Section 8: Rehabilitation-mediated reorganisation after stroke

It was shown in Section 4 that movement of an affected limb after stroke is associated with altered patterns of motor-related FMRI activation. The dentate nucleus of the cerebellum was shown to be more active during affected hand movements and laterality in this region was correlated with hand impairment. This suggests that some of the altered patterns of brain activity during movement after stroke may be associated with recovery. The current section explored this further with a longitudinal study designed to assess whether changes in motor function as a result of rehabilitative therapy are associated with changes in FMRI activation.

8.1 Introduction and rationale

Intensive rehabilitation interventions are being used more commonly as delivery of post-stroke care improves and they can reduce long term disability (Stroke Unit Trialists' Collaboration 1997; Indredavik *et al.* 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; Nelles *et al.* 2001; Liepert *et al.* 2001). These 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 (Section 4, Cramer and Bastings 2000; Cramer *et al.* 1997; Weiller *et al.* 1992; Chollet *et al.* 1991; Cao *et al.* 1998; Cao *et al.* 1994; Pineiro *et al.* 2001; Seitz *et al.* 1998; Traversa *et al.* 2000; Rossini *et al.* 1998; Cicinelli *et al.* 1997;

Traversa *et al.* 1997; Caramia *et al.* 1996; Honda *et al.* 1997; Marshall *et al.* 2000; Netz *et al.* 1997) 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 (Cramer *et al.* 1997; Weiller *et al.* 1992; Cao *et al.* 1998; Caramia *et al.* 1996; Honda *et al.* 1997; Chollet *et al.* 1991). Whereas some studies have identified changes either in the extent (Cao *et al.* 1998) or the location (Rossini *et al.* 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.* 2001; Nelles *et al.* 1999) and animals (Liu and Rouiller 1999) have concluded that altered 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 subjects, 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 reorganisation 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 emphasise that such reorganisation 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 reorganisation (Liepert *et al.* 2000; Liepert *et al.* 1998; Kopp *et al.* 1999). However, the nature of this reorganisation 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.* 2000; Liepert *et al.* 1998). 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 to 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 localisation 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.

The experiment presented in this section aimed to define the changes in movement-related brain activity that occur with successful rehabilitation after stroke. Serial FMRI scans were used 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 assessment of the involvement of individual motor cortical regions and correlation of behavioural benefits with FMRI changes for individual subjects.

8.2 Methods

Subjects: Seven patients with mild to moderate hemiparesis at least 6 months after a first ischaemic stroke participated (Table 8.1). Subjects gave informed consent in accordance with the declaration of Helsinki and local ethical approval from the Central Oxford Research Ethics Committee. Subjects attended seven testing sessions (1 practice, 4 pre- and 2 post-therapy, at 2-weekly intervals).

Patient	Sex	Age	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 middle MCA	60	0.32	72
5	F	59	L	84	Right middle 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

Table 8.1: Patient details. Abbreviations: M=male, F=female, R=right, L=left, MCA=middle cerebral artery

Movement Therapy: After five testing sessions subjects performed a 2 week home-based therapy programme based on some of the principles of the constraint-induced technique (Taub *et al.* 1993). Subjects were asked to wear a restraint on their unaffected arm for 90% of waking time. Subjects used either a sling (subjects 1-3, Table 8.1), a ski mitten (subjects 4-6) or a thick gardening glove (subject 7) for restraint. Subjects were instructed to complete an explicitly defined 30 minute graded exercise programme (Table 8.2) with the affected arm twice daily.

Movement testing: Movement testing (Motricity Index (Demeurisse *et al.* 1980), Grip Strength (Sunderland *et al.* 1989) and 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). Grip strength was measured with a Baseline Hydraulic Hand Dynamometer (Fabrication Enterprises Inc, NY, USA). For grip strength and the Jebsen test a normalised 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 subject and for each measure ([[mean pre-therapy ratio – mean post-therapy ratio]/[mean pre- + mean post-therapy ratio]]*100). The relationship between measures was tested by calculating a Pearson correlation coefficient between changes in mean scores pre- and post-therapy for each measure.

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

Table 8.2: Progressive exercises used during rehabilitation therapy

FMRI scanning: Subjects were scanned on four of the testing session occasions, two weeks apart, twice before and twice after movement therapy. Five of the subjects were also scanned in the initial practice session to familiarise them with the magnet environment. A 3T Varian/Siemens MRI system was used. A T1-weighted anatomical scan was acquired for each subject in session one (IR 3D Turbo Flash, 64x3mm axial slices, TR=30ms, TE=5ms, TI=500ms, flip angle=15°, FOV=256x256, matrix=256x256). A 6 minute echo-planar imaging (EPI) run was performed first

with movement of the unaffected hand, then with movement of the affected hand (21x6 mm axial slices, TE=30ms, TR = 3000ms, FOV = 256x256, matrix = 64x64). For patients 1-3 the movement task was visually cued flexion-extension of the metacarpalphalangeal joints of the pronated hand against a flat surface. Movements were performed with the hand resting on a wooden board with a bridge 3 cm above the board. The amplitude of movements was limited by instructing subjects to move between the board and the bridge. Movements were cued at 25% and 75% of each subject's maximum tapping rate measured at the time of the first scan. The tasks were presented in alternating 30-second periods of rest and movement. The data from the blocks with slower movements were not fully analysed, as the amount of significant brain activation for slow movements was very small. For patients 4 to 7 the movement task was modified slightly to allow better monitoring of performance. Subjects 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 subject's maximum compression on the first scanning session. The maximum rate at which the subject could repeatedly produce this force over a 24-second period was measured during the first session. Movements in the scanner were cued at 40% of this maximum rate. Thus while the force and rates of movements were set individually for each subject at the beginning of the study, they did not change over sessions. The movement task was presented in 24-second blocks alternating with 24 second rest periods.

Image analysis Image analysis was carried out using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl) and MEDx (Sensor Systems Inc., VA, USA).

Individual level fMRI analysis: Data from each subject 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 5mm full-width half maximum; mean-based intensity normalisation; nonlinear highpass temporal filtering (Gaussian-weighted least squares straight line fit, with sigma = 72.0s). Statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich *et al.* 2001). For each subject 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.* 2001). A statistical image of "therapy-related decreases" was also created (pre- versus post-therapy sessions) for each subject.

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

To identify the group baseline activation pattern associated with movement Z statistic images were produced ([sum of the initial pre-treatment Z statistic images for movement versus rest for each subject]/ √[number of subjects]). The resulting group Z statistic images were thresholded at $Z>3.1$ and significant clusters defined according to extent (at $p<0.005$) (Worsley *et al.* 1992; Friston *et al.* 1992; Forman *et al.* 1995). The number of suprathreshold voxels within the motor and premotor cortices were used to calculate laterality indices ([C-I]/[C+I], where C = contralateral and I = ipsilateral to hand being moved).

To identify brain regions where change in fMRI activity correlated with change in arm function after therapy a "recovery-weighted" group image was created. First, for each subject the Z statistic image of therapy-related increases was multiplied by their individual normalised 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 normalised across the group by subtracting the group mean and dividing by group standard deviation). The seven resulting images were summed and divided by √[number of subjects]. 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) (Worsley *et al.* 1992; Friston *et al.* 1992; Forman *et al.* 1995). These clusters were then masked by the group baseline movement-related activity. This identified volumes across the whole sensorimotor system where increased activity after therapy correlated with improved affected hand function. The same procedure was repeated with individual subject images of therapy-related decreases to identify volumes where *decreased* activity correlated with improved affected hand function.

8.3 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 8.3. The relationship between the different behavioural measures was tested. Therapy-related changes in grip strength ratio were 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 subject 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. The statistical significance of the functional improvement across the group or within individuals was not tested, 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.

Patient				Affected hand			Unaffected hand		
	Mean Grip Strength Ratio			Mean Grip Strength			Mean Grip Strength		
	pre	post	change	pre	post	% change	pre	post	% change
1	0.12	0.05	42.3	53	57	7.5	67.25	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	46.25	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	49.75	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
s.d.	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

Table 8.3: Effect of therapy on grip strength. Improvement in mean grip strength ratio from pre- to post-therapy varied between subjects. As grip strength ratio is a measure of relative performance between the two hands we have shown grip strength scores (in arbitrary units) separately for the affected and the unaffected hands. For most subjects, 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]]*100], for absolute grip strength values change is calculated as % change.

Effect of therapy as assessed by fMRI:

Movement performance during scanning: For the 4 patients who performed the flexion-extension movement while holding a rubber bulb it was possible to confirm that a consistent force (60% of maximum) and rate (40% of maximum) was maintained in the scanner throughout 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 subjects performing hand flexion-extension in pronation was assessed less directly by monitoring with a video camera throughout each scanning session. For the latter group it was possible to confirm that a consistent rate and amplitude was maintained.

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 (Figure 8.1). Activation patterns produced using the two movements were similar (Figure 8.1). Data from all 7 subjects therefore were pooled to produce group baseline movement maps for the affected and the unaffected hands (Figure 8.2). Movement of the affected hand consistently produced a more bilateral pattern of activity in sensorimotor and premotor cortices (Figure 8.2B); the laterality index on the group baseline activation image for affected hand movements was 0.15, compared to 0.63 for movement of the unaffected hand.

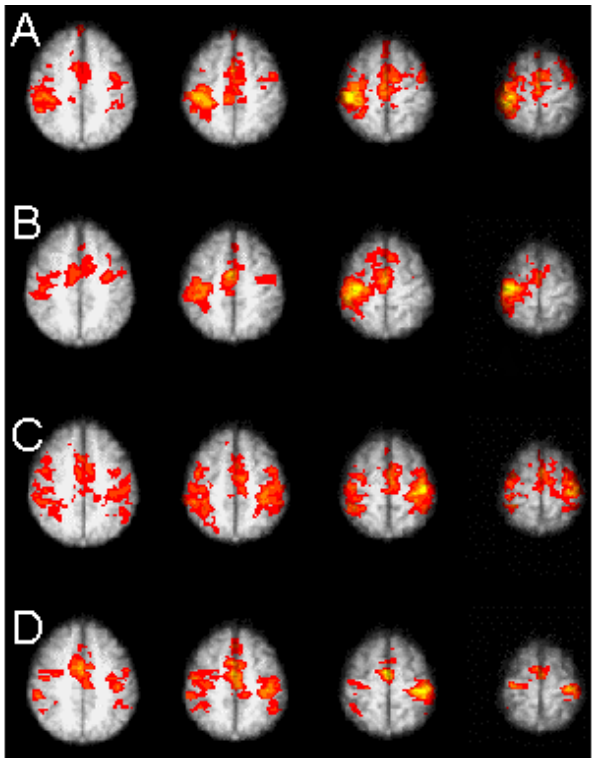

Figure 8.1: Baseline fMRI activation patterns for the two flexion-extension tasks used demonstrate that there is little difference between the tasks in the pattern of activation of the motor cortices. A,B: Activation patterns for the unaffected hand for flexion-extension against a rubber bulb (A) and 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).

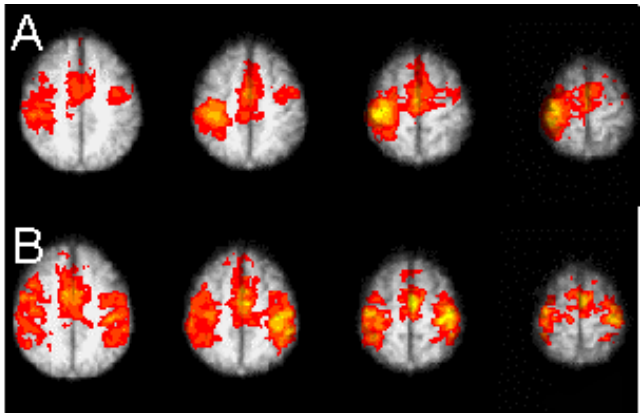

Figure 8.2: Baseline fMRI activation patterns for the group of 7 subjects. Movement of the affected hand (B) produces a more bilateral pattern of activation than movements of the unaffected hand (A).

Therapy-related changes in brain activity for the affected hand: A "recovery-weighted" correlation image was created (see methods). This analysis identified 3 clusters in which increased fMRI signal change correlated significantly with improved function (Figure 8.3A, Table 8.4): the cerebellum (bilaterally), the contralateral secondary somatosensory cortex and the contralateral dorsal premotor cortex.

Anatomical region	cluster size (voxels)	mean Z score	max Z score	Talairach co-ordinates of maximum Z statistic		
				x	y	z
Positive Correlation – affected hand						
Bilateral cerebellum	863	3.74	6.02	22	-62	-28
L precentral gyrus (PMC)	184	3.66	5.13	-38	-8	58
L superior bank of sylvian fissure (S2)	24	3.42	3.89	-44	-34	18
Negative correlation – affected hand						
L 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						
R primary sensorimotor cortex	1231	4.37	9.53	32	-24	64
L superior temporal gyrus	29	3.81	4.71	-62	-22	2

Table 8.4: Extent, magnitude and location of clusters where changes in grip strength after therapy correlate with changes in FMRI activation after therapy. Positive correlations refer to improvements in grip strength correlating with increases in FMRI. Negative correlations refer to improvement in grip strength correlating with decreases in FMRI. To combine data across the group, images from subjects with right hemisphere stroke were rotated about the midline. Therefore the affected hemisphere is by convention the left, and Talairach co-ordinates are reported accordingly.

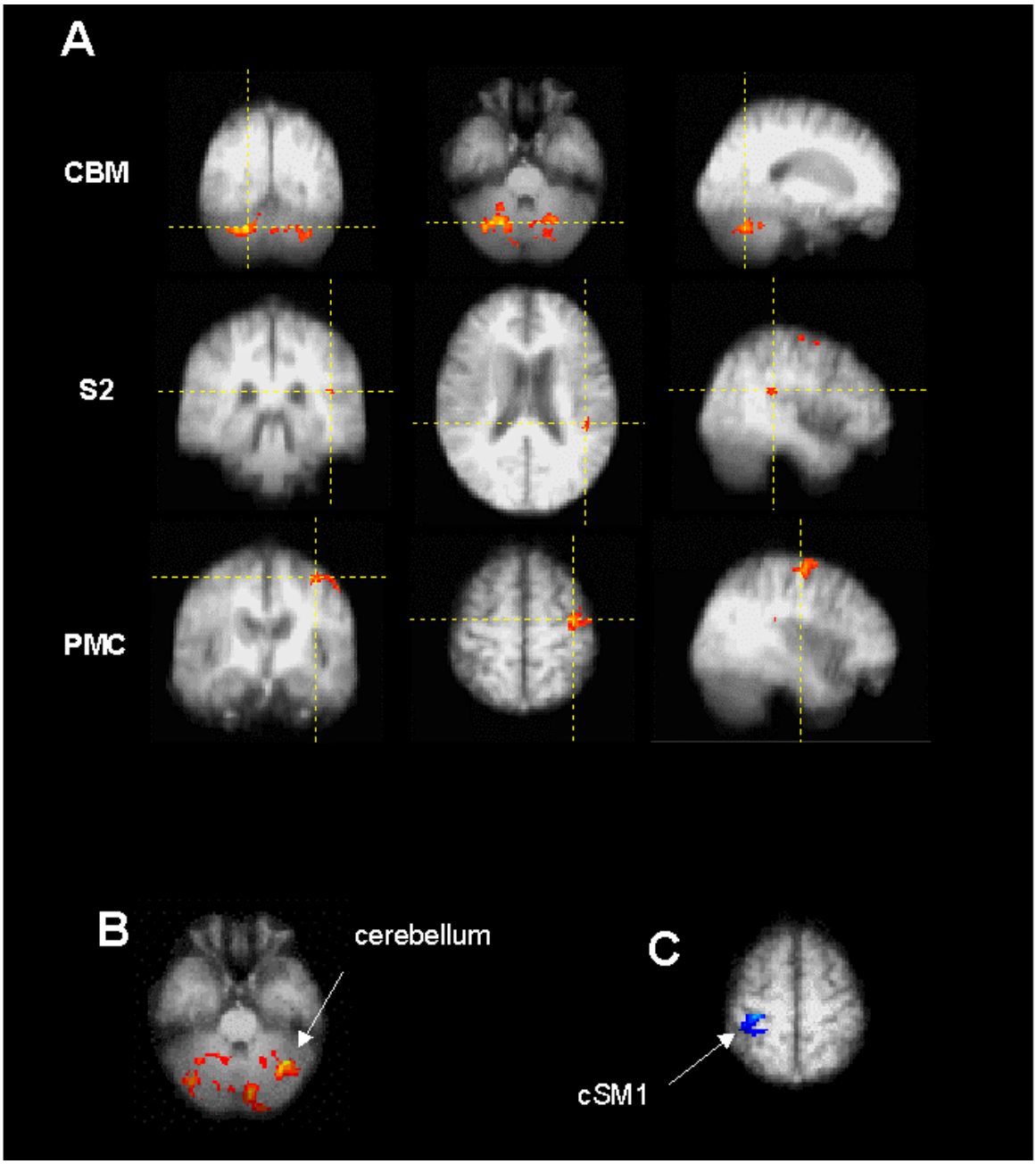

Figure 8.3: Areas where changes in grip strength ratio after therapy correlate with changes in fMRI activation (see Table 3). **A.** Increased fMRI activity in cerebellum (CBM), secondary somatosensory cortex (S2) and contralateral premotor cortex (PMC) during movements of the affected hand correlated with improvements in grip strength ratio. Cross hairs are at location of maximum z statistic within each cluster (see Table 4 for co-ordinates). **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 (SM1) during movements of the unaffected hand correlated with improved grip strength ratio.

In order to better visualise the variation of responses across subjects, 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 (Figure 8.4). A significant correlation was found between mean Z statistic and improvement in grip in all three regions (cerebellum: r=0.915, p=0.004; premotor cortex: r=0.927, p=0.003; S2: 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; premotor cortex: r=0.841, p=0.036; S2: r=0.896, p=0.016).

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 8.4).

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 (Figure 8.3B, Table 8.4). 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 (Figure 8.3C, Table 8.4).

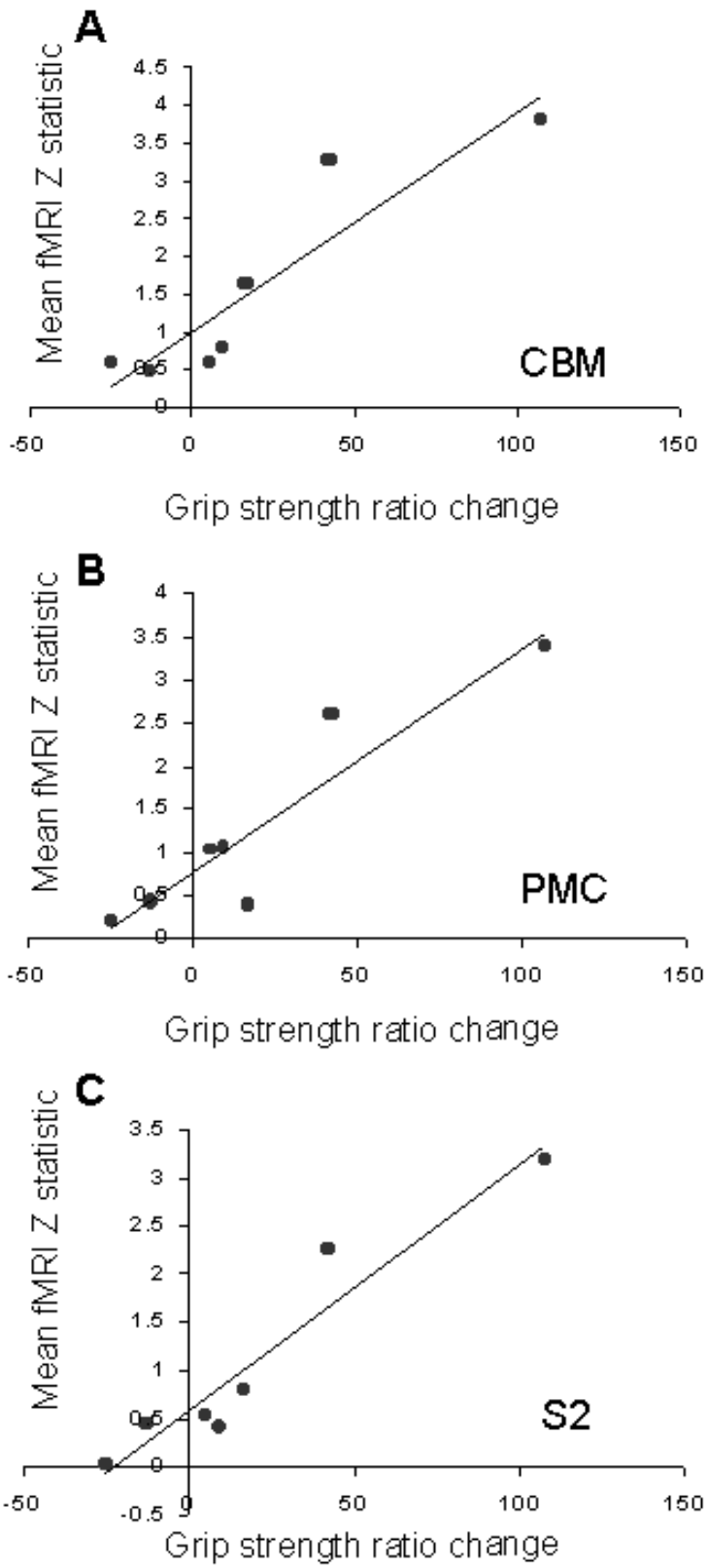

Figure 8.4: Spread of individual subject values of change in grip strength and change in FMRI in the cerebellum (A), premotor cortex (B) and secondary somatosensory cortex (C)

8.4 Discussion

This section demonstrates 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 also in the bilateral superior 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 transcranial magnetic stimulation (TMS) (Liepert *et al.* 2000; Liepert *et al.* 2001). Liepert et al mapped the extent of the motor output map in patients before and after constraint-induced therapy (Liepert *et al.* 2000; Liepert *et al.* 2001; Liepert *et al.* 1998). 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 its conclusions as it was possible 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 for identification of changes across the whole brain. The increased spatial resolution of fMRI compared to techniques such as TMS or EEG enabled specific identification of premotor and parietal cortices and the cerebellum as the sites showing the strongest correlation with improvements in function after therapy.

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 et al 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 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 (Liu and Rouiller 1999; Seitz *et al.* 1998). 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* primary motor cortex) with the 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 primary sensorimotor cortex (Seitz *et al.* 1998). Changes in premotor and parietal areas are also associated with dynamic recovery. A PET study assessed regional cerebral blood flow (rCBF) 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 rCBF in bilateral premotor and parietal cortex and contralateral sensorimotor cortex compared to 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 FMRI changes reported 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 sensori-motor 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 to controls (Weiller *et al.* 1993) but the majority of studies have focussed purely on cortical changes, possibly due to problems of complete coverage of motor cortices and cerebellum. In section 4 it was reported that movement of an affected arm in patients was associated with relatively increased activity in the dentate nucleus of the cerebellum.

There have also been 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) 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 subjects 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. Functional improvement after therapy also correlated with *decreased* activity in 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 which 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. As the patients in the study presented in this section 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 might 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 (although evidence for therapy-related changes in the ipsilateral hemisphere was not found here). 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 reorganisation 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 about 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 S2 (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. Attempts were made to control basic movement parameters (e.g., force, rate) 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 comfortably continue 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 the changes reported in this section 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. In section 6 it was established that attention to sensory stimulation modulates somatosensory cortical areas including S2. However, although attention to movement was shown to modulate activity in motor cortical areas in section 7, it was not shown 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 subjects performed slightly different movement tasks in the current study. However, the pattern of activation associated with the two tasks were similar (Figure 8.1). In addition, the differences in motor tasks are unlikely to explain the observed correlations. The size of the FMRI signal change in individual subjects was quantified within the regions where FMRI increases correlated with behavioural improvements (Figure 8.4). 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 2,6,7).

In conclusion, in subjects receiving rehabilitative therapy there was a correlation between changes in sensorimotor brain activation and improvement in motor function. Specifically, behavioural improvement was associated with increased activity in contralateral premotor and secondary somatosensory cortex and bilateral cerebellum during movement of the affected hand. Behavioural improvement was also correlated with decreased activity in 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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