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CASE STUDY

Assessing recovery in middle cerebral artery stroke using functional MRI

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Abstract

Primary objective: To understand the temporal evolution of brain reorganization during recovery from stroke.
Research design: A patient who suffered left middle cerebral artery stroke 9 months earlier was studied on three occasions, ~1 month apart.
Methods and procedures: Brain activation was studied using functional Magnetic Resonance Imaging (fMRI). During each session, the patient performed a finger-to-thumb opposition task, which involved one bimanual and two unimanual conditions. Each condition consisted of overt movement of fingers and imagery of the same task.
Results: With recovery, greater recruitment was observed of the affected primary motor cortex (M1) and a decrease in activation of the unaffected M1 and supplementary motor area. In addition, the widespread activation of brain areas seen during the initial session changed to a more focused pattern of activation as the patient recovered. Imagery tasks resulted in similar brain activity as overt execution pointing to imagery as a potential tool for rehabilitation.

Keywords: *Stroke, motor recovery, fMRI, finger-sequencing, motor imagery*

Introduction

Stroke remains one of the prime causes of adult disability for a number of reasons. First, patients affected by stroke rarely achieve complete recovery. This is primarily due to the inability to reverse the ischemic process and also in part, to the failure to institute effective treatment at an early phase of the ischemic attack. A second, but related reason is the lack of understanding of the neural mechanisms that contribute to recovery of function following stroke. Thirdly are various contributing factors such as diet, habits and drugs. In the past, clinical, animal and pharmacological studies have enabled researchers to identify many basic mechanisms of stroke pathology. With the advent of imaging tools such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI),

functional reorganization of the brain after stroke can now be studied using a non-invasive technique while subjects perform simple tasks. This serial fMRI case study examines a patient with left middle cerebral artery (MCA) stroke using a finger-sequencing paradigm, with the aim of understanding the temporal evolution of brain reorganization during recovery from stroke and the contribution of different brain areas in the recovery process.

Several studies in the recent past have identified neural activation patterns corresponding to recovery from stroke. Earlier studies included patients with good motor recovery and were cross-sectional [1–4], while later studies were longitudinal and included patients who were in the process of recovery [5–13]. As can be expected, brain activation observed in these studies differed depending on the

task employed, time after the onset of stroke and the nature and location of the lesion. In addition to primary sensorimotor cortex (SM1) and cerebellum, greater activation was also observed in other motor-related areas such as the inferior parietal lobe, supplementary motor area (SMA), insula, cingulate, basal ganglia and cerebellum [1, 2, 5, 12]. Patients with cortical infarcts activated bilateral pre-motor regions while performing tasks with the affected hand [4]. Several longitudinal studies also demonstrated over activation of motor and motor association areas in both the hemispheres [5–7, 11, 12]. However, the initial over recruitment decreased over time and resulted in focusing of activation as patients improved. With functional recovery, focusing of activation mainly occurred to the ipsilesional primary sensorimotor cortex (SM1). Another study that examined patients recovering from stroke during the first 6 months [11] concluded that the degree of motor recovery was related to the extent of corticospinal tract damage, as measured by the degree of Wallerian degeneration observed in MRI images of the cerebral peduncles.

In order to better characterize changes in neural activation and to quantify dynamic changes in brain activation patterns over time, Cramer et al. [3] formulated the Laterality Index (LI), defined as $(C - I)/(C + I)$, where C and I represent contralateral and ipsilateral activation volumes, respectively. Generally, most studies have found greater variability in LI values in patients than controls [3, 6–8, 14]. Interestingly, longitudinal studies [6–9, 15] have reported changes in LI values over time, with most patients exhibiting a change from contralesional to ipsilesional activation over time, as they improve. Cramer et al. [3] also observed increased peri-infarct activation, which was interpreted as recruitment of the surviving neuronal elements for task execution. Recently, Luft et al. [16], in an fMRI study, reported peri-infarct activation in chronically impaired patients with cortical infarcts.

In summary, the activation patterns observed by previous studies can be broadly grouped into three categories

(1) *Focusing of activation*: initial widespread activation of primary motor and motor-related areas (SMA, cerebellum, pre-motor, parietal, insula) become focused when patients improve;
(2) *Change in laterality*: an initial increase in activity in the contralesional (normal hemisphere) primary sensorimotor (SM1) changes to more ipsilesional activity over time, as the patient improves; and
(3) *Peri-infarct activation*.

A previous study in normal subjects [17] showed that execution of bilateral finger-sequencing movements recruited a large network of brain areas including the SM1, SMA, superior and inferior parietal lobes and the cerebellum. Imagery of the same tasks recruited the same network of brain areas (generally less active), but resulted in decreased activity in the cerebellum. The finger-sequencing task used in a previous study was cognitively very demanding in that it involved at least the following: planning the sequence of execution, remembering the order of movement—both temporal and spatial, monitoring movements both mentally and using sensory/proprioceptive feedback, detecting errors in the executed sequence and correcting them if necessary. Fine movements such as finger sequences are usually the last to recover in patients with stroke [18, 19] and, hence, qualify as an optimal task to monitor motor recovery over time. That motor execution and imagery share many cortical and sub-cortical mechanisms including the primary somatosensory cortex has been shown in many previous studies [17, 20–22]. This observation provides clues as to why motor performance improves in individuals who mentally practice a motor task [23]. If patients with hemiplegia retain the ability to represent movements even when not being able to actually execute movements, motor imagery would provide a means of stimulating those damaged neural networks despite difficulties in producing limb movements. When patients with stroke perform goal-directed action sequences (both actual execution and imagery), brain activity within these partially damaged neural regions could provide a mechanism for functional recovery. In other words, even motor imagery could have potential therapeutic significance. Execution and imagery of the finger-sequencing task were, hence, considered an ideal task to understand how recruitment of different brain areas would change over time. By using unimanual and bimanual action sequences, this study also addresses the question of whether bimanual tasks and their motor/cognitive demands help improve neural reorganization. The following hypotheses were pursued:

(a) More ipsilateral activation occurs while performing sequencing tasks using the affected hand than the normal hand, at least during the initial sessions. If this ipsilateral activation represents one of the functional compensatory mechanisms, it should decrease over time when the patient shows functional improvement.
(b) If de-masking and recruitment of several brain areas occurs during the initial period of stroke, then brain activation might become more focused over time.
(c) Imagining movements involves similar brain mechanisms and neural recruitment as actual execution and, hence, facilitates recovery.

(d) Using both hands together (bimanual task) recruits more neural elements in M1 of the affected hemisphere than the unimanual, right-handed task.

Materials and methods

Subject

The subject, N.G. was a 65 year-old, right-handed male who suffered from a left middle cerebral artery stroke (Figure 1) 9 months before the first scanning session. All procedures followed in the study were in accordance with the institutional guidelines. Informed consent was obtained from the patient after explaining the experimental protocol to him. He was examined on three occasions—at post-stroke months 9, 11 and 12. Although recovery is believed to happen only during the initial weeks or months after the neurological insult [24], there are several reasons for choosing a patient 9 months into the episode. Six months or later, initial vascular adjustments including luxury perfusion, altered vasoreactivity, peri-infarct oedema and diaschisis usually subside [24]. During the acute phase of stroke, there is profound mismatch between cerebral metabolism and blood flow, with varying degrees of relative or absolute hyperemia [25]. Hence, cerebral blood flow does not reflect the actual cerebral function during the early phase of injury. Transcranial Doppler ultrasound studies [26, 27] have recently verified these changes in blood flow

that occur during the early post-stroke period. The severity of hemiparesis early after stroke precludes the possibility of using motor tasks for functional brain imaging.

Physiotherapy

The patient's current physiotherapy methods were based on the Feldenkrais method® [28, 29]. Therapy started after the first scan, twice a week for ~8 weeks and each session lasted ~45 minutes. There were no home exercises or tasks beyond these therapeutic sessions. This method claims to utilise functionally-based variation, innovation and differentiation in sensorimotor activity in order to free subjects from habitual patterns and allow for new patterns of thinking, moving and feeling to emerge.

Physical examination and objective measurement of stroke

Initial examination revealed right hemiparesis with mild expressive aphasia, but no hemianopsia or heminegelect. N.G. was physically active within the impairment, was independently ambulant without any assistive devices or orthotics. His right upper extremity was non-functional during ambulation and supporting reactions were absent. He did not experience pain during active or passive range of movements of the arm. The results of a detailed motor examination and functional profile of the right upper extremity during the first and the last sessions are given in Tables I and II, respectively. Manual muscle testing was done and graded according to the Medical Research Council (MRC) scale [30]. No other systemic abnormalities were detected by a detailed clinical examination.

Task

The experiment consisted of three tasks, two unimanual and one bimanual. During the unimanual task, the subject performed movements with the right or left hand alone, whereas the bimanual task was carried out using both hands simultaneously. Each experimental task consisted of overt movement of the fingers in a prescribed sequence followed by imagery of the same task. During overt movement, N.G. was instructed to make the requested finger sequences as accurately as possible at an approximate movement frequency of one finger per second. During the imagery task, he was asked to imagine doing the same, but to remain relaxed without actually moving the fingers. During the experiment, the hands were kept in a semi-prone position by the subject's side, so that the experimenters were able to see his finger
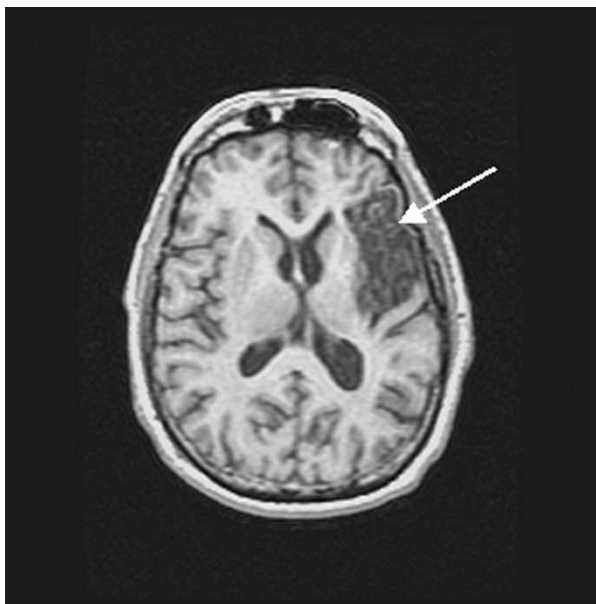

Figure 1. An axial slice of the brain from the patient showing the extent of the lesion (arrow). Note that the left side of the brain is on the right.

Table I. Results of motor examination of the patient.

Test	fMRI Session 1	fMRI Session 3
Cervical spine	Limited	Limited
Thoracic spine		
Kyphosis	Severe	Severe
Thoracic cage expansion	Severely limited	Improved
Thoracic mobility	Stiff and limited	Improved
Breathing	Paradoxical	Normal
Righting reactions	Minimal	Improved
Shoulder		
External rotation (loss of range)	50%	35%
Flexion (loss of range)	30%	20%
Elbow and forearm		
Flexion and extension	5	5
Supination	3	4
Pronation	3	4
Wrist and hand		
Wrist flexion	2	3
Wrist radial deviation	0	0
Wrist ulnar deviation	0	3
Wrist extension	0	3
Wrist extension with ulnar deviation	0	2
Wrist extension with radial deviation	0	3
Abductor pollicis longus/brevis	0	3
Abductor digiti minimi	0	2
Adductor pollicis	0	2
Flexor digiti minimi	0	3
Opponens digiti minimi	0	3
Opponens pollicis	0	3
Extensor indicis	0	3
Flexor pollicis longus	2	3
Flexor pollicis brevis	2	2
Flexor digitorum superficialis	2	2
Flexor digitorum profundus	2	3
Palmar interossei	0	3
Lumbricals	0	2
Extensor digitorum	0	3

Numbers correspond to the MRC manual muscle testing scale.

Table II. Functional improvement in motor control.

Functional profile of the right extremity	First session	Last session
Shoulder girdle movement without synergy	Yes	Yes
Reaching from right to left without grasping	Yes	Yes
Isolated thumb movement (flexion)	Yes	Yes
Very weak and unco-ordinated grasping	Yes	Yes
Isolated finger movement in flexion	Yes	Yes
Isolated thumb/finger movement in extension	No	Yes
Hand gesturing	No	Yes/No
Close chain supporting reactions	No	No
Grasping of a small object	No	Yes
Pinch	No	Yes
Thumb and finger opposition	No	Yes
Power grip	No	No
Open and close a door	No	Yes
Open and close a car door	No	Yes
Turn an ignition key	No	Yes
Hold a tennis racquet	No	Yes
Dress independently	Yes	Yes
Catch a tennis ball with both hands	No	Yes
Button a shirt using both hands	No	Yes/No
Arm swing with gait	No	Yes/No
Writing with a pen	No	No
Using a feeding utensil with the right hand	No	Yes/No
Holding a coffee cup	No	No
Tie a shoe string	No	No
Tighten a belt	No	No
Carrying using his right forearm, if asked	Yes	Yes
Carrying using right hand	No	Yes/No
Driving holding steering wheel with left hand	Yes	Yes
Driving holding steering wheel with right hand	No	No
Swing a golf club	No	Yes
Play golf	No	Yes

Yes/No means that the subject was not able to complete the task but there was observable muscle contraction in an attempt to perform the task and the response was better than that during the first session.

movements at all times (and lack of such during imagery conditions). The fingers were labelled 1–5 from the thumb to the little finger (anatomical convention) and the sequences employed were 5342, 2435 and 4253 for left, right and bimanual conditions, respectively. Task instructions were given to the subject just before the beginning of each experimental condition. He was asked to keep his eyes closed during the entire experiment and to concentrate on the task, opposing thumb to fingers as firmly and accurately as possible. The authors were unable to use an Electromyograhic (EMG) recording to monitor muscle activity during these tasks. Nevertheless, one of the authors stood inside the scanner room beside the patient to monitor movement speed and precision during the overt sequencing tasks and lack of movement during the imagery tasks.

Image acquisition protocol

The patient was scanned on three occasions (sessions I, II and III at 9, 11 and 12 months post-stroke, respectively). For each session, whole brain fMRI data acquisition was carried out using a 1.5 Tesla Signa scanner (General Electric Medical Systems, Milwaukee, WI), equipped with echo planar imaging (EPI) capabilities. Images were acquired with the patient lying supine inside the scanner. Before entering the scanner, he was briefed about the tasks to be performed. The sequence of finger movements was explained to him when he was inside the scanner. Each task (unimanual and bimanual) lasted for 3 minutes and was comprised of three periods of activation (ON, task) during which the subject performed the task and three baseline (OFF, rest) periods in which he heard only the ambient machine noise. Alternating periods of task and rest

were cued to the subject through instructions to 'move' and 'rest', respectively, delivered through a speaker system. There were two phases—overt execution and imagery—for each task. This resulted in six conditions—execution and imagery of right, left and bimanual action sequences, respectively. Scans were randomized across sessions. Throughout the experiment, the subject's head was supported by a comfortable foam mold. Head movement was further minimized using foam padding and forehead restraining straps.

Scanning started with the acquisition of full head, 3D SPGR anatomical images, with the following imaging parameters: field of view (FOV) = 26 cm, frequency-phase matrix = 256 × 256, repetition time (TR) = 34 ms, echo time (TE) = 5 ms, flip angle (FA) = 45°, slice thickness 2 mm and one excitation per phase encoding step. T2*-weighted gradient echo, echo planar multi-slice datasets were acquired during performance of the finger sequencing tasks. (TR = 3000 ms; TE = 60 ms; FA = 90°; 20 axial slices, frequency-phase matrix = 64 × 64; FOV = 24 cm; slice thickness = 5 mm and inter-slice gap = 2.5 mm). Thus, the voxel size was 3.75 × 3.75 × 7.5 mm. High-resolution background images (same 20 slices, frequency-phase matrix size = 512 × 512) were also acquired for overlaying the functional data.

Data analysis

The software packages used for data analysis were AFNI (Analysis of Functional NeuroImages, Medical College of Wisconsin) for display and analysis [31] and SPM (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London) for co-registration. Pre-processing consisted of movement correction of the functional datasets using a Fourier method [32], low pass filtering of the corrected time-series (cut-off = 0.1 Hz) and spatial smoothing of each volume using a Gaussian kernel (FWHM = 6 mm). Alternating periods of baseline and movement-related activation were modeled using a boxcar reference function shifted by 6 seconds to account for the haemodynamic response delay. This delay was determined by examining the raw time series data. Regions of task-related activity were determined by cross-correlation of the image time series with the reference waveform. Voxels with a correlation value (with zero time lag) less than 0.5 were masked and discarded form further analysis. The functional datasets were then coregistered to a full-head T1-weighted scan and resliced into 1 mm cubic voxels (done in SPM). An activated region was defined by an individual voxel probability less than 0.01 and a minimum cluster size threshold of 630 μl

(six original voxels) for session one and 735 μl (seven voxels) for sessions 2 and 3. These thresholds were established based on 1000 Monte Carlo simulations demonstrating that the probability of obtaining such activation cluster for an entire volume (type I error) was less than 0.0001 [33]. Finally, the functional datasets were transformed into the stereotaxic space of Talairach and Tournoux [34].

ROI analysis

One of the striking observations between brain activation in this study compared to normal subjects [17] is the general spread of activation and increase in size of clusters of activation in this patient. Such a general increase in task-related activation in patients with stroke relative to control subjects has been reported in several previous studies [1–4]. Regions of interest (ROI) were identified based on the results of previous work on normal subjects using the same finger-sequencing paradigm [17]. The following 11 ROI were selected—for SMA, both hemispheres were considered as a single ROI and the remaining 10 ROI comprised of five regions in the right and their homologous regions in the left hemisphere. These were the pre-central gyrus (BA4), post-central gyrus (BA3), superior parietal lobe (precuneus), inferior frontal gyrus (peri-infarct area; BA 44/45) and culmen of the cerebellum. Voxels in each ROI which satisfied the cluster identification criteria were counted.

Comparison across sessions

To compare data across sessions, clusters of brain activation were identified at the statistical criterion of $p < 0.01$ (corrected) in each session. However, since the primary interest was to understand the temporal evolution of brain activation as stroke resolves and to see how different brain regions are engaged and disengaged over time a laterality index (LI) was used to compare brain activation across sessions. For each ROI, LI was defined as the number of voxels in the left (affected) hemisphere/(voxels in the left + voxels in the right), thus giving LI for five ROI (except SMA). This index essentially provided a better way of understanding the contribution of each brain area (ROI) to the overall task-related activation in one session and its changes over time. The mean intensity of activation of all active voxels within each region of interest was also computed.

Results

N.G. performed all tasks correctly. Movements involving the affected (right) hand were difficult for

him during the first session as the motor weakness due to stroke limited finger opposition movements to execute the task correctly. However, during the second and third sessions, he was able to perform the tasks much better, as muscle power improved. He reported the bimanual imagery task to be the most difficult one. No mirror movements were observed in the normal hand when he performed the task using the affected hand.

Unimanual tasks

During task execution using the unimpaired hand (left-move) and while imagining the same movements (left-image), there was more contralateral than ipsilateral cortical activation, as revealed by the Laterality Index (LI) (always less than 0.5 in any brain area for all sessions). This is the expected pattern of brain activation for such motor tasks in normal subjects. A similar pattern of activation (contralateral > ipsilateral) was observed in the sensorimotor cortex (SMC) for the right-handed execution (right-move) task too. Figure 2 shows brain activation in an axial slice ($Z = 50$ of the Talairach atlas) during the right-handed execution task across sessions. It can be seen that activation in the contralateral (left) SMC is always greater than that of the ipsilateral (right) side in all three sessions. However, activation in the precuneus (superior parietal lobe) exhibited the opposite pattern—ipsilateral (right) > contralateral.

Figure 2 also illustrates a general decrease in the spread of activation over sessions; i.e. compared to the first session, brain activation became more localized by the third session. Interestingly, the LI values during the right-handed execution task showed an increase over sessions (0.58, 0.65, 0.82 in sessions I, II and III, respectively). It should be noted that, in right-handed tasks, LI depicts the contribution of the contralateral (affected, left) hemisphere towards total activation (left + right) and 1 minus LI (denoted $1 - LI$ in future) that of the ipsilateral hemisphere. Hence, an increase in LI during the right-handed execution task over sessions suggests greater contribution of the affected hemisphere and a progressive decrease in the contribution of the right (ipsilateral) M1 to total activation (left + right). A similar decrease in activation over sessions was also observed in the Supplementary Motor Area (SMA) (Figure 2). The right-handed imagery task (right-image) resulted in a pattern of cortical activation very similar to that of the right-handed execution task across sessions, but almost always with less intensity of activation in bilateral M1 (Table III).

Recruitment of precuneus (superior parietal lobe) occurred in a different manner than sensorimotor cortex during left-move and right-move tasks and their imagery counterparts. As can be seen in Figure 2, more ipsilateral than contralateral precuneus activation was evident during the right-move task during all sessions. In fact, when the contribution of the ipsilateral precuneus ($1 - LI$) was compared with that of ipsilateral M1 during the right-handed execution task, an inverse relationship was observed ($r = -0.99$) (see Figure 3). Interestingly, a larger cluster of activation in the ipsilateral
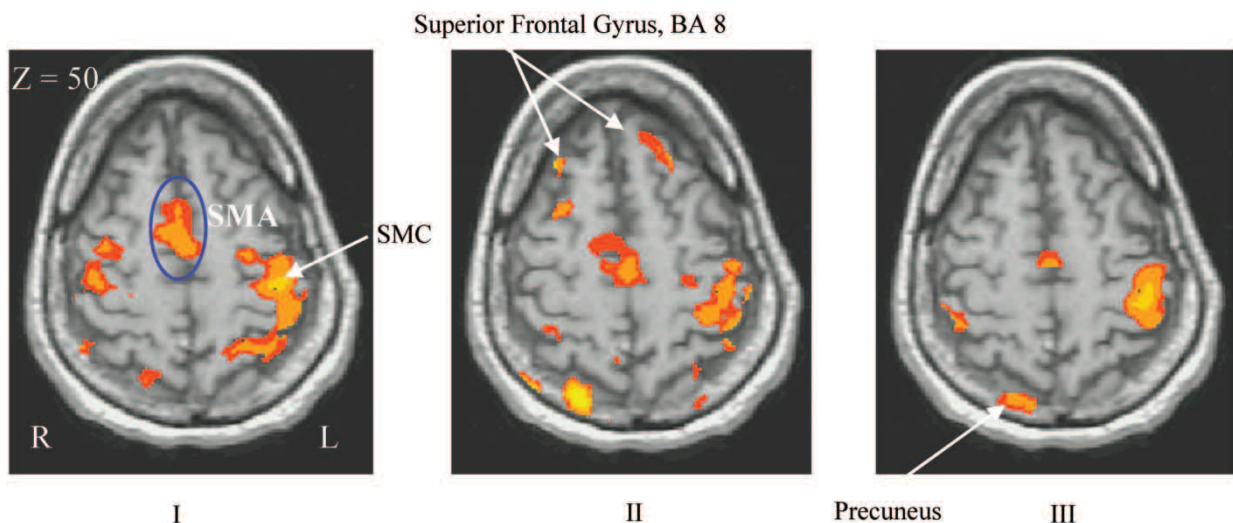

Figure 2. Comparison of brain activation during the right-move task (bad hand) across sessions I, II and III. SMC: Sensorimotor Cortex; SMA: Supplementary Motor Area; $Z = 50$ indicates the inferior–superior co-ordinate of the axial slice in the Talairach atlas. In all sessions, contralateral (left) sensorimotor cortex shows stronger activation than ipsilateral (right). SMA activation decreases with session; Precuneus activity increases during the last two sessions, when compared to the first. Activity is more diffuse in the first session and an overall decrease in the spread of neural activation is seen over sessions.
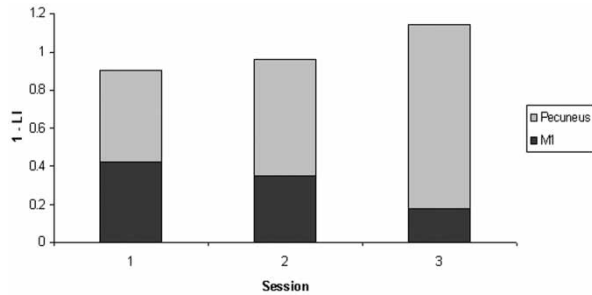
Figure 3. Contribution of ipsilateral M1 and superior parietal lobe (Precuneus) as shown by $1 - LI$ values, to their corresponding total activation (left + right hemisphere) during the right-handed execution task. M1 activation decreases while activity in the Precuneus increases with session. A negative correlation ($r = -0.99$) was observed between these two activations over time.

Table III. Laterality Index (LI) and intensity of activation.

	Session I	Session II	Session III
Part A: Intensity of activation in right M1			
Right-move	0.69	0.68	0.68
Right image	0.53	0.68	0.41
Intensity of activation in left M1			
Right-move	1.2	0.84	0.98
Right-image	0.61	1.00	0.87
Part B: Ipsilateral precuneus activation			
Right-move ($1 - LI$)	0.48	0.61	0.96
Left-move (LI)	0.17	0.41	0.39
Part C: Intensity of activation in ipsilateral precuneus			
Right-move	0.63	1.14	0.9
Left-move	0.61	0.76	0.63
Right-image	0.46	0.57	0.83
Left-image	0	0.45	0.25
Part D: Laterality Index in cerebellum			
Right-move	0.84	0.56	0.77
Left-move	0.59	0.67	0.7
Part E: Laterality Index (LI) in M1			
Right-image	0.42	0.53	0.49
Bimanual-image	0.46	0.54	0.72

precuneus was found when N.G. executed the task using the affected hand (right) compared to the good (left) hand (as indicated by $1 - LI$ of right move greater than LI of left-move—see Table III). Comparing the intensity of activation in precuneus, it was also noted that executing and imagining sequences using the affected (right) hand resulted in stronger ipsilateral activation than while using the good (left) hand (Table III).

An increase in fMRI signal occurred in the inferior frontal gyrus (BA 44/45) including the peri-infarct region during the right-move task, but no specific pattern of change could be observed over sessions. In all sessions, when the subject performed the task using the affected (right) hand, more voxels were active in the contralateral (left) cerebellum than the ipsilateral (Table III; LI always > 0.5). However,

for the left move task, more ipsilateral cerebellar activation consistent with the normal pattern was observed.

Bimanual tasks

Performing the bimanual tasks recruited several brain areas in both hemispheres. In this stroke patient, who was on treatment and was functionally improving, the extent to which different brain areas are recruited over time is likely to change depending on the degree of recovery in these areas. Hence, rather than comparing LI of bimanual tasks across sessions, it was more interesting to compare the LI of the right-move task in each session with that of the bimanual-move task of the same session. This yields more useful information as the basic vascular changes consequent to functional improvement remain the same for all tasks (unimanual and bimanual) in one session and the contribution of different brain areas in each hemisphere (during right-move and bimanual-move tasks) is almost entirely due to the difference in the task demands; i.e. one is able to assess how much of the difference in brain activation in the side of the lesion is due to a change in task from unimanual to bimanual alone. In other words, this helps one understand whether the bimanual task facilitates the recovery process. When comparing the LI in primary sensorimotor cortex during right move and bimanual move tasks, no increase for the bimanual task was observed (i.e. no increased activation in the left side). However, the value of LI was always greater than 0.5 in right move and bimanual move tasks, indicating that more voxels were active in the sensorimotor cortex of the left side (side with the lesion) than the right. Both during right-move and bimanual-move tasks, M1 of the affected side (left) showed higher intensity activation than the right side (Figure 4, gray > dark during right-move and dotted > stripes during bimanual-move). Also during the second and third sessions, bimanual execution of the task resulted in increased intensity of activation in the left M1 compared to right-handed execution (Figure 4, compare the dotted and gray bars).

Between right-image and bimanual-image, laterality index in M1 showed an increase during bimanual-image in all sessions (Table III). This suggests that the bimanual task recruits more voxels in the damaged hemisphere than the unimanual task.

Brain activation during bimanual execution and imagery tasks is shown in Figure 5. A decrease in the spread of activation by the third session is evident both during bimanual execution and imagery (row 1 indicates activation in the first session and row 2 that in the third). It is interesting to note that execution
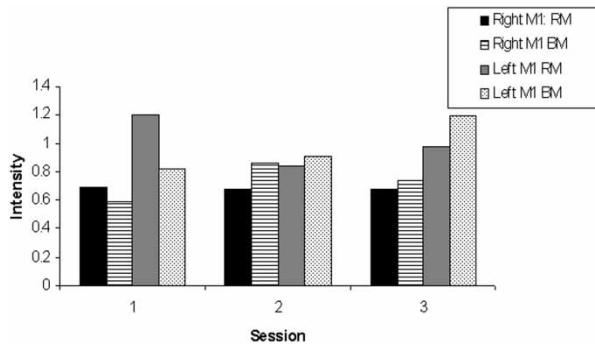
Figure 4. Intensity of activation in primary motor cortex (M1, Brodmann's area 4) during the right-handed and bimanual overt execution tasks. Although in the first session more intensity of activation is seen in the right-handed than the bimanual task in both hemispheres, this pattern reverses in sessions 2 and 3 (compare dark and striped bars; and gray and dotted bars). A higher intensity of activation was observed in the lesion hemisphere (left) than the right hemisphere, both during the right-handed and bimanual execution tasks (gray > dark and dotted > striped). RM: Right-Move; BM: Bimanual-Move.

and imagery result in quite similar patterns of activity across sessions.

Discussion

One of the important features of this study is that it monitored changes in the pattern of brain activation over time in a patient recovering from left MCA stroke, using the same spatiotemporal finger-sequencing task. It also related neural activation patterns with clinical recovery using the standard MRC scale and a functional profile of his activities.

Increased reliance on brain structures involved in motor control may be an integral part of reorganization of motor systems and result in the wide distribution of neural activation observed during the first session [6, 35, 36]. This phenomenon occurs as part of adaptive plasticity, which has been proposed as a principal mechanism of recovery from stroke [37, 38]. The results support several previous studies
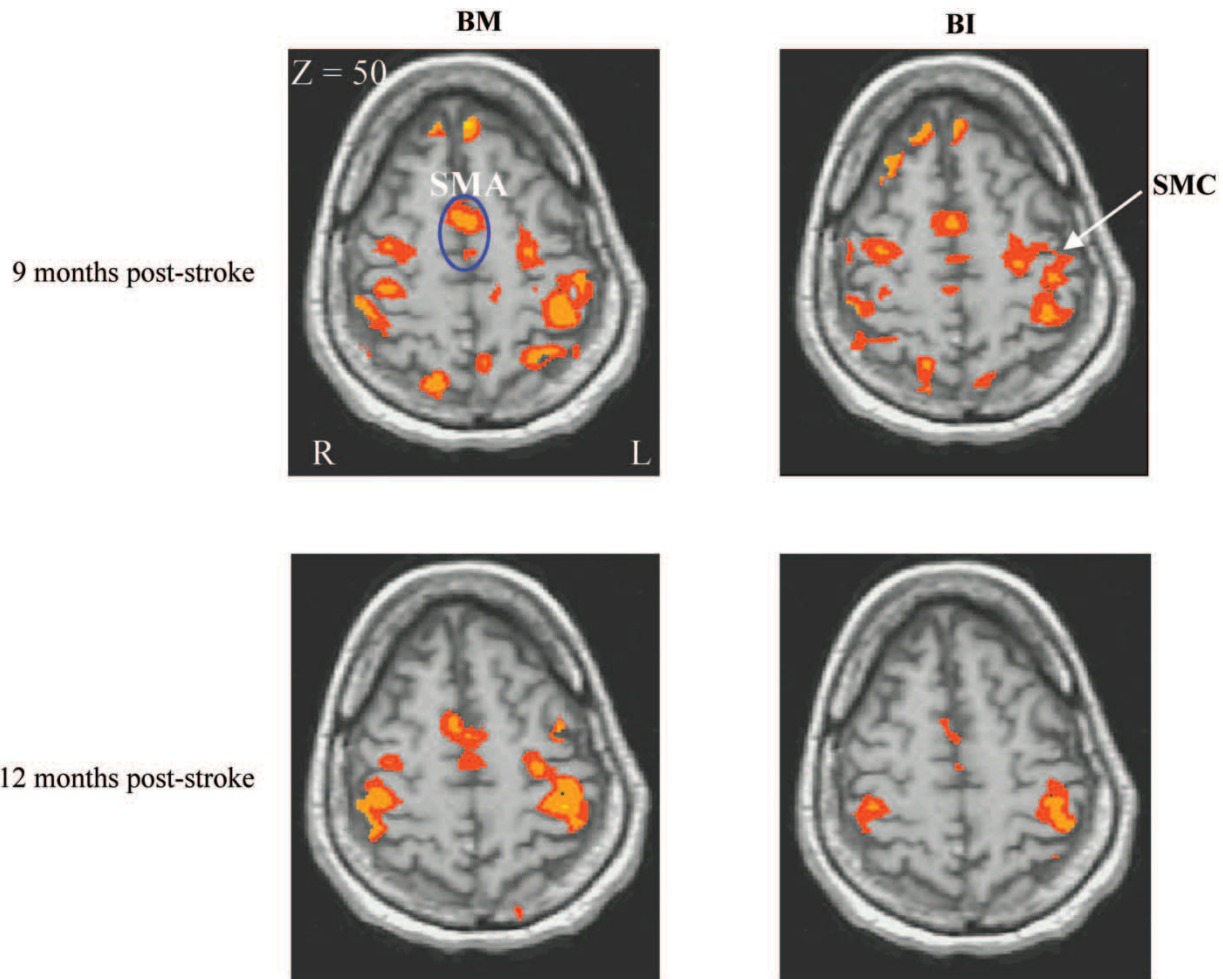

Figure 5. Comparison of brain activation during bimanual-move (left column) and bimanual-image (right column) tasks in the first and last sessions (first and second row, respectively) shows that the primary sensori-motor cortex (SMC) of the lesion side (left, L) is more active than the right, during both tasks and across sessions. A general decrease in the spread of activation and decreased activity in the supplementary motor area (SMA) by the third session is also seen.

that reported greater and widespread brain activation in early, compared to the later stages of stroke [5–7, 12]. An initial increase in dendritic branching, number of synapses and hyper-excitability has been suggested as being responsible for this general spread of activation [39, 40]. However, Buchkremer-Ratzmann et al. [41] reported in rodent studies that, over time, this increase is followed by a pruning back of neurons and a decrease in hyper-excitability. With improvement in function of the stroke-affected neural areas, it is likely that similar mechanisms contribute to a reversal of the initial demasking that was observed in the patient.

The activation of the ipsilateral motor pathways during the initial session in this subject is an interesting phenomenon, although it is yet unclear how the non-stroke hemisphere contributes to recovery [42, 43]. One possibility is that when brain regions in one hemisphere suffer damage due to stroke, homologous regions in the other hemisphere are recruited more, to compensate for the loss of function. This is consistent with animal studies that demonstrated expansion of neural elements in the non-injured hemisphere in animals recovering from a unilateral lesion [44, 45]. Although when compared to control subjects, Transcranial Magnetic Stimulation (TMS) parameters (such as lower motor threshold, easier to obtain ipsilateral motor evoked potentials—MEPs, reduced intra-cortical inhibition) [46] point to increased cortical excitability in the contralesional sensorimotor cortex (SMC) following stroke, this is not essentially associated with good recovery [35, 47, 48]. It is the development of contralateral MEPs by stimulation of the affected hemisphere that heralds return of function in the hand [49]. Using TMS, Werhahn et al. [50] recently demonstrated that recovered motor function in the paretic hand of chronic stroke patients relies predominantly on reorganized activity within motor areas of the affected hemisphere. Therefore, TMS studies indicate that it is the survival of the contralateral, not ipsilateral corticospinal tract that correlates with recovery, a finding that is supported by clinical and anatomical imaging data [51, 52]. FMRI following rehabilitation therapy has also shown decreased contralesional and increased ipsilesional activation associated with improved motor performance [8, 9, 53].

Another reason for an increased activation in the contralesional hemisphere is the loss of inhibition (disinhibition) from the stroke-affected hemisphere to the unaffected hemisphere [46, 54, 55] following stroke. Indeed, previous studies have established that, in normal subjects, inhibitory trans-callosal conduction occurs between the contralateral and ipsilateral motor cortices during unilateral motor tasks [56, 57]. Several researchers have also demonstrated bilateral brain activation with an increase in task complexity in normal subjects [58, 59] and suggested that the ipsilateral motor cortex may be responding to an increase in perceived task complexity. Suppression of unwanted movements may well be another role of the non-stroke hemisphere.

In both execution and imagery tasks, the subject had his eyes closed and, hence, had to rely on knowledge of the spatial dimensions of the task along with the sensory feedback experienced during movement. Accessing this memorized spatial information may have contributed primarily to the parietal lobe activation observed during execution and imagery. However, it is unusual for ipsilateral activation to be larger than contralateral activation, especially when right-handed individuals perform the task using their preferred hand. In this subject, even when the pattern of blood flow to the left sensorimotor cortex had been restored closer to normal in later sessions (as evidenced by LI values in the left sensorimotor cortex greater than 0.5 and increasing over sessions during the right-move task), blood flow to ipsilateral (right) parietal cortex appeared to increase during the right-move task. These observations suggest ongoing vascular readjustments and vicariousness of function in the parietal cortex of this patient. Reciprocal activation of M1 and superior parietal lobule over time during the right-handed execution task demonstrates a major role of the connections between these two regions in the process of recovery. Recent imaging studies have verified the functional connectivity of such pathways during motor tasks in the human brain *in vivo* [60]. Data tend to indicate that the undamaged parietal cortex (right) takes over the function of the affected side even when the left sensorimotor cortices are normal, to help maintain optimal motor performance. Parietal cortex (especially the superior parietal lobule, Brodmann's area 7, the precuneus) is engaged especially for action sequences that rely on remembering and executing the correct ordering of task components along with processing the sensory consequences of action. Using motor imagery, Johnson [61] demonstrated in early hemiplegic patients that they retained the ability to accurately represent movements of both their healthy and paralysed limbs. These patients could use motor imagery to activate damaged motor networks, except when the lesion involved the right posterior parietal and left frontal areas. This highlights the role of the parietal cortex in representation of movements and also as a key element of functional reorganization during recovery from stroke.

Since the bimanual task engages brain areas in both hemispheres, it may serve to improve functions of the affected hemisphere through cortico-cortical and trans-callosal connections. As observed in animal studies, it may be that, through these

bihemispheric connections, there is a reduction in GABA receptors or bilateral increases in glutamate NMDA receptors [62] in areas functionally connected to the infarcted region. These in turn act to unmask latent horizontal connections and aid in functional recovery [63, 64]. The existence of these horizontal connections throughout M1 has been verified by Donoghue et al. [65, 66] using intra-cellular recordings and field potential recordings of *in-vitro* preparations. Jacobs and Donoghue [63] also showed that local blockade of GABAergic inhibition in one part of M1 unmasks existing horizontal connections that then reveal hidden representations of limb movements in other parts of M1. This data revealed stronger M1 activation in the lesion hemisphere both during bimanual execution and imagery tasks. This observation, along with the superior parietal lobe activation observed during bimanual tasks, support the proposition that bimanual tasks aid in neural reorganization and functional recovery from stroke. In this process, several brain areas including, but not limited to the primary sensorimotor cortex, superior parietal lobule, SMA and cerebellum are involved. It is interesting to note that the bimanual imagery task too results in similar activation patterns as overt execution. This observation warrants attention as it opens the possibility of using imagery as a potential therapeutic/rehabilitative tool for functional improvement while recovering from stroke.

One interesting observation is that chronic stroke patients maintain the ability to recover and be functionally independent, even months after the neurological insult. The success of therapy depends on identifying rehabilitative measures that improve motor control by exploiting the inherent plasticity of the brain. This in turn enhances communication between brain areas within and across hemispheres and activates motor pathways that lie dormant in patients with stroke due to limb disuse or neglect. This work supports the idea that motor imagery and bimanual movements of complex finger sequences are useful in this regard. Results also reveal that recovery involves coupling and decoupling of brain areas such as the affected M1, SMA and parietal cortex into the functional neural network over time. Quantitative measurements of finger movements such as force of contraction, if measured during each session, may help test the results observed in this study. It is encouraging to see that the Feldenkrais method® has been able to contribute to recovery in this patient. However, it should be remembered that the results of this study might pertain to this patient alone. Similar studies need to be done in a larger population of patients, not only to study the applicability of such treatment protocols in different types of stroke and motor disabilities, but also to better understand the evolution of brain activation as patients recover.

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