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Compensatory Motor Network Connectivity is Associated with Motor Sequence Learning after Subcortical 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 behaviour 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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Keywords

Constrained Principal Component Analysis; Motor Sequence Learning; Functional Magnetic Resonance Imaging; Stroke; Functional Connectivity

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 age = 63.8 ± 6.2 years; mean Fugl Meyer motor upper extremity score = 54.3 ± 13.0) and nine age-matched healthy controls (HC; 4 men, mean age = 63.1 ± 7.0 years) were recruited for the present study (Table 1; Figure 1). Exclusion criteria included: (1) a score below the 25th percentile on the Mini-Mental Status Exam using age adjusted norms [16] (2) left handedness, (3) neurological impairment or disease of individuals in the HC group [17], (4) inability to perform the task due to any orthopedic condition or color-blindness, or (5) ineligibility to undergo magnetic resonance imaging (MRI). Participants were recruited from the University of British Columbia, the local community and the Brain Behaviour Lab database. Each participant's consent was obtained according to the Declaration of Helsinki; the research ethics boards at the University of British Columbia approved all aspects of this work.

2.2 Behavioral Task

Participants tracked a moving, white circular target on a computer monitor that followed a sine-cosine waveform. The ST group operated a joystick with their hemiparetic left arm; the HC group used their non-dominant left arm. Movements were represented as a red dot on a 19" computer monitor placed directly in front of participants. Unbeknownst to participants, one segment of each tracking trial of the moving target followed a predefined pattern constructed from a modified version of the method introduced by Wulf and Schmidt [18]. This pattern repeated throughout practice (days 2–6) and during fMRI acquisition (baseline and retention). The random segments of the tracking task did not contain a pattern and a different random sequence was used for every trial; however, the same set of random movements was used across participants. During each day of practice participants executed a total of 250 repetitions of the random and repeated sequences partitioned over five blocks each containing 10 sequence repetitions. The task was performed in a block design during fMRI acquisition. Each block contained either random or repeated sequences (40s rest/150s stimulation/40s rest/150s stimulation/40s rest) presented in a counterbalanced order within a run, and a total of four runs were performed (Figure 2). Following the fMRI retention test on day 7, a test was performed to assess whether participants had gained explicit awareness of the repeating sequence. Participants were asked if they recognized any of the ten, 10s blocks of the sequence presented to them as they repeated the pattern they had practiced. Three of

the 10 blocks presented during the test were the “true” repeating sequences and 7 were randomly generated sequences. If a participant correctly identified the repeated sequence at a better than chance level (i.e., correctly identified 2 of 3 repeated sequences as being repeated, and correctly identified 4 of the 7 novel sequences as having never been seen before) then the participant was considered to have gained explicit awareness of the repeating sequence and was excluded from the final sample [19, 20]. In the current study, all individuals in both groups failed to gain explicit awareness, thus none were excluded from the analyses.

To evaluate motor performance, our behavioural outcome measure for the continuous tracking task was root mean squared error (RMSE). RMSE is representative of the overall tracking error integrating both temporal and spatial measurements of time lag and distance from the moving target, respectively [4].

2.3 Imaging Protocol

MR imaging was performed at UBC MRI Research Center on a Philips Achieva 3.0 T whole body MRI scanner (Philips Healthcare, Andover, MD) using a sensitivity encoding head coil (SENSE). Blood oxygenation level dependent (BOLD) images were acquired axially using echo-planar images (EPI) with a single-shot readout (TR = 2,000 ms, TE = 30 ms, flip angle $\theta = 90^\circ$, FOV = 240 mm, 36 slices, 3 mm thickness with a 1 mm gap). A high-resolution anatomical scan was collected (TR = 12.4 ms, TE = 5.4 ms, flip angle $\theta = 8^\circ$, FOV = 256 mm, 170 slices, 1 mm thickness) for later co-registration with the functional maps.

2.4 fMRI data analysis

2.4.1 Preprocessing—Brain images were preprocessed using statistical parametric mapping (SPM 8) software (Wellcome Department of Cognitive Neurology, London, UK) in the MATLAB environment (Mathworks 7.6, Sherbon, MA). Images were corrected for slice timing and realigned for motion correction. The functional and anatomical images were co-registered, normalized into MNI space (Montreal Neurological Institute, Quebec, Canada) and spatially smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM). The fMRI-CPCA results were converted to Talairach space.

2.4.2 fMRI-CPCA—fMRI-CPCA Matlab-based software was applied to extract functionally-connected brain networks associated with motor sequence learning at the baseline (day 1) and retention (day 7) (Matlab version 13.0. Natick, Massachusetts: The MathWorks Inc., 2013). The theory and proofs of CPCA are detailed in previously published work [12, 13]; for applications to fMRI data, refer to [14, 15, 21, 22]. In short, when applied to fMRI data, three main steps are carried out (see figure 3). In the first step, referred to as the external analysis, a multivariate least-square multiple regression is carried out to isolate the BOLD signal variability that is predictable from the stimulus timing model; in this case, the stimulus timing model is a hemodynamic response (HDR) shape derived from the timing of the blocks in the tracking task convolved with a hemodynamic response function obtained from SPM 8. In the second step, the predicted scores from the multivariate multiple regression are submitted to a PCA using singular value decomposition. In a third step, weights are computed that, when applied to the stimulus timing model, produce the

component scores. These weights, termed “predictor weights”, reflect the intensity of the functional network for each subject and condition (i.e. repeated vs. random). Further statistical analyses can then be performed on the predictor weights to examine group- and condition-level connectivity differences on the functional network(s) derived from the PCA.

2.4.2 Secondary ROI fMRI-CPCA—The whole brain functional network that explained the most variance from each of the baseline and retention fMRI CPCA analyses was used to perform a region of interest (ROI) analyses exclusively within stroke patients. This secondary analysis assessed stroke-specific spatial distribution of activation within the task-dependent networks. Binary masks including the most extreme 30% of voxels (highest component loadings) were created for each day. New masked baseline and retention fMRI-CPCA analyses were performed for the stroke group data.

2.4.3 Statistical inference procedure—Inspection of the scree plot [23, 24] of singular values suggested that a single functional network should be extracted for further analysis for both baseline and retention whole brain analyses. Similarly, a single functional network was extracted for the secondary ROI fMRI-CPCA analyses at baseline and retention as demonstrated by the scree plots. To test for differences in the estimated BOLD response associated with motor performance, separate Group (HC, ST) by Sequence (repeated, random) ANOVAs for each Day (baseline, retention) were performed on the predictor weights of the functional network resulting from the PCA. In the secondary analysis, to test for differences in the estimated BOLD response within the motor network for the stroke group, separate Sequence (repeated, random) ANOVAs for each Day (baseline, retention) were performed on the predictor weights of the functional network. Post-hoc linear contrasts were used to further examine significant interactions from the ANOVA. All statistical procedures were conducted using SPSS software (SPSS 19.0).

To assess the relationship between level of functional connectivity within the motor network and implicit motor learning for the stroke group, a Pearson’s correlational analysis was conducted on predictor weights extracted from the secondary analysis and mean RMSE on retention for both repeated and random conditions. In addition, age, post-stroke duration and Fugl Meyer (FM) were correlated with predictor weights as these measures have been previously shown to have a strong relationship with neurophysiological measures, such as white matter integrity (fractional anisotropy; FA) [25]. All statistical procedures were conducted using SPSS software (SPSS 19.0).

3. RESULTS

3.1 Whole brain functional connectivity during motor sequence learning

At baseline, the functional network included right precentral gyrus, left superior parietal lobule and the cerebellum bilaterally (Table 2 and Figure 4). This component accounted for 32.91% of the variance predictable from the HDR model of the block design on baseline.

The functional network distinguished at retention (day 7) included right postcentral gyrus, superior parietal lobule, occipital lobe and the cerebellum bilaterally (Table 3 and Figure 4).

This component accounted for 23.8% of the variance predictable from the HDR model of the block design at retention.

Separate ANOVAs were conducted on component one-predictor weights from baseline and retention. The results indicated a significant group by sequence interaction for retention, but not for baseline (non-significant baseline main effect; $p > 0.05$). At retention, analysis of the predictor weights showed a significant main effect of sequence, $F_{(1, 16)} = 14.86, p < 0.001, \eta^2 = 0.481, \sigma = 0.951$ and a significant group $\times$ sequence interaction, $F_{(1, 16)} = 4.36, p = 0.05, \eta^2 = 0.214, \sigma = 0.501$. Contrasts showed a significant increase in network activity for healthy participants during repeated relative to random sequence performance $t_{(1, 8)} = 4.136, p = 0.003$, while no differences were observed for individuals with stroke ($p = 0.24$) (Figure 4).

3.2 Secondary ROI functional connectivity for the ST group

At baseline, the functional network included left lingual gyrus and right parietal lobule, middle temporal gyrus, superior and inferior frontal gyri (Table 2 and Figure 4). This component accounted for 36.79% of the variance predictable from the HDR model of the block design at baseline. The functional network noted at retention (day 7) included left medial frontal gyrus and right insular cortex, lateral occipital cortex, inferior temporal gyrus and bilateral cerebellum (anterior lobe and culmen; Table 3 and Figure 4). This component accounted for 30.36% of the variance predictable from the HDR model of the block design on retention.

Separate ANOVAs were performed on the predictor weights for baseline and retention. Neither of these analyses revealed a main effect of sequence ($p > 0.05$) for the ST group.

3.3 Behavioral task performance

Participants in the ST group had higher RMSE scores during early practice on baseline (day 1) than the HC group ($F_{1,16} = 4.7, p = 0.046$). During the practice, acquisition phase, both the ST and the HC groups reduced RMSE ($F_{1,16} = 9.2, p = 0.008$) and greater improvement was demonstrated for the repeated sequence compared to the random sequence ($F_{1,16} = 3.5, p = 0.038$). Furthermore, there was a significant main effect of Group, with the ST group demonstrating a greater RMSE than the HC group ($F_{1,16} = 8.1, p = 0.012$). At retention, both the ST and HC groups were more accurate for the repeated sequence compared to the random sequence ($F_{1,16} = 14.4, p = 0.002$) and the HC group performed the tracking task with less error than the ST group ($F_{1,16} = 6.7, p = 0.020$), with no significant Group by Sequence interaction ($p = 0.194$) (figure 5).

3.4 Relationship between stroke functional connectivity and implicit motor learning

In the ST group, there was a significant relationship between the ROI fMRI-CPCA predictor weights and RMSE during implicit motor learning on retention testing. Individuals who demonstrated less tracking error during implicit motor learning showed greater motor network connectivity on retention ($r = -0.733, p = 0.025$; Figure 6). Age, post-stroke duration and Fugl-Myer were not significantly correlated with implicit motor learning.

4. DISCUSSION

The current study used fMRI-CPCA to evaluate the neural networks involved in implicit motor sequence learning in healthy individuals and individuals with chronic stroke. Due to the novelty of the analytic approach, task-dependent networks were assessed using a whole brain functional connectivity analysis. This exploratory analysis demonstrated a well-defined and characteristic large-scale motor network during the performance of a continuous tracking task (Figure 4b). Separate analyses at baseline and retention testing following 5 days of skilled motor practice resulted in activation of a motor network for both repeated and random conditions. At baseline, repeated and random conditions shared similar levels of connectivity within this motor network. At retention, a comparable motor network demonstrated higher functional connectivity during the repeated condition in the healthy control group and was accompanied by superior motor performance of the implicit motor sequencing task. There was no overlap between lesion location and clusters of activation; however individuals with chronic subcortical stroke did not engage the motor network to the same extent as controls. The HC group showed activation in the motor network during the performance of both repeated and random sequences with greater functional connectivity observed during the repeated sequence. The motor network in healthy individuals included a large cluster of bihemispheric activation encompassing the sensory and motor cortices, and parietal lobule. Bilateral cerebellar activation and occipital lobule activation was also found in this network (Table 3). While individuals with stroke demonstrate the ability to implicitly learn motor sequences [4, 26], our whole brain fMRI-CPCA results suggest high inter-subject variability in the spatial distribution of neural activity during motor learning after stroke.

Our secondary analysis constrained connectivity within the, now defined, motor network to assess the level of functional connectivity specific to the ST group. At retention, the results of the ROI fMRI-CPCA analysis demonstrated similar activation patterns of a subset of regions within the motor network during repeated and random conditions. This subset predominately included larger clusters of functional integration within the left medial frontal gyrus and right cerebellar lobule as well as the in the right insular cortex, occipital lobule, middle temporal gyrus, and left cerebellar culmen (Table 3). The level of inter-regional functional connectivity was significantly correlated with performance during the continuous tracking task; demonstrating individuals with higher network connectivity performed the task with less tracking error following 5 days of skilled motor practice. Constraining our analysis to a defined network yielded clusters of regions that demonstrated behavioral significance, which remained undetected in the whole brain analysis, perhaps due to the inter-subject variability in brain activity in the ST group.

4.1 Motor Network

This is the first study to use fMRI-CPCA to assess the functional networks associated with implicit motor sequence learning after stroke. The motor network that was recruited during the performance of the repeated sequence in healthy individuals agrees with previous work using other functional connectivity analysis methods [8, 27]. fMRI-CPCA allows for whole brain analysis of functionally-connected areas that are specifically related to the

experimental task employed, and, in the current study, revealed a task-related motor network previously characterized as the M1-premotor-parietal-cerebellar circuit [28]. This network has been shown to demonstrate substantial inter- and intra-hemispheric functional connectivity as spatial and motor representations are established during non-dominant hand motor sequence learning [27, 29]. Absolute activation level of brain regions within this network has been shown to decrease with increasing practice, which is believed to reflect improved efficiency in visuospatial processing, spatio-motor integration and motor execution for the repeated sequence [28–30]. A similar motor network was observed in a separate analysis during baseline performance. However, no significant difference between repeated and random conditions was observed in this network. Our findings from the retention test analysis revealed an increase in coordinated neural activity in healthy controls that was associated with the performance of implicit sequence tracking during the repeated condition. Unlike traditional functional connectivity analysis methods, fMRI-CPCA extracts networks exclusively from variance in BOLD signal predictable from the hemodynamic response modeled from the task timing [31]. In the present study, there was an improvement in neural efficiency demonstrated by the expression of a motor network. This reflects greater synchronization within the M1-premotor-parietal-cerebellar circuit that was associated with more accurate tracking for the repeated condition at retention.

In the present study we did not observe a relationship between functional connectivity within the motor network as measured with the BOLD response in the cortical grey matter of the HC group. Neuroplastic change has recently been observed within the white matter microstructure of the brain following motor learning in young healthy individuals [32] and animals [33]. Future studies are needed to evaluate the integral relationship between changes in white matter microstructure, BOLD gray matter response and degree of motor skill learning in the healthy individuals as well as individuals with chronic stroke.

4.2 Lesion disruption of neural networks

Unlike healthy controls, individuals with stroke did not demonstrate a similar pattern of coordinated activity within the whole brain motor network. This finding supports other work suggesting that a high degree of inter-participant variability exists during motor learning in the stroke-affected brain [5, 34]. Different reorganization patterns may emerge within a group of individuals with stroke, potentially due to the diverse repertoire of disrupted connections remote of the lesion site [9]. It is possible that changes within disrupted networks progress towards a randomized, less optimized network as the brain repairs itself [9]. Network randomization has been shown to occur in various brain pathologies such as brain tumors [35], Alzheimer's disease [36, 37], schizophrenia [38], epilepsy [37] and severe traumatic brain injury [39]. Resting-state connectivity within the motor network appears to become less optimized with greater time following the recovery from stroke (1 week to 1 year post-stroke); areas within the network become less clustered and the degree of randomization has been positively related to motor recovery after stroke [9]. In the current study individuals in the stroke group were in the chronic phase of stroke recovery, and thus it is possible that network randomization may also be evident during motor sequence learning. The degree of network randomization, or the final common pathway, may be highly variable as individual brains undergo varied reorganization strategies to

create unique, operable functional networks during motor sequence learning. The structural integrity of transcallosal pathways in individuals with chronic stroke are highly individualized [40]. Differences in corpus callosum integrity connecting the gray matter of the hemispheres, may have contributed to the lack of coordinated activation within the whole brain motor network. Transcallosal tract microstructure, measured by fractional anisotropy (FA; white matter integrity) and neurophysiological function (measure by mean amplitude in muscle activity during the ipsilateral silent period evoked by TMS; transcallosal inhibition) accounts for a high degree of variance in motor impairment and function (measured by Fugl-Meyer score and Wolf Motor Function Test, respectively) [40]. Disruptions in transcallosal pathways in individuals with stroke may be the result of indirect, slowly progressing secondary degeneration of white matter [40]. Subsequently, although variability increases after brain injury, our masked secondary analysis may have isolated regions of preserved structural integrity, resulting in commonalities in connectivity functional important in implicit motor learning.

We tested the relationship between the variability of network connectivity and motor learning in our secondary analysis by constraining (i.e. masking) the brain to assess the intraregional connectivity within the motor network in individuals with stroke. The spatial distribution of this analysis was limited to voxels within the motor network, thus reducing irrelevant activation and maximizing the variance of the BOLD within the motor network. This method elucidated a more restricted functional network with a high level of intrinsic functional connectivity as compared to the whole brain analysis in the stroke group. There were overlaps between the regions that comprised the multivariate and univariate compensatory motor networks in the current study and our previous study [4], respectively, which included ipsilesional insula cortex and contralesional temporal gyrus activation. In our secondary analysis, the largest cluster of activation was within the left medial frontal gyrus (Brodmann's area 6; BA 6). Meehan et al. [4] performed a post-hoc analysis evaluating the percent signal change of the BOLD response in the left medial frontal gyrus, which contains the dorsal premotor cortex (PMd; BA 6), as this region demonstrated significant activation in the whole brain univariate analysis during repeated tracking at retention for the healthy control group. Similarly to the present study, activation in the frontal medial gyrus after stroke significantly correlated with tracking error (i.e. RMSE) at retention [4]. However, the specific region of activity within the medial frontal gyrus in the two studies did not overlap. This difference likely stems from methodological differences between the two analytical approaches. The secondary analysis in the Meehan et al. study relied on coordinates from the peak activation derived from the healthy control group whole brain univariate analysis to determine and illustrate the relationship between level of activation of the medial frontal gyrus and behavioral performance at retention [4]. In the present paper our secondary analysis relied on multiple regions derived from the healthy control group whole brain multivariate analysis to determine and illustrate the relationship between level of intraregional connectivity and behavioral performance. Findings from both univariate and multivariate analyses demonstrate importance of the medial frontal gyrus during motor learning following stroke; however sub-regional discrepancies exist between the coordinates associated with the level of peak activation and those associated with coordinated activity with other regions.

Applying a multivariate analysis to the present data set allowed the BOLD signal in regions that followed similar temporal patterns of activation to emerge as a part of the task-dependent network. Multivariate analysis increases the sensitivity of signal detection, as regions with weaker signals that still contribute to a task-dependent network might be negated in whole brain analysis due to voxel-wise statistical inference [41]. At retention, the stroke group demonstrated task-dependent variance of the BOLD response within a larger cluster of activation in the left medial frontal gyrus as well as the right cerebellar lobule, which was not observed in the whole brain univariate analysis [4]. Compared to connectivity within the motor network demonstrated by the HC group, a different pattern of lateralization of brain activity was observed in the stroke group as contralesional cortical involvement of the motor cortex and subcortical involvement of the ipsilesional cerebellum were noted during tracking performance at retention. The hemispheric laterality of connectivity observed within the motor network in the secondary analysis in the ST group, in comparison to the whole-brain analysis in the HC group, may be the result of disruption within the ipsilesional dentatothalamocortical and corticopontine tracts, which are known to connect the ipsilesional motor cortex with the contralesional cerebellar hemisphere [42, 43]. Our lab has previously studied the relationship between corticospinal tract integrity, as measured by white matter tractography in the posterior limb of the internal capsule (PLIC), and motor skilled learning in a cohort of individuals with chronic stroke affecting the middle cerebral artery using diffusion tensor imaging (DTI; [44]. The findings from Borich et al. [40] demonstrated that the degree of motor learning-related change in the performance of a complex visuomotor task is associated with post-training ipsilesional white matter integrity as measured by fractional anisotropy (FA) in the PLIC. The contralesional cortical to ipsilesional cerebellum functional connectivity pattern observed in the compensatory motor network may indicate underlying structural damage of the ipsilesional tractography as the internal capsule encompasses fibers of the dentatothalamocortical and corticopontine tracts [45]. Future studies should assess the underlying tractography of the motor network (dentatothalamocortical and corticopontine tracts) and the relationship of the underlying white matter integrity and skilled motor learning in individuals with chronic stroke.

Individuals with stroke who demonstrated greater connectivity within the compensatory network tracked with less error during the repeated sequence condition at retention (Figure 6). This finding differs from previous literature, which reported that greater activation of the ipsilesional, and reduced activation of the contralesional hemispheres predicts motor recovery following stroke [46]. However, the functional network is highly dependent on the nature of the task, as motorically challenging tasks have been shown to recruit different brain regions [47]. The continuous tracking task employed in the present study is a complex visuomotor task that involves a high level of motor dexterity and control to manipulate a joystick at a specified range of movements and given velocity. Our findings are in accordance with Schaechter and Perdue [43], which concluded that increased activation in the contralesional cortical network was dependent on motor skill challenge in chronic stroke patients that were deemed to have good motor recovery based on their level upper limb function. In the present study, the contralesional motor and ipsilesional cerebellar connectivity may reflect the demands of the task as well as alterations in the structural white matter of the underlying ipsilesional PLIC.

5. CONCLUSION

Findings from the present study support the existence of a motor network for healthy individuals and a variable compensatory motor network for individuals with chronic stroke. Recruitment of this motor network was observed during a retention test for healthy individuals, but after stroke we noted a high degree of inter-participant variability in network activity within the stroke affected brain. An increase in coordinated neural activity within the M1-premotor-parietal-cerebellar circuit observed for the healthy control group may have been limited in the stroke group due to lesion related changes in functional connectivity. Our secondary analysis of the motor network demonstrated greater connectivity of a compensatory network following stroke. Individuals with stroke demonstrated the capacity to implicitly learn a motor sequence, and functional connectivity within the compensatory motor network may be a neurophysiologic biomarker of implicit motor learning. Individuals with greater functional connectivity within this network had superior motor performance following 5 days of motor practice. The findings from the present study provide a baseline for comparison of an optimal efficiency motor network, setting the stage for further fMRI-CPCA motor learning studies. fMRI-CPCA is a task-based multivariate approach that provides statistical information about the importance of functional brain networks to each condition and subject, allowing direct group comparisons. Thus, future studies can evaluate individualized predictor weight values of the motor network in larger populations of stroke groups to determine if subgroups have different levels of connectivity. To enhance the ecological validity of fMRI studies in rehabilitation settings, future work may use longer practice paradigms to determine if a common network can be identified with an increased number of repetitions in individuals with chronic stroke. Thus, the present study provides insights into novel task-based fMRI methods to evaluate the reorganization of functional networks following 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.

Figure 1. T1 weighted images with lesion location

Participants' anatomical images including highlighted lesions in red for the ST group.

Figure 2. Continuous Tracking Task

a) Pictorial of the continuous tracking task apparatus used to perform the task during the 5 days of practice. Participants operated a joystick to move a closed red dot inside an open black circle to track 20 s waveform segments (multiple overlapping lines represent different trials) separate by random and repeating sequences on a computer screen. The fMRI design performed during baseline (day 1) and retention (day 7) used random and repeated sequences that were counterbalanced across scans and performed over 150 s blocks.

Figure 3. fMRI-CPCA Methodology

The fMRI-CPCA methods are delineated for whole brain (WB) and masked analyses outlining the chronological steps (input, analytic processing, output) used to derive the functional connectivity networks (see methods for details).

Figure 4. Plots of whole brain (WB) and masked predictor weights on retention, and images for component one networks revealed by fMRI-CPA at baseline and retention

a) The graph displays the mean predictor weights plotted as a function of condition (repeat, random) and group (stroke, healthy) and analysis (WB and masked) (error bars are standard errors) for baseline (day 1) and retention (day 7). b) The top panel displays the positive loadings of component one for baseline (day 1). The WB network is displayed in red for the dominant 5% of loadings (red, min = 0.21; white, max = 0.40) and the masked network in blue for the dominant 5% of loadings (blue, min = 0.12; turquoise, max = 0.15) of the motor network overlaid on a structural image. The bottom panel displays the positive loadings of component one for retention (day 7). The WB network is displayed in red for the dominant 5% (red, min = 0.17; white, max = 0.30) of the motor network and the masked network in blue for the dominant 5% (blue, min = 0.11; turquoise, max = 0.14) of the motor network overlaid on a structural image.

Figure 5. Tracking performance for baseline (day 1), 5 days of practice and retention (day 7) for the HC and ST group

The average root mean square error (RMSE) is displayed across days for the continuous tracking task (bars represent standard error).

Figure 6. Relationship between functional connectivity in the masked motor network and repeated tracking performance for the ST group at retention (day 7)

This graph depicts the significant negative correlation between the predictor weights for the masked motor network and tracking performance (average root mean squared error (RMSE)) at retention (day 7) for the ST group.

Table 1

Participants' Characteristics

	Sex	Age Mean (SD)	Post-Stroke ^a Mean (SD)	Fugl-Meyer motor UE ^b Mean (SD)
ST Group	6 Males; 3 Females	63.88 (6.214)	53.22 (49.789)	54.33 (12.952)
HC Group	4 Males; 5 Females	63.11 (7.001)		

^a Post-stroke duration is in months.

^b UE, upper extremity (range for Fugl-Meyer UE motor test 0–66; lower scores denote less hemiparetic arm function).

Table 2

Cluster volumes for whole brain (WB) and masked component one at baseline (day 1) for the HC and ST group and ST group, respectively, with anatomical descriptions, Montreal Neurological Institute (Talairach) coordinates for peaks within each cluster.

Day 1: Cortical Regions	Cluster Volume (mm ³)	Talairach Coordinate (x, y, z)	Peak Locations	
WB HC and ST group				
Component 1: <i>Positive Loadings</i>				
Right Precentral Gyrus	4130	39	-13	60
Left Cerebellum Anterior Lobe	794	-18	-48	-24
Left Cerebellum Posterior Lobe	152	-25	-80	-20
Right Cerebellum Anterior Lobe	77	21	-57	-28
Right Postcentral Gyrus	50	3	-56	73
Left Superior Parietal Lobule	42	-33	-59	54
Masked ST Group				
Component 1: <i>Positive Loadings</i>				
Left Lingual Gyrus	1654	-12	-76	-3
Right Inferior Parietal Lobule	488	47	-41	37
Right Middle Temporal Gyrus	254	43	-60	3
Right Superior Frontal Gyrus	199	19	-1	69
Right Inferior Frontal Gyrus	175	45	2	20
Right Superior Frontal Gyrus	153	9	-13	64

Table 3

Cluster volumes for whole brain (WB) and masked component one at retention (day 7) for the HC and ST group and ST group, respectively, with anatomical descriptions, Montreal Neurological Institute (Talairach) coordinates for peaks within each cluster.

Day 7: Cortical Regions	Cluster Volume (mm ³)	Talairach Coordinate (x, y, z)	Peak Locations
WB HC and ST group			
Component 1: <i>Positive Loadings</i>			
Right Postcentral Gyrus	4171	31 -34	31
Left Cerebellum Anterior Lobe	704	-16 -48	-16
Left Superior Parietal Lobule	124	-32 -59	-32
Left Middle Occipital Pole	119	-29 -89	-29
Right Cerebellum (Culmen)	114	23 -56	23
Left Occipital Cortex (Cuneus)	77	-20 -85	-20
Right Lingual Gyrus	52	2 -69	2
Right Inferior Occipital Gyrus	50	19 -91	19
Right Occipital Lobe (Cuneus)	42	21 -83	21
Masked ST group			
Component 1: <i>Positive Loadings</i>			
Left Medial Frontal Gyrus	1630	-6 -23	72
Right Cerebellum (Culmen)	971	25 -61	-25
Right Insular Cortex	167	41 3	14
Right Lateral Occipital Cortex	136	23 -81	20
Left Cerebellum Anterior Lobe	74	-32 -55	-28
Right Middle Temporal Gyrus	41	41 -57	-6
Left Cerebellum (Culmen)	33	-34 -40	-27