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Authors

Stewart, Jill
Dewanjee, Pritha
Shariff, Umar
et al.

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Dorsal Premotor Activity and Connectivity Relate to Action Selection Performance after Stroke

Jill Campbell Stewart,^{1*} Pritha Dewanjee,³
Umar Shariff,³ and Steven C. Cramer^{2,3}

¹Department of Exercise Science, Program in Physical Therapy,
University of South Carolina, Columbia

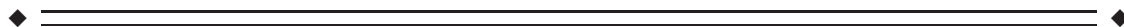
²Department of Neurology, University of California, Irvine

³Department of Anatomy & Neurobiology, University of California, Irvine



Abstract: Compensatory activation in dorsal premotor cortex (PMd) during movement execution has often been reported after stroke. However, the role of PMd in the planning of skilled movement after stroke has not been well studied. The current study investigated the behavioral and neural response to the addition of action selection (AS) demands, a motor planning process that engages PMd in controls, to movement after stroke. Ten individuals with chronic, left hemisphere stroke and 16 age-matched controls made a joystick movement with the right hand under two conditions. In the AS condition, participants moved right or left based on an abstract, visual rule; in the execution only condition, participants moved in the same direction on every trial. Despite a similar behavioral response to the AS condition (increase in reaction time), brain activation differed between the two groups: the control group showed increased activation in left inferior parietal lobule (IPL) while the stroke group showed increased activation in several right/contralateral regions including right IPL. Variability in behavioral performance between participants was significantly related to variability in brain activation. Individuals post-stroke with relatively poorer AS task performance showed greater magnitude of activation in left PMd and dorsolateral prefrontal cortex (DLPFC), increased left primary motor cortex-PMd connectivity, and decreased left PMd-DLPFC connectivity. Changes in the premotor-prefrontal component of the motor network during complex movement conditions may negatively impact the performance and learning of skilled movement and may be a prime target for rehabilitation protocols aimed at improving the function of residual brain circuits after stroke. *Hum Brain Mapp* 37:1816–1830, 2016. © 2016 Wiley Periodicals, Inc.

Key words: motor planning; upper extremity; imaging; functional connectivity



INTRODUCTION

The performance of skilled actions recruits a number of nodes in a distributed neural network that is behavior

specific. For skilled movement, this network often includes cortical regions in both hemispheres, especially for complex tasks [Catalan et al., 1998; Verstynen et al., 2005]. A commonly reported compensatory activation pattern in

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*Correspondence to: Jill Campbell Stewart, PhD, PT, University of South Carolina, 921 Assembly Street, Room 301D, Columbia, SC 29208. E-mail: jcstewar@mailbox.sc.edu

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older adults and in individuals with neurologic diagnoses is an increase in the number and magnitude of nodes recruited to support behavioral performance [Rehme et al., 2012; Seidler et al., 2010; Spreng et al., 2010]. This increase in activation is often bilateral and has been found across a variety of cognitive and motor tasks.

After stroke, persistent motor deficits are common and often associated with changes in activation in the motor network. Compensatory brain activation during movement within both ipsilesional and contralesional brain regions has been frequently reported [Carey et al., 2002; Lotze et al., 2006; Schaechter and Perdue, 2008; Schaechter et al., 2008; Ward et al., 2003]. One often cited region of compensatory activation is bilateral dorsal premotor cortex (PMd) [Bestmann et al., 2010; Fridman et al., 2004; Johansen-Berg et al., 2002; Ward et al., 2006], although the precise role of PMd in the control of movement after stroke is not fully known. Studies to date have reported an important role for PMd in movement execution after stroke that is increased in individuals with greater motor impairment [Ward et al., 2006, 2007]. However, PMd plays a variety of roles in the control of skilled movement beyond simple execution, especially in movement planning [Kantak et al., 2012]. It is not currently known how the stroke damaged brain responds to task conditions that target the PMd node of the motor network.

One well-studied role for PMd in movement planning in nondisabled individuals is in the process of action selection (AS). AS, or selection of a movement response, is a critical feature of voluntary action. Task conditions that relatively increase AS demands for movement result in longer planning times than simple motor execution tasks, with a corresponding increase in bilateral PMd and bilateral parietal cortex activation [Grafton et al., 1998; Grol et al., 2006; O’Shea et al., 2007; Toni et al., 2002]. Selection of a movement response based on external, visual cues that are abstract in nature and require some degree of visuomotor transformation have been shown to engage PMd to a greater extent [Hanakawa et al., 2006]. However, the neural correlates of AS and the role of PMd for AS after stroke have not been reported.

Response to behavioral interventions aimed at improving arm motor function varies greatly after stroke [Cramer, 2008; Prabhakaran et al., 2008; Stinear, 2010]. Both degree of motor impairment and residual corticospinal tract integrity have been shown to be significant predictors of response to treatment [Chen and Winstein, 2009; Riley et al., 2011; Stinear, 2010; Stinear et al., 2007]. However, continued difficulty incorporating the affected arm and hand into everyday life can persist, even in individuals deemed to have “good” motor recovery [Stewart and Cramer, 2013], suggesting additional factors play a role. One important factor may be the ability to effectively engage a node or set of nodes of the motor network based on selected changes in task demands. Structuring practice during rehabilitation to engage specific neural resources may serve as an adjunct to repetitive movement training after stroke [Cramer et al., 2011; Dodakian et al., 2013]. Given the role PMd is hypothesized to play in motor recovery after stroke, this region is a prime candidate for a targeted rehabilitation protocol aimed at improving the function of residual brain circuits.

The purpose of this study was to determine the behavioral and neural correlates of motor AS in individuals with motor system damage due to stroke. We hypothesized that individuals post-stroke would show a significant increase in planning time that corresponded to an increase in bilateral PMd and parietal cortex activation for AS compared to simple movement execution. We also hypothesized that variability in AS task performance between individuals would correlate with variability in brain activation (magnitude and functional connectivity), specifically in relation to PMd. Since AS task performance could have had a positive or negative correlation with PMd activation, this behavior-brain function hypothesis was two-tailed.

MATERIALS AND METHODS

Participants

Ten individuals in the chronic phase of stroke recovery and sixteen age-matched nondisabled controls were recruited from the local community. Potential participants had to be at least 18 years old and right-hand dominant [Oldfield, 1971] (determined by pre-stroke handedness). Participants with stroke were included if they had a history of stroke at least 6 months prior to enrollment and mild to moderate motor impairment in the right arm as demonstrated by a score between 30 and 60 on the upper extremity Fugl-Meyer (UE FM) motor section [Fugl-Meyer et al., 1975]. Potential participants were excluded if they had a Mini-Mental State Exam [Folstein et al., 1975] score less than 26, history of any non-stroke neurologic diagnosis in participants with stroke and any neurologic diagnosis in controls that affected movement of the arms, or contraindication to magnetic resonance imaging (MRI) [Kleim et al., 2007]. Participants with stroke were excluded

Abbreviations

ANOVA	Analysis of variance
AS	Action selection
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor images
EO	Execution only
FA	Fractional anisotropy
IPL	Inferior parietal lobule
MRI	Magnetic resonance imaging
MT	Movement time
PPI	Psychophysiological interaction
ROI	Region of interest
RT	Reaction time

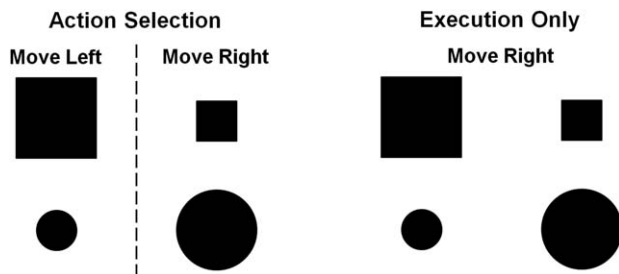


Figure 1.

Participants moved a joystick under two experimental conditions. During *action selection*, movement direction was dictated by an abstract rule (large square or small circle = move left; small square or large circle = move right). During *execution only*, movement direction was the same on every trial regardless of visual cue. Movement direction (right/left) for execution only was counterbalanced across participants.

if they had significant sensory loss (<50% of normal on the Nottingham sensory scale [Lincoln et al., 1998]) or severe ideomotor apraxia (score <65 on the Test of Upper Limb Apraxia (TULA) [Vanbellingen et al., 2010]). All participants provided informed consent on a form approved by the university institutional review board.

Motor Task

All participants performed the motor task with the dominant/paretic, right hand. The task involved right or left movement of a standard joystick based on a visual cue in two different conditions. In the AS condition, the individual moved right or left based on an abstract rule (Fig. 1). When a small square or large circle was shown, a joystick movement to the right was made; when a large square or small circle was shown, a joystick movement to the left was made. Small cues were 50×50 pixels in size while large cues were 200×200 pixels. In the execution only (EO) condition, the visual cues were the same, however, the participant made a joystick movement in the same direction on every trial irrespective of the size/shape of the cue. Movement direction for EO was counterbalanced across participants. In both conditions, a single cue was presented for 2 sec in a pseudorandom order such that each cue was presented six times in each block (36 trials per block). The inter-trial interval varied between 2.0 and 3.25 sec to minimize anticipatory responses prior to the cue.

Prior to MRI, a training session in the laboratory was completed to ensure understanding of both task conditions. First, verbal and visual instruction on the AS condition was provided followed by a practice block of the AS condition. Three blocks of each condition were then completed in alternating order; the condition completed in the first block (AS/EO) was counterbalanced across participants. After completion of the training blocks, the participant practiced the MRI version of the task. This version

alternated periods of movement (cues were green) with periods of view only (cues were red) in a block design (see below) and included a total of 10 movement trials (five trials per movement epoch).

Brain Imaging

All brain imaging sessions were performed on a 3T Achieva MRI scanner (Phillips Medical System, Best, Netherlands). Functional MRI (fMRI) data were acquired using a block design while the participants performed the AS and EO tasks with an MRI compatible joystick (Current Designs, Philadelphia, PA). Periods of movement (Move, 24 sec) alternated with periods of view only (View, 24 sec) with a fixation period (red cross, 8 sec) between each epoch. Cue duration (2 sec) and the inter-trial interval (varied between 2.0 and 3.5 sec) were the same as during practice in the laboratory. Just prior to entering the scanner, the movement rule for the AS condition was reviewed; no additional reminders of the rule were provided during scanning. Each participant completed four fMRI runs, two in the AS condition and two in the EO condition in alternating order; the condition completed in the first run (AS/EO) was counterbalanced across participants. Functional runs lasted for 2 minutes 10 seconds during which 65 brain volumes were acquired (TR = 2000 ms, TE = 30 ms); each volume included 31 slices that were 4 mm thick with a slice gap of 1 mm (acquisition voxel size $2.5 \text{ mm} \times 2.5 \text{ mm} \times 4 \text{ mm}$). Next, a high resolution structural MPRAGE image was acquired (TR = 8.4 ms, TE = 3.9 ms) which included 150, 1 mm thick slices with no interslice gap (acquisition voxel size $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$). Diffusion tensor images (DTI) were acquired using echo planar imaging (TR = 11,190 ms, TE = 69 ms) and included 60, 2 mm axial slices with no interslice gap, 32 directions, and a b value of 800 s/mm^2 . Total scan time for each session was approximately 45 minutes.

Data Analysis

Behavioral data

Data from the joystick were used to determine task accuracy, reaction time (RT), and movement time (MT) using a custom script in Matlab (Matworks, Inc., Natick, MA). Position data (x, y) were recorded throughout each trial (60 Hz in the laboratory, 30 Hz in the MRI) and used to derive movement velocity [Winter, 2005]. RT, the primary behavioral outcome measure, was the time between cue presentation and movement onset. Movement onset was determined by searching backward in time from initial peak velocity until velocity dropped below $5^\circ/\text{sec}$ for two consecutive samples or the change in velocity dropped below $1^\circ/\text{sec}$ for two consecutive samples, whichever was identified first. Movement offset was determined by searching forward in time from peak velocity until velocity dropped below $10^\circ/\text{sec}$ for two consecutive

samples. AS RT was normalized to EO RT to determine RT cost (AS RT – EO RT), a measure of the relative increase in planning time for the AS condition for each participant. MT was the time between movement onset and movement offset. All movement data were analyzed with a mixed model analysis of variance (ANOVA) that included two within group factors (condition, trial block) and one between group factor (control, stroke). Data collected during fMRI were analyzed separately with an ANOVA to determine differences between conditions and groups during scanning. Significant level was set at $P < 0.05$ for all statistical tests. JMP 8 (SAS, Cary, NC) statistical software was used for analyses.

Corticospinal tract integrity

Corticospinal tract integrity was quantified using the DTI images. Analysis was completed in FSL (FMRIB Center, Oxford, UK) using the FDT toolbox [Behrens et al., 2003]. Diffusion images were corrected for eddy currents and head motion followed by removal of the skull and dura [Smith, 2002]. A voxelwise map of fractional anisotropy (FA) was then created. FA is a measure of the structural integrity of white matter with values ranging between 0 and 1 with higher values indicating greater structural integrity [Mori and Zhang, 2006]. To determine corticospinal tract integrity, a region of interest (ROI) mask was manually drawn on the axial slice that showed the largest cross-sectional area of the cerebral peduncle [Burke et al., 2014; Mark et al., 2008]. Mean FA was extracted from each ROI using a threshold of $FA > 0.2$ and used to determine FA asymmetry between the lesioned and nonlesioned side ($FA_{\text{contralesional}} - FA_{\text{ipsilesional}} / FA_{\text{contralesional}} + FA_{\text{ipsilesional}}$) [Stinear et al., 2007].

Functional imaging data

All functional imaging data were analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). First, volumes from each run were realigned to the first volume and resliced to account for motion artifact. The mean image for each participant was then normalized to the standard Montreal Neurological Institute EPI template in SPM. The normalization parameters were then applied to all of the functional volumes for that participant, and the normalized images were resampled to $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$ voxels. Images were then spatially smoothed with an isotropic Gaussian filter (FWHM = 8 mm) and a temporal filter was applied (1/128 Hz) to remove low frequency confounds. Data from each functional run were inspected for outliers due to excessive head motion ($> 1 \text{ mm}$ translation or > 0.2 radians rotation between each volume) or signal noise ($Z > 3$ from the mean image intensity) using the Artifact Detection Tool toolbox (http://www.nitrc.org/projects/artifact_detect); outliers were de-weighted during statistical analysis. A single run from two participants in the stroke group were excluded from data analysis due to excessive noise (both for the EO

conditions); all remaining runs for all participants were included in analyses.

First-level statistical analysis was performed separately for each participant using a general linear model [Friston et al., 1995a,b]. For each run, Move and View epochs were modeled separately against fixation for later contrast. To determine the regions active during each condition (EO, AS), Move was contrasted with View (Move $>$ View); both runs for each condition were weighted equally in all contrasts. For first-level analyses, the first derivative of head motion for all six directions, which was uncorrelated with stimulus presentation, was added as a regressor of no interest to account for the effect of head motion in the data.

The contrast maps for each participant and each condition (Move $>$ View contrasts for EO and AS) were moved to a second-level random effects analysis. Group analyses were performed using a factorial design that included a factor for group (control, stroke) and a factor for condition (EO, AS). This design allowed for the analysis of main effects (group, condition) as well as group \times condition interactions. Additionally, a t contrast between conditions (EO $>$ AS, AS $>$ EO) was run for each group separately. MT (mean during all fMRI trials) was included as a regressor of no interest to account for differences in movement response unrelated to RT. To examine the relationship between variability in behavioral performance and variability in brain activation between individuals, regression analysis was performed between RT cost and the AS contrast map. RT cost represents the relative increase in RT for each individual participant for the AS condition after controlling for EO RT. Age and MT were included as regressors of no interest. For group comparisons, statistical significance was set at $P < 0.001$ uncorrected for multiple comparisons.

Functional connectivity analysis

Psychophysiological interaction (PPI) analysis was performed to identify brain regions in which the connectivity with M1 and PMd changed as a function of task condition [Friston et al., 1997; Gitelman et al., 2003]. PPI is a measure of functional connectivity that identifies changes in correlation between the seed region and other regions based on a psychological variable (e.g., task condition: EO, AS); analyses were carried out separately using M1 and PMd as seed regions. For each subject, after carrying out a GLM statistical analysis, the time series of the mean corrected, high-pass filtered BOLD signal was extracted from M1 and PMd (4 mm radius sphere centered on each participants peak of activation determined using previously defined masks of M1 and PMd [Mayka et al., 2006]). This time series and the psychological vector of interest (action selection minus execution only) were used to create the PPI interaction term. The interaction term as well as the seed region time series and psychological vector were entered into a first-level model of connectivity. Brain areas showing an increase in connectivity with the seed region

in the AS condition were determined by testing for significant positive changes in slope of the PPI regressor (t -contrast with +1 for the PPI regressor). Regions showing a decrease in connectivity with the seed regions in the AS condition were determined by testing for significant negative changes in slope of the PPI regressor (t -contrast -1 for the PPI regressor). Contrast images from both comparisons (increased connectivity in AS, decreased connectivity in AS) were then entered into separate second-level random effects analyses (one-sample t -test) to determine regions whose connectivity with M1 or PMd changed between task conditions. Statistical significance was set at $P < 0.001$ without correction for multiple comparisons.

To further explore the relationship between variability in behavior and variability in brain activation, we examined the correlation between brain connectivity and RT cost. PPI analysis is designed to test for differences in the regression slope between the seed region and other brain areas based on task condition. Therefore, the time series data from one ROI was plotted against the time series data of another ROI and the slope of the regression line was extracted separately for each of the two conditions (EO, AS) [Lin et al., 2013]. The change in slope from EO to AS was the measure used to define the effect of task condition on functional connectivity. If the slope increased, the activity in the two brain regions was more correlated in the AS condition than the EO condition. If the slope decreased, the activity between the two brain regions was less correlated in the AS condition. To determine if change in connectivity related to variability in task performance between participants, the change in slope between left M1 (centered on the group peak derived from average activation across conditions) and each region identified in the regression analysis was correlated with RT cost. Significance level was set at $P < 0.05$ and the strength of correlations were interpreted based on the value of the correlation coefficient: $r < 0.25$ = little or no relationship; r of 0.25 to 0.50 = fair; r of 0.50 to 0.75 = moderate; $r > 0.75$ = strong [Portney and Watkins, 2009].

RESULTS

Participants

Participant demographics are presented in Table I. Overall, the stroke group presented with mild to moderate motor impairment (mean UE FM motor score = 52.3), reported moderate difficulty in using the paretic hand to perform functional activities (mean Stroke Impact Scale hand domain score = 3.6), and did not have apraxia (mean TULA score = 230.8). Stroke lesions were subcortical except for a single participant who had injury into temporoparietal cortex (Fig. 2). M1 and PMd were not injured by stroke in any participant. The stroke and control groups did not differ in age or cognitive status (total digit span

score) but did differ in motor status (Box & Blocks ratio) and FA asymmetry in the corticospinal tract.

Motor Task Performance

Accuracy, RT, MT, and RT cost in both conditions across blocks are shown in Figure 3. As expected, participants in both groups were very accurate during performance of the EO task. Accuracy on the AS task was overall lower in the stroke group compared to the control group during pre-scan behavioral testing ($P = 0.007$), however, both groups showed an improvement in accuracy over successive blocks ($P = 0.006$) such that by the time of fMRI scanning, task accuracy for the AS condition averaged >90% and did not differ between groups ($P = 0.4$). Across groups, RT for the AS task was significantly longer than for the EO task ($P < 0.0001$). Action selection RT significantly decreased over practice blocks ($P < 0.0001$) while EO RT did not change ($P = 0.1002$). Therefore, changes in RT cost over practice blocks ($P < 0.0001$) were driven by faster RT during AS. There was no significant difference between groups for RT or RT cost ($P > 0.311$), however, MT was significantly longer in the stroke group ($P = 0.005$).

During fMRI, motor performance was stable and similar to performance in the laboratory (Fig. 3). In both groups, RT for AS was significantly longer than for EO ($P < 0.0001$) while MT did not differ between conditions ($P = 0.535$). While RT for both conditions was longer during MRI testing compared with in the laboratory, RT cost during fMRI was consistent with the end of practice in the laboratory across groups ($P = 0.927$). MT was longer in the stroke group compared to controls during fMRI ($P = 0.023$), but RT and RT cost did not differ between groups ($P > 0.119$). For the control group, age had a moderate, positive correlation with AS RT ($r = 0.508$, $P = 0.044$) and RT cost ($r = 0.494$, $P = 0.052$) but not EO RT ($r = 0.205$, $P = 0.447$) during fMRI. In the stroke group, EO RT, AS RT and RT cost did not significantly correlate with age, UE FM motor score or Box & Blocks ratio ($r < 0.31$, $P > 0.417$ for all comparisons), or corticospinal tract integrity as measured by FA asymmetry ($r < 0.482$, $P > 0.158$).

Brain Activation during Task Performance

Brain activation during the EO and AS task conditions is shown in Figure 4. Performance of the EO task (repetitive movement in the same direction) activated the expected motor network including left M1, PMd, supplemental motor area, thalamus, and cerebellum (Table II). Overall, across control and stroke groups, activation increased during performance of the AS task in both hemispheres. However, for comparisons of activation between the two conditions (AS > EO; EO > AS), no significant clusters were found at the predefined significance level ($P < 0.001$). When a more liberal threshold was applied ($P < 0.005$), differences between groups were found in how

TABLE I. Participant demographics

	Stroke	Control
N	10	16
Age	66.3 ± 5.8	65.0 ± 9.0
Gender	4F/6M	10F/6M
Corticospinal FA Asymmetry	0.11 ± 0.08	0.00 ± 0.03 ^a
Box & Blocks Ratio (R/L)	0.64 ± 0.31	1.03 ± 0.05 ^a
Digit Span Total	13.9 ± 4.8	17.0 ± 2.8
Months post-stroke	42.5 ± 24.7	
UE FM Motor	52.3 ± 9.1	
Stroke Impact Scale Hand Domain	3.6 ± 1.1	
TULA Total	230.8 ± 6.8	

Values represent group mean ± standard deviation.

^a $P < 0.05$ between groups.

brain activation changed from the EO to the AS task (Fig. 4; Table III). In the control group, performance of the AS task corresponded to increased activation in left inferior parietal lobule (IPL). In the stroke group, performance of the AS task corresponded to increased activation in several regions in the right, contralesional hemisphere including inferior frontal gyrus, fusiform gyrus, anterior cingulate cortex, and IPL along with the left cerebellum. A group by condition interaction revealed three significant clusters where change in activation from the EO to the AS condition differed by group: right anterior cingulate cortex, right visual association cortex, and right fusiform gyrus. For all three clusters, this difference between groups was driven by no change in activation between conditions in the control group and an increase in activation from the EO to the AS condition in the stroke group.

Whole brain PPI analysis was carried out separately with left M1 (mean peak coordinates: -32 -20 64) and left PMd (mean peak coordinates: -24 -7 69) used as the seed region. This analysis was performed to determine changes in the correlation between M1/PMd and other

brain regions based on task condition (EO > AS; AS > EO). There were no significant clusters that changed their relationship with M1 or PMd between the EO and AS conditions across participants in the whole brain analysis, both when the groups were analyzed separately and when the groups were combined.

Neural Correlates of Interindividual Variability in Task Performance

Whole brain regression analysis was run in order to determine if variability in task performance between participants was related to variability in brain activation. Since RT cost did not significantly differ between the control and stroke groups during fMRI, all participants from both groups were included in a single regression analysis. Three clusters were found where activation significantly correlated with RT cost: left dorsolateral prefrontal cortex (DLPFC), left PMd, and left visual association cortex (Fig. 5; Table IV). All three clusters showed a positive correlation with RT cost, i.e. individuals who took relatively longer to prepare a response in the AS condition had greater activation in each of these regions. A post-hoc analysis determined that the relationship between brain activation and RT cost was similar in the stroke and control groups (no group by activation interaction for explaining RT cost; see Fig. 5). Additionally, within the stroke group, variability in brain activation between participants was not significantly related to clinical measures of arm function (no relationship between percent signal change and UE FM motor score or Box & Blocks ratio; $P > 0.1$ for all comparisons) or corticospinal tract integrity as measured by FA asymmetry ($P > 0.82$).

To further explore the relationship between variability in behavioral performance and variability in brain activation, the correlation between brain connectivity and RT cost was examined. This analysis focused on changes in

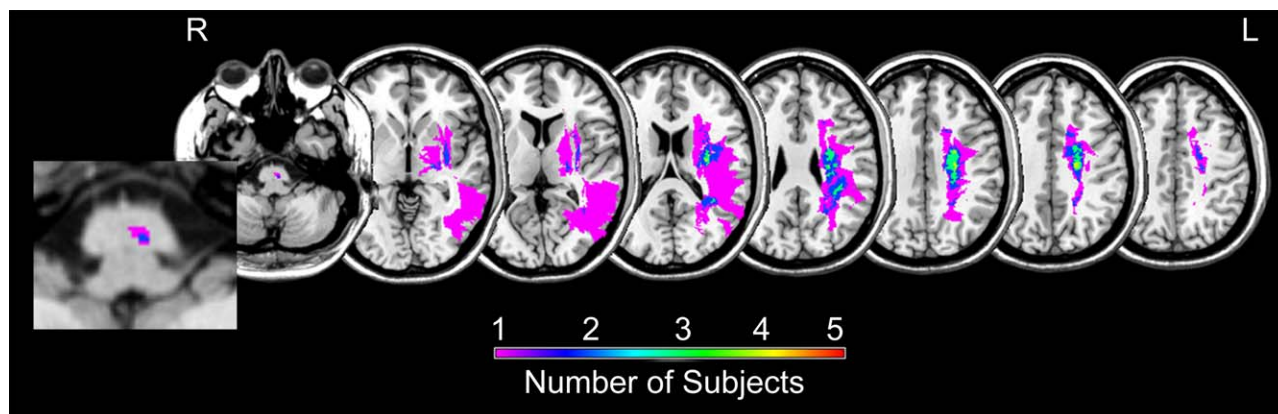


Figure 2.

Summary mask of stroke lesions created using MRIcron (www.mccauslandcenter.sc.edu/micromicron/). Color represents number of participants with a stroke in that region.

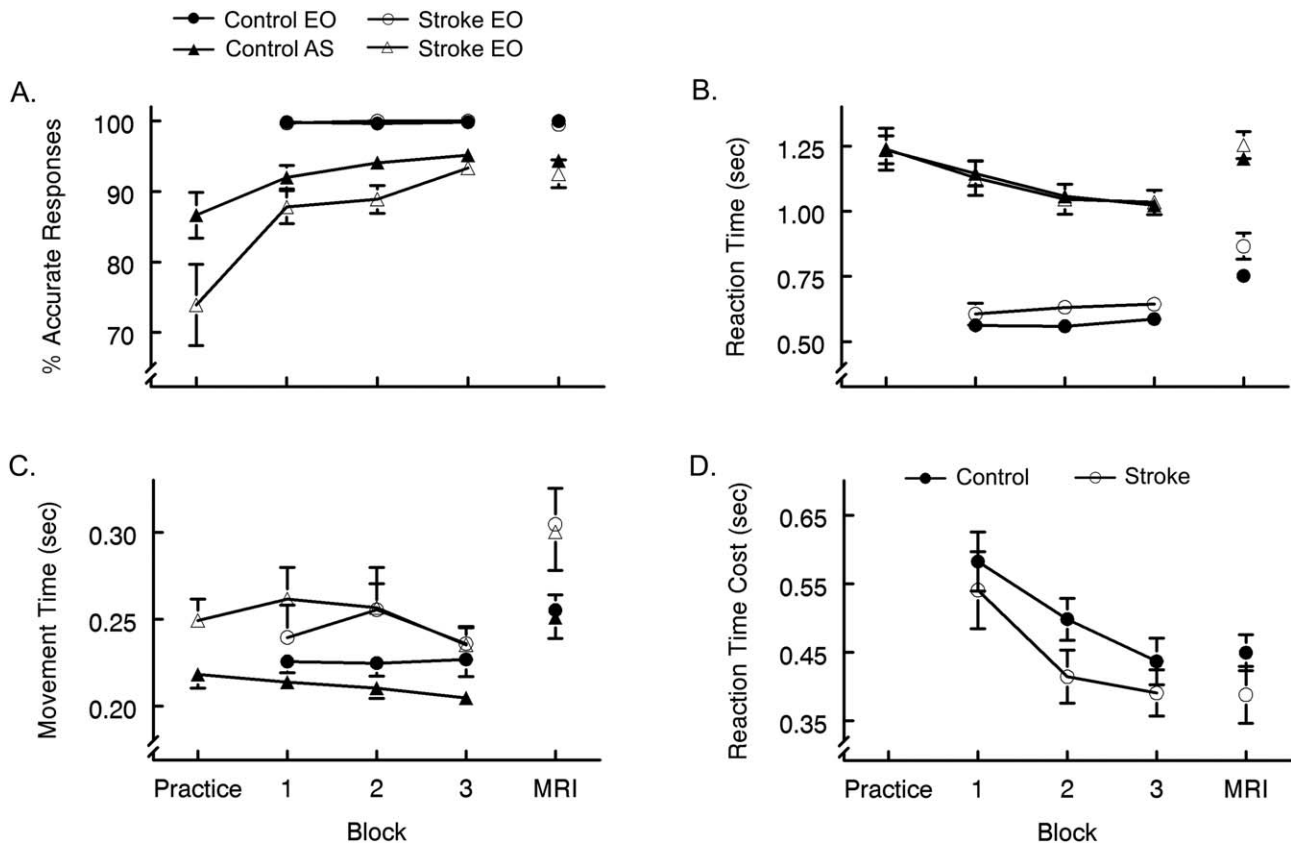


Figure 3.

Behavioral performance for both experimental conditions and groups shown for task accuracy (A), RT (B), MT (C), and RT cost (D). Each data point represents the group mean with standard error bars. Practice through Block 3 was completed in the laboratory prior to MRI.

connectivity from the EO to the AS task condition between left M1, PMd, and DLPFC (Fig. 6A,B) based on the results of the regression analysis above. For controls, no significant correlation between change in connectivity and RT was found for any comparison. In the analysis of PMd-M1 connectivity, two groups of control participants emerged (increase in connectivity, decrease in connectivity) that was explored in a previous analysis [Stewart et al., 2014]. For the stroke group, a relationship between change in connectivity and RT cost was found. Change in PMd-DLPFC connectivity showed a significant negative correlation with RT cost ($r = -0.640$, $P = 0.046$); individuals with longer RT cost tended to show a decrease in connectivity between these two brain regions during AS (Fig. 6D). Change in PMd-M1 connectivity showed a relationship with RT cost in the opposite direction; individuals with longer RT tended to show an increase in PMd-M1 connectivity (Fig. 6C). While the relationship between PMd-M1 connectivity and behavior was fair in strength, the correlation was not statistically significant. However, when an outlier was removed (stroke subject with the lowest RT cost across all participants), the relationship between PMd-

M1 connectivity and RT cost was strong and significant ($r = 0.842$, $P = 0.004$). Therefore, overall, individuals who had relatively lower RT cost (better performance), showed a decrease in PMd-M1 connectivity and an increase in PMd-DLPFC connectivity; individuals who had relatively higher RT cost (worse performance) showed an increase in PMd-M1 connectivity and a decrease in PMd-DLPFC connectivity. These relationships were not related to clinical presentation; connectivity between regions did not correlate with UE FM motor or Box & Blocks ratio ($P > 0.62$ for all comparisons) or with corticospinal tract integrity as measured by FA asymmetry ($P > 0.381$).

DISCUSSION

This study examined the behavioral and neural correlates of motor AS after stroke. Similar to controls, there was a significant increase in movement preparation time to perform the AS task compared to simple movement execution (EO) in the stroke group. However, despite a similar increase in RT in the stroke and control groups,

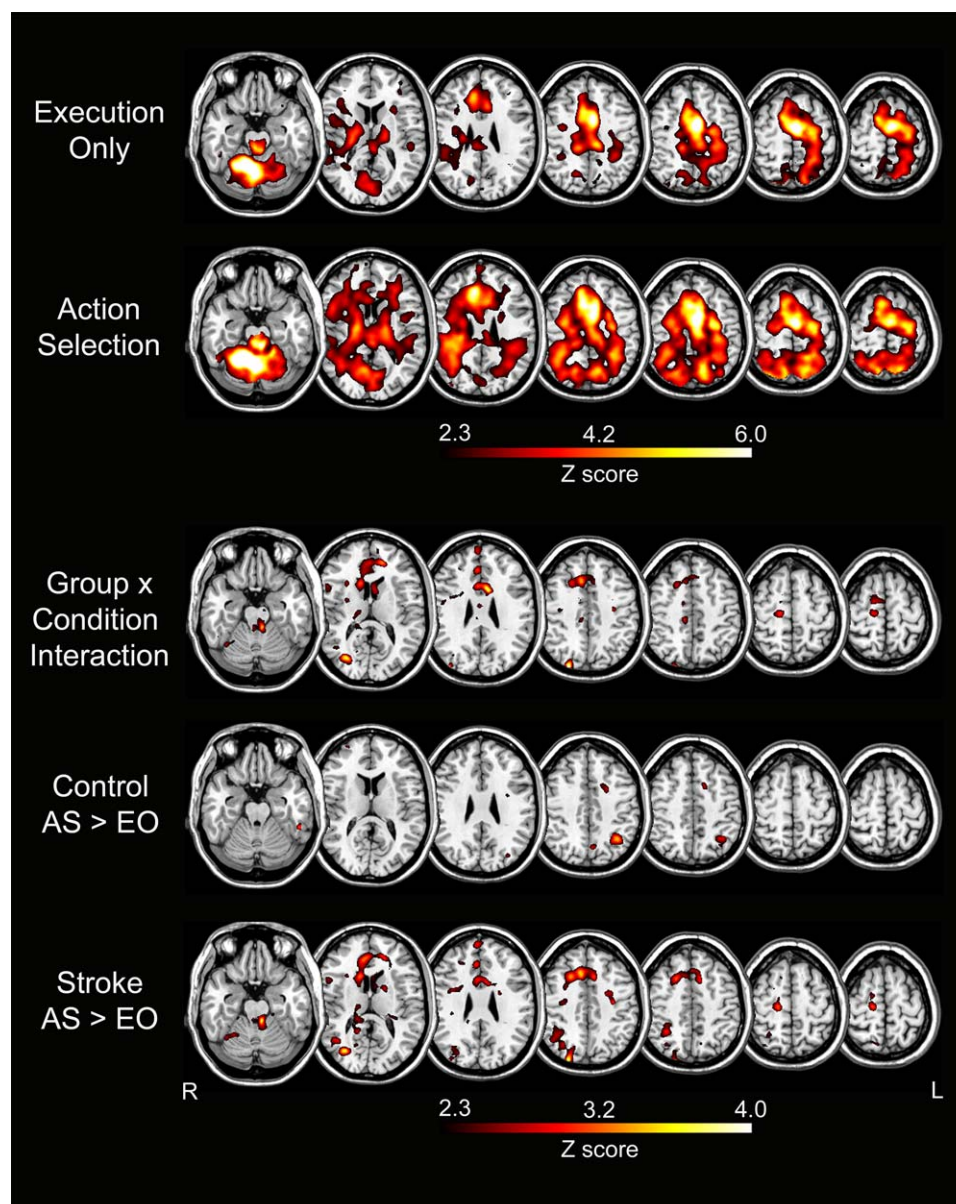


Figure 4.

Group analysis of brain activation including main effect of condition (execution only, action selection) for the control and stroke groups combined, group \times condition interaction, and a t-contrast of conditions (AS > EO) for each group separately (Control, Stroke). MT was included as a regressor of no interest in all comparisons.

the neural resources utilized to perform the AS task differed between groups. In the control group, the increase in planning time for the AS condition corresponded to increased activation in the IPL *contralateral* to the moving hand similar to previous studies in young controls [Grafton et al., 1998; Grol et al., 2006; O’Shea et al., 2007; Toni et al., 2002] and discussed in a previous paper [Stewart et al., 2014]. In the stroke group, the increase in planning

time for the AS condition corresponded to increased activation in several *contralateral* brain regions that were *ipsilateral* to the moving hand. Additionally, variability in behavioral performance on the AS task between participants with stroke correlated with brain activation in ipsilateral premotor and prefrontal cortices. Specifically, relatively *better* performers (lower RT cost) showed decreased activation magnitude in left PMd and DLPFC,

TABLE II. Location of significant clusters for each condition

Condition	Brain region	Volume	Peak Z	MNI coordinates		
				x	y	z
Execution only	R cerebellum	2630	Inf	10	-54	-18
	L supplementary motor area	2553	7.43	-4	-8	54
	R supplementary motor area			10	4	50
	R anterior cingulate cortex			6	12	40
	L dorsal premotor cortex			-24	-12	56
	L cerebellum	185	6.16	-32	-50	-36
	R midbrain	192	5.61	5	-25	-14
	L thalamus	129	5.41	-16	-18	4
	R thalamus	40	4.96	16	-12	8
	R anterior cingulate cortex	31	4.90	10	30	28
Action selection	L primary motor cortex	23	4.78	-30	-28	52
	R cerebellum	6483	Inf	8	-54	-16
	L cerebellum			-32	-50	-34
	R midbrain			4	-30	-16
	L midbrain			-2	-30	-20
	L supplementary motor area	4204	7.05	-6	0	48
	R supplementary motor area			4	16	66
	L dorsal premotor cortex			-28	-16	58
	L anterior cingulate cortex			10	30	28
	R anterior cingulate cortex			-8	22	36
	L precuneus	420	5.63	-12	-62	50
	L inferior frontal gyrus	169	5.42	-30	22	-6
	R inferior parietal lobule	531	5.25	38	-48	36
	R precuneus	73	5.08	10	-66	60
L inferior parietal lobule	64	4.94	-30	-46	42	
R dorsal premotor cortex	30	4.85	32	-8	42	

All clusters were significant at $P < 0.05$ with familywise error correction for analysis of each condition with control and stroke groups combined. Volume = number of 8 mm^3 voxels in cluster; Peak Z = peak Z value within the cluster; L = Left; R = Right; Inf = Infinity. For large clusters, the locations of several local maxima within the cluster are listed.

decreased left PMd-M1 connectivity, and increased left PMd-DLPFC connectivity. On the other hand, relatively worse performers (higher RT cost) showed increased activation magnitude in left PMd and DLPFC, increased left PMd-M1 connectivity, and decreased left PMd-DLPFC

connectivity. Overall, the findings of the current study suggest that the behavioral response to the addition of AS demands to movement after stroke relates to the pattern of engagement of ipsilesional premotor and prefrontal brain regions.

TABLE III. Location of significant clusters for group analyses

Comparison	Brain region	Volume	Peak Z	MNI coordinates		
				x	y	z
Control group AS>EO	L inferior parietal lobule	147	3.52	-34	-56	44
Stroke group AS>EO	R inferior frontal gyrus	789	4.06	24	30	0
	R fusiform gyrus	1121	4.02	26	-50	-12
	L cerebellum	448	3.66	-4	-48	-18
	R dorsal anterior cingulate	623	3.57	10	24	44
Group \times condition interaction	R inferior parietal lobule	253	3.35	42	-56	38
	R dorsal anterior cingulate	429	4.02	8	20	44
		665	3.46	4	44	8
	R visual association cortex	290	3.84	30	-76	12
	R fusiform gyrus	488	3.41	30	-54	-14

All clusters were significant at $P < 0.005$ uncorrected for multiple comparisons. Volume = number of 8 mm^3 voxels in cluster; Peak Z = peak Z value within the cluster; R = Right; L = Left; AS = Action Selection; EO = Execution Only.

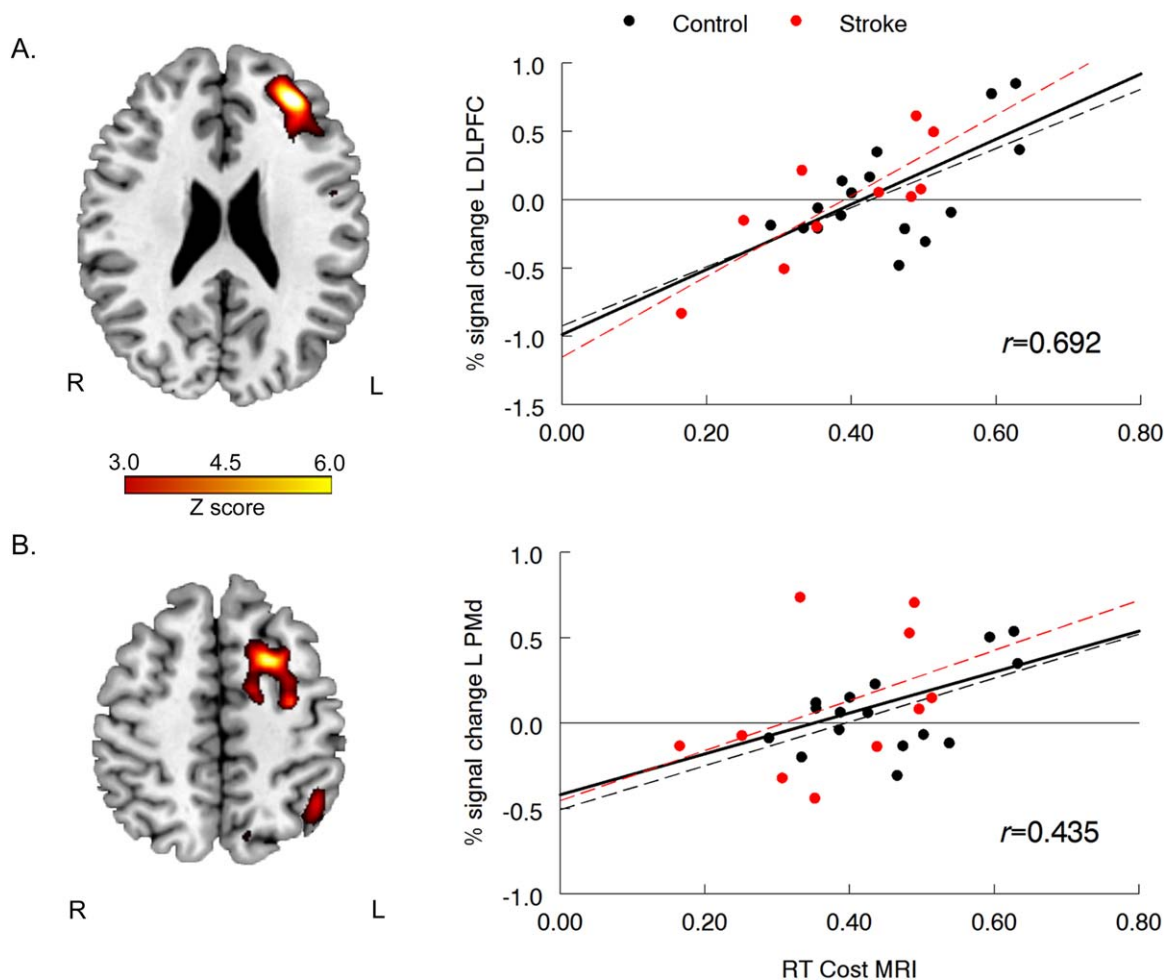


Figure 5.

Results of whole brain regression analysis between RT cost during MRI and brain activation during the action selection condition with age and MT included as regressors of no interest: **(A)** left dorsolateral prefrontal cortex (DLPFC), and **(B)** left dorsal premotor cortex (PMd). For scatter plots, percent signal change was extracted from the significant cluster ($P < 0.001$ uncor-

rected for multiple comparisons) during action selection; each data point represents performance for a single participant. Solid regression line and r value = all participants combined; black dashed regression = Control group only; red dashed regression line = Stroke group only.

As a group, performance of the AS task with paretic, right hand corresponded to increased activation in several right, contralesional brain regions and left cerebellum

using a threshold of $P < 0.005$. Since behavioral response to the AS task did not differ between the stroke and control groups (no difference in RT cost), the engagement of

TABLE IV. Location of significant clusters for regression analyses

	Brain Region	Volume	Peak Z	MNI Coordinates		
				x	y	z
AS with RT Cost (+)	L dorsolateral prefrontal cortex	956	5.06	-32	44	24
	L dorsal premotor	301	4.49	-32	-10	54
	L visual association cortex	154	3.93	-48	-70	-16

All clusters were significant at $P < 0.001$ uncorrected for multiple comparisons. Volume = number of 8 mm^3 voxels in cluster; Peak Z = peak Z value within the cluster; L = Left; AS = Action Selection; RT = Reaction Time; (+)=positive relationship.

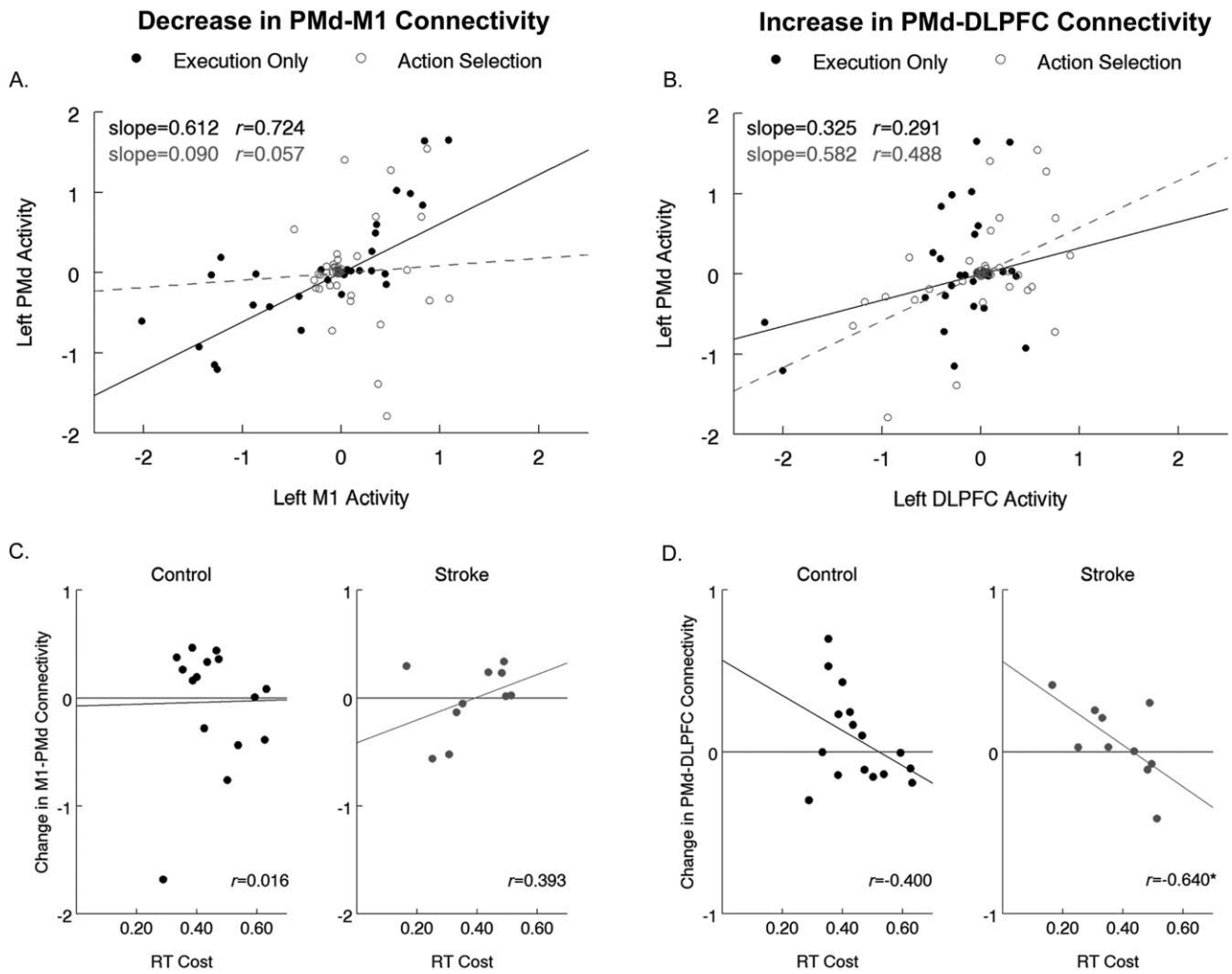


Figure 6.

Results of PPI analysis. **(A)** Exemplary data from an individual participant who had a decrease in left primary motor (M1) - left dorsal premotor cortex (PMd) connectivity during the action selection (AS) condition compared to the execution only (EO) condition (each data point represents activity for a single brain volume). Slope and correlation coefficient (r) were extracted for each participant and condition. **(B)** The same participant showed an increase in PMd - left dorsolateral prefrontal (DLPFC) con-

nectivity during AS compared to EO. **(C)** Change in M1-PMd connectivity (AS slope - EO slope) plotted against RT cost separately for each group. A positive change equates to an increase in connectivity while a negative change equates to a decrease in connectivity from the EO to the AS conditions. **(D)** Change in PMd-DLPFC connectivity (AS slope - EO slope) plotted against RT cost separately for each group. *significant correlation at $P < 0.05$.

contralateral brain regions after stroke likely reflects compensatory activation to maintain task performance [Lotze et al., 2006; Schaechter and Perdue, 2008]. This increase in contralateral activation in the AS condition is consistent with a previous study that showed increased contralateral activation after stroke in response to an increase in task difficulty of a hand movement [Schaechter and Perdue, 2008]. Additional research is needed to fully understand modulation of brain activity based on changes in task conditions after stroke and whether this modulation

changes with targeted practice. Increased neural resource utilization in the contralateral hemisphere during AS after stroke may impact motor learning under training conditions that relatively increase AS demands.

The contralateral brain regions activated in the AS condition included the right IPL, fusiform gyrus, inferior frontal gyrus, anterior cingulate gyrus, and visual association cortex. These brain regions have been previously reported be active during the performance of a motor AS task [Grafton et al., 1998; Grol et al., 2006; O'Shea et al., 2007;

Toni et al., 2002], performance of a motor task that has increased planning demands [Lin et al., 2012; Lin et al., 2011], and completion of a complex motor task in older adults [Heuninckx et al., 2005]. The task in the current study was visually cued. The increase in visual cortex and IPL activation during the AS condition may represent an increase in visual attention [Cross et al., 2007; Kahlbrock et al., 2012] or visuomotor processing [Fogassi and Lupino, 2005; Grefkes and Fink, 2005] in response to the increase in planning demands. Activation in the fusiform gyrus, inferior frontal gyrus, and anterior cingulate cortex suggest an increase in the cognitive control of movement during motor AS after stroke through increased attention and response inhibition [Hampshire et al., 2010; Picton et al., 2007; Sebastian et al., in press] or processing of feedback [Amiez et al., 2012; Holroyd et al., 2004]. Overall, the increase in activation in these regions on the contralesional side may indicate slower learning such that participants with stroke remained at an earlier phase of learning for the AS task despite the same number of practice trials as controls prior to scanning [Patel et al., 2013].

Magnitude of activation in ipsilesional PMd and DLPFC varied between individuals post-stroke and this variability in activation correlated with task performance. Better performance (lower RT cost) was related to lower magnitude of activation in PMd and DLPFC while worse performance (higher RT cost) was related to higher activation magnitude in these regions. The increase in activation magnitude in PMd and DLPFC in poorer performers was not related to age (age was included as a covariate in regression analyses), level of motor impairment, or corticospinal tract integrity, and was similar in the control and stroke groups. This relationship suggests a similar compensatory increase in activation magnitude to maintain task performance in older adults with and without stroke. Increased activation to maintain behavioral performance during movement has previously been reported in older adults [Heuninckx et al., 2008; Mattay et al., 2002; Noble et al., 2011; Ward and Frackowiak, 2003] and after stroke [Carey et al., 2002; Lotze et al., 2006; Schaechter and Perdue, 2008; Schaechter et al., 2008; Ward et al., 2003]. The current study extends this finding to a task that has increased planning demands through the addition of AS demands to movement.

Variability in AS task performance between individuals in the stroke group also correlated with variability in the functional connections in the premotor-prefrontal component of the motor network. PMd connectivity with M1 and DLPFC varied between participants in a manner that related to task performance. In individuals with better performance, left PMd showed increased connectivity with left DLPFC and decreased connectivity with left M1 in the AS condition compared to the EO condition. In individuals with worse performance, however, the relationship was opposite: left PMd showed decreased connectivity with left DLPFC and increased connectivity with left M1. Overall, these results suggest that PMd may have played a

greater role in movement execution during the AS task in some individuals (increased connectivity with M1) and a greater role in movement planning in other individuals (increased connectivity with DLPFC). In individuals who are using PMd to support movement execution [Fridman et al., 2004], this region may be limited in its ability to support other movement related processes such as AS. It has been suggested that PMd may serve as a region of interaction between the motor and cognitive systems [Abe and Hanakawa, 2009; Hanakawa, 2011]. The current study suggests that the ability to effectively allocate PMd resources between the motor and cognitive systems may vary after stroke and that this ability may have an effect on the performance of skilled motor tasks that require both systems. The role of PMd in motor planning after stroke and how this role changes with practice warrants further investigation.

Increased utilization of the cognitive system during movement has been shown in older, nondisabled adults [Heuninckx et al., 2005; Li and Lindenberger, 2002]. Changes in motor performance or neural activation during movement may be a better indicator of aging than chronological age [Schaefer, 2015; Talelli et al., 2008]. The current study suggests a similar relationship in older adults with motor impairment after stroke. Altered patterns of ipsilesional PMd and DLPFC activity during motor AS may indicate changes in the attention and cognitive resources needed to complete a motor planning task that has clinical implications. If the performance of a motor task under conditions of increased complexity requires increased premotor and prefrontal neural resources, less resource may be available to perform additional cognitive tasks (e.g. dual task), to monitor task performance, or to anticipate and plan for the next motor task. Such changes in neural resource utilization may help explain why some individuals post-stroke do not use their arm for the performance of everyday, functional activities despite having minimal to no motor impairment [Han et al., 2013; Stewart and Cramer, 2013]. With the current study design, we cannot determine whether this increased in premotor-prefrontal activation changes with targeted practice; future studies can investigate this question.

We did not find an increase in the magnitude of PMd activation when moving from the EO to the AS condition, ipsilesionally or contralesionally, for the stroke group as hypothesized. There are several possible reasons for this finding. First, PMd was significantly active during the EO condition consistent with previous work showing increased PMd activation with movement execution tasks in older adults [Mattay et al., 2002; Ward and Frackowiak, 2003] and after stroke [Ward et al., 2003; Ward et al., 2006]. Increased PMd activation during the EO condition in participants post-stroke may have made it more difficult to find statistically significant increases in activation during performance of the AS task. Second, modulation of brain activity to meet a change in task demands may be altered after stroke. The control participants in the current study showed limited changes in brain activation between task conditions consistent with previous

work showing a decrease in the modulation of brain activation to meet changes in motor task demands in older adults [Heuninckx et al., 2010; Ward et al., 2008]. This decrease in modulation may also be present in older adults who have had a stroke. Third, level of PMd activation during AS in the current study may reflect the stage of learning. Brain activation changes with practice in nondisabled adults [Floyer-Lea and Matthews, 2004; Karni et al., 1995; Lin et al., 2011; Wu et al., 2004] and after stroke [Boyd et al., 2010; Carey et al., 2002; Meehan et al., 2011]. Additional practice may be needed in individuals post-stroke to achieve a level of task performance that corresponds to PMd activation that is similar to previous studies in young adults. Finally, this study may have not had enough power to detect a significant difference between conditions given the sample size of the stroke group.

This study was cross-sectional by design and cannot provide insight into how brain activation during motor AS changes with practice. Future research might examine whether contralesional brain activation changes with practice and determine whether the brain-behavior relationships between individuals found here persist or are altered over time. The measure of connectivity used in this analysis provides information on functional connections between brain regions but does not give an indication of the direction of these connections. Future analyses may be able to determine whether the PMd connections with M1 and DLPFC found during AS are facilitatory or inhibitory. The sample size in the current study was small and only included individuals in the chronic stage of stroke recovery with a mild to moderate degree of motor impairment. Therefore, inferences of the current results to the larger population of individuals with motor impairment due to stroke and analyses of possible covariates such as lesion location and extent are limited. The results of the current study suggest additional studies that address such variables are warranted.

In conclusion, individuals post-stroke showed an increase in planning time and engaged several contralesional brain regions to successfully perform a motor AS task. Individuals who took longer to respond (poorer performance) showed increased magnitude of activation in PMd and DLPFC and decreased functional connectivity between these two regions. The ability to efficiently engage neural resources during motor planning tasks may have implications for motor training after stroke. Structuring practice during rehabilitation to engage specific behavioral processes and neural resources (e.g., motor AS) may serve as an adjunct to repetitive movement execution [Cramer et al., 2011; Dodakian et al., 2013]. The premotor-prefrontal component of the motor circuit may be a prime candidate for a targeted rehabilitation protocol aimed at improving the function of residual brain circuits after stroke.

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