Disruption of resting-state functional connectivity in acute ischemic stroke: comparisons between right and left hemispheric insults

Marilise Katsurayama
University of Campinas
Lucas Scárdua Silva
University of Campinas
Brunno Machado Campos
University of Campinas
Wagner Mauad Avelar
University of Campinas
Fernando Cendes
University of Campinas
Clarissa Lin Yasuda (cyasuda@unicamp.br)
University of Campinas

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Abstract

Background: Few resting-state functional magnetic resonance imaging (RS-fMRI) studies evaluated the impact of acute ischemic changes on cerebral functional connectivity (FC) and its relationship with functional outcomes after acute ischemic stroke (AIS), considering the side and size of lesions.

Objective: To characterize alterations of FC of patients with AIS by analyzing 12 large-scale brain networks (NWs) with RS-fMRI. Additionally, we evaluated the impact of side (right (RH) or left (LH) hemisphere) and size (lacunar or non-lacunar) of insult on the disruption of brain NWs.

Materials and Methods: 38 patients diagnosed with AIS (19 RH and 19 LH) who performed 3T MRI scans up to 72 hours after stroke were compared to 44 healthy controls. Images were processed and analyzed with the software toolbox UF^2C with SPM12. For the first level, we generated individual matrices based on the time series extraction from 70 regions of interest (ROIs) from 12 functional NWs, constructing Pearson's cross-correlation; the second-level analysis included an analysis of covariance (ANCOVA) to investigate differences between groups. The statistical significance was determined with $p<0.05$, after correction for multiple comparisons with false discovery rate (FDR) correction.

Results: Overall, individual with LH insults developed poorer six months clinical outcomes. A high degree of FC disruption was observed in LH insults (widespread pattern), mainly in non-lacunar lesions. Changes in FC for RH insults did not survive FDR corrections.

Conclusion: Our findings demonstrated that LH stroke causes severe FC alterations in the network topological properties, presumably related to impairment in their long-term recovery.

Introduction

Ischemic stroke is a leading worldwide cause of mortality; new perspectives on clinical intervention (implementation of stroke units, mechanical thrombectomy, and improved hypertension control) have increased the survival rate in the last years [33]. Although some predictors of the outcome of stroke have been identified (such as the National Institute of Health Score Scale [NIHSS][29], such as infarct characteristics [29], age, uncontrolled hypertension[30], hyperglycemia and inflammation)[44] the relationship between lateralization and the functional outcome is still unclear. Until now, some of the studies considered the right hemisphere (RH) lesion had a more unsatisfactory evolution when compared to the left-sided. Given cerebral hemispheric asymmetry and specific functions on each side, clinical changes in the presence of cortical dysfunction can influence rehabilitation and outcome differently. Aphasia from the left hemisphere (LH) stroke and hemispatial or unilateral neglect in RH stroke can result in structural and functional alterations involving ipsilateral and contralateral brain regions [32,43].

Recently, resting-state functional magnetic resonance imaging (rs-fMRI) has been widely used to investigate brain connectivity. It provides information about the functional integrity of brain networks (NWs) [12] characterized by a pairwise temporal integration between brain regions promoting integrative information processing, being a practical approach to detecting Functional Connectivity (FC) alterations after stroke [12]. This technique can examine brain connectivity without subjecting individuals to cognitive tasks [5]; this fundamental characteristic has facilitated the design of studies for patients in various clinical conditions [11,18].

Some rs-fMRI studies performed during the chronic phase of the stroke have been applied to estimate functional impairment and predict recovery in stroke survivors [22,46]. Unfortunately, few rs-fMRI have been conducted during the acute stage [20], providing little evidence of whether the dysfunction between local and remote cortical regions can start during this period and follows a distinct pattern in AIS patients [10,40]. While intuitively, we hypothesize that larger infarcts associate with severe FC disruption, it is unclear what is the impact of the side of ischemic insult on FC.

Dynamic changes of FC have been reported according to the stroke evolution: in the acute phase of stroke (less than 24 hours), the FC between bilateral motor cortices decreases; in other stages (between 7 and 90 days after stroke, when motor function start to recover), the FC increases reaching near normality [20]. These data are similar to a previous RS fMRI study, which included mild-to-moderate motor deficits in the subacute phase (up to four weeks since stroke) [7]. On the other hand, Puig [40] scanned patients on day three after stroke onset. Using an ROI-Based analysis, they showed that the severely injured brain presented decreased interhemispheric connectivity associated with an increase of ipsilateral FC, involving cortico-subcortical connections and crossed connections (right and left cerebellum). One recent study [6] demonstrated that severely stroke patients (scanned in the first two weeks from stroke onset) had significantly reduced connectivity between cortical sensorimotor components, suggesting that severe injury may promote excessive disruption of cortical motor areas. In contrast (and contrary to expectation), moderately affected patients presented more remarkable alterations of FC [6].

Due to la ack of studies about rs-fMRI in the acute stage of AIS, we investigated the impact of an early brain insult on acute resting state Functional Connectivity and the relationship with the late functional outcome. For more detailed analyses, we separately evaluated the effects of side and size lesions on the disruption of 12 large-scale brain resting-state networks.

Materials And Methods

Subjects

We recruited a total of 50 consecutive subjects with acute ischemic stroke (25 women, median of 63 years, range [33–96]) evaluated at the Emergency Department of the University of Campinas who performed a 3T MRI protocol (detailed below) including RS-fMRI scan (with 3D-T1-weighted) up to 72 hours after the stroke event, between March 2017 and May 2019. We had to exclude 12 individuals due to movement artifacts during MRI acquisition. The comparisons of clinical characteristics between groups of included and excluded subjects are presented in Supplemental table 1. Inclusion criteria included:

aged > 18 years, admitted in the acute stage (less than 72 hours) with an anterior circulation stroke, presenting a single new lesion in the structural MRI. We excluded patients with contraindications to MRI (pacemakers, metallic prostheses, or claustrophobia), psychiatric disorders, cognitive impairment, previous chronic infarction, and other neurological disorders. Some ischemic stroke (IS) factors were also considered exclusion criteria, such as acute posterior circulation stroke, wake-up stroke (or ischemic event with more than 72h), non-collaborative patients, and those who refused to participate. The clinical characteristics of the 38 included subjects (21 women; median of 63 years, range [33–89]) are described in Table 1. They were divided into two groups according to the affected hemisphere (Right Hemisphere, RH = 19; Left Hemisphere, LH = 19) and compared to 44 controls (never presented stroke, other neurological or psychiatric dysfunction) (22 women; the median age of 61 years, range [50–80]); patients and controls were balanced for age (p = 0.4) and sex (p = 0.8). The group of controls included individuals with known risk factors for acute ischemic stroke; however, we could not obtain information about associated risk factors from 12 subjects in this group.

After classifying the patients according to Trial of Org 10172 in Acute Stroke Treatment (TOAST)[1], we separated them into two groups: Lacunar (deep and small infarcts most involving basal ganglia or other white matter region supplied by penetrating arteries, not measuring more than 15mm)[1], and Non-Lacunar AIS (larger lesions resulting from cardioembolic etiology, large artery atherosclerosis and other causes)[1]. As we considered separately the side of the lesion (left and right), we had four groups: Lacunar (left and right) and non-Lacunar (left and right). With these groups, we analyzed both the effect of lateralization and the lesion size.

We registered demographic data from all patients (including sex, age, and comorbidities) and stroke data (age at onset, etiologic classification, and functionality measures [Rankin Score]). Additionally, after six months from the acute event, we applied the modified Rankin Scale (mRS, a measurement of recovery of motor function after stroke), which comprehends seven levels covering functional outcomes from ‘no symptoms = 0’ to ‘death = 6’, assessing the effectiveness and ineffectiveness of acute stroke therapies. [23]

Ethics Approval

The Research Ethics Committee of the University of Campinas previously approved this study (Certificate of Ethical Appreciation Presentation - CAAE 68052316.4.0000.5404), and we obtained written informed consent from all subjects or families.

MRI Acquisition

All images were acquired at the University of Campinas’ Clinical Hospital using a 3T Philips Achieva MRI scanner, including two image protocols:

The *Neurovascular Protocol* includes volumetric/structural acquisitions in T1, T2, FLAIR, SWI, DWI, ADC, and Magnetic Resonance Angiography (MRA) with “*time of flight*” (TOF). The parameters were: three-dimensional T1 weighted turbo field echo images (WI) (180 slices, 1 mm^3 isotropic voxels, acquired on the sagittal plane, 1mm thickness, flip angle = 8^o, TR = 7.1ms, echo time (TE) 3.2 milliseconds, matrix = 240 × 240, field of view (FOV) = 240 × 240); T2 weighted image (1.5 mm^3 isotropic voxels, 180 axial slices, no gap, TR = 1.8ms, TE = 340ms, FOV = 230 × 230mm^2); fluid-attenuated inversion recovery (FLAIR) image (voxel size = 1.2 × 1.2 × 0.6mm^3, FOV = 250 × 250 mm^2, TE = 276ms, TR = 4.8ms, TI = 1.650ms) [42]. Additionally, we applied a *resting-state protocol* acquired with echo-planar imaging sequence, with isotropic voxels of 27mm^3, on axial plane, with 40 axial slices, no gap, TR = 2 seconds, TE = 30 milliseconds, flip angle = 90^o, resulting in 180 dynamics in a 6 minutes scan with FOV = 240x240 mm^2 [14]. Patients were instructed to rest with closed eyes, not think about anything in particular, and not fall asleep. Subjects were not sedated and did not receive contrast [18].

Image Preprocessing and Analysis

Images were analyzed with the software toolbox (UF^2C, http://www.lniunicamp.com/uf2c/) running on MATLAB (2019b, The MathWorks, Inc. USA) with SPM12 (www.fil.ion.ucl.ac.uk/MATLAB2019b)[3]. The protocol includes the following steps of pre-processing according to UF^2C standard protocol[14].

All images were pre-processed according to the standard UF^2C toolbox pipeline [14], based on dynamic realignments of fMRI images, spatial normalization to the MNI- space (Montreal Neurologic Institute Standard template), co-registration of fMRI mean image with volumetric T1-weighted image of each subject, framewise displacement (FD) estimation, and smoothing with 6x6x6 mm^3 (FWHM) smoothing kernel. Besides, the structural images were segmented in different tissues (grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF)), and normalized to the MNI space. The segmented GM maps were interpolated to match the functional images and used to mask the analysis, removing non-GM regions. We also regressed for six head movement parameters (three rotational and three translational), censoring vectors (framewise displacement (FD) > 0.5mm), and the average of the cerebrospinal fluid and white matter signals. Furthermore, we detrended (removed linear trends) the time series and filtered them with band-pass (0.008-0.1 Hz) [13].

We performed an exploratory investigation of functional connectivity (FC) dysfunction in the acute stage of ischemic stroke, including 12 functional resting-state networks (Anterior and Posterior Salience, Basal Ganglia, Dorsal and Ventral Default Mode, Left and Right Executive Control Network, Auditory, Visual, Language, Sensorimotor and Visuospatial/Dorsal Attention). These 70 ROIs (regions of interest) were selected to evaluate FC in widespread brain areas, considering relevant functional NWs.[3,14].

Statistical Analysis

Demographic group variables and stroke specificities were analyzed with SPSS23. We used Chi-Square tests to analyze categorical variables (sex, co-morbidities, and stroke specificities) and Mann-Whitney tests to compare continuous variables with non-normal distribution (Table 1).

The statistical analyses of functional connectivity were performed with the UF^2C toolbox[14], which allowed the analysis of resting-state parameters in two levels: at the first level, individual matrices were generated based on the extraction of time series from the 70 ROIs. These time series were used for constructing Pearson's Cross-Correlation matrices; in other words, every pair of ROIs (ROI-ROI analysis) were included in the connectivity matrix of each subject and converted to z-score using Fisher z-transformation. The second-level analyses were performed with comparisons between patients and controls (group comparisons of ROI-to-ROI FC), using analysis of covariance (ANCOVA) tests with age and sex as covariates. Statistical significance was determined with $p < 0.05$, corrected for multiple comparisons using FDR (False Discovery Rate) procedure.[4]

Results

Demographic and Clinical Data

Thirty-eight patients (19 RH-AIS and 19 LH-AIS) were included and compared to forty-four controls without previous AIS. The three groups were balanced in terms of age, sex, and co-morbidities, as seen in Table 1.

Table 1
Demographic and Clinical Data from Patients and Controls

Data	RH Stroke (19)	LH Stroke (19)	Controls* (44)	P-value
Male/Female	9 /10	8 /11	22 /22	0.85
Median Age (range) 95% CI [lower-upper limits]	63 (33–89) [54–73]	63 (46–85) [51–81]	61 (50–80) [60–63]	0.69
Hypertension (yes/no)	12/7	12 /7	18/14	0.84
Smoking (yes/no)	4 /15	5 /14	2/30	0.12
Atrial Fibrillation (yes/no)	3 /16	1 /18	2/30	0.42
Diabetes (yes/no)	7 /12	8 /11	6/26	0.16
Hyperlipidemia (yes/no)	8 /11	9 /12	8/24	0.22
Data presented as median (range); CI: confidence interval *We were unable to recover information about comorbidities for 12 volunteers				

Stroke Data

Information about the stroke was collected through medical records, and structural MRIs were visually inspected by a neurovascular physician (to determine the classification of the stroke -lacunar or non-lacunar); telephone contact was performed after six months (to classify the outcome). All stroke data (size, treatment, and outcome) is exposed in Table 2.

Table 2
Stroke Data

	RH Stroke (19)	LH Stroke (19)	P-value
Non-lacunar/Lacunar	9 /10	13 /6	0.32
NIHSS at admission Median (range) 95% CI [lower-upper limits]	8 (1–23) [6–14]	10 (3–20) [6–16]	0.56
Treated with rTPA (yes/no)	7/12	8/11	1
Modified Rankin after 6 months Median (range) 95% CI [lower-upper limits]	1 (0–5) [0–1]	3 (0–6) [1–5]	0.006
0–2(Good Outcome)/3–6(Poor Outcome)	17 / 2	8 / 11	0.006
RH: right hemisphere; LH: left hemisphere; CI: confidence interval			

Although the size of stroke (lacunar/non-lacunar, $p = 0.32$) and proportion of thrombolysis ($p = 1$) were balanced between RH and LH groups, the two groups (LH/RH) differ in terms of the outcome. While 58% (n = 11) of the LH-AIS group presented a poor outcome (considering mRs 3 to 6), only 11% (n = 2) of the RH-AIS group evolved with a poor outcome ($p = 0.006$). The separate analysis clarified that the poor outcome in the LH group was most related to individuals with non-lacunar lesions. Figure 1.

Functional connectivity analysis

We initially performed the analysis based on the side of the stroke. Subsequently, we investigated each group (LH and RH) according to the size of the stroke lesion.
1) According to the side of the stroke (RH/LH):

While the whole LH-AIS exhibited bilateral and widespread abnormal interactions among all 12 networks (including executive control, salience, basal-ganglia, and others) ($p < 0.05$, FDR corrected) (Fig. 2A, Supplemental tables 2 and 3), the alterations in the RH-AIS group (compared to controls) did not survive correction for multiple comparisons (Supplemental Fig. 1A).

2) Analyses according to the type of lesion (Lacunar or Non-lacunar) and side (RH/LH):

After the primary analyses, we performed additional tests to disentangle the interaction between size (Lacunar × Non-Lacunar Lesions) and side (RH × LH) since we suspected non-lacunar lesions could result in a widespread pattern of FC disruption.

The LH-AIS group presented significant abnormalities in both the lacunar and non-lacunar subgroups. While the Non-lacunar subgroup exhibited a bilateral and widespread abnormal FC pattern, disrupted intra and interhemispheric interactions among all 12 NWs (including executive control, salience, basal-ganglia, and others) (Fig. 2B, Supplemental Tables 2 and 4), the Lacunar subgroup presented decreased FC in four RS NWs (Anterior and Posterior Salience, Right and Left ECN) (Fig. 2C, Supplemental tables 2 and 5) ($p < 0.05$, corrected with FDR).

The analyses of the RH-AIS group according to the size did not survive the correction for multiple comparisons, consistent with the findings of the whole group analysis. These results are displayed in Supplemental Figs. 1B and C.

Discussion

In our sample, considering the homogeneity of clinical factors between the two groups (patients and controls), we observed a high degree of FC disruption associated with a poor outcome when the lesion is on the left hemisphere, displaying a bilateral and widespread pattern of FC disruption proportional to the lesion size. Given the higher number of patients with extensive injuries on the left side, we decided to proceed with a counterproof by subdividing them according to the side and size of the lesion (Lacunar Right and Left, Non-Lacunar Right and Left). These sub-analyses confirmed the importance of laterality in the FC disruption in the acute phase of stroke, being the degree of disturbance proportional to the lesion's size.

Many fMRI studies have been performed in the scope of rehabilitation, involving the FC on chronic stroke patients´ recovery. Most of these investigated the complex process related to cerebral structural and functional reorganization.[34,39,41,46,47] However, fewer evaluated the impact of lateralization and type of lesion in the FC of the stroke´s hyperacute phase. Lately, RS-fMRI studies with stroke patients demonstrated disturbances in interhemispheric connectivity.[7,20] Previous studies identified a correlation between severe motor symptoms and a significant reduction of connectivity between cortical sensorimotor components. Thus, interhemispheric connectivity in stroke patients is considered an important indicator of recovery [41,46]. Meanwhile, the majority included patients in the subacute phase[6,8] and chronic phase [26,36,45]; the few which enrolled patients in the hyperacute phase evaluated FC related to prognosis[10,40] and reperfusion treatment.[9], without emphasizing the role of the side of ischemic insult.

There is no consensus in the literature about which hemisphere affected by stroke is related to the worst outcome, and evidence is still inconclusive. A series of studies investigate laterality influence (addressing specific symptoms of each hemisphere, such as hemispatial neglect and aphasia, in addition to NIHSS) on the outcome and motor recovery of these patients, without homogeneous results, possibly due to the heterogeneity of the population.[17,19,28,43]

Considering both RH and LH were balanced for pre-stroke comorbidities, we inferred that the disruption of FC was associated with the poor outcome (58%) in the LH-AIS group compared to the RH-AIS outcome (11%). Although we do not have complete explanations for such findings, we speculate that differences may be partially explained by the relation between inter and intra-hemisphere connectivity and brain reorganization in post-stroke patients [21,37]. LH stroke has been described in the literature as more frequent and more severe (based on higher NIHSS scores on admission and more severe neurological deficits) [16,24] with a worse outcome (and higher mortality) [24,32]. It is mainly justified by the incidence of large vessel ischemic stroke in the territory of the left middle cerebral artery [24] and the symptom of aphasia related negatively to the outcome [32]. In contrast, some authors considered the right-sided hemisphere insult had a more unsatisfactory outcome when compared to left-sided. There may be some role of unilateral neglect on functional recovery and the time when the patient arrives at the hospital (later than left-sided stroke), which delays the start of treatment[16,17,35].

After subdividing the groups according to the type/size of stroke (Lacunar RH and LH-AIS and Non-lacunar RH and LH-AIS), we demonstrated that the left hemisphere lesion yields a more severe pattern of FC disruption, proportionally to the size of the lesion. Given that our samples' Left side Stroke presented a worse outcome, we speculate a possible relationship between the initial disruption and poor long-term outcome. There is clear evidence of structural and functional brain asymmetry since fetal stages, sedimented later by language acquisition [25]; additionally, a higher number of large pyramidal cells are localized in language regions on the left side [27]. One study with children up to two years suggested that the LH has a higher metabolic demand which may leave this hemisphere more vulnerable to reduced blood flow; this demand may eventually impact poststroke neuroplasticity (in adults)[2]. We speculate that the dominant LH (for language and handedness) is metabolically demanding, presents more bilateral stronger connections, and is, therefore, more susceptible to insults that cause widespread disruption of functional connectivity.

Contrary to some studies [15,38], our results showed that the lacunar stroke infarct was not always correlated to a better outcome compared to infarcts involving the main territory. In other words, lacunar lesions located in the LH were also related to significant disruption of functional connectivity. The importance of lesion in the LH has been investigated, and some studies reported aphasia – an impairment of language comprehension and expression (a major consequence of an LH lesion) – as an independent factor associated with functional status, increased length of hospital stay, and complication during acute stroke admission [31].

Some limitations should be considered when interpreting the results. First, it is a cross-sectional study that can only provide preliminary evidence and not the relationship's causality. Second, our sample size was relatively small, considering the difficulties of performing MRI scans in a clinical emergency setup. Some patients could not perform MRIs within our time window due to the need for critical assistance (medications in continuous infusion or frame instability). Third, the ROI-ROI approach gives us a hypothesis-based investigation of brain areas but determines a statistical correction for the multiplicity of comparisons that may reject more minor effects (true positives). Finally, considering our small sample size, the requirements for a robust statistical analysis may have underpowered our comparison.

Conclusion

The abnormalities in the network connectivity presented in the LH group can imply that LH stroke causes alterations in the whole brain's networks' topological properties, presumably related to impairment in their recovery. Rs-fMRI emerges as a promising tool in the AIS scenario as it can be used in a wide range of patients with different levels of cognitive capability or dysfunction since it does not require the ability to perform a particular task. Further studies with larger samples may contribute to better understand the physiopathology of the impact of ischemic insult on brain connectivity and eventually provide biomarkers related to future diagnostic and therapeutic strategies for an individualized rehabilitation plan.

Abbreviations

Acute Ischemic Stroke (AIS); Functional Resonance Magnetic Imaging (fMRI); Resting State (RS).

Declarations

Author Contribution

1. Study concept and design: CLY, MK, FC, WMA
2. acquisition of data: MK, BMC, WMA
3. analysis and interpretation: MK, CLY, LSS, FC, WMA, BMC
4. critical revision of the manuscript for important intellectual content: MK, CLY, LSS, FC, WMA, BMC
5. study supervision CLY

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Data availability: data collected and analyzed for this study will be available at the university database and will be available upon reasonable request.

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Figures

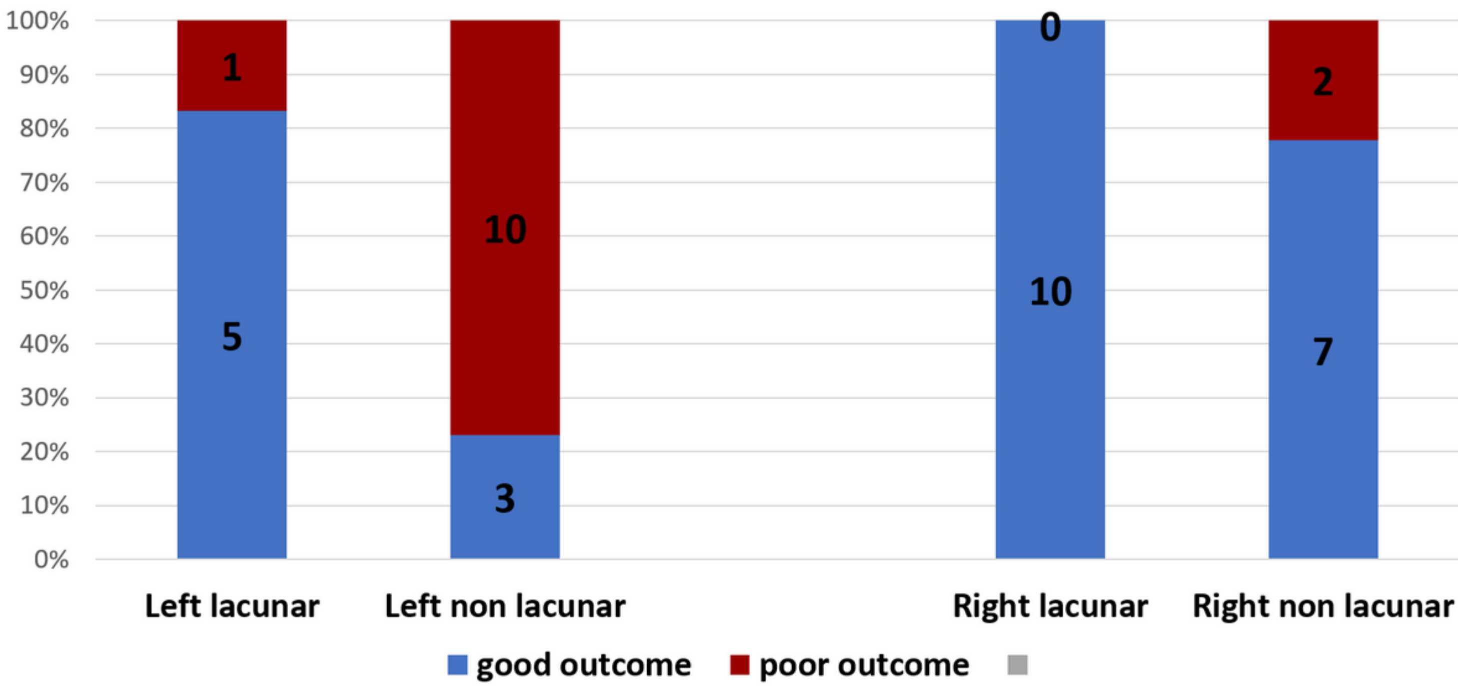

Figure 1

Stroke Outcome (6 months) based on the side and size of the stroke lesion.

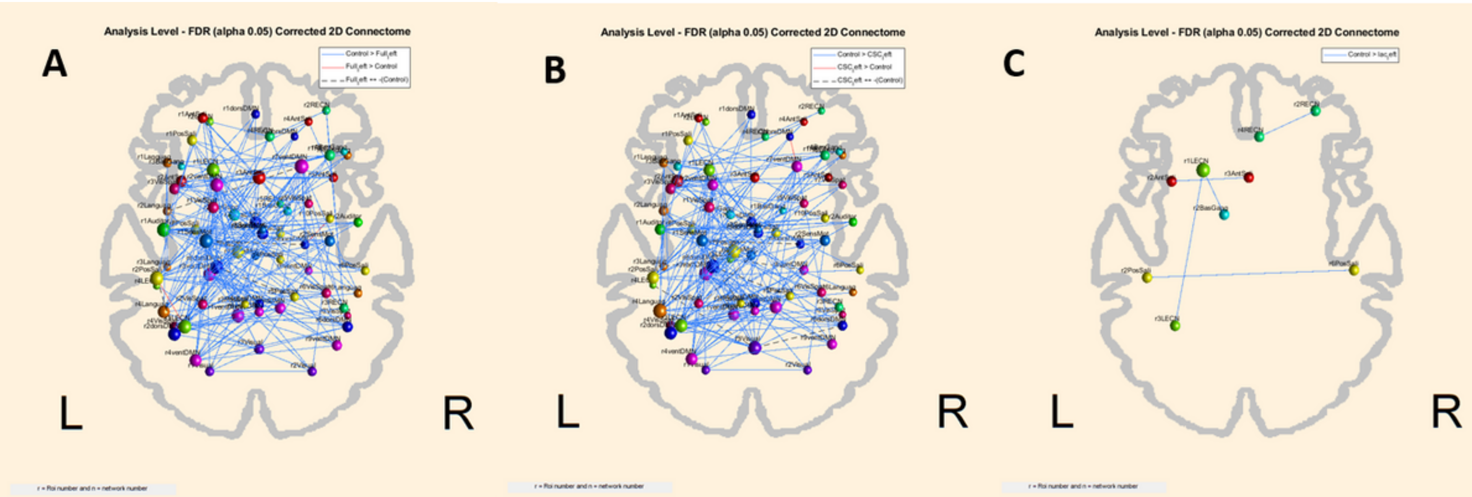

Figure 2

Abnormalities of FC in the LH-AIS group, according to size of insult.

A) Whole group; B) non-Lacunar; C) lacunar

Results are corrected for multiple comparisons with FDR (p<0.05)

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