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Stroke. 2008;39:1507-1513; originally published online March 13, 2008;
doi: 10.1161/STROKEAHA.107.501999
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Background and Purpose—Although knowledge concerning cortical reorganization related to upper limb function after ischemic stroke is growing, similar data for lower limb movements are limited. Previous studies with hand movement suggested increasing recruitment of motor areas in the unlesioned hemisphere with increasing disability. We used ankle movement as a lower limb analog to test for similarities and differences in recovery patterns.

Methods—Eighteen subjects were selected with chronic residual gait impairment due to a single subcortical ischemic stroke. Functional MRI scans were obtained at 3.0 T during active and passive ankle dorsiflexion in the patients (8 females, 10 males; mean age, 59.9±13.5 years; range, 32 to 74 years) and 18 age-matched healthy control subjects.

Results—We observed substantial neocortical activity associated with foot movement both in the patients with stroke and in the healthy control subjects. Our primary finding was increased cortical activation with increasing functional impairment. The extent of activation (particularly in the primary sensorimotor cortex and the supplementary motor area of the unlesioned hemisphere) increased with disability. The changes were most prominent with the active movement task.

Conclusions—Using ankle movement, we observed increased activation in the unlesioned hemisphere associated with worse function of the paretic leg, consistent with studies on movement of paretic upper limbs. We interpret this finding as potentially adaptive recruitment of undamaged ipsilateral motor control pathways from the supplementary motor area and (possibly maladaptive) disinhibition of the ipsilateral sensorimotor cortex. (***Stroke*. 2008;39:1507-1513.)**

Key Words: disability ■ fMRI ■ lower extremity ■ plasticity ■ stroke

The potential of functional MRI (fMRI) to identify changes in cortical activation patterns associated with different levels of recovery has been demonstrated in several studies probing functional consequences of brain damage. In fMRI studies of upper limb movements, a more bihemispheric pattern of motor cortex activation has been reported in patients with poor motor function after both early and chronic stroke.[1,2] Bilateral activation was seen to decrease with improvements in function in chronic stroke both spontaneously and after rehabilitation.[3–6]

Although knowledge concerning cortical reorganization related to upper limb function after ischemic brain damage is extensive, analogous data for lower limb movements are still limited.[7,8] However, fundamental differences in the neural control of hand and leg movement have to be expected, eg, considering the role of spinal interneurons in central pattern generation for gait[9] versus the almost exclusively cerebral–cerebellar control of fine hand movements.[10,11] Patterns of brain activation associated with recovery, specifically of lower limb function, after stroke therefore may be different from those for hand movements.[5,10,12,13] Brain responses to ankle movements in healthy subjects have been characterized using fMRI,[7,8,14,15] but studies in patients with gait impairment have been limited to multiple sclerosis[16] and patients with stroke with heterogenous lesion types (subcortical, cortical, brainstem).[7,17,18]

We therefore used fMRI and an active and passive ankle dorsiflexion paradigm to test for cortical functional reorganization in patients with gait impairment and chronic disability after stroke. We focused specifically on subcortical ischemic strokes affecting efferent motor tracts without cortical involvement to limit the pathological heterogeneity. Our aims were to use ankle dorsiflexion as an analog of hand flexion–extension to test for evidence of potentially compensatory activation in patients with lower limb paresis after stroke as has been found for the upper limb and to determine whether

Received August 23, 2007; accepted September 20, 2007.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.107.501999**

Table. Coordinates (in MNI standard space) and Activation Significance (Z statistics) for Contrasts

Group Contrast	Region		Maximum Z Score	MNI Coordinates of Maximum Z Score		
				X	Y	Z
Active versus rest						
Patients; paretic foot	SMC	L	6.01	−4	−18	74
	Cerebellum	VI	5.09	0	−70	−14
		L; V	4.79	−26	−62	−30
	Insula	R	5.35	44	4	−2
Patients; unaffected foot	SMC	R	5.60	4	−6	58
	Cerebellum	L; VI	5.69	2	−48	−10
	Insula	R	5.63	48	2	−6
		L	4.61	−48	2	−4
	SII	R	5.04	58	−34	20
		L	4.71	−46	−34	12
Patients; paretic foot versus control subjects	Not significant					
Patients; unaffected foot versus control subjects	Not significant					
Lower motricity patients; paretic foot versus control subjects	SMC	R	4.45	−2	−34	−74
	Cerebellum	R; VII, Cr II	5.14	30	−78	−52
	SMA	L	4.46	−6	−18	66
Lower versus higher motricity patients; paretic foot	SMC	R	4.45	6	−26	64
Patients; correlation with Motricity Score affected leg	SMC/SMA	R	4.76	0	−32	54
Passive versus rest						
Patients, paretic foot	SMC	L	6.31	−2	−16	70
	SII	L	6.08	−50	−32	12
		R	4.51	58	−32	14
Patients, unaffected foot	SMC	R	5.74	14	−22	74
	SII	R	4.68	64	−30	14
		L	5.30	−48	−34	12
	Cerebellum	L; V, VI	4.41	−24	−32	−28

Regions of the cerebellum are designated according to the convention provided by Schmahmann et al.[26]
SII indicates secondary somatosensory cortex; L, left; R, right.

interindividual differences in the poststroke fMRI response are correlated with the degree of functional impairment of the lower limb.

Subjects and Methods

Patients

Inclusion Criteria

We included patients with residual gait impairment attributable to a single MRI-visible subcortical ischemic stroke, which had occurred 6 months or more before study entry. The study was approved by the local ethics committee. Subjects had to score 3 or above on the Functional Ambulatory Capacity rating scale.[19] Their mean (SD) Functional Ambulatory Capacity score was 4.4±0.6 (median, 4.0; range, 3 to 5; Functional Ambulatory Capacity 5: normal; 4: independent on level, help on slopes, stairs, uneven surfaces; 3: verbal/standby of one person; 2: continuous or intermittent support of one person; 1: firm continuous support of one person; 0: help of 2 or more persons/cannot walk). Patients had to have a degree of residual gait impairment due to stroke. This was defined by an abnormal 10-m walk time for age (age <60=10 seconds or longer or 1 m/s; age 60 to 69: 12.5 seconds or longer or 0.8 m/s; age ≥70: 16.6 seconds or longer, <0.6 m/s).[20] To allow use of the active fMRI paradigm, patients were selected who were able to actively ankle dorsiflex to a minimum of 10°.

Exclusion Criteria

Cognitive impairment precluding full engagement with the experimental paradigm (Mini Mental State Examination score <27), extensive leukoaraiosis (ie, confluent white matter lesions according to the Fazekas scale),[21] other clinically significant causes for reduced mobility (eg, disabling arthritis, musculoskeletal or cardiorespiratory disease), present rehabilitation or previous rehabilitation within 4 months before inclusion, common contraindications for MRI, somatosensory or proprioceptive abnormalities apparent on neurological examination (including somatosensory tests of light touch, pin prick, and vibration sensitivity; proprioception of the great toe and ankle; and tests for extinction with light touch on the dorsum of the feet), or neuroleptic or anticonvulsive medication were exclusion criteria.

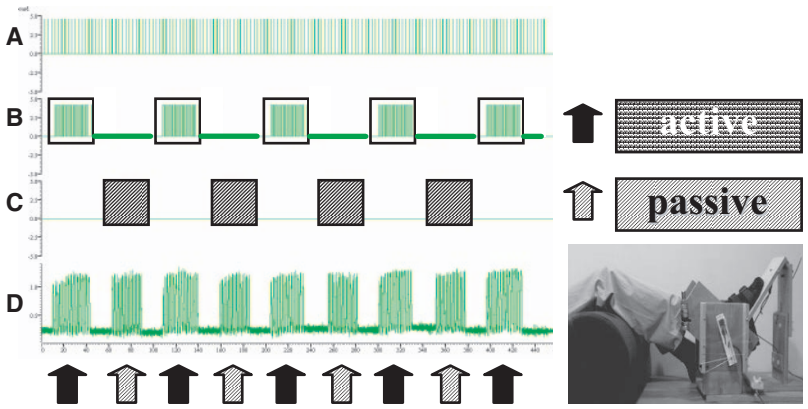

Figure 1. fMRI paradigm. Over 150 volumes (A, scanner triggers), 5 blocks of active foot movement (B) alternated with 4 blocks of passive foot movement (C) and interspersed rest periods. The inset shows the purpose-built wooden ankle support and the movement apparatus providing an electronic signal giving the angular displacement at the joint for continuous monitoring of individual performance in the scanner through a potentiometer (D; y-axis: time in seconds).

Demographics and Clinical Characteristics

The patient group comprised 18 individuals (8 females, 10 males) having a mean (SD) age of 59.8±13.5 years (median, 63.0 years; range, 32 to 74 years). The mean (SD) time interval since stroke was 37.3±36.8 months (median, 21.0 months; range, 6 to 144 months). Patients had spent 67.1±60.9 days (median, 62.0 days; range, 0 to 180 days) in inpatient rehabilitation.

The mean values (SD) for the Motricity Score,[22] a neurological deficit score with lower values indicating worse function (maximum, 99), were 77.7±10.5 for the affected leg (median, 77.0; range, 58 to 91) and 71.3±23.9 for the affected arm (median, 76.0; range, 9 to 99). Two functional outcome scales were used to quantify the patients' ability to perform tasks of daily living. The mean (SD) Rivermead Mobility Index,[23] a measure of mobility disability, was 12.8±1.9 (median, 13.0; range, 8 to 15; maximum, 15) and the mean (SD) modified Barthel Index score,[24] reflecting functional outcome after stroke, was 18.6±1.6 (median, 19.0; range, 15 to 20; higher scores reflecting better outcome; maximum, 20).

Twelve subjects had right-sided and 6 subjects had left-sided hemiparesis. The ischemic lesions affected the posterior limb of the internal capsule (n=11) or efferent corticospinal tracts within the corona radiata (n=7). Sixteen patients were right-handed, one patient was left-handed, and one ambidextrous.[25]

The 10-m timed walk and the 2-minute walk were used as measures of speed and of endurance, respectively. Assessed twice serially after 5-minute periods of rest to limit variability, the averaged mean (SD) values were 15.9±20.3 seconds for the 10-m timed walk and 101.9±37.7 m for the 2-minute walk, reflecting a mean (SD) walking speed of 0.74±0.23 m/s. Twelve subjects used a walking stick and 6 had an ankle–foot orthosis.

Healthy Control Subjects

Eighteen age-matched and right-handed[25] subjects (12 females, 6 males) with a mean (SD) age of 58.8±13.8 years (median, 61.0 years; range, 30 to 79 years) served as a control group. All had a normal neuropsychiatric history and neurological examination. None had any major health problems. One subject was on antihypertensive monotherapy and none of the remainder used chronic medication. Structural brain scans were reported as normal in all subjects. The healthy subjects also underwent gait measurements as described previously. As expected, the average time needed for the 10-m timed walk was shorter (7.3±22.1 seconds) and the distance completed during the 2-minute walk was longer (166.19±22.14 m) than in the stroke patient cohort, reflecting a mean walking speed of 1.36±0.23 m/s.

MRI

Data acquisition was performed on a 3.0-T Varian INOVA MRI system (Siemens, Erlangen, Germany) using a multislice gradient-echo echoplanar image sequence (TR=3000 ms, TE=30 ms, 24×6-mm axial slices, voxel dimensions 4×4×6 mm, field of view 256×256, matrix 64×64, spin angle 90°). Care was taken to cover both brain regions near the vertex and the cerebellum as inferiorly as possible. Conventional T2-weighted scans and a high-resolution T1-weighted structural image (IR3D Turbo Flash, 64 3-mm axial slices, TR=30 ms, TE=5 ms, TI=500 ms, flip angle 15°, field of view 256×256, matrix 256×256) also were acquired for each subject to allow functional image registration for precise localization of activations and to assess the topography of structural brain damage caused by the ischemic infarcts.

Paradigm Design

The paradigm (based on that used previously in our laboratory)[15] involved unilateral foot movements in a purpose-built wooden apparatus in a block design with 2 conditions: active ankle dorsiflexion and passive movement of the ankle by the experimenter (Figure 1). Active and passive movement blocks alternated with interspersed periods of absolute rest (21 seconds each). Each block was 30 seconds long, there being 5 active movement blocks and 4 passive movement blocks. The total scanning time for unilateral movement of one foot was approximately 450 seconds.

During the active movement blocks, the subject was paced by a visual cue. Vision was corrected with prism lenses if necessary. In an attempt to reduce stimulus-correlated motion, the subjects' heads were secured with Velcro straps in a foam-cushioned holder and their knees were flexed to approximately 135° using a soft roll placed beneath the knees. There were no significant differences between patients and control subjects in parameters of head motion during the fMRI paradigm.

Before entering the scanner, subjects practiced the paradigm using the same apparatus. In patients, a self-paced comfortable rate of movement in the apparatus (based on the self-selected walking speed) was assessed for each foot for dorsiflexion and plantarflexion and then used to determine the frequency for the visual cue for movement during the scanning paradigm. This approach was chosen to match the amount of "effortfulness" of the movements rather than the rate of movement. Movements for the paretic feet were paced at a mean rate of 1127±364 ms (range, 800 to 1800 ms) for dorsiflexion and 1236±364 ms (range, 850 to 1200 ms) for plantarflexion. Respective values for movements of the unaffected feet were 1016±257 ms (range, 800 to 1500 ms) and 1138±250 ms (range, 900 to 1800 ms). These parameters were then kept constant across all sessions of the experiment. In control subjects, the pacing was fixed at a rate of 1000 ms for dorsiflexion and plantarflexion.

The mean dorsiflexion in the apparatus for patients was 22.1±5.6° (range, 10 to 30°) for active ankle movement. Dorsiflexion was fixed at 30° for passive movement. Healthy control subjects used the full range of movement in the apparatus (30°) for both tasks. Patients were observed and corrected for any synkinetic movement of the opposing limb during familiarization outside the scanner. After initial training, none of the patients exhibited a clinically detectable radiation of movement (synkinesia) to the unaffected side or upper limbs with the experimental task. This clinical impression was additionally checked with surface electromyography outside the scanner. Direct observation during imaging confirmed that movements were limited to the test foot. During the passive movement

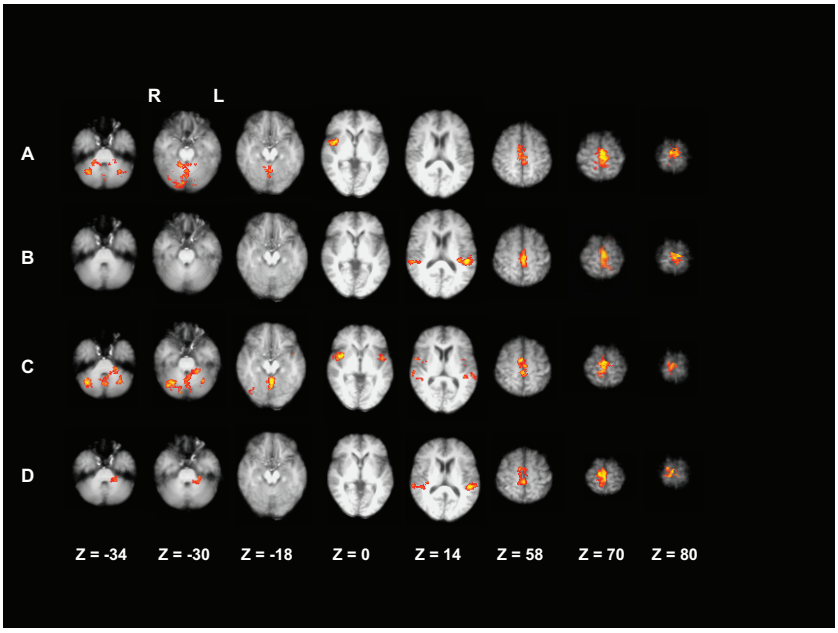

Figure 2. Mean maps of brain activation in patients associated with active (A) and passive (B) movements of the paretic foot and of the unaffected foot (C and D, respectively). Data were grouped with images adjusted so that brain activation contralateral to the paretic foot was in the left hemisphere displayed on the right side of the image in this radiological convention (mixed effects higher level analyses; Z >3.1; corrected cluster significance threshold P=0.01).

condition, dorsi- and plantarflexion of the foot was paced by a visual cue (not visible to the subjects) at a rate of 1.0 Hz. The paradigm was first performed for one foot with pseudorandom selection of the right or left leg.

Data Analysis

fMRI analysis was carried out using FEAT (FMRI Expert Analysis Tool; version 5.63, www.fmrib.ox.ac.uk/fsl). The following prestatistical processing was applied: motion correction using MCFLIRT; nonbrain removal using BET; spatial smoothing using a Gaussian kernel of 5 mm full-width half maximum; global (volumetric) multiplicative mean intensity renormalization (which forces every fMRI volume to have the same mean intensity by calculating the mean intensity for each volume and then scaling the intensity across the whole volume to a preset constant value); and high-pass temporal filtering (Gaussian-weighted least squares straight line fitting with sigma=50.0 seconds). Time-series statistical analysis was carried out using FILM with local autocorrelation correction. Registration to high-resolution and/or standard images was carried out using FLIRT. Higher level analysis was done using FLAME (FMRIB's Local Analysis of Mixed Effects). Z (Gaussianized T/F) statistical images were thresholded using clusters determined by Z >3.1 and a (corrected) cluster significance threshold of $P=0.01$.

In a first-level analysis, the effects of the active and passive movement blocks versus rest were determined for each subject, session, and limb (paretic or control). Absolute head motion as assessed from displacement in the head images was integrated in the models at the first level as a covariate of no interest. Registration results were checked visually. Functional and structural images of subjects with right hemispheric strokes were flipped right to left so that the image on the left represented the "damaged" hemisphere (corresponding to "paresis" in a notional right foot for all patients). Age was used as a covariate of no interest in higher level models. A functional region of interest (ROI), selected from an activation cluster defined by a higher level mixed effects analysis (sensorimotor cortex [SMC] region of activation in the contrast between patients with lower Motricity Score and matched healthy control subjects during active movement versus rest), was applied to the first-level analyses to compute mean signal changes within the ROI for the active and passive movement conditions versus rest. For representation, activation clusters were overlaid on the group mean normalized high-resolution brain image. All images are shown in radiological convention in which the left side of the image is the right side of the brain.

General Statistical Analyses

The Statistical Package of Social Sciences (PC+, version 11.5; SPSS Inc, Chicago, Ill) was used to test categorical variables by Pearson's χ^2 test and continuous variables by Student t test or the Mann-Whitney U test. Bivariate correlations were tested using Spearman's Rho nonparametric test in the absence of normal distribution. The level of significance was set at 0.05.

Results

Active Foot Movement Versus Rest in Patients and Control Subjects

The mixed effects contrast of the active movement versus the rest conditions was associated with similar activation patterns in patients and control subjects. The functional network included the primary SMC and secondary sensorimotor cortices, supplementary (SMA) and cingulate motor areas, and the ventral premotor cortices (Table and Figure 2A–C; findings for healthy control subjects as described previously).[15] Significant infratentorial activation was found in the midline and paramedian sectors of the anterior and posterior lobes of the cerebellum (vermis), ipsilateral to foot movement in lobules IV, V, and VI of the cerebellum (near the middle cerebellar peduncle), and bilaterally in the cerebellar hemispheres (lobules IV, V, and VI; culmen and declive).[26]

Higher level mixed effects group contrasts of active movement conditions versus rest across the entire group of patients compared with control subjects did not show significant differences (Z>3.1; corrected cluster significance threshold $P=0.01$) with movement of either the paretic or of the unaffected foot. Group-level contrasts of active movement versus rest of the paretic foot versus active movement versus rest of the unaffected foot within the patients with stroke also did not show significant differences (data not shown).

Passive Foot Movement Versus Rest in Patients and Control Subjects

Brain activation patterns during passive movement versus rest showed activation in brain areas partly overlapping with

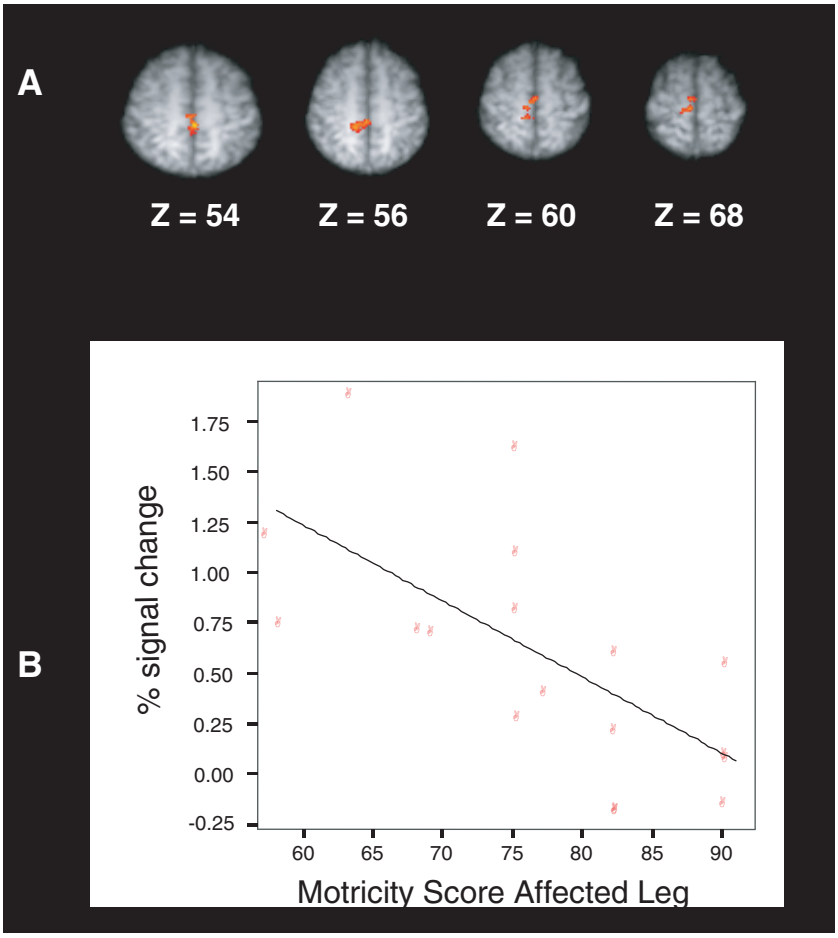

Figure 3. Influence of lower limb function on brain activation. A, Brain regions in which active movement-associated brain activation shows a significant negative correlation with Motricity Score of the affected leg. Increased activation in SMC and SMA of the unlesioned hemisphere ipsilateral to movement is noted with decreasing functional strength (mixed effects analyses; $Z > 3.1$; corrected cluster significance threshold $P = 0.01$). B, Correlation between activation signal changes within the unlesioned hemisphere and disability for active movement. Activation data from an SMC ROI in the undamaged hemisphere (defined by the SMC region of activation found in the contrast between patients with lower Motricity Score and matched healthy control subjects during active movement versus rest) using the entire patient group was strongly correlated ($r = -0.76$) with Motricity Score for the affected leg (COPE, coefficient of parameter estimates).

patterns of activation observed with active movement versus rest. Both in patients and control subjects, significant activations were observed in SMC, the precuneus, the cingulate gyrus, and secondary sensorimotor cortices bilaterally (Table and Figure 2B–D, as described for control subjects previously).[15] The MNI coordinates of the peak activation within the SMC for the active ($x = -4$, $y = -18$, $z = 74$) and passive ($x = -2$, $y = -16$, $z = 70$) movement conditions of the paretic limb versus rest were not meaningfully different. No significant activations in the cerebellum or in subcortical brain structures were found. There were no significant differences between patients and control subjects in the group contrast of passive foot movement relative to rest. Within patients, contrasts of brain activation during movement of the paretic versus the unaffected foot also showed no significant differences (data not shown).

Effects of Lesion Location and Laterality

No significant differences were found in the patterns of activation between patients with internal capsule ($n = 11$) or centrum semiovale ($n = 7$) lesions or between patients with left ($n = 12$) and right ($n = 6$) hemispheric lesions.

Influence of Lower Limb Function

To further explain the variability in the fMRI activation related to lower limb function, a higher level mixed effects analysis of patients contrasting active movement of the paretic foot versus rest using the demeaned Motricity Score of the affected leg of each patient as a continuous variable was performed. Figure 3A shows brain regions where active movement-associated activation showed a negative correlation with Motricity Score (ie, an increase of activation with more impaired leg function; see Table for coordinates). Variations in the self-paced movement rate within the scanner were moderately correlated with the Motricity Score of the affected leg ($r = -0.54$, $P = 0.02$ for dorsiflexion and $r = -0.59$, $P = 0.01$ for plantarflexion). Differences in movement rate alone (assuming that higher movement rates [greater numbers of movements per block] are associated with greater activation) therefore cannot account for the differences seen. Significant changes were not found with the same contrasts in data for passive movement of the affected foot or for active or passive movement of the unaffected foot.

Region of Interest Analysis

To further define relations between variations of activation with impairment and to better understand the distribution of results across subjects, we performed a ROI analysis using active and passive movement data versus rest from individual subjects. Activation data from an SMC region of interest in the unlesioned hemisphere (defined by the contrast between patients with lower Motricity Score and matched healthy control subjects during active movement versus rest; see Table for coordinates; imaging data not shown) using the

entire patient group demonstrated a strong correlation ($r=-0.76$) with Motricity Score for the affected leg (Figure 3B). The ROI analysis for the passive movement condition versus rest showed a moderate correlation between signal change in the same ROI and the Motricity Score of the affected leg ($r=-0.57$).

Discussion

We report use of an fMRI ankle dorsiflexion paradigm to test for cortical reorganization in patients with chronic stroke with varying degrees of residual gait impairment. In line with studies on movement of paretic upper limbs,[1–6] our primary finding was increased cortical activation in the unlesioned hemisphere of the patients with stroke (ipsilateral to the paretic lower limb) with increasing functional impairment. Increased activation was found in SMC and SMA. We interpret this as reflecting mixed effects of a loss of normal interhemispheric inhibition of SMC[27] and potentially adaptive recruitment of undamaged motor control pathways from the SMA in the ipsilateral hemisphere,[28] but direct testing (eg, using transcranial magnetic stimulation interference)[29] is needed to evaluate this hypothesis further.

Few previous studies have examined lower extremity movement in stroke using fMRI.[7,17,18] The main finding of the largest study by Luft and coworkers suggested differences in brain activation associated with knee movement of the paretic leg determined by lesion location.[18] In contrast to our observations, the authors also reported a correlation between better functional outcome and greater activation of the ipsilateral SMC in their subcortical patients. Differences in the paradigms used (unilateral knee versus ankle movements), clinical correlates (speed of gait versus functional strength), the nature of the patients with subcortical stroke studied, or the high percentage of subjects with mirror movements (58% in Luft et al versus none in our study) might explain this discrepancy. In the subgroup of patients with subcortical strokes without mirror movements from the Luft et al study, larger ipsi- and contralateral motor cortex recruitment was found. Alternatively, consideration of the full results from the 2 studies together could be considered as evidence that the increased ipsilateral SMC activation is either a functionally nonspecific finding (eg, reflecting "effortfulness") or one with little independent effect on function (eg, loss of selectivity of interhemispheric cortical control for a movement in which subcortical control may be strongly dominant).[27] Further work is needed to address these possibilities.

Although increased brain activation with pyramidal tract injury was most prominent in the SMC and the SMA, it is unlikely that injury-related activation differences are confined to these brain regions. Although the direct contrasts did not demonstrate significance, comparison of the thresholded group maps of patients and control subjects (data not shown) suggested that other areas of activation difference might be distinguished (eg, greater cerebellar and right parietal activation in control subjects compared with patients) with greater study power.

The hypothesis that changes in neocortical motor network function are closely associated and perhaps causally related to lower limb function was further supported by the finding that activation changes elicited by passive movement were also correlated with functional impairment, albeit to a weaker extent. Here, despite absence of any volitional, active movement (supported by the fact that no significant basal ganglia or cerebellar activation was observed), changes in SMC activation also associated with the neurological deficit were found. The patients did not have proprioceptive or somatosensory loss detectable with neurological testing. One possibility is that there are subclinical changes in central sensory processing as a direct consequence of sensory afferent or efferent injury. However, cortical sensorimotor systems are closely integrated.[30,31] As discussed previously (for upper[5,32] and more recently for lower limb movements),[14,15] the changes also may indirectly reflect injury-induced plastic changes affecting functional connectivities involved in motor control.[33] To date, the literature comparing active and passive motor paradigms appears conflicting; whereas in some situations active and passive task changes appear equivalent,[5] in others, active activation maps decrease, whereas sensory maps increase with recovery.[12,13]

We did not find evidence for significant premotor activation differences between patients and healthy subjects or between patients with different degrees of disability in this study of lower limb paresis despite the consistency of this finding in studies of upper limb impairments.[2,34–36] Several studies have emphasized a role for premotor activity in differentiated movements of the distal upper limb.[37,38] Enlargements of premotor cortex representations proportional to the amount of primary motor cortex injury from ischemic infarcts have been reported in monkeys.[39] Studies in humans have suggested similar changes.[3,29] Our finding would be consistent with differences in cortical control of movement for the distal upper and lower limbs.[40] Further work to confirm differential involvement in upper and lower limb recovery after stroke could make use of variants of previous transcranial magnetic stimulation transient interference approaches.[27]

Although there are novel elements of interest, limitations of this study need to be considered in the interpretation of our findings. Active movement rates in the scanner were fixed in control subjects but variably adjusted to a rate that each patient was able to maintain. This performance difference complicates interpretation of activation differences solely in terms of differences in brain mechanisms. However, this difference in movement rate cannot account for the primary results reported; as noted previously, despite fewer movements per block, more disabled patients showed greater and more widespread activation. Future work could explore differences using less "efficient" single-event designs to fully disambiguate the influence of rate. Sensitivity to differences also might have been enhanced with use of a more demanding or graded task design.[41]

Sources of Funding

This work has been supported by the Austrian Science Fund (C.E., S.R.); the UK Medical Research Council (P.M.M.) and Wellcome Trust (H.J.B.). P.M.M. became an employee of GlaxoSmithKline after completion of the experimental phase of this project.

Disclosures

None.

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Correction

In the article entitled "Functional MRI Correlates of Lower Limb Function in Stroke Victims With Gait Impairment" by Enzinger et al[1] that published in *Stroke* (Volume 39, Issue 5) should have included the following financial information: We are grateful for financial support from the Oxford NIHR Biomedical Research Centre.

This has been corrected for the print and online versions. The authors regret this error.

The corrected version can be viewed online at http://stroke.ahajournals.org/cgi/reprint/39/5/1507.

[1] *[Correction for Vol 39, Number 5, May 2008. Pages 1507–1513.]*
(*Stroke*. 2011;42:e403.)

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STR.0b013e31821b1443**