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Disrupted functional network integrity and flexibility after stroke: Relation to motor impairments

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ABSTRACT

Previous studies investigating brain activation present during upper limb movement after stroke have greatly detailed activity alterations in the ipsi- and contralesional primary motor cortices (M1). Despite considerable interest in M1, investigations into the integration and coordination of large-scale functional networks subserving motor, sensory, and cognitive control after stroke remain scarce. The purpose of this study was to assess non-static functional connectivity within whole-brain networks involved in the production of isometric, visually-paced hand grips. Seventeen stroke patients and 24 healthy controls underwent functional MRI while performing a series of 50 isometric hand grips with their affected hand (stroke patients) or dominant hand (control subjects). We used task-based multivariate functional connectivity to derive spatial and temporal information of whole-brain networks specifically underlying hand movement. This technique has the advantage of extracting within-network commonalities across groups and identifying connectivity differences between these groups. We further used a nonparametric statistical approach to identify group differences in regional activity within these task-specific networks and assess whether such alterations were related to the degree of motor impairment in stroke patients. Our whole-brain multivariate analysis revealed group differences in two networks: (1) a motor network, including pre- and postcentral gyri, dorsal and ventral premotor cortices, as well as supplementary motor area, in which stroke patients showed reduced task-related activation compared to controls, and (2) a default-mode network (DMN), including the posterior cingulate cortex, precuneus, and medial prefrontal cortex, in which patients showed less deactivation than controls. Within-network group differences revealed decreased activity in ipsilesional primary sensorimotor cortex in stroke patients, which also positively correlated with lower levels of motor impairment. Moreover, the temporal information extracted from the functional networks revealed that stroke patients did not show a reciprocal DMN deactivation peak following activation of their motor network. This finding suggests that allocation of functional resources to motor areas during hand movement may impair their ability to efficiently switch from one network to another. Taken together, our study expands our understanding of functional reorganization during motor recovery after a stroke, and suggests that modulation of ipsilesional sensorimotor activity may increase the integrity of a whole-brain motor network, contribute to better motor performance, and optimize network flexibility.

1. Introduction

Stroke is a cerebrovascular injury often resulting in sensorimotor and cognitive impairments (Broeks et al., 1999; Desmond et al., 1996). While some patients achieve good motor recovery, up to 40% of stroke survivors are left with permanent motor disabilities (Krueger et al., 2015). A key impediment to the development of effective treatment interventions lies in the lack of empirical evidence linking residual motor functions to observed functional connectivity changes in widely distributed regions outside the lesion site (Fornito et al., 2015). Stroke research grounded in network analysis is therefore crucial to understand the mechanisms that enable motor recovery after an infarct. Identification of network abnormalities in stroke patients can be leveraged using task-based functional neuroimaging paradigms, which, as opposed to resting-state (i.e., task-free) recordings, have the ability to detect brain alterations that may only manifest during the

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performance of motor actions. Despite considerable interest in the role of the primary motor cortex (M1) after a stroke, our knowledge on the integrative and cooperative properties of functionally connected, large-scale brain networks involved in the execution of hand movement in stroke patients remain scarce (Bernhardt et al., 2016; Rehme et al., 2015).

Recent developments in the field of network neuroscience have revealed that an optimal brain requires a dynamic and flexible balance between unimodal (e.g., sensorimotor, visual) and transmodal (e.g., attention, default-mode) large-scale networks (Bressler and Menon, 2010; Margulies et al., 2016). Network flexibility, which reflects the brain's ability to switch between different network configurations, has been demonstrated to change dynamically during a simple motor learning task, balancing between attention- and motor-driven processes (Bassett et al., 2011). Efforts to characterize motor recovery mechanisms in stroke individuals, however, have focused almost exclusively on static patterns of functional connectivity in individual networks. Several lines of research comparing stroke patients to healthy controls, for instance, have reported decreased interhemispheric motor network connectivity (Park et al., 2011; Thiel and Vahdat, 2015), disruption of the dorsal attention network (Carter et al., 2010; He et al., 2007), and an inability to regulate default-mode network (DMN) activity (Dacosta-Aguayo et al., 2015; Tuladhar et al., 2013). Although the majority of these findings correlated with behavioral measures of cognition, attention, and motor impairment, these observations also raise the possibility that connectivity alterations in diverse cerebral systems may lead to impaired network flexibility after a stroke.

A large proportion of the studies on stroke have used univariate analysis methods which limit the observations of brain activity to individual regions that are largely independent of each other. However, because motor and cognitive networks are active in parallel during a hand motor task (Bressler and Menon, 2010), univariate task-based regression methods may lead researchers to overlook important information embedded in the functional integrity and cooperation of large-scale networks. In contrast, multivariate methods can separate multiple distinct, simultaneously active brain networks while quantifying each network's unique spatial and temporal properties. In this study, we derived task-specific functional brain networks with subject- and condition-specific hemodynamic response (HDR) shapes using constrained principal component analysis for functional MRI (fMRI-CPCA; www.nitrc.org/projects/fmricpca), a method that integrates multivariate multiple regression analysis and principal component analysis into a unified framework. Notably, fMRI-CPCA has the advantage of identifying brain networks that are (1) specifically underlying isometric hand grips, and (2) shared across all subjects, thus allowing direct comparison of network connectivity between groups. Previous studies employing similar approaches to examine whole-brain patterns of functional connectivity have reported a progressive increase in motor network connectivity and integrity during the recovery process after stroke (Wadden et al., 2015; Wang et al., 2010). While these studies have documented connectivity anomalies extending beyond individual motor regions, the consequences of stroke on functional integrity and coordination between motor and cognitive networks remain to be investigated.

Our purpose was to compare non-static functional connectivity changes in whole-brain networks between stroke patients and healthy controls during the production of isometric hand grips. We used fMRI-CPCA to generate shared functional networks that activate (or deactivate) during hand movement and extract each network's spatial and temporal patterns of activation. In line with previous studies highlighting regional activity decreases in several functionally segregated motor areas (for comprehensive reviews, see Lake et al. (2016) and Grefkes and Fink (2011)), we hypothesized that patients would show reduced whole-brain motor network functional connectivity relative to controls. Furthermore, based on evidence from resting-state and hand motor task studies suggesting altered activity in sensorimotor and default-mode regions (Dacosta-Aguayo et al., 2015; Liu et al., 2014; Wang et al., 2010; Ward et al., 2003), we postulated that differential patterns of network connectivity in stroke patients may lead to impaired network flexibility. In light of the notion that reinstatement of previously reduced functional activations can predict post-stroke motor recovery (Kim and Winstein, 2017), we also assessed the relationship between regional brain activity changes and variability in behavioral motor performance in stroke patients.

Table 1
Participants' demographic information and behavioral scores. *Note: standard deviations are in parentheses. BBT, Box and Block Test; NHPT, Nine-Hole Peg Test.

Variable	Control subjects	Stroke patients
Sex (male/female)	14/10	14/3
Handedness (right/left)	23/1	17/0
Age (years)	46.7 (17.5)	53.2 (12.3)
Time since stroke (months)	–	44.9 (56.6)
Lesion side (right/left)	–	11/6
Hand affected (right/left)	–	6/11
BBT % of unaffected	–	52.1 (26.6)
NHPT % of unaffected	–	40.8 (35.5)
Grip strength % of unaffected	–	56.0 (33.7)

2. Materials and methods

2.1. Participants

A total of 41 subjects (17 stroke patients and 24 healthy controls) were included in this study. All patients had suffered from first ischemic stroke; individual patient characteristics are presented in Supplementary Table 1. Group-specific demographic information is listed in Table 1; groups were matched on gender, handedness, and age. Full written consent was obtained from all subjects in accordance with the Declaration of Helsinki. The study was approved by the Joint Ethics Committee of the Institute of Neurology, UCL and NHNN, UCL Hospitals NHS Foundation Trust, London.

2.2. Experiment protocol

2.2.1. Behavioral assessment

Motor impairment was assessed based on measurements of (1) hand grip strength (Mathiowetz et al., 1984), (2) finger dexterity (Nine Hole Peg Test; Mathiowetz et al., 1984), and (3) unilateral gross manual dexterity (Box and Block Test; Mathiowetz et al., 1985). As depicted in Table 1, these measurements were calculated as a percentage of the score obtained with the unimpaired hand (Sunderland et al., 1989). These scores were then entered into a principal component analysis (PCA) and the first component was used as a single impairment score for each patient, with lower motor score values corresponding to greater motor impairment.

2.2.2. Motor task

While undergoing fMRI, all subjects performed a series of 50 visually cued isometric hand grips, using an MR-compatible manipulandum as described elsewhere (Ward and Frackowiak, 2003). Healthy controls carried out the task with their dominant hand while patients performed the task with their affected (i.e., contralesional) hand. Each subject performed a total of 50 isometric hand grips at a target pressure of 10% or 30% of their maximum voluntary contraction in a randomized order. Hand grips were sustained for 3 s and were followed by a variable interstimulus interval between 3 and 7 s.