Subacute functional connectivity correlates with cognitive recovery six months after stroke

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ABSTRACT

Background and purpose: Cognitive impairment is a common consequence of stroke, and the rewiring of the surviving brain circuits might contribute to cognitive recovery. Studies investigating how the functional connectivity of networks change across time and whether their remapping relates to cognitive recovery in stroke patients are scarce. We aimed to investigate whether resting-state functional connectivity was associated with cognitive performance in stroke patients and if any alterations in these networks were correlated with cognitive recovery.

Methods: Using an fMRI ROI-ROI approach, we compared the ipsilesional, contralesional and interhemispheric functional connectivity of three resting-state networks involved in cognition – the Default Mode (DMN), Salience (SN) and Central Executive Networks (CEN), in subacute ischemic stroke patients (time 1, n = 37, stroke onset: 24.32 ± 7.44 days, NIHSS: 2.66 ± 3.45) with cognitively healthy controls (n = 20). Patients were reassessed six months after the stroke event (time 2, n = 20, stroke onset: 182.05 ± 8.17 days) to verify the subsequent reorganization of functional connections and whether such reorganization was associated with cognitive recovery.

Results: At time 1, patients had weaker interhemispheric connectivity in the DMN than controls; better cognitive performance at time 1 was associated with stronger interhemispheric and ipsilesional DMN connectivity, and weaker contralesional SN connectivity. At time 2, there were no changes in functional connectivity in stroke patients, compared to time 1. Better cognitive recovery measured at time 2 (time 2 – time 1) was associated with stronger functional connectivity in the DMN, and weaker interhemispheric subacute connectivity in the SN, both from time 1.

Conclusions: Stroke disrupts the functional connectivity of the DMN, not only at the lesioned hemisphere but also between hemispheres. Six months after the stroke event, we could not detect the remapping of networks. Cognitive recovery was associated with the connectivity of both the DMN and SN of time 1. Our findings may be helpful for facilitating further understanding of the potential mechanisms underlying post-stroke cognitive performance.

1. Introduction

Worldwide, cerebrovascular accidents (stroke) are the second leading cause of death and the third leading cause of disability (WHO, 2012). Cognitive impairment after stroke is a frequent but neglected consequence compared to other neurological deficits such as sensory or motor impairment (Jacova et al., 2012). Although not all strokes result in cognitive impairment, it significantly increases the risk of dementia (Pendlebury, 2009; Pendlebury and Rothwell, 2009). Memory, visuo-constructional and executive functions are the most commonly impaired domains (Jokinen et al., 2015) and even mild cognitive deficits can affect patients’ quality of life, independent functioning and occupational abilities.

The risk of post-stroke cognitive impairment and subsequent

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recovery has been related to demographic factors such as age and previous cognitive performance/education (del Ser et al., 2005; Patel et al., 2003; Tham et al., 2002). Although the underlying biological mechanism of cognitive recuperation following stroke events is not well understood, animal studies have shown that vascular repair (Horie et al., 2011), structural plasticity (Carmichael, 2006) as well as angiogenesis and neurogenesis (Chopp et al., 2007) have been reported as crucial factors. In addition, lesions caused by a stroke event go beyond those in focal regions, but entire brain networks might get disrupted (Jiang et al., 2018; Rehme and Greknes, 2013). Previous research, for example, has shown acute (Jiang et al., 2018) and chronic disruptions (Dacosta-Aguayo et al., 2015; Tuladhar et al., 2013) in the Default Mode Network (DMN) and other resting-state networks (Wang et al., 2014) after a stroke event. In this context, the rewiring of the surviving brain circuits can also contribute and predict cognitive recovery after stroke (Carter et al., 2010, 2012; Dacosta-Aguayo et al., 2014b; Ding et al., 2014; Puig et al., 2018; Siegel et al., 2016). The DMN, Salience Network (SN) and Central Executive Network (CEN) are functional networks involved in the cognitive processing, presenting antagonistic roles depending on the cognitive task (Jilka et al., 2014).

Studies investigating how the functional connectivity of networks change across time and whether their remapping relates to cognitive recovery in stroke patients are scarce (Crofts et al., 2020). Here, our cognitive task (Jilka et al., 2014). We ensured written consent to participate in the study. We excluded young adults (45 years old), since stroke epidemiology for ictus occurrence may vary and potentially be a research bias (Griffiths and Sturm, 2011), and those much older than 80 years old, due to greater chances of accelerated brain atrophy (Peters, 2006). Neuropsychological testing and MRI were acquired during the first-month post-stroke (subacute phase, 

2. Material and methods

2.1. Subjects

After approval by the local Ethics Committee, we recruited Brazilian participants at the emergency unit of the Hospital of Clinics of the University of Campinas (UNICAMP) personally or by phone contact. Patients who experienced their first unilateral ischemic stroke provided written consent to participate in the study. We excluded young adults (<45 years old), since stroke epidemiology for ictus occurrence may vary and potentially be a research bias (Griffiths and Sturm, 2011), and those much older than 80 years old, due to greater chances of accelerated brain atrophy (Peters, 2006). Neuropsychological testing and MRI were acquired during the first-month post-stroke (subacute phase, time1) and six months after the ictus (chronic phase, time2). We excluded patients with severe aphasia/dysarthria, previous neurologic disorder, and any contraindications to submit to an MRI exam. The cognitively healthy control group underwent the same MRI scanning session as the stroke patients, but only once. Controls were excluded if they presented any neurological disorders. All structural images were visually inspected for abnormalities. Demographic and clinical information can be found in Table 1.

2.2. Stroke lesion assessment

A stroke neurologist (L.V.), blinded to the demographic and clinical results, assessed stroke lesion characteristics through T1-, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted images. Fazekas scale (Fazekas et al., 1987) in T2 and FLAIR images were evaluated to confirm white matter lesion. The laterality and location of the lesion were determined for each patient. The latter was used to exclude participants from the study if their lesion overlapped with any ROI of a given network (exclusions based on this criterion were pairwise, i.e., patients could be excluded from the analysis of one network but are included for the others).

2.3. Clinical assessment

Stroke severity assessment, using the National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989) was applied by a physiotherapist (S.R.A.). Barthel index (Mahoney and Barthel, 1965), Beck Depression Inventory (Beck et al., 1961), Beck Anxiety Inventory (Beck and Ward, 1961), and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) were evaluated by a neuropsychologist (J.E.V.).

2.4. MRI data acquisition

MRI acquisition was performed in a 3 T scanner (Philips Achieva®, Best, Netherlands) on the same day of clinical assessment. The acquisition protocol included a 3D T1-weighted images (WI) (isotropic voxels of 1 mm3, acquired in the sagittal plane; 1-mm thick, flip angle = 8°, repetition time (TR) = 7 ms, echo time (TE) = 3.2 ms, matrix = 240 × 240 × 240 FOV = 240 × 240 × 180 mm3); a 3D T2-WI (isotropic voxels of 1.5 mm3, reconstructed with 0.96 × 0.96 × 1.5 mm3, TR = 1800 ms, TE = 340 ms, FOV = 230 × 230 × 180 mm3, number of sampling averages (NSA) = 2); a 3D FLAIR (voxel size = 1.2 × 1.2 × 0.6 mm3, reconstructed with 0.58 × 0.58 × 0.6 mm3 TR/inversion time (TI) = 4800/1650 ms, TE = 276 ms, FOV = 250 × 250 × 190 mm3, NSA = 2); a diffusion WI (voxel size = 1.2 × 1.2 × 0.4 mm3, reconstructed with 0.9 × 0.9 × 4 mm3, TR = 3486 ms, TE = 71 ms, FOV = 230 × 230 × 139 mm3); and an echo-planar imaging (EPI) functional acquisition (isotropic voxel of 3x3x3 mm3, 39 slices, no gap, FOV = 240 × 240 × 117 mm3, flip angle = 90°, TR = 2 s, TE = 30 ms and 180 dynamics). During the resting state protocol, patients were instructed to keep their eyes closed, relax, not to move, and not to fall asleep.

2.5. MRI data analysis

To improve the statistical power, MRI datasets from 16 patients with lesions on the left hemisphere were flipped along the midsagittal line (so for all patients the left side corresponded to the contralesional hemisphere, and the right side corresponded to the ipsilesional hemisphere). We performed image preprocessing and analysis using UF-C (version 7.3beta, www.lnionicamp.com/uf2c) (de Campos et al., 2016), an
SPM12-based toolbox that runs within Matlab (version 2019b, The MathWorks, Inc., Natick, Massachusetts, United States). The UF2C pre-processing pipeline was based on fMRIs realignment, images coregistration (fMRI mean image and T1-WI), T1-WI tissue segmentation and normalization (MNI-152), fMRIs spatial normalization (MNI-152) and smoothing (Gaussian kernel of $6 \times 6 \times 6$ mm$^3$ at FWHM). At this point, fMRI datasets were visually inspected for any normalization abnormalities related to the impact of damaged stroke tissue. Then, fMRIs were regressed to the 6 head motion parameters and to the 3 principal components of the cerebrospinal fluid and white matter time series aiming to control for noise arising from physiological signals. Additionally, functional images were band-pass filtered to the 0.008–0.1 Hz interval. Finally, fMRI volumes were ranked based on their framewise displacement and derivative variance and removed if they exceeded UF2C suggested thresholds (0.75 mm and 7.5%, respectively, UF2C NoVolEx procedure) (de Campos et al., 2020). The number of volumes removed was forced to be the same for all participants and was determined by the worst dataset (final number of included volumes = 156).

A total of 18 ROIs were used to extract the average time-series: 7 from the DMN, 5 from the SN, and 6 from the CEN (FINDLab; http://findlab.stanford.edu/functional_ROIs.html) (Shirer et al., 2011) (Fig. 1, Table 2). We calculated Pearson’s correlation coefficient for every pair of ROIs (ROI-ROI analysis) to create the functional connectivity matrices of all subjects. Subsequently, the correlation values were converted to z-score using Fisher z-transformation. Finally, ROI pairs were divided into three groups: ROI pairs on the ipsilesional side, ROI pairs on the contralesional side, and interhemispheric/medial ROI pairs. All imaging results were statistically significant when $p < 0.05$, False Discovery Rate corrected for multiplicity.

2.6. Statistical analysis

Normality of the data was verified with the Shapiro-Wilk test and parametric or non-parametric tests were performed accordingly. Two sample t-test, Chi-Square, and Mann–Whitney U test were used to

![Fig. 1. Selected regions of interest (ROIs) for the A) Default Mode Network, B) Central Executive Network and C) Salience Network (MNI coordinates). Figure rendered with MRicroGL (https://www.mccauslandcenter.sc.edu/mricrogl/home).](image_url)
### Table 2
Regions of interest (ROIs) used for functional connectivity analysis.

| Network         | ROI     | Hemisphere (after image flipping) | Approximate anatomic location | size (voxels) |
|-----------------|---------|-----------------------------------|------------------------------|--------------|
| Salience Network* | SN 1    | Contralesional                    | Left middle frontal gyrus    | 651          |
|                 | SN 2    | Contralesional                    | Left insula                  | 305          |
|                 | SN 3    | Medial                            | Anterior cingulate cortex, medial prefrontal cortex | 2887          |
|                 | SN 4    | Ipsilesional                      | Right middle frontal gyrus   | 470          |
|                 | SN 5    | Ipsilesional                      | Right insula                 | 319          |
| Default Mode Network* | DMN 1   | Medial                            | Medial prefrontal cortex, anterior cingulate cortex | 5257          |
|                 | DMN 2   | Medial                            | Posterior cingulate cortex, precuneus | 1555          |
|                 | DMN 3   | Contralesional                    | Left parahippocampal gyrus   | 134          |
|                 | DMN 4   | Contralesional                    | Left middle occipital gyrus, angular gyrus | 491          |
|                 | DMN 5   | Medial                            | Precuneus                    | 1921         |
|                 | DMN 6   | Ipsilesional                      | Right parahippocampal gyrus  | 90           |
|                 | DMN 7   | Ipsilesional                      | Right middle occipital gyrus, angular gyrus | 752          |
| Central Executive Network* | EN 1    | Contralesional                    | Left middle frontal gyrus, superior frontal gyrus | 1501          |
|                 | EN 2    | Contralesional                    | Left inferior frontal gyrus   | 437          |
|                 | EN 3    | Contralesional                    | Left angular gyrus           | 2110         |
|                 | EN 4    | Ipsilesional                      | Right middle frontal gyrus, superior frontal gyrus | 2093          |
|                 | EN 5    | Ipsilesional                      | Right inferior frontal gyrus  | 356          |
|                 | EN 6    | Ipsilesional                      | Right angular gyrus          | 1873         |

*These regions belong to the following networks from the FINDLab website ([http://findlab.stanford.edu/functional_ROIs.html](http://findlab.stanford.edu/functional_ROIs.html)): Anterior and Posterior Salience, Dorsal and Ventral Default Mode, and Left and Right Executive networks. DMN = Default Mode Network; SN = Salience Network; CEN = Central Executive Network.

### 3. Results

#### 3.1. Clinical and demographic data

The stroke group presented a median of 2 days (interquartile range: 1–2) in-hospital length stay. Anterior circulation stroke was found in most of the sample and neurological deficit measured by NIHSS at the subacute stage (median: 5, interquartile range: 2–8). The degree of microangiopathy on the Fazekas scale had a median of 2, interquartile range: 1.25–3. Stroke lesions were found in cortical region (64.9%) in the frontal (n = 10), parietal (n = 8), temporal (n = 5) and insular (n = 1) lobes; in subcortical region (29.7%) in the basal nuclei (n = 1) and corona radiata (n = 10); and in brainstem (5.4%) in the midbrain (n = 1) and pons (n = 1).

For the cross-sectional study, the cognitively healthy control group did not differ from patients in age, years of education, or sex. According to the parameters that MoCA scores ≤25 indicate cognitive impairment ([Cecato et al., 2014; Ciesielska et al., 2016]), all participants met the criteria for this condition at time 1. Patients presented significant cognitive improvement at time 2 (ΔMoCA), in which 15 out of 20 patients had improved scores. No significant differences were found between time 1 and time 2 for Barthel index, Beck Depression Inventory and Beck Anxiety Inventory scores (Table 1).

#### 3.2. Functional connectivity and cognition at subacute stroke (time 1)

After visual inspection for overlapping lesion tissue with the network ROIs, we finished with 37 subjects in the DMN analysis (flipped images = 16), 32 in the CEN (flipped images = 15), and 31 in the SN (flipped images = 15). The stroke group showed weaker interhemispheric DMN functional connectivity between right middle occipital gyrus and left middle occipital gyrus when compared to cognitively healthy controls (p = 0.028, FDR-corrected). We found a positive correlation between MoCA scores and interhemispheric DMN functional connectivity (between left middle occipital gyrus and right middle occipital gyrus), and a positive correlation between ipsilesional DMN connectivity and MoCA scores (between posterior cingulate cortex and right middle occipital gyrus). CONTRALESIONAL SN functional connectivity was negatively correlated with MoCA scores (between left middle frontal gyrus and left insula, and between left insula and anterior cingulate cortex) (Fig. 2, Cross-sectional). FDR-corrected p values and r values can be found in Table 3. Correlation between CEN and MoCA scores in subacute stroke did not survive correction for multiplicity.

#### 3.3. Functional connectivity and cognition at chronic stroke (time 2)

A subgroup of subjects was lost to follow-up due to exclusion criteria (recurrent stroke, n = 2; MRI acquisition problems, n = 3) or no show (n = 12), and we finished with 20 subjects in the DMN analysis (6 flipped images), 16 in the CEN (5 flipped images), and 15 in the SN (5 flipped images).

No significant differences between time 1 and time 2 were found in the connectivity of the DMN, SN, and CEN. As we found a significant cognitive recovery at time 2, we analyzed whether changes in MoCA scores (ΔMoCA) could be related to changes in functional connectivity (ΔFC), or functional connectivity at time 1 (FCtime1). Correlations between ΔMoCA and ΔFC did not survive FDR correction, but cognitive recovery (ΔMoCA) positively correlated with DMN functional connectivity (between anterior cingulate cortex and precuneus) and negatively correlated with SN functional connectivity (between left and right insulums) from time 1, in the respective subgroups (Fig. 2, Longitudinal). FDR-corrected p values and r values for longitudinal comparison can be found in Table 5.

compare sociodemographic data (age, gender, and education respectively) between stroke patients and controls. To compare MoCA, Barthel index, Beck Depression Inventory and Beck Anxiety Inventory scores across time within patients, we used the Wilcoxon signed rank test. Cognitive recovery (ΔMoCA) and remapping of networks (ΔFC) were calculated as a difference between values in the chronic and subacute phases (ΔMoCA = MoCAtime2 − MoCAtime1; ΔFC = FCtime2 − FCtime1). Pearson’s correlation was used to measure any associations between α) the performance in MoCA at the subacute stage (MoCAtime1) and ROI-ROI functional connectivity at the subacute phase (FCtime1); b) cognitive recovery (ΔMoCA) and network remapping (ΔFC); c) cognitive recovery (ΔMoCA) and ROI-ROI functional connectivity at the subacute phase (FCtime1). All analyses were controlled for years of education and age, and correlation with neuropsychological results were deemed statistically significant when p < 0.1 ([Fisher, 1950], False Discovery Rate corrected for multiplicity. We particularly opted for a more liberal p-value in neuropsychological analysis since correlation of clinical scales with fMRI is not expected to be as high as in other domains ([Vul et al., 2009]), which yields greater p-values. Statistical analyses were carried out in SPSS Statistics v.20 (IBM Corp., 2011).
4. Discussion

Using an interhemispheric, contralesional and ipsilesional ROI-ROI approach, we evaluated how the functional connectivity of resting-state networks gets disrupted after a stroke event, and whether their remapping relates to cognitive recovery 6 months after the stroke. At time 1, we found that stroke disrupted the interhemispheric connectivity of the DMN. Cognitive performance was related to stronger interhemispheric and ipsilesional DMN connectivity, and weaker contralesional SN connectivity. At time 2, we did not detect any reorganization of the networks despite a significant cognitive improvement. However, cognitive recovery could be associated with stronger connectivity of the DMN, and weaker connectivity of the SN both at time 1.

Leading to cognitive impairment and dementia, stroke is the foremost cause of morbidity in the elderly (Jokinen et al., 2015; Tamam et al., 2008). Given that even mild cognitive deficits affect the patients’ quality of life and functional abilities, it is important to understand not only how stroke events disrupt brain networks, but also whether their remapping correlates with good cognitive recovery. According to our results and others (Jiang et al., 2018; Tuladhar et al., 2013), stroke patients presented weaker functional connectivity within the DMN compared to healthy individuals, a feature observed even in patients with transient ischemic attack (Zhu et al., 2019) - an important risk factor for stroke. In addition, our approach allowed us to find that a stroke event affects not only the lesion site but also distant connections between hemispheres, corroborating with previous reports of interhemispheric disruptions post stroke (Carter et al., 2010; Siegel et al., 2016).

A better performance in cognitive tests at time 1 related to a stronger interhemispheric and ipsilesional DMN connectivity and a weaker SN contralesional connectivity. Here, for a better understanding of our results, we shall give a brief explanation of the role of DMN and SN in cognitive processing. The DMN is one of the most prominent resting-state functional networks and is ostensibly dominated by internally directed self-referential cognitive processes (Buckner et al., 2008). The SN, in turn, is involved in the maintenance of homeostasis between internal and external stimuli (Menon and Uddin, 2010), playing a critical role in allocating attentional resources between the DMN and CEN (Goulden et al., 2014). The responses of these networks can increase or decrease antagonistically, according to the demands of cognitive tasks (Jilka et al., 2014). Decreased connectivity (Wang et al., 2013) and deactivation (Anticevic et al., 2012) in the DMN, as well as increased connectivity of the SN (Balthazar et al., 2014) have been associated with poor cognitive processing. Corroborating with the view of antagonistic roles between the two networks in cognition, we found that patients with good cognitive performance at time 1 presented stronger connectivity within the DMN and weaker connectivity within the SN.

Although ipsilesional hemispheric reorganization is traditionally
thought to be crucial for successful recovery, definitive conclusions into the role and importance of the contralesional hemisphere remain under debate. Other authors have noted, for example, structural (Dacosta-Aguayo et al., 2014a) and functional (Crofts et al., 2011) abnormalities in the contralesional hemisphere after the stroke event. Beyond that, hyperexcitability of the contralesional hemisphere correlated with lesser recovery elsewhere (Dodd et al., 2017). Taken together, these results suggest that stroke not only functionally affects the lesioned hemisphere but that integrity of the contralesional site might play an important role in recovery.

Six months after the stroke event, a general cognitive recovery was observed among patients, yet no changes in functional connectivity were detected. In other words, the cognitive recovery observed among patients was not accompanied nor could be predicted by network remapping. A failure in observing changes in connectivity at time 2, although detected. In other words, the cognitive recovery observed among patients, yet no changes in functional connectivity were observed among subacute and chronic phases.

| Cross-sectional Classification | ROI – ROI | Correlation between | Pearson’s r | FDR p-value |
|-------------------------------|-----------|---------------------|-------------|-------------|
| Interhemispheric | DMN | FC_{time1} and MoCA_{time1} | 0.409 | 0.058 |
| | 4 – DMN | 7 | | | |
| Contralesional | SN 1 – SN 2 | FC_{time1} and MoCA_{time1} | −0.398 | 0.049 |
| | SN 2 – SN 3 | MoCA_{time1} | −0.426 | 0.049 |
| Ipsilesional | DMN | FC_{time1} and MoCA_{time1} | 0.449 | 0.068 |
| | 2 – DMN | 7 | | | |

| Longitudinal Classification | ROI – ROI | Correlation between | Pearson’s r | FDR p-value |
|-------------------------------|-----------|---------------------|-------------|-------------|
| Interhemispheric | SN 2 – SN 5 | FC_{time1} and ΔMoCA | −0.638 | 0.076 |
| Medial | DMN | FC_{time1} and ΔMoCA | 0.511 | 0.090 |
| | 1 – DMN | 5 | | | |

ROI: Regions of interest; DMN = Default Mode Network; SN = Salience Network; FC_{time1} = Functional connectivity at the subacute phase; MoCA_{time1} = Montreal Cognitive assessment scores at the subacute phase; ΔMoCA = changes in Montreal Cognitive assessment scores between subacute and chronic phases.

5. Conclusions

Stroke disrupts the functional connectivity of the DMN, not only at the lesioned hemisphere but also between hemispheres. Six months after the stroke event, we could not detect the remapping of networks. Cognitive recovery was correlated with the connectivity of both the DMN and SN of time 1. Our findings may be helpful for facilitating further understanding of the potential mechanisms underlying post-stroke cognitive performance.

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CRediT authorship contribution statement

Jéssica Elias Vicentini: Conceptualization, Investigation, Methodology, Writing - original draft. Marina Weiler: Conceptualization, Methodology, Writing - original draft. Raphael Fernandes Casseb: Conceptualization, Formal analysis, Visualization, Writing - original draft. Sara Regina Almeida: Investigation, Writing - original draft. Lenise Valler: Visualization. Bruno Machado de Campos: Software, Formal analysis. Li Min Li: Conceptualization, Supervision, Resources.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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