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Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke

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Summary

An experimental lesion in the primary motor or sensory cortices in monkeys leads to functional reorganization in areas surrounding the lesion or in contralateral homologous regions. In humans, task-dependent brain activation after motor stroke seems to be multifocal and bilateral. Although many active structures are seen after stroke, their roles are unclear. For instance, the uninjured primary motor cortex may play a significant role in recovery or may be associated with mirror movements. Other motor areas, particularly those outside the affected middle cerebral artery distribution, have also been thought to play such a role, including the medial pre-motor areas and both cerebellar hemispheres. The lateral pre-motor areas might also contribute but the demarcation of primary motor and pre-motor cortices is not trivial. It is not known from existing studies how brain activation relates to behavioural change over the time course of recovery. We used functional MRI (fMRI) to study 12 patients longitudinally over the first 6 months of stroke recovery. All subjects had acute stroke causing unilateral arm weakness and had some ability to move the impaired hand within 1 month. Each patient had both motor testing and fMRI during finger and wrist movements at four points during the observed period. Six of these patients showed good motor recovery, whereas the other six did not. The imaging results support a role for the cerebellum in mediating functional recovery from stroke. The data suggest that patients with good recovery have clear changes in the activation of the cerebellar hemisphere opposite the injured corticospinal tract. Patients with poor recovery do not show such changes in cerebellar activation. No other brain region had a significant correlation with recovery. Interestingly, activation in the cerebellum ipsilateral to the injury increases transiently after stroke, independently of the success of recovery. The present work suggests a possible link between cerebellar activation and behavioural recovery from hand weakness from stroke. The underlying mechanism is not known, but it could relate to haemodynamic changes such as diaschisis or to the postulated role of the cerebellum in motor skill learning.

Keywords: cerebellum; stroke recovery; functional brain imaging; plasticity

Abbreviations: CRB = cerebellum; M1 = primary motor cortex; M2/3 = supplementary motor and cingulate motor cortices; PM = pre-motor cortex; S1 = primary sensory cortex; SM1 = primary sensory and motor cortex; SMA = supplementary motor area

Introduction

Despite success in reducing the mortality and morbidity from ischaemic stroke by early intervention, many stroke survivors continue to have serious functional impairments, particularly in motor function. Unfortunately, neither basic research nor clinical therapeutics has made tremendous inroads into chronic aspects of stroke. A major limitation in the current approach to stroke neurorehabilitation is the predominance of an educational, rather than a biological, perspective. This has led to attempts to 're-educate' patients through a variety of intuitive methods, without knowledge of the basic neurophysiology of stroke recovery. The present research aims to begin the development of a neurobiological theory of stroke recovery through the longitudinal investigation of brain anatomy after stroke.

Most patients with stroke have unilateral weakness, due to involvement of the motor system (corticospinal) at the level of the motor cortices, the subcortical nuclei or the axons that project to the spinal cord. Such patients typically have significant weakness in the extremities contralateral to the brain infarction, which recovers over a period of time ranging from several months to several years (Twitchell, 1951). The most significant amount of recovery is thought to occur in the first 6 months after the stroke (Jorgensen *et al*., 1995), and it is this time period that was the focus of the present study.

It is an underlying assumption of this work that the recovery of impaired behavioural functions, e.g. motor skill, is accompanied by changes in brain neurophysiology, and that studying the neurobiology will lead to both theoretical insights into stroke rehabilitation and novel treatment strategies based on biological, rather than longstanding empirical principles.

Although recovery is thought to be associated with major changes in regional cerebral blood flow (rCBF), some of these changes relate to alterations in cerebral haemodynamics that characteristically accompany ischaemic stroke, and could be short or long lived (Gideon *et al*., 1994; Toyoda *et al*., 1994), whereas others are thought to reflect neural reorganization that might have long-lasting effects on recovery. It is believed that therapy might affect this reorganization (Taub *et al*., 1993), both positively and negatively (Feeney *et al*., 1982; Goldstein, 1998; Small *et al*., 1998).

Studies in animal models suggest that with small lesions in the primary motor or sensory cortices (M1 or S1), reorganization takes place locally, adjacent to the injury (Jenkins and Merzenich, 1987; Nudo *et al*., 1996; Xerri *et al*., 1998). Other studies suggest that the homologous regions of the contralateral hemisphere undergo specific changes, including sprouting of new synapses (Jones and Schallert, 1992), but that these changes may be dependent on the additional activity by the unimpaired limb (Jones and Schallert, 1994).

With the advent of functional neuroimaging, *in vivo* studies of human stroke recovery have become possible. Initial studies showed that regional brain metabolism, unrelated to specific task performance, was altered after stroke (Heiss and Herholz, 1994; Heiss *et al*., 1984) and changed over the course of recovery (Toyoda *et al*., 1994). These rCBF studies, conducted with single photon emission computed tomography (SPECT) or PET have lent support for the concept of diaschisis (von Monakow, 1914), developed early in the century to describe the modification of neural activity in brain regions functionally connected to impaired regions. Such studies also supported the notion that functional recovery might be associated with measurable neural phenomena (e.g. decreased activity as reflected in glucose metabolism or oxygen consumption), rather than the static size and location of a brain lesion (Metter *et al*., 1984, 1987; Seitz *et al*., 1999). Due to the radiation exposure associated with these methods, longitudinal changes were not investigated.

Both PET (Raichle *et al*., 1983) and functional MRI (fMRI) (Kwong *et al*., 1992) can be used to demonstrate task-dependent brain activation in both normal subjects and patients with brain injury. PET studies investigating patients at a single time point after motor system stroke have shown that the changes in the functional anatomy involve diffuse bilateral networks (Weiller *et al*., 1992), possibly involving the cerebellar/thalamic pathway (Azari *et al*., 1996). An fMRI study suggested an important role for the uninjured M1 (Cramer *et al*., 1997). Although an earlier study suggested that such ipsilateral activation might be associated with mirror movements (Weiller *et al*., 1993), one current theory is that this activation is actually compensatory activation and/or reorganization and is instrumental to recovery (Cramer *et al*., 1997). Although this result is quite plausible, given the longstanding theories in the neurology of motor and language rehabilitation (Sparks *et al*., 1974; Lee and van Donkelaar, 1995), involving compensation by homologous brain structures opposite areas of damage, these studies are difficult to generalize for three reasons. First, they have examined patients at different and often unmatched times since stroke, thus including quite variable physiological systems. Secondly, they generally have not examined the degree of behavioural impairment or of behavioural recovery in the studied patients, to see if in fact the observed changes are functionally important. Thirdly, they have not examined these patients longitudinally, to see if the anatomical or behavioural effects change during the time course of stroke recovery.

To address these questions, we used fMRI and neuropsychology to study both behaviour and neurophysiology over the time course of recovery from ischaemic motor system stroke. Any patient with a single stroke and unilateral weakness, who was able to move the impaired hand by the end of the first month post-stroke, was eligible for the study. Each such patient was examined behaviourally and physiologically four times during the first 6 months post-stroke. The behavioural evaluation included tests of both strength and fine motor skill. The basic physiological evaluation used fMRI to examine changes in brain activation patterns during wrist and index finger movements.

Hypotheses for the present work were that over the course of stroke recovery, brain activation would increase in one or more of the following primary sites: (i) in the M1 contralateral to the injury; (ii) in the M1 ipsilateral to the injury; and (iii) in cortical regions functionally connected to the impaired M1, particularly the supplementary motor (SMA) and lateral pre-motor cortices (PMs) and cerebellum (CRB). We hypothesized that functional (behavioural) motor recovery would correlate with the neurobiological changes, such that better recoverers but not poorer recovers would demonstrate such changes.

Methods

Subjects

Twelve patients were recruited from a stroke rehabilitation service of an academic medical centre. All patients had a first stroke within the previous 3 months (range 26–97 days; mean 44 days) documented by history and brain imaging (T_2-weighted structural MRI taken at the beginning of the research study). The group consisted of seven males and five females, mean age 54 years (range 44–74; median 52 years), and 11 out of 12 were right handed. Six of the patients had strokes affecting their dominant hand. Anatomically, the group had a high degree of heterogeneity but, behaviourally, all patients were able to perform index finger–thumb opposition at one flexion per second with the hemiparetic hand. All patients gave written consent for their participation according to the Declaration of Helsinki (Nylenna and Riis, 1991) and the study was approved by the Institutional Review Boards of the University of Maryland and The University of Chicago.

Behavioural evaluation

All patients performed a set of behavioural tests with each hand: index finger tapping (Shimoyama *et al*., 1990), nine-hole peg test (Mathiowetz *et al*., 1985) and hand grip strength. The peg test and hand grip strength were tested three times on each hand (alternating hands) and the results averaged.

Functional MRI

Functional image acquisition consisted of three stages. First, structural scout images were acquired in each of the three orthogonal planes, with normalization of head position based on the positions of the third ventricle (coronal plane) and the longitudinal fissure (axial plane). This permitted normalized axial image acquisition that was reliable over long periods of time. Following this alignment, (oblique) in-plane structural (T_1-weighted) and pathological (T_2-weighted) images were collected. Secondly, functional scans were performed using spiral imaging, a method allowing rapid image acquisition, and with less sensitivity to movement and flow artefacts than other methods (Nishimura *et al*., 1995; Noll *et al*., 1995). In spiral imaging, magnetic field inhomogeneities do not cause geometric image distortions and can be corrected efficiently (Noll *et al*., 1992, 1993). The third step in acquisition consisted of acquiring a high resolution brain volume scan and a venous phase angiogram.

Tasks

During each imaging experimental session, subjects performed simple repetitive movements of fingers (index finger–thumb opposition) and wrist (flexion/extension). These were paced auditorily at 1 Hz, a slow pace for a normal subject but a quick pace for a paretic hand. Movement blocks were separated by blocks of rest within a standard order (rest, finger, rest, wrist). The rest block included the auditory pacing signal. Each experimental run consisted of eight repetitions of the four blocks: a rest block (12 s), a finger block (24 s), another rest block (12 s) and a wrist block (24 s), for a total of $8 \times (12 + 24 + 12 + 24) = 576$ s = 9 min 36 s. Each subject had two experimental runs with the impaired hand in each imaging session. All task performance during scanning was monitored visually by a member of the research staff. All trials containing errors in task performance were aborted and restarted.

Electromyography (EMG)

EMG examination using surface electrodes placed over the *extensor digitorum communis* of both arms was used to address concerns that bilateral activation of motor cortical areas is partly caused by mirror movements that have been observed during complex finger movements in normal people (Hopf *et al*., 1974). Mirror movements may be very subtle, and EMG provides a sensitive method to detect their presence.

Analysis

Following reconstruction of the spiral k-space data (Noll *et al*., 1995), all experimental trials from each session were co-aligned first to each other and then to the (aligned) trials from the other sessions (Woods *et al*., 1998). This meant that images collected 6 months apart were co-registered.

Statistical image analysis was performed using multiple linear regression, utilizing square wave predictors of wrist and finger movements, along with corrections for linear trends (Haxby *et al*., 2002). Haemodynamic response was modelled using a Gaussian, and effective degrees of freedom were estimated (Maisog *et al*., 1995). *F*-maps associated with each regressor were converted into individual *Z*-maps. For illustration purposes, data with $Z > 2$ are shown. For statistical analysis of regional activation, however, these maps were thresholded at a minimum cluster size of 4 and a *Z* score of 3, with all subsequent numerical analysis based on this threshold.

Each resulting area of activation was located anatomically and named by consensus of (at least) two of the authors (S.L.S. and A.S.). Each brain image was examined separately, and localization decisions made with respect to each subject's individual anatomy. Based on the hypotheses of the study, a mapping was then made from this array of brain regions into four regions of interest capturing the cerebral cortical and cerebellar motor areas, including the primary sensory and motor cortices (SM1s), the lateral PM, the supplementary motor and cingulate motor cortices (M2/3) and the CRB. These regions were delimited according to accepted anatomical landmarks (Picard and Strick, 1996; White *et al*., 1997; Yousry *et al*., 1997; Hlustik *et al*., 2001; Solodkin *et al*., 2001) (see Appendix 1).

Table 1 *Subject demographics for motor stroke recovery study*

No.	Lesion side	Lesion location	Sex	Age (years)	Lesion volume (mm^3)	Dominance
Better recoverers						
2	L	Capsule	M	46	364	D
4	L	Pons	M	45	1034	D
5	L	Putamen/capsule	F	73	3665	D
8	R	Cortex	M	44	255 767	N
9	R	Cortex	F	54	92 428	N
11	L	Pons	F	54	1118	D
	4L/2R	Heterogeneous	3M/3F	52.67	59 063	4D/2N
Poorer recoverers						
1	R	Cortex	M	48	10 716	N
3	L	Capsule	M	55	411	D
6	R	Pons	F	50	1656	N
7	L	Capsule	M	74	838	D
10	R	Caudate/capsule	M	57	16 058	N
12	L	Thalamus	F	50	1419	N
	3L/3R	Heterogeneous	4M/2F	55.67	5183	2D/4N
All subjects						
Mean	7L/5R	Heterogeneous	7M/5F	54.17	32 123	6D/6N

The first column indicates the identification number of the individual research participant. The last column refers to whether the affected hand was dominant (D) or non-dominant (N).

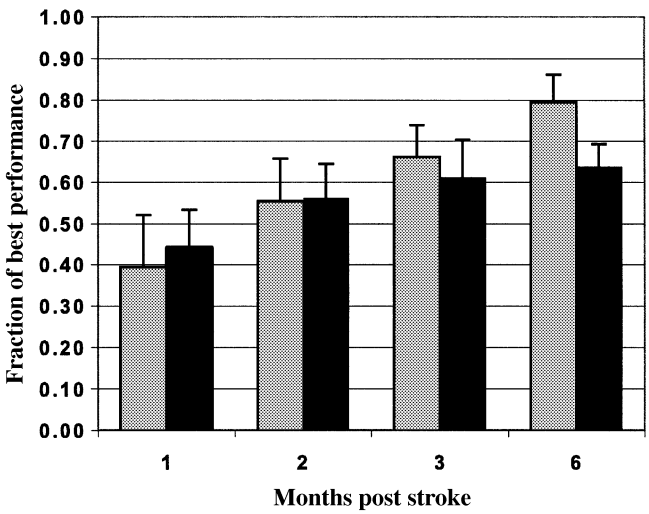

Fig. 1 Behavioural results. Nine-hole peg test: fraction of best performance (either hand) on the nine-hole peg test (timed motor task) for better recovery group (grey) and poorer recovery group (black).

Statistical analysis of the behavioural data is described during presentation of the results, including a procedure in which each measure of hand performance is normalized to the best performance by either hand, and then compared across time to gauge improvement. Secondary analysis of the brain activation maps included three steps: (i) a direct comparison of the raw counts in each region by each subject; (ii) the execution of a multiple level ANOVA (analysis of variance) to assess the important contributions to the differences in activation volumes across lateralized brain region, type of hand movement and magnitude of behavioural recovery, all over the time course of recovery; and (iii) the use of a multivariate model that attempted to relate behavioural recovery over time to the regional activation values during the task-dependent imaging.

Results

Behavioural findings

Raw dynamometer scores (hand and pinch) were transformed into normalized scores by dividing the raw (impaired hand) score by the maximum (unimpaired hand) score over the entire 6 months. Nine-hole peg test scores (times) were normalized by dividing the minimum (unimpaired hand) by the raw (impaired hand) score. The normalized performance in the impaired hand ranged from 9 to 66% on these measures (pinch, 10–65%; hand, 9–62%; peg, 13–66%). The behavioural data showed that all subjects improved their performance on all three primary measures, grip strength (hand dynamometer), pinch strength (pinch dynamometer) and timed fine motor performance (nine-hole peg test).

Improvement scores were calculated as the difference between the best and worst performance in the impaired hand on each of the three tasks. Subjects who had more than average improvement on two or three measures were classified as 'better', and those with less than average improvement on two or three measures were classified as 'worse'. This heuristic led to an equal number of subjects (six) in each group. A descriptive characterization of the subjects in each group is shown in Table 1.

Using normalized performance change as the dependent variable, a two-level ANOVA (two performance groups $\times$ three tests) was performed at the 6 month time point, and demonstrated that indeed the two groups differed

Table 2 *Brain activation results*

ROI	Group	Contralateral				Ipsilateral			
		1	2	3	6	1	2	3	6
SM1	Better	1354 (4)	3241 (5)	2053 (6)	3779 (4)	28 (1)	0	0	0
	Worse	1657 (6)	2004 (3)	1557 (5)	1658 (6)	166 (3)	0	0	0
CRB	Better	42 (1)	429 (2)	457 (3)	257 (3)	777 (4)	2616 (5)	1522 (5)	2275 (5)
	Worse	305 (2)	565 (3)	466 (3)	489 (3)	366 (2)	1239 (4)	1019 (5)	857 (4)
M2/M3	Better	123 (2)	267 (4)	169 (2)	141 (2)	35 (1)	0	63 (1)	67 (1)
	Worse	229 (2)	29 (1)	225 (2)	144 (2)	0	0	0	0
PM	Better	91 (1)	137 (2)	169 (1)	197 (1)	397 (2)	35 (1)	35 (1)	39 (1)
	Worse	116 (2)	0	0	28 (1)	35 (1)	0	35 (1)	0

Mean volumes of activation (mm^3) in each region of interest (SM1, CRB, M2/M3, PM) in each hemisphere (contralateral or ipsilateral to hand movements) for each group (better recoverers, worse recoverers), at each time point (1, 2, 3 and 6 months post-stroke) on combined finger and wrist movements are given. In parentheses are the total number of subjects with activation in that particular condition.

significantly in the amount of recovery as assessed on these measures ($F = 18.823$; $P < 0.0001$), but that the specific tests used did not distinguish the groups (i.e. no main effect of test or interaction between test and group). Further, with normalized starting performance as the dependent variable, an analogous two-level ANOVA at the 1-month time point demonstrated no difference in severity of impairment between the two groups (prior to recovery) ($F = 0.456$; $P = 0.5045$). Figure 1 shows the difference between the two groups in the mean level of performance on the nine-hole peg test over time. This test result played an important role in our multivariate model (see below).

The results of EMG examination demonstrated no evidence of mirror movements in any subject during task performance.

Brain activation

The hypotheses of the study related to the motor cortices and CRB, and four regions based on these functional anatomical sites formed the basis of the analysis. The regions used for this analysis included several coalescent areas that are distinguishable anatomically (Solodkin *et al*., 2001), but are less clearly distinguishable on routine fMRI (but for an example of high resolution imaging see Hlustik, 1999, 2001), namely the SM1 and the M2/3 in each hemisphere. The other two regions are the lateral PM areas and the CRB. The anatomical landmarks delimiting these regions of interest are described in Appendix 1.

In order to compare these results with those of previous non-longitudinal studies, a count was made of how many subjects showed activation in any of these regions at any time point during recovery, as well as the mean volume of this activation. These tabulated results are shown in Table 2, which also arranges the data by behavioural recovery group, showing the difference between subjects with 'better' recovery and those with 'worse' recovery.

Using activation volume as the dependent variable, and restricting attention to the impaired hand, a five-level ANOVA incorporated these two groups of subjects (better and worse), two tasks (wrist and finger), four brain regions (SM1, PM, M2/3 and CRB), four time points (1, 2, 3 and 6 months post-stroke) and two hemispheres (ipsilateral and contralateral). Hemispheric data were coded as ipsilateral or contralateral to the hand movement, rather than as left and right.

First, this ANOVA reveals regional brain activation on hand motor function post-stroke (without regard to body part or time course of brain injury) through the presence of a two-way interaction between region and hemisphere of activation [$F(1,1,3) = 48.04$; $P < 0.0001$]. *Post hoc* analysis of this interaction showed that the two regions accounting for this difference were the contralateral SM1 ($P < 0.0001$) and the ipsilateral CRB ($P < 0.0001$). Figures 2 and 3 show the mean activation in the M1 (Fig. 2) and the CRB (Fig. 3) for both groups of subjects.

This ANOVA further demonstrated a three-way interaction among degree of recovery, hemisphere of activation and region of activation [$F(1,1,3) = 4.55$; $P = 0.0036$]. Thus, without taking into consideration the amount of time post-stroke or whether the subject was moving the wrist or fingers, the group with the better recovery differed from the group with worse recovery in the regional pattern of activation among the four motor regions of interest in each hemisphere. *Post hoc* analysis of this interaction showed that a single lateralized regional activation accounted for the effect: The good recoverers had significantly more activation in the ipsilateral cerebellum than did poor recoverers ($P = 0.0434$).

Statistical model relating brain activation and behaviour

In this analysis, we restricted our attention to the two regions with the highest level of brain activation across most subjects, namely the SM1 and the CRB. In each of the other regions of interest examined (i.e. the pre-motor areas), interesting and suggestive subject-specific effects were evident, but the overall degree of activation was small, and it was difficult to

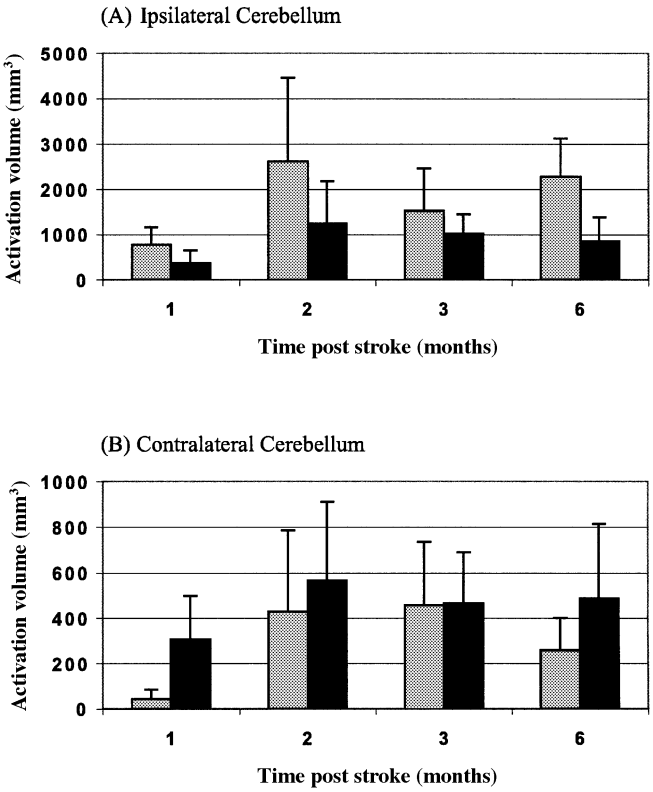

Fig. 2 Cerebellar activation. (**A**) Ipsilateral cerebellum: mean volume of activation for better recovery group (grey) and poorer recovery group (black). (**B**) Contralateral cerebellum: mean volume of activation for better recovery group (grey) and poorer recovery group (black). Note different scales on the ordinates.

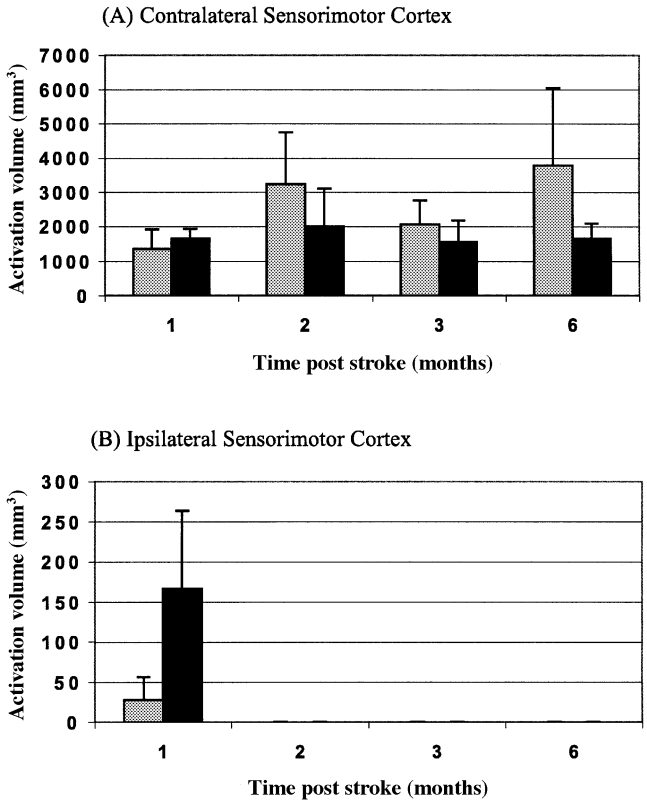

Fig. 3 Primary sensorimotor activation. (**A**) Contralateral sensorimotor cortex: mean volume of activation for better recovery group (grey) and poorer recovery group (black). (**B**) Ipsilateral sensorimotor cortex: mean volume of activation for better recovery group (grey) and poorer recovery group (black). Note different scales on the ordinates.

draw firm conclusions about the effects without *post hoc* grouping of the data. We intend to follow up these leads in further studies.

Ipsilateral CRB

All subjects but one (Subject 5) exhibited robust patterns of activation over time in the ipsilateral CRB. Exploratory data analysis suggested that a simple linear model,

$$V^* = k(1/\text{peg})$$

where V* represents the cube root of the volume, had good predictive value ($k = 2.21 \pm 0.96$; $T = 2.3$; $P = 0.0232$). The correlation of this model with V* ($r = 0.232$) reflects a large component of unexplained variance in the data. Figure 4 compares the mean activation volume over time in the ipsilateral CRB with the prediction of this simple model.

Contralateral CRB

The CRB contralateral to the impaired hand movements (i.e. ipsilateral to the brain injury) also exhibited significant effects, but rather than correlating with recovery, these fits show that the behavioural measures explain a transient spike in brain activation at the 2–3 month point during recovery. In this case, no simple model explained a significant amount of the data, although a complex log-linear additive model (capturing non-linear effects) was able to explain a significant portion of the data. Figures 5 and 6 illustrate the difference between the increasing ipsilateral activation and the transient contralateral activation in two single subjects, the first a 'better' recoverer and the second a 'worse' recoverer. As predicted by the model, the better recoverer shows an increasing activation in the ipsilateral CRB, whereas the worse recover does not show this pattern.

Contralateral SM1

The SM1 contralateral to hand movements is the brain area of highest activation (both signal and volume) in studies of normal subjects (Roland *et al*., 1980; Colebatch *et al*., 1991; Kim *et al*., 1993; Rao *et al*., 1995; Solodkin *et al*., 2001) as well as in patients with brain injuries (Weiller *et al*., 1992, 1993; Cramer *et al*., 1999). As we saw in the previous section of results, this is also true here. However, with this analysis, we examine a more specific question, namely, what is the relationship of this activation to recovery of function?

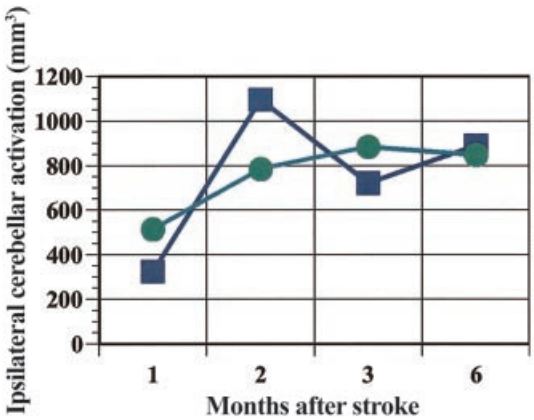

Fig. 4 Multivariate model of ipsilateral cerebellar activation. Model data (green circle) compared with actual data (blue square) in which ispilateral cerebellum activation is related to behaviour by a simple formula based on the inverse of the nine-hole peg test score (i.e. more activation related to faster performance). This model accounts for a significant portion of the data.

Using our statistical models, we found that activation in the contralateral SM1 has a complex relationship with behavioural recovery. No simple model was able to explain the activation patterns in these 12 subjects. In particular, the time course of SM1 activation does not easily fit (and could not be modelled without non-linear components) into either of the two hypothesized patterns, i.e. either a straightforward relationship with the indices of behavioural recovery (as with ipsilateral CRB) or a transient increase or decrease during the course of recovery (as with contralateral CRB). This was true despite the significant correlation found in ipsilateral CRB, to which it is highly interconnected.

Ipsilateral SM1

As noted above, a very limited amount of activity was detected in this region. As a result of this paucity of ipsilateral activation, there was insufficient information available to relate behavioural changes to activation changes.

Discussion

Previous research in primates and humans has studied the differences in the neural circuit organization after stroke. It is known that following a small experimental lesion in the S1 of the macaque, the cortical receptive field maps, ascertained by direct electrical recording, change to maintain complete somatotopic coverage of the skin surface (Jenkins and Merzenich, 1987). A similar lesion in the M1 leads to analogous changes (Nudo *et al*., 1996). The biological changes accompanying stroke recovery (Weiller *et al*., 1992, 1993; Chollet and Weiller, 1994; Small *et al*., 1996; Cramer *et al*., 1997; Small and Solodkin, 1998; Weiller, 1998; Johansson, 2000) are thought to occur in ipsilateral brain regions adjacent to the lesion site (Jenkins *et al*., 1990; Nudo *et al*., 1996) and in contralateral homologous regions (Nudo *et al*., 1996; Cramer *et al*., 1997). Other brain regions, including the PM, CRB, putamen and parietal cortex have all been postulated to play a role in such recovery (Weiller *et al*., 1992, 1993).

Studies of hand motor function in normal subjects (Solodkin *et al*., 2001) have shown that very simple hand motor behaviours, such as finger–thumb opposition of the dominant (right) hand in a right-hander, activate the M1 contralateral and the cerebellar hemisphere ipsilateral to the movements (Colebatch *et al*., 1991; Rao *et al*., 1995, 1996; Deiber *et al*., 1996; Fink *et al*., 1997; Wexler *et al*., 1997; Cramer *et al*., 1999; Hlustik *et al*., 2002). From this base network, additional brain areas can be recruited by altering various parameters of movement, such as complexity or use of the non-dominant hand (or of either hand in left-handers). Such extended networks include the SMA, the cingulate motor area, the lateral pre-motor area, the M1 ipsilateral to the movement and the CRB contralateral to the movement (Solodkin *et al*., 2001). Certain of these areas seem to play greater roles in particular circumstances, such as the SMA in tasks that are self-paced (Rao *et al*., 1997), or the left lateral pre-motor area in tasks that are more complex (Hlustik *et al*., 1998, 2002).

At a neuronal level, stroke recovery incorporates multiple components (Lee and van Donkelaar, 1995; Small and Solodkin, 1998). The first neural mechanism of recovery is the sprouting of fibres from surviving neurones and formation of new synapses. At the time of writing, it is controversial if this could also involve the growth of new neurones (Rakic, 1985; Gould *et al*., 1999; Kornack and Rakic, 2001). Such local development of new neurones or neural connections potentially could lead to re-establishment of previously existing neural pathways and mechanisms. The other two neural mechanisms of recovery are closely related, the unmasking of existing but functionally inactive pathways and the use of alternative functional pathways that comprise the normal system of cerebral circuit redundancy (Lee and van Donkelaar, 1995).

Stroke recovery also involves haemodynamic changes. Blood flow following stroke is decreased in the CRB contralateral to the infarction (Weiller *et al*., 1992; Jenkins and Frackowiak, 1993), presumably due to diaschisis, the phenomenon first described by von Monakow in 1914 (von Monakow, 1914; Meyer *et al*., 1993), in which brain function is depressed at sites remote from focal lesions, but not directly affected by the lesion *per se*. Patients with motor recovery within the first month appear to have a partial recovery of metabolism in this cerebellar hemisphere (contralateral to the infarction) (Azari *et al*., 1996), as well as in the thalamus on the other side.

The M1 is highly interconnected with the cerebellar hemisphere on the opposite side of the brain via the dentatothalamocortical and corticopontine tracts (Middleton and Strick, 1994, 1997), and normal subjects show a highly

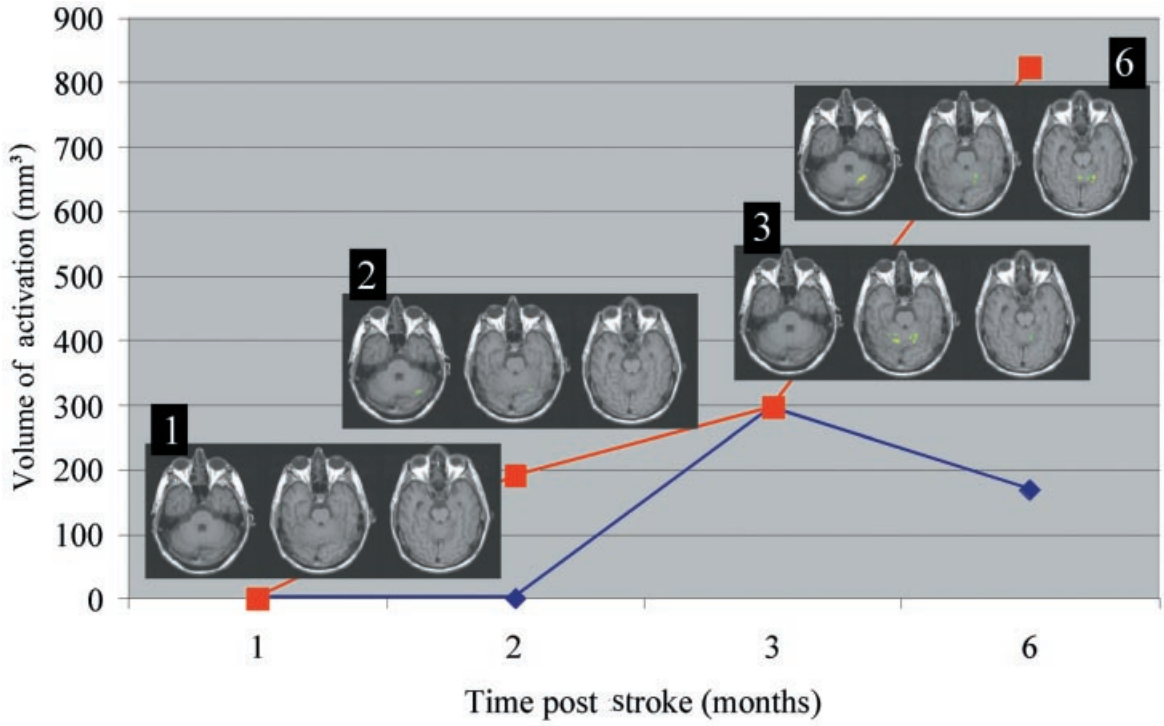

Fig. 5 Cerebellar activation over time in a 'better recoverer' during movements of the hemiparetic left hand. Actual fMRIs are superimposed on top of a graph of activation volume in the ipsilateral cerebellum (red square) and contralateral cerebellum (blue diamond). Note the increasing ipsilateral cerebellar activation and the transient contralateral cerebellar activation, both in the graphs and in the brain images.

correlated rCBF in these two regions (Junck *et al*., 1988). Thus, it may be unsurprising that 'crossed cerebellar diaschisis' (Baron *et al*., 1980) is considered a common sequela of corticospinal tract infarctions. The relationship between the degree of such crossed cerebellar hypometabolism and stroke recovery has been examined previously (Serrati *et al*., 1994; Seitz *et al*., 1999), showing no relationship early after stroke, but showing a correlation with lesion size at 2 months.

Stroke recovery may thus be related to the processes of neural recovery, haemodynamic recovery or functional (behavioural) recovery, which themselves may occur at independent rates and even at cross purposes (Taub *et al*., 1993). Recovery itself may be either restorative (direct) or compensatory (indirect) (Friel and Nudo, 1998). For direct recovery, the injured neural tissue would itself recover, or tissue nearby the injured or permanently damaged tissue would take over identical neural functions to the original tissue. For indirect recovery, completely different neural circuits permit the re-enablement of the lost or impaired function. Since the neural mechanism of such recovery could be vastly different from the original, both the brain activation pattern and the quality of the recovered function would differ substantially from the original.

Our results highlight the relationship between dynamic changes in brain activation and those in motor recovery after stroke: following a stroke affecting the corticospinal motor tracts, as in normal adults, movement of the fingers and wrist leads to widespread brain activation in motor areas, as demonstrated previously (Chollet *et al*., 1991; Weiller *et al*., 1992; Cramer *et al*., 1997). As in normal adults, the most significant regions of activation are the SM1 contralateral to the movements and the cerebellar hemisphere ipsilateral to the movements. Not predicted previously is that the degree of recovery from motor stroke appears to be significantly correlated with brain activation in the CRB ipsilateral to movements of the impaired hand (i.e. contralateral to the infarction), but not in the injured M1 with which this region has extensive connections, albeit indirectly. A second unexpected finding is that the CRB contralateral to the movements of the paretic hand has a transient increase in activation during the course of recovery, but that this is not correlated with recovery. A third finding is that the SM1 ipsilateral to impaired hand movements (i.e. contralateral to the infarction) may not play a role in motor recovery from stroke. Activation in these regions was not significant (except in some subjects early in recovery) and did not correlate with success of recovery. A fourth finding is that activation in contralateral M1, which is quite pronounced during movements of the paretic hand, did not differ between better and worse recoverers.

Previous imaging studies of patients with motor system stroke, assessed at a single time point after injury, have suggested important roles for the M1s bilaterally and the CRB

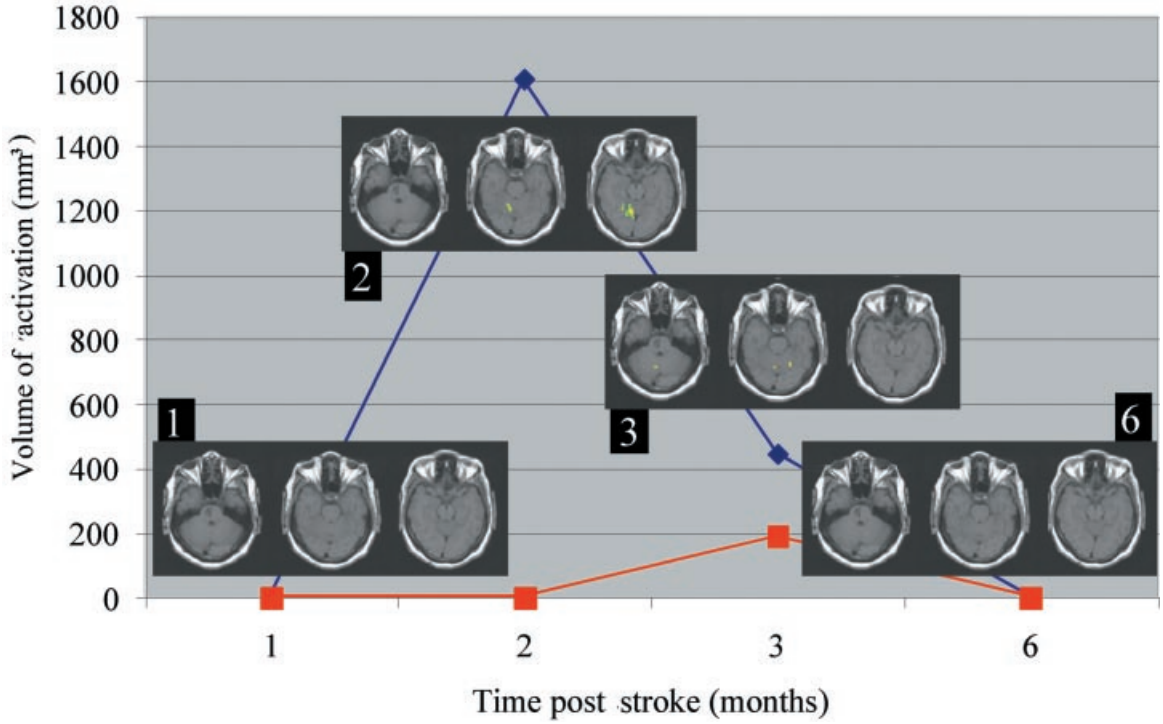

Fig. 6 Cerebellar activation over time in a 'poorer recoverer' during movements of the hemiparetic left hand. Actual fMRIs are superimposed on top of a graph of activation volume in the ipsilateral cerebellum (red square) and contralateral cerebellum (blue diamond). Note the transient cerebellar activation in both cerebellar hemispheres both in the graphs and in the brain images.

contralateral to the movements of the impaired hand (i.e. ipsilateral to the infarction) (Weiller *et al*., 1992; Jenkins and Frackowiak, 1993). The present study suggests that changes in activation in these regions do not follow the same temporal course as the behavioural changes. Although contralateral CRB was commonly activated after stroke, this activation was transient, peaking at 2–3 months after stroke, and declining by the final imaging session at 6 months. These changes were not correlated with changes in motor performance.

Nevertheless, it is possible to speculate on the origins of this transient activation. We know that this region is heavily interconnected with the M1 contralateral to the injury (i.e. ipsilateral to the weak hand), but that this region was poorly activated during stroke recovery: Half of the poor recoverers (three out of six) had some activation in ipsilateral M1 and only one of the good recoverers (out of six) had any such activation, and, in all cases, activation occurred early in recovery. One possibility is that the cerebellar activation could have originated in subcortical structures (basal ganglia and thalamus), which can be missed in single subject fMRI, and which have been suggested to play a role in recovery after stroke (Weiller *et al*., 1992; Azari *et al*., 1996).

In the case of ipsilateral M1, our results are not consistent with a previous fMRI study that suggested a primary role for this cortex in recovery (Cramer *et al*., 1999). We did not observe significant activation in this area. The reasons for this lack of activation could be 2-fold. (i) Our task was not complex enough for this patient population, since in normal subjects, complex finger movements typically lead to activation of M1 in both hemispheres (Solodkin and Small, 1998; Solodkin *et al*., 2001). In animal models, studies that have shown a possible role of M1 contralateral to a sensorimotor cortical injury (Jones and Schallert, 1992) have also shown it to be correlated with a significant increase in the use of the uninjured limb (Jones and Schallert, 1994). This suggests that such ipsilateral activity reflects compensatory limb activity (Jones *et al*., 1996), rather than circuit reorganization. (ii) The studies used different criteria to delimit M1 and PM. The borders between these two regions are difficult to determine, and thus the activation observed in M1 in the previous study could be labelled PM in the present work. Moreover, although brain activation of the ipsilateral motor cortex occurs to a limited degree in studies incorporating complex movements, it seems to occur most commonly in situations where the pre-motor areas are also active (Solodkin and Small, 1998). Since it is primarily the premotor (rather than the M1) cortices of the two hemispheres that are interconnected (Rouiller *et al*., 1994), it may be that the ipsilateral activation is a secondary effect of transcallosal activation through PM.

In addition to studies using single time points after stroke, several imaging studies investigated the time course, in each case comparing two time points after stroke (Nelles *et al*., 1999; Marshall *et al*., 2000; Calautti *et al*., 2001). Although these studies provide only two time points after stroke,

making it impossible to compare the temporal dynamics of activation patterns, some interesting results emerge from these papers. First, it is clear that brain activation after stroke is not a static phenomenon (as in control subjects) but a dynamic one (Nelles *et al*., 1999). Secondly, the SM1 may play a role in recovery since the activation in this area increased when considering the ratio between the two hemispheres (Marshall *et al*., 2000). Without behavioural assessment of the subjects, however, it is not possible to compare these results with those presented here. Although we see an increase in M1 activation after stroke, this increase did not differ between the groups of better and worse recoverers. Thirdly, there may be overactivation of the injured hemisphere during finger movements, which tends to decrease after recovery (Calautti *et al*., 2001). The borderline statistical significance of this result, combined with the presence of mirror movements in a large number of subjects (two out of four of the patients showing the effect), makes this result more difficult to interpret.

In the present study, activation in the ipsilateral CRB was the only significant correlate to behavioural recovery. Of the possible underlying mechanisms that could link this structure with motor recovery, two mechanisms seem the most plausible, although the methodology of the present study does not lend support for either hypothesis directly.

One explanation is that changes in cerebellar activation could be a consequence of haemodynamic alterations such as diaschisis. One study used principal component analysis to describe networks at two points during recovery, and suggested a role for both thalamus and visual association areas in the network active during the movements of the impaired hand (Seitz *et al*., 1999). These areas were also part of the network affected by the lesion (through diaschisis), suggesting that diaschisis might play a critical role in behavioural recovery.

A second possibility is that perhaps the CRB plays a more direct role in recovery through its postulated role in motor learning. Neurologists have long assessed cerebellar function through tests that emphasize motor control and timing (Joynt and Griggs, 1999; Tesche and Karhu, 2000). Data from patients with focal brain lesions in the CRB have shown some impairment in learning new motor skills (Sanes *et al*., 1990; Doyon *et al*., 1998; Bracha *et al*., 2000). Imaging studies have also lent some support for the role of the CRB in motor learning, with cerebellar activation prominent in motor learning studies (Jenkins and Frackowiak, 1993; Jenkins *et al*., 1994). Although some studies postulate a role for the CRB in early stages of motor learning (Thach, 1998; Bracha *et al*., 2000), others have shown the CRB to be involved in the 'automatization' (improvement of motor performance) of learned skills, the establishment of movement strategies and the consolidation of this motor knowledge (Doyon *et al*., 1998; Jueptner and Weiller, 1998; Schweighofer *et al*., 1998; Nixon and Passingham, 2000).

If the role of the CRB in motor learning involves the improvement of motor performance by the establishment of automatic motor skills, then we might expect changes in cerebellar activity after stroke to occur with some delay. Further, we should expect this change to be present for an extended period, until such time as the skill is automatic or, at a minimum, until reaching a plateau. Although it is difficult to quantify these times precisely, the temporal course of the changes in the ipsilateral activation of CRB in good recoverers seems to fit this model. The increase in activation did not start until the second or third months after stroke and persisted for at least 6 months. Interestingly, it has been reported that at the cellular level, there is an increase in the number of cerebellar cortical synapses with complex motor skill learning but not with gross motor use without learning (Kleim *et al*., 1998), and these synapses seem to persist even without continued exposure to the complex motor tasks that were used in learning (Kleim *et al*., 1997).

The relative role of haemodynamics versus that of neuronal reorganization remains unclear. Certainly the animal model supports a role for both angiogenesis and neuronal sprouting, depending on the motor learning requirements (Black *et al*., 1990). Further, the manifestations of crossed cerebellar diaschisis (Pantano *et al*., 1986; Baron, 1989) as demonstrated by the BOLD effect (Thulborn *et al*., 1982; Ogawa *et al*., 1990, 1993; Bandettini *et al*., 1994) are not known. Since these two processes are not necessarily mutually exclusive, it could be interesting in future studies to determine the relationship between them.

The present data also suggest that activation in the CRB on the same side as the injured corticospinal tract (i.e. contralateral to hand movement) as well as the activation in contralateral M1 might relate to general recovery processes independently of the success of these processes. It is possible that this activity is related to vascular and/or haemodynamic factors, since it does not correlate with degree of recovery and is transient, falling off after a peak in the 2–3 month time frame.

The CRB appears to play an important role in motor recovery from stroke, with the cerebellar hemisphere opposite the damaged corticospinal tract playing the clearer role. Of course, the current patients comprise a heterogeneous group, and additional research is needed to understand the differences among patients with lesions of different sizes and locations. Although this mixed group of subjects showed significant effects in the CRB, perhaps particular subgroups would show additional changes for which there was insignificant power in the present study.

Finally, although it is premature to attempt treatments based on these findings, the present result suggests an emerging possibility of interventions aimed at increasing activity at particular anatomical sites. If the present result withstands the tests of replicability and confirmation, a logical next step would be to attempt specific treatment approaches, both behavioural and pharmacological, aimed at enhancing cerebellar hemispheric function on the same side as the hemiparetic hand. By monitoring such therapy with brain imaging, a new science of stroke neurorehabilitation,

based on brain–behaviour relationships and quantifiable neurobiological outcomes, will be possible.

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Appendix 1: parcellation of anatomical areas

The anatomical parcellation of regions was accomplished according to standard techniques, using published landmarks. The hand area of M1 was centred on the knob of the precentral gyrus (Yousry *et al*., 1997) where M1 and S1 areas interdigitate (White *et al*., 1997). The lateral limit of this area was positioned at the point of intersection of the central sulcus and the precentral gyrus. The vertical centres of S1, lateral PM, SMA and pre-SMA were all defined to be in the same plane as M1. The horizontal centre of S1 was placed across the central sulcus from that of M1. The A/P limits of S1 were defined to include the area between the central and the postcentral sulci. The anterior limit of lateral PM and SMA proper were defined using a coronal plane perpendicular to the commissural line through the anterior commissure. The posterior limit of lateral PM was defined as the precentral sulcus. Posteriorly, SMA was limited by the paracentral lobule (Picard and Strick, 1996). The inferior limit was the cingulate sulcus. The cingulate motor area (CMA) was defined as the region on both banks of the cingulate sulcus, on the midline, inferior to SMA, the anterior limit at the level of the genu of the corpus callosum (Picard and Strick, 1996). The CRB was not parcellated further and was taken as a whole.