Neural Substrates of Cognitive Load Changes During a Motor Task in Subjects with Stroke

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Purpose: A critical component to rehabilitation is the degree to which we challenge patients to facilitate learning without providing excessive competition for cognitive resources. The purpose of this study was to examine brain activation and motor performance during changes in cognitive load in a continuous motor task in subjects with stroke (n = 7) and healthy subjects (n = 17).

Methods: Subjects participated in a joystick drawing task during functional magnetic resonance imaging. Subjects attempted to continuously draw a square under three conditions of varying cognitive demands.

Results: In subjects with stroke, results showed significantly less activation in contralateral primary motor area when the task did not require working memory demands and no change when the condition required online visual feedback processing. Bilaterally, the premotor cortex also demonstrated a significant decrease in activation when the task did not require working memory and then an increase in activation when online visual feedback processing was required. Despite these changes in activation, the accuracy of performance was maintained across the three conditions. Healthy subjects demonstrated no significant differences in activation between conditions.

Conclusion: These data suggest that the sensorimotor areas investigated have the greatest demand when the task requires working memory, but that only the bilateral premotor area has increased demands when online visual feedback processing is required. Use of working memory and visual feedback should be carefully considered when designing rehabilitation programs to balance challenging patients with overwhelming their potentially limited cognitive resources.

Key words: *stroke, neuroimaging, functional magnetic resonance imaging, working memory, feedback, human, rehabilitation, motor, cognitive load*

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INTRODUCTION

Learning or relearning motor skills is an essential priority during recovery from stroke. Robust findings from many sources suggest that "active engagement" during repetitive motor retraining is a critical component to promote neural plastic changes in a damaged brain.[1–6] However, which components a therapist should manipulate to facilitate this recovery and which may overwhelm an already compromised nervous system are unknown. The term used to describe the extent of cortical resources required to perform a task is cognitive load. In other words, the more processing of information that is required to perform a task, the greater is the cognitive load. Understanding how cortical activation changes with altered cognitive demand during motor task performance will help to elucidate the neural substrates of task performance and determine the neurologic underpinnings of rehabilitation strategies. This study investigated brain activation and motor performance in healthy subjects and subjects with stroke while manipulating two conditions that change cognitive load: feedback and working memory.

Feedback is information regarding performance or results.[7] This can take many forms including visual, auditory/verbal, tactile, kinesthetic, and proprioceptive. Timing of feedback can be given after task performance, as well as online or during the event. Relatedly, explicit instruction about a task can be given before performance. Several studies have shown feedback and explicit instruction to be beneficial for motor performance in healthy subjects.[8,9] However, in stroke populations, the research is more variable. Some studies suggest more feedback is beneficial for motor learning[10–13] and others suggest that too much feedback is detrimental to motor performance.[14,15] The variability in results likely is due, in part, to the type and amount of feedback given, the type of task performed, and the type of learning or performance investigated. The current experiment used online visual feedback during a motor drawing task.

Another component that can increase demands on cortical processes is working memory. Working memory is the process of actively holding information in the brain and manipulating it to guide behavior.[16] Baddeley and Hitch[17] theorized there to be two pathways involved in working memory. The first is the phonological loop, which is responsible for acoustic and linguistic memory. The other pathway is the visuospatial sketch pad, which holds memories of visual images and allows for recall of characteristics. In our experiment, we examined the latter type of working memory, whereby a subject had to "hold" an image in working memory and attempt to reproduce it.

Thus, the purpose of this study was to determine brain activation and motor performance associated with different cortical demands and the relationship between these during a motor task in healthy subjects and subjects with stroke. Our investigation centered on the following regions of interest (ROIs) both ipsilaterally and contralaterally to the moving hand: primary motor area (M1), primary sensory area (S1), supplementary motor area (SMA), and premotor cortex (PMC). These areas were selected because of their role in motor planning and execution of movement. The M1 is primarily responsible for the execution of movement and the S1 is responsible for sensory perception. The SMA is an area that is important in the temporal organization and planning of movements.[18] Our defined PMC region included the superior and posterior aspects of the frontal lobe which includes Brodmann's areas 6, 8, and parts of 9 and 46. The PMC is classically considered the center for motor preparation and programming and has been shown to be active during sensorimotor transformations including visually guided movements[19,20] and movement choice[21] and is thus an important anatomical region for rehabilitation. The dorsal lateral prefrontal cortex (DLPFC) is the anatomical center for working memory.[22] However, the borders of DLPFC are not easily defined, and given the strong connectivity of this region with PMC, the ROI for PMC was extended to be inclusive of this area.[23,24]

Our hypothesis was that in subjects with stroke, there would be a decrease in accuracy and an increase in cortical activation with higher cognitive load because of competition for cognitive resources. We further hypothesized that healthy subjects would show no change in activation but an improvement in accuracy with visual feedback, given an intact nervous system that is able to process the increased load requirements.

METHODS

Subjects

Seven right-handed subjects with chronic (more than one year after) stroke (four males, three females; mean $\pm$ SD age: 60 ± 14.28 years) and 17 healthy subjects (seven males, 10 females; mean $\pm$ SD age: 29 ± 10.33 years) participated in the experiment. This study was approved by the University of Minnesota's Institutional Review Board. Subjects were recruited through flyers, presentations, and a previous research subject database. Subjects were excluded if they had any other neurologic disorder, had magnetic resonance image (MRI) contraindications, did not speak English, or had a cognitive status below Mini-Mental State Examination score of 26[25] (Table 1). Subjects were screened for visual field integrity and color blindness to ensure ability to perform the task adequately. Subjects with stroke were all living independently and were able to walk 60 m without assistance. They had severe upper extremity hemiplegia on their affected side with trace or no active movement of their affected hand. Spasticity was evident in four of seven subjects with stroke (Ashworth median: 2). Informed consent was obtained from all subjects according to the Declaration of Helsinki.

Task

The task performed, Squarecopy, was a custom-designed program that consisted of four of 12-second conditions, with a 12-second fixation period presented before each condition. The conditions were (1) vision, whereby a square was presented around a dot, which remained blue, indicating that the subjects were to fixate on the image in front of them and produce no movement; (2) draw (from memory), whereby a green dot in the center of the screen was presented, signaling subjects to draw the square as seen in the vision condition without the actual image of a square shown; (3) copy (without feedback), whereby a square was presented around a green dot and subjects copied the square while viewing the template but did not see feedback regarding their performance; and (4) feedback, whereby the square template was presented, the dot was green, and the subjects received visual feedback of their drawing performance by seeing a red cursor on the screen indicating the real-time movements made by the subject with the joystick (Fig. 1). The instructions to the subjects were "draw the square continuously when the dot turns green and do not draw when the dot is blue." This task has been used previously with good reliability in subjects with stroke.[26] The conditions were presented three consecutive times in the same order for all subjects. Subjects were able to practice the task before entering the magnet to ensure that they had full understanding and the task was well learned. Understanding was assessed by the investigator as accurate performance of the task without hesitation.

Functional Magnetic Resonance Image (fMRI)

The task was performed during a fMRI scan. Images of the brain were collected with a 3.0-T research MRI system (Magnetom Trio, Siemens, Germany). A head volume radiofrequency coil was used to collect images over the entire volume of the brain. Padding was used around the head to minimize movement. Subjects with stroke performed with their less affected hand, stabilizing the joystick box that

TABLE 1. Subjects with Stroke Demographics

Age (yr)	Gender	Stroke Location	Stroke Hemisphere
57	Female	Inferior parietal, superior/posterior temporal	Right
76	Male	Thalamic	Right
55	Male	Frontal > parietal, including BG and internal capsula, insula, and operculum	Right
68	Male	Putamen, ALIC + MCA, frontal, parietal, temporal lobes, and deep nuclei	Right
61	Female	Posterior putamen and PLIC	Left
78	Male	Centrum semiovale	Left
53	Male	Thalamic with subtle involvement of PLIC and cerebral peduncle	Right

Abbreviations: BG, basal ganglia; ALIC, anterior limb internal capsule; MCA, middle cerebral artery; PLIC, posterior limb internal capsule.

rested on their stomach with their more affected hand, and healthy subjects performed the task with their right (dominant) hand, stabilizing with their left hand. Previous work determined this method allowed for the greatest movement consistency across subjects.[26,27] The joystick was connected to a laptop computer that displayed the task program and recorded the performance data. The task program generated by the computer was presented to the subjects in the MRI by a rear-projection screen and mirror attached to the head-gradient set. Once in the magnet, the subjects were proprioceptively oriented to the joystick and allowed to practice for approximately 10 minutes or until they felt comfortable and understood the task. During the practice period and the experiment, subjects were visually monitored to determine whether any extraneous movement was produced. Any subject displaying extraneous movements was excluded from the study ($n = 0$).

A high resolution (1 mm^3), T1-weighted, three-dimensional (3D) anatomical image data set (3D FLASH, TR = 20 ms, FA = 25 degrees, total acquisition time = 10:44) was acquired over the entire area of the brain to allow for identification of the anterior and posterior commissures. For functional imaging, a T2-weighted, single-shot, echo-planar imaging sequence was employed (TE = 30 msec, TR = 3000 msec, resolution = $3 \times 3 \times 3$ mm). The total imaged volume extended from the superior pole of the cortex to a depth of 162 mm in 36 interleaved slices. During the experiment, 96 repeated measurements were acquired, for a total scan time of 4.8 minutes. Whole brain imaging data were collected, but for the purposes of this investigation, analysis was focused on the following ROIs: M1, S1, SMA, and PMC. The ROIs were outlined on the anatomical scans of each subject according to previously published boundaries[27–29] (Fig. 2).

Analysis

Brain Voyager (Brain Innovation, Maastricht, the Netherlands) software was used to perform 3D head motion correction, preprocessing, registration, statistical analysis, and fMRI data presentation for each subject. The processed functional images were then used to reconstruct the 3D functional volume for each subject. The 3D functional volume was then overlaid and aligned (coregistered) with the 3D anatomical volume. The ROI designation was performed on the anatomical image and included both ipsilateral and contralateral (defined in relation to the hand used during task performance) M1, S1, SMA, and PMC.

The aligned volumes were normalized to standard Talairach space,[30] but no spatial smoothing was performed. Motion parameters for the fMRI scans were examined and subjects who exceeded 2 mm of head motion were excluded from the study. The change in blood oxygen level dependent signal intensity from the fixation condition was analyzed separately for each trial using a general linear model with 10 predictors. Four of the predictors were the vision, draw, copy, and feedback conditions. Three additional predictors accounted for translational movement of the head in the sagittal, coronal, and transverse planes, and the remaining three predictors accounted for rotational movement in the same three planes. The last six predictors were entered as covariates in the model and served to exclude the effect of any movement artifact in the variability of blood oxygen level dependent signal. Activation was determined by selecting contrasts for those areas unique to the draw, copy, and feedback predictor by determining the difference from the fixation condition with a false discovery rate of <0.05. The activation data for subjects with stroke were analyzed individually. These activation data were not grouped because of anatomical variability secondary to stroke location and size. The healthy subjects were analyzed with a group analysis whereby all subjects' functional scans are overlaid onto a single anatomical scan. The percentage of change from baseline was then determined from the same procedure as above.

Accuracy

A custom-designed program, Squarerror, was used to evaluate the subjects' accuracy of performance via a square of best fit. This program determined the centermost point of each subject's performance by determining the point that had the greatest angle of rotation between any two adjacent points. The square of best fit was then determined based on each subject's performance centered on the centermost point. The SE was then calculated by determining the distance between each point of the actual square and the closest point of the ideal square. This number is then minus log transformed according to the Weber-Fechner law regarding the approximately logarithmic thesis about human perception. This serves to accentuate differences at the higher end of the scale.[26] Higher values represent greater accuracy.

Statistical Analysis

Analyses of variance for repeated measures (RM-ANOVAs) were performed for the percentage of change in signal

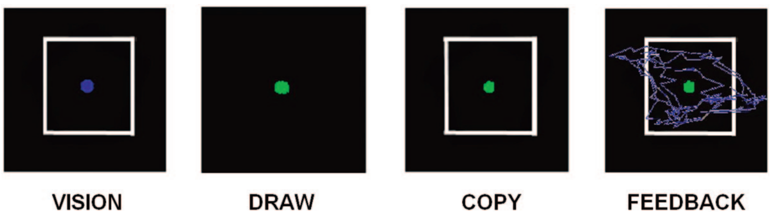

FIGURE 1. Task presentation. All subjects used a joystick to draw a square. Four 12-second conditions were examined: (1) vision, no movement produced; (2) draw, square was drawn from memory without template and without feedback; (3) copy, square was drawn with template provided but with no feedback about performance given; and (4) feedback, square was drawn with template shown and online visual feedback was provided. Preceding each task condition was a fixation period of equal duration (not shown).

intensity from baseline to examine for differences in trial, condition, and ROI. RM-ANOVAs were also executed to examine for differences in trial or condition. Post hoc analyses and paired *t* tests, with Bonferroni corrections for multiple comparisons (corrected $P = 0.016$), were performed if the condition showed significant differences, defined as $P < 0.05$, in order to find where the differences existed between the three conditions of interest (draw, copy, and feedback).

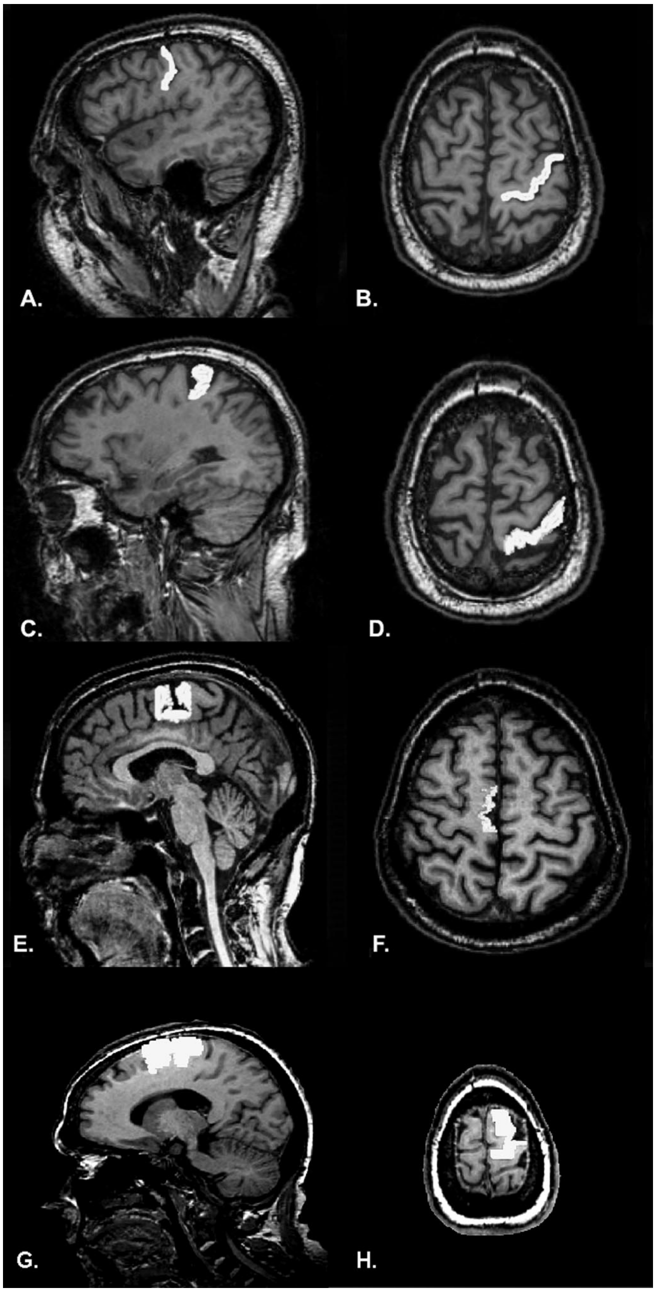

FIGURE 2. Regions of interest (ROIs). The following ROIs were examined because of their role in motor planning and execution of movement. Shown are the sagittal (left column) and transverse (right column) slice from a single subject of primary motor area (M1) (A and B); primary sensory area (S1) (C and D); supplementary motor area (SMA) (E and F); premotor cortex (PMC) (G and H).

RESULTS

Brain Activation

Subjects with Stroke

The RM-ANOVAs revealed that trial was not a significant factor; however, there was a significant interaction between ROI and condition. This suggests that there was consistent activation across the three trials for a given person, but that different regions in the brain behaved differently given the task condition. Figure 3A shows the general decline in activation from draw to the remaining conditions in the contralateral cortex in subjects with stroke. However, M1 was the only region to show a significant difference. Post hoc tests revealed a significant difference between the draw and copy conditions ($P = 0.004$) and between the draw and feedback conditions ($P = 0.011$) in contralateral M1 with no difference between the copy/feedback comparison. Additionally, the contralateral PMC showed a trend toward significance between draw and copy ($P = 0.056$) and an increase in activation between copy and feedback.

Figure 3B shows a general decrease in activation between draw and copy across the ROIs in the ipsilateral cortex. The M1, S1, and SMA showed almost identical decreases in activation. In the M1 there was a significant decrease between the draw and feedback conditions ($P = 0.015$). Similar to the contralateral side, ipsilateral PMC showed a decrease between draw and copy and an increase between copy and feedback.

The PMC has been shown to be activated bilaterally during motor tasks.[31–33] Thus, additional analysis was performed combining the contralateral and ipsilateral PMC. There was a significant change in activation ($P = 0.038$) with a significant decrease in activation between draw and copy ($P = 0.0025$) and then a significant increase between the copy and feedback conditions ($P = 0.0008$) (Fig. 3C). The change in activation can be seen in Figure 4. This fMR image is a representative example showing the activation in one subject with stroke using the right hand during the copy condition and feedback condition. A greater amount of activation is evident in the feedback condition, particularly in the PMC region bilaterally when the subject was required to process the visual feedback.

Healthy Subjects

The healthy subjects' activation was lower than that of subjects with stroke. In the contralateral hemisphere, there was a slight decrease in activation in all ROIs between the draw and copy conditions (Fig. 3D). The ipsilateral hemisphere showed virtually no activation difference from baseline. There was no significant difference across trials or condition. Table 2 shows activation means and SDs for healthy subjects and subjects with stroke.

Accuracy

Trial was not a significant factor for either group in accuracy values, meaning that performance did not change within a condition across the three trials. Within the three active conditions, there were no significant differences in the subjects with stroke. That is, subjects drew equally accurate squares regardless of the amount of feedback received. In healthy subjects, however, there was in increase in accuracy during the feedback condition (when they could see their performance). Overall, subjects with stroke performed with less accuracy than healthy subjects (Table 3).

DISCUSSION

This study examined the effect of working memory and visual feedback on accuracy of drawing and cognitive load as measured by fMRI in healthy subjects and subjects with stroke. The most salient findings were the evidence related to high activation in all examined areas when working memory was required in a task, and the exclusively high activation in PMC when visual feedback processing was required.

Brain Activation

In the task requiring the most working memory challenge (draw condition), subjects with stroke displayed the greatest activation in all cortical areas assessed both ipsilaterally and contralaterally. The breadth of the higher activation level is interesting because the DLPFC (included in our PMC ROI) is considered to be the locus of working memory. Our findings clearly show high levels of activation in other areas as well. The M1 displayed significant decreases both contralaterally and ipsilaterally between the draw and feedback conditions and contralaterally between the draw and copy condition. Other areas, including S1 and SMA, displayed a similar pattern, but without statistical significance. A similar decrease in activity was observed in PMC between the draw and copy conditions, however, and an increase was observed between copy and feedback. Given these findings, one can reason that the task of holding the image in working memory required the greatest amount of cortical resources.

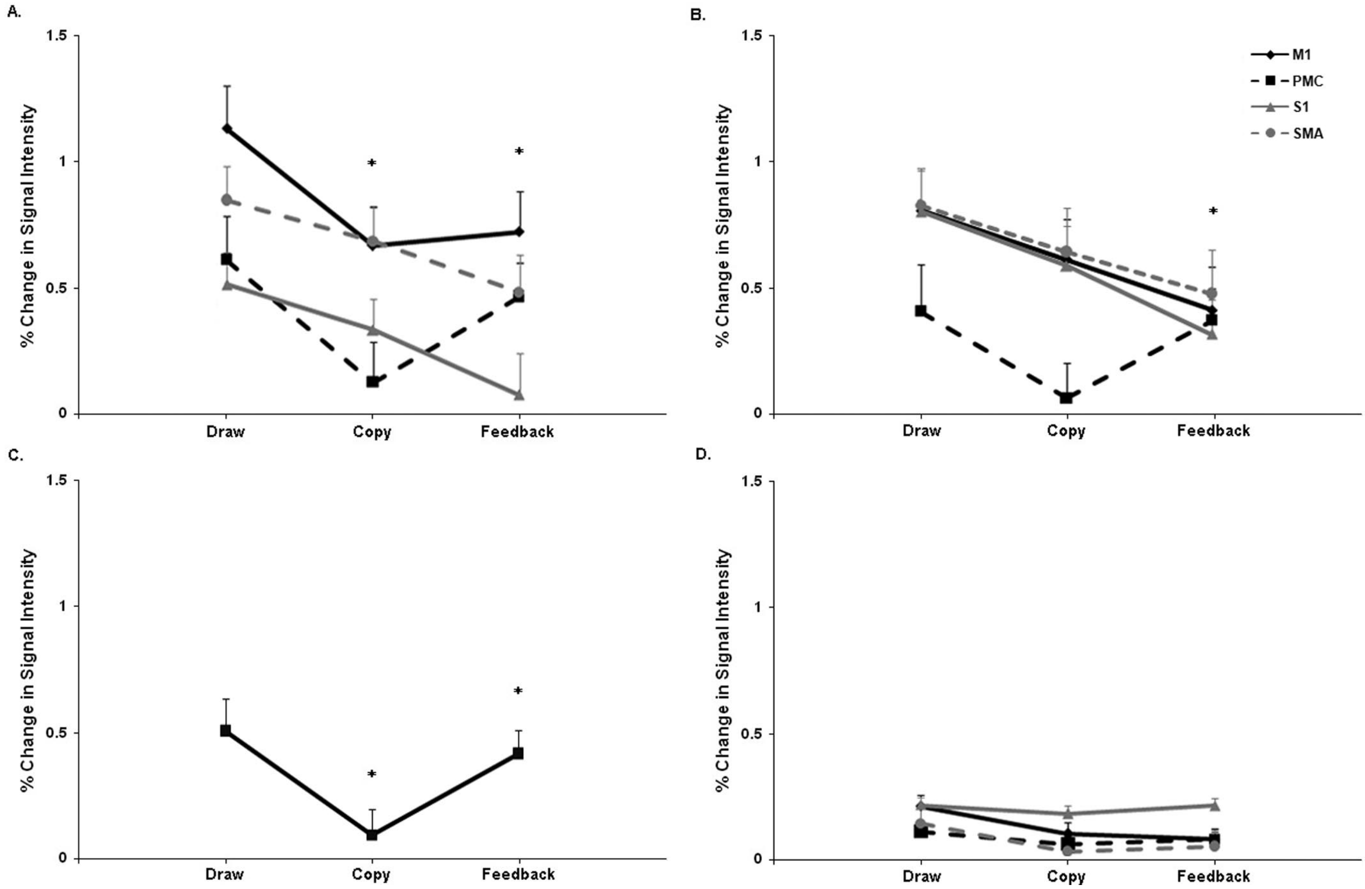

FIGURE 3. Cortical activation in percentage of change in signal intensity. All data are means ± SEs. A. In the subjects with stroke, activation contralateral to the moving hand (nonlesioned hemisphere) showed a general decline across conditions with significance in primary motor area (M1) between draw and copy ($P = 0.004$) and between draw and feedback ($P = 0.011$). Additionally, there was a trend toward significance in premotor cortex (PMC) ($P = 0.056$). B. The activation ipsilateral to the moving hand (lesioned hemisphere) also demonstrated a general decline across conditions with significance in M1 between draw and copy (*$P = 0.015$) and with a trend in PMC ($P = 0.061$). C. Bilateral activation in PMC. There was a significant decrease in activation between draw and copy ($P = 0.0025$), and a significant increase between copy and feedback ($P = 0.0008$). D. In the healthy subjects, activation was lower than in subjects with stroke with no differences across conditions.

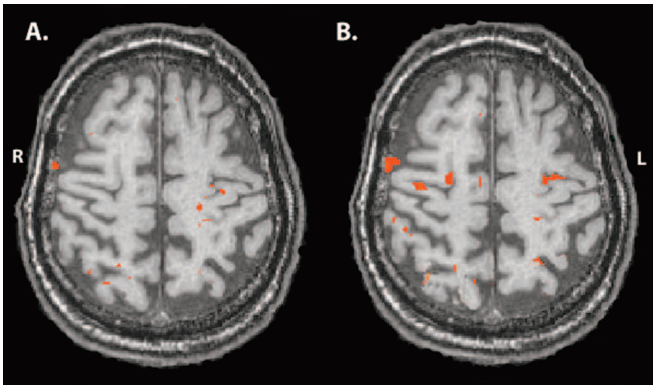

FIGURE 4. Functional magnetic resonance image (fMRI). A horizontal slice from a subject with stroke illustrating less activation during the copy task which required less cognitive load (A) and bilateral premotor cortex (PMC) activation during the feedback task when the subject was provided with online visual feedback (B). The subject was performing the task with the right hand.

No activation change was found in M1, S1, or SMA for either hemisphere between the copy and feedback conditions. In these tasks, there was a template to follow; thus, working memory demands were the same. The only difference was the online visual feedback processing required in the latter task, which did not change the cortical demands in these ROIs. This suggests that the processing of visual feedback does not increase the cortical demands in these areas and that the critical region for that feedback processing is in the PMC, which did demonstrate increased signal during the feedback processing task.

Premotor Cortex

There is a robust literature to suggest that the PMC works bilaterally to plan movement and allocate attentional resources including working memory.[34–37] Indeed, direct connections between the PMC of each hemisphere have been found in monkeys.[38] In humans, Ryou and Wilson[39] reported bilateral increases in the PMC activation during spatial tasks in visual modalities. In a positron emission tomography study, verbal online feedback was used with tasks involving working memory, which demonstrated bilateral activation of the PMC during conditions similar to those of the present study.[40] Additionally, increased PMC activation has been reported with increased working memory demands.[41] Relatedly, inhibition to one PMC via transcranial magnetic stimulation demonstrated alterations in performance in both the contralateral and ipsilateral hand[21] and has been shown to produce a compensatory increase in the contralateral PMC.[42]

In the current study, bilateral PMC data (along with M1, S1, and SMA) demonstrated a significant decrease between draw and copy conditions, which supports the role of PMC as one associated with spatial working memory. A significant increase in activation between the copy and feedback conditions was also found in bilateral PMC in subjects with stroke. This finding supports the role of PMC in visual feedback processing. Similar results of increased PMC excitability have been reported in studies examining the effects of verbal feedback processing in healthy subjects (Lee and van Donkelaar,[43] and Toni et al[44]). This would suggest that the present findings could extend to other types of feedback commonly used during rehabilitation. These findings support the role of PMC, and not other sensorimotor areas, in processing explicit information involved with sensorimotor adaptation (error correction) and visual integration.

TABLE 3. Mean Accuracy Scores ± SD

Stroke	
Draw	0.287 ± 0.04
Copy	0.279 ± 0.06
Feedback	0.303 ± 0.05
Healthy	
Draw	0.305 ± 0.09
Copy	0.316 ± 0.17
Feedback	0.371 ± 0.05

TABLE 2. Mean Beta Weight Values ± SD

	M1	S1	SMA	PMC
Healthy contralateral				
Draw	0.214 ± 0.17	0.218 ± 0.12	0.145 ± 0.27	0.113 ± 0.12
Copy	0.105 ± 0.17	0.184 ± 0.12	0.034 ± 0.27	0.064 ± 0.12
Feedback	0.082 ± 0.17	0.215 ± 0.12	0.054 ± 0.27	0.081 ± 0.12
Stroke ipsilateral				
Draw	0.67 ± 0.34	0.68 ± 0.35	0.59 ± 0.43	0.64 ± 0.39
Copy	0.55 ± 0.50	0.63 ± 0.33	0.47 ± 0.44	0.45 ± 0.37
Feedback	0.66 ± 0.55	0.53 ± 0.29	0.52 ± 0.44	0.63 ± 0.38
Stroke contralateral				
Draw	0.66 ± 0.30	0.64 ± 0.28	0.65 ± 0.40	0.66 ± 0.39
Copy	0.49 ± 0.27	0.55 ± 0.29	0.56 ± 0.35	0.51 ± 0.37
Feedback	0.53 ± 0.26	0.44 ± 0.30	0.56 ± 0.43	0.62 ± 0.41

All regions of interest are contralateral to the performing hand.
Abbreviations: M1, primary motor area; S1, primary sensory area; SMA, supplementary motor area; PMC, premotor cortex.

Clinically, there is evidence to suggest that the dorsal PMC may play a role in motor recovery.[45] Johansen-Berg et al[46] have demonstrated that recovered manual performance was mediated by increased activation of the contralesional dorsal PMC. The anatomical basis of this may be due to direct connections between PMC and the spinal cord[47] or interhemispheric connections with the contralateral M1.[48] These connections may enable the PMC to exert some influence on hand movements in recovering stroke patients. It is thus reasonable to suggest that activities, such as working memory and feedback processing, leading to increased PMC activation could help to facilitate these connections. Indeed, the bilateralality of PMC may be an important factor mediating functional recovery from unilateral injury.[42]

This area of the brain is also responsible for divided attention, the allocation of attentional resources, and, to some extent, executive function. Although not explicitly studied in this experiment, it has other important clinical implications worth considering when devising a rehabilitation program to increase cognitive load. It has been shown that during balance experiments in older subjects, when a dual task is added, thus dividing attention, there are increased demands on postural muscles[49] and subjects have more difficulty maintaining balance.[50–52] Thus, all potential implications of the task need to be considered, including safety.

Healthy Subjects

The healthy subjects displayed relatively low amounts of activation, and, thus, no significant differences were found between tasks. This indicates that the task was not of adequate difficulty to produce widespread activation. Indeed, task difficulty is a factor in determining the extent of activation elicited during fMRI.[34] In other words, this group did not require the same level of cognitive resources to hold the image in working memory or to process the visual feedback.

Motor Performance

It is interesting to note that the accuracy of square drawing did not change across conditions in subjects with stroke. We had hypothesized that accuracy would decrease in the final feedback condition in subjects with stroke, given the competition for cortical resources. Although this did not occur, when compared with healthy subjects, whose performance improved in the feedback condition, it could be stated that the visual online feedback provided in this study may have had a negative effect on subjects with stroke because more cortical activation was required with no improvement in performance.

One advantage to the finding of consistent performance in subjects with stroke is that there was no confounding variable related to motor output. This lends greater confidence that the fMRI findings were due to changes in the cortical demands across task and not due to performance differences. In comparison with the healthy population, our task did increase cortical demands in subjects with stroke, suggesting that a threshold may have been approached. These findings support the theory that there is a threshold of feedback that patients with stroke can process,[14] as the level of feedback provided in this study caused an increase in cortical demands, but the task performance did not deteriorate. This supports other work that has shown that the costs associated with additional cognitive load differ according to a subject's level of executive function and the type of task.[51]

Clinical Implications

The amount and type of cognitive load to give patients with stroke is a critical component to the creation of a treatment plan. Increased cortical demands are beneficial to facilitate with plastic changes, but excessive load may provide competition for limited cognitive resources. There is evidence that suggests that active engagement is required to promote cortical plasticity in the neurologically damaged brain.[2–4] In other words, simple repetition of a movement does not promote the plastic changes necessary for neural reorganization, but rather the task must have other components of complexity. This research demonstrates that requiring a task to be held in working memory elicits the greatest total amount of activation in the cortical motor areas investigated and that visual feedback processing specifically may enhance bilateral premotor activation. Premotor regions have been shown to work bilaterally, particularly when the task is challenging[53] or the learners have access to explicit information.[14,44] Thus, adding this aspect to a rehabilitative task may facilitate bilateral activation and thus increase PMC projections to the motor cortex and/or spinal cord.

CONCLUSION

In summary, how a given component of complexity affects the neurologically damaged brain is not fully understood, nor is it known which components of task complexity are most beneficial to facilitate neural plastic changes. It appears clear, however, that to affect neural plastic changes, cognitive load should be maximized and one method of facilitating that is through working memory and feedback processing. Future work should explore the effects of manipulating other parameters and types of feedback to determine how to maximize rehabilitation potential to promote adaptive plastic changes in the brain.

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