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Correlation between motor improvements and altered fMRI activity after rehabilitative therapy

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Summary

Motor rehabilitation therapy is commonly employed after strokes, but outcomes are variable and there is little specific information about the changes in brain activity that are associated with improved function. We performed serial functional MRI (fMRI) on a group of seven patients receiving a form of rehabilitation therapy after stroke in order to characterize functional changes in the brain that correlate with behavioural improvements. Patients were scanned while performing a hand flexion–extension movement twice before and twice after a two-week home-based therapy programme combining restraint of the unaffected limb with progressive exercises for the affected limb. As expected, the extent of improvement in hand function after therapy varied between patients. Therapy-related improvements in hand function correlated with increases in fMRI activity in the premotor cortex and secondary somatosensory cortex contralateral to the affected hand, and in superior posterior regions of the cerebellar hemispheres bilaterally (Crus I and lobule VI). fMRI offers a promising, objective approach for specifically identifying changes in brain activity potentially responsible for rehabilitation-mediated recovery of function after stroke. Our results suggest that activity changes in sensorimotor regions are associated with successful motor rehabilitation.

Keywords: stroke; fMRI; rehabilitation; premotor cortex; cerebellum

Abbreviations: fMRI = functional MRI; TMS = transcranial magnetic stimulation

Introduction

Stroke is a major cause of disability in adults. Intensive rehabilitation interventions are being used more commonly as delivery of post-stroke care improves and can reduce long-term disability (Indredavik *et al*., 1997; Stroke Unit Trialists' Collaboration, 1997). Unfortunately, objective evaluation of the specific effects of rehabilitation remains challenging (Tallis, 2000). While advances are being made, too little is known about the basis for post-stroke functional recovery to provide a firm neurobiological foundation for most strategies employed.

Successful rehabilitation may alter the way in which the brain controls movement. Animal studies have demonstrated remapping of movement representations in the primary motor cortex after effective rehabilitative training of hand movement following an ischaemic lesion (Nudo *et al*., 1996). A few studies have already attempted to define the changes in brain activity responsible for successful rehabilitation after stroke in humans (Liepert *et al*., 2000, 2001; Nelles *et al*., 2001). These rehabilitation-related changes may be related to the brain activity changes that occur with spontaneous functional recovery. There is growing evidence from human brain imaging studies that movement of an affected limb with partial recovery after a stroke is associated with altered activity in motor cortical regions (Chollet *et al*., 1991; Weiller *et al*., 1992; Cao *et al*., 1994, 1998; Caramia *et al*., 1996; Cicinelli *et al*., 1997; Cramer *et al*., 1997; Honda *et al*., 1997; Netz *et al*., 1997; Traversa *et al*., 1997, 2000; Rossini *et al*., 1998; Seitz *et al*., 1998; Cramer and Bastings, 2000; Marshall *et al*., 2000; Pineiro *et al*., 2001), but the exact pattern of change reported varies between studies. Most studies have shown that increased activity in the undamaged hemisphere is associated with movement of a recovered limb (Chollet *et al*., 1991; Weiller *et al*., 1992; Caramia *et al*., 1996; Cramer *et al*., 1997; Honda *et al*., 1997; Cao *et al*., 1998). Whereas some studies have identified changes either in the extent (Cao *et al*., 1998) or the location (Rossini *et al*.,

Table 1 *Patient details*

Patient	Sex	Age (years)	Handedness	Time post stroke (months)	Stroke location	Stroke volume (cm^3)	Baseline grip ratio	Baseline motricity
1	M	44	R	12	Left anterior MCA	36	0.12	76
2	M	57	R	6	Right MCA	230	0.52	58
3	F	52	R	70	Left MCA	120	0.16	76
4	M	59	R	49	Right MCA	60	0.32	72
5	F	59	L	84	Right MCA	24	0.40	76
6	M	57	R	6	Left MCA temporal-parietal	4	0.35	76
7	M	61	R	36	Left centrum semiovale lacune	<0.1	0.33	91

F = female; L = left; M = male; MCA = middle cerebral artery; R = right.

1998; Pineiro *et al*., 2001) of activity in primary motor cortices (Netz *et al*., 1997), other studies of recovery after ischaemic infarcts in both humans (Seitz *et al*., 1998; Nelles *et al*., 1999, 2001) and animals (Liu and Rouiller, 1999) have concluded that the function of premotor and parietal cortices is associated with movement recovery.

It is clear that the pattern of activity associated with movement of an affected limb after recovery is different to that seen in control patients, or in patients moving an unaffected limb. However, it remains unclear what the altered pattern of activation signifies. It has been tempting to claim that such changes reflect the adaptive reorganization of the brain that has allowed recovery to take place. However, it is difficult to demonstrate this convincingly in a cross-sectional study that does not look at changes over the course of recovery. Recent years have seen more attempts to carry out serial studies of recovery processes after stroke (Cicinelli *et al*., 1997; Marshall *et al*., 2000). These studies emphasize that such reorganization is dynamic. The largest changes in cortical maps have been seen in the first few months after stroke, which is also when the steepest recovery curves are seen (Traversa *et al*., 2000).

There has been some success in improving motor function in stroke patients even years after stroke (Taub *et al*., 1993). It is thought that this improvement in function is mediated by cortical reorganization (Liepert *et al*., 1998, 2000; Kopp *et al*., 1999). However, the nature of this reorganization is imperfectly understood. An evoked potential study of patients before and after constraint-induced therapy demonstrated a relative shift in dipole towards the ipsilateral hemisphere, but this change was only seen at a 3 month follow-up and not immediately after therapy, even though behavioural improvements were evident immediately (Kopp *et al*., 1999). Transcranial magnetic stimulation (TMS) studies have shown an increase in the area of excitable contralateral motor cortex and an increase in motor evoked responses after the same therapy (Liepert *et al*., 1998, 2000). A PET study demonstrated that, in patients who had received arm training, there was relatively increased blood flow in premotor, parietal and primary motor cortex after therapy compared with control patients (Nelles *et al*., 2001). Together, these studies support the hypothesis that functional brain changes accompany therapy-mediated behavioural improvements. However, the limited spatial specificity of some of these methods does not allow clear neuroanatomical localization of these functional changes. In addition, the fact that all patients improved substantially with therapy means that it is not possible to determine whether the neural changes associated with therapy correlate with the degree of behavioural improvement that the therapy induces.

We wished to define the changes in movement-related brain activity which occur with successful rehabilitation after stroke. We used serial functional MRI (fMRI) to quantify neural changes associated with behavioural changes in a group of chronic stroke patients receiving rehabilitation therapy for hand function. The sensitivity and spatial resolution of fMRI allowed us to make specific conclusions about individual motor cortical regions involved and to correlate behavioural benefits with fMRI changes for individual patients.

Methods

Patients

Patients with mild to moderate hemiparesis at least 6 months after a first ischaemic stroke were asked to take part in the study. Of 10 patients approached, seven agreed to participate in the full study (Table 1). Reasons for non-participation included claustrophobia in the scanner or unavailability for all testing sessions. Stroke location and extent varied between patients (Table 1, Fig. 1). Infarct volumes did not include the hand area of the primary motor cortex or the region of dorsal premotor cortex anterior to the primary hand area in any of the patients. Patients gave informed consent in accordance with the Declaration of Helsinki and local ethical approval from the Central Oxford Research Ethics Committee. Patients attended seven testing sessions (one practice, four pre- and two post-therapy, at two-weekly intervals).

Movement therapy

After five testing sessions, Patients performed a two-week home-based therapy programme based on some of the principles of the constraint-induced technique (Taub *et al*.,

1993). Patients were asked to wear a restraint on their unaffected arm for 90% of waking time. Patients 1–3 were given a sling that enclosed the fingers of the unaffected arm and held the arm against the body. Some patients reported difficulties walking and carrying out daily tasks without being able to use the affected arm for stabilization. Therefore, Patients 4–7 were given a mitten that enclosed the fingers of the unaffected arm but left the arm free for stabilization if required. Patient 7 chose to use his own thick gardening glove instead of the mitten provided. Patients were instructed to complete an explicitly defined 30 min graded exercise programme (Table 2) with the affected arm twice daily. Patients were given self-report questionnaires to fill in daily to report how many hours they wore the restraint and how many times they completed the exercises. Given the limited reliability of self-report, these questionnaires were intended in part as an encouragement for patients to comply as fully as possible and were not relied on as a quantitative measure of compliance with the treatment protocol. The relationship between compliance and outcome was beyond the scope of this study, which was designed only to assess the correlation between fMRI and behavioural changes.

Movement testing

Movement testing [Motricity Index (Demeurisse *et al*., 1980), grip strength (Sunderland *et al*., 1989) and the Jebsen arm test (Jebsen *et al*., 1969)] was performed during all seven testing sessions. The card turning, cone stacking and bean spooning elements of the Jebsen arm test were timed (Jebsen *et al*., 1969). The upper limb section of the Motricity Index for the affected arm was used (Demeurisse *et al*., 1980). Grip strength was measured with a baseline hydraulic hand dynamometer (Fabrication Enterprises Inc, NY, USA). For grip strength and the Jebsen test, a normalized ratio score was calculated [Grip: (U – A)/(U + A); Jebsen: (A – U)/(A + U) where U = unaffected, A = affected]. The change in motor ability with therapy was calculated for each patient and for each measure [(mean pre-therapy ratio – mean post-therapy ratio)/(mean pre- + mean post-therapy ratio)]. The relationship between measures was tested by calculating a Pearson correlation coefficient between changes in mean scores pre- and post-therapy for each measure.

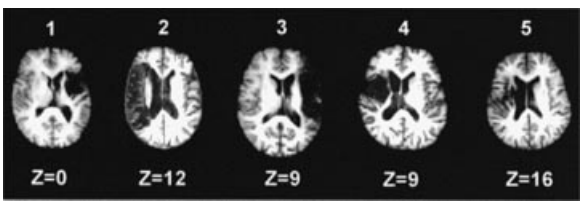

Fig. 1 Location of lesions for patients with cortical strokes (Patients 1–5). Single axial slices in the centre of the lesion volume are shown for illustration. Talairach *Z* coordinates are given for each slice. Total lesion volume is given in Table 1. No lesions included the hand area of primary motor cortex or the dorsal premotor cortex.

fMRI scanning

Patients were scanned on four of the testing session occasions, two weeks apart—twice before and twice after movement therapy. Five of the patients were also scanned in the initial practice session to familiarize them with the magnet environment. We used a 3T Varian (Palo Alto, CA, USA)/Siemens (Erlangen, Germany) MRI system. A T_1-weighted anatomical scan was acquired for each patient in session one [IR (inversion recovery) 3D TurboFLASH (turbo flast low ange shot), 64 × 3 mm axial slices, TR (repetition time) = 30 ms, TE (echo time) = 5 ms, TI (inversion time) = 500 ms, flip angle = 15°, FOV (field of view) = 256 × 256, matrix = 256 × 256]. A 6 min EPI (echo-planar imaging) run was performed first with movement of the unaffected hand, then with movement of the affected hand (21 × 6 mm axial slices, TE = 30 ms, TR = 3000 ms, FOV = 256 × 256, matrix = 64 × 64). For Patients 1–3, the movement task was visually cued flexion–extension of the metacarpal–phalangeal joints of the hand. Movements were performed with the pronated hand resting initially on a wooden board. A plastic 'bridge' was positioned above the fingers of the hand, 3 cm above the board. The amplitude of movements was limited by instructing patients

Table 2 *Progressive exercises used during rehabilitation therapy*

Exercise description	Progression of exercise with improvement
Lifting cones	Increase number of cones lifted
Cutting plastic dough	Increase number of slices
Pouring water from jug	Increase size of jug and repetitions
Unscrewing jar lids	Increase size of jar and repetitions
Lifting dumbbells:	Increase weight and repetitions
wrist pronation/supination	
wrist abductions/extension	
Folding paper into envelope	Decrease size of envelope and increase repetitions
Placing small objects into a box	Increase repetitions
Spooning water to mouth	Increase repetitions and size of spoon
Stretching	None

to move all four fingers between the board and the bridge. Movements were cued at 25% and 75% of each patient's maximum tapping rate measured at the time of the first scan. The tasks were presented in alternating 30-s periods of rest and movement. When data was combined across all patients, only the data from the fast movement task was included as this task provided greater overall activation and better reproducibility as expected based on previous literature (Wexler *et al*., 1997). Faster movements produce activation with higher signal-to-noise because a greater proportion of the sampling time is occupied by the task (i.e. there is an increase in 'duty cycle'). The fast tapping task is therefore a more powerful task design. For Patients 4–7, the movement task was modified slightly to allow better monitoring of performance. Patients performed visually cued flexion–extension of the supinated hand around an air-filled rubber bulb connected to a pressure sensor. The force required for bulb compression was adjusted to be 60% of the patient's maximum compression on the first scanning session. The maximum rate at which the patient could repeatedly produce this force over a 24 s period was measured during the first session. Movements in the scanner were cued at 40% of this maximum rate. The movement task was presented in 24 s blocks alternating with 24 s rest periods. Thus, for both tasks we chose to set the rate (Patients 1–3) or both force and rate (Patients 4–7) of movements for each patient at the beginning of the study and then not to change these movements over sessions. Maintaining test performance constant was essential for determining whether the brain activation patterns associated with performing the movements changed over time.

Image analysis

Image analysis was carried out using tools from the Functional Magnetic Resonance Imaging of the Brain Centre software library (www.fmrib.ox.ac.uk/fsl) and MEDx (Sensor Systems Inc., VA, USA).

Individual level fMRI analysis

Data from each patient and each session were initially analysed separately. The following pre-statistical processing was applied: motion correction using MCFLIRT (Jenkinson and Smith, 2001); spatial smoothing using a Gaussian kernel of 5 mm full-width half maximum; mean-based intensity normalization; non-linear high-pass temporal filtering (Gaussian-weighted least squares straight line fit, with $\sigma = 72.0$ s). Statistical analysis was carried out using FILM (Woolrich *et al*., 2001) with local autocorrelation correction. We quantified the degree to which activation changed before versus after therapy; for each patient, a statistical image of 'therapy-related increases' was created which was a fixed effects comparison of the two post- versus two pre- therapy sessions (Frackowiak *et al*., 1997). A statistical image of 'therapy-related decreases' was also created (pre- versus post-therapy sessions) for each patient. Correlations between the changes in fMRI activation and changes in behaviour were carried out at the group level.

Group level analysis

For group analyses, the individual level Z statistic images for all patients and all sessions were registered into standard space using FLIRT (Jenkinson and Smith, 2001). Images from the three patients with right hemisphere strokes were mirrored about the midline so that the lesioned hemisphere could be overlaid with images from the patients with left hemisphere strokes.

To identify the group baseline activation pattern associated with movement, we produced Z statistic images [(sum of the initial pre-treatment Z statistic images for movement versus rest for each patient)/$\sqrt{}$(number of patients)]. The resulting group Z statistic images were thresholded at $Z > 3.1$ and significant clusters defined according to extent (at $P < 0.005$ (corrected for multiple spatial comparisons according to random field theory) (Worsley *et al*., 1992; Friston *et al*., 1994; Forman *et al*., 1995). The number of suprathreshold voxels within the motor and premotor cortices were used to calculate a group laterality index [(C – I)/(C + I)], where C = contralateral and I = ipsilateral to hand being moved). This anatomical region was defined as the anterior bank of the central sulcus, the precentral gyrus and precentral sulcus, extending from the dorsal surface of the lateral ventricles to the dorsal surface of the brain. The group laterality index was used to assess the relative laterality of activation during movements of the affected and unaffected hands at the baseline scan.

A 'recovery-weighted' group image was created to identify brain regions where change in fMRI activity correlated with change in arm function after therapy. First, for each patient, the Z statistic image of therapy-related increases was multiplied by their individual normalized grip strength ratio change. This was calculated as [(mean pre-therapy – mean post-therapy grip strength ratio)/(mean pre- + mean post-therapy grip ratio)] and normalized across the group by subtracting the group mean and dividing by the group standard deviation. The seven resulting images were summed and divided by the square root of the number of patients. This analysis effectively performs a correlation between activation change (after versus before therapy) and behavioural (i.e. grip strength) change (after versus before therapy) at each voxel. This gave a 'recovery-weighted' Z score image for the group which was thresholded at $Z > 3.1$ and significant clusters defined according to extent (at $P < 0.005$; corrected for multiple spatial comparisons according to random field theory) (Worsley *et al*., 1992; Friston *et al*., 1994; Forman *et al*., 1995). We then masked these clusters by the group baseline movement-related activity, i.e. we constrained our search volume to only consider regions which fell within the group activation map at baseline. This identified volumes across the whole sensorimotor system where increased

Table 3 *Effect of therapy on grip strength*

	Mean grip strength ratio			Affected hand			Unaffected hand		
				Mean grip strength			Mean grip strength		
	Pre	Post	Change	Pre	Post	Percentage change	Pre	Post	Percentage change
1	0.12	0.05	42.3	53	57	7.5	67.3	63	–6.3
2	0.47	0.39	9.4	25	31	24	69.5	70	0.7
3	0.09	0.15	–25.0	38.5	42	9.1	46.3	57	23.2
4	0.35	0.45	–13.0	22.75	17.5	–23.1	47	46	–2.1
5	0.50	0.36	16.7	16.5	20	21.2	49.8	42.5	–14.6
6	0.31	–0.01	107.3	26.5	50	88.7	50.5	49	–3
7	0.35	0.32	5.3	37	42.5	14.9	76.5	82	7.2
Mean	0.31	0.24	20.4	31.3	37.1	20.3	58.1	58.5	0.7
SD	0.16	0.18	43.9	12.3	14.9	33.9	12.5	14.2	11.9
Median	0.35	0.32	9.4	26.5	42	14.9	50.5	57	–2.1

As grip strength ratio is a measure of relative performance between the two hands, we have shown grip strength scores separately for the affected and the unaffected hands. For most patients, changes in grip strength ratio are largely a consequence of changes in the affected hand. The change in grip strength for the affected hand is significantly greater than the change for the unaffected hand (Mann–Whitney $Z = –1.73$, one-tailed $P = 0.04$). For grip strength, ratio change is calculated as [(pre – post)/(pre + post)], for absolute grip strength values change is calculated as [(post – pre)/(post + pre)].

activity after therapy correlated with improved affected hand function. The same procedure was repeated with individual patient images of therapy-related decreases to identify volumes where decreased activity correlated with improved affected hand function.

Results

Effect of therapy on motor function

As expected, the degree to which hand function improved after therapy was variable. To illustrate the variable outcomes, mean grip strength ratios before and after therapy are given in Table 3. We tested the relationship between the different behavioural measures and found that therapy-related changes in grip strength ratio correlated with therapy-related changes in the Jebsen test and arm motricity (Jebsen: $r = 0.816$, $P = 0.013$; motricity: $r = 0.795$, $P = 0.017$), consistent with previous studies in both acute (Sunderland *et al*., 1989) and chronic (Boissy *et al*., 1999) stroke patient groups. Grip strength ratio was chosen as the primary behavioural measure for correlation with brain activation results as it was the most precisely measurable outcome. Table 3 shows that therapy-related changes in the grip strength ratio (a measure of relative performance in the affected and unaffected hands) were predominantly a consequence of functional changes in the affected, rather than the unaffected hand (affected versus unaffected hand: Mann–Whitney $Z = –1.73$, one-tailed $P = 0.04$). We did not attempt to assess the statistical significance of the functional improvement across the group or within individuals as the study was designed simply to correlate individual behavioural and fMRI changes rather than to assess the overall behavioural effects of the rehabilitation procedure.

Effect of therapy as assessed by fMRI

Movement performance during scanning

For the four patients who performed the flexion–extension movement while holding a rubber bulb (Patients 4–7), we were able to confirm that a consistent force and rate was maintained through scanning sessions. There were no differences in the force produced before (mean ± SD: 19.3 ± 9.4, arbitrary units) and after (18.9 ± 8.1) therapy. Consistency of performance for patients performing hand flexion–extension in pronation (Patients 1–3) was assessed less directly by monitoring with a video camera (Webcam, RS Components, Corby, Northants, UK) throughout each scanning session. We were able to confirm that a consistent rate and amplitude was maintained for the latter group.

Movement-related brain activation pattern prior to therapy

Both types of flexion–extension movements produced activation in the expected sensorimotor network when performed with either the affected or the unaffected hand (Fig. 2). We confirmed that activation patterns produced using the two movements were similar (Fig. 2).

Data from all seven patients were pooled to produce group baseline movement maps for the unaffected (Fig. 3A) and affected hands (Fig. 3B). Movement of the affected hand consistently produced a more bilateral pattern of activity in sensorimotor and premotor cortices (Fig. 3B); the laterality index on the group baseline activation image for affected hand movements was 0.15 compared with 0.63 for movement of the unaffected hand. There were only minor differences between the two pre-therapy scans (data not shown).

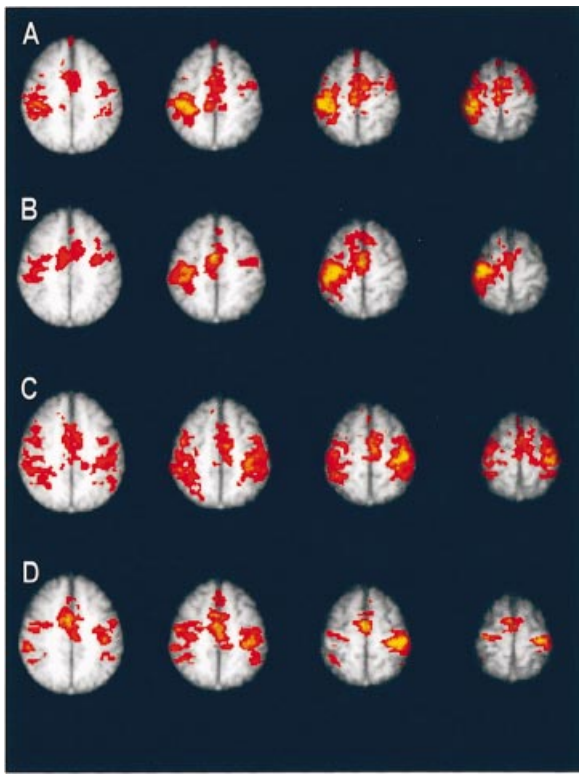

Fig. 2 Baseline fMRI activation patterns for the two flexion–extension tasks used to demonstrate that there is little difference between the tasks in the pattern of activation of the motor cortices. (**A**, **B**) Activation patterns for the unaffected hand for flexion–extension against a rubber bulb (**A**) and a flat surface (**B**). (**C**, **D**) Activation patterns for the affected hand for flexion–extension against a rubber bulb (**C**) and a flat surface (**D**). Images have been thresholded at $Z > 3.1$ and significant clusters defined according to extent (at $P < 0.005$).

Differences were mainly found in visual areas and were not consistent between the two hands, making their significance as 'session' effects questionable.

Therapy-related changes in brain activity for the affected hand

We created a 'recovery-weighted' correlation image (see Methods). This analysis identified three clusters in which increased fMRI signal change correlated significantly with improved function (Fig. 4A, Table 4): the cerebellum (bilaterally), the contralateral secondary somatosensory cortex and the contralateral dorsal premotor cortex.

To better visualize the variation of responses across patients, the relation between the mean positive Z statistic from each patient's statistical map of therapy-related increases within the three clusters identified by the 'recovery-weighted' correlation and improvement in grip strength was tested directly (Fig. 5). A significant correlation was found between mean Z statistic and improvement in grip in all three regions (cerebellum: $r = 0.915$, $P = 0.004$; dorsal premotor cortex: $r = 0.927$, $P = 0.003$; secondary somatosensory cortex: $r = 0.958$, $P = 0.001$). The correlations remain significant even if results from Patient 3 (who showed the greatest behavioural improvement) were not included (cerebellum: $r = 0.872$, $P = 0.023$; dorsal premotor cortex: $r = 0.841$, $P = 0.036$; secondary somatosensory cortex: $r = 0.896$, $P = 0.016$).

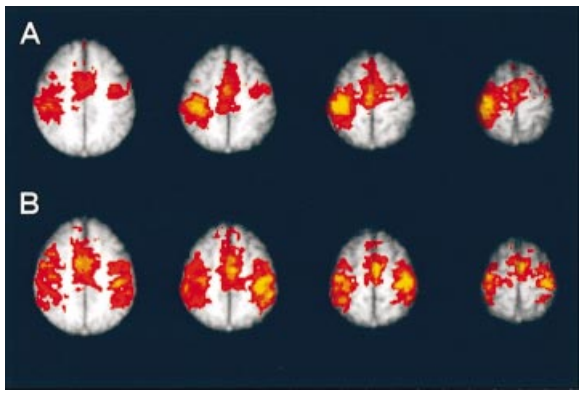

Fig. 3 Baseline fMRI activation patterns for the group of seven patients. Movement of the affected hand (**B**) produces a more bilateral pattern of activation than movements of the unaffected hand (**A**). Images have been thresholded at $Z > 3.1$ and significant clusters defined according to extent (at $P < 0.005$).

The areas showing significant positive correlation with recovery were overlaid onto individual high-resolution T_1-weighted scans in standard space in order to determine whether lesions occurred in these areas for any patient. The clusters in the cerebellum and dorsal premotor cortex did not overlap with lesions in any patients. The cluster in the secondary somatosensory cortex overlapped with the lesion in Patient 2 and with the posterior border of the lesion in Patient 5.

The 'recovery-weighted' correlation analysis also identified a single small cluster in the posterior orbital gyrus that showed a decrease in fMRI signal change after therapy that correlated with recovery scores (data not shown, Table 4).

Therapy-related change in brain activity for the unaffected hand

The 'recovery-weighted' correlational analysis identified increased activity after therapy bilaterally in the cerebellum that correlated with recovery scores (Fig. 4B, Table 4). There was a large cluster in the contralateral primary motor cortex and a small area in the superior temporal gyrus where decreased activity correlated with therapy-related improvement in grip strength (Fig. 4C, Table 4).

Discussion

We have shown that improved hand function after rehabilitation therapy is associated with increased fMRI activity in the premotor cortex and secondary somatosensory cortex contralateral to the affected hand, and in the bilateral superior

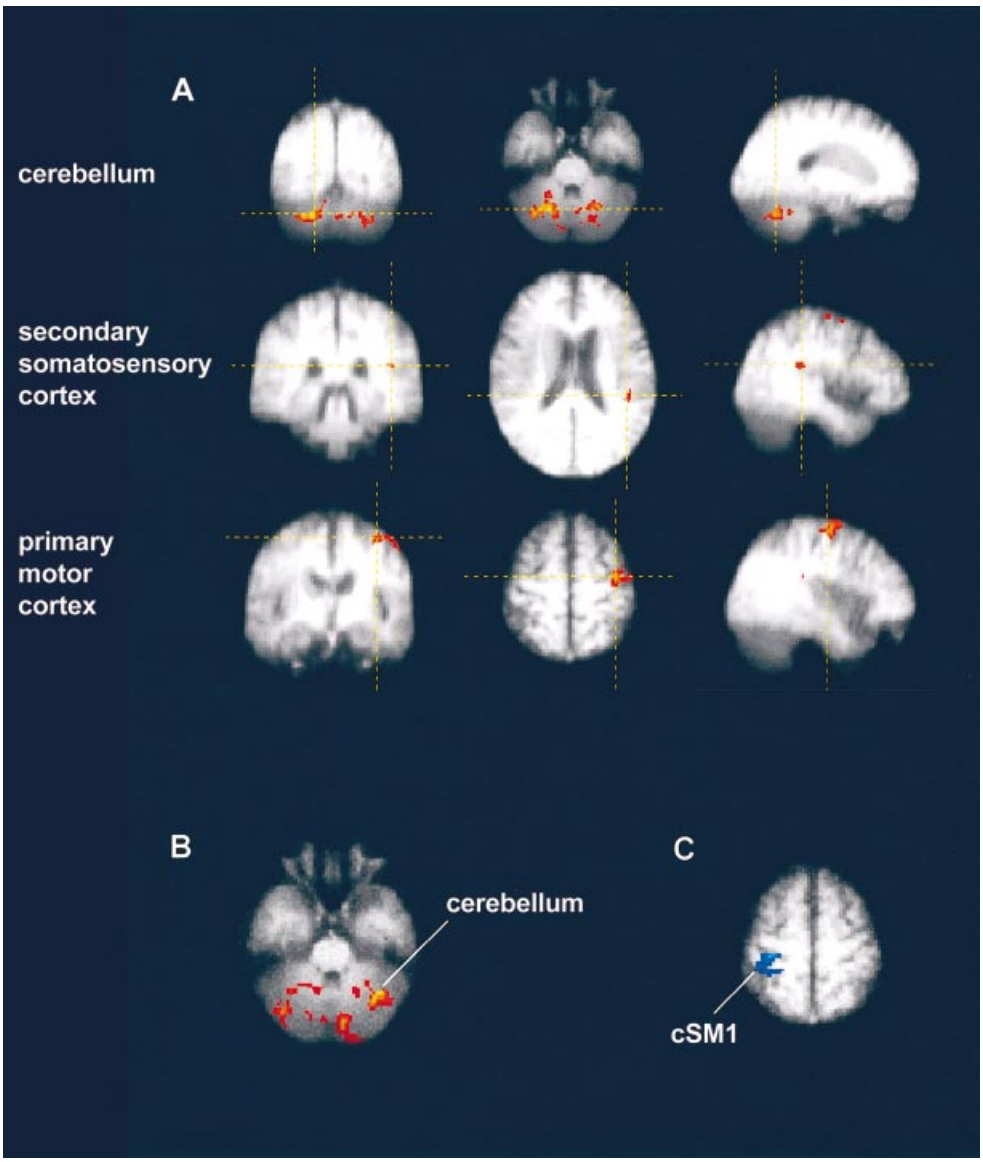

Fig. 4 Areas where changes in grip strength ratio after therapy correlate with changes in fMRI activation (see Table 3). (**A**) Increased fMRI activity in cerebellum, secondary somatosensory cortex and contralateral premotor cortex during movements of the affected hand correlated with improvements in grip strength ratio. Cross hairs are at location of maximum *Z* statistic within each cluster (see Table 4 for coordinates). (**B**) Increased fMRI activity in the cerebellum during unaffected hand movement correlated with improved grip strength ratio. (**C**) Decreased fMRI activity in contralateral primary sensorimotor cortex (cSM1) during movements of the unaffected hand correlated with improved grip strength ratio. Images have been thresholded at $Z > 3.1$ and significant clusters defined according to extent (at $P < 0.005$).

posterior cerebellar hemispheres. This suggests that altered recruitment of sensorimotor cortices and the cerebellum may contribute to recovery after this therapy. This result complements those from recent studies using TMS (Liepert *et al*., 2000, 2001). Liepert and colleagues mapped the extent of the motor output map in patients before and after constraint-induced therapy (Liepert *et al*., 1998, 2000, 2001). All patients benefited from the therapy and the group as a whole showed an enlargement in excitable cortex volume and shift in centre of the motor output area in the damaged hemisphere. The range of recovery outcomes in the current study lends strength to our conclusions, as we were able to perform a direct correlation between the degree of recovery and the degree of fMRI activation increase in specific brain regions. Using fMRI to assess functional brain changes allowed us to identify changes across the whole brain. The increased spatial resolution of fMRI compared with techniques such as TMS or EEG enabled us to specifically identify premotor and parietal cortices and the cerebellum as the sites showing the strongest correlation with improvements in function after therapy.

Table 4 *Extent, magnitude and location of fMRI clusters*

Anatomical region	Cluster size (voxels)	Mean *Z* score	Maximum *Z* score	Talairach coordinates of maximum *Z* statistic		
				x	*y*	*z*
Positive correlation – affected hand						
Bilateral cerebellum	863	3.74	6.02	22	–62	–28
Left precentral gyrus	184	3.66	5.13	–38	–8	58
Left superior bank of sylvian fissure	24	3.42	3.89	–44	–34	18
Negative correlation – affected hand						
Left posterior orbital gyrus	26	3.49	3.81	–26	22	–18
Positive correlation – unaffected hand						
Bilateral cerebellum	1473	3.75	6.61	–36	–54	–30
Negative correlation – unaffected hand						
Right primary sensorimotor cortex	1231	4.37	9.53	32	–24	64
Left superior temporal gyrus	29	3.81	4.71	–62	–22	2

Positive correlations refer to improvements in grip strength correlating with increases in fMRI clusters. Negative correlations refer to improvement in grip strength correlating with decreases in fMRI clusters. To combine data across the group, images from patients with right hemisphere stroke were rotated about the midline. Therefore, the affected hemisphere is by convention the left, and Talairach coordinates are reported accordingly.

The relationship between patterns of brain activity and dynamic recovery has been tested in a complementary way by serial monitoring of functional changes over the first few months after stroke. Marshall and colleagues reported a shift in laterality of motor cortical activity over the early, more rapid recovery period with greater relative contralateral activity when the paretic hand had recovered (Marshall *et al*., 2000). The laterality of this effect concurs with the results presented here (i.e. increased activity in motor cortical areas of the damaged hemisphere) but, while changes in the study of spontaneous recovery were confined to primary sensorimotor cortex, the effects reported in the current study were found in the premotor and parietal areas of the cortex.

However, the importance of premotor and parietal cortices rather than primary motor cortex for recovered movement is consistent with data from human and animal studies (Seitz *et al*., 1998; Liu and Rouiller, 1999). Recovery of dexterity after unilateral motor cortex lesions in macaques appears to be mediated by the premotor cortex in the damaged hemisphere, as inactivation of this region (and not the primary motor cortex) with the γ-aminobutyric acid (GABA) agonist muscimol abolishes recovered movement (Liu and Rouiller, 1999). One PET study reported that movement of a recovered limb in patients after middle cerebral artery stroke that spared the dorsolateral part of the precentral gyrus was associated with activation in premotor and supplementary motor areas, but not in the primary sensorimotor cortex (Seitz *et al*., 1998). Other imaging studies have also demonstrated that there is increased activity in the supplementary motor areas during affected hand movements after stoke compared with controls, suggesting that this region may play a role in recovery (Weiller *et al*., 1993; Cramer *et al*., 1997). However, in the current study we found no evidence for a correlation between the degree of recovery and activation in the supplementary motor areas. Changes in premotor and parietal areas are also associated with dynamic recovery. A PET study assessed regional cerebral blood flow in response to passive movements of the hand before and after task-oriented arm training for severely hemiparetic patients after subcortical stroke (Nelles *et al*., 2001). After training, patients showed increased regional cerebral blood flow in the bilateral premotor and parietal cortex and contralateral sensorimotor cortex compared with a group who did not receive therapy (Nelles *et al*., 2001). However, although there were significant differences in fMRI activation between therapy and non-therapy groups, there was not a significant difference between the groups in change in motor function over time (Nelles *et al*., 2001). It is therefore difficult to assess whether the reported fMRI changes reflect behavioural changes. The current study is novel in providing data on patients with a range of recovery outcomes. This allowed direct correlation of recovery outcome and fMRI change in specific sensorimotor areas.

In addition to effects in sensorimotor cortical areas, the current study found a correlation between recovery and fMRI activity in the superior posterior cerebellar hemispheres. There have been a few reports of increased cerebellar activity in stroke patients compared with controls (Weiller *et al*., 1993), but the majority of studies have focused purely on cortical changes, possibly due to problems of complete coverage of motor cortices and cerebellum.

There have been some other suggestions that the specific regions of the cerebellum found in the current study (Crus I and lobule VI) may be important for recovery of movement, at least in the case of early brain damage. Although cortical damage in adults is associated with resting hypometabolism in the contralesional cerebellum (Baron *et al*., 1980), there have been reports of symmetrical metabolism and even paradoxically increased contralesional cerebellar metabolism in brain damaged children (Shamoto and Chugani, 1997)—

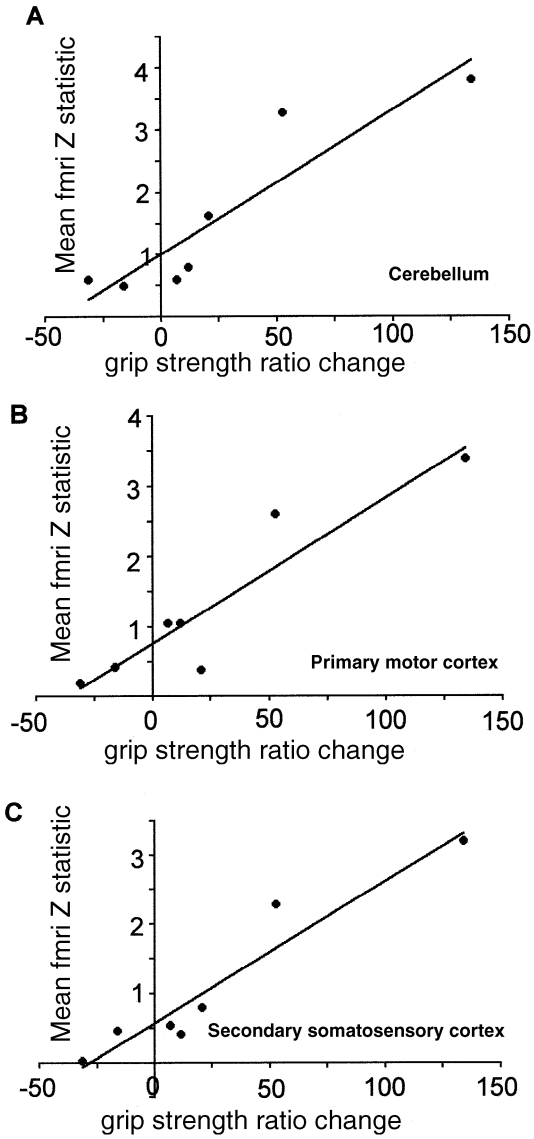

Fig. 5 Spread of individual patient values of change in grip strength and change in fMRI in (**A**) the cerebellum, (**B**) premotor cortex and (**C**) secondary somatosensory cortex.

specifically in lobules VI and Crus I (Niimura *et al*., 1999). These specific regions have also been implicated in normal motor learning (Ramnani *et al*., 2000). In addition, the premotor cortex in normal patients is involved in visually-cued movements particularly when the association between cue and movement is learnt (Wise *et al*., 1996; Schluter *et al*., 1998).

Brain functional correlates of therapy-mediated improvement in hand function were not only related to movements of the affected hand. We also showed that functional improvement after therapy correlated with decreased activity in the contralateral motor cortex during movements of the unaffected hand. This is consistent with one of the previous TMS studies that mapped motor cortex representations before and after constraint-induced movement therapy (Liepert *et al*., 1998): in this study the extent of motor cortex from which TMS evoked contralateral muscle responses increased in the affected hemisphere after therapy, but decreased in the unaffected hemisphere. It was suggested that the decreased motor representation in the unaffected hemisphere might be a result of the non-use of the unaffected limb (Liepert *et al*., 1998). As our patients also had their unaffected limb constrained during the therapy period, it is intriguing that this decrease in activity with movement of the unaffected limb correlated with functional gains. It is possible that non-use of the unaffected limb may contribute directly to recovery by enhancing plasticity for the affected limb; if the representation of the unaffected limb is reduced in the unaffected motor cortex, this might allow for an increased ipsilateral representation of the affected limb. Alternatively, the prime importance of non-use of the unaffected limb may be to encourage behavioural reliance on the affected limb and fMRI may simply be detecting an incidental consequence of this non-use.

The interpretation of increased activity in premotor and parietal cortices is not unequivocal. It is tempting to conclude that these patterns reflect adaptive reorganization that mediates recovery. An attractive possibility is that the increased activity reflects altered recruitment of non-primary motor corticospinal projections. Retrograde labelling studies in macaque have shown that, although ~30–50% of corticospinal projections originate in primary motor cortex, there are also contributions from non-primary motor areas including dorsal premotor cortex (6–7%) (Dum and Strick, 1991; Galea and Darian-Smith, 1994) and sensory areas including secondary somatosensory cortex (3%) (Galea and Darian-Smith, 1994).

An alternative interpretation is that brain functional changes reflect subtle differences in the way the task is performed after therapy. We have tried as far as possible to control the basic parameters (e.g. force, rate) of the movements made from session to session to keep them as similar as possible. For both tasks, movements were cued at a proportion of patients' maximum original movement rate so that all patients would be able to continue comfortably the task throughout testing periods and to help maintain consistency of performance from session to session. In addition, movement amplitude (for patients performing the pronated flexion–extension movement) or force (for patients performing the movement around a rubber bulb) was also controlled. Despite these efforts, it is possible that a less controlled aspect of the movement (e.g. acceleration, hand posture) could have changed from session to session. However, although there is therefore a possibility that some of the fMRI changes might be due to changes in basic movement parameters, it is unlikely that movement changes, if they occurred, would be able to explain all the fMRI differences observed. Variations in simple movement parameters such as force (Dettmers *et al*., 1995) or frequency (Wexler *et al*., 1997) tend to modulate processing in primary motor cortex rather than the dorsal premotor cortex where our changes occurred. Another

possibility is that rehabilitative therapy may direct attention to the affected side. Therefore, although basic movement parameters were controlled before and after therapy, psychological factors such as the amount of attention necessary may have changed. It is known that attention to sensory stimulation modulates somatosensory cortical areas including secondary somatosensory cortex (Mima *et al*., 1998; Johansen-Berg *et al*., 2000). However, although attention to movement modulates activity in motor cortical areas (Jueptner *et al*., 1997; Johansen-Berg and Matthews, 2002), it has not been reported to produce significant effects in the region of dorsal premotor cortex associated with motor recovery in the current study.

It is not ideal that different patients performed slightly different movement tasks in the current study. Although the patterns of activation associated with the two tasks were similar (Fig. 2), direct comparison of the two tasks did reveal some differences. Flexion–extension movements around a rubber bulb produced more sensory cortex (insula, secondary somatosensory cortex) activation, whereas movement against a flat surface produced slightly greater activation of contralateral precentral gyrus. However, differences in motor tasks are unlikely to explain the observed correlations. The size of the fMRI signal change in individual patients was quantified within the regions where fMRI increases correlated with behavioural improvements (Fig. 5). There was no suggestion that the different motor tasks elicited different sized increases in activation after therapy. The three patients performing the flexion–extension task of the pronated hand are ranked second, third and seventh in terms of the increase in contralateral premotor cortical activity for example (for the cerebellum they are ranked 2, 4 and 6 and for the secondary somatosensory cortex 2, 6 and 7).

We were specifically interested in sensorimotor regions that changed their activity in line with therapy-related behavioural changes and therefore masked the therapy-related activation changes by the group baseline activation patterns (see Fig. 3B). The group baseline activation maps includes a large distributed network of sensorimotor regions (Fig. 3B). However, we cannot rule out the possibility that additional changes occurred in regions outside this mask.

A strength of the current study was that we were able to use 3 T fMRI to investigate recovery after stroke whereas the majority of previous fMRI studies of motor recovery have been conducted on 1.5 T scanners (Cramer *et al*., 1997; Cao *et al*., 1998; Marshall *et al*., 2000). Higher field strength provides greater sensitivity to blood oxygen level dependent (BOLD) signal because field strength increases result in both increased signal-to-noise and increased BOLD contrast-to-noise (Gati *et al*., 1997). Another advantage of higher field strength is the increased relative contribution of capillaries (as opposed to draining veins, which may be distant from the site of neuronal activation) to the observed signal. This occurs because, as magnetic field strength increases, there is a greater than linear increase in signal from extravascular tissue around small vessels whereas the increase of intravascular signal from large vessels is linear (Ogawa *et al*., 1993).

In conclusion, we have shown a correlation between changes in sensorimotor brain activation and therapy-mediated improvement in motor function. Specifically, behavioural improvement was associated with increased activity in the contralateral premotor and secondary somatosensory cortex and bilateral cerebellum during movement of the affected hand. Behavioural improvement was also correlated with decreased activity in the primary motor cortex during movement of the unaffected hand. These findings add to our understanding of rehabilitation-mediated recovery and could assist in development of neurobiologically-informed rehabilitation strategies.

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