 will survive a stroke during their lifetime (8). While more than half of stroke patients survive ischemic stroke, a smaller number suffer from hemorrhagic stroke. The morbidity resulting from stroke is reduced by investing in the quality of primary healthcare services and education for stroke prevention; however, stroke remains the third leading cause of death worldwide. Unfortunately, only 10% of stroke survivors manage to make a full recovery, while the remaining patients may be left disabled for life (9). Only a small portion of stroke survivors, approximately 5 to 15%, can be subjected to thrombolysis or thrombectomy during the acute phase.

As a mechanism to cope with injury, the brain develops a method called neuroplasticity. Neuroplasticity is the ability of the nervous system to restore functionality by making structural reorganizations or changes in the connections and communication between different brain regions (28). This leads to an event known as cortical

reorganization. It is the process by which new neural pathways form as a result of learning and practicing new skills (29). This event occurs most frequently during the acute phase of stroke, specifically, in the first 6-12 months. The mechanism of cortical reorganization occurs in two ways: either through the transcallosal pathway, which collects fibers from the intact hemisphere necessary for the planning and execution of movement, or through the uncrossed pyramidal pathway, since 10-15% of the fibers remain uncrossed.(22) Since neurons remain locked in the G0 phase, meaning they do not enter the division phase of the cell cycle, this explains the loss of nerve tissue due to brain damage. However, recovery depends not on the number of neurons, but on the number and type of synapses formed. It is very important to start rehabilitation in this acute phase of stroke, because it is possible to take advantage of the cortical reorganization process.

Since the connections formed during cortical reorganization are formed randomly, the individual's recovery may be negatively affected if it is not guided by planned and skill-specific rehabilitation methods (22). The importance of task-specific rehabilitative interventions in the early post-stroke period was shown in a groundbreaking study conducted by Nudo and others in 1996. In the monkey group that received a 4-week task-specific retraining program, researchers compared the cortical representation of the hand to that in an untrained monkey group. They observed that, following ischemic stroke, the cortical representation of the hand was damaged. However, the cortical representation of the digits, wrist, and forearm expanded toward the intact cortex, unlike in the untrained group.

Recently, changes have emerged in neurological sciences. These changes can be considered a revolution in our traditional localizationist/asociationist understanding of the brain as a multidimensional network from a structural/anatomical and functional point of view. As a result of this, the clinical picture and behavioral disorders in neurological diseases are now increasingly attributed to changes in structural and functional brain networks. Naturally, this approach also applies to stroke, where a focal lesion may be accompanied by widespread structural and functional network changes (1-2). Dysfunction in distant areas of the brain, classically resulting from a focal lesion, is referred to as 'diaschisis', a term introduced by von Monakow.

Today, with new neuroimaging methods, the concept of 'diaschisis' has been expanded to include changing network connections (3).

Stroke is one of the most common neurological manifestations of this condition. Although the structural damage caused by a stroke may be localized in a specific brain area, dysfunction may occur in areas of the brain that are distant from the area of damage. This framework suggests that a lesion in a single location in the brain has the ability to disrupt brain function well beyond the lesion's boundaries (4-5).

It is observed that there is an attempt to improve methodological approaches in this field. Recent studies have followed Salvalaggio et al. in comparing the accuracy of four neuroimaging methods in predicting symptoms (lesion localization, indirect estimates of structural and functional disconnections, and direct functional connectivity analysis) (55) Yue et al. took a different approach, assessing changes in functional network connectivity using fMRI and evaluating cognitive outcomes with the MMSE following stroke.

This methodological evolution lays the foundation for more nuanced investigations into how disruptions in brain networks contribute to cognitive impairments. In this context, Yue et al.'s study, takes a novel approach by utilizing fMRI to assess functional network connectivity and its relationship with cognitive outcomes, as measured by the MMSE. Their findings reveal significant changes within static and dynamic functional networks and illustrate a negative correlation between the Default Mode Network (DMN) and cognitive performance, reinforcing the importance of advanced neuroimaging techniques in elucidating the complex relationship between

brain connectivity and cognitive deficits post-stroke. Together, these studies underscore the significance of integrating various neuroimaging methods to gain deeper insights into stroke-related cognitive impairments, thus fostering a more comprehensive understanding of neurological recovery processes.

In previous studies investigating the relationship between cognitive impairment and the default mode network (DMN), researchers observed significant changes in both static and dynamic functional networks. They also reported a negative correlation between the DMN, the visual spatial network, and Mini-Mental State Examination (MMSE) scores, which assess cognitive function (6). In contrast, our study focuses on examining the correlation between disruptions in resting state networks and the severity of motor impairment during the acute phase of stroke.

5. METHODOLOGY

5.1. Participants of the Study.

An assessment was performed to evaluate the National Institutes of Health Stroke Scale (NIHSS) scores of 20 patients, ranging in age from 30 to 75 years, who were diagnosed with their first stroke and fulfilled the inclusion criteria. Later, the Montreal Cognitive Assessment (MoCA) (34) test is administered only once to asses cognitive status of a patient, it is not used for analyses related to functional network characteristics. Following the evaluations, functional MRI scans were conducted to assess both the anatomical and resting states of the patients. The assessments were repeated upon the patients' discharge. Finally, patients were classified according to the location of the infarction, whether it was in the cortical/subcortical region, which hemisphere the infarction occurred in, and whether they received thrombolytic therapy or not.

5.1.1. Inclusion criteria

- Right-handedness
- First-time and ischemic stroke (ischemic/hemorrhagic
- Aged 30-75
- Stable vital signs, no progression of neurological symptoms

5.1.2. Exclusion criteria

- Left-handedness
- Previous history of stroke
- Having undergone cranial surgery
- being illiterate
- Brain tumor, brain trauma, ischemic foci and a history of seizures
- Decline of cognitive functions before stroke/dementia
- Any neuropsychiatric and affective disorders that may affect the test results
- Inability to tolerate MRI scanning

5.2 . Evaluation Methods

The study used the Montreal Cognitive Assessment (MoCA) (34) and the National Institutes of Health Stroke Scale (NIHSS) (33) as evaluation methods.

5.2.1. Montreal Cognitive Assessment Scale (MoCA)

MoCA (Montreal Cognitive Assessment): The Montreal Cognitive Assessment is a simple assessment of seven cognitive domains and consists of eleven questions. This test is good at detecting mild cognitive impairment (MCI) or early signs of dementia (35).

5.2.2. National Health Stroke Scale

NIHSS (National Institutes of Health Stroke Scale):

It is a 15-item impairment scale used to measure the severity of stroke

This scale includes the following domains: level of consciousness, eye movements, integrity of visual fields, facial movements, muscle strength in arms and legs, sensation, coordination, language, speech, and neglect. Each area is scored on a scale ranging from 0-2,0-3 or 0-4. The points of each item are added to the total score, which ranges from 0-42.. The severity of the stroke is directly proportional to the score obtained (33).

5.5. fMRI Analysis

MRI Data Acquisition

Structural and resting-state fMRI data were acquired using a Signa Explorer MR device (General Electric Company, USA) at Alanya Alaaddin Keykubat University. T1-weighted structural scans consisted of 190 slices (TR/TE: 8.1/3.7 ms), with a field of view (FOV) of 256 × 256 × 190 mm (FH × AP × RL) and an isotropic voxel size of 1 × 1 × 1 mm. Resting-state fMRI data were collected with eyes open using an echo-planar imaging (EPI) sequence. Each scanning session lasted approximately 12 minutes, during which 300 volumes were acquired with the following parameters: TR = 2,230 ms, TE = 30 ms, FOV = 240 × 240 × 140 mm (RL × AP × FH), voxel size = 3 × 3 × 4 mm, flip angle = 77°, and 35 slices. Prior to scanning, participants were instructed to keep their eyes open, remain relaxed with minimal movement, clear their minds, and avoid falling asleep.

Analysis of Resting-State Functional Connectivity (rsFC)

Functional MRI data were analyzed using CONN (34, 35) (RRID:SCR_009550) release 21.a (34,35) and SPM (41) (RRID:SCR_007037) release 12.7771.

Preprocessing

Functional and anatomical data were preprocessed using a modular preprocessing pipeline (35) comprising realignment with correction of susceptibility distortion interactions, slice-timing correction, outlier detection, direct segmentation, MNI-space normalization, and spatial smoothing. Functional data were realigned using the SPM realign-and-unwrap procedure (36), in which all scans were co registered to a reference image (first scan of the first session) via a least-squares approach using a six-parameter rigid-body transformation (37), and resampled using B-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between slices acquired in ascending order was corrected with SPM slice-timing correction (43,44), employing since temporal interpolation to resample each slice BOLD time series to a common mid-acquisition time. Potential outlier scans were identified using ART (34) as acquisitions with frame wise displacement exceeding 0.9 mm or global BOLD signal changes exceeding 5 standard deviations (38,35). A reference BOLD image was computed for each subject by averaging all non-outlier scans. Functional and anatomical data were then normalized to standard MNI space, segmented into gray matter, white matter, and cerebrospinal fluid (CSF)

tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure (35,39) using the SPM unified segmentation and normalization algorithm (40,41) with the default IXI-549 tissue probability map template. Finally, functional data were smoothed using a Gaussian kernel of 6 mm full width at half maximum (FWHM).

Denoising

Functional data were denoised using a standard pipeline (35) that included regression of potential confounding effects: white matter time series (5 CompCor noise components), CSF time series (5 CompCor noise components), motion parameters and their first-order derivatives (12 factors) (37), outlier scans (up to 20 factors) (38), session effects and their first-order derivatives (2 factors), and linear trends (2 factors) within each functional run. This was followed by band pass frequency filtering of the BOLD time series between 0.008 Hz and 0.09 Hz (45). CompCor noise components (46,47) within white matter and CSF were estimated by computing the average BOLD signal and the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. Based on the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 89.1 to 111.7 (mean: 104.9) across subjects (35).

First-Level Analysis

Group-level independent component analyses (group-ICA; 39) were performed to identify 20 temporally coherent networks from the fMRI data pooled across all subjects and conditions. The BOLD signal across all time points and voxels was concatenated along the temporal dimension. Subject-level dimensionality reduction was performed using singular value decomposition (SVD) with 64 components separately for each subject and condition. The concatenated data were further reduced using a group-level SVD retaining 20 components, and a fast-ICA fixed-point algorithm (48) with hyperbolic tangent (G1) contrast function was applied to extract spatially independent group-level networks. Individual subject and condition ICA maps were subsequently derived using GICA3 back-projection (49). Relevant components were identified using CONN's network-identification procedure, which automatically matches each estimated ICA component to a set of reference networks by selecting the component with the highest spatial correlation to each canonical network template, consistent with previously established resting-state network topographies (50,51). Of the 20 estimated components, the Default Mode Network (DMN; ICA_2), Visual Network (ICA_8), and Sensorimotor Network (ICA_19) yielded the highest correspondence with their respective reference templates and were thus selected for further analysis.

Group-Level Analyses

Group-level statistical inference was performed using a General Linear Model (GLM) (35). For each voxel, a separate GLM was estimated with first-level connectivity measures as the dependent variable and group or subject-level identifiers as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random effects across subjects and sample covariance estimation across multiple measurements. Statistical inferences were performed at the cluster level (contiguous

groups of suprathreshold voxels), based on parametric statistics derived from Gaussian Random Field theory (52,35). Age, education, sex,
and MoCA scores were included as covariates of no interest. To examine the relationship

between resting-state network connectivity and stroke severity, NIHSS scores were entered as a continuous covariate of interest within the GLM framework, with ICA maps from all subjects entered as dependent variables separately for each identified resting-state network. Results were thresholded using a cluster-forming voxel-level threshold of p < 0.001 combined with a cluster-size threshold of p-FDR < 0.05 (familywise corrected) (53).

5.5.2. ICA analysis

The aim of ICA analysis is to identify resting state networks. Resting state connectivity analysis was performed using the CONN toolbox. Group independent component analysis (ICA) was performed using Calhoun's group-level ICA approach within the CONN toolbox. . The process included variance normalization preconditioning, combining BOLD signal data across subjects or conditions along the temporal dimension, dimensionality. A decrease was observed at the group level. Fast ICA was used to estimate independent spatial components, and GICA1 back projection was applied to predict spatial maps at the individual subject level (37)

The number of independent components to be estimated was set to 20. To discover the estimated ICA networks, the summary option in the second-level results was used. The relevant components were identified through visual inspection, guided by previous literature (38-39) and the frequency spectra of the components' time courses. Of the 20 components analyzed, the figures demonstrate that the Default Mode Network (DMN, ICA_2), Visual Network (ICA_8), and Sensorimotor Network (ICA_19) were identified as the most appropriate components. To measure the correlation between the connectivity values of the identified networks and NIHSS scores, a general linear model (GLM) was implemented. In this second-level analysis, the ICA maps of all subjects were processed as a group for each resting state network. .Additionally, age, education, gender, and MoCA scores were included as covariates. Statistical significance for all comparisons was determined as cluster level (cluster threshold) false finding.

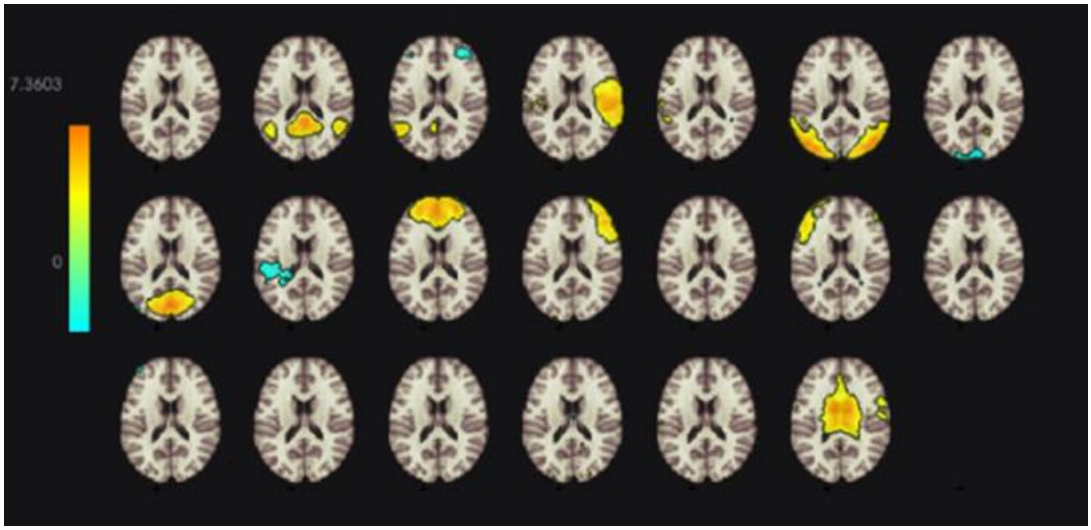


Figure 5.5.2.1. 20 Component Group ICA Images

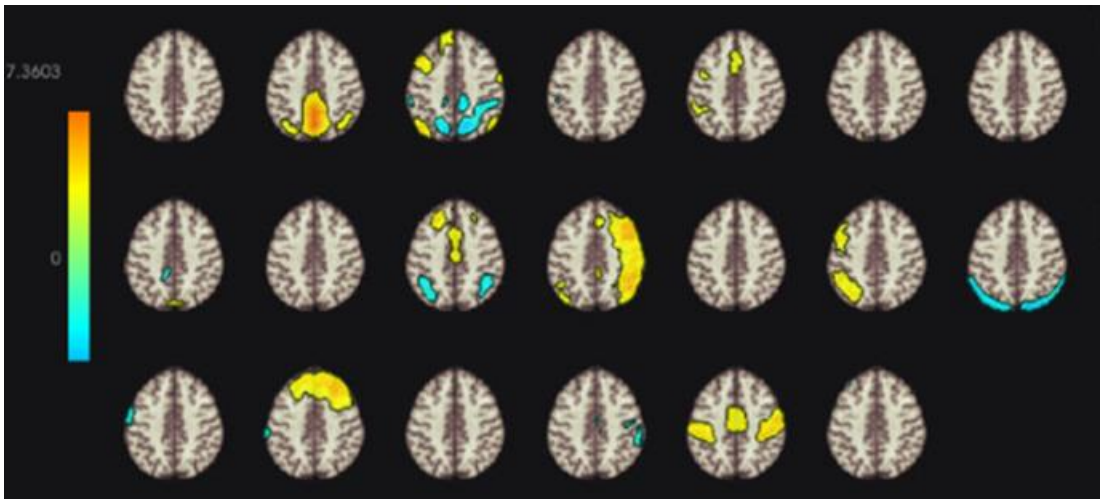


Figure 5.5.2.2. Images of the 20-component Group ICA images from a different section

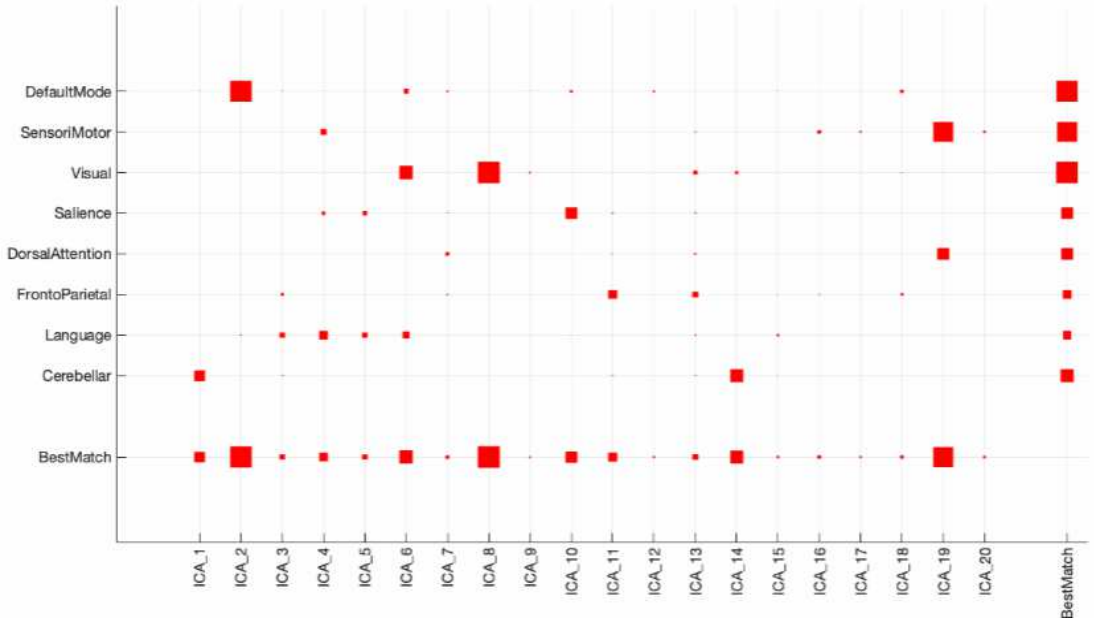


Figure 5.5.2.3. Selection of Appropriate Components by Matching 20-Component Group ICA Images with Resting State Networks

5.5.3. Resting State Functional MRI Acquisition

The resting state fMRI will be performed using a multiband echo-planar imaging (EPI) sequence: TR =2000 ms; TE=30 ms; 40 slices; slice thickness, 3 mm; gap 1 mm; flip angle, 83°; FOV=234×234mm2; pixel size= 3.0mm×3.0 mm; matrix= 64×64; duration: 6 min. The participants were instructed to relax during the screening.

5.5.4 Statistical Analysis

IBM SPSS Statistics 25 was used as the statistical tool. The Non-Parametric Wilcoxon Signed Ranks Test was used to investigate the difference between pre- and post-test scores. Furthermore, the

Spearman correlation method was employed to explore potential relationships between the scores, while the partial correlation method was applied to account for confounding variables

6. RESULTS

6.1 Demographic and Clinical Data

The demographic and clinical characteristics of the 20 patients included in the study, along with their NIHSS subscores and MoCA subscores, are presented in Table 1. The total NIHHS score at admission was 2.65 (±1.47), while the mean NIHHS total score at discharge, repeated after an average of 5 days (±1.2), was 1.70 (±1.66). Additionally, Table 1 presents details regarding the side of the stroke, the characteristics of cortical and subcortical localization, as well as the rates of thrombolytic treatment administered.

Table 6.1 Clinical and Demographical characteristics

Area	N
Age	58.80(7.30)
Education	6.45 (3.0)
Gender M/F	17/3
NIHSS Total(42)	2.65(1.47)
NIHSS Motor	1.35(1.19)
NIHSS Facial Paralysis	0.6(0.8)
NIHSS Sensory	0.05(0.21)
NIHSS Ataxia	0.25(0.43)
NIHSS Dysarthria	0.40(0.73)
Total NIHSS Discharge	1.7
Motor NIHSS Discharge	0.95(1.31)
F.P. NIHSS Discharge	0.45(0.88)
Sensory NIHSS Discharge	0(0)
Ataxia NIHSS Discharge	0.15(0.36)
Dysarthria NIHSS Discharge	0.10(0.30)
Hemispheric Infarct (Right/Left)	7:13
Infarct (Cortical/Subcortical)	7:13
Thrombectomy(done/not done)	4:16
MoCA(Total)	20.89(4.01)

Spearman's Rho, a non-parametric statistical method, was employed to assess the relationship between evaluations and Deci-sive values. The analysis revealed a significant negative correlation between the NIHSS score at hospitalization and the MoCA score (r (2 Dec) = -0.508, p = 0.026). This

relationship was further upheld in the partial correlation analysis, which accounted for variables such as gender, age, thrombolytic treatment status, cortical or subcortical involvement, and hemisphere. Furthermore, the analysis revealed a significant positive correlation between education level and MoCA scores ($r(20) = 0$, $p = 0.001$), as well as a significant negative correlation with NIHSS scores ($r(20) = -0.56$, $p = 0.010$).

Table 6.2. Correlation results of Spearman's Rho test between variables

Variable	N	r	P
NIHSS-MoCA	20	-0.508	0.026
NIHSS- Education	20	-0.56	0.01
MoCA- Education	20	-0.707	0.004

Table 6.3. Results of Partial Correlation Analysis for Gender, Age, Thrombolytic Status, and Infarct Location (including Hemisphere and Cortical/Subcortical classification).

Variable	N	r	P
NIHSS-MoCA	20	-0.565	0.35

Conducted during the patients' hospitalization, a significant improvement in the average NIHHS scores was observed when compared between the repeated assessments taken approximately 5 ± 1.2 days later. The Non-Parametric Wilcoxon Marked Orders Test was conducted to assess the difference in average rankings between NIHSS scores at hospitalization and discharge for patients diagnosed with stroke. The results revealed a statistically significant difference, with $p = 0.013$, indicating significance at the 0.05 level ($r(20) = 0.54$). This finding indicates a significant difference in NIHSS scores between hospitalization and discharge. Table 6.5 presents the results of the Non-Parametric Wilcoxon Marked Orders Test, which was performed to assess the significance of the differences in NIHSS scores at admission and discharge.

Table 6.4. The results of the Non-Parametric Wilcoxon Marked Decrees Test conducted to determine the significance of the difference between the time of admission and discharge of NIHSS scores

Score	Ranks	N	S.O	Z	p
NIHSS Total	Negative	20	73.5		
	Positive	0	4.5		
		0		-2.799	0.005
NIHSS Total Discharge Equal Total		20			

6.2. Comparison of Neuroimaging Results

Following the ICA analysis, we investigated the relationship between the connectivity values of the selected components and the NIHSS scores. Our findings revealed a prominent association between the Default Mode Network (DMN) and the Sensor-Motor Network (SMN), as detailed in Table 6.

Table 6.5. The clustering results of the correlation analysis of the determined components with NIHSS scores

Network	Region	Cluster (x,y,z)	size	size p-FDR	Effect Sizes
ICA2/DMN	Left Cerebellum/Precuneus Cortex	(+02) (-70)(-48)	100	0.014317	-0.8498
ICA19/SMN	Left Frontal Operculum Cortex	(-22)(-40)(-52)	94	0.014317	-0.9011
	Left Inferior Frontal Gyrus	(+14)(-50)(+08)	82	0.017017	-0.9679
	Left Insular Cortex	(-26)(+16)(+08)	67	0.02741	-1.3501
		238			

The analysis reveals that the functional connectivity of the Default Mode Network (DMN) with the left Cerebellum and Precuneus cortex diminishes as NIHSS scores rise. Clustering analysis indicated that, according to the CONN atlas, there are 164 voxels associated with the Cerebellum and 42 voxels associated with the Precuneus.

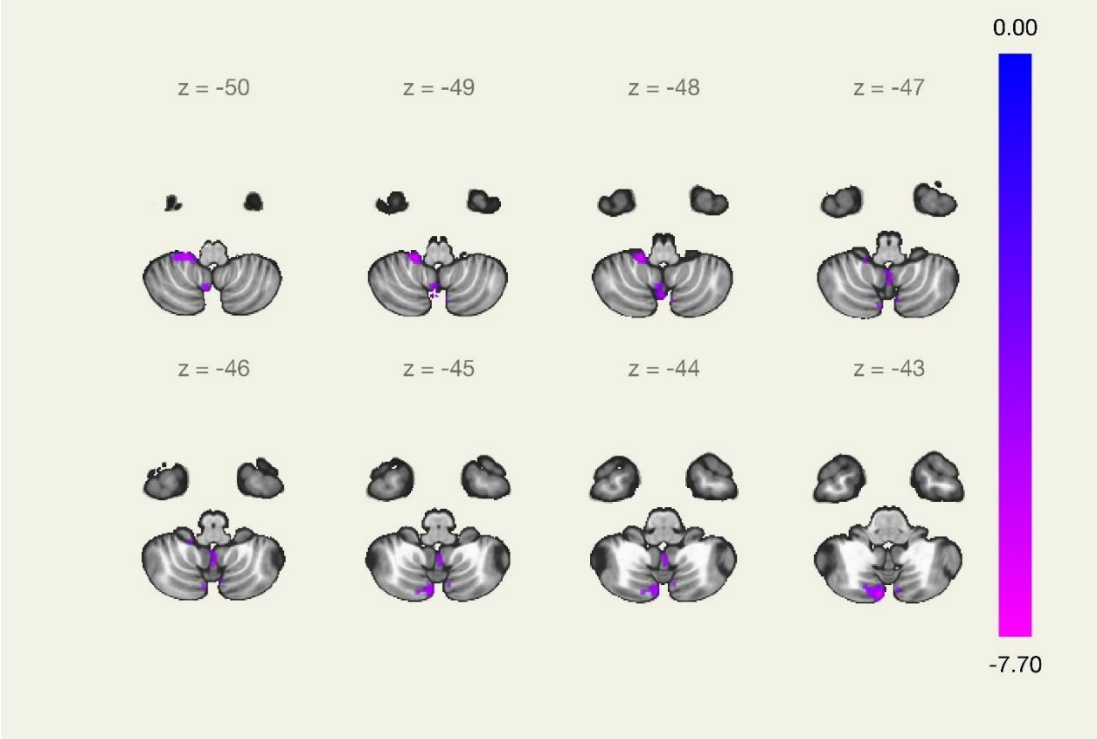
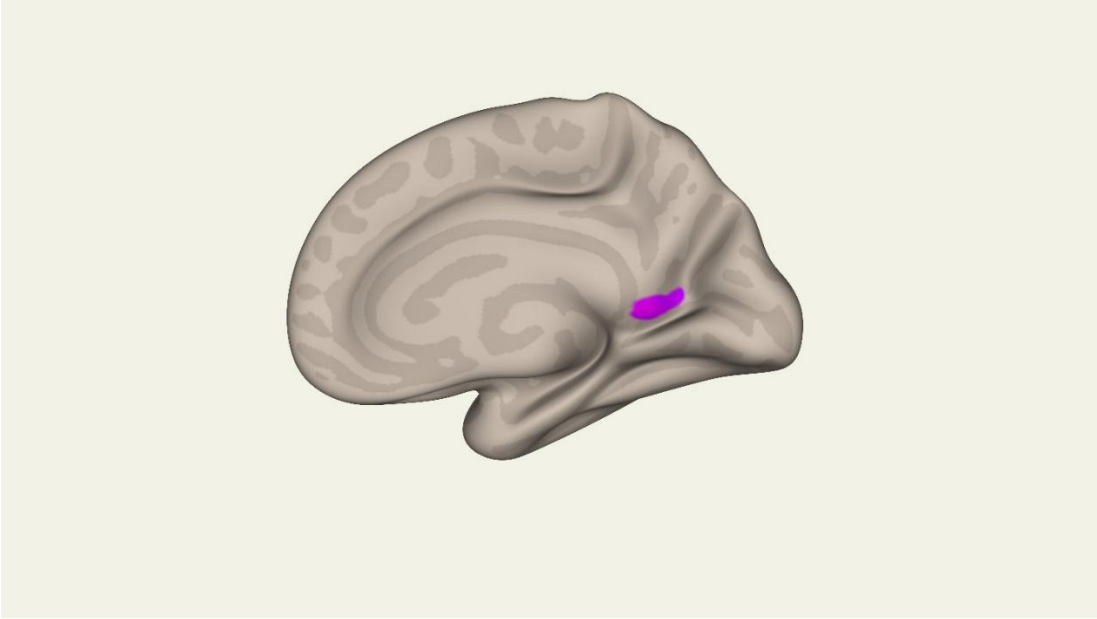


Figure 6.1. Cerebellar areas showing negative correlation with NIHSS scores in the Resting State Network



6.2. Representation of the Resting State Network on the brain surface of the region covering the Precuneus cortex, which is negatively correlated with NIHSS scores

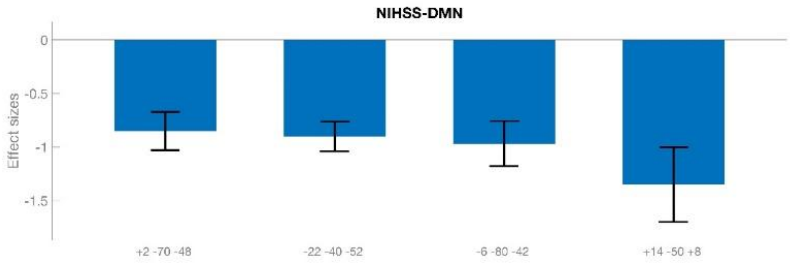


Figure 6.3. Graph showing the effect sizes and direction of clustering results in the correlation results of the Resting State Network with NIHSS scores

In a secondary finding, we observed that the functional connectivity of the Sensorimotor Network exhibited heightened activity with the Frontal Operculum, Inferior Frontal Gyrus, and Insular Cortex as NIHSS scores increased. Clustering analysis revealed that this connectivity encompassed 93 voxels within the Left Frontal Operculum, 46 voxels in the Inferior Frontal Gyrus (pars triangularis), 40 voxels in the Left Insular Cortex, 20 voxels in the Left Inferior Frontal Gyrus (pars opercularis), and 17 voxels in the Left Frontal Orbital Cortex, as per the CONN atlas.



Figure 6.4. Representation of the regions where the Sensory-Motor Network has a positive correlation with NIHSS scores from axial sections

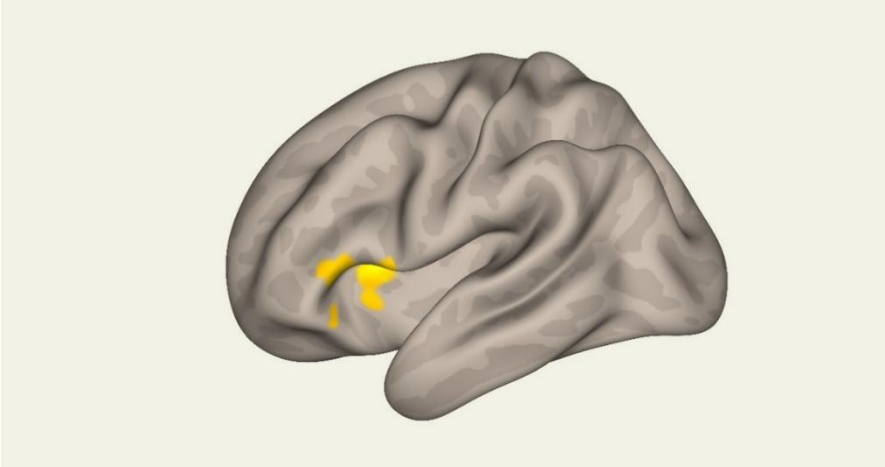


Figure 6.5. Representation of regions on the brain surface where the Sensory-Motor Network shows positive correlation with NIHSS scores



Figure 6.6. Graph displaying the effect sizes and directional trends of clustering results related to the correlation between the Sensorimotor Network and NIHSS scores.

7. Discussion

This study aims to examine the relationship between reduced activity in the default mode network (DMN) and motor decline in acute stroke patients. Following exclusion of patients with cognitive impairment based on MOCA test and NIHSS scale results, ICA analysis identified the DMN and sensorimotor network (SMN) as the most relevant networks, which were subsequently analyzed. .Correlation analyses with NIHSS scores revealed that connectivity between the DMN and both the cerebellum and precuneus decreased as NIHSS scores increased (40). In contrast, connectivity between the SMN and regions including the frontal operculum, frontal gyrus, and insular cortex increased with higher NIHSS scores. These findings provide evidence that disruption of the Default Mode Network is associated with motor impairment following stroke (41). Previous research has primarily focused on the Default Mode Network (DMN) in the context of cognitive impairments, including Parkinson's disease, Alzheimer's disease, or Mild Cognitive Impairment. Brain homeostasis relies on the harmonious activity

of resting-state networks, and any disruption to this equilibrium can lead to a functional neurological disorder (FND) (42). Notably, damage to this network hierarchy may be reversible, as rehabilitation can promote the formation of new synapses. An individual's recovery is determined not by the quantity of neurons, but by the number of synaptic connections formed (43). These new synapses arise through neuroplastic changes that drive cortical reorganization (44). Although network disruption leads to a loss of coordinated brain function, this process is not irreversible. Importantly, the number of neurons remains largely constant from birth, as nerve cells do not undergo cell division and may instead be lost through apoptosis following injury.

Studies have demonstrated that disruptions in resting-state functional connectivity are associated with impaired motor function following stroke (45). Alterations in neural motor networks and their relationship to post-stroke recovery can be explored through resting-state correlation and connectivity analyses (46). Furthermore, stroke patients with motor impairments consistently exhibit changes in interhemispheric connectivity within motor networks, suggesting a link between these alterations and motor dysfunction (47). Dysfunctional connectivity resulting from damage to the corticospinal tract may also contribute to diminished motor performance (48). Changes in resting-state functional connectivity have been linked to motor recovery after stroke, indicating that evaluating the temporal variability of brain networks may serve as a valuable tool for predicting motor recovery outcomes (49). Moreover, alterations in functional connectivity among resting-state networks have been proposed as potential biomarkers for estimating clinical outcomes in post-stroke motor function (50).

Our study identified two networks—the Default Mode Network (DMN) and the Sensorimotor Network (SMN)—as most significant in relation to NIHSS and ICA scores. Both are resting-state networks. Jiang et al. (12) used independent component analysis (ICA) to examine the integrity of the DMN in patients with brainstem ischemic stroke and risk of cognitive dysfunction. They found that, compared to healthy controls, patients with acute ischemic stroke exhibited significantly reduced functional connectivity in the right medial prefrontal cortex (mPFC) and right precuneus, as well as anterior and posterior regions of the DMN. This reduction in functional connectivity provides important clues about how damage to these brain regions may contribute to the neural mechanisms underlying cognitive decline. While our primary focus is not cognitive function, our patients had low MoCA scores, and we observed a negative correlation between NIHSS and MoCA scores. Our findings, showing altered DMN connectivity to regions associated with cognition (precuneus) and motor function (cerebellum), support the results reported by Jiang et al.

Our findings regarding the sensorimotor network (SMN) are consistent with the results of Chi et al., who observed a similar relationship between the ipsilesional primary motor cortex (M1) and the contralesional dorsal premotor area within functional motor networks in acute stroke patients. Chi et al. also demonstrated that this inter-regional connectivity is associated with prognostic outcomes (54). More recently, Salvalaggio et al. investigated the predictive value of both structural and functional networks for post-stroke behavioral outcomes (55). Direct approaches, such as structural or functional MRI, assess connectivity and its deterioration by imaging stroke patients; in contrast, indirect methods utilize functional MRI and diffusion tensor imaging data from healthy individuals to construct connectomes that represent typical functional or structural brain connections.

By mapping a patient's lesion onto these datasets, it is possible to estimate the structural and functional disconnections within the healthy connectome and thereby predict the disruptions caused by the lesion (56). Salvalaggio et al. found that basic lesion maps and indirect structural disconnection maps performed similarly, and adding indirect maps to lesion maps did not improve predictive accuracy. Indirect functional disconnection maps were weak predictors of behavioral outcomes, whereas direct measurement of functional disruption, as conducted in our study, proved significantly more effective in predicting patient behavior—further supporting our results (55).

In conclusion, stroke remains one of the leading causes of chronic disability, frequently impairing motor and sensory functions. Brain network analysis goes beyond simple disconnection mapping, and comprehensive

evaluation of lesion maps offers valuable insights for predicting stroke outcomes, making it a critical tool (56). As a non-invasive and functional neuroimaging technique, resting-state fMRI (rs-fMRI) can provide therapeutically relevant information for stroke patients by identifying both focal vascular lesions and connectivity-based reorganization, thus informing models of functional recovery and neuroplasticity (57). Our findings are consistent with and support these perspectives and results.

The limitations of this study include the small sample size, which represents a primary constraint. Additionally, the absence of a normal control group for comparison of functional networks poses another limitation. Our sample also consisted exclusively of patients with minor stroke, which may have facilitated the identification of subtle regional effects as opposed to global ones. However, this could also limit the generalizability of our findings, as compensatory mechanisms in minor stroke cases may obscure more meaningful results.

Our findings demonstrate a correlation between neurological symptoms observed during the acute phase of stroke and resting-state functional brain networks. This suggests that analysis of resting-state brain networks can provide a foundation for predicting, prognosis and tailoring rehabilitation strategies after stroke. Damage resulting from disruption in neural networks is observed as a loss of voluntary movement control, impaired communication within the musculoskeletal system, or maladaptive neuroplasticity, which is often characterized by spasticity. The strong correlation between disruption of resting - state networks and the onset of motor impairment in the acute phase of stroke aligns with findings from previous research, underscoring the importance of further investigation into the role of resting - state networks. Assessing brain networks at rest in stroke patients may improve the prediction of motor deficits and inform more effective rehabilitation strategies. Both behavioral correlations and the degree of connectivity loss between primary motor cortices are frequently used as specific biomarkers for the severity of motor impairment and the extent of corticospinal tract damage .

9. REFERENCES

1. Siegel JS, Ramsey LE, Snyder AZ, Metcalf NV, Chacko RV, Weinberger K, Baldassarre A, Hacker CD, Shulman GL, Corbetta M. (2016). Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. Proceedings of the National Academy of Sciences, 113(30), 4367-76.
2. Cheng B, Dietzmann P, Schulz R, Boenstrup M, Krawinkel L, Fiehler J, Gerloff C, Thomalla G. (2020). Cortical atrophy and transcallosal diaschisis following isolated subcortical stroke. Journal of Cerebral Blood Flow & Metabolism, 40(3), 611-621.
3. Carrera E, Tononi G. (2014) Diaschisis: past, present, future. Brain, 2408-22.
4. Fornito A, Zalesky A, Breakspear M. (2015). The connectomics of brain disorders. Nature Reviews Neuroscience, 16(3):159-72.
5. Boes AD, Prasad S, Liu H, Liu Q, Pascual-Leone A, Caviness VS Jr, Fox MD. (2015). Network localization of neurological symptoms from focal brain lesions. Brain, (10), 3061-75.
6. Yue X, Li Z, Li Y, Gao J, Han H, Zhang G, Li X, Shen Y, Wei W, Bai Y, Xie J, Luo Z, Zhang X, Wang M. (2023). Altered static and dynamic functional network connectivity in post-stroke cognitive impairment. Neuroscience Letter, 16;799.
7. Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Anderson, C. A., Arora, P., Avery, C. L., ... & American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. (2023). Heart disease and stroke statistics—2023 update: a report from the American Heart Association. Circulation, 147(8), e93-e621.
8. Third annual northwestern medicine comprehensive stroke and cerebrovascular CME conference. Breakthroughs for Physicians. (n.d.). (2022) https://breakthroughsforphysicians.nm.org/3rd-annual-nm-comprehensive-stroke-and-cerebrovascular-conference.html
9. Raghavan
10. Jiang, L., Geng, W., Chen, H., Zhang, H., Bo, F., Mao, C. N., ... & Yin, X. (2018). Decreased functional connectivity within the default-mode network in acute brainstem ischemic stroke. European journal of radiology, 105, 221-226.
11. Benjamin, E. J., Muntner, P., Alonso, A., Bittencourt, M. S., Callaway, C. W., Carson, A. P., ... & American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke

Statistics Subcommittee. (2019). Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation, 139(10), e56-e528.

12. Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. Nature reviews neuroscience, 2(10), 685-694.
13. Feeney, D. M., & Baron, J. C. (1986). Diaschisis. Stroke, 17(5), 817-830.
14. Morgan, M. (2023). Matt Morgan: The NHS needs to be less efficient. bmj, 383.
15. Schone HR, Maimon Mor RO, Kollamkulam M, Gerrand C, Woollard A, Kang NV, Baker CI, Makin TR. Stable Cortical Body Maps Before and After Arm Amputation. bioRxiv [Preprint]. 2023 Dec 14:2023.12.13.571314. doi: 10.1101/2023.12.13.571314. PMID: 38168448; PMCID: PMC10760201
16. Winship, I. R., & Murphy, T. H. (2009). Remapping the somatosensory cortex after stroke: insight from imaging the synapse to network. The Neuroscientist, 15(5), 507-524.
17. Wilson, A. D., Coleby, D., Taub, N. A., Weston, C., & Robinson, T. G. (2014). Delay between symptom onset and clinic attendance following TIA and minor stroke: the BEATS study. Age and ageing, 43(2), 253-256.
18. Sebastianelli, L., Versace, V., Martignago, S., Brigo, F., Trinka, E., Saltuari, L., & Nardone, R. (2017). Low-frequency rTMS of the unaffected hemisphere in stroke patients: A systematic review. Acta Neurologica Scandinavica, 136(6), 585-605.
19. Kwah, L. K., & Diong, J. (2014). National institutes of health stroke scale (NIHSS). Journal of physiotherapy.
20. Cheng, B., Dietzmann, P., Schulz, R., Boenstrup, M., Krawinkel, L., Fiehler, J., ... & Thomalla, G. (2020). Cortical atrophy and transcallosal diaschisis following isolated subcortical stroke. Journal of Cerebral Blood Flow & Metabolism, 40(3), 611-621.
21. Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage, 37(1), 90-101.
22. Bi, X. A., Sun, Q., Zhao, J., Xu, Q., & Wang, L. (2018). Non-linear ICA analysis of resting-state fMRI in mild cognitive impairment. Frontiers in neuroscience, 12, 413.
23. Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. Proceedings of the national academy of sciences, 103(37), 13848-13853.
24. Tong, D. C., Yenari, M. A., Albers, G. W., O'brien, M., Marks, M. P., & Moseley, M. E. (1998). Correlation of perfusion-and diffusion-weighted MRI with NIHSS score in acute (< 6.5 hour) ischemic stroke. Neurology, 50(4), 864-869.
25. Larivière, S., Ward, N. S., & Boudrias, M. H. (2018). Disrupted functional network integrity and flexibility after stroke: relation to motor impairments. NeuroImage: Clinical, 19, 883-891.

26. Rai, A. T., Link, P. S., & Domico, J. R. (2023). Updated estimates of large and medium vessel strokes, mechanical thrombectomy trends, and future projections indicate a relative flattening of the growth curve but highlight opportunities for expanding endovascular stroke care. Journal of neurointerventional surgery, 15(e3), e349-e355.
27. Liu, L., Chen, W., Zhou, H., Duan, W., Li, S., Huo, X., ... & Wang, Y. (2020). Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. Stroke and vascular neurology, 5(2).
28. Kraeutner, S. N., Rubino, C., Rinat, S., Lakhani, B., Borich, M. R., Wadden, K. P., & Boyd, L. A. (2021). Resting state connectivity is modulated by motor learning in individuals after stroke. Neurorehabilitation and Neural Repair, 35(6), 513-524.
29. Rehme, A. K., & Grefkes, C. (2013). Cerebral network disorders after stroke: Evidence from imaging-based connectivity analyses of active and resting brain states in humans. The Journal of physiology, 591(1), 17-31.
30. Zhao, Z., Wu, J., Fan, M., Yin, D., Tang, C., Gong, J., ... & Jia, J. (2018). Altered intra-and inter-network functional coupling of resting-state networks associated with motor dysfunction in stroke. Human Brain Mapping, 39(8), 3388-3397.
31. Carter, A., Patel, K., Astafiev, S., Snyder, A., Rengachary, J., Strube, M., … & Corbetta, M. (2011). Upstream dysfunction of somatomotor functional connectivity after corticospinal damage in stroke. Neurorehabilitation and Neural Repair, 26(1), 7-19.
32. Hu, J., Du, J., Xu, Q., Yang, F., Zeng, F., Weng, Y., ... & Zhang, Z. (2018). Dynamic network analysis reveals altered temporal variability in brain regions after stroke: a longitudinal resting-state fMRI study. Neural plasticity, 2018.
33. Yue, X., Li, Z., Li, Y., Gao, J., Han, H., Zhang, G., ... & Wang, M. (2023). Altered static and dynamic functional network connectivity in post-stroke cognitive impairment. Neuroscience Letters, 799, 137097.
34. Fischer, U., Arnold, M., Nedeltchev, K., Brekenfeld, C., Ballinari, P., Remonda, L., … & Mattle, H. (2005). Nihss score and arteriographic findings in acute ischemic stroke. Stroke, 36(10), 2121-2125.
35. Mistry, E. A., Yeatts, S., de Havenon, A., Mehta, T., Arora, N., De Los Rios La Rosa, F., ... & Khatri, P. (2021). Predicting 90-day outcome after thrombectomy: baseline-adjusted 24-hour NIHSS is more powerful than NIHSS score change. Stroke, 52(8), 2547-2553.
36. Mikulik, R., Ribo, M., Hill, M. D., Grotta, J. C., Malkoff, M., Molina, C., ... & Alexandrov, A. V. (2007). Accuracy of serial National Institutes of Health Stroke Scale scores to identify artery status in acute ischemic stroke. Circulation, 115(20), 2660-2665.

37. Chi, N. F., Ku, H. L., Chen, D. Y. T., Tseng, Y. C., Chen, C. J., Lin, Y. C., ... & Hu, C. J. (2018). Cerebral motor functional connectivity at the acute stage: an outcome predictor of ischemic stroke. Scientific reports, 8(1), 16803.
38. Salvalaggio, A., De Filippo De Grazia, M., Zorzi, M., Thiebaut de Schotten, M., & Corbetta, M. (2020). Post-stroke deficit prediction from lesion and indirect structural and functional disconnection. Brain, 143(7), 2173-2188.
39. Umarova, R., & Thomalla, G. (2020). Indirect connectome-based prediction of post-stroke deficits: Prospects and limitations. Brain, 143(7), 1966-1970.
40. Christidi, F., Orgianelis, I., Merkouris, E., Koutsokostas, C., Tsiptsios, D., Karavasilis, E., ... & Vadikolias, K. (2024). A Comprehensive Review on the Role of Resting-State Functional Magnetic Resonance Imaging in Predicting Post-Stroke Motor and Sensory Outcomes. Neurology International, 16(1), 189-201.
41. Ruiz Pardo AC, Minda JP. Reexamining the "brain drain" effect: A replication of Ward et al. (2017). Acta Psychol (Amst). 2022 Oct;230:103717. doi: 10.1016/j.actpsy.2022.103717. Epub 2022 Aug 22. PMID: 36007374.
42. Andersson, J. L. R., Hutton, C., Ashburner, J., Turner, R., & Friston, K. (2001). Modeling geometric deformations in EPI time series. NeuroImage, 13(5), 903–919.
43. Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage, 37(1), 90–101.
44. Bi, X. A., Sun, Q., Zhao, J., Xu, Q., & Wang, L. (2018). Non-linear ICA analysis of resting-state fMRI in mild cognitive impairment. Frontiers in Neuroscience, 12, 413.
45. Calhoun, V. D., Miller, R., Pearlson, G., & Adalı, T. (2014). The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron, 84(2), 262–274.
46. Chai, X. J., Castañón, A. N., Öngür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. NeuroImage, 59(2), 1420–1428.
47. Chumbley, J., Worsley, K., Flandin, G., & Friston, K. (2010). Topological FDR for neuroimaging. NeuroImage, 49(4), 3057–3064.
48. Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. Proceedings of the National Academy of Sciences, 103(37), 13848–13853.
49. Erhardt, E. B., Rachakonda, S., Bedrick, E. J., Allen, E. A., Adali, T., & Calhoun, V. D. (2011). Comparison of multi-subject ICA methods for analysis of fMRI data. Human Brain Mapping, 32(12), 2075–2095.
50. Friston, K. J., Ashburner, J., Frith, C. D., Poline, J. B., Heather, J. D., & Frackowiak, R. S. J. (1995). Spatial registration and normalization of images. Human Brain Mapping, 3(3), 165–189.
51. Henson, R. N. A., Buechel, C., Josephs, O., & Friston, K. J. (1999). The slice-timing problem in event-related fMRI. NeuroImage, 9(6), S125.
52. Hyvarinen, A. (1999). Fast and robust fixed-point algorithms for independent component analysis. IEEE Transactions on Neural Networks, 10(3), 626–634.
53. Nieto-Castanon, A., & Whitfield-Gabrieli, S. (2022). CONN functional connectivity toolbox: RRID SCR_009550, release 22. https://doi.org/10.56441/hilbertpress.2246.5840

54. Penny, W. D., Friston, K. J., Ashburner, J. T., Kiebel, S. J., & Nichols, T. E. (Eds.). (2011). Statistical parametric mapping: The analysis of functional brain images. Elsevier.
55. Sladky, R., Friston, K. J., Tröstl, J., Cunnington, R., Moser, E., & Windischberger, C. (2011). Slice-timing effects and their correction in functional MRI. NeuroImage, 58(2), 588–594.
56. Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connectivity, 2(3), 125–141.
57. Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. Human Brain Mapping, 4(1), 58–73.