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Neural correlates of motor recovery after stroke: a longitudinal fMRI study

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Summary

Recovery of motor function after stroke may occur over weeks or months and is often attributed to cerebral reorganization. We have investigated the longitudinal relationship between recovery after stroke and task-related brain activation during a motor task as measured using functional MRI (fMRI). Eight first-ever stroke patients presenting with hemiparesis resulting from cerebral infarction sparing the primary motor cortex, and four control subjects were recruited. Subjects were scanned on a number of occasions whilst performing an isometric dynamic visually paced hand grip task. Recovery in the patient group was assessed using a battery of outcome measures at each time point. Task-related brain activations decreased over sessions as a function of recovery in a number of primary and non-primary motor regions in all patients, but no session effects were seen in the controls. Furthermore, consistent decreases across sessions correlating with recovery were seen across the whole patient group independent of rate of recovery or initial severity, in primary motor cortex, premotor and prefrontal cortex, supplementary motor areas, cingulate sulcus, temporal lobe, striate cortex, cerebellum, thalamus and basal ganglia. Although recovery-related increases were seen in different brain regions in four patients, there were no consistent effects across the group. These results further our understanding of the recovery process by demonstrating for the first time a clear temporal relationship between recovery and task-related activation of the motor system after stroke.

Keywords: stroke recovery; longitudinal functional MRI; motor system; neuronal plasticity

Abbreviations: ADL = activities of daily living; ARAT = Action Research Arm Test; BA = Brodmann area; BOLD = blood oxygen level dependent; EMG = electromyogram; EPI = echoplanar image; fMRI = functional MRI; M1 = primary motor cortex; MI = Motricity Index; MNI = Montreal Neurological Institute; MVC = maximum voluntary contraction; NHPT = nine hole peg test; OPSS = Orpington Prognostic Stroke Scale; SMA = supplementary motor area; SPM = statistical parametric mapping; VAS = visual analogue scale

Introduction

In those patients who survive stroke, there is invariably some degree of functional recovery, ranging from minimal to complete (Twitchell, 1951). In animals, there is evidence that this recovery is facilitated by neuronal reorganization (Schallert *et al*., 2000), but the tools available for studying the working human brain, such as functional imaging, are very different from those available in animals. Functional imaging studies of the motor system in previously hemiparetic patients have described task-related brain activation in recovered patients over and above control subjects in contralesional sensorimotor and premotor cortex, ipsilesional cerebellum, bilateral supplementary motor area (SMA) and parietal cortex (Chollet *et al*., 1991; Weiller *et al*., 1992, 1993; Cramer *et al*., 1997; Seitz *et al*., 1998). Recently, we have demonstrated that chronic stroke patients with less than full recovery are more likely to activate a number of primary and non-primary motor regions over and above the normal population, whereas in those with complete recovery, motor-related activation patterns indistinguishable from the normal population are seen (Ward *et al*., 2003). However, the dynamic process of changing brain activation patterns and the relationship of this process to recovery is less well understood. Two studies in which patients were scanned early after stroke, and then again some months later, demonstrated an initial increase followed by an overall reduction of task-related brain activation, but results were not correlated with

recovery (Marshall *et al*., 2000; Calautti *et al*., 2001a). Feydy *et al*. (2002) described differential evolution of motor-related activation in stroke patients depending on whether primary motor cortex (M1) was involved, but no relationship to recovery was found. Another study found no correlates of functional improvement outside of the ipsilateral cerebellum, in which increases in task-related activation were seen with recovery (Small *et al*., 2002). We postulated that by scanning patients at more frequent time points, particularly during periods of greatest behavioural change (i.e. early after stroke), and by obtaining detailed outcome measures relating to different aspects of the recovery process, we would be able to identify changes in motor-related brain activation patterns occurring not as a function of time after stroke, but as a function of recovery.

Methods

Subjects

Patients were recruited from the acute stroke and rehabilitation services at the National Hospital for Neurology and Neurosurgery, Queen Square, London. All patients had suffered from first-ever ischaemic stroke resulting in weakness of at least wrist and finger extensors, and hand interossei to ⩽4+ on the Medical Research Council scale, for at least 48 h after onset of symptoms. Exclusion criteria consisted of (i) carotid artery occlusion or stenosis ⩾70%; and (ii) language or cognitive deficits sufficient to impair cooperation in the study.

The age-matched control group was recruited from the volunteer database at the Wellcome Department of Imaging Neuroscience. They reported no history of neurological illness or psychiatric history and were not taking regular medication. Neurological and rheumatological examinations were normal in all control subjects.

All patients and control subjects were right handed according to the Edinburgh handedness scale (Oldfield, 1971). Full written consent was obtained from all subjects in accordance with the Declaration of Helsinki. The study was approved by the Joint Ethics Committee of the Institute of Neurology, UCL and National Hospital for Neurology and Neurosurgery, UCL Hospitals NHS Trust, London.

Behavioural evaluation

In addition to full neurological examination, all patients were scored on the following outcome measures on the same day as MRI: (i) Rankin disability scale; (ii) Barthel activities of daily living (ADL) index; (iii) Orpington Prognostic Stroke Scale (OPSS); (iv) Motricity Index (MI) for upper and (v) lower limbs; (vi) nine hole peg test (NHPT); (vii) grip strength; (viii) Action Research Arm Test (ARAT); and (ix) timed 10 m walk. In comparing these scores, the Rankin disability scale and OPSS were converted such that increasing scores reflected improvement, by subtracting the measured score from the maximum score possible for that scale. NHPT was performed by measuring the time to place nine pegs with each hand. If patients failed to place all nine pegs within 60 s, the number of pegs successfully placed was recorded. Scores were recorded as pegs per second for each hand (averaged over three trials). The score for the impaired hand was corrected within subject by dividing by the score for the unimpaired hand. Maximum grip strength was measured using the same manipulandum as for MRI scanning. The maximum of three trials was taken as the maximum grip strength for each hand. The score for the impaired hand was again corrected within subject by dividing by the score for the unimpaired hand (Sunderland *et al*., 1989).

Thus, for each patient, nine measures of recovery were recorded at each assessment, creating nine recovery curves (one each for Barthel, Rankin, OPSS, etc.) per patient. Each patient's set of recovery curves was normalized (giving unit variance and zero mean) and a principal component analysis was performed on the data set of each patient. The first principal component was taken as the representative recovery curve across sessions for each patient. This recovery curve was used to examine for correlations between task-related activations and recovery for each patient. This method has been used successfully to correlate overall recovery with task-related brain activations across subjects, in a group of chronic stroke patients (Ward *et al*., 2003).

Motor paradigm

Patients were first scanned at 10–14 days post-stroke onset, then weekly for at least the next 4 weeks. Subsequent scans were then carried out at least 3 and 6 months, and in some cases 12 months, post-stroke onset. Control subjects (two using the dominant hand and two using the non-dominant hand) were scanned at weekly intervals for 4 weeks, then again 2 and 5 months later. During scanning, subjects performed a dynamic isometric hand grip task using an MRI-compatible manipulandum as described previously (Ward and Frackowiak, 2003). Patients used their impaired hand. At each session, prior to scanning, but whilst lying in the scanner, subjects were asked to grip the manipulandum with maximum force to generate a maximum voluntary contraction (MVC). During a continuous scanning session, subjects performed paced isometric dynamic hand grips in blocks of 20 s, alternating with 20 s rest. A total of 10 blocks of hand grip, and 10 rest blocks were performed per session. Target forces and rates of hand grip were constant within each 20 s block, but were presented in two different forms within each session. In hand grip task A, the target force was 20% of MVC performed at 40% of the patient's maximum rate, as measured on the day of scanning. Thus, in a recovering patient, the absolute force generated per hand grip would increase in task A over sessions, but would remain at 20% of their MVC on that day. In hand grip task B, the target force was 40% of MVC performed at 40% of the patient's maximum rate as measured at the first session. Thus, in a

recovering patient, the absolute performance parameters (target force and rate) were unaltered in task B across sessions. Five blocks of each task A and task B were performed in each scanning session in a pseudorandomized counterbalanced order. Our primary interest was in task A, but task B was included in order to address the hypothesis that maintaining absolute task parameters across sessions will lead to over-estimation of session effects. Target forces during scanning were indicated by a horizontal target bar on the screen. The required rate of hand grip was indicated visually by a cross displayed at the bottom of the screen for 0.3 s at the appropriate rate. The appearance of the cross indicated that the subject was to perform a single brief hand grip, to be continued until the column representing force applied came into contact with the horizontal target bar on the screen, at which point the grip could be released. Subjects were asked specifically to attend to this continuous feedback. Prior to scanning, subjects were pre-trained until comfortable with the task.

All patients performed the motor task outside the scanner in order that they might be observed for the presence of associated movements or mirror movements. To aid this assessment, patients held two identical hand grip manipulanda, one in each hand, during the performance of repetitive hand grip with the affected hand. These simultaneous recordings from both hands enabled us to detect true mirror movements (Nelles *et al*., 1998). In addition, surface electromyogram (EMG) electrodes were positioned on biceps, triceps and latissimus dorsi bilaterally, to detect more proximal muscle activation.

Data acquisition

A Siemens VISION system (Siemens, Erlangen, Germany), operating at 2 T, was used to acquire both T_1-weighted anatomical images (1 × 1 × 1.5 mm voxels) and T_2*-weighted MRI transverse echoplanar images (EPIs) [64 × 64 3 × 3 mm^2 pixels, echo time (TE) = 40 ms] with blood oxygenation level-dependent (BOLD) contrast. Each EPI comprised forty-eight 1.8 mm thick contiguous axial slices taken every 3 mm, positioned to cover the whole cerebrum. A total of 116 volumes were acquired continuously during each session, with an effective repetition time (TR) of 3.649 s per volume. The first six volumes were discarded to allow for T_1 equilibration effects.

Image analysis

Imaging data were analysed using statistical parametric mapping (SPM99, Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/) (Friston *et al*., 1995*a*; Worsley and Friston, 1995) implemented in Matlab5 (The Mathworks Inc., USA). All volumes were realigned spatially to the first volume in order to correct for interscan movement. No subject moved more than 2 mm in any direction, but some of this movement was task related. In order to remove some of this unwanted movement-related variance without removing variance attributable to the motor task, realigned images were processed using the 'unwarp' toolbox in SPM99 (Andersson *et al*., 2001) which is predicated on the assumption that susceptibility × movement interaction is responsible for a sizeable part of residual movement-related variance. Given the observed variance (after realignment) and the realignment parameters, estimates of how deformations changed with subject movement were made, which subsequently were used to minimize movement-related variance.

To correct for their different acquisition times, the signal measured in each slice was shifted relative to the acquisition of the middle slice using sinc interpolation in time. For control subjects, resulting volumes were then normalized to a standard EPI template based on the Montreal Neurological Institute (MNI) reference brain in Talairach space (Talairach and Tournoux, 1988), and resampled to 3 × 3 × 3 mm^3 voxels. This normalization process may result in incorrect normalization (and therefore incorrect localization of activations) in brains with abnormal structure. In order to take account of this in our stroke patients, a mask of the lesion was created using MRIcro software (MRIcro, Nottingham University, http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). This mask was then incorporated into the normalization step for all patients (Brett *et al*., 2001). All normalized images were then smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel to allow valid statistical inference according to Gaussian random field theory (Friston *et al*., 1995*b*). The time series in each voxel were high pass filtered at 1/100 Hz to remove low frequency confounds and scaled to a grand mean of 100 over voxels and scans within each session.

Statistical analysis was performed in two stages. In the first stage, using a single subject fixed effects model, all hand grips were defined as a single event type, and modelled as delta functions. Hand grips during task A and hand grips during task B were included as separate covariates. These covariates were convolved with a canonical synthetic haemodynamic response function, and were used in a general linear model (Friston *et al*., 1995*a*) together with a single covariate representing the mean (constant) term over scans. The parameter estimates for each covariate resulting from the least mean squares fit of the model to the data were calculated, and statistical parametric maps of the *t* statistic (SPM{*t*}) resulting from linear contrasts of each covariate (Friston *et al*., 1995*a*) were generated and stored as separate images for each subject.

The first experimental question related to whether a correlation exists between the voxel-wise task-related changes in BOLD signal and the degree of recovery across sessions in each subject. This question was addressed using one multiple session fixed effects model per patient, employing the same covariates as described for single session analysis, with appropriate corrections made for non-sphericity (as the data for each session came from the same subject).

Table 1 *Patient characteristics*

Patient	Age (years)	Sex	Affected hand	Site of lesion	No. of fMRI sessions	PMH	Medication
1	53	F	L	R pons	6	Hypertension	Aspirin, metoprolol
2	56	M	L	R IC (posterior)	7	Nil	Aspirin
3	63	M	L	R IC (anterior)	7	Hypertension	Aspirin, atenolol, amlodipine, simvastatin
4	71	M	R	L pons	10	IHD, COPD	Aspirin
5	52	M	R	L corona radiata	6	Hypertension	Aspirin, atenolol, ramipril
6	60	M	L	R IC (posterior)	10	Hypertension	Aspirin, bendrofluazide
7	29	M	R	L pons	10	Nil	Aspirin
8	38	M	L	R striatocapsular region and insular cortex	8	Nil	Aspirin

M = male; F = female; R = right; L = left; IC = internal capsule; MCA = middle cerebral artery; NIDDM = non-insulin-dependent diabetes mellitus; IHD = ischaemic heart disease; COPD = chronic obstructive airways disease; PMH = past medical history.

We examined for voxels in which there is a linear correlation between the recovery score and the parameter estimates for the covariates representing the main effects of hand grip (task A or task B) across sessions. The specific contrasts across each covariate were weighted according to the mean corrected recovery scores (either positively or negatively) appropriate for each patient, in order to generate an appropriate SPM{*t*} representing a 'recovery map' [i.e. brain regions in which task-related activations correlate (either positively or negatively) with the degree of recovery across sessions] for each patient. For significant voxels, the correlation coefficient for the plot of parameter estimate against recovery for each subject, together with the corresponding *P* value, was calculated.

The second experimental question related to whether task-related activation in specific regions of the brain would correlate with recovery across subjects in a group analysis. This was addressed in a second stage of analysis, for which the data comprised the pooled parameter estimates for the specific linear combination of covariates representing the 'recovery maps' for each patient. For these group analyses, the images of patients with left-sided infarcts (right hand weakness) were flipped about the mid-sagittal line, such that all subjects were considered to have right-sided infarcts. Thus, contrast images for each subject were entered into a one-sample *t* test, and SPM{*t*}s generated.

The third experimental question concerned the direct comparison between 'recovery maps' for task A and task B. We contend that in a longitudinal study of this kind, the notion of maintaining the same motor task across sessions is best dealt with by maintaining %MVC as target force, rather than maintaining absolute force. Thus, using the same multiple session fixed effects models as above, a combination of weighted contrasts (derived from the mean corrected recovery scores) across covariates for task A and task B was used, representing the direct comparison of recovery-related changes in task-related brain activation across sessions for task A and task B. Previous attempts at characterizing longitudinal changes have often done so in terms of shifts in task-related activation between contralesional and ipsilesional sensorimotor and premotor cortices (Marshall *et al*., 2000; Feydy *et al*., 2002). Therefore, we limited our comparison of tasks A and B to these regions using a small volume correction. The regions of interest were defined as spheres of radius 20 mm centred on coordinates $x = \pm 38$, $y = -26$, $z = 56$, representing hand M1 (Fink *et al*., 1997).

In addition to the above questions, we were interested to see whether a correlation existed between task-related activation patterns and the degree of impairment in the post-acute phase, similar to the correlation we previously described in the chronic phase (Ward *et al*., 2003). For this analysis, a multi-subject single session (earliest session for each patient, i.e. 10–14 days post-stroke) fixed effects model was employed, using the same covariates as described for single subject analysis. We examined for voxels in which a linear correlation between severity of stroke scores and the parameter estimates for the covariates representing the main effects of hand grip across subjects existed. The specific contrast across the appropriate covariates was weighted according to a mean corrected severity score, which was generated using principal component analysis across subjects rather than within subjects as used above.

It was not possible to generate 'recovery maps' for the control subjects as no change in function occurred, but we were able to examine for session effects across each subject. These maps of session effects were generated using the same single subject, multi-session fixed effects model as described above, and examining for linear changes in task-related activation as a function of session for each subject. Only indirect comparisons could be made between patient's 'recovery maps' and control's 'session maps'.

The resulting SPM{*t*}s were thresholded at $P < 0.05$, corrected for multiple comparisons across whole brain. All SPM{*t*}s were transformed to the unit normal *Z*-distribution

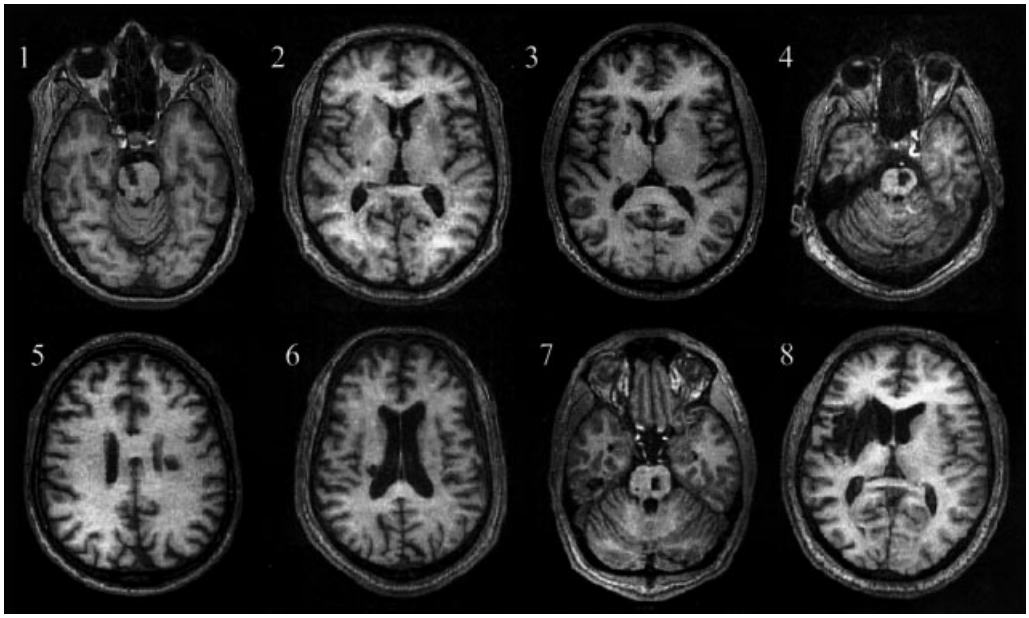

Fig. 1 Axial structural T_1-weighted MRI scans at the level of maximum infarct volume for each patient.

to create a statistical parametric map (SPM{*Z*}). All *t* tests carried out within SPM were one tailed.

Anatomical identification was carefully performed by superimposing the maxima of activation foci both on the MNI brain and on the normalized structural images of each subject, and labelling with the aid of the atlas of Duvernoy (1991).

Results

Clinical data

The control group were aged between 27 and 67 years (mean age 47.3 years), and comprised two male and two female subjects. Eight stroke patients were recruited (range 29–71 years, mean age 52.8 years). Patient characteristics are listed in Table 1. Patients attended for between six and 10 sessions (mean 8), and controls attended for six sessions each. The site of cerebral infarction was determined from the T_1-weighted structural MRI (Fig. 1). Five patients had right-sided infarcts, three had left-sided infarcts. Three patients had infarcts isolated to the internal capsule (two posterior, one anterior), one patient had an infarct in the corona radiata, three patients had pontine infarcts and one patient had an infarct in the striatocapsular region with extension to the insular cortex, as a result of a branch middle cerebral artery occlusion. No patient had damage to M1. Incomplete sensory deficit, described as a slight reduction in sensation compared with the unaffected side, was detected in two patients.

All patients received both in-patient and out-patient post-stroke rehabilitation therapy appropriate to their clinical needs. The outcome measures demonstrated improvement in performance in all patients (Table 2). The first principal component of each patient's set of recovery curves accounted for between 78.2 and 90.5% of the variance within each data set (Table 2), and were taken as the overall patient-specific recovery curves for the purposes of correlation analysis (Fig. 2).

Behavioural results

All controls and patients were able to perform the task adequately. No patients displayed mirror movements at bedside observation. When performing the motor paradigm outside the scanner, there was no evidence of mirror movements or surface EMG activity in biceps, triceps or latissimus dorsi muscles on the side opposite the affected hand. However, patients 1 and 2 did exhibit synergistic wrist flexion, but not elbow flexion, nor shoulder adduction during rehearsal of the motor paradigm at sessions 1 and 2. A 100 mm visual analogue scale (VAS) (where 0 = 'no effort' and 100 = 'maximum effort') was completed by patients after practising task A (target grip force set at 20% of MVC on day of scanning) prior to each scanning session, and suggested no significant differences existed in the perceived effortfulness of the task across sessions. There was no correlation between the rating for effort and the overall recovery score for each patient (Table 2).

Changes in motor-related brain activation as a function of recovery

The neural correlates of this hand grip task were not examined explicitly in the current study, but have been described in previous studies, together with relative differences in activation patterns in older subjects (Ward and

Table 2 *Early and late outcome scores for stroke patients*

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Average contribution of each measure to first principal component [mean (SD)]
	Early (11)	Late (200)	Early (10)	Late (197)	Early (9)	Late (207)	Early (14)	Late (174)	Early (14)	Late (193)	Early (10)	Late (191)	Early (13)	Late (370)	Early (10)	Late (312)	
Barthel	12	20	19	20	19	20	12	20	19	20	18	20	11	20	14	20	11.4% (0.4)
Rankin	3	1	2	1	2	1	4	2	2	1	4	1	4	1	4	1	11.4% (0.3)
Orpington Prognostic Stroke Scale	2.4	1.6	2	1.6	2	1.6	3.2	2	2	1.6	2.4	1.6	3.6	1.6	2.8	1.6	11.3% (0.7)
Action Research Arm Test	33	57	56	57	56	57	53	57	56	57	54	57	13	57	28	57	10.6% (1.4)
Grip strength (% unaffected side)	41.2	88.6	48.1	101.2	71.3	93.1	47.9	98.7	91.8	103.3	71.3	104.9	3.2	100.9	49.1	106.9	10.6% (1.1)
Motricity Index—upper limb	67	100	93	100	93	100	72	92	93	100	77	100	62	100	73	100	11.1% (0.7)
Motricity Index—lower limb	73	100	92	100	92	100	64	92	92	100	73	100	40	100	92	100	11.4% (0.3)
Nine Hole Peg Test (% unaffected side)	3.8	74.3	35.9	75.4	62.7	108.2	30.1	86.7	90.3	102.8	29.9	78.7	0	78.1	0	67.1	11.0% (1.1)
10 m walk (m/s)	0.45	1.33	0.4	1.4	1.01	1.6	0	1.15	1.95	2.25	0	1.02	0	1.68	0	1.4	11.2% (0.6)
Sensory loss	No	No	Face/hand	Hand	No	No	No	No	No	No	Hand	Hand	No	No	No	No	
Neglect*	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	
Mirror movements	None	None	None	None	None	None	None	None	None	None	None	None	None	None	None	None	
% variance explained by first principal component†	87.50%		83.30%		87.40%		78.50%		78.20%		84.30%		90.50%		83.60%		
Correlation between VAS score for effort and overall recovery scores‡	$r^2 = 0.07$ P = NS		$r^2 = 0.11$	P = NS	$r^2 = 0.04$	P = NS	$r^2 = 0.21$	P = NS	$r^2 = 0.02$	P = NS	$r^2 = 0.06$	P = NS	$r^2 = 0.02$	P = NS	$r^2 = 0.16$	P = NS	

Outcome scores for earliest and latest study sessions (days post-stroke onset given in parentheses). *Detected by line bisection and cancellation tasks. †The first principal component of the whole data set of outcome scores for each patient was taken as the set of overall recovery scores for that patient. The amount of variance in the original data set explained by the first principal component is given in this row. ‡Correlation between VAS score for effort exerted during task A and overall recovery score obtained by principal component analysis across all sessions.

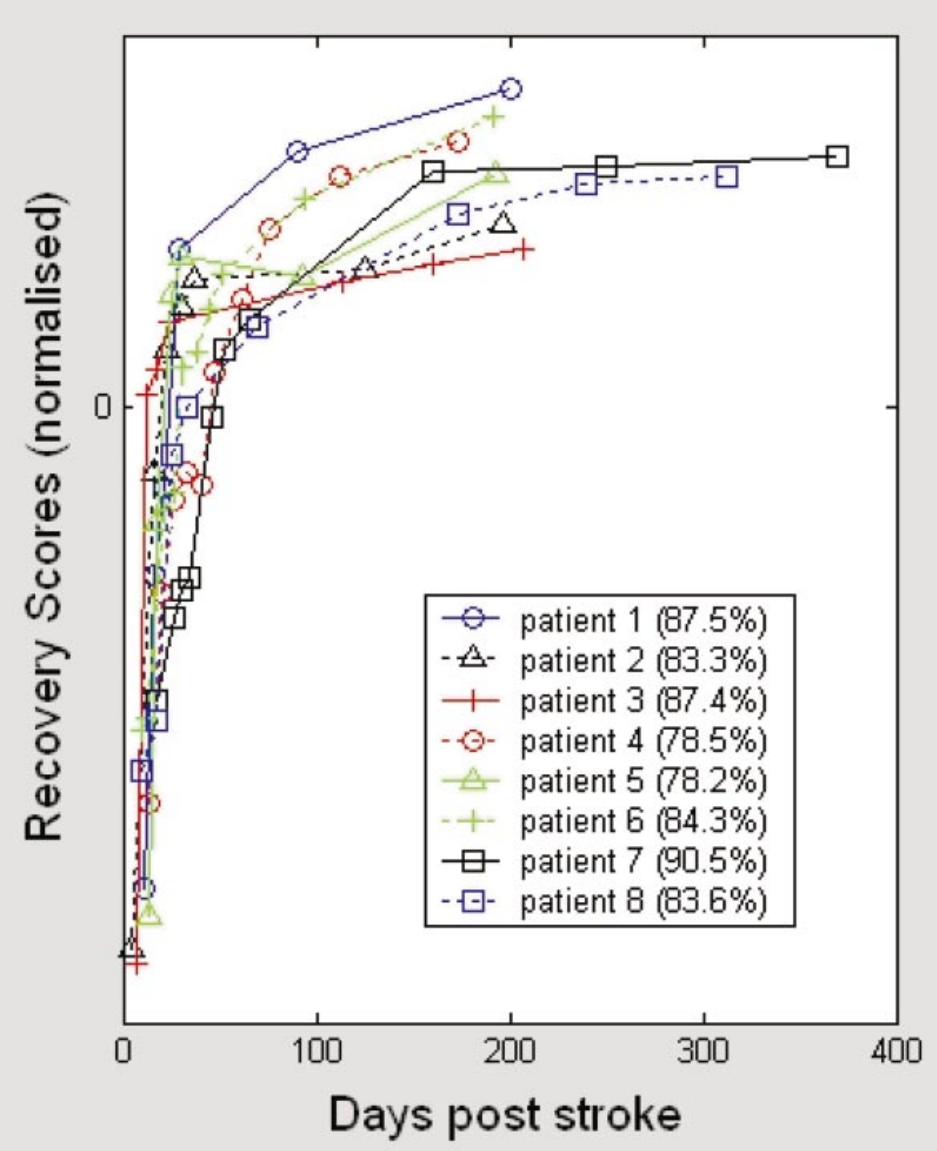

Fig. 2 Plots of normalized overall recovery scores for each patient across sessions. Each patient had nine separate performance scores recorded at each fMRI session (Rankin, Barthel, OPSS, etc.), creating nine recovery curves per patient. The overall recovery score represents the first principal component of a principal component analysis of these nine recovery curves. The amount of variance in the original data set explained by the first principal component is given in parentheses. There is no scale on the *y*-axis because the scores are normalized, and have no meaningful absolute value, only relative value, within subject.

Frackowiak, 2003) and chronic stroke patients (Ward *et al*., 2003).

We were interested primarily in the 'recovery maps' for task A, which will now be described. Brain regions will be described as either ipsilesional (i.e. contralateral to the moving hand) or contralesional. A negative correlation between task-related increases in brain activation and recovery across sessions (i.e. recovery-related decreases in task-related activations) was seen in a number of brain regions in all eight patients (Fig. 3 and Table 3), and was particularly common in motor-related regions, in particular ipsilesional M1 (five patients), contralesional M1 (four patients), dorsal and ventral premotor cortex (seven and five patients, respectively), SMA (six patients), cingulate motor regions (four patients) and cerebellum (seven patients). In addition, recovery-related decreases were observed in both inferior and superior parietal cortex, as well as intraparietal sulcus (seven patients) and prefrontal regions (six patients). Brain activations in both temporal and occipital lobe have been observed with this hand grip task (Ward and Frackowiak, 2003) and, interestingly, task-related activity in these regions also decreased with recovery in some subjects, as well as in subcortical structures such as thalamus and basal ganglia structures. In the group analysis, recovery-related decreases in task-related activation across sessions were seen throughout ipsilesional M1, from z = 36 to 52, and in inferior

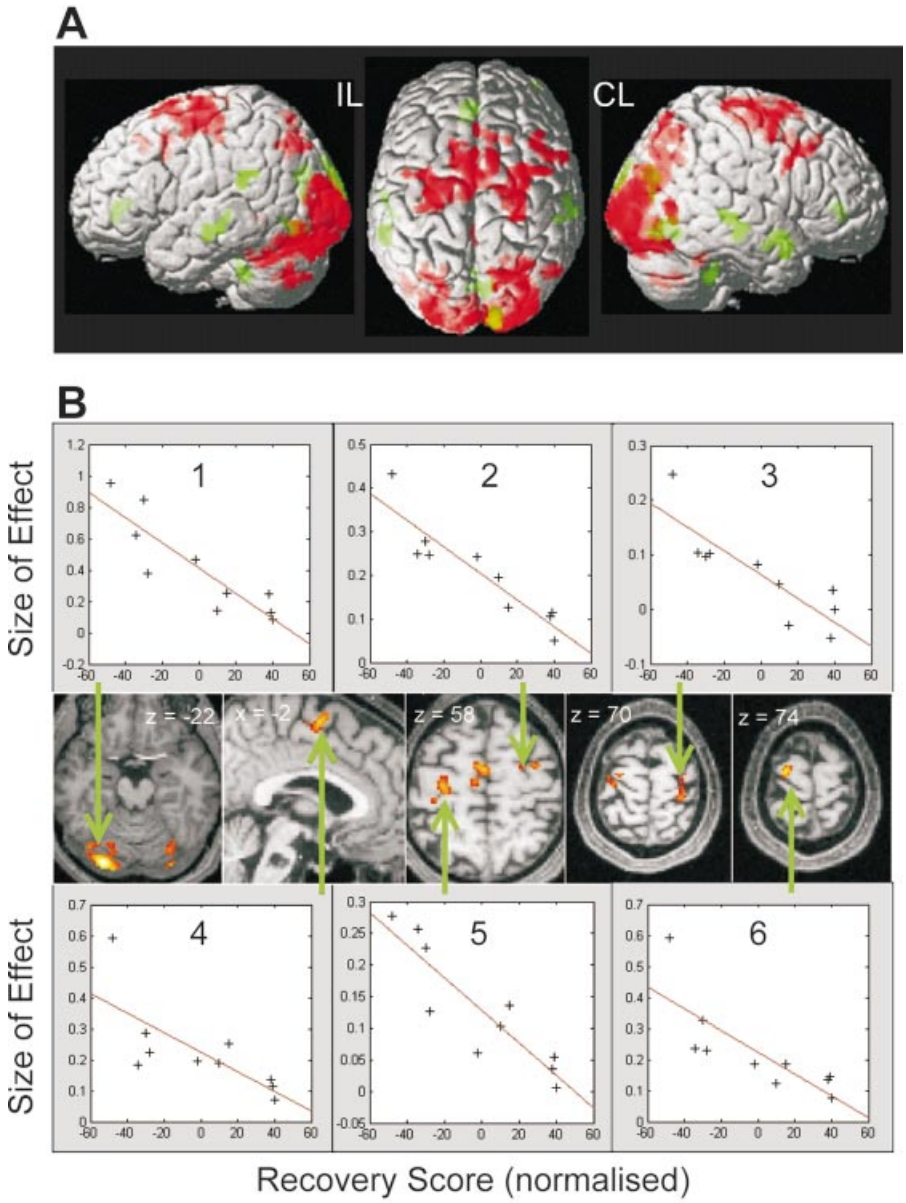

Fig. 3 Results of single subject (patient 7) longitudinal analysis examining for linear changes in task-related brain activations over sessions as a function of recovery. Patient 7 suffered from a left-sided pontine infarct resulting in right hemiparesis. (**A**) Results are surface rendered onto a canonical brain; red areas represent recovery-related decreases in task-related activation across sessions, and green areas represent the equivalent recovery-related increases. All voxels are significant at $P < 0.001$ (uncorrected for multiple comparisons) for display purposes. The brain is shown (from left to right) from the left (ipsilesional, IL) side, from above (left hemisphere on the left), and from the right (contralesional, CL). (**B**) Results are displayed on patient's own normalized T_1-weighted anatomical images (voxels significant at $P < 0.05$, corrected for multiple comparisons across the whole brain), with corresponding plots of size of effect against overall recovery score (normalized), for selected brain regions. Coordinates of peak voxel in each region are followed by the correlation coefficient and the associated P value: (1) ipsilesional cerebellum ($x = –26$, $y = –84$, $z = –22$) ($r^2 = 0.77$, $P < 0.01$), (2) contralesional dorsolateral premotor cortex ($x = 38$, $y = 0$, $z = 58$) ($r^2 = 0.85$, $P < 0.01$), (3) contralesional M1 ($x = 28$, $y = –14$, $z = 70$) ($r^2 = 0.74$, $P < 0.01$), (4) ipsilesional SMA ($x = –2$, $y = –2$, $z = 60$) ($r^2 = 0.53$, $P = 0.02$), (5) ipsilesional M1 ($x = –30$, $y = –14$, $z = 58$) ($r^2 = 0.80$, $P < 0.01$), (6) contralesional dorsolateral premotor cortex ($x = –18$, $y = –10$, $z = 74$) ($r^2 = 0.63$, $P = 0.01$).

contralesional M1, as well as in anterior and posterior dorsolateral premotor cortex bilaterally [Brodmann area (BA) 6 and BA 8], contralesional ventrolateral premotor cortex, and ipsilesional SMA-proper, pre-SMA, prefrontal cortex (superior frontal sulcus) and caudal cingulate sulcus (Fig. 4 and Table 4). In addition, these decreases were also seen in parietal, temporal and occipital lobes, as well as thalamus and globus pallidus.

A positive correlation between task-related activation and recovery across sessions (i.e. recovery-related increases in

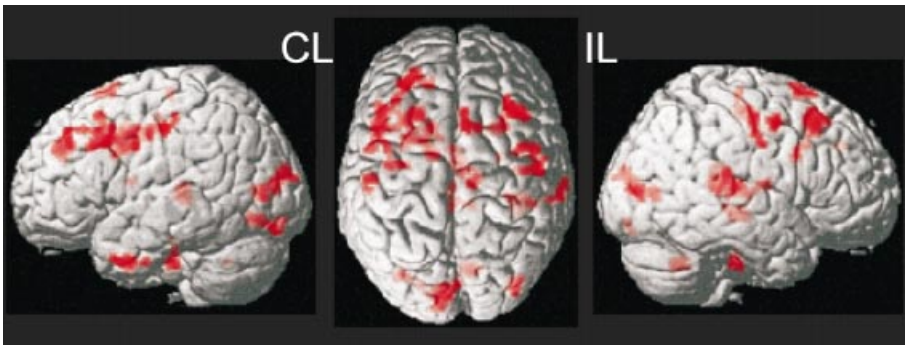

Fig. 4 Group 'recovery map': brain regions in which linear reductions in task-related activation across sessions as a function of recovery were consistently detected for the whole group. This represents the random effects group analysis, in which the data representing the individual 'recovery maps' were pooled across all subjects. Images for patients with left-sided lesions were flipped about the mid-sagittal line, so that all patients were assumed to have a lesion on the right side, with initial left hand weakness. Results are surface rendered onto a canonical brain. The brain is shown (from left to right) from the left (contralesional, CL) side, from above (left hemisphere on the left), and from the right (ipsilesional, IL). All clusters are significant at $P < 0.05$, corrected for multiple comparisons across whole brain.

task-related activations) was seen in some brain regions in four patients [with lesions involving pons (two), anterior internal capsule and corona radiata]. No such increases were seen in the other four patients with lesions involving either posterior internal capsule (two), pons or striatocapsular region with extension to the insular cortex. The severity of deficit at presentation was matched between these two groups. A number of regions demonstrated these recovery-related increases in task-related activations across sessions (Table 3), including ipsilesional ventrolateral premotor cortex and anterior cingulate cortex, and cerebellum (in two patients each). Three patients demonstrated increases in ipsilesional superior temporal sulcus in the mid to posterior segment. In the group analysis, no brain regions demonstrated a significant recovery-related increase in activation, suggesting the lack of a consistent pattern across patients.

Comparison of constant effort or constant force across sessions

This comparison was made only in patients in whom the initial affected grip force was <50% of the final affected grip force, in order to ensure significant differences between target forces used in tasks A (constant effort) and B (constant force and rate). Five patients fulfilled this criterion (Table 2).

The direct comparison of recovery-related decreases in task-related activations across sessions for task A and those for task B revealed significant voxels which showed greater recovery-related decreases across sessions in ipsilesional sensorimotor cortex (three out of five patients, $P < 0.05$ corrected for multiple comparisons) and contralesional sensorimotor cortex (two out of five patients, $P < 0.05$ corrected for multiple comparisons), for the comparison task B versus task A, but no significant voxels for the comparison task A versus task B. This result indicates that decreases in sensorimotor cortex activation across sessions as a function of recovery are more likely to be seen if the absolute target force is maintained across sessions despite improving function.

Correlation between early task-related activations and initial severity across all patients

A correlation analysis was performed between task-related activation at the first scanning session and an overall measure of initial severity. This measure was obtained by performing a principal component analysis of all nine sets of outcome scores for each patient (first principal component, 77.7% of variance). A significant negative linear correlation between task-related activation and early performance levels was observed in several regions (Table 5). Thus, in the post-acute phase, patients with more severe strokes are more likely to activate a number of brain regions during the hand grip task. These include bilateral M1, postcentral sulcus, premotor cortex, superior temporal sulcus and cerebellum, contralesional postcentral gyrus, SMA, pre-SMA, rostral cingulate sulcus, parietal cortex and cerebellar vermis. In addition, this negative correlation was seen in bilateral striate cortex and contralesional middle occipital lobe (close to area V5), and also in the deep structures bilateral thalamus and ipsilesional globus pallidus.

A significant positive correlation between task-related activation and early performance levels was observed in ipsilesional anterior superior temporal sulcus, contralesional inferior parietal cortex and head of caudate (Table 5).

Comparison with normal subjects

None of the four control subjects demonstrated linear increases or decreases in task-related activation across sessions at a threshold of $P < 0.05$ (either voxel or cluster), corrected for multiple comparisons across whole brain.

Table 3 (A) *Single subject analysis (patients 2, 3, 5 and 6): regions in which activations correlate linearly with recovery*

Region	Patient 2							Patient 3							Patient 5							Patient 6						
	Side	Talairach coordinates in MNI space			Z–value	Correlation analysis		Side	Talairach coordinates in MNI space			Z–value	Correlation analysis		Side	Talairach coordinates in MNI space			Z–value	Correlation analysis		Side	Talairach coordinates in MNI space			Z–value	Correlation analysis	
		x	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value
Negative correlation																												
Central sulcus (M1)	I	36	–22	60	4.99	0.8	<0.01	I	58	–12	44	6.99	0.9	<0.01	I	–18	–28	66	4.33*	0.6	0.05	I	40	–22	66	>8.0	0.8	0.01
	I	50	–16	58	4.81	0.7	0.03	C	–58	–8	44	>8.0	0.8	0.01	C	20	–26	72	5.75	0.6	0.04	I	40	–28	52	6.75	1	<0.01
PMd	I	54	0	50	6.49	0.7	0.03	I	18	–14	78	6.68	0.7	0.02								I	38	16	54	5.22	0.6	0.05
Anterior PMd (BA 6/8)								C	–46	14	50	5.96	0.9	<0.01	I	–26	16	44	6.36	0.6	0.05							
								C	–16	8	68	5.73	0.7	0.02	C	22	20	62	6.26	0.9	<0.01							
Caudal PMv								I	52	4	28	5.37	0.7	0.01	I	–52	–6	16	4.42*	0.7	0.05	I	58	0	18	4.21*	0.8	0.01
								C	–48	12	34	6.31	0.9	<0.01														
								C	–50	–2	28	5.02	0.6	0.05														
Rostral PMv (BA 44)	I	50	16	14	4.88	0.6	0.03																					
SMA	I	6	0	62	5.84	0.7	0.01	C	–8	–4	72	6.17	0.8	<0.01	I	–4	–18	64	4.45*	0.7	0.04							
Pre–SMA	I	10	14	64	5.79	0.6	0.03																					
	C	–6	8	60	5.01	0.7	0.03																					
Cingulate sulcus	I	12	16	42	5.52	0.6	0.04	C	–6	30	24	7.11	0.9	<0.01														
								C	–12	–18	44	6.19	0.8	0.01														
Anterior cingulate gyrus								I	8	12	26	6.81	0.8	0.01														
Inferior parietal cortex	I	62	–26	44	5.65	0.9	<0.01	I	58	–32	48	6.89	0.9	<0.01	I	–50	–68	38	5.07	0.8	0.02	C	–34	–68	34	3.80*	0.6	0.05
	I	50	–62	44	4.97	0.9	<0.01	C	–48	–68	34	<8.0	0.9	<0.01														
	C	–52	–20	38	4.82	0.7	0.02	C	–58	–42	48	7.54	0.9	<0.01														
Intraparietal sulcus	I	46	–42	44	5.51	0.8	<0.01	I	28	–68	56	7.39	0.9	<0.01								I	28	–68	50	6.97	0.8	0.01
	C	–34	–42	56	5.95	0.9	<0.01																					
Superior parietal cortex								I	14	–78	48	7.02	0.9	<0.01								I	36	–40	66	5.73	0.8	0.01
								C	–16	–78	48	<8.0	0.9	<0.01														
								C	–10	–56	72	5.32	0.9	<0.01														
Superior temporal gyrus								C	–50	20	–14	6.66	0.9	0.01								C	–66	–24	10	4.92	0.9	<0.01
Superior temporal sulcus								I	60	–56	14	6.76	0.8	0.01	C	36	–50	26	5.51	0.8	0.02							
								C	–58	–42	8	7.59	1	<0.01														
Insula	I	42	–4	–10	4.79	0.8	<0.01															I	40	0	2	4.56*	0.9	0.01
Parietal operculum (S II)	I	60	–18	26	6.17	0.8	<0.01	I	58	–26	16	5.99	0.9	<0.01	C	52	–32	20	5.49	0.8	0.02							
								C	–54	–28	22	6.01	0.8	0.01														

Table 3A *Continued*

Region	Patient 2							Patient 3							Patient 5							Patient 6						
	Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis		Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis		Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis		Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis	
		x	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value
Prefrontal cortex	I	46	54	8	6.82	0.6	0.03	I	40	42	28	5.83	0.7	0.01														
	I	56	22	36	6.2	0.6	0.04	C	–42	32	36	> 8.0	0.9	<0.01														
	I	54	24	0	7.09	0.8	0.01	C	–54	28	20	6.51	0.9	<0.01														
	C	–52	38	18	5.05	0.7	0.05																					
Striate cortex	I	18	–84	12	5.16	0.8	<0.01	I	10	–62	16	6.76	0.9	<0.01	I	–12	–70	10	5.62	0.6	0.05	I	10	–72	–10	5.32	0.9	<0.01
								C	–6	–72	12	6.54	0.9	<0.01	C	24	–70	10	5.54	0.6	0.05							
Middle occipital gyrus	I	28	–96	6	>8.0	0.9	<0.01	I	50	–78	10	5.57	0.9	<0.01								I	32	–92	4	6.32	0.8	0.02
	C	–24	–94	20	6.13	0.9	<0.01	C	–36	–74	16	7.39	0.9	<0.01								C	–34	–76	10	5.19	0.9	0.01
Cerebellum	I–VIIIA	26	–38	–48	5.41	0.7	0.02	I–VIIIB	30	–40	–44	7.53	0.9	<0.01								I–VI	20	–58	–24	5.76	0.8	0.02
	I–V	12	–56	–10	5.02	0.6	0.04	I–CrI	28	–78	–32	6.06	1	<0.01								C–VI	–22	–66	–20	6.16	0.8	0.01
								C–CrI	–30	–88	–20	6.36	1	<0.01								C–CrI	–24	–72	–30	5.03	0.7	0.04
								C–CrI	–48	–66	–36	5.68	0.8	<0.01														
Cerebellar vermis	VIIB	4	–72	–26	5.36	0.9	<0.01	VIIIA	–2	–64	–32	5.14	0.6	0.04	V	–4	–60	0	5.43	0.8	0.02	VI	0	–62	–28	4.93	0.8	0.01
Thalamus								I	6	–2	2	7.67	0.9	<0.01														
								I	6	–22	4	6.21	0.8	<0.01														
								C	–16	–16	16	6.11	0.8	<0.01														
Caudate								I	12	20	2	4.93	0.7	0.01	C	18	6	16	4.64*	0.9	<0.01							
								C	–14	6	18	5.88	0.7	0.02														
Globus pallidus								I	18	8	–8	5.94	0.8	0.01														
Positive correlation																												
PMd								C	–18	–10	76	7.18	0.9	<0.01														
PMv															I	–42	32	42	5.11	0.9	0.01							
Superior parietal cortex								C	–22	–50	58	> 8.0	0.9	<0.01														
Intraparietal sulcus															I	–26	–68	38	5.25	0.8	0.02							
Superior temporal sulcus								I	54	–24	–2	6.64	0.8	<0.01														
								C	–64	–20	–2	5.54	0.6	0.03														
Cerebellum															C–V	22	–50	–24	4.87	0.9	<0.01							

Regions in which there is a correlation between recovery score and task-related activation across all sessions for patients with internal capsule (patients 2, 3 and 6) or corona radiata (patient 5) infarcts. Voxels significant at $P < 0.05$, corrected for multiple comparisons across whole brain volume. *Coordinates represent peak voxels within a significant cluster ($P < 0.05$, corrected for multiple comparisons across whole brain volume). The correlation coefficient (r^2) and corresponding *P* value for the correlation analysis are also given. I = ipsilesional; C = contralesional; M = midline; PMd = dorsolateral premotor cortex; PMv = ventrolateral premotor cortex; SMA = supplementary motor area. Roman numerals for cerebellar activations refer to cerebellar lobules (Schmahmann *et al*., 1999).

Table 3 (B) *Single subject analysis (patients 1, 4, 7 and 8): regions in which activations correlate linearly with recovery*

Region	Patient 1							Patient 4							Patient 7							Patient 8						
	Side	Talairach coordinates in MNI space			Z–value	Correlation analysis		Side	Talairach coordinates in MNI space			Z–value	Correlation analysis		Side	Talairach coordinates in MNI space			Z–value	Correlation analysis		Side	Talairach coordinates in MNI space			Z–value	Correlation analysis	
		x	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value
Negative correlation																												
Central sulcus (M1)															I	–30	–14	58	5.6	0.8	<0.01	I	22	–34	60	7.19	0.7	0.01
															C	28	–14	70	5.25	0.7	<0.01	I	44	–14	58	6.95	0.9	<0.01
																						C	–40	–26	60	7.7	0.7	0.01
PMd								C	42	0	58	6.18	0.8	<0.01	I	–18	–10	74	6.88	0.6	0.01	I	38	–6	64	5.63	0.9	<0.01
								I	–28	–20	70	5.49	0.6	0.01	I	–28	–8	68	5.14	0.6	0.01	I	24	0	66	5.62	0.9	<0.01
															C	32	–10	68	4.96	0.7	<0.01	C	–26	–12	68	6.16	0.9	<0.01
															C	38	0	58	5.02	0.9	<0.01							
Anterior PMd (BA 6/8)								C	24	14	68	5.34	0.5	0.02								I	50	24	42	5	0.8	<0.01
Caudal PMv															C	48	10	34	4.45*	0.8	<0.01	I	42	–2	40	6.76	0.7	0.01
																						C	–52	10	34	5.39	0.8	<0.01
Rostral PMv (BA 44)								C	58	12	4	5.16	0.5	0.03														
SMA								C	10	–2	56	5.11	0.5	0.04	I	–2	–2	60	6.12	0.5	0.02	I	6	–10	70	>8.0	0.7	0.01
															I	–6	–12	58	5.03	0.9	<0.01	C	–2	–18	64	>8.0	0.8	<0.01
								C	8	12	68	4.94	0.7	<0.01	C/I	0	10	48	4.50*	0.5	0.03	I	4	22	52	6.53	0.5	0.04
Cingulate sulcus								I	–10	0	46	5.22	0.5	0.03								I	8	0	44	7.7	0.7	0.01
																						C	–8	–12	42	5.61	0.6	0.02
Anterior cingulate gyrus	I	14	54	–4	5.31	1	<0.01																					
Inferior parietal cortex																						I	38	–62	48	7.91	0.9	<0.01
Intraparietal sulcus								C	32	–44	42	5.01	0.5	0.03	C	30	–74	38	6.14	0.7	<0.01	C	–54	–40	42	6.85	0.9	<0.01
															I	–24	–74	42	4.50*	0.4	0.05	I	44	–50	56	7.35	0.9	<0.01
Superior parietal cortex								I	–30	–56	66	5.12	0.7	0.01	C	18	–70	60	4.58*	0.5	0.02	C	–20	–74	52	>8.0	0.9	<0.01
								C	36	–64	58	4.83	0.6	0.01								I	20	–76	52	>8.0	0.9	<0.01
Superior temporal gyrus																						C	–56	6	–6	6.63	0.7	0.01
Superior temporal sulcus																						I	62	–6	–16	5.37	0.6	0.02
Insula	C	–32	12	–14	4.18*	0.9	0.02	C	42	18	–2	5.21	0.5	0.02								C	–36	–6	–6	5.07	0.7	0.01
Frontal operculum															C	68	–10	14	5.25	0.5	0.02	C	–64	–32	20	7.62	0.9	<0.01
Prefrontal cortex	C	–42	34	22	5.35	0.8	0.03	C	42	52	20	5.29	0.6	0.01	I	–38	58	–10	5.05	0.5	0.02	I	38	50	22	>8.0	0.8	<0.01
								I	–34	48	28	5.41	0.7	<0.01								C	–34	48	32	6.12	0.7	0.01
																						C	–32	28	6	7.2	0.9	<0.01
Middle occipital gyrus															C	48	–66	4	6.6	0.8	<0.01							
Cerebellum	I–CrI	50	–52	–36	6.13	0.8	0.05								I–CrI	–26	–84	–22	> 8.0	0.8	<0.01	I–VI	12	–86	–22	>8.0	0.9	<0.01
	I–CrII	48	–48	–44	4.97	1	<0.01								I–VI	–20	–66	–18	6.05	0.8	<0.01	C–VI	–16	–72	–18	>8.0	0.8	<0.01
Cerebellar vermis															VI	–2	–44	–2	5.32	0.8	<0.01	VIIIB	0	–72	–42	> 8.0	0.9	<0.01
															VIIIB	0	–70	–46	4.79*	0.6	0.01							
Thalamus								I	–10	–14	8	5.78	0.5	0.02														
Caudate	I	16	20	–6	6.04	0.8	0.03																					
Putamen	I	22	4	–10	4.83*	0.8	0.03																					
Positive correlation																												
M1	I	46	–18	40	5.87	0.8	0.04																					
Caudal PMv	I	52	6	40	5.06	0.8	0.03																					
Parietal operculum (SII)	I	58	–26	26	4.98	1	<0.01																					

Table 3B *Continued*

Region	Patient 1							Patient 4							Patient 7							Patient 8						
	Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis		Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis		Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis		Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis	
		x	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value		*x*	*y*	*z*		r^2	*P* value
Rolandic operculum	I	60	–6	16	5.2	0.8	0.05																					
Superior temporal sulcus	I	58	–20	–8	6.09	0.8	0.03								I	–64	–40	6	6.39	0.8	<0.01							
															I	–52	–18	4	5.64	0.5	0.03							
Prefrontal cortex															C	36	54	24	5.8	0.7	<0.01							
															C	46	20	52	5.23	0.5	0.03							
Anterior cingulate gyrus	C	–10	14	30	4.64*	0.8	0.04								I	–2	42	4	5.09	0.5	0.02							
Cerebellum	I–CrII	42	–60	–44	4.56*	0.8	0.03																					
	C–CrII	–24	–40	–44	5.48	0.8	0.04																					
Thalamus	I	16	–14	0	4.51*	1	<0.01																					
	C	–14	–14	0	4.41*	1	<0.01																					

Regions in which there is a correlation between recovery score and task-related activation across all sessions for patients with pontine infarcts (patients 1, 4 and 7) and a patient with middle cerebral artery territory infarct (patient 8). Voxels significant at $P < 0.05$, corrected for multiple comparisons across whole brain volume. *Coordinates represent peak voxels within a significant cluster ($P < 0.05$, corrected for multiple comparisons across whole brain volume). The correlation coefficient (r^2) and corresponding *P* value for the correlation analysis are also given. I = ipsilesional; C = contralesional; M = midline; PMd = dorsolateral premotor cortex; PMv = ventrolateral premotor cortex; SMA = supplementary motor area. Roman numerals for cerebellar activations refer to cerebellar lobules (Schmahmann *et al*., 1999).

Table 4 *Group analysis: regions in which activations correlate linearly with recovery*

Region	Side	Talairach coordinates in MNI space			*Z*–value
		x	*y*	*z*	
Negative correlation					
Central sulcus (M1)	I	44	–14	42	3.88
	I	52	–10	36	3.75
	I	50	–12	52	3.57
	C	–42	–10	42	3.82
PMd	I	48	–6	50	4.18
	C	–42	0	42	3.97
Anterior PMd (BA 6/8)	I	32	24	50	4.76
	C	–20	20	50	4.21
Caudal PMv	C	–46	14	38	4.05
SMA	I	8	–22	66	3.85
Pre-SMA	I	6	12	66	4.31
Cingulate sulcus	I	4	–16	50	3.33
Prefrontal cortex	C	–24	42	32	4.01
Inferior parietal cortex (BA 40)	C	–54	–22	44	5.15*
Intraparietal sulcus	I	30	–50	50	4.23
Superior temporal gyrus	I	64	–24	8	4.19
Middle temporal gyrus	C	–50	8	–34	4.17
Striate cortex	I	6	–74	8	4.25
Middle occipital gyrus	I	36	–84	6	3.91
	C	–32	–78	4	3.84
Cerebellum	I	8	–62	–36	3.64
Thalamus	C	–2	–6	12	4.19
Putamen/globus pallidum	I	24	–8	12	4.08
Positive correlation					
No significant voxels					

Group analysis demonstrating regions in which there is a correlation between recovery and task-related activation for all patients. Images for patients with left-sided lesions were flipped about the mid-sagital line, so that all patients were assumed to have a lesion on the right side, with initial left hand weakness. Coordinates represent peak voxels within a significant cluster ($P < 0.05$, corrected for multiple comparisons across whole brain volume). *Voxels significant at $P < 0.05$, corrected for multiple comparisons across whole brain volume. I = ipsilesional; C = contralesional; M1 = primary motor cortex; PMd = dorsolateral premotor cortex; PMv = ventrolateral premotor cortex; SMA = supplementary motor area. Roman numerals for cerebellar activations refer to cerebellar lobules (Schmahmann *et al*., 1999).

Discussion

We have demonstrated for the first time that there is a clear relationship between changes in motor-related brain activation and changes in performance parameters over time in patients who have suffered from ischaemic hemiparetic stroke sparing M1. After stroke, there is an early and widespread recruitment of brain regions during motor performance, followed by a progressive reduction in this task-related recruitment over sessions that correlates with recovery scores in individual patients. This process occurs primarily in motor-related regions, in particular involving bilateral sensorimotor cortex, premotor cortex, SMA, cingulate motor areas, cerebellum, basal ganglia and thalamus, but also in parietal cortex, prefrontal cortex, and striate and extrastriate cortex. Progressive increases in task-related activation were seen in different brain regions as a function of recovery in half of our patients, but there were no consistent effects across the group. Such 'focusing' of brain activation has been reported before (Marshall *et al*., 2000; Calautti *et al*., 2001a; Feydy *et al*., 2002), but has never been described in relation to both the recovery process and the specific brain regions in which it occurs. A number of processes may contribute to this observation, and these will be discussed.

Patient selection

Although no stroke type was actively excluded on anatomical grounds, there are clearly sources of bias in our patient selection. None of our patients had significant language or other cognitive deficit, because of the need to understand the experimental instructions. Furthermore, all patients had regained at least some ability to grip with the affected hand by 10–14 days post-stroke. As a result, our cohort consists largely of patients with subcortical infarcts, and none had infarcts involving the hand region of M1. Thus our results pertain only to such patients, and are not directly applicable to

Table 5 *Correlation between early outcome scores and task related brain activation after stroke*

Region	Side	Talairach coordinates in MNI space			*Z*–value	Correlation analysis	
		x	*y*	*z*		r^2	*P* value
Negative correlation							
Central sulcus (M1)	I	36	–26	64	>8.0	0.66	0.01
	C	–34	–26	70	6.91	0.49	0.05
Postcentral gyrus	C	–48	–16	54	6.14	0.51	0.04
Postcentral sulcus	I	32	–36	48	7.81	0.58	0.03
	C	–36	–34	52	7.53	0.8	<0.01
	C	–48	–22	48	6.14	0.8	<0.01
PMd	I	32	0	60	>8.0	0.58	0.03
	I	32	–16	68	>8.0	0.67	0.01
	C	–30	0	62	7.66	0.58	0.03
	C	–26	–14	68	7.24	0.49	0.05
Anterior PMd (BA 6/8)	I	44	22	42	5.84	0.73	0.01
SMA	C	–2	–4	58	>8.0	0.65	0.02
Pre-SMA	C	–4	28	56	7.14	0.52	0.04
Rostral cingulate sulcus	C	–2	10	38	>8.0	0.58	0.03
Superior parietal cortex	C	–28	–68	56	>8.0	0.73	0.01
Intraparietal sulcus	C	–28	–72	32	>8.0	0.56	0.03
Parietal operculum (SII)	I	64	–16	18	6.36	0.62	0.02
Prefrontal cortex (BA 10)	I	34	60	–4	7.03	0.54	0.04
Inferior frontal sulcus	C	–42	46	–4	6.08	0.65	0.02
Superior temporal sulcus	I	58	–48	14	6.23	0.66	0.01
	C	–50	–44	10	6.16	0.69	0.01
Middle occipital gyrus	C	–50	–64	–4	>8.0	0.85	<0.01
Striate cortex	I	2	–84	14	5.67	0.51	0.05
	C	–4	–96	14	>8.0	0.56	0.03
Cerebellum—VI	C	–30	–76	–18	>8.0	0.64	0.02
	I	22	–62	–18	>8.0	0.64	0.02
Cerebellum—V	C	–24	–30	–34	5.59	0.66	0.01
Cerebellum—CrI	I	48	–60	–28	>8.0	0.69	0.01
Cerebellar vermis—VIIIB	n/a	–2	–68	–40	>8.0	0.51	0.04
Cerebellar vermis—VI	n/a	–4	–62	–22	6.02	0.56	0.03
Thalamus	I	2	–14	10	7.23	0.72	0.01
	C	–4	–2	6	5.25	0.59	0.02
Putamen/globus pallidum	I	26	–16	8	5.66	0.52	0.04
Positive correlation							
Superior temporal sulcus	I	48	18	–30	7.22	0.6	0.02
Inferior parietal	C	–50	–70	36	6.36	0.6	0.02
Caudate	C	–10	8	18	5.48	0.62	0.02

Regions in which there is a correlation between early (10–14 days) outcome scores and task-related activation across all first sessions for all stroke patients. Images for patients with left-sided lesions were flipped about the mid-sagital line, so that all patients were assumed to have a lesion on the right side, with initial left hand weakness. Voxels significant at $P < 0.05$, corrected for multiple comparisons across whole brain volume. The correlation coefficient (r^2) and corresponding *P* value for the correlation analysis are also given. I = ipsilesional; C = contralesional; M1 = primary motor cortex; PMd = dorsolateral premotor cortex; PMv = ventrolateral premotor cortex; SMA = supplementary motor area; BA = Brodmann area. Roman numerals for cerebellar activations refer to cerebellar lobules (Schmahmann *et al*., 1999).

those with the behavioural consequences of widespread cortical damage.

Study design

After hemiparetic stroke, the ability to perform hand grip returns relatively early compared with fractionated finger movements (Heller *et al*., 1987), and compares well with other measures of upper limb function (Heller *et al*., 1987; Sunderland *et al*., 1989). The use of a hand grip task, rather than a finger tapping task, therefore enabled us to study patients with significant neurological deficit early after stroke.

A comparison of brain activation in patients requires that they all perform an equivalent motor task. Equivalence may be considered in terms of absolute performance parameters (task B) or motor effort (task A) across sessions. The principle of comparing brain activations elicited by a motor task in which effort is controlled has been applied successfully in studying correlations between motor-related brain

activations and outcome in a group of chronic stroke patients with variable recovery (Ward *et al*., 2003). In order to compare equivalent tasks across sessions within subject, we applied the same principles in task A (20% MVC on the day of scanning across sessions). That this strategy succeeded in controlling for effort across sessions is supported by the results of the VAS ratings for effort completed by each subject at each session for task A. In task B, however, the absolute force and rate were maintained across sessions, similar to the designs of previous longitudinal motor studies in stroke patients (Calautti *et al*., 2001a; Feydy *et al*., 2002; Small *et al*., 2002). The direct comparison of recovery-related decreases in brain activation for tasks A and B suggests that if absolute performance parameters are maintained and the task becomes easier over sessions, there is an increased likelihood of observing recovery-related decreases in ipsilesional and to a lesser extent contralesional sensorimotor cortex with time. This is consistent with the observation that difficult motor tasks result in greater recruitment within the motor system than simple motor tasks (Catalan *et al*., 1998). Thus the results with task B can be explained by a decrease in task difficulty, or by neuronal reorganization, and it is not possible to differentiate between the two mechanisms *post hoc* (Price and Friston, 1999). The results for task A, however, are not confounded by decreasing effort over time. Although some aspects of cognitive performance, such as attention, may change with time, we argue that by performing a motor task (hand grip) that is more dependent on intrinsic motor recovery than adaptation (Sunderland *et al*., 1989), and controlling for motor effort as much as possible, our findings within known motor-related regions are more likely to reflect neuronal reorganization.

Previous longitudinal studies

Our main finding relates to longitudinal decreases in task-related activation over sessions as a function of recovery in patients with cerebral infarcts not involving M1. Reduction in motor-related activations over time has been described before. Marshall *et al*. (2000) and Calautti *et al*. (2001a) both studied a similar case mix of stroke patients, and reported differences in motor-related brain activation patterns at one early and one late time point after stroke. The first described an increase in the ratio of ipsilesional to contralesional sensorimotor cortex activations, whereas the latter noted a decrease in activation of non-primary motor regions largely in the affected hemisphere. These shifts in laterality of activation were subsequently correlated with changes in motor performance (Calautti *et al*., 2001*b*). Feydy *et al*. (2002) described four cases similar to our own (good recovery, non-M1 lesions), all of whom had early bilateral activation during a motor task followed by a focusing towards a relatively normal activation pattern over three sessions. Small *et al*. (2002) found only increases in ipsilateral cerebellar activation in a group analysis of patients with better recovery compared with poorer. The *post hoc* separation of patients into groups of good or poor recoverers, and the small number of recovery tests used may have contributed to a lack of sensitivity in that study. Johansen-Berg *et al*., (2002) reported increases in task-related premotor cortex and cerebellar activation over two scanning sessions in chronic stroke patients responding to modified constraint-induced therapy. This result is not directly comparable with ours because it was performed in chronic, previously stable stroke patients, but does illustrate the utility of examining for recovery-related rather than time-related changes.

Our *a priori* intention was to relate changes in brain activation patterns to changes in performance, not time, after stroke. An overall picture of recovery is best provided by a range of measures, each reflecting a different aspect of recovery (Turton and Fraser, 1986; Duncan *et al*., 2000). Combining these measures is problematic, not least because some scales are linear and some not. However, by performing a principal component analysis, it is possible to say how much of the variance described by all the outcome scores is attributable to the first, second, third, etc. principal components of the data set. The first principal component of each patient's outcome data set accounted for between 78.2 and 90.5% of the variance in each data set. Our approach therefore provides a useful, complete and robust measure of relative overall recovery with which to examine for correlations in task-related brain activations.

Early post-acute changes

When comparing post-acute and chronic phase task-related brain activations, our data and those of others clearly demonstrate greater and more widespread brain activation in early compared with late stages (Marshall *et al*., 2000; Calautti *et al*., 2001a; Feydy *et al*., 2002). Findings in animal models of focal cerebral infarction may account for such observations. For example, an increase in both dendritic branching (Jones and Schallert, 1992) and synaptic number (Stroemer *et al*., 1995; Jones *et al*., 1996) has been noticed in both the damaged and undamaged hemispheres days after a lesion. This branching may overshoot and be followed by pruning back, as seen during normal development (Kolb, 1995), which might explain some of our time-related reductions in activation size.

In addition, widespread areas of cortical hyperexcitability appear days after cerebral infarction, reducing over subsequent months (Buchkremer-Ratzmann *et al*., 1996). These changes occur in regions structurally connected to the lesion in both hemispheres as a consequence of downregulation of the $\alpha 1$ GABA receptor subunit and a decrease in GABAergic inhibition (Neumann-Haefelin *et al*., 1998). The BOLD signal measured by fMRI represents primarily input and processing within a region and not the output signal (Logothetis *et al*., 2001), so that a state of hyperexcitability will result in increased and more diffuse BOLD signal. The functional consequence of hyperexcitability is a facilitation of activity-dependent plastic change (Hagemann *et al*., 1998).

Although these phenomena have been reported in animals with cortical lesions, there is evidence from human studies that subcortical damage to the corticospinal pathway has a similar effect. Enlargement of the motor output zone was observed as a consequence of degeneration of the corticospinal tract (Kew *et al*., 1994), possibly as a result of loss of recurrent inhibition onto surrounding pyramidal cells (Ghosh and Porter, 1988). There is also evidence for hyperexcitability in the contralesional motor cortex after both cortical and subcortical stroke in humans with at least moderate recovery (upper limb MI score $\geqslant$61) (Bütefisch *et al*., 2003). Such hyperexcitability decreases with time after infarction, in keeping with the data from animals (Witte, 1998; Shimizu *et al*., 2002). Whether these changes result in increased and more diffuse task-related BOLD signal in the early human post-stroke phase, as one would predict, and whether they subserve the recovery process requires further investigation.

The early recruitment of a number of brain regions not normally activated by a motor task also requires explanation. We have demonstrated such overactivations previously in chronic stroke patients compared with normal subjects, particularly those with poorer recovery, during the performance of a hand grip task (Ward *et al*., 2003). We have observed the same relationship between task-related activations and clinical deficit at 10–14 days post-stroke in very similar regions, i.e. patients with greater initial deficit seem to recruit more widely and to a greater extent in a number of regions than those with less early deficit (Table 5). Stroke patients with motor weakness may rely on independent parallel motor loops (Strick, 1988) in proportion to the degree of damage to the direct projection from M1 to spinal motor neurons. Our results in post-acute patients suggest that the brain regions within these parallel motor loops may participate in the generation of a motor act very early, possibly immediately after stroke, rather than slowly being recruited over time. Furthermore, the increased recruitment of non-motor regions such as occipital cortex indicates that other modalities, e.g. sensory, are increasingly utilized in those with greatest deficit in an attempt to optimize task performance.

Longitudinal changes

If recruitment of independent parallel non-primary motor loops is the consequence of impairment to direct M1 corticomotoneuronal pathways, then the most parsimonious explanation for the reduction of such recruitment is that recovery of motor function is a direct result of restitution of this direct anatomical link. Several studies using transcranial magnetic stimulation in stroke patients have demonstrated changes in neurophysiological parameters from the affected hemisphere suggestive of improving corticospinal function (in particular motor threshold, motor evoked potential amplitude in a hand muscle, and central motor conduction time) that correlate with recovery of hand function (Heald *et al*., 1993; Turton *et al*., 1996; Traversa *et al*., 1997; Pennisi *et al*., 2002). However, it is clear that abnormalities in neurophysiological parameters can persist in patients with complete recovery (Pennisi *et al*., 2002), suggesting that preservation of fast direct cortico-motoneuronal pathways is not the only means of achieving full recovery, and that cerebral reorganization may play an important role in generating motor output. A number of mechanisms may be involved in driving this reorganization.

Changes in cortical motor representation may provide alternative motor output

Recruitment of more ischaemia-resistant small diameter myelinated corticospinal fibres, such as those from premotor cortex, may compensate loss of large diameter fibres. Alternatively, changes in cortical representations may enable the lesioned brain to take advantage of considerable redundancy within the somatotopy of M1 (in that a number of combinations of pyramidal cells may produce the same movement; Sanes and Donoghue, 2000) to generate an output to the spinal cord via an intact portion of the pyramidal tract. Shifts in the peak ipsilesional sensorimotor task-related activations in post-stroke patients have been observed in previous studies (Weiller *et al*., 1993; Pineiro *et al*., 2001), and additional areas of M1 have been recruited in incompletely recovered patients (Ward *et al*., 2003). In a *post hoc* analysis, shifts in the peak sensorimotor activation from the first session to the last in six of our patients (all except patients 5 and 6) were observed, but in no consistent direction, nor seemingly correlated with the lesion site. In the group analysis, we observed recovery-related reductions in activation in M1 ventral to the hand area ($z = 52$), and deep in central sulcus corresponding to area 4p ($z = 42$ and 36). We speculate that early changes such as hyperexcitability may increase the amount of M1 that is activated, facilitating subsequent refocusing towards a shifted sensorimotor representation, with access to undamaged fast cortico-motoneuronal pathways in those with better recovery. In those with poorer recovery, recruitment of additional M1 regions may persist, as we have observed previously (Ward *et al*., 2003). Such a mechanism could not occur with damage to the entire M1 cortical region. In this respect, patients such as ours with preserved M1 are clearly different from those with substantial M1 damage. Clinical improvement in patients with (near) complete M1 damage does occur, but is more limited, and 'reorganized' motor output is likely to come from the undamaged hemisphere. Even in our patients with subcortical infarcts, we observe task-related activations in contralesional M1 early after stroke that are not accountable for by mirror movements. This activation tends to diminish across sessions as a function of recovery. It is likely, therefore, that contralesional M1 plays some part in the recovery process, although there is no evidence that it is more important than recruitment of non-primary parallel motor networks.

Does attention to motor performance contribute to cerebral reorganization?

Increases in task-related brain activation as a result of increased attention to a simple motor task have been observed in a number of motor regions, including SMA, cingulate cortex, insula, postcentral sulcus and deep central sulcus (putative area 4p) (Binkofski *et al*., 2002; Johansen-Berg and Matthews, 2002). It could be argued, therefore, that our results are largely due to the fact that early after stroke, when deficit is greatest, patients need to pay more attention to a task. We attempted to control for attention within a scanning session by incorporating visual feedback to which all subjects were asked to attend. However, reductions in both striate and extrastriate activations occurred in several patients, suggesting attention to the visuomotor task was greater early on. It is possible that increased attention to a task is a key strategy early after stroke when deficit is greatest. This attentional mechanism will contribute to increased activation in non-primary motor regions, thereby providing a substrate for activity-dependent plastic changes in somatotopic representations within the motor system, and consequently increasing access to alternative motor pathways. While this is not a factor we set out to manipulate experimentally, it clearly needs to be examined in future longitudinal studies.

Do stroke patients re-learn motor performance?

Current models of motor learning suggest that during early learning, there is a dynamic interaction between a frontoparietal network encoding movement in terms of spatial coordinates, that requires high levels of attention, and motor cortex which encodes movement in terms of a kinematic system of joints, muscles, limb trajectories, etc. Motor cortex is dominant once learning has occurred and a movement has become automatic (Hikosaka *et al*., 2002). Each of these cortical systems is engaged in loops that include different regions of cerebellum and basal ganglia. Attempted movements by hemiparetic patients will result in significant discrepancies between predicted and actual performance, generating error signals that in normal subjects are used by the cerebellum to optimize subsequent sensorimotor accuracy (Blakemore *et al*., 2001). Interactions between these parallel systems occur not only in cerebellum and basal ganglia, but also via intracortical connections involving particularly premotor cortex and pre-SMA (Hikosaka *et al*., 1999, 2002). A number of empirical findings support such a model. Decreases in brain activation as a function of motor learning have been reported in lateral premotor cortex, prefrontal cortex, pre-SMA, superior parietal cortex, anterior cingulate, cerebellum, cerebellar vermis and caudate, (Jenkins *et al*., 1994; Nakamura *et al*., 1998; Toni *et al*., 1998); the cerebellum is involved in detecting error between internal models of movement and the sensory consequences of actual movement (Imamizu *et al*., 2000; Blakemore *et al*., 2001); activation in pre-SMA has been explicitly associated with new motor sequence learning (Nakamura *et al*., 1998; Hikosaka *et al*., 1999; Sakai *et al*., 1999); and a variety of changes in M1, predominantly increases in recruitment, have been observed (Grafton *et al*., 1995; Karni *et al*., 1995; Honda *et al*., 1998; Toni *et al*., 1998; Muellbacher *et al*., 2002). We describe decreases in activation with recovery in similar networks, both in individuals and across the whole group, consistent with the notion of a transfer of reliance from the frontoparietal to the primary motor system. We did not see consistent increases in activation with recovery, although they were seen in individuals. Increases and decreases in recovery-related activations in the same functional region may represent shifts in somatotopic representations. Increased activation in M1 during motor learning is predicted in the normal brain by such a model, and has been observed in normal subjects when learning occurs over weeks (Karni *et al*., 1995), but we have observed such an increase in only one patient. However, damage to direct connections between M1 and spinal cord motor neurons may prevent normal responses and result in shifts of peak M1 activation by re-mapping instead. The need to re-learn simple motor tasks after stroke is likely to engage such a mechanism, but the degree to which this can occur will depend on the degree of overall damage to the motor network. Issues such as the role of error signal generated in the damaged motor system are important and unexplored, though they may have significant implications for rehabilitative interventions.

Conclusions

We have correlated longitudinal changes in motor-related brain activation and recovery of function in individual patients for the first time. We have been able to do this because of the large number of study sessions accompanied by detailed measurement of a variety of aspects of functional recovery in each patient. One aim of this study was to identify changes in activation patterns of relevance to the recovery of individual patients. The differences in results between patients are likely to be a result of differences in (i) anatomical damage and (ii) cognitive parameters such as motivation, concentration and attention. We have attempted to control for the latter, in order to make inferences about the former. We have not studied enough patients to be able to draw firm conclusions. However, within our patient group, we have observed some remarkably consistent patterns in recovery-related changes in brain activation patterns, which are independent of the initial severity and rate of recovery. Our data suggest that in stroke patients with infarcts not involving M1, there is a clear linear relationship between recovery scores and task-related brain activation in many parts of the motor system. It has been assumed that this relationship is linear, perhaps because of the lack of detailed studies previously. However, this may not be the case given that different mechanisms may facilitate recovery at different time points after stroke. Nevertheless, our analysis shows that

the assumption of linearity is a robust first-pass approximation.

We do not imply that the relationship we describe is causative, but suggest that our results reflect a number of processes occurring after focal brain damage at both cellular and systems levels which contribute to cerebral reorganization and functional recovery. Early on following cerebral infarction, any voluntary movement is associated with massive recruitment of areas in the motor system, possibly because of alterations in the tonic reciprocal influence of anatomically connected motor-related regions upon each other. In addition, a number of mechanisms described in animal models of focal cerebral damage, such as local and distant cortical hyperexcitability, may play a role. Thereafter, it is likely that surviving elements of highly preserved neural systems subserving motor learning are employed to facilitate the transition from attention-dependent movement to a more automated performance. This is accompanied by recovery-dependent decreases in the initial pattern of activation. The degree to which any of these elements are employed successfully in the recovery process will depend on a number of other variables, not least the precise amount and site of anatomical damage caused by the infarct. Cerebral reorganization undoubtedly contributes to functional recovery after stroke, but it is clear that we require a more detailed understanding of the process and the factors that influence it, before we can utilize such information to rationalize therapeutic strategies in individual patient groups. To that end, these results further our understanding of the likely dynamic mechanisms underlying functional recovery after stroke.

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