Section 4: Motor-related activation after stroke

A number of studies have used functional brain imaging techniques to explore patterns of activity related to movement of a recovered limb (Section 2.4.3). However, there is little consensus on the precise pattern of cortical reorganisation associated with motor recovery. Furthermore, few studies have attempted to relate patterns of activity to recovery processes and there are some motor areas, such as the cerebellum, that have been largely ignored by previous studies. The overall aim of this thesis is to investigate reorganisation of the cortical motor system after stroke. This first experiment was therefore designed to characterise more fully the patterns of movement-related activation in a group of recovered stroke patients and to assess the degree to which altered activation patterns are related to the level of impairment.

4.1 Introduction and rationale

Some recovery of movement often occurs after stroke (e.g. (Skilbeck *et al.* 1983), see Section 2.2). There is growing evidence from human functional imaging studies that movement of a recovered limb after a stroke is associated with altered activity in motor cortical regions (see Section 2.4.3). The majority of these studies have used positron emission tomography (PET). (Chollet *et al.* 1991; Weiller *et al.* 1992; Weiller *et al.* 1993; Seitz *et al.* 1998; Nelles *et al.* 1999) and only a few have made use of the greater spatial resolution possible with FMRI (Cramer *et al.* 1997; Marshall *et al.* 2000; Cao *et al.* 1998). Reported altered patterns of activity include local remapping around an area affected by an infarct (Weiller *et al.* 1993; Pineiro *et al.* 2001; Section 2.4.3.1), increased recruitment of intact non-primary motor regions in the damaged hemisphere (Seitz *et al.* 1998; Section 2.4.3.2) and increased involvement of the undamaged hemisphere, ipsilateral to the recovered limb (Cramer *et al.* 1997; Weiller *et al.* 1992; Chollet *et al.* 1991; Cao *et al.* 1998; Section 2.4.3.3). However, there is little consensus on the precise pattern of cortical reorganisation associated with motor recovery (see Section 2.4.3.4).

Such changes are typically interpreted as evidence for adaptive reorganisation that underlies recovery. However, the lack of consensus over the patterns of reorganisation makes the differences difficult to interpret. In addition, few studies have attempted to relate patterns of activity to recovery processes and therefore the functional relevance of the changes is unclear. The experiment presented in this section aimed to characterise more fully the changes in motor-related activation patterns in stroke patients and to assess the degree to which altered patterns of activity are related to motor impairments.

4.2 Methods

Subjects: 8 patients (all originally right-handed, 6 male, 2 female, age 58 ± 14, table 4.1) at least 6 months after first unilateral ischaemic stroke and 12 right-handed control subjects (7 male, 5 female, age 53 ± 21) participated in accordance with local ethics committee consent.

Subject	Sex	Age	Time post stroke (months)	Stroke location	Stroke volume (cm^3)	Affected arm motricity	Max tap rate		% Increase in 9-hole peg
							A	U	
1	m	50	6	Right MCA	36	58	2.1	3.4	61.0
2	m	42	12	Right corona radiata lacune	<0.1	100	7.7	6.5	-7.1
3	m	62	10	Right MCA	120	83	2.4	3.6	23.9
4	f	58	10	R corona radiata lacune	<0.1	76	4.1	6.1	11.3
5	m	78	15	Left MCA with some bilateral periventricular changes	18	100	2.2	2.6	38.0
6	m	78	14	Left middle MCA	36	28	0.9	2.5	99.6
7	m	44	12	Left anterior MCA	36	76	4.2	6.1	63.6
8	f	52	70	Left MCA	120	76	3.4	5.9	25.5

Table 4.1: Subject details. Abbreviations: m=male, f=female, MCA=middle cerebral artery, A=affected. U=unaffected. % increase in 9-hole peg is the increase in the time taken to complete the test with the affected hand compared to the unaffected hand.

Movement testing: Arm function was assessed with the motricity index (Demeurisse *et al.* 1980) and with the 9 hole peg test (Sharpless 1982).

FMRI scanning: A 3T Varian/Siemens MRI system was used. Axial echo-planar volumes were acquired (21x6 mm slices, TE=30ms, TR = 3000ms, FOV = 256x256, matrix = 64x64). A T1-weighted anatomical image was also acquired for each subject (IR 3D Turbo Flash, 64x3mm axial slices, TR=30ms, TE=5ms, TI=500ms, flip angle=15°, FOV=256x256, matrix=256x256).

Subjects performed a visually cued flexion-extension of the pronated hand against a flat surface. Hand movements were performed with the wrist 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 by a large flashing star displayed on a projection screen visible through prism glasses. Movements were cued at 25% and 75% of each subject's maximum tapping rate. The tasks were presented in alternating 30-second periods of rest and movement.

Image analysis: Analysis was performed using tools from FSL (www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: Motion correction using MCFLIRT (Jenkinson and Smith 2001); spatial smoothing with a Gaussian kernel of 5mm full-width at half-maximum; mean-based intensity normalisation of all volumes by the same factor; nonlinear high pass temporal filtering (Gaussian-weighted least squares straight line fitting with sigma =72 seconds). Statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich *et al.* 2001). Registration to T1-weighted high-resolution individual subject images, and to standard template images was carried out using FLIRT (Jenkinson and Smith 2001).

So that left and right hemisphere stroke patients could be grouped together, the images from the patients with left hemisphere strokes were rotated about the midline.

Random effects group analysis was carried out using FEAT to produce within and between group activation maps. Z (Gaussianised T) statistic images were thresholded at $Z>2.3$ and significant clusters were determined with a threshold of $p<0.05$ (Friston *et al.* 1994; Worsley *et al.* 1992; Forman *et al.* 1995).

A mean high-resolution image was created by averaging the T1-weighted images from all 20 subjects. The following anatomical volumes of interest (VOIs) were drawn on the mean high-resolution image for the left and right hemisphere:

1. Primary sensorimotor cortex (SMC): The cortex including the central sulcus, the postcentral gyrus and the posterior half of the precentral gyrus, extending from the level of the dorsal surface of the lateral ventricles to the most dorsal point of the brain and from the lateral surface of the brain to the interhemispheric fissure.

2. Premotor cortex (PMC): The cortex including the anterior half of the precentral gyrus and the precentral sulcus, extending from the level of the dorsal surface of the lateral ventricles to the most dorsal point of the brain and from the lateral surface of the brain to the interhemispheric fissure.

3. Cerebellum (CBM): For each VOI and each contrast (i.e. slow movement versus rest and fast movement versus rest), the mean positive parameter estimate (i.e. height of activation, PE) was found and used to calculate a laterality index ([C-I]/[C+I], where C = mean contralateral PE and I = mean ipsilateral PE). A mean of slow and fast movement LI was also calculated for each VOI. For the patient group, the affected hand was the right hand for half of the subjects and the left hand for the other half. For this reason, for control subjects a mean of the LI for left and right hands was calculated for each subject to compare to the affected hand LI in the patients.

To test whether FMRI activation in patients was less lateralised than controls, LIs were compared using one-tailed unpaired t-tests. One-tailed paired t-tests were used to test whether affected hand LI was lower than unaffected hand LI. Correlations between laterality indices for different VOIs, and between laterality indices and impairment measures were tested by calculating a Pearson correlation coefficient.

4.3 Results

As expected, performance of the motor task produced activation in a network of motor cortical regions in patients and controls (Figure 4.1, Tables 4.2 - 4.6). Overall, conclusions for controls are based on group statistical maps showing a greater volume of significantly activated voxles (range 11,000-16,000 voxels across different movement conditions) - than patients moving their unaffected (5,000-5,500 voxels) or affected hand (6,000-11,000, Tables 4.2-4.6). This difference probably partially reflects the greater statistical power with this larger group of control subjects, greater variability in haemodynamic responses from patients (Pineiro *et al.* 2002) and/or the absence of activation in infarcted regions in patients. However, there are specific brain regions in which there is greater activation in the patient group (Figure 4.1). For example, movement of the affected hand in patients is associated with bilateral ventral cerebellar activation, whereas hand movement in controls is associated with predominantly ipsilateral and more dorsal cerebellar activation (Figure 4.1a,b). In addition, movements of the affected hand in patients produced a more bilateral pattern of motor cortical activation than the equivalent movement in controls (Figure 4.1d).

Anatomical region	Co-ordinates of max Z score			Max Z
	X	y	z	
Controls right hand:				
Slow tapping: (total suprathreshold voxels: 11637)				
Cortical areas:				
L pre-post central gyri	-34	-26	60	5.3
SMA	-4	-10	74	4.9
L superior bank of sylvian fissure (S2)	-48	-34	24	4.7
R superior bank of sylvian fissure (S2)	44	-30	18	3.8
L middle temporal gyrus	-50	-62	-4	4.9
L inferior frontal gyrus	-54	4	30	4.0
R insula	52	8	20	4.3
L insula	-52	8	-2	3.4
Subcortical areas:				
R thalamus	10	-6	0	3.8
L thalamus	-14	-16	4	3.7
R globus pallidus	12	-6	-2	3.8
L putamen	-24	-12	-10	4.3
R cerebellum	10	-52	-24	4.3
Fast tapping: (total suprathreshold voxels: 13253)				
Motor cortices:				
L pre-post central gyri	-28	-22	60	5.6
SMA	-6	-18	50	4.1
Other cortical areas:				
R superior bank of sylvian fissure	30	-38	12	4.2
L superior bank of sylvian fissure (S2)	-58	-28	14	5.2
Subcortical areas:				
R thalamus	-50	4	-4	4.5
L thalamus	-16	-22	4	5.1
R putamen	22	-2	0	3.2
L putamen	-30	-8	0	4.4
R cerebellum	26	-54	32	4.0
Cerebellum - vermis	6	-60	-26	5.6

Table 4.2: Location and z-statistic of peak voxels for control right hand tapping (at a magnitude threshold of Z>2.3 and a corrected cluster extent threshold of p<0.05)

Anatomical region	Co-ordinates of max Z score			Max Z
	X	y	z	
Controls left hand:				
Slow tapping: (total suprathreshold voxels: 13148)				
Cortical areas:				
R pre-post central gyri	36	-20	58	4.9
SMA	8	-4	62	4.3
R inferior parietal lobule	40	-52	46	4.0
L middle frontal gyrus	-30	38	10	5.3
Posterior cingulate gyrus	0	-36	26	3.9
R insula	58	14	-12	3.9
L insula	-44	-2	-6	3.9
Subcortical areas:				
R thalamus	26	-22	4	4.4
L thalamus	-2	-32	0	4.3
R putamen	30	-14	-8	4.3
L putamen	-28	-20	-6	4.1
L cerebellum	-10	-44	-26	5.2
Cerebellar vermis	0	-60	-16	4.6
Fast tapping: (total suprathreshold voxels: 15788)				
Cortical areas:				
R pre-post central gyri	1	30	-20	4.1
SMA	8	0	68	4.6
R insula	54	12	2	3.4
L supramarginal gyrus	-52	-34	44	3.5
L superior bank of sylvian fissure (S2)	-50	-24	28	3.4
R superior bank of sylvian fissure (S2)	52	-30	18	4.8
Subcortical areas:				
R thalamus	22	-20	-10	4.8
L thalamus	-20	-14	14	4.3
R putamen	28	-18	8	5.1
L putamen	-22	-4	12	4.8
Cerebellum – vermis	-2	-56	-34	3.2
L cerebellum	-8	-44	-32	3.6
R cerebellum	36	-38	-36	4.0

Table 4.3: Location and z-statistic of peak voxels for control left hand tapping (at $Z>2.3$, $p<0.05$)

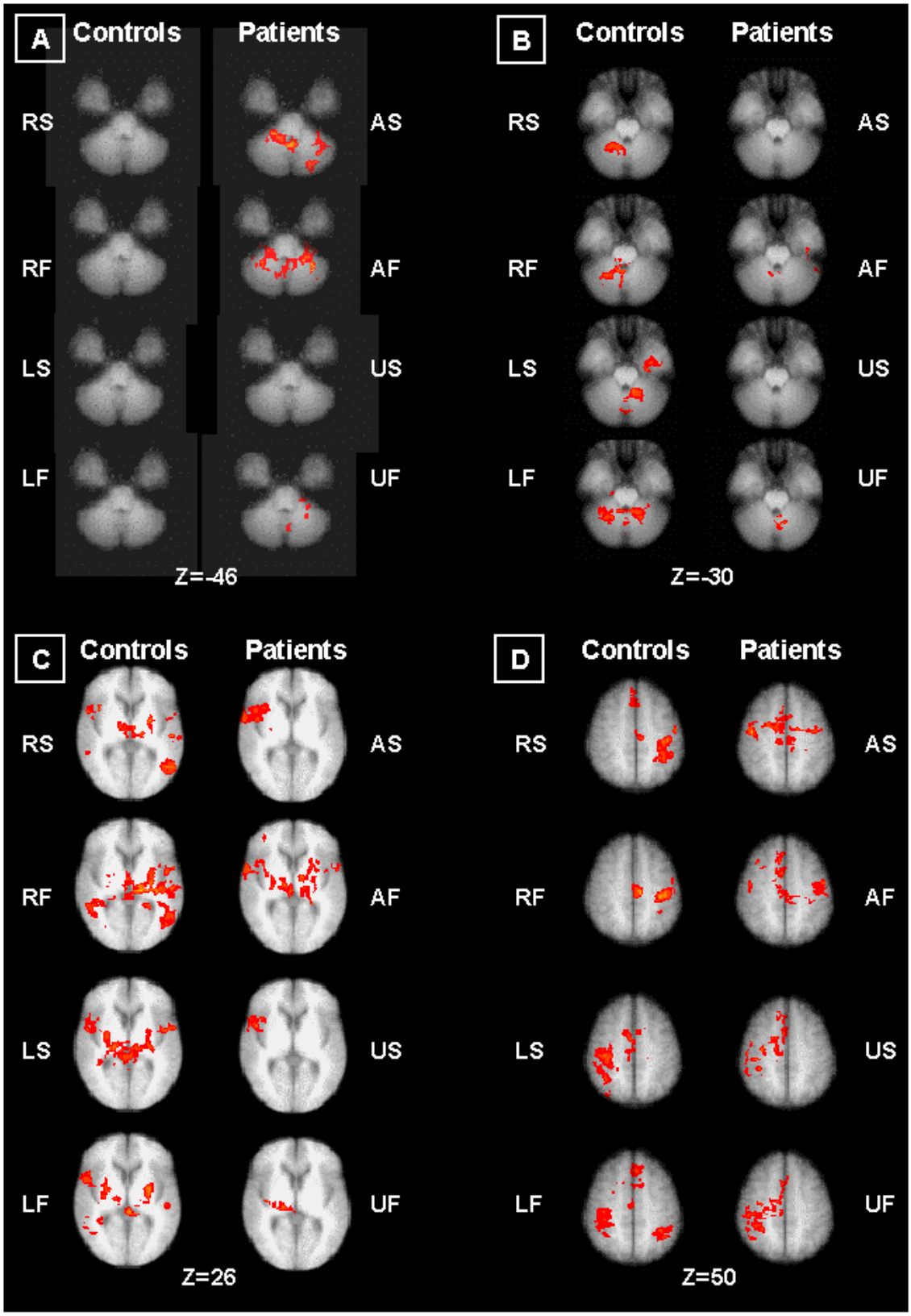
Anatomical region	Co-ordinates of max Z score			Max Z
	X	y	z	
Patients affected hand:				
Slow tapping: (total suprathreshold voxels: 6447)				
Cortical areas:				
L pre-post central gyri	46	-8	48	4.8
R pre-central gyrus/superior pre-central sulcus	28	-16	68	4.0
SMA	10	0	54	4.2
R insula	52	4	6	4.0
Subcortical areas:				
R cerebellum	22	-38	-46	3.8
L cerebellum	-22	-78	-44	3.7
Cerebellum – vermis	2	-52	-46	4.5
Fast tapping: (total suprathreshold voxels: 11200)				
Cortical areas:				
R pre-central gyrus	18	-14	66	4.2
R post-central gyrus	30	-30	66	4.2
L pre-central gyrus	-30	-30	54	3.9
SMA	6	8	42	3.9
R inferior frontal	36	48	16	3.7
R insula	58	24	-10	4.9
L insula	-44	0	-6	4.0
Subcortical areas:				
R thalamus	12	-14	0	4.0
L thalamus	-20	-22	4	3.5
L putamen/globus pallidus	-10	-4	2	3.8
L cerebellum	-34	-52	-46	4.4
R cerebellum	22	-28	-52	4.5
Cerebellum - vermis	-2	-64	-42	3.2

Table 4.4: Location and z-statistic of peak voxels for patients affected hand tapping (at a magnitude threshold of $Z>2.3$ and a corrected cluster extent threshold of $p<0.05$)

Anatomical region	Co-ordinates of max Z score			Max Z
	X	y	z	
Patients unaffected hand:				
Slow tapping: (total suprathreshold voxels: 5049)				
Cortical areas:				
R pre-post central gyri	32	-12	42	4.0
SMA	4	-6	58	3.3
R superior parietal lobule	34	-60	60	4.6
R insula	50	12	-2	3.9
Fast tapping: (total suprathreshold voxels: 5425)				
Cortical areas:				
R pre- and post-central gyri	36	-38	56	4.2
R post-central gyrus				
L pre-central gyrus				
SMA	6	-6	60	3.8
L superior bank of sylvian fissure (S2)	50	-38	22	3.8
Subcortical areas:				
R thalamus	12	-20	-4	4.7
R cerebellum	-28	-38	-42	3.2
Cerebellum – vermis	-4	-58	-32	4.0

Table 4.5: Location and z-statistic of peak voxels for patients unaffected hand tapping (at a magnitude threshold of Z>2.3 and a corrected cluster extent threshold of p<0.05)

Figure 4.1 (over page): Example images from patient and control group activation maps (at a magnitude threshold of Z>2.3 and a corrected cluster extent threshold of p<0.05). On the whole controls had a greater volume of activation than patients. However, there were specific regions that were activated in patients and not in controls. For controls, RS=right hand slow, RF=right hand fast, LS=left hand slow, LF=left hand fast. For patients, AS=affected hand slow, AF=affected hand fast, US=unaffected hand slow, UF=unaffected hand fast. **A, B:** Activation within the cerebellum was at different levels for the two groups. Controls consistendly activated the ipsilateral superior parts of the cerebellum **(B)**. Patients showed little cerebellar activaiton during unaffected hand movements; during affected hand movements patients activated bilateral, more ventral parts of the cerebellum **(A)** that were not activated in controls. **C:** Hand movement in controls was associated with extensive thalamic, basal ganglia and insula activation that was less prominent in patients. **D:** Activation of the pre- and post-central gyrus for controls, and for unaffected hand movements in patients, was purely contralateral to the hand moved. However, movement of the affected hand in patients was associated with bilateral activation of the precentral gyrus. (Fast, left hand movement in controls does produce ipsilateral activation at the level of the hand area, but it is caudal to the sensorimotor cortex, in the supramarginal gyrus)


A
Controls
Patients
RS
AS
RF
AF
LS
US
LF
UF
Z=-46
B
Controls
Patients
RS
AS
RF
AF
LS
US
LF
UF
Z=-30
C
Controls
Patients
RS
AS
RF
AF
LS
US
LF
UF
Z=26
D
Controls
Patients
RS
AS
RF
AF
LS
US
LF
UF
Z=50

A between groups random effect analysis provides a quantitative test for differences between patients and controls. Slow movement of the affected hand was associated with significantly greater activation in the cerebellum (including the contralateral dentate nucleus and bilateral lobule X (flocculus)) and the primary visual cortex in patients compared to controls (Figure 4.2, Table 4.6). No further differences were found between patients and controls for movement of the affected hand. Slow movements of the *unaffected* hand were associated with significantly less activation in the pulvinar nucleus of the thalamus and the cingulate gyrus in patients compared to controls (Figure 4.2, Table 4.6).

Anatomical region	**Co-ordinates of max Z score**			**Max Z**
	X	y	z	
Patients versus controls:				
Affected hand				
Slow tapping:				
Total number suprathreshold voxels: 1540				
Cerebellum – flocculus	0	-52	-44	3.8
Cerebellum –contralateral dentate nucleus	-26	-48	-44	3.3
Calcarine sulcus	12	76	2	4.0
Fast tapping: none				
Unaffected hand: none				
Controls versus patients:				
Affected hand: none				
Unaffected hand:				
Slow tapping:				
Total number suprathreshold voxels: 989				
Thalamus – pulvinar	-2	-30	-2	3.6
Anterior cingulate gyrus	-12	36	18	3.6
Fast tapping: none				

Table 4.6: Results of between group analyses

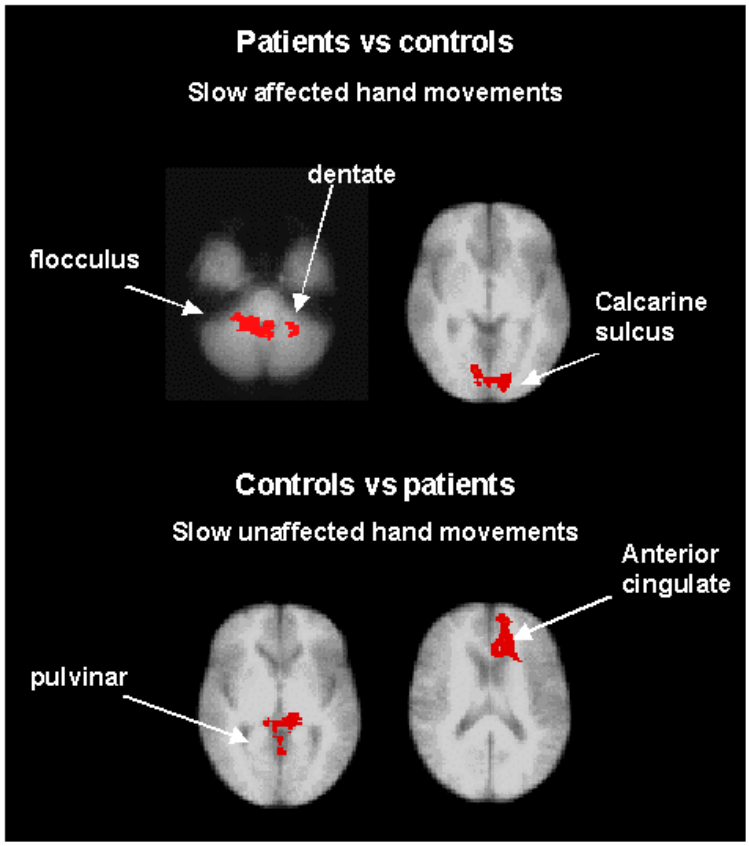


Figure 4.2: Random effects analysis of differences between activation responses to hand movements in patients and controls.**Top:** Slow movement of the affected hand in patients was associated with significantly greater activation than controls in bilateral inferior regions of the cerebellum (see also Figure 4.3) and the calcarine sulcus. **Bottom:** slow movement of the unaffected hand in patients was associated with significantly less activation than controls in the pulvinar nucleus of the thalamus/posterior part of the cingulate gyrus and the anterior part of the cingulate gyrus.

In order to more fully investigate differences between patients and controls specifically in motor areas a volumes of interest (VOI) analysis was carried out. This used anatomically defined VOIs (see methods) and also a VOI functionally-defined by the between groups analysis (patients versus controls) reported above. The between groups analysis revealed a cluster in the dentate nucleus of the cerebellum contralateral to the hand moved where patients produced significantly greater activation than controls during slow movements of the affected hand (Figure 4.3). This cluster (smoothed with a kernel of 7x7x7mm full width at half maximum) was used to create a binary mask that was employed

in the same way as the anatomically-defined masks. The mask was mirrored about the midline to produce a mask of the ipsilateral dentate that was used to calculate laterality indices.

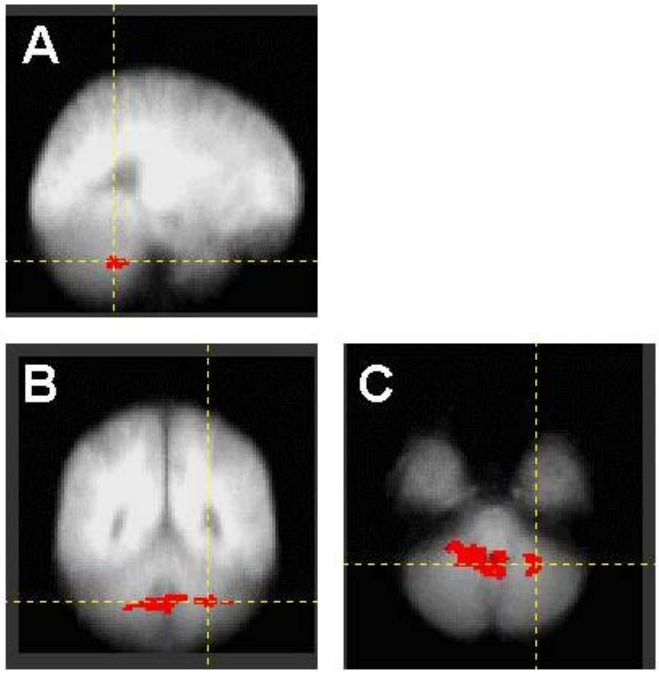


Figure 4.3: Areas where slow movement of the affected hand led to increased motor-related activity in patients compared to controls included the ventral part of the dentate nucleus of the cerebellum contralateral to the hand moved, shown by the cross hairs in saggital (**A**), coronal (**B**) and axial (**C**) sections. The cluster in the dentate nucleus was smoothed to define a mask that was used in later analyses. The cross hairs are at x=-26, y=-48, z=-44, Z-statistic=2.9). (The midline cerebellar activation visible in B and C is in lobule X (flocculus)),

The mean laterality index (LI) averaged across slow and fast movements for each VOI for patients and controls was calculated (Figure 4.4, Table 4.7). The affected hand was the left (non-dominant) hand for half of the patient group. Some studies have found that movement of the non-dominant hand in control subjects is associated with more bilateral motor cortical activation than dominant hand movement (Kawashima *et al.* 1993; Singh *et al.* 1998). The affected hand was therefore separately compared to the control left and right hand, as well as to the mean of left and right hand LI. Affected hand movements in patients were associated with lower absolute laterality indices than controls in all four VOIs (Figure 4.4, Table 4.7). Differences were tested against a Bonferroni corrected one-tailed probability

threshold for four VOIs (i.e. p<0.0125). There were significant differences and trends for differences between patients and control LIs in the primary sensorimotor cortex (versus control mean LI: t=-2.4, df=18, p=0.013; versus control right hand LI: t=-2.9, df=18, p=0.005) and the cerebellum (versus control mean LI: t=2.107, df=8.8, p=0.033, corrected for unequal variances; versus control left hand LI: t=2.53, df=18, p=0.01). No significant differences in laterality between patients and controls were found for movements of the unaffected hand, or for the laterality in the premotor cortex or the functionally-defined dentate nucleus. There was a trend for movements of the affected hand to be associated with lower LIs than the unaffected hand in the cerebellum (t=2.0, df=7, p=0.043).

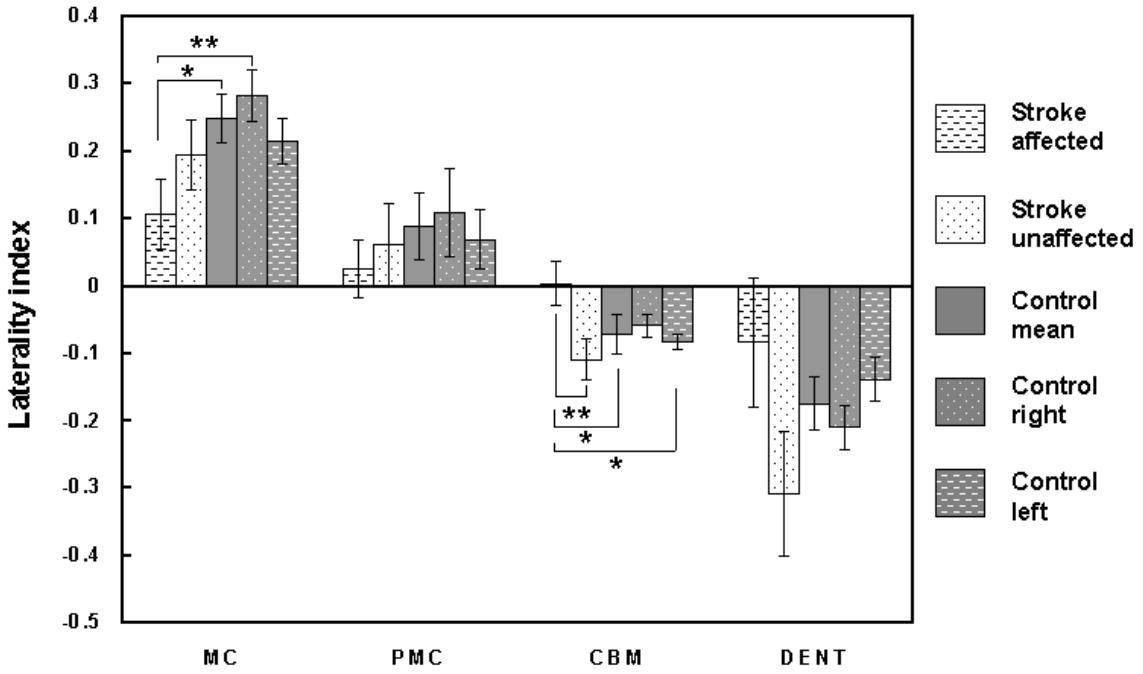


Figure 4.4: Mean Laterality indices within volumes of interest. LI for patients is shown separately for the affected and unaffected hands. LI for controls is shown separately for the left and right hand, and as a mean of left and right hand. For the cortical areas LI tends to be positive (i.e. greater contralateral activation). For the cerebellar areas LI tends to be negative (i.e. greater ipsilateral activation). Movement of the affected hand is associated with a more bilateral pattern of activation (lower magnitude LI) than controls and than unaffected hand movements in all four VOIs. The difference between patients and controls is significant in the primary motor cortex (MC) and the cerebellum (CBM) (p<0.05) but not in the premotor cortex (PMC) or functionally-defined dentate (DENT). ** represents differences significant at p<0.0125; * represents differences significant at p<0.05. Error bars represent standard errors of group means.

Subject		Laterality Index			
		MC	**PMC**	**CBM**	**DENT**
Control group	Right	0.28 (0.04)	0.11 (0.05)	-0.06 (0.03)	-0.21 (0.04)
	Left	0.22 (0.04)	0.07 (0.07)	-0.08 (0.02)	-0.14 (0.03)
	Mean	0.25 (0.03)	0.09 (0.04)	-0.07 (0.01)	-0.18 (0.03)
Patient group - Affected hand	1	-0.03	0.01	0.09	0.20
	2	0.22	-0.06	-0.14	-0.49
	3	0.15	0.08	-0.07	-0.18
	4	0.15	0.26	-0.02	-0.31
	5	-0.04	-0.12	0.15	0.11
	6	-0.10	-0.04	0.04	0.32
	7	0.29	-0.02	0.04	-0.15
	8	0.23	0.10	-0.05	-0.16
Mean		0.11	0.03	0.005	-0.08
Patient group – Unaffected hand	1	0.45	0.28	-0.16	-0.56
	2	0.16	0.07	-0.03	-0.09
	3	0.09	-0.12	-0.18	-0.62
	4	0.17	-0.13	-0.04	-0.17
	5	0.16	0.34	-0.25	-0.46
	6	-0.004	-0.05	-0.12	-0.32
	7	0.38	0.03	-0.02	0.15
	8	0.16	0.08	-0.06	-0.41
Mean		0.19	0.06	-0.11	-0.31

Table 4.7: Laterality indices for individual patients and for group of controls.

In addition to comparing the laterality of activation between patients and controls, the relationship between the laterality of activation in cortical and cerebellar motor regions within the different subject groups was tested. For movements of the affected hand in patients there was a highly significant correlation between laterality index in the primary motor cortex and the functionally-defined dentate nucleus of the cerebellum (r=-0.839, p=0.009, Figure 4.5, Table 4.6). There was no correlation between cortical and cerebellar LI for the left or right in the control group moving the left or the right hand or in patients moving their unaffected hand (Table 4.6).

			Dentate nucleus		Whole cerebellum	
			r	p	r	p
Primary motor	patients	affected	-0.84	0.009**	-0.66	0.08
cortex		unaffected	0.17	0.69	0.11	0.79
	controls	left	-0.28	0.38	-0.23	0.48
		right	-0.15	0.64	-0.07	0.84
Premotor cortex	patients	affected	-0.38	0.35	-0.36	0.38
		unaffected	-0.24	0.56	-0.49	0.22
	controls	left	0.21	0.51	-0.13	0.70
		right	0.20	0.53	0.27	0.39

Table 4.8: Results of correlations between cortical and cerebellar laterality indices. There is highly significant correlation between laterality in the primary motor cortex and the dentate nucleus of the cerebellum for patients moving the affected hand.

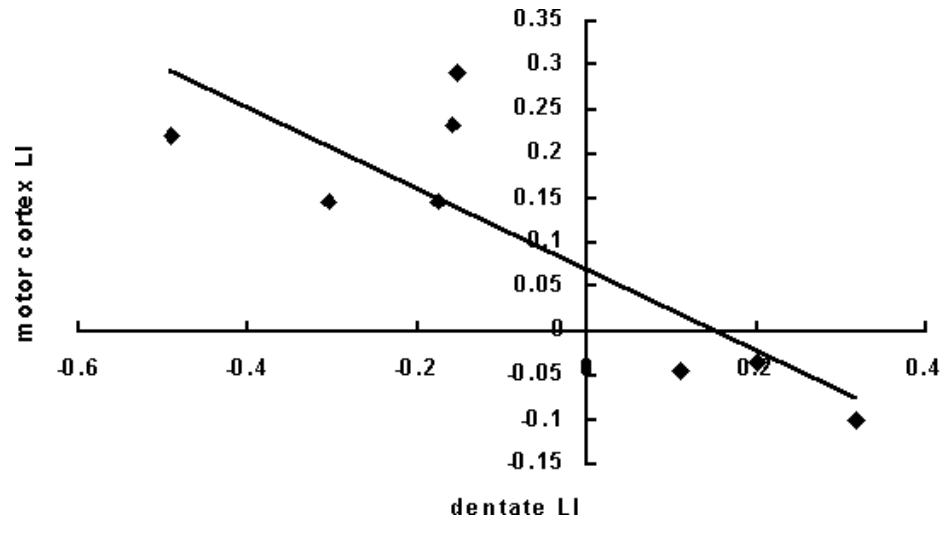


Figure 4.5: For movement of the affected hand in patients there was a significant correlation between LI in the dentate nucleus of the cerebellum and LI in the primary motor cortex (r=-0.84, p=0.009)

In order to assess the relationship between motor impairment and FMRI activation in the patient group the correlation between impairment (% change from unaffected to affected 9-hole peg test score) and LI was calculated for each VOI. There was a significant correlation between LI in the functionally-defined dentate nucleus of the cerebellum during affected hand movement and impairment (r=0.868, p=0.005, Figure 4.6). There was no evidence for a relationship between LI in motor cortical areas and impairment (MC: r=-0.56; NS; PMC, r=-0.36, NS).

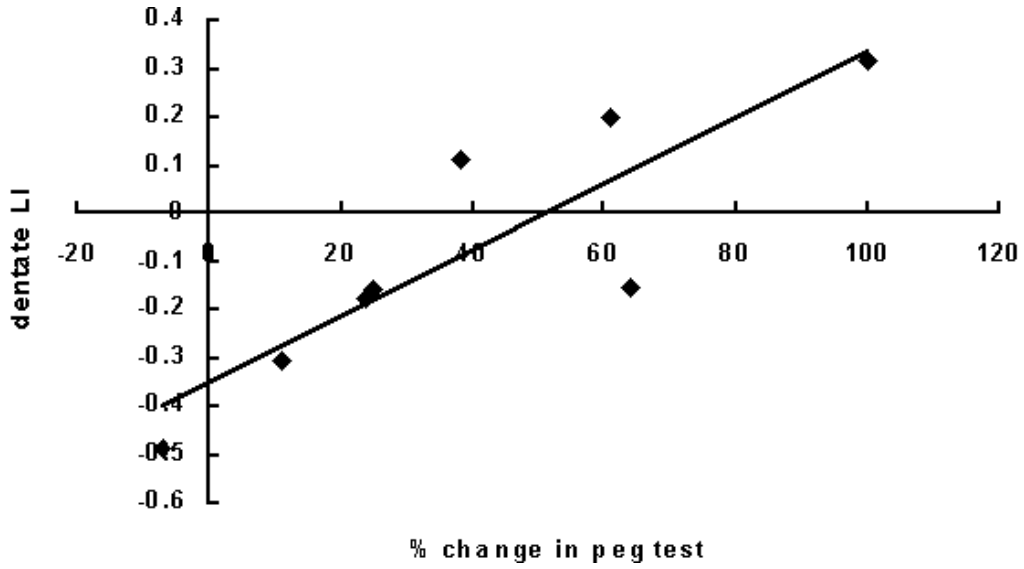


Figure 4.6: There was a significant correlation between a measure of hand impairment (% change in peg test) and laterality index in the dentate nucleus of the cerebellum during affected hand movement (p=0.005)

4.4 Discussion

This study demonstrated a number of differences in movement-related FMRI activation in patients and controls, and ways in which patterns of FMRI activity were related to impairment in the patient group. Specifically, movement of the affected hand in patients was associated with increased activity in bilateral inferior regions of the cerebellum and in the calcarine sulcus (primary visual cortex). A volumes of interest (VOI) analysis was performed to assess laterality of activation in anatomically-defined (primary sensorimotor cortex (SMC), premotor cortex (PMC) and the cerebellum) and functionally-defined (the region of the dentate nucleus with increased activation in patients) regions. This analysis found that movement of the affected hand in patients produced significantly less lateralised activation in the SMC and cerebellum compared to controls.

Relatively increased activity in the ipsilateral sensorimotor cortex during movements of an affected hand in stroke has been reported previously in studies using positron emission tomography (Cramer *et al.* 1997; Weiller *et al.* 1992; Nelles *et al.* 1999; Weiller *et al.* 1993;

Honda *et al.* 1997) and a few studies using FMRI (Cramer *et al.* 1997; Cao *et al.* 1998; Marshall *et al.* 2000). Although some studies found that ipsilateral motor responses appeared only in patients with mirror movements (Weiller *et al.* 1993) most studies have interpreted the increase in ipsilateral motor activity as evidence for adaptive altered recruitment of alternative motor networks.

However, few studies have attempted to relate the degree of involvement of the ipsilateral hemisphere to the extent of recovery. All of the imaging studies above have looked for differences between groups of patients and groups of controls, or between activation patterns for affected versus unaffected hands. By contrast, the experiment reported in this section also aimed to explore interactions between motor areas, and to assess the functional relevance of the activation patterns in the patient group by relating them to motor impairment.

Interactions between elements of the motor system were assessed by correlating laterality indices between different regions. This revealed further differences between patients and controls: for patients and not controls there was a significant correlation between laterality in the dentate nucleus of the cerebellum and the primary motor cortex. This raises the possibility that tight coupling between cortical and cerebellar activation may play an increased role in patient groups performing simple movements of the affected hand. Further evidence that laterality of activation in the dentate nucleus specifically is related to recovery is found from the significant correlation between impairment in motor function and LI in the dentate nucleus and no other volume of interest.

A striking result from the current study therefore was the importance of the cerebellum in movement of the affected hand. The strict between-groups comparison of motor-related activation for movement of the affected hand in patients versus controls only revealed increased activity in bilateral cerebellum and the primary visual area during slow

movements. The increased visual cortical activity may reflect increased attention paid to the flashing visual cue by the patients. The increased activity in the contralateral dentate nucleus of the cerebellum may reflect increased recruitment of cerebellar motor circuits. The dentate projects to the contralateral ventrolateral nucleus of the thalamus (Asanuma *et al.* 1983) which projects to sensorimotor cortical areas including supplementary motor area (Matelli and Luppino 1996) premotor and primary motor cortex (Matelli *et al.* 1989). The dentate therefore has neuroanatomical connectivities appropriate to influence ongoing motor cortical activity. Motor cortical areas give rise to corticopontine fibres and the pontine nuclei project back to the contralateral cerebellar hemispheres which project to the dentate. The dentate nucleus therefore forms part of a cortico-cerebellar loop with the motor areas of the opposite hemisphere (Middleton and Strick 1997). The anatomy concurs with the finding of correlated laterality between dentate and motor cortex. Patients who showed relatively increased contralateral cerebellar activity (i.e. increasingly positive LI) also showed relatively increased ipsilateral motor cortex activity (i.e. increasingly negative LI). This raises the possibility that the ipsilateral motor cortical changes that are frequently reported (Cramer *et al.* 1997; Weiller *et al.* 1992; Nelles *et al.* 1999; Weiller *et al.* 1993; Honda *et al.* 1997) may be modulated or even driven by changes in contralateral cerebellar activity.

The importance of the cerebellum for movement of a recovered limb has largely been overlooked by previous studies that have mainly concentrated on altered recruitment of cortical motor networks. Nevertheless, a few studies have reported increased activity in the bilateral cerebellum, along with a number of cortical motor areas (Weiller *et al.* 1993; Chollet *et al.* 1991). In addition, one study using a principle component analysis to identify patterns of spatial covariance in resting-state and movement-state PET data found a component expressed during movement that differentiated between patients and controls and correlated with lower motor scores initially after stroke (Seitz *et al.* 1999). This 'recovery-related'

component included bilateral occipital and prefrontal areas, contralesional cingulate, hippocampal formation, dorsal thalamus and bilateral cerebellum. The current study found correlations between laterality in the dentate nucleus of the cerebellum and motor impairment score.

In normal subjects the cerebellum plays a role in motor learning (Marr 1969; Ito 1984). Human imaging studies have demonstrated increased activation in the cerebellum during learning of new movement sequences (Jenkins *et al.* 1994), acquisition of eye-blink conditioning (Ramnani *et al.* 2000) and rhythm learning (Ramnani and Passingham 2001). Permanent lesions of the dentate nucleus in monkeys impairs new learning of a motor sequence (Nixon and Passingham 2000). Temporary inactivation of the dentate nucleus impairs monkeys ability to adapt to visual distortions in a visuo-motor task (Robertson and Miall 1999). The role of the dentate is thought be in the automation of movement sequences, rather than the association of one movement with the next (Nixon and Passingham 2000). This is consistent with the proposed role of the cerebellum in movement timing and motor co-ordination: FMRI activation increases in the bilateral dentate as performance at an eye-hand co-ordination task improves (Miall *et al.* 2001); the cerebellum is active during performance of a movement sequence with remembered timing (Kawashima *et al.* 2000).

The cerebellum is also involved in predicting the sensory consequences of movements (Blakemore *et al.* 2001; Blakemore *et al.* 1998). It is activated when there is a mismatch between expected and actual outcomes and in this way can be seen as an 'error detector'. Ascending projections from the cerebellum to motor cortices modulate ongoing motor activity to minimise error. It is possible that this mechanism would be particularly involved in movement of an affected limb, if there is often a mismatch between intended movement and movement outcome.

4.4.1 Conclusions

Overall, the results presented here suggest that movement of a recovered hand after stroke is associated with a more bilateral pattern of activation across the motor system and particularly in the primary motor cortex and cerebellum. There is a relationship between laterality of activation in the primary motor cortex and the dentate nucleus of the cerebellum during affected hand movement that is not seen in control subjects or in patients moving their unaffected hand. Finally, the laterality of activation in the dentate nucleus was tightly coupled to recovery, with relatively increased contralateral dentate activation (i.e. opposite to the normal pattern) associated with greater motor impairment.

It is tempting to suggest that the altered patterns of activation seen in the patient group reflect adaptive reorganisation that contributes to the recovery process. The correlations found suggest that FMRI activation specifically in the dentate nucleus of the cerebellum is related to the degree of impairment. However, it is impossible to determine whether the pattern of FMRI activation is the cause or effect of impairment. In addition, there are a number of potential confounds to interpretation that need to be considered. First, it is possible that patients would find the movement more effortful than controls and that this could result in relatively more ipsilateral activation. The experiment presented here tried to address this to some degree by cueing movements at a proportion of subjects maximum rate in order to normalise performance. However, it remains possible that patients found the movement more difficult or more complex due to other aspects of the movement. Second, it is possible that cognitive factors, such as the amount of attention paid to the movement affects the degree of motor cortical activation. It is conceivable that a patient whose limb is or has been hemiparetic would differ in the amount of attention paid to movement of the affected limb.

In addition, investigation of patients at a single time point does not provide any insight into dynamic recovery processes, and makes it difficult to relate the FMRI activation patterns to behavioural recovery.

Lastly, the technique of FMRI demonstrates which patterns of brain activity correlate with performance of a particular task. However, it cannot tell us whether activation of a given region is necessary or sufficient for task performance. Thus, the increased ipsilateral activation in stroke patients could simply reflect an incidental by-product of the lesion (such as disinhibition of the unaffected hemisphere by reduced transcallosal input) rather than adaptive reorganisation.

Some of these alternative possibilities are explored in the following sections. Section 5 assesses the effect of movement factors on motor cortical activation. Sections 6 and 7 assess the impact of attentional factors. Section 8 reports a longitudinal study of a patient group that investigates dynamic brain changes in response to rehabilitation. Section 9 assesses the functional relevance of the ipsilateral FMRI activation seen by disrupting activity in ipsilateral motor regions using transcranial magnetic stimulation.

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