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The relationship between brain activity and peak grip force is modulated by corticospinal system integrity after subcortical stroke

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Abstract

In healthy human subjects, the relative contribution of cortical regions to motor performance varies with the task parameters. Additionally, after stroke, recruitment of cortical areas during a simple motor task varies with corticospinal system integrity. We investigated whether the pattern of motor system recruitment in a task involving increasingly forceful hand grips is influenced by the degree of corticospinal system damage. Nine chronic subcortical stroke patients and nine age-matched controls underwent functional magnetic brain imaging whilst performing repetitive isometric hand grips. Target grip forces were varied between 15% and 45% of individual maximum grip force. Corticospinal system functional integrity was assessed with transcranial magnetic stimulation. Averaged across all forces, there was more task-related activation compared with rest in the secondary motor areas of patients with greater corticospinal system damage, confirming previous reports. However, here we were primarily interested in regional brain activation, which covaried with the amount of force generated, implying a prominent executive role in force production. We found that in control subjects and patients with lesser corticospinal system damage, signal change increased linearly with increasing force output in contralateral primary motor cortex, supplementary motor area and ipsilateral cerebellum. In contrast, in patients with greater corticospinal system damage, force-related signal changes were seen mainly in contralesional dorsolateral premotor cortex, bilateral ventrolateral premotor cortices and contralesional cerebellum, but not ipsilesional primary motor cortex. These findings suggest that the premotor cortices might play a new and functionally relevant role in controlling force production in patients with more severe corticospinal system disruption.

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Keywords

fMRI; human; motor cortex; premotor; stroke; transcranial magnetic stimulation

Introduction

Motor system reorganization after focal brain damage has been demonstrated using functional brain imaging techniques. Compared with healthy volunteers, patients with stroke have more task-related brain activation in secondary motor regions such as premotor cortex, supplementary motor area (SMA) and cingulate motor areas, particularly in the contralesional hemisphere (Chollet *et al.*, 1991; Weiller *et al.*, 1993; Cramer *et al.*, 1997; Seitz *et al.*, 1998; Newton *et al.*, 2002; Ward *et al.*, 2003; Gerloff *et al.*, 2006). Furthermore, secondary motor system overactivity is particularly prominent in more impaired patients (Ward *et al.*, 2003).

There are two ways to investigate the functional relevance of secondary motor region recruitment. One approach uses transcranial magnetic stimulation (TMS) to disrupt activity transiently in targeted cortical regions whilst measuring differential behavioural effects in patients and healthy controls. In patients with subcortical stroke, TMS to the dorsolateral premotor cortex (PMd) in either hemisphere increases simple reaction times (Johansen-Berg *et al.*, 2002; Fridman *et al.*, 2004) and impairs timing of complex finger movements when delivered to the contralesional side (Lotze *et al.*, 2006). TMS to the contralesional primary motor cortex (M1), however, affects only the timing of complex finger movements (Lotze *et al.*, 2006). These effects are more prominent in patients with greater motor impairment, suggesting that the relative contribution of each brain region to recovered function depends on the degree of motor system damage as well as the demands of the task.

A second way of assessing the functional contribution of brain regions is to measure how task-related activity covaries with modulation of task parameters. In healthy humans, for example, functional imaging experiments have shown that increasing force production is associated with linear increases in blood oxygen level-dependent (BOLD) signal in contralateral M1 and medial motor regions, implying that they have a functional role in force production (Dettmers *et al.*, 1995; Thickbroom *et al.*, 1999; Ward & Frackowiak, 2003).

We recently showed that when patients with a subcortical stroke grip with their affected hands there is a shift in average motor system recruitment from primary to secondary networks in those with greater corticospinal system disruption (Ward *et al.*, 2006). This result suggests that average task-related activity in a region is related to individual corticospinal integrity, but does not indicate whether this activity contributes towards recovered motor function. Here we assess each cortical motor region's contribution to recovered grip by using functional magnetic resonance imaging (fMRI) to examine how activity in each area covaries with increasing force production. We then tested how the pattern in individual patients was related to a measure of corticospinal integrity assessed independently using TMS.

We hypothesized that, as in healthy controls, activity in ipsilesional M1 would covary positively with the amount of force output in patients with lesser degrees of corticospinal system damage. In contrast we expected in patients with greater corticospinal disruption, who were nevertheless still able to modulate grip force, that activity in secondary motor areas would show novel force-modulated characteristics, suggesting a behaviourally relevant role in the post-stroke functional motor network.

Materials and methods

Subjects

Patients were recruited from the National Hospital for Neurology and Neurosurgery, Queen Square, London. The patient group comprised nine male patients (range 22–69 years, mean 48.1 ± 14.3 years). Patient characteristics are listed in Table 1. All patients had suffered from first-ever 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: (1) cortical infarction; (2) carotid artery occlusion or stenosis ≥ 70%; (3) language or cognitive deficits sufficient to impair co-operation in the study; (4) inability to perform the motor task; (5) previous seizures.

Age-matched control subjects were also recruited, comprising nine male subjects (range 21–74 years, mean 49.3 ± 15.6 years). They reported no history of neurological or psychiatric illness, and were not taking regular medication.

All control subjects and patients 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 Foundation Trust, London.

Behavioural evaluation

Subjects were evaluated with the nine-hole peg test (NHPT) and maximum grip strength (GRIP). Maximum grip strength was measured using the same manipulandum as used for MRI scanning. Scores for the affected hand were divided by scores for the unaffected hand and expressed as a percentage.

TMS

The functional integrity of the corticospinal system was measured in each patient using motor cortical stimulus/response curves (Devanne *et al.*, 1997; Ridding & Rothwell, 1997; Boroojerdi *et al.*, 2001), as described previously (Ward *et al.*, 2006). At least 10 resting motor-evoked potentials were obtained at each of four stimulus intensities (90%, 110%, 130% and 150% of resting motor threshold, or up to a maximum of 100% of stimulator output). Maximum amplitude M-waves were elicited from first dorsal interosseus by supramaximal electrical stimulation of the ulnar nerve at the wrist. Peak-to-peak motor-evoked potential amplitudes were expressed as a fraction of the M-wave for each patient and were plotted against stimulus intensity. The gradient of the line of best fit (RC_{AH}) was obtained for each patient using the least-squares method, and used as a measure of the functional integrity of the corticospinal system originating primarily from that hemisphere (Devanne *et al.*, 1997; Ridding & Rothwell, 1997; Boroojerdi *et al.*, 2001).

fMRI scanning

Motor paradigm—A 3T Siemens ALLEGRA system (Siemens, Erlangen, Germany) was used to acquire both T1-weighted anatomical images and T_2*-weighted MRI transverse echo-planar images (EPI) (64 × 64, 3 × 3 mm pixels, TE = 30 ms) with BOLD contrast, as previously described (Ward *et al.*, 2006). During scanning, all patients performed a series of dynamic isometric hand grips of different forces with their impaired hand (five left, four right) using a MRI-compatible manipulandum. The age-matched control group used either their right or left hand (five left and four right, to match the patient group). Continuous visual feedback about the force exerted was provided. Prior to scanning, but whilst lying in the scanner, subjects were asked to grip the manipulandum with their affected hand using

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maximum force to generate a maximum voluntary contraction (MVC). A single scanning session comprised 30 visually cued hand grips interspersed with 30 null events in a randomized and counterbalanced order (intertrial interval = 5.72 s, scanning time = 6 min 14 s). Each hand grip was visually cued. The target force was varied such that 10 grips at each of 15%, 30% and 45% of MVC were performed (30 in total). All subjects performed the motor task outside the scanner to look for the presence of associated or mirror movements. To look for bilateral movements during scanning, patients held identical hand grip manipulanda in both hands while carrying out the task unimanually. Simultaneous recordings from both hands enabled detection of true mirror movements (Nelles *et al.*, 1998). After scanning, a 100-mm visual analogue scale (where 0 = 'no effort' and 100 = 'maximum effort') was used to assess the perceived effortfulness of the task.

Data preprocessing—Imaging data were analysed using Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 6 (The Mathworks, USA) (Friston *et al.*, 1995b; Worsley & Friston, 1995). All volumes were realigned, unwarped (Andersson *et al.*, 2001) and slice-time corrected. The resulting volumes were then normalized to a symmetrical EPI template (the average of the EPI template and the EPI template flipped about the mid-sagittal line) based on the Montreal Neurological Institute (MNI) reference brain in Talairach space (Talairach & Tournaux, 1998) and resampled to 3 × 3 × 3 mm voxels. All normalized images were then smoothed with an isotropic 8-mm full-width half-maximum Gaussian kernel to account for intersubject anatomical differences and allow valid statistical inference according to Gaussian random field theory (Friston *et al.*, 1995a). The time series in each voxel were high-pass filtered at 1/128 Hz to remove low-frequency confounds and scaled to a grand mean of 100 over voxels and scans within each session.

Images from those subjects using their right hand were flipped about the midsagittal plane so that all subjects were assumed to have performed the task with the left hand, consistent with previous published work (Ward *et al.*, 2006).

Statistical analysis

Imaging data from each single subject were modelled using two orthogonal covariates. Firstly, all hand grips were defined as a single event type and modelled as delta functions (grip covariate). A second covariate (force covariate) comprised a delta function scaled by the peak force exerted for each hand grip. The force covariate was mean corrected and orthogonalized with respect to the first covariate ensuring that parameter estimates derived from each covariate are independent. Both covariates were convolved with a canonical synthetic haemodynamic response function and used in a general linear model (Friston *et al.*, 1995b, 1998) together with a single covariate representing the mean (constant) term over scans. Thus, for each subject, voxel-wise parameter estimates for each covariate resulting from the least mean squares fit of the model to the data were generated. Parameter estimates (or 'betas') for the grip covariate reflect the size of increase in the BOLD signal during all hand grips compared with rest (B_G). Parameter estimates for the force covariate represent the partial correlation coefficient of BOLD signal plotted against hand grip force (B_F), i.e. the degree to which BOLD signal changes linearly with hand grips of different force (Buchel *et al.*, 1998). For the control group, statistical parametric maps of the *t*-statistic (SPM{*t*}) resulting from a linear contrast of each covariate (Friston *et al.*, 1995b, 1998) were generated to determine: (1) the main effects of hand grip; and (2) brain regions in which signal varies linearly with hand grip force The resulting SPM{*t*}s were thresholded at $P < 0.05$ (family wise error), corrected for multiple comparisons.

The experimental question in the patient group was whether an interaction between corticospinal system integrity (RC_{AH}) and B_G or B_F can be detected. In a previous experiment, a subset of the current patients was scanned to examine for the main effects of hand grip (B_G) only (Ward *et al.*, 2006), but not the parametric modulation of BOLD signal with increasing force output (B_F) as in this study. In the previous study, owing to the lack of comparable data, we assumed that the relationship between brain activity and corticospinal system integrity would be linear as a first-pass approximation. Although the correlation was significant, it was clear that the relationship was not linear. A *post hoc* analysis of those data found that using log RC_{AH} rather than RC_{AH} as the independent variable resulted in a stronger linear correlation. Thus, we chose *a priori* to use log RC_{AH} as the independent variable in this study for the correlation analysis with B_F.

We used a multisubject fixed effects model for our patient group. The fixed effects model allows 'task by corticospinal integrity' interactions to be examined, although the results are specific to the group studied. Thus, the specific contrasts across each covariate were weighted according to the mean corrected log RC_{AH} scores for each patient (either positively or negatively). When applied to the model these contrast weightings identified voxels in which the correlation between B_G or B_F and log RC_{AH} was significant. The resulting SPM{*t*}s for positive and negative correlations were thresholded at $P < 0.05$, corrected for multiple comparisons.

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

All subjects were able to perform the task adequately. The duration of hand grips for low (target 15% MVC), medium (target 30% MVC) and high (target 45% MVC) hand grips are given in Table 2, along with the mean force and range of forces exerted for each patient. There was no significant correlation between log RC_{AH} and duration of hand grip for low ($r^2 = 0.16$, P = ns), medium ($r^2 = 0.03$, P = ns) or high ($r^2 = 0.05$, P = ns) target forces.

No subject displayed mirror movements or synergistic flexor movements in more proximal joints as assessed outside the scanner by direct observation, and during scanning by inspection of the force recordings from the unaffected hand during movement of the affected hand.

TMS results

M-wave, resting motor threshold and RC_{AH} values for each patient are given in Table 3.

A significant positive correlation was found between log RC_{AH} and GRIP ($r^2 = 0.81$, $P < 0.001$) and between log RC_{AH} and NHPT ($r^2 = 0.51$, $P = 0.03$) (Fig. 1). No correlation was found between log RC_{AH} and the visual analogue scale rating for effort by each patient ($r^2 = 0.03$, P = ns).

Imaging results

Control subjects—The main effects of hand grip were consistent with previous reports using this paradigm (Ward & Frackowiak, 2003) and so are not reported here. Regions in which the magnitude of task-related signal covaried positively with grip force output in this visuo-motor task were seen in contralateral M1, SMA, ipsilateral cerebellum (lobule VI),

and primary visual cortex (Table 4). There were no regions in which task-related signal decreased with increasing grip force.

Stroke patients—A positive correlation between the parameter estimates for grip covariate (B_G) and log RC_{AH} was seen in ipsilesional M1 and contralesional cerebellum (lobule VI) (Table 5). A negative correlation between B_G and log RC_{AH} was seen in contralesional M1, bilateral premotor cortices (both dorsal and ventral), SMA, parietal and prefrontal cortices, contralesional insula cortex, posterior cingulate sulcus, and in both cerebellar hemispheres; ipsilesional lobule VI and contralesional crus I (Table 5).

There were no suprathreshold voxels in which a positive correlation between log RC_{AH} and the parameter estimates for the force covariate (B_F) was found. However, we had hypothesized that we would observe a positive correlation between log RC_{AH} and B_F in brain regions in which task-related activity covaried positively with grip force output in the control group. In other words we expected more 'normal' behaviour of the motor system with greater functional integrity of the corticospinal system. Our *a priori* anatomical hypothesis therefore allowed us to restrict our search volume for a positive correlation between log RC_{AH} and B_F. We used spheres of 10 mm diameter centred on the coordinates of the four peak regions described in Table 4 to define the search volumes. Using this approach, the only region in which there was a positive correlation between log RC_{AH} and B_F in the patient group was in ipsilesional M1 (Table 6 and Fig. 2). Trends towards a significant positive correlation were seen in contralesional cerebellum (lobule VI, $x = -30$, $y = -62$, $z = -22$, Z-score = 2.89, $P = 0.091$) and SMA ($x = 0$, $y = -2$, $z = 52$, Z-score = 3.00, $P = 0.064$), but not in the visual cortex.

Negative correlations between log RC_{AH} and B_F were found in contralesional PMd and cerebellum (crus I), and in the middle frontal gyrus (within the ventral precentral sulcus) bilaterally at the threshold $P < 0.05$, corrected for multiple comparisons across the whole brain (Table 6 and Fig. 3). In the ipsilesional hemisphere, the significant cluster ($P < 0.05$ corrected) extended from $z = 32$ to 42, and in the contralesional hemisphere from $z = 30$ to 46. A location within the precentral sulcus below $z = 50$ is likely to represent the ventral premotor cortex (PMv) (Rizzolatti *et al.*, 2002).

Discussion

In this study we have characterized two aspects of motor system activity during hand grip in nine subcortical stroke patients. Thus, for each brain region we have determined: (1) the average increase in activity during hand grip with the affected hand; and (2) the degree to which brain activity covaries with the amount of force produced. These two parameters can vary independently from one another. Thus, activity in one region might be high on average during hand grip, but might not vary greatly when hand grips of different forces are used. Conversely, activity in another region might be moderate on average, but vary a great deal depending on the amount of force produced.

We have previously reported a negative correlation between average brain activity in secondary motor regions during affected hand grip and a measure of corticospinal system integrity (RC_{AH}) in chronic subcortical stroke patients (Ward *et al.*, 2006). Here we have repeated this finding and confirmed that the shift from primary to secondary motor area recruitment is non-linear, occurring predominantly in the face of marked corticospinal disruption. We have previously interpreted this recruitment of secondary motor areas as an attempt to generate motor output to spinal cord motoneurons in the face of increasing disconnection of ipsilesional M1. However, secondary motor regions are less efficient at

generating motor output so this reorganization can only be considered partially successful in reducing motor impairment after stroke.

In this study we have extended these findings by demonstrating for the first time that after subcortical stroke, the degree to which activity in brain regions covaries with the amount of force produced is related to the extent of corticospinal system damage. In patients with less corticospinal damage (and in normal subjects) brain activity in ipsilesional (contralateral) M1covaries positively with the amount of force produced, as expected. In other words, M1 is behaving more normally in these patients. However, in patients with greater damage to the corticospinal system this force-related modulation of activity is seen in bilateral PMv and contralesional PMd, but less so in ipsilesional M1. This shift suggests that premotor regions have taken on some of the executive properties of M1, which supports the notion that they are contributing to recovered function. Increasing executive properties of contralesional PMd in patients with greater corticospinal damage is consistent with the finding that TMS-induced disruption of this region has greater behavioural effect in more impaired patients (Johansen-Berg *et al.*, 2002). Force-related modulation of brain activity in non-primary motor regions has been demonstrated previously in chronic stroke patients (Dettmers *et al.*, 1997), but here we demonstrate that the relationship between changes in force production and brain activity within the distributed motor system is modulated by the functional integrity of the major motor output pathway. Taken together, the results of these studies indicate that our subcortical stroke patients with greater damage to the corticospinal tract are left with a motor system that is not only configured differently, but one that behaves differently in response to demands to increase relative force output.

Our results must be viewed in the context of the patients studied. We were interested in characterizing differences in motor system organization in a wide range of subcortical stroke patients. This variability does not lend itself to examining for average group effects, but is essential for a correlation analysis of the type we have employed. However, our cohort is by no means representative and thus it is difficult to generalize the results to all stroke patients.

We characterized the variability in the patient group using both TMS and fMRI. TMS was used to obtain motor cortical stimulus/response curves, which plot the size of the motor potential evoked by magnetic stimulation of a fixed site on the scalp across a range of intensities (Ridding & Rothwell, 1997). For an intrinsic hand muscle the relationship is sigmoidal (Devanne *et al.*, 1997) and most likely reflects increasing recruitment of the elements comprising the corticospinal system, namely cortical circuitry, the motoneuron pool and spinal interneuronal relays (Burke *et al.*, 1994). Although the exact contribution of each of these elements is not well understood, the resulting stimulus/response gradient is a sensitive reflection of the functional integrity of the corticospinal system (Devanne *et al.*, 1997; Ridding & Rothwell, 1997; Boroojerdi *et al.*, 2001). Our measure of corticospinal system integrity accounted for over 80% of the variability in grip strength and over 50% of the variability in a measure of manual dexterity (NHPT) in our patient group. Thus, although there is some variability in subcortical lesion location, our metric of corticospinal system integrity captures a large proportion of clinically relevant anatomical damage in our patient group.

When using fMRI, a potential problem that arises from the variation in motor impairment seen in the patient group is that of performance confounds in the experimental design (Baron *et al.*, 2004). It is increasingly recognized that several cortical motor regions contribute to motor planning and execution via neurons that can encode multiple parameters of the task (Riehle & Requin, 1989; Alexander & Crutcher, 1990; Fu *et al.*, 1993, 1995; Johnson *et al.*, 1999; Kakei *et al.*, 2001; Xiao *et al.*, 2006). For example, the discharge of PMd neurons can be influenced by kinematic (Fu *et al.*, 1993; Scott *et al.*, 1997; Johnson *et al.*, 1999; Gomez

et al., 2000), visuospatial (di Pellegrino & Wise, 1993; Johnson *et al.*, 1996; Shen & Alexander, 1997) and contextual (Hepp-Reymond *et al.*, 1999) aspects of the movement. Thus, any differences in the way a task was performed in patients with marked impairment in comparison to those with less impairment could account for our results. Our experiment was therefore carefully designed to minimize this possibility. There were no differences between patients in terms of the range or average of relative forces exerted or the visual feedback provided. There was no relationship between the duration of hand grips and log RC_{AH}, suggesting that the small differences in time on task between patients could not have explained our results. Neither was there a correlation between the perceived effort involved in the task and log RC_{AH} or impairment (as measured by grip strength or NHPT). Thus, in terms of perceived effort our design ensured equivalence of task across all subjects, so that the changes in force modulatory areas observed are likely to be a consequence of differences in corticospinal system integrity rather than task difficulty. Our results reflect differences in brain activity over the relative range of forces available to each individual patient (i.e. 15–45% of maximum voluntary contraction).

However, the range and average of absolute force levels were smaller in patients with greater corticospinal damage. An alternative explanation of our result lies in the finding that premotor regions, particularly ventral, are more active during precision compared with power grip (Ehrsson *et al.*, 2000, 2001). It is possible that the more impaired patients were performing the force modulation task more like a precision grip task, thus accounting for increased modulatory behaviour in ventral premotor cortices. Nevertheless, whether it is the change in absolute or relative force levels that is more important, it still suggests that these regions become increasingly functionally useful, in the face of greater corticospinal damage.

Single-cell recordings in macaque monkeys have demonstrated positive linear correlations between firing rates of cortical neurons and force during grip tasks in contralateral M1 (Evarts, 1968; Smith *et al.*, 1975; Hepp-Reymond *et al.*, 1978; Evarts *et al.*, 1983; Wannier *et al.*, 1991; Georgopoulos *et al.*, 1992). Experiments in humans using fMRI have found similar results (Dettmers *et al.*, 1995; Thickbroom *et al.*, 1999; Ward & Frackowiak, 2003). We observed a linear increase in BOLD signal with increasing force in contralateral M1 in our control group and in patients with greater functional integrity of the corticospinal system. In patients with greater damage, however, force modulatory behaviour in ipsilesional (contralateral) M1 diminished, suggesting reduced functional utility. These patients generally exhibit greater motor impairment (Fig. 1), and yet are still able to modulate hand grip force. Modulation of grip force in the face of increasing corticospinal damage must therefore be mediated by non-M1 sites. Our results suggest the premotor cortices are able to take on this role.

In single-cell recordings, a quarter of PMd cells demonstrated force-related activity in an isometric task (Werner *et al.*, 1991). A small proportion of PMv cells may either increase or decrease neuronal firing rates with increasing precision grip force (Hepp-Reymond *et al.*, 1994). The fMRI signal from a region is effectively an average of the local responses, which might explain why force modulation was not seen in premotor cortices in our control group using fMRI. However, our results demonstrate that a consistently positive correlation between force and BOLD signal was more likely to be seen in premotor cortices rather than M1 as corticospinal integrity diminished, indicating an increase in the number of premotor neurons involved in force-related activity.

The adopted role of the premotor regions within the residual functional architecture is less clear. In primates, M1, PMd and PMv form a densely interconnected network subserving hand motor function (Dum & Strick, 2005). Although the laminar distribution of the corticocortical connections suggests these regions operate at the same hierarchical level,

their corticospinal projections are significantly different (Dum & Strick, 2005). Spinal cord motor neurons to the hand originate from lower cervical/upper thoracic cord. A large proportion of direct cortico-motoneuronal fibres to the lower cervical cord originate from M1 (He *et al.*, 1993; Porter & Lemon, 1993; Maier *et al.*, 2002). PMd provides projections to the upper and lower cervical cord, whilst PMv provides projections mainly to the upper cervical cord (He *et al.*, 1993). Thus, premotor projections are unlikely to completely substitute for those from M1 to hand muscles. However, the ability to modulate applied forces, even if those forces are lower, will increase the functionality of hand grip. Our results suggest that the premotor regions play a role in maintaining this capability.

It is possible that premotor regions are exerting their modulatory effect directly on M1 by increasing the gain of residual M1 output. When higher grip forces are required, partial damage to the corticospinal system may render existing inputs to M1 insufficient to increase output to spinal cord motor neurons. In this situation, additional premotor cortex input to M1 could facilitate an increase in residual M1 output. In normal primates, rostral PMv (area F5) is able to facilitate motor cortex output to upper limb motor neurons (Cerri *et al.*, 2003; Shimazu *et al.*, 2004). The human homologue of primate area F5 remains controversial but is likely to be close to Brodmann area (BA)44 (Rizzolatti *et al.*, 2002). Our ventral premotor clusters are situated just dorsal and caudal to this region in the normal human brain (Tomaiuolo *et al.*, 1999), although the border between BA44 and ventral BA6 remains uncertain (Amunts *et al.*, 1999). Enlargement of the PMv hand area has been observed in primates after M1 damage (Frost *et al.*, 2003; Dancause *et al.*, 2005), together with the appearance of novel connections between PMv and primary somatosensory cortex (Dancause *et al.*, 2005). The possibility of shifts in PMv/BA44 representation in some of our patients cannot therefore be excluded.

An alternative explanation is that premotor regions exert their modulatory effect through non-monosynaptic pathways to spinal cord motor neurons. In stroke patients with poorer recovery (and greater damage to the corticospinal system) a greater proportion of the descending motor command is mediated through propriospinal projections (Mazevet *et al.*, 2003; Stinear & Byblow, 2004). Both PMd and PMv have direct and indirect (via bilateral reticulospinal pathways) projections to the propriospinal premotoneurons in the upper cervical cord (Benecke *et al.*, 1991; He *et al.*, 1993). Movements elicited through the propriospinal system tend to involve multiple joints rather than fractionated finger movements (Mazevet & Pierrot-Deseilligny, 1994; Mazevet *et al.*, 2003). Thus, the appearance of flexor synergistic movements in some patients when gripping harder could be explained by increased activation through propriospinal pathways.

The shift in executive force modulation from M1 to premotor regions is reflected in changes in cerebellar activation. In control subjects, force modulation was seen in lobule VI, but in patients with increasing corticospinal disruption appeared more ventrally in crus I. Cerebellar outputs from the dentate nucleus to premotor regions are ventral to those targeting M1 (Middleton & Strick, 1997). Thus, our result may reflect increased force-related activity in contralesional premotor-cerebellar loops as a consequence of increased task-related connectivity in contralesional motor loops (Gerloff *et al.*, 2006).

In conclusion, we have previously demonstrated that increasing corticospinal damage results in less dependence on ipsilesional M1, but greater dependence on secondary motor regions (Ward *et al.*, 2006). This is likely to reflect recruitment of surviving motor regions that are able to influence spinal cord motoneurons and thus motor output. Our current results characterize this response to corticospinal injury further by demonstrating that motor-related activity in contralesional PMd and bilateral PMv is not only increased in patients with more damage to the corticospinal system, but that this activity now covaries with force output in a

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way not seen in healthy controls or in patients with less damaged corticospinal systems. Furthermore, covariation between force output and brain activity in ipsilesional M1 diminishes with increasing corticospinal system damage. Thus, there is a shift in brain regions involved in modulating grip force from contralateral (ipsilesional in the patients) M1 towards premotor regions in this group of patients. Our finding suggests that premotor regions might therefore play a new and functionally relevant role in optimizing motor output in the face of major corticospinal disruption. Thus, reconfiguration of functional neural networks post-stroke is a dynamic process dependent on both the anatomy of the damage and the demands of a task.

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Abbreviations

BA	Brodmann area
BOLD	blood oxygen level-dependent
EPI	echo-planar image
fMRI	functional magnetic resonance imaging
M1	primary motor cortex
MNI	Montreal Neurological Institute
MVC	maximum voluntary contraction
NHPT	nine-hole peg test
PMd	dorsal lateral premotor cortex
PMv	ventral lateral premotor cortex
RC_{AH}	recruitment curve gradient – affected hemisphere
SMA	supplementary motor area
TMS	transcranial magnetic stimulation

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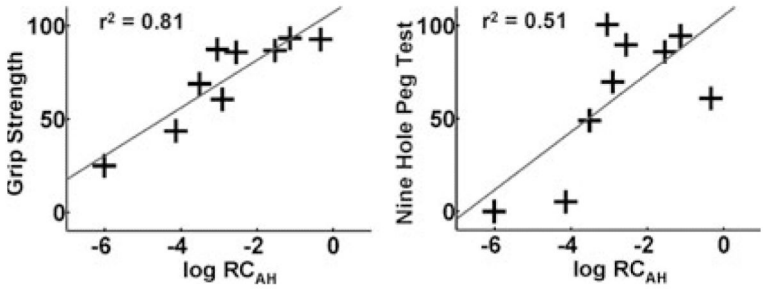

Fig. 1.

Maximum hand grip (GRIP) and nine-hole peg test (NHPT) scores for the affected hand (expressed as percentage of the values for the unaffected hand) plotted against log RC_{AH}.

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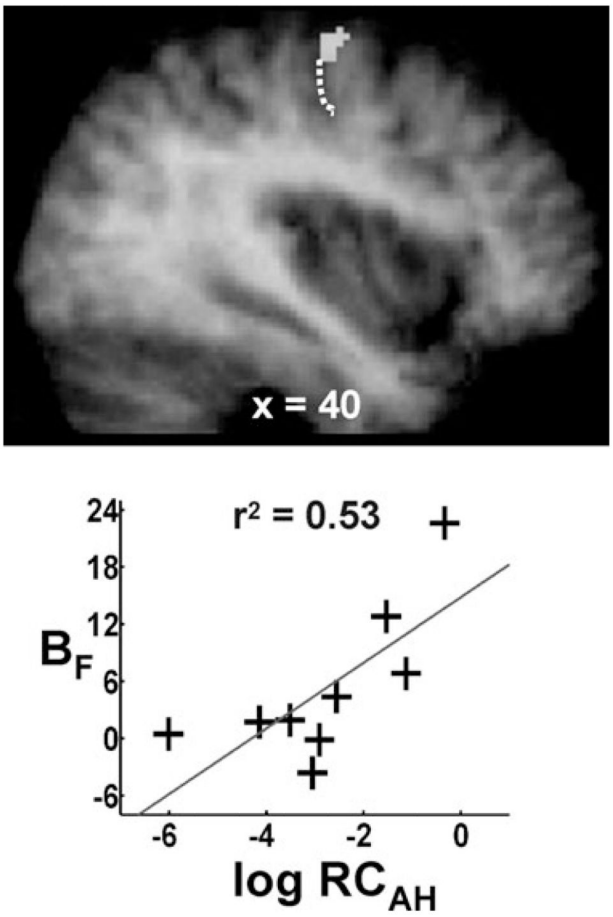

Fig. 2.

A positive correlation between RC_{AH} and B_F was seen in ipsilesional primary motor cortex on the anterior bank of central sulcus ($x = 40$, $y = -16$, $z = 62$, $r^2 = 0.53$). Results are overlaid onto the average T1-weighted structural scan obtained from all stroke patients. The position of the central sulcus is marked by a dotted white line. The plot of B_F vs. RC_{AH} for the peak voxel in the cluster is also shown.

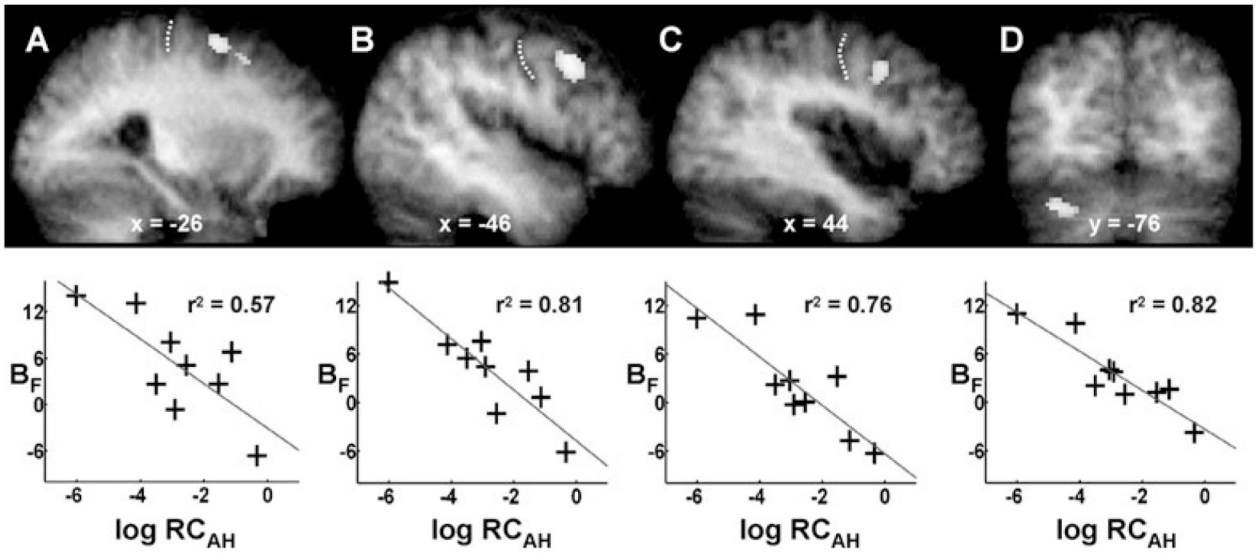

Fig. 3.

Brain regions in which there is a negative correlation between RC_{AH} and B_F. (A) Contralesional PMd ($x = -26$, $y = -4$, $z = 60$, $r^2 = 0.57$). (B) Contralesional PMv ($x = -46$, $y = 8$, $z = 38$, $r^2 = 0.81$). (C) Ipsilesional ventral premotor cortex ($x = 44$, $y = 6$, $z = 40$, $r^2 = 0.76$). (D) Contralesional cerebellum (crus I) ($x = -34$, $y = -76$, $z = -32$, $r^2 = 0.82$). Results are overlaid onto the average T1-weighted structural scan obtained from all stroke patients. The position of the central sulcus is marked by a dotted white line in (A–C). The plot of B_F vs. RC_{AH} for the peak voxel in each cluster is shown underneath each brain slice.

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Table 1

Patient characteristics

Patient	Age (years)	Sex	Site of lesion	Time since stroke (months)	Initial severity	Grip strength (%)*	NHPT (%)*	Past medical history
1	62	M	R striatocapsular	5	0	24.9	0	Hhypertension
2	46	M	R internal capsule	8	0	87.3	100.5	Nil
3	69	M	L striatocapsular	9	4	61.5	69.7	Hypertension
4	44	M	R striatocapsular	8	0	43.6	5.1	Nil
5	33	M	L pons	46	0	68.7	48.9	Nil
6	51	M	L corona radiata	6	4	85.7	89.6	Hypertension
7	58	M	R internal capsule	7	0	93.3	94.5	Hypertension
8	22	M	L pons	4	0	86.6	85.8	Nil
9	48	M	R striatocapsular	116	0	92.6	60.8	Nil

L, left; M, male; R, right. Initial severity represents strength of finger extension (Medical Research Council scale) at time of stroke as recorded in the medical notes. NHPT, nine-hole peg test.

*Values measured at the time of study.

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Table 2

Hand grip performance

Patient	Grip duration (ms)			Mean force (% MVC)	Range (% MVC)
	Low grip	Medium grip	High grip		
1	1309 ± 204	1675 ± 179	2199 ± 216	27.9 ± 9.6	8.4–45.6
2	1047 ± 78	1305 ± 137	1567 ± 194	26.3 ± 10.5	14.7–47.7
3	1179 ± 207	1540 ± 155	2030 ± 190	27.1 ± 10.4	12.1–43.0
4	1116 ± 215	1360 ± 209	2129 ± 172	31.9 ± 11.3	13.4–57.0
5	981 ± 130	1345 ± 158	1789 ± 192	29.5 ± 9.9	13.2–45.5
6	937 ± 173	1236 ± 263	1606 ± 253	25.5 ± 10.8	8.6–44.7
7	1206 ± 171	1761 ± 204	2238 ± 249	29.2 ± 11.6	12.3–51.4
8	1066 ± 141	1307 ± 146	1620 ± 153	32.6 ± 14.3	10.8–58.2
9	1093 ± 106	1457 ± 101	1896 ± 134	28.8 ± 12.4	8.7–51.9

Data are presented as means ± SD or range.

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Table 3

TMS data

Patient	M-wave (mV)	rMT_{AH}	RC_{AH}
1	6.86	80	0.003
2	13.34	41	0.048
3	18.2	39	0.055
4	11.04	85	0.016
5	10.81	52	0.031
6	18.04	65	0.078
7	13.42	44	0.324
8	16.79	54	0.216
9	15.45	47	0.716

M-waves are from the paretic hand first dorsal interosseus muscle. RC_{AH}, affected hemisphere stimulus/response gradient from first dorsal interosseus (corrected for M-wave amplitude); rMT_{AH}, resting motor threshold for first dorsal interosseus from affected hemisphere.

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Table 4

Increasing signal change with increasing hand grip force in healthy controls

		Talairach coordinates in MNI space			
Region	**Side**	***x***	***y***	***z***	***Z*-value**
Primary motor cortex	C	40	−16	56	> 8.0
Supplementary motor area	C	0	−6	46	7.71
Cerebellum (lobule VI)	I	−30	−70	−22	7.29
Primary visual cortex	C	0	−90	6	> 8.0

Brain voxels in which hand grip-related signal change increases linearly with increasing hand grip force. For the group analysis, control subjects are assumed to have used their left hands, and brains flipped about the mid-sagittal line accordingly. Voxels are significant at $P < 0.05$, corrected for multiple comparisons. C, contralateral; I, ipsilateral.

Table 5

Correlation between the main effects of hand grip and corticospinal system integrity in chronic stroke patients

Region	Side	Talairach coordinates in MNI space			*Z*-value	(r^2)
		x	*y*	*z*		
Positive correlation						
Primary motor cortex	I	40	−16	64	4.31	0.45
Cerebellum (lobule VI)	C	−16	−46	−24	4.22	0.45
Negative correlation						
Primary motor cortex	C	−32	−26	66	> 8.0	0.74
Premotor cortex (dorsal)	C	−36	−12	66	> 8.0	0.63
	C	−26	−10	56	> 8.0	0.86
	I	42	−2	54	> 8.0	0.73
Premotor cortex (ventral)	C	−52	4	18	5.56	0.36
	I	50	12	18	7.17	0.57
Supplementary motor area	I	2	0	64	> 8.0	0.69
	C	−6	0	54	7.39	0.75
Cingulate sulcus	C	−6	−24	58	6.87	0.55
Intraparietal sulcus	C	−36	−54	56	> 8.0	0.49
	I	40	−52	56	> 8.0	0.72
Inferior parietal cortex	C	−44	−42	24	> 8.0	0.76
Superior parietal cortex	I	24	−40	70	5.28	0.49
Prefrontal cortex (dorsolateral)	I	38	38	36	6.91	0.61
	C	−36	34	40	5.35	0.54
Insula cortex	C	−28	16	10	5.19	0.69
Cerebellum (lobule VI)	I	28	−70	−28	5.85	0.61
	I	32	−40	−42	5.73	0.73
Cerebellum (Cr I)	C	−36	−72	−34	5.95	0.66

Brain voxels in which there is a correlation between log RC_{AH} and the parameter estimates for the grip covariate (B_G) within the patient group. Voxels are significant at $P < 0.05$, corrected for multiple comparisons. C, contralesional; I, ipsilesional.

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Table 6

Correlation between size of force modulation effect and corticospinal system integrity in chronic stroke patients

		Talairach coordinates in MNI space			Correlation analysis	
Region	**Side**	***x***	***y***	***z***	***Z*-value**	**(r^2)**
Positive correlation						
Primary motor cortex	I	40	−16	62	3.92‡	0.53
Negative correlation						
Premotor cortex (ventral)	C	−46	8	38	5.49*	0.81
	I	44	6	40	5.17*	0.76
Premotor cortex (dorsal)	C	−26	−4	60	4.88*	0.57
Cerebellum (crus I)	C	−34	−76	−32	4.77*	0.82

Brain voxels in which there is a correlation between log RC_{AH} and the parameter estimates for the force covariate (B_F) within the patient group. Voxels are significant at $P < 0.05$, corrected for multiple comparisons

*across the whole brain

‡across a restricted search volume defined by spheres of 10-mm diameter centred on the coordinates of the four peak regions described in Table 4.
C, contralesional; I, ipsilesional.