Cognitive Context Determines Dorsal Premotor Cortical Activity During Hand Movement in Patients After Stroke

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Background and Purpose—Stroke patients often have difficulties in simultaneously performing a motor and cognitive task. Functional imaging studies have shown that movement of an affected hand after stroke is associated with increased activity in multiple cortical areas, particularly in the contralesional hemisphere. We hypothesized patients for whom executing simple movements demands greater selective attention will show greater brain activity during movement.

Methods—Eight chronic stroke patients performed a behavioral interference test using a visuo-motor tracking task without a simultaneous cognitive task. The magnitude of behavioral task decrement under cognitive motor interference (CMI) conditions was calculated for each subject. Functional MRI was used to assess brain activity in the same patients during performance of a visuo-motor tracking task alone; correlations between CMI score and movement-related brain activation were then explored.

Results—Movement-related activation in the dorsal precentral gyrus of the contralesional hemisphere correlated strongly and positively with CMI score ($r^2$ at peak voxel=0.92; $P<0.05$). Similar but weaker relationships were observed in the ventral precentral and middle frontal gyrus. There was no independent relationship between hand motor impairment and CMI.

Conclusions—Results suggest that variations in the degree to which a cognitive task interferes with performance of a concurrent motor task explains a substantial proportion of the variations in movement-related brain activity in patients after stroke. The results emphasize the importance of considering cognitive context when interpreting brain activity patterns and provide a rationale for further evaluation of integrated cognitive and movement interventions for rehabilitation in stroke. (Stroke. 2011;42:1056-1061.)

Key Words: cognitive motor interference ■ functional magnetic resonance imaging ■ rehabilitation

Manual dexterity involves grasping and applying muscular forces with the digits on objects, a skill that is important for activities of daily living. After a stroke, a large proportion of patients will experience motor problems with the contralateral hand, which can affect their performance of activities of daily living. An added challenge for performing manual dexterity tasks in everyday life arises from the fact that functional tasks are rarely performed alone, but rather are often executed under distracting conditions that require attention to be divided between multiple tasks. Cognitive context influences performance even of simple movement tasks; decrements in performance of a manual dexterity task performed at the same time as a demanding cognitive task can be seen even in healthy subjects. Such decrements are typically even greater after stroke. Such “cognitive motor interference” (CMI) can cause great difficulties in successful performance of activities of daily living and limit independence. Performance of manual dexterity tasks is associated with altered patterns of motor cortical activation in stroke patients compared to age-matched controls, with increased activity of motor areas in the contralesional hemisphere most common in patients with the greatest impairment. It is possible that this reflects adaptive plasticity mediated by recruitment of intact motor output pathways from nonprimary motor cortical areas or from the contralesional hemisphere. However, it is also possible that changes in patterns of activation arise from associated differences in cognitive demands of the task for patients and healthy controls. Motor imagery after stroke is associated with greater bilateral activation of primary and premotor cortical areas and with increased coupling between the ipsilesional (contralateral) prefrontal cortex (PFC) and premotor cortex, even when individuals have intact motor areas. Performance of a visuo-motor tracking task is associated with greater PFC activation as well. Differences in activity between the two tasks correlated strongly with CMI, and this activity was associated with functional impairments in the affected hemisphere.
activity in stroke patients compared to healthy controls. Increased activity in patients is seen in the dorsolateral PFC during early learning of the task and in more superior parts of PFC, including middle frontal and superior frontal gyrus after 5 days of task practice.15 Differences in attention to movement modulate activity in the primary motor cortex and supplementary motor area, even in healthy subjects.16,17 Together, these results suggest that cognitive aspects of motor control are associated with modulation of activity across widespread motor cortical and association areas.

Given that behavioral evidence suggests that patients require greater attention resources to execute even simple movements,5,18,19 and that attention to movement is associated with modulation of motor cortical activity,16,20 we hypothesized that some of the brain activity associated with simple movement after stroke could be explained by enhanced attention to movement. To test this hypothesis, we calculated a behavioral measure of the attention demands of a simple hand movement using a CMI dual-task paradigm. Specifically, stroke patients performed a visuo-motor tracking task with and without a simultaneous cognitive distracter task. To assess brain activity associated with simple motor performance, we then acquired blood oxygen level-dependent functional MRI (fMRI) data in the same patients while they performed the visuo-motor task alone. We tested whether greater CMI in the behavioral assessment was associated with greater brain activity during simple motor task performance in specific brain regions.

Materials and Methods

Patients

Eight individuals with chronic left hemisphere subcortical ischemic stroke took part in the study. All gave written consent before participation, in accordance with the Declaration of Helsinki (1983). Inclusion and exclusion criteria are provided in full in the Supplementary information (available online at http://stroke.ahajournals.org). Hand motor ability was assessed using the Fugl-Meyer (FM) motor assessment.21 Demographic data can be found in Table 1.

CMI Behavioral Testing

After a period of task familiarization, the participants were asked to perform, in a random order, a visuo-motor tracking task using the impaired (right) hand and the “clock faces” cognitive task. Full details of both tasks are provided in the Supplementary information. In brief, the tracking task required subjects to squeeze a hand-held force device to control a visually displayed bar to match the height of a computer-controlled target bar that moved in a predictable repeated sine wave pattern (Figure 1). After single task performance of each task, subjects performed the 2 tasks simultaneously for 3 additional 60-second blocks. Both tasks were initiated simultaneously and subjects were instructed to give equal emphasis to the motor and cognitive task and thus perform both tasks to the best of their ability.

fMRI Paradigm

Participants performed a similar visuo-motor tracking task with the right (impaired) hand in a block design with 12 blocks of 30-second duration interspersed with 30-second rests for each condition. During tracking blocks, participants performed a variant on the visuo-motor tracking task described using the same hand-held device, but instead of regular movements the target moved in a pseudorandom, unpredictable fashion (constrained so that the movements were always smooth) to maintain participants’ attention to the task throughout the scan session. During rest blocks, participants passively viewed both bars moving but made no responses. Vision was corrected using corrective lenses as necessary.

fMRI Data Acquisition

Imaging data were acquired using a 3.0-T Varian (Siemens, Erlangen, Germany) MRI system. A total of 256 T2*-weighted blood oxygen level-dependent-sensitive echo planar imaging images were acquired during task performance (40 axial slices per volume; repetition time=3500 ms; echo time=30 ms; matrix=64×64; in-plane resolution=3×3 mm²; flip angle=90°). A T₁-weighted anatomic image was also acquired (repetition time=30 ms; echo time=5 ms; inversion time=500 ms; flip angle 15°, field of view, 256×256; matrix=256×256).

Data Analysis: Behavioral Data

Motor performance was evaluated by calculating the average root mean-squared error (RMSE) of the difference between the target sequence pattern and the participant’s movement. The mean absolute tracking error for the middle 30 seconds of each 60-second block was calculated and averaged over the 3 blocks. We focused on the middle 30 seconds because this was when more stable performance tended to be achieved, rather than at the initiation and finish of the motor and cognitive task. Motor task data satisfied tests for normality; therefore, the difference in motor task performance from single to dual task conditions across the group was compared using a paired *t*-test.
Test. To quantify the interference effects of the cognitive task on the visuo-motor tracking task, a CMI index score was calculated for each participant as (errorsingle - errordual)/errordual. Each subject's CMI score was normalized (giving unit variance and zero mean) and then analyzed for relationship to hand motor ability (FM score) using 2-tailed Spearman correlation.

fMRI

Data from each subject were initially analyzed separately using tools from the FMRIB software library (www.fmrib.ox.ac.uk/fsl). Standard preprocessing and individual-level statistical analysis was applied (Supplementary information). The first level results were registered into standard space (based on the Montreal Neurological Institute 152 template) via each subject's T₁-weighted anatomic scan using FMRIB's nonlinear image registration tool. Higher-level analyses on the resulting aligned images used mixed effects with outlier de-weighting23 to calculate group average patterns of movement-related activity and to test for correlations between movement-related activity and CMI. Because we were interested in correlations with CMI over and above any correlations with motor ability, FM score was included in the model and shared variance between CMI, FM was assigned to the FM regressor by orthogonalizing the score was found in the right (contralesional) dorsal premotor cortex (PMd), right ventral premotor cortex (PMv), and in the right middle frontal gyrus (DLPFC). Consideration of individual subject data highlighted a participant with extreme values for both CMI and movement-related activity. Although the impact of this subject should be limited by the automatic outlier de-weighting included in our analysis,23 to more fully assess the dependence of our results on this single subject correlations at the peak voxels were reassessed without the subject. There was still a positive relationship between CMI and activation in the dorsal premotor area \((r^2=0.45; P=0.05)\), although no meaningful relationship remained for the PMv or DLPFC.

Discussion

We found an association between CMI and patterns of movement-related brain activity in chronic stroke patients. Patients who showed greater interference effects of a distracting cognitive task on motor performance had increased activation in specific premotor and dorsolateral prefrontal areas during performance of a motor task alone. These associations could not be explained by differences in motor impairment. No relationship was found between CMI and motor impairment (FM score) and the correlations between CMI and brain activity were over and above any relationships between FM and brain activity.

Previous functional imaging studies of simple hand movement after stroke have reported increased activity in contralateral areas, including premotor and prefrontal cortex, but the functional role played by these areas is unclear. The current results suggest that increased activity, most convincingly in contralesional PMd and possibly also the PMv and DLPFC, may partly reflect increased cognitive demands of even simple

Figure 2. Thresholded images \((Z>2.3)\) of group mean activation for movement vs rest. Significant clusters defined according to extent (at corrected \(P<0.05\)).

Neural Correlates of Cognitive Motor Interference Score

Correlations between increased fMRI signal change and CMI score were found in the right (contralesional) dorsal premotor cortex (PMd), right ventral premotor cortex (PMv), and in the right middle frontal gyrus (DLPFC) (Figure 3, Table 2).

To estimate how much of the variance in brain activity at each location can be explained by CMI, we calculated \(r^2\) values between CMI scores and the percent signal change at the voxel of maximal correlation in each cluster. CMI score explained 52% \((P<0.05)\), 92% \((P<0.01)\), and 69% \((P<0.05)\) of the variance in fMRI activity for the contralesional PMv, PMd, and DLPFC, respectively. Consideration of individual subject data highlighted a participant with extreme values for both CMI and movement-related activity. Although the impact of this subject should be limited by the automatic outlier de-weighting included in our analysis,23 to more fully assess the dependence of our results on this single subject correlations at the peak voxels were reassessed without the subject. There was still a positive relationship between CMI and activation in the dorsal premotor area \((r^2=0.45; P=0.05)\), although no meaningful relationship remained for the PMv or DLPFC.

Results

Behavioral

Analysis of error scores revealed a tendency for greater tracking error under dual-task conditions compared to single-task conditions \((t=1.86; P=0.053)\), although they were not significant. CMI scores quantifying the dual-task effects were generally positive (reflecting greater error in the dual task condition; range, -0.09 to 2.77; Table 1). No significant relationships were identified between motor task error and FM score \((P=0.29; P=0.49)\) or between CMI score and FM score \((P=0.26; P=0.53)\).

fMRI: Movement-Related Brain Activity

The visuo-motor tracking activated the expected sensorimotor and visual network (Figure 2), including sensorimotor, posterior parietal, prefrontal and visual cortices, and the cerebellum.
movements for patients. Performance of a concurrent cognitive task disrupts motor performance in patients to a greater extent than in healthy controls, although evidence is mixed for upper limb movements.

Previous fMRI studies have reported increased activity in PMd even in simple movements after stroke, whereas a recent study emphasized the importance of PMd and DLPFC for motor learning after stroke. Studies in healthy volunteers show that movement-related activity in premotor and prefrontal cortices depends on cognitive context even in the healthy brain. Activity in motor and prefrontal areas increases with increased attention to simple movements. PMd activity is associated with increased action selection demands and DLPFC is involved in maintenance of task performance in the presence of a competing cognitive task.

Our findings underline the importance of considering cognitive demands when designing rehabilitation interventions. Movements are typically made in the context of multiple distracting task demands such as talking while walking. Our behavioral data show that patients with a relatively homogeneous clinical profile (FM scores ranging from 42–64) and stroke pathology (left hemisphere subcortical stroke) vary widely in the degree to which a distracting cognitive task impairs motor performance. In conjunction with previous data, our observation that variation in these distraction effects explains some of the variability in fMRI activity during a movement task alone suggests that the cognitive context of a movement is an important determinant of brain activity during motor task performance. If PMd, for example, is required even to perform a simple motor task, then this will place limits on how well a patient can perform everyday activities in which additional activation demands are placed on the PMd by competing simultaneous cognitive tasks. Our results support a rationale for further development of rehabilitation strategies integrating cognitive and motor training. The potential effects of cognitive control training are suggested by a recent report that such an intervention can shift the pattern of brain activity associated with performance of a cognitive task from activation of a widespread network of brain regions including the lateral PFC to a more focal pattern relying on the lateral PFC.

There are several limitations to our study. Only a small number of patients were studied and all of the patients had left hemisphere subcortical stroke with mild to moderate impair-
ments. Although use of a relatively homogeneous patient group allows for clearer interpretation of voxel-wise analysis of brain imaging data, it limits the degree to which our findings can be immediately generalized to the wider stroke population. One patient had a particularly high CMI score and, although the correlations found in PMd were robust to removal of this extreme subject, results were no longer significant in DLPFC or PMv; a larger follow-up study would help to clarify whether the DLPFC and PMv effects found here are meaningful. In addition, we did not study healthy controls, so we do not know whether the patients studied showed greater CMI effects than controls. However, previous studies have shown that CMI effects are typically greater in stroke patients compared to controls.\(^\text{19,36}\) We used a slightly different visuo-motor tracking task for fMRI and behavioral testing. During fMRI (single task only), the target bar moved in an unpredictable random fashion, whereas during behavioral testing (single and dual task) the target bar moved in a predictable repeating manner. The study was designed in this way because piloting suggested that participants were unable to sustain dual-task performance with the more demanding unpredictable motor sequence, but the unpredictable sequence was more effective for limiting boredom during scanning sessions. We propose that the behavioral measure of CMI obtained can be considered a general probe of the attention demands of tracking movements and therefore is of interest to compare to fMRI activity during a similar task. However, given that activity in PMd and/or DLPFC could differ in magnitude for these 2 variants of tracking, it would also be of interest to compare CMI behavioral measures with fMRI data acquired during a predictable tracking sequence. We also did not assess behavioral performance of the cognitive task because we were primarily interested in changes in motor task performance, but a more complete picture of interference effects could be gained from monitoring performance in both tasks. Finally, we were primarily interested in the dual-task paradigm as a behavioral means to assess the performance in both tasks. Finally, we were primarily interested in interference effects could be gained from monitoring performance. Although use of a relatively homogeneous patient group allows for clearer interpretation of voxel-wise analysis of brain imaging data, it limits the degree to which our findings can be immediately generalized to the wider stroke population. One patient had a particularly high CMI score and, although the correlations found in PMd were robust to removal of this extreme subject, results were no longer significant in DLPFC or PMv; a larger follow-up study would help to clarify whether the DLPFC and PMv effects found here are meaningful. In addition, we did not study healthy controls, so we do not know whether the patients studied showed greater CMI effects than controls. However, previous studies have shown that CMI effects are typically greater in stroke patients compared to controls.\(^\text{19,36}\) We used a slightly different visuo-motor tracking task for fMRI and behavioral testing. During fMRI (single task only), the target bar moved in an unpredictable random fashion, whereas during behavioral testing (single and dual task) the target bar moved in a predictable repeating manner. The study was designed in this way because piloting suggested that participants were unable to sustain dual-task performance with the more demanding unpredictable motor sequence, but the unpredictable sequence was more effective for limiting boredom during scanning sessions. We propose that the behavioral measure of CMI obtained can be considered a general probe of the attention demands of tracking movements and therefore is of interest to compare to fMRI activity during a similar task. However, given that activity in PMd and/or DLPFC could differ in magnitude for these 2 variants of tracking, it would also be of interest to compare CMI behavioral measures with fMRI data acquired during a predictable tracking sequence. We also did not assess behavioral performance of the cognitive task because we were primarily interested in changes in motor task performance, but a more complete picture of interference effects could be gained from monitoring performance in both tasks. Finally, we were primarily interested in the dual-task paradigm as a behavioral means to assess the attention demands of simple movements; therefore, dual tasks were not performed during fMRI scanning. Further research could directly contrast brain activity patterns during single-task and dual-task performance to shed more light on the neural correlates of CMI in chronic stroke.

Conclusions

Our results suggest that variation in the degree to which a competing cognitive task interferes with performance of a concurrent motor task explains variation in movement-related brain activity, particularly in PMd, in patients after stroke. These associations are found over and above any associations with motor impairment and suggest that the cognitive demands of even simple movement execution should be considered when interpreting brain activity patterns in stroke patients. Additional work is needed to further evaluate the cognitive neuroscientific basis for integrated cognitive and movement therapy in rehabilitation of patients after stroke.

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Disclosure

None.

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Supplemental methods

Participant inclusion and exclusion criteria

Individuals with stroke were identified by consultant referral with inclusion criteria of: right-handed (Edinburgh Handedness Miniscale -2 to 2); evidence of subcortical ischemic infarct (greater than 5 mm in diameter) on CT or MRI (T1- or T2-weighted) scan with a localisation consistent with new motor symptoms and signs; grip strength (dynamometer) in impaired hand of >20% and <80% of that in unimpaired hand (based on the best performance in three repeated trials) with sensation to light touch and ability to give informed consent. Individuals were excluded if they had a clinical history of dementia or aphasia significantly limiting communication (NIH Stroke Scale rating >2), a history of previous symptomatic strokes or active neurological disease, a known active, major psychiatric disease or claustrophobia; any other conditions precluding safe MRI (e.g., pacemaker or other metal implant) or other condition having a functional impairment that would interfere with assessment of motor performance.

Behavioural testing

Participants were asked to perform the following two tasks in random order.

- A visuo-motor tracking task using the impaired (right) hand while seated: Participants viewed a computer screen displaying two moving bars: a computer-controlled target bar and a participant-controlled bar.
The participant’s task was to match the height of the participant-controlled bar with the height of the target bar by altering grip force applied to a plastic isometric pressure-sensing device held in their right hand (see fig 1). An increase in applied pressure by the participant caused an increase in the participant-controlled bar height. Stimuli were presented and movements recorded using custom software developed on a Labview platform (National Instruments, Austin, TX) with a sampling rate of 100 Hz. Prior to beginning the task, the maximum amplitude of the target bar was calibrated to approximately 80% the individual’s maximum grip strength. During CMI trials the tracking sequence was a predictable repeated sine-wave as pilot studies had suggested that participants were unable to sustain performance of an unpredictable tracking task while concurrently performing a cognitive task. Participants performed the task in 3 blocks of 60 seconds each.

- The ‘clock-faces’ cognitive task: A visuo-spatial decision task in which participants heard a time of day such as “one fifteen”, every 5 seconds, and responded verbally whether the hands of the clock would be on the same or opposite side of the clock face. Participants performed the task in 3 blocks of 60 seconds.

Following single task performance of each task, subjects performed the two tasks simultaneously for a further three 60 second blocks. Both tasks were initiated simultaneously and subjects were instructed to give equal emphasis
to the motor and cognitive task and thus perform both tasks to the best of their ability.

**Individual level FMRI analysis**

The following pre-statistical processing was applied: Motion correction using MCFLIRT \(^1\); non-brain removal using BET \(^2\), spatial smoothing using a Gaussian kernel of 5 mm full-width half maximum; mean based intensity normalisation; non-linear high-pass temporal filtering (Gaussian-weighted, least squares straight line fitting with sigma = 50.0 seconds). Individual data sets were checked visually to confirm that excessive head motion had not occurred. Statistical analysis of the images was performed in two stages. The first level (within subject) analysis was carried out using FILM with local autocorrelation correction \(^3\) to produce effect size images of movement related activity versus rest for each subject that were carried up to the group level analysis.

**Supplemental Results**

**Behavioural**

Analysis of error scores revealed a tendency for greater tracking error under dual-task conditions compared to single-task conditions (t=-1.86, p=0.053), although not significant. Although the data passed tests of normality, analysis was also conducted using Wilcoxon matched pairs. The result remained not significant (z =-1.68, p=0.093).
Supplemental References


