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# Improved understanding of cortical injury by incorporating measures of functional anatomy

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## Summary

**Volume of injury is often used to describe a brain insult. However, this approach assumes cortical equivalency and ignores the special importance that certain cortical regions have in the generation of behaviour. We hypothesized that incorporating knowledge of normal brain functional anatomy into the description of a motor cortex injury would provide an improved framework for understanding consequent behavioural effects. Anatomical scanning was performed in 21 patients with a chronic cortical stroke that involved the sensorimotor cortex. Functional MRI (fMRI) was used to generate separate average activation maps for four tasks including hand, shoulder and face motor tasks in 14 controls. For each task, group average maps for contralateral sensorimotor cortex activation were generated. Injury to these maps was measured by superimposing each patient's infarct. These measurements were then correlated with behavioural assessments. In bivariate analyses, injury to fMRI maps correlated with behavioural assessments more strongly than total infarct volume. For example, performance on the Purdue pegboard test by the stroke-affected hand correlated with the fraction of hand motor map injured ($r$ = –0.79) more strongly than with infarct volume ($r$ = –0.60). In multiple linear regression analyses, measures of functional map injury, but not infarct volume, remained as significant explanatory variables for behavioural assessments. Injury to >37% of the hand motor map was associated with total loss of hand motor function. Hand and shoulder motor maps showed considerable spatial overlap (63%) and similar behavioural consequences of injury to each map, while hand and face motor maps showed limited overlap (10.4%) and disparate behavioural consequences of injury to each map. Lesion effects support current models of broad, rather than focal, sensorimotor cortex somatotopic representation. In the current cross-sectional study, incorporating an understanding of normal tissue function into lesion measurement provided improved insights into the behavioural consequences of focal brain injury.**

**Keywords**: motor cortex map; stroke; somatotopy

**Abbreviations**: fMRI = functional magnetic resonance imaging; MCP = metacarpophalangeal

## Introduction

A large amount of study has been dedicated to understanding the relationship between brain injury and behavioural sequelae. Experimental animal (Lyden *et al*., 1997; Rogers *et al*., 1997) and human (Brott *et al*., 1989; Saver *et al*., 1999) studies of brain infarction have consistently found that behavioural deficits correlate significantly with acute or with chronic measurement of infarct volume. This approach to understanding brain injury assumes an equivalency of cortical function, akin to theories of cerebral mass action (Lashley, 1950).

However, a range of methods have provided substantial evidence that certain regions of peri-Rolandic gyri have special importance in movement generation in humans (Penfield and Boldrey, 1937; Cohen and Hallett, 1988; Grafton *et al*., 1993; Urbano *et al*., 1996). In some cases, therefore, understanding the behavioural effects of brain injury might be best achieved by incorporating information related to function of such cortical regions. The current study hypothesized that an improved understanding of the behavioural effects of brain injury in humans can be gained when the description of brain injury incorporates information on the normal function of affected brain areas.

Experimental animal studies sometimes perform cortical mapping before introducing injury (Hoffman and Strick,

**Table 1** *Subject demographics*

| | Patients | Controls |
|---|---|---|
| n | 21 | 14 |
| Age (years) | 58 ± 15 | 51 ± 19 |
| Gender (male/female) | 8/13 | 8/6 |
| Handedness | 20 right-handed, 1 left-handed | 14 right-handed |
| Hemisphere studied with fMRI | | left |
| Hemisphere affected by stroke | 11 left/10 right | |
| Time from stroke to structural imaging and examination (months) | 4.5 (range 1.7 – 115) | |

Results are mean ± SD, except for time from stroke to exam (median). Age and gender distribution were not significantly different between groups.

1995; Nudo and Milliken, 1996; Nudo *et al*., 1996; Friel and Nudo, 1998; Schieber and Poliakov, 1998; Liu and Rouiller, 1999)—an approach not possible in most human study designs. In the current study, functional anatomy was determined in age-matched normal subjects and assumed to approximate pre-infarct functional organization of stroke patients. In the normal controls, functional maps in contralateral peri-Rolandic gyri were obtained for four different motor or sensory activation tasks using functional MRI (fMRI). Injury to these maps was then assessed by superimposing the infarct from 21 patients in stereotaxic space (Talairach and Tournoux, 1988).

## Subjects and methods

### *Subject selection and evaluation*

Entry criteria for patients were a chronic cortical stroke that: (i) had been radiologically verified; (ii) involved precentral and/or postcentral gyri; (iii) did not extend to internal capsule; and (iv) was associated with arm sensorimotor deficits at stroke onset. Control subjects with no stroke history or active neurological disease were enrolled. Consent was obtained according to the Declaration of Helsinki and with approval of the University of Washington Human Subjects Committee.

A total of 14 controls and 21 stroke patients meeting these criteria were studied (Table 1). Patients were >10 weeks post-stroke except for a 47 year-old who was 7 weeks post-stroke but showed substantial early recovery. One patient with left hemisphere infarct was left-handed. Seven patients had a history of prior stroke that in each case did not involve primary sensorimotor cortex. Patients had been admitted to a large number of different hospitals, where initial stroke deficits varied from mild to severe. The majority of the patients (14 out of 21) had undergone an inpatient rehabilitation program after acute stroke hospitalization. Patients were all >1 month beyond acute and rehabilitation therapies for stroke. By the time of study entry, patients had a broad range of deficits that on average were mild–moderate in extent (Table 2).

Ten clinical measures were used to assess various aspects of sensorimotor function (Table 2), as probing several features of motor skill can improve understanding of post-infarct recovery (Nudo *et al*., 2001).

(i) The number of pegs placed by each hand in the Purdue pegboard test (Spreen and Strauss, 1991) during a 30 s trial was measured as a test of fine sensorimotor function, with results normalized to unaffected hand performance.

Standardized scales included: (ii) the Fugl–Meyer arm motor scale (Duncan *et al*., 1983), an assessment of 33 aspects of motor function from fine motor to primitive functions such as motor synergy, hyperreflexia and range of motion; (iii) the National Institute of Health (NIH) Stroke Scale (Adams *et al*., 1999), which assesses a broad range of neurological functions after stroke; and (iv) the Stroke Impact Scale (Duncan *et al*., 1999) hand motor sub-score, a self assessment of hand function. (v) Tone measurement used a four-tier modification of the Ashworth Scale (Bohannon and Smith, 1987). Strength in (vi) proximal arm, (vii) distal arm, (viii) proximal leg and (ix) distal leg was assessed using the Medical Research Council (MRC) grading system, 1986. (x) Index finger proprioception at the metacarpophalangeal (MCP) joint was assessed using a four-tier scale: a score of 3 was normal; 2 was any error with movement <1 cm; 1 was any error with movement >1 cm but some correct answers; and 0 was absent proprioception.

In the hour prior to fMRI, control subjects rehearsed the four tasks to be used during fMRI scanning. During this time, a recording was made from bipolar surface electromyography (EMG) leads placed over 14 muscles: the mentalis and corrugator supercilii, plus right and left pectoralis major, biceps, wrist flexors, wrist extensors, first dorsal interosseus and tibialis anterior. EMG was recorded as subjects performed two active–rest cycles for each task, amplified (Nihon-Kohden, Foothill Ranch, CA, USA), filtered from 5 Hz to 3000 Hz, recorded at 1000 samples/second/channel and digitized using an analog-to-digital converter card plus Labview software (National Instruments, Austin, TX, USA).

### *MRI*

In stroke patients, a $T_1$-weighted anatomical MRI scan was obtained with in-plane resolution of 0.94 mm and 7 mm thickness. A total of 14 axial slices were obtained ventral to

**Table 2** *Correlation between behaviour and MRI measures*

| Behavioural evaluations | Patient mean (range) | Infarct volume | Hand motor map injury | Hand sensory map injury | Shoulder motor map injury | Face motor map injury |
|---|---|---|---|---|---|---|
| Affected hand Purdue pegboard score (normal = 1) | 0.62 (0–1.25) | –0.60 | –0.79 | –0.65 | –0.76 | –0.64 |
| Fugl–Meyer arm motor score (normal = 66) | 55 (4–66) | | | | | |
| NIH Stroke Scale score (normal = 0) | 2.5 (0–9) | 0.69 | 0.75 | 0.75 | 0.69 | 0.72 |
| Hand motor subscore, Stroke Impact Scale (normal = 5) | 3.2 (1–5) | | –0.78 | –0.65 | –0.81 | |
| Affected arm tone (normal = 3) | 2.4 (0–3) | –0.65 | –0.69 | –0.68 | –0.64 | –0.73 |
| Strength, affected hand interossei (normal = 5) | 4.0 (0–5) | | –0.74 | | –0.71 | |
| Strength, affected arm deltoid (normal = 5) | 4.7 (0–5) | | –0.65 | | –0.66 | |
| Strength, affected leg psoas (normal = 5) | 4.9 (4–5) | | | | | |
| Strength, affected leg tibialis anterior (normal = 5) | 4.7 (0–5) | | | | | |
| Proprioception, affected hand index finger (normal = 3) | 2.5 (0–3) | –0.63 | –0.68 | –0.71 | . | –0.71 |

Describing the stroke in terms of injury to normal functional anatomy improves the number and degree of correlations compared with describing the stroke in terms of infarct volume. Ten behavioural assessments were measured, representing a spectrum of objective and subjective motor and sensory behaviours. Each was then correlated with anatomical assessments of stroke or with measures of injury to normal fMRI activation maps. The Spearman rank order statistic, $r$, is shown for significant ($P < 0.005$) correlations. Note that Purdue pegboard results are normalized to findings in the unaffected hand.

brain vertex that included the entire infarct. All imaging in the current study was performed on the same 1.5 T GE scanner (General Electric, Waukesha, WI, USA).

In control subjects, collection of these anatomical data was accompanied by acquisition of fMRI data during performance of four functional tasks: hand motor, hand sensory, shoulder motor and face motor. With the head restrained, fMRI scanning used a gradient echo echoplanar pulse sequence with $T_2$*-weighting for blood oxygenation level dependent (BOLD) contrast and a boxcar design that alternated 20 s of rest with 20 s of active state. Scanning parameters included TR (repetition time) = 2000 ms, TE (echo time) = 50 ms, in-plane resolution 3.75 × 3.75 mm, 14 axial brain slices of 7 mm thickness with no gap that were in plane with the anatomical scan. All fMRI scans began with four TRs to establish magnetic field homogeneity, after which either 100 images/slice (five rest-active cycles for the three motor tasks) or 200 images/slice (10 rest-active cycles for the sensory task) were obtained. The subject's eyes were closed for all four tasks. Movements were guided by a headphone metronome. A single light touch on the knee toggled subjects between rest and tapping. An examiner at the subject's side during scanning verified task performance as instructed.

The first fMRI scan contrasted rest with 2 Hz tapping by the right index finger. Arms were extended and pronated, bilateral splints kept wrists mildly extended and provided a slot for index finger movements isolated to the flexion/extension plane, and Velcro straps restricted movement to the index MCP joint. The splint was attached to a stand with a force transducer (SSL5, Interface, Scottsdale, AZ, USA) that measured motor task performance during fMRI and limited movement to 25°. Force transducer output was amplified (ETH-200, CB Sciences, Dover, NH, USA), left the scanner room via a filter that shorted high frequency signals to ground through a shunt capacitor, and was then digitized and recorded using methods described previously (Cramer *et al*., 2002*b*).

The second fMRI scan contrasted rest with 2 Hz passive movement of the right index finger. Thick tape was placed around the index finger distal interphalangeal joint. A string was looped atop this and taped in place. The string connected to a wooden pole extending out of the scanner bore across a hinged fulcrum. The pole limited movement to a range of 25° of motion in the flexion/extension plane. The examiner then alternated rest with 2 Hz finger movement.

The third fMRI scan contrasted rest with 1 Hz right shoulder movement. The elbow was flexed so that the hand was atop the subject's mid-abdomen. Foam pads were placed beneath the elbow so that the plane of the arm at rest was parallel to the plane of the scanner bed. With each beep, the subject externally rotated the shoulder 20°. The fourth fMRI scan contrasted rest with 1 Hz contraction of the corner of the mouth. This involved contraction of the risorius, mentalis and zygomaticus major muscles.

During scanning, subjects performed tasks as instructed. Motor task performance during fMRI, available in 10 subjects, showed actual tapping frequency was 2.06 ± 0.23 Hz (mean ± SD) and the tapping force was 1.07 ± 0.31 newtons, highly consistent across subjects. In one subject, bilateral face movements were generated, but only in <10% of face movements. There was no resistance or active movement during the hand sensory task. Two subjects requested briefer imaging and thus only completed three out of four tasks, one omitting hand sensory and one, face motor task. Head motion resulted in excess artifact in two subjects for hand motor, none for hand sensory, eight for shoulder motor and six for face motor; a higher rate of excess head motion during fMRI tasks involving more proximal muscles is consistent with a prior report (Cramer *et al*., 2001). This left for analysis 12 subjects for the hand motor map; 13

for hand sensory, six for shoulder motor and seven for face motor.

### *Data analysis*

All images were motion corrected to the fifth volume of the finger-tapping task using Automated Image Registration and MED× 3.3 (Sensor Systems, Sterling, VA, USA). This process corrupts the top and bottom functional data slices, in anticipation of which the top slice was selected to be above the brain. Images were linear detrended. For each of the four scans, a voxelwise *t*-test then contrasted active and rest states, with results expressed as a *Z*-map. Data were spatially smoothed with a 4 mm Gaussian filter. Studies with excess head motion, evident as a circumferential ring of activation or total absence of any activated voxels, were excluded.

Each *Z*-map was then converted to stereotaxic space (Talairach and Tournoux, 1988) by registering to the standard image supplied with MEDx 3.3 software using FLIRT (www.fmrib.ox.ac.uk/fsl/). A group composite map was generated (Bosch, 2000) for each of the four tasks. The activation cluster of interest, with the largest number of activated voxels in the area composed of precentral plus postcentral gyri, was identified and isolated in its entirety. The volume and coordinates for centre of activation were noted at a significance threshold of $Z = 4.2$ ($\sim 10^{-5}$). Secondary analyses repeated this using significance thresholds of $Z = 3$ ($\sim 10^{-3}$) and $Z = 7$ ($\sim 10^{-12}$). In addition, the size and location were noted at $Z = 4.2$ threshold for areas of overlapping activation for four task pairs of interest.

For stroke patients, the volume of infarction was outlined, measured and saved as a binary mask. Next, the anatomical images were then transformed into stereotaxic space as above, and the details of this transform were then applied to the stroke mask. For strokes occurring in the right hemisphere, maps were flipped about the *y*-axis. For each patient, the stroke mask was multiplied by each of the control subjects' group activation maps in order to determine what fraction of each control map was injured by the stroke. The current study used the approach that stroke masks were multiplied by control subject fMRI maps, rather than by fMRI maps derived from unaffected hemisphere of patients during tasks by the unaffected body side. This was because unilateral infarction often changes sensorimotor organization, neurophysiological properties and behavioural output of the non-infarcted hemisphere (Weiller *et al*., 1992; Cramer *et al*., 1997; Nelles *et al*., 1998; Bury and Jones, 2002; Shimizu *et al*., 2002). Note that in four patients, a small infarct verified radiologically at the time of acute stroke admission had atrophied to the extent that it could not be seen on the chronic $T_1$-weighted images. These patients were assigned a mask volume of zero voxels, and secondary analyses repeated all assessments without these four patients. Finally, across the stroke patient population, the fraction of the controls' functional map injured by stroke, and the volume of infarction, were each correlated with each of the 10 clinical measures.

EMG data were analysed as described previously (Cramer *et al*., 2002*a*). Briefly, data were filtered digitally using a first order, high-pass, 20 Hz Butterworth filter. Next, root mean square values were determined for rest and active epochs for each task. For each muscle during each task, the ratio of active:rest EMG signal was then calculated.

### *Statistical analysis*

A Spearman rank-order statistic was used for all bivariate correlation analyses (JMP-4, SAS Institute, Cary, NC, USA). An $\alpha$ value of 0.05 was used. To correct for the use of 10 clinical measures, $P = 0.005$ was used to define significance. Correlations between clinical measures and control map injury were performed using $Z = 4.2$ threshold maps, and secondarily using $Z = 3$ and $Z = 7$ threshold maps; results were compared using the $\kappa$ statistic. Multiple linear regression was performed for each behavioural measure using the behavioural measure as the dependent variable and two regressors: infarct volume and injury to a single functional map. This was repeated for each functional map. A Wilcoxon rank sum test was used to compare EMG activity in each muscle across tasks; for any task where overall analysis of EMG data showed a $P < 0.05$, pairwise comparisons were then made.

## Results

Results of EMG assessments support the conclusion that each of the four tasks activated a distinct set of muscles that were appropriate for the task being performed (Table 3). Compared with the other three tasks, the hand motor task had significantly greater EMG activity in distal muscles, the shoulder task had significantly greater EMG activity proximally, and the face task had significantly greater EMG activity in the lower face. The hand sensory task was not associated with any significant increases in EMG activity. Results showed specificity, as upper face and bilateral leg muscles showed no activity during any task.

The functional maps of the cluster of interest from control subjects are shown in Fig. 1A and their volumes of activation appear in Table 4. The centre of activation showed a dorsal-ventral gradient across tasks, from shoulder (Talairach $z = +55$) to face (Talairach $z = +35$). For all tasks, most of the activation within the sensorimotor cortex cluster of interest was located on precentral + postcentral gyri, and in no case did this cluster extend to midline cortex or deep grey structures. At a threshold of $Z = 4.2$, the hand and shoulder motor maps extended anterior to the precentral sulcus dorsally, probably corresponding to the premotor cortex. The hand sensory and, to a lesser extent the hand motor, maps extended ventrally to the parietal operculum, probably corresponding to the secondary somatosensory area. At its ventral extent, the face motor map extended anteriorly to the frontal operculum (including the ventral premotor cortex) and

**Table 3** *EMG activity according to task*

| Muscle | Hand motor task | Hand sensory task | Shoulder motor task | Face motor task | Significant pairwise comparisons |
|---|---|---|---|---|---|
| Right FDI | 7.76 | 1.06 | 2.23 | 1.09 | Hand motor > three others |
| Right WF | 4.29 | 0.98 | 2.52 | 1.07 | Hand motor, shoulder > face > hand sensory |
| Right WE | 6.89 | 1.07 | 3.44 | 1.12 | Hand motor > three others; shoulder > hand sensory, face |
| Right BC | 1.08 | 1.04 | 1.74 | 1.06 | Shoulder > three others |
| Right PEC | 1.05 | 0.99 | 1.27 | 1.02 | Shoulder > three others |
| Left BC | 1.09 | 1.03 | 1.81 | 1.02 | Shoulder > hand sensory, face |
| Left PEC | 1.05 | 1 | 1.04 | 0.99 | Shoulder > face |
| Mentalis | 0.94 | 0.92 | 1.28 | 2.21 | Face > both hand tasks; shoulder > hand motor |

A unique and appropriate profile of muscle activity was seen for each of the four tasks, which was contrasted with rest during fMRI generation of normal functional anatomy maps. During fMRI rehearsal, surface EMG data were collected from 14 muscles. Data are presented for the eight muscles in which an overall difference across tasks was significant. All but two muscles were on the right; during shoulder movement, there were slight but significant increases in two proximal left-sided muscles. The rightmost column presents pairwise comparisons for these eight muscles. Values express task:rest EMG activity. BC = biceps brachii; FDI = first dorsal interosseus; PEC = pectoralis; WE = wrist extensors; WF = wrist flexors. Data are from 13 subjects, as EMG data could not be collected from one control due to technical reasons.

posteriorly to the parietal operculum (including the secondary somatosensory area). There was a modest degree of inter-subject variability, as indicated by voxelwise maps of variance for each task (Fig. 1B), as well as by review of the individual maps contributing to the group composite map for one of the tasks (Fig. 1C).

Voxels showing activation on more than one task were also examined for four pairwise task combinations. Some pairwise comparisons showed substantial overlap (Table 4). For the hand sensory and shoulder motor tasks, most of the area activated was also activated during the hand motor task; for example, 63% of the area activated during the shoulder motor task was also activated during the hand motor task. Overlap between hand and face motor tasks was small (10.4%). Overlap between shoulder and face motor tasks was virtually absent (1.2%).

The volume of infarction showed a significant bivariate correlation with a number of clinical measures (Table 2). Median infarct volume was 6.3 $cm^3$ (range 0–282 $cm^3$). The strongest correlation of infarct volume was with the NIH Stroke Scale, a measure that reflects motor and non-motor deficits, but significant correlation was also found with sensorimotor measures.

The proportion of each normal functional map injured by stroke also showed significant bivariate correlation with clinical measures. Compared with correlations between total infarct volume and clinical measures, the correlations between functional map injury and clinical measures were generally stronger, i.e. they had higher correlation coefficients (Table 2 and Fig. 2). The former also tended to be more common, as clinical measures were significantly correlated with functional map injury in 22 out of 40 (55%) of instances compared with 4 out of 10 (40%) for stroke volume, though this difference was not significant ($P$ = not significant by Fisher's exact test). In several cases, the pattern of behavioural deficits showed a logical relationship to the specific functional map injured by stroke. For example, strength of hand interossei correlated with injury to the hand motor map, but not the face motor map. Arm muscle strength was related to injury to shoulder and hand motor maps, but not injury to the hand sensory map. Proprioceptive function was related more to hand sensory map injury than hand or shoulder motor map injury. None of the functional map injury measures correlated with assessments of leg strength. Injury to the hand motor map showed a very similar profile of relationships with behavioural results compared with injury to the shoulder motor map, but this was not true for injury to the face motor map. With regard to injury to cortical regions that represent overlap of two tasks' maps, correlations were overall the same or weaker compared with correlations between behaviour and injury to individual task maps. Results were nearly identical when all analyses were repeated excluding the four patients in whom a small infarct had atrophied to the point where it could not be seen on the $T_1$-weighted anatomical scans. Because normal maps overlapped, partial correlations were calculated to explore the relationship of functional map injury with behavioural outcome after adjusting for correlations between functional map injury measures. Only 1 out of 22 correlations remained significant at $P < 0.005$.

Use of multiple linear regression analysis also found that the proportion of each normal functional map injured by stroke was a stronger descriptor of behaviour than infarct volume. When the proportion of normal hand motor map injured and the infarct volume were entered as regressors in a model for each behavioural evaluation, the proportion of hand motor map injured remained as a significant explanatory variable for the same seven behavioural evaluations. However, infarct volume remained as a significant explanatory variable for only one behavioural measure. When using injury to the other three normal functional maps, infarct volume remained a significant parameter in zero cases.

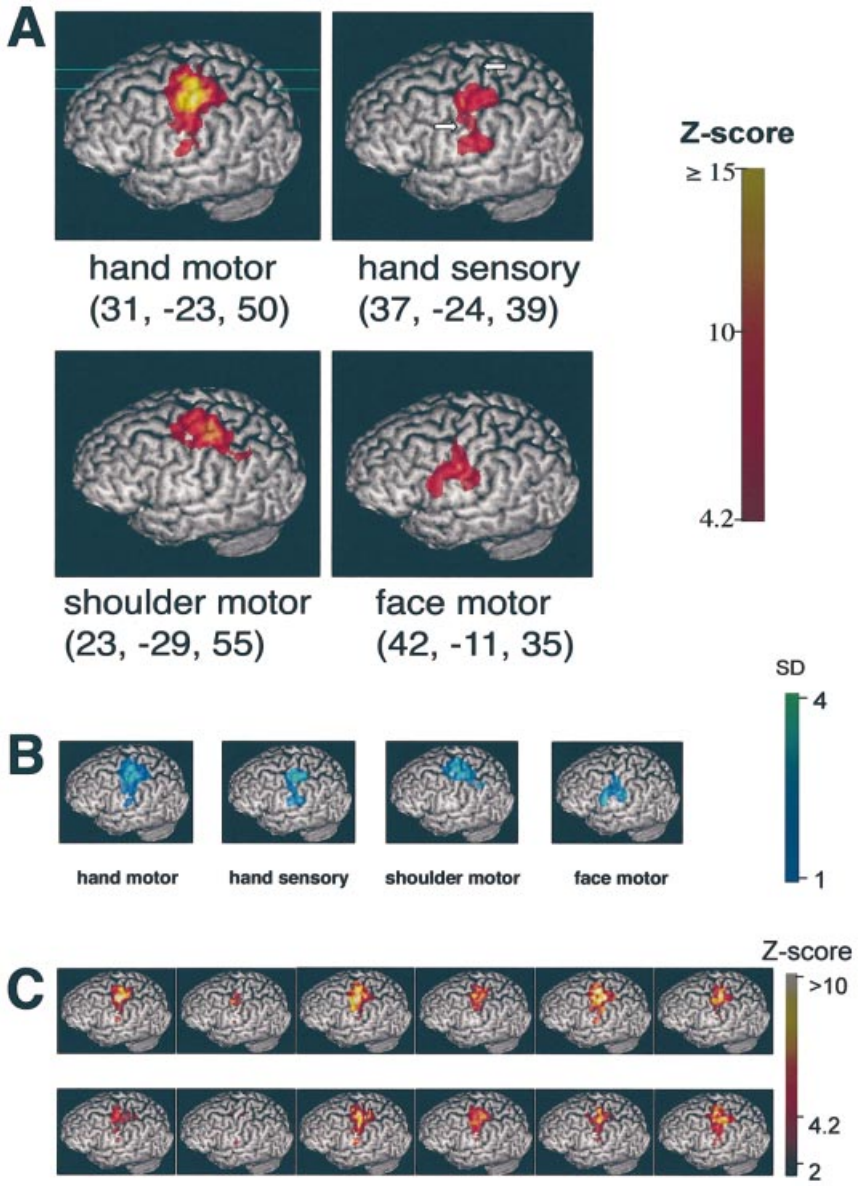


**Fig. 1** (**A**) Activation by control subjects during hand motor, hand sensory, shoulder motor and face motor tasks. For each task, the largest activation cluster in contralateral (left) sensorimotor cortex activation is superimposed upon a normal control brain. Numbers in parentheses are Talairach coordinates for the centre of the activation cluster. The green lines indicate the two axial planes shown in Fig. 2. The white arrows indicate dorsal and ventral aspects of the central sulcus. (**B**) For each of the group composite maps in **A**, variance is presented voxel-wise as the number of SD. (**C**) Inter-subject variability is further depicted by presenting the 12 individual hand motor activation maps that were used to generate the group composite map for this task in **A**. Voxels within the hand motor group map are presented for each subject.

**Table 4** *Activation volumes (mm³) for each task and for pairwise combinations of tasks*

| *Z*-value used to define activation (approximate *P* value) | Hand motor | Hand sensory | Shoulder motor | Face motor | Hand motor and sensory overlap | Hand and shoulder motor overlap | Hand and face motor overlap | Shoulder and face motor overlap |
|---|---|---|---|---|---|---|---|---|
| 3 ($10^{-3}$) | 27615 | 16800 | 27931 | 13739 | | | | |
| 4.2 ($10^{-5}$) | 17526 | 8127 | 10697 | 7021 | 5430 | 6689 | 1826 | 126 |
| 7 ($10^{-12}$) | 7755 | 133 | 3351 | 268 | | | | |

The volume of contralateral (left) sensorimotor cortex, in $mm^3$, is presented using either $Z = 3$, $Z = 4.2$ or $Z = 7$ as the threshold to define significant activation. In addition, at $Z = 4.2$ threshold, volumes are shown for areas with overlapping activation for four pairwise task combinations of interest.

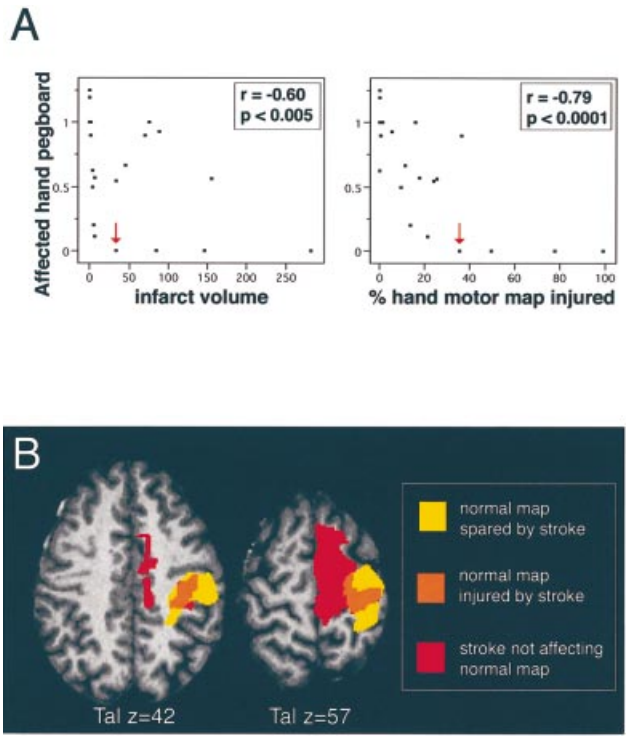


**Fig. 2** (**A**) Infarct volume (top left) and fraction of hand motor map injured by stroke (top right) each show a significant inverse relationship with pegboard performance by the affected hand (normalized to pegboard results for the unaffected hand). However, correlation is stronger and more significant in the latter case. Note that injury to >37% of the hand motor map was associated with total loss of hand motor function. The arrow indicates the patient whose images are displayed below. (**B**) Images from a patient whose stroke was mild–moderate in size (33 $cm^3$), but injured 35% of the hand motor area and was associated with total loss of hand motor function.

Results of multiple linear regression analyses therefore suggest that functional map injury is significantly related to behavioural outcome after controlling for infarct volume, but infarct volume is not significantly related to behaviour after controlling for injury to normal functional maps.

Use of the less stringent threshold of $Z = 3$ to define significant activation in control maps was associated with larger activation volumes, with functional map size increasing by a factor of 1.58–2.61 (Table 4). Despite this change in size of control functional maps, injury to each map showed a significant correlation with the very same behavioural measures. The κ statistic for this comparison was 1.0 for all four maps, indicating perfect consistency. Use of a more stringent threshold of $Z = 7$ to define significant activation was associated with smaller activation volumes, with functional map size decreasing by a factor of 0.02–0.44. The κ statistic was 0.2 for hand sensory and 0.4 for face motor tasks [indicating a fair level of agreement (Landis and Koch, 1977)], where activation volumes at this threshold were quite small. Kappa was 0.52 for hand motor (moderate agreement) and 1.0 for shoulder motor (perfect agreement).

The current approach also allowed interrogation of functional map injury to determine whether a threshold of injury exists beyond which useful motor function is lost. At the $Z = 4.2$ threshold, infarction of >37% of the control hand motor functional map was associated with total loss of hand motor function, as measured by the pegboard test (Fig 2A), the hand motor sub-score of the Stroke Impact Scale, or affected hand interossei strength. The volume of infarction among the four patients with no hand motor function had a wide range, 33 to 282 $cm^3$. Though the control hand motor functional map was larger at a $Z = 3$ threshold, the fraction of control hand motor map injury associated with total loss of hand motor function was similar (>44%). The map was smaller at a $Z = 7$ threshold, but results were also similar, with >33% of hand motor map injury associated with total loss of hand motor function.

## Discussion

The current study approached the relationship between human brain injury and behavioural deficits by defining injury in relationship to normal functional anatomy. Total infarct volume has long been used as a measure of injury and predictor of outcome in stroke studies (Brott *et al*., 1989; Saver *et al*., 1999). However, the principal finding in the current patient cohort is that correlation between total infarct volume and behaviour was weaker compared with correlation between injury to functional maps and behaviour (Table 2). When functional map injury and infarct volume were both included as explanatory variables in multiple linear regression models, only functional map injury remained significantly related to behavioural outcome.

The increase in deficits with greater injury to cortical motor maps (Table 2) is concordant with prior studies in which motor cortex injury was introduced under controlled conditions, either experimentally in primates or surgically in human patients. In primates, larger injury to motor cortex produces enduring substantial arm weakness while smaller insults produce a mild distal paresis that shows substantial recovery (Kennard, 1942; Hines, 1943; Sperry, 1947; Hoffman and Strick, 1995; Friel and Nudo, 1998; Schieber and Poliakov, 1998; Liu and Rouiller, 1999). Current findings are also concordant with results of precentral gyrus surgical resection in human patients with neurosurgical conditions, with extensive precentral gyrus resection producing persistent major arm weakness, and a small resection resolving to mild hand motor deficits (Sachs, 1935; Penfield and Erickson, 1941; Bucy, 1944; Laplane *et al*., 1977). Several of these studies were able to define the cortical insult in terms of functional map injury because these maps were defined before introducing the lesion (Penfield and Erickson, 1941; Bucy, 1944; Hoffman and Strick, 1995; Friel and Nudo, 1998; Schieber and Poliakov, 1998; Liu and Rouiller, 1999).

In some cases, results may have provided insight into the anatomical basis of the behavioural measures. Proprioceptive sensory testing correlated with injury to the hand sensory map

more than with injury to hand or shoulder motor maps, suggesting that postero-ventral areas activated during passive finger movement (the hand sensory task) are of greater functional significance to this sensory function. Functional map injury did not correlate with the Fugl–Meyer score. This suggests that the anatomical basis for this scale may be largely subcortical, consistent with the scale's content. Arm tone correlated with injury to all four maps and with total infarct volume, suggesting that a broad area of cortex can modify tone when injured.

Correlation between behavioural deficits and injury to areas where cortical representation maps overlap was not stronger than correlation between behavioural deficits and injury to individual task maps. This suggests that areas of overlap, as defined at the resolution of fMRI, do not have extra importance in the organization of motor behaviours. However, the specific behaviours related to activity in motor representation overlap regions may have been incompletely probed by current methods.

The current study measured brain insult on the basis of injury to normal cortical motor and sensory maps. Previous studies have also assessed brain injury in terms more specific than total volume of injury, though with alternative approaches. In patients with stroke (Pendlebury *et al*., 1999) or multiple sclerosis (Lee *et al*., 2000), motor status correlated with MRI spectroscopic measures of axonal injury in the posterior limb of the internal capsule. Such an approach may lack some of the specificity obtained by measuring damage to cortical maps derived from moving a single body part. However, assessment of capsular integrity may be complementary to the current approach by measuring injury across a broad range of motor-related tracts and by virtue of subcortical measurement site. Language deficits after stroke correlated with perfusion abnormalities in Wernicke's area (Hillis *et al*., 2001). This study defined the region of interest using standard templates and it is possible that injury–behaviour correlations would have been improved by instead estimating the location of Wernicke's area from brain mapping studies of normal subjects. Motor status was related to degree of cerebral peduncle shrinkage chronically after stroke (Warabi *et al*., 1990). Recovery was severely reduced when cerebral peduncle loss was >40%, similar to the value found in the current study for total loss of hand motor function, >37% injury to hand motor map (Fig. 2).

The current findings based on lesion effect support models that describe a broad, rather than focal, cortical organization of movement (Strick and Preston, 1982; Donoghue *et al*., 1992; Nudo and Milliken, 1996; Nudo *et al*., 1996). Use of a more liberal threshold to define significance increased map size by a factor of 1.58–2.61 (Table 4), but did not change the relationship between behaviour and functional map injury, as reflected by $\kappa = 1.0$ for each functional map. Changing threshold also had little effect on the amount of hand motor map injury associated with total loss of hand motor function. If functions such as hand interossei strength were localized within a restricted patch of cortex, examining injury over a larger stretch of cortex would be expected to reduce the injury–behaviour correlation, but this was not seen. A broad localization may be particularly in evidence for the hand sensory and face motor tasks, where use of a more restrictive threshold to define significance reduced correlations between functional map injury and behaviour.

The current findings also support models of motor cortex organization whereby somatotopy is present between body segments, but limited within a body segment (Nudo *et al*., 1996; McKiernan *et al*., 1998; Georgopoulos *et al*., 1999; Sanes and Donoghue, 2000). The hand motor map overlapped extensively with the shoulder motor map, but not with the face motor map. Similarly, hand motor map injury had similar relationships with behaviour compared with shoulder map injury, but different relationships compared with face motor map injury (Table 2). In addition, the overlap observed between normal maps might explain some unexpected findings, such as the relationship of face map injury to pegboard performance, the similar relationship to behaviour found for hand sensory and face motor map injury, and results of partial correlation analyses. Considerable spatial overlap of normal maps was present in several areas including precentral gyrus, postcentral gyrus, ventral premotor cortex and secondary somatosensory area. Spatial overlap across different tasks' normal maps may reflect use of a common cortical resource, but at the spatial resolution of the current approach, it can not be concluded that the very same neuronal pools were active across tasks.

There are several limitations to the current approach. Future studies might be improved by adding measures of injury at the subcortical level (Makris *et al*., 1997; Pendlebury *et al*., 1999; Lee *et al*., 2000). Current methods did not establish which cortical layers were activated for each task. The control functional maps were each derived from a different number of subjects due to issues in fMRI data collection, resulting in different power to detect activation in the group composite maps across tasks. Right hemisphere infarcts were flipped and then superimposed upon left hemisphere control maps for 10 patients. Differences in contralateral sensorimotor organization between right and left hemispheres might thus cloud data interpretation. The region of sensorimotor cortex evaluated in the current study gives rise to the vast majority of corticospinal tract fibres (Passingham, 1993; Porter and Lemon, 1993; Galea and Darian-Smith, 1994), and is thus a major contributor to final behaviour. However, changes in the activity of other foci in relevant cortical networks can affect final behaviour (Price *et al*., 1999; Chen *et al*., 2002; Rijntjes and Weiller, 2002), and measuring changes in function of these distant foci might further explain the relationship between behaviour and sensorimotor cortex injury. Finally, superimposing each lesion on control activation maps assumes patients had normal functional anatomy prior to stroke, and does not consider premorbid variability across patients. Unmeasured changes in the function of distant motor network foci and in inter-subject variability in premorbid brain organization are

limitations that might have reduced correlations between behaviour and cortical injury as assessed in the current study.

The current results based on lesion assessment support current models of broad motor cortex organization, as well as substantial overlap within a body segment but limited overlap across body segments. The effects of injury to sensorimotor cortex in humans are better described by incorporating measures of normal functional anatomy. Future therapeutic trials might achieve more precise characterization of a brain insult, such as stroke, by incorporating a measure of functional map injury.

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