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Research report

Compensatory motor network connectivity is associated with motor sequence learning after subcortical stroke

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HIGHLIGHTS

- We evaluated brain connectivity during motor tracking in healthy and stroke participants.
- Healthy subjects demonstrated connectivity within a widely disturbed motor network.
- A mask of the motor network was created to assess connectivity for the stroke group.
- The connectivity within a smaller motor network correlated with motor performance in the stroke group.
- Motor network connectivity may be a predictor of motor learning and recovery following stroke.

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ABSTRACT

Following stroke, functional networks reorganize and the brain demonstrates widespread alterations in cortical activity. Implicit motor learning is preserved after stroke. However the manner in which brain reorganization occurs, and how it supports behavior within the damaged brain remains unclear. In this functional magnetic resonance imaging (fMRI) study, we evaluated whole brain patterns of functional connectivity during the performance of an implicit tracking task at baseline and retention, following 5 days of practice. Following motor practice, a significant difference in connectivity within a motor network, consisting of bihemispheric activation of the sensory and motor cortices, parietal lobules, cerebellar and occipital lobules, was observed at retention. Healthy subjects demonstrated greater activity within this motor network during sequence learning compared to random practice. The stroke group did not show the same level of functional network integration, presumably due to the heterogeneity of functional reorganization following stroke. In a secondary analysis, a binary mask of the functional network activated from the aforementioned whole brain analyses was created to assess within-network connectivity, decreasing the spatial distribution and large variability of activation that exists within the lesioned brain. The stroke group demonstrated reduced clusters of connectivity within the masked brain regions as compared to the whole brain approach. Connectivity within this smaller motor network correlated with repeated sequence performance on the retention test. Increased functional integration within the motor network may be an important neurophysiological predictor of motor learning-related change in individuals with stroke.

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1. Introduction

The ability to acquire a movement skill without conscious awareness of improvements in certain aspects of performance is a fundamental aspect of motor learning. This process, known as implicit motor learning, is preserved in individuals with stroke and encompasses a large portion of motor skill rehabilitation [1–4]. However, it is unclear how the brain reorganizes to support the behavioral improvements observed after skilled motor practice in individuals with stroke [4]. In part our failure to fully understand how the stroke damaged brain reorganizes to support motor learning stems from methodological approaches in previous work that focused on understanding functionally-segregated brain structures (i.e. region of interest-based and voxel-wise analyses) based on the locus of the lesion [4]. However, recent advances in neuroimaging analysis techniques promote a shift away from mapping brain function to individual areas, and place a greater emphasis on the assessment of integrated and reorganized networks [5]. For the present study, we used a novel multivariate applied to functional magnetic resonance imaging (fMRI) analysis to identify networks underlying implicit motor sequence learning for healthy controls and individuals with stroke.

In previous work, our laboratory illustrated differences in regional brain activation between healthy and stroke individuals during implicit motor learning [4]. A comparison of differences in regional brain activation between these groups provides an indication of maladaptive recruitment, or lack of recruitment, following motor sequence learning in individuals with chronic stroke. However, a differential approach, and somewhat of a counter view, would be to investigate functional connectivity commonalities within a motor network across groups and then identify the connectivity differences between these groups. In our previous study, the results from our whole-brain, univariate fMRI analysis following a motor learning task revealed differences in activation of the premotor dorsal (PMd) area and dorsal lateral prefrontal cortex (DLPFC) between healthy and stroke participants [4]. Separate ANOVAs for baseline and retention were performed on voxel-wise activation maps, comparing group (healthy controls, stroke participants) by sequence (repeated, random). Based on this approach, we observed a significant increased activation of the PMd and decreased activation of the DLPFC on retention for the healthy controls compared to individuals with stroke. This activation pattern suggests a transition from feedback mechanisms to feed-forward memory-based control during motor learning in healthy adults [6,7]. Individuals with stroke did not show a concomitant decrease in activation in the DLPFC with motor learning, which may indicate continued reliance on the prefrontal-based attentional network and compensatory regions that encompassed the primary somatosensory cortex, ipsilesional insula and bilateral superior frontal, middle temporal gyri [4]. This past work hypothesized that variances exist within the DLPFC-premotor network between healthy individuals and individuals with chronic stroke, yet it did not allow us to consider changes in network connectivity supporting implicit learning after stroke. Thus, in our current study a multivariate approach was applied to fMRI analysis to allow for the direct characterization of functional network connectivity across groups. Subsequently, this network was used to identify the differences in connectivity between groups that may explain differences in motor skill learning.

Functional connectivity analyses of fMRI data can be used to investigate the temporal correlations between the hemodynamic responses (HDR) of spatially distant brain areas. Past work in this field has used methods such as independent component analyses (ICA; [8]), principal component analyses (PCA; [9]), and functional connectivity matrices and graph theory methods [9] to study activation patterns based on models of motor skill learning [10]. Limitations of standard ICA and PCA approaches involve difficulties with (1) relating derived brain networks to behavioral tasks carried out while subjects are in the scanner, and (2) simultaneously comparing activity between two groups on one task-related network [11]. These limitations can be addressed using constrained principal component analysis (CPCA), a statistical technique that combines multivariate multiple regression and principal component analysis in a unified framework [12–14]. When applied to fMRI (fMRI-CPCA; www.nitrc.org/projects/fmricpca; [14,15]) this technique allows isolation of task-relevant blood oxygenation level dependent (BOLD) signal. The analyzed BOLD signal is constrained to the aspect of variance in BOLD signal that is predictable from the experimental design (i.e. presentation of stimuli), producing the derivation of images based on the degree to which one or more task-related functional networks are involved in each experimental condition for each subject. The computations of functional networks are based on the analysis of interrelationships among cortical structures involved in the experimental task [15].

In past work using fMRI-CPCA to study working memory in schizophrenia [11], researchers were able to identify differential activation patterns between schizophrenia patients and healthy controls in shared functional networks. For the present study, we used whole brain fMRI-CPCA to evaluate shared functional networks that may activate (or deactivate) during implicit motor sequence learning for healthy controls and individuals with stroke. We selected individuals with similar brain lesions for this study as the inclusion of individuals with right subcortical stroke enabled the evaluation of connectivity within whole brain networks rather than restricting our connectivity analysis to predefined regions of interests. This factor was key to our ability to run an unrestricted whole brain connectivity analysis. It is known that whole brain connectivity at rest is altered in the lesioned brain, and functional connectivity within specific nodes is reduced [9]. However, specific changes are influenced by lesion location, and little is known about how implicit motor learning task-based networks are altered in the injured brain. fMRI-CPCA has the advantage of identifying shared functional networks underlying the performance of repeated versus random tracking movements, and thereby allows for comparison of the degree of functional connectivity associated with learned sequences of movement as compared to changes in generalized motor control. Using between-groups comparisons, this method provides a statistical test of the degree to which brain reorganization after stroke is affecting each shared functional network. Due to the novelty of this task-based functional connectivity approach, we also performed a secondary analysis to examine functional connectivity within the motor functional networks exclusively for the stroke group. Given the results from previous multivariate analyses [8,9], we hypothesized that in our primary whole brain analysis greater connectivity within a motor network would be observed during repeated compared to random performance at a retention test. In addition, we predicted that a secondary analysis that exploits functional connectivity within regions restricted to the motor network from our primary analysis would reveal a specific compensatory stroke affected motor network. Finally, we hypothesized that the level of connectivity within this stroke affected motor network would be related to the level of implicit motor learning during the retention test following five days of skilled motor practice.

2. Methods

2.1. Participants

Nine first-time, right-hemisphere ischemic stroke (ST) participants with chronic (>6 months) subcortical lesions (6 men, mean