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Neural coupling between contralesional motor and frontoparietal networks correlates with motor ability in individuals with chronic stroke

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ABSTRACT

Movement is traditionally viewed as a process that involves motor brain regions. However, movement also implicates non-motor regions such as prefrontal and parietal cortex, regions whose integrity may thus be important for motor recovery after stroke. Importantly, focal brain damage can affect neural functioning within and between distinct brain networks implicated in the damage. The aim of this study is to investigate how resting state connectivity (rs-connectivity) within and between motor and frontoparietal networks are affected post-stroke in correlation with motor outcome. Twenty-seven participants with chronic stroke with unilateral upper limb deficits underwent motor assessments and magnetic resonance imaging. Participants completed the Chedoke-McMaster Stroke Assessment as a measure of arm (CMSA-Arm) and hand (CMSA-Hand) impairment and the Action Research Arm Test (ARAT) as a measure of motor function. We used a seed-based rs-connectivity approach defining the motor (seed = contralesional primary motor cortex (M1)) and frontoparietal (seed = - contralesional dorsolateral prefrontal cortex (DLPFC)) networks. We analyzed the rs-connectivity within each network (intra-network connectivity) and between both networks (inter-network connectivity), and performed correlations between: a) intra-network connectivity and motor assessment scores; b) inter-network connectivity and motor assessment scores. We found: a) Participants with high rs-connectivity within the motor network (between M1 and supplementary motor area) have higher CMSA-Hand stage ($z = 3.62$, $p = 0.003$) and higher ARAT score ($z = 3.41$, $p = 0.02$). Rs-connectivity within the motor network was not significantly correlated with CMSA-Arm stage ($z = 1.83$, $p > 0.05$); b) Participants with high rs-connectivity within the frontoparietal network (between DLPFC and mid-ventrolateral prefrontal cortex) have higher CMSA-Hand stage ($z = 3.64$, $p = 0.01$). Rs-connectivity within the frontoparietal network was not significantly correlated with CMSA-Arm stage ($z = 0.93$, $p = 0.03$) or ARAT score ($z = 2.53$, $p = 0.05$); and c) Participants with high rs-connectivity between motor and frontoparietal networks have higher CMSA-Hand stage ($r_s = 0.54$, $p = 0.01$) and higher ARAT score ($r_s = 0.54$, $p = 0.009$). Rs-connectivity between the motor and frontoparietal networks was not significantly correlated with CMSA-Arm stage ($r_s = 0.34$, $p = 0.13$). Taken together, the connectivity within and between the motor and frontoparietal networks correlate with motor outcome post-stroke. The integrity of these regions may be important for an individual's motor outcome. Motor-frontoparietal connectivity may be a potential biomarker of motor recovery post-stroke.

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1. Introduction

The study of movements has traditionally focused on the motor system [43,46]. However, the execution and learning of movements also engages prefrontal and parietal cortex, brain regions not directly implicated in motor control but cognitive functions [12,23,43,46]. In individuals with stroke, little is known about how neural functioning in prefrontal and parietal cortex may influence the recovery of movement [40,61]. The present study investigates the relationship between motor and frontoparietal (FP) resting state networks with motor outcome, in individuals with chronic stroke. Here, we refer to motor outcome as the clinical status of the upper limb at one time point after stroke. A better understanding of this brain-behavior relationship may have implications for the assessment and prediction of motor ability post-stroke. Furthermore, it may inform the development of interventions that facilitate neural functioning in both motor and FP regions, leading to enhanced motor recovery [32,42].

Performing a movement involves brain regions such as the primary motor cortex (M1), supplementary motor area (SMA), and premotor cortex. The M1 is involved in motor execution [38] while the SMA and premotor cortex are associated in planning and sequencing movements [24,54]. Collectively, these regions constitute the motor network [4]. A network comprises brain regions whose blood oxygen level-dependent (BOLD) signals are temporally coupled [50]. Thus, these regions are considered 'connected'. In individuals with stroke, damage to regions of the motor network is common and leads to motor deficits [27]. Motor network connectivity is reduced in individuals with stroke relative to healthy persons [18]. To examine the relationship between motor network connectivity and motor behavior post-stroke, studies have employed seed-based connectivity analyses with seed placement in ipsilesional [6,18,37,63] or contralesional [62,63] motor cortex. Using a whole-brain analysis approach, seed regions show resting state connectivity (rs-connectivity) with other areas of the motor network, namely the premotor and supplementary motor cortex, and this motor network connectivity correlates with clinical motor outcomes [6,37,63]. Similarly, seed-to-seed based approaches reveal that people with stroke with higher interhemispheric connectivity have less severe motor deficits than those with lower connectivity [6,8]. Thus, a positive relationship between motor network connectivity and motor outcome supports the notion that communication between motor regions is important for recovery post-stroke. In the present study, we implement a connectivity strategy with the seed defined in contralesional motor cortex. This allows us to study connectivity patterns that relate to the structurally intact contralesional motor cortex, which can be interpreted to represent a compensatory response. Furthermore, seed placement in the contralesional hemisphere avoids a scenario in which the seed and lesion overlap. In this situation, the blood-oxygenation level dependent (BOLD) signal extracted from the seed-lesion overlap region may be difficult to interpret.

However, performing movements also requires the prefrontal and parietal regions, which provide cognitive and visual information to the motor system [43,46]. Prefrontal areas, such as the dorsolateral prefrontal cortex (DLPFC), are involved in attention, working memory, and decision-making, among other functions, together which enable individuals to perform meaningful actions [33,53]. Parietal areas, such as the intraparietal sulcus and inferior parietal lobule, are involved in integrating visuospatial information that enable individuals to perceive and interact with objects in the environment [2,19]. Together, these regions form the FP network [14]. While prior work has established a relationship between motor outcome and motor network connectivity post-stroke [6,8,55], investigations about FP network connectivity have been more limited. FP network connectivity decreases in people with stroke relative to healthy controls [60]. Individuals with stroke who have higher M1-prefrontal connectivity [37] and M1-parietal connectivity [63] have better motor outcome. However, the relationship between FP network connectivity and motor outcome has not, to our knowledge, been studied. Importantly, it is also unknown whether connectivity between networks, such as motor and FP, are altered post-stroke, and whether this inter-network connectivity relates to an individual's motor outcome. Thus, the FP network warrants further study given the promising, yet preliminary evidence of this network's role in motor outcome post-stroke.

The aim of our proof-of-principle study is to test the hypothesis that differences in connectivity within and between the motor and FP networks correlate with motor outcome in individuals with chronic stroke. The novel aspect of this study is that it examines whether the connectivity between these networks relate to motor outcome post-stroke. We used resting state functional magnetic resonance imaging (rs-fMRI) to measure spontaneous BOLD signal fluctuations between spatially distinct brain regions that are temporally correlated [50]. Our objectives were: 1) To confirm prior findings whereby connectivity within the motor network (i.e., intra-network connectivity) correlates with motor outcome; 2) To determine whether intra-network FP connectivity correlates with motor outcome; and 3) To determine whether connectivity between the motor and FP networks (i.e., inter-network connectivity) correlates with motor outcome. We hypothesized that the connectivity within and between the motor and FP networks will positively correlate with motor outcome.

2. Methods

2.1. Participants

Twenty-seven participants with chronic stroke gave informed written consent for a study approved by the Baycrest Research Ethics Board. This cohort was part of a clinical trial (NCT01721668) conducted to study the efficacy of a ten-week arm and hand intervention in individuals with chronic stroke. The present study, unrelated to the clinical trial objectives, involved the analysis of a subset of the baseline (pre-intervention) data. Details of the clinical trial will be reported in a future publication.

We list here the study inclusion/exclusion criteria relevant for the current study. Inclusion criteria were: first-time ischemic stroke at least six-months post-onset with unilateral upper limb motor deficit, and fluency in English. Participants were included if their residual motor impairment was stage 2 on the Chedoke-McMaster Stroke Assessment Impairment Inventory (CMSA) Stage of Arm and Hand [20], and they were additionally able to complete at least one task in stage 3. Participants were also required to have near-normal hearing verified by clinical audiometry (< 40 dB 250–2000 Hz). Exclusion criteria were: moderate to severe apraxia and/or aphasia, sensory loss, clinically significant spatial neglect, dementia, psychiatric disorders, severe pain and/or fatigue, formal music training for > 2 years within the past 10 years or for > 10 years in total, concurrently participating in another clinical intervention trial during the study period, and had significant depression (< 27, Center for Epidemiological Studies-Depression scale) [41]. If a participant was on antidepressants, he/she had to be on a stable dosage for at least 3 months with no change during the study period.

2.2. Assessments

All participants underwent a battery of motor assessments: CMSA Stage of Arm (CMSA-Arm) [20], CMSA Stage of Hand (CMSA-Hand) [20], and the Action Research Arm Test (ARAT) [64]. The CMSA assesses motor impairment using seven stages from 1 (flaccid paralysis) to 7 (normal movement) and has good validity with the Fugl-Meyer Assessment [20]. The ARAT assesses motor function and is scored from 0 (no motor function) to 57 (normal motor function) [64].

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