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doi:10.1093/brain/awh713 *Brain* (2006), **129**, 791–808

Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke

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Clinical recovery after stroke can be significant and has been attributed to plastic reorganization and recruitment of novel areas previously not engaged in a given task. As equivocal results have been reported in studies using single imaging or electrophysiological methods, here we applied an integrative multimodal approach to a group of well-recovered chronic stroke patients (n = 11; aged 50–81 years) with left capsular lesions. Focal activation during recovered hand movements was assessed with EEG spectral analysis and $H_2{}^{15}O$-PET with EMG monitoring, cortico–cortical connectivity with EEG coherence analysis (cortico–cortical coherence) and corticospinal connectivity with transcranial magnetic stimulation (TMS). As seen from comparisons with age-matched controls, our patients showed enhanced recruitment of the lateral premotor cortex of the lesioned hemisphere [Brodmann area (BA) 6], lateral premotor and to a lesser extent primary sensorimotor and parietal cortex of the contralesional hemisphere (CON-H; BA 4 and superior parietal lobule) and left cerebellum (patients versus controls, $Z > 3.09$). EEG coherence analysis showed that after stroke cortico–cortical connections were reduced in the stroke hemisphere but relatively increased in the CON-H (ANOVA, contrast analysis, $P < 0.05$), suggesting a shift of functional connectivity towards the CON-H. Nevertheless, fast conducting corticospinal transmission originated exclusively from the lesioned hemisphere. No direct ipsilateral motor evoked potentials (MEPs) could be elicited with TMS over the contralesional primary motor cortex (iM1) in stroke patients. We conclude that (i) effective recovery is based on enhanced utilization of ipsi- and contralesional resources, (ii) basic corticospinal commands arise from the lesioned hemisphere without recruitment of ('latent') uncrossed corticospinal tract fibres and (iii) increased contralesional activity probably facilitates control of recovered motor function by operating at a higher-order processing level, similar to but not identical with the extended network concerned with complex movements in healthy subjects.

Keywords: Plasticity; stroke; recovery; motor control; motor cortex

Abbreviations: APB = abductor pollicis brevis muscle; BA = Brodmann area; COG = center of gravity; CON-H = contralesional hemisphere; DAM-H = damaged (stroke) hemisphere; EOI = electrode of interest; EDC = extensor digitorum communis; ERD = event-related desynchronization; FWHM = full width at half maximum; iM1 = ipsilateral (= contralesional) primary motor cortex; M1 = primary motor cortex; MEP = motor evoked potential; MRC = Medical Research Council; MT = motor threshold; NAP = number of active positions (from which TMS responses are elicited); OP = optimal point for eliciting a defined muscle response with TMS; POI = (electrode) pairs of interest; PT = pyramidal tract; rCBF = regional cerebral blood flow; ROI = region of interest; SMA = supplementary motor area; SPL = superior parietal lobule; SPM = statistical parametric map; tDCS = transcranial direct current stimulation; $\tanh^{-1}$ = inverse hyperbolic tangent; TMS = transcranial magnetic stimulation; TRCoh = task-related coherence; TrlogPow = task-related log-transformed power; TRPow = task-related power; TR$\tanh^{-1}$Coh = task-related inverse hyperbolic tangent-transformed coherence

Received July 31, 2005. Revised September 29, 2005. Accepted November 7, 2005. Advance Access publication December 19, 2005

Introduction

Clinical recovery after stroke can be significant and has been attributed to plastic reorganization in the adult human CNS (Chollet *et al.*, 1991; Weiller *et al.*, 1992; Hamdy and Rothwell, 1998; Xerri *et al.*, 1998; Calautti and Baron, 2003; Cramer, 2003; Nudo, 2003; Ward *et al.*, 2003; Rossini and Dal Forno, 2004). Reorganization commonly refers to recruitment of areas previously not (or less) engaged in a given task, in order to substitute for directly lesioned or disconnected areas (Merzenich and Jenkins, 1993; Nudo *et al.*, 1996; Cramer *et al.*, 2001; Ward *et al.*, 2003; Baron *et al.*, 2004; Rossini and Dal Forno, 2004). A clinically relevant model for recovery is capsular stroke, with loss of corticospinal control from the primary motor cortex (M1) after a subcortical lesion of the efferent pyramidal tract (PT) fibers. In addition to areas located in the hemisphere of the ischaemic lesion (damaged hemisphere, DAM-H), homologous areas of the intact (contralesional) hemisphere (CON-H) have been considered candidates for taking over motor function after hemiparetic stroke (Chollet *et al.*, 1991; Feydy *et al.*, 2002; Fujii and Nakada, 2003) or language processing in patients with aphasia (Weiller *et al.*, 1995; Karbe *et al.*, 1998; Winhuisen *et al.*, 2005). It has been demonstrated that an extended premotor and sensorimotor network including those areas shows high metabolic activity during early clinical improvement with a linear decrease of activation towards later stages of recovery (Ward *et al.*, 2003; Fridman *et al.*, 2004). For capsular infarction with contralateral hemiparesis, a relevant candidate region is the M1 of the CON-H, ipsilateral to the paralysed limb (also referred to as 'ipsilateral M1', iM1). The present study specifically addresses the hypothesis that iM1 contributes to recovered motor function of the paretic hand in subcortical stroke.

It has been suggested that pre-existing uncrossed motor pathways originating from the iM1 may be accessed or recruited to compensate for damage to the crossed pathways after ischaemic stroke (Fisher, 1992; Cao *et al.*, 1998; Ago *et al.*, 2003). However, the data concerning the contribution of iM1 and other cortical regions of the CON-H are inconsistent. Evidence for involvement of iM1 in successful reorganization after stroke has been found in some studies (Chollet *et al.*, 1991; Cao *et al.*, 1998; Green *et al.*, 1999; Feydy *et al.*, 2002; Fujii and Nakada, 2003; Ward *et al.*, 2003) but not in others (Weiller *et al.*, 1992), and, in some, only if movements of the recovered limb were accompanied by mirror movements in the healthy limb (Weiller *et al.*, 1993). The latter finding points to a critical uncertainty in imaging studies on iM1 function after stroke, that is, the lack of sufficient control for mirror activity in the healthy limb when the paralysed limb is moved (Wittenberg *et al.*, 2000). The situation is complicated further because several investigations have pooled data from various types of lesions, for example, cortical and subcortical, supra- and infra-tentorial, left and right hemisphere of right- and left-handed patients with varied clinical outcomes (Cramer *et al.*, 1997; Ward *et al.*, 2003). Some findings with transcranial magnetic stimulation (TMS) have even suggested that enhanced ipsilateral responses to TMS over the iM1 are associated with poor clinical outcome (Netz *et al.*, 1997; Turton *et al.*, 1996). These data raised the possibility that iM1 activation could be interfering with recovery rather than helping it in some patients with predominantly subcortical lesions and moderate to good recovery (Martin *et al.*, 2004; Murase *et al.*, 2004; Ward and Cohen, 2004; Hummel *et al.*, 2005). More recently, studies have pointed to a functionally relevant contribution of the ipsilateral dorsal premotor cortex (iPMd) to recovered motor behaviour after stroke predominantly in patients with more prominent impairment rather than of the iM1 (Johansen-Berg *et al.*, 2002*a*).

To clarify some aspects of the contribution of iM1 and related motor structures (e.g. premotor cortex) of the CON-H to recovery after capsular stroke, we conducted a multimodal study combining clinical, anatomical, functional imaging and neurophysiological information in 11 patients with chronic ischaemic lesions of the left internal capsule. These methods provide complementary, rather than just mutually validating information, as they assess different aspects of information processing (PET, EEG) and functional connectivity (EEG, TMS). The identification of regions engaged in the recovery of function after focal CNS lesions is important not only from a basic science perspective but also from a clinical point of view. Approaches are evolving that might in the future allow for controlled focal enhancement of plastic adaptation in the cortex (e.g. repetitive TMS, convergent pair-pulse stimulation, epidural stimulation, transcranial direct current stimulation (tDCS)) (Stefan *et al.*, 2002; Brown *et al.*, 2003; Kobayashi *et al.*, 2003; Hummel and Gerloff, 2005) or for feeding cortical signals into prosthetic devices (Wessberg *et al.*, 2000; Wolpaw *et al.*, 2002; Friehs *et al.*, 2004; Kennedy *et al.*, 2004). To apply these techniques effectively, the target regions and their potential contributions must be known.

Patients and methods

All participants gave their written informed consent to each experiment according to the declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm), and the National Institute of Neurological Disorders and Stroke Institutional Review Board approved the study protocol. Patients were recruited by advertising in newspapers, to local doctors and by talking at local stroke clubs.

Patient inclusion criteria and clinical data

Inclusion criteria were (i) clinical diagnosis of a first-ever ischaemic stroke in the chronic stage (>8 months after the event; 'first-ever' stroke was clinically defined, small lacunar lesions without clinical consequences were not excluded), (ii) right-handedness according to the Edinburgh handedness inventory and (iii) subcortical lesion affecting the posterior limb of the left internal capsule. The lesions were documented by magnetic resonance imaging

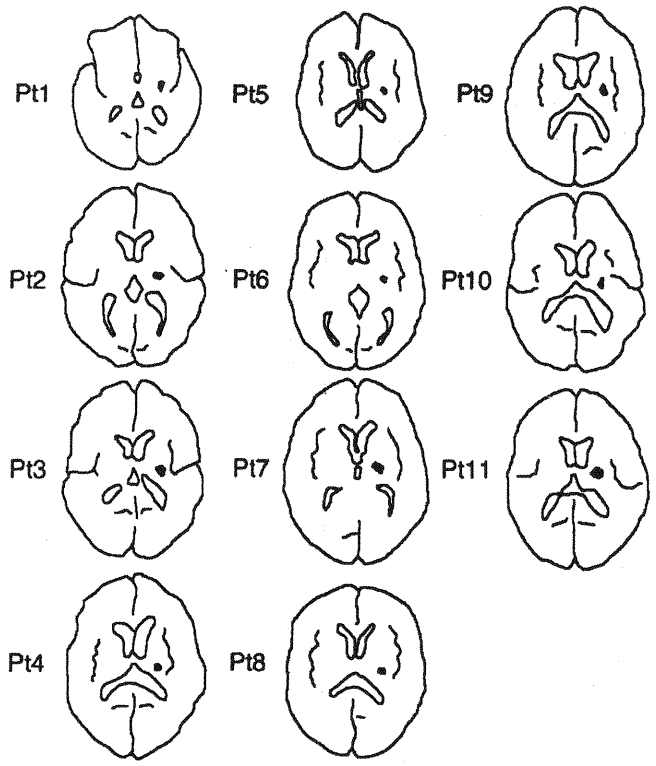

Fig. 1 Schematic representation of MRI lesion sites. Patient numbers correspond with those in the Table 1.

(MRI, T_1- and T_2-weighted images; 1.5 T GE scanner) (schematic drawings of the lesions are given in Fig. 1). Additional lacunar lesions were accepted only if there had not been any previous clinical stroke-like event, and if they were not located in the course of the PT of either hemisphere. The inclusion criterion for muscular strength at the time of the study was '>3/5' assessed clinically using the Medical Research Council (MRC) scale. Further, clinical motor recovery of '>1/5' on the MRC scale and regaining the capacity of individual finger movements were required. Excluded were patients with neurological diseases other than stroke or with neuropsychiatric or neuropsychological deficits which could potentially compromise informed consent or compliance during the experiments. Exclusion criteria were also history of seizures (because of TMS) and professional use of musical instruments prior to the stroke.

Time since stroke was 2.5 years (median, range 1–9 years). The median age in the patient group (n = 11, 2 females) was 70 years (50–81), in the EEG control group (n = 11, 2 females) 59 (48–79), in the PET control group (n = 11, 2 females) 63 (27–75). All controls were also right handed. The initial motor deficit of the patients is documented in Table 1. All patients had experienced substantial clinical recovery. For the stroke patients' right hand the mean ± SD MRC score was 4.1 ± 0.4, for elbow flexion/extension 4.3 ± 0.5, for shoulder movements 4.3 ± 0.5 and for the right leg 4.0 ± 0.0. The left side was not affected in any of the patients. As for skilled movements, all patients needed to be able to perform a finger opposition task (index-to-thumb, middle finger-to-thumb, etc.), finger tapping and finger extensions at a rate of 1–2 per second without mirror activity in the concomitantly recorded EMG. All patients made use of their recovered hand in daily life activities (like holding a cup, tying shoe laces, buttoning a shirt). Grip force in patients was also quantified by a dynanometer. For the stroke patients' right hand the mean ± SD was 59 ± 32 lbs, for their healthy (left) hand the corresponding value was 84 ± 27 lbs. Deep tendon reflexes were increased on the right-hand side in 9 out of 11 patients, a slight somatosensory deficit (hypesthesia) was reported in 2 out of 11 patients.

EEG

EEG was recorded during two conditions: (i) metronome-paced extensions of fingers II–V at a rate of 1 per second with the right hand (MOVE) and (ii) listening to the metronome beats at 1 per second without moving (REST). Subjects were seated comfortably in an armchair with the right arm relaxed and resting on a pillow. The right hand was positioned palm down at the edge of the pillow so that the fingers could be moved freely. Subjects performed repetitive, brisk simultaneous finger extensions followed by brief relaxation (rather than voluntary flexion) (Fig. 2). To avoid intra-session learning effects, subjects practised the required movement before the EEG recording, using online EMG feedback. Five to ten blocks of 100 movements (corresponding to 100 s) and REST (also 100 s) were recorded, alternating with breaks of 1–5 min between blocks to avoid muscular fatigue. During all conditions, subjects looked at a stationary fixation point to prevent eye movements, and were instructed to avoid eye blinks, swallowing or any movement other than the required finger movements. Continuous EEG was recorded from 28 surface electrodes, mounted in a cap (Electro-Cap International Inc., Eaton, OH). Impedances were kept below 8 kΩ. Data were sampled at 250 Hz, low-pass filter was set at 50 Hz and the time constant was set to DC (DC amplifiers and software by Neuroscan, Inc., El Paso, TX). Linked earlobe electrodes served as reference. Four bipolar EMG channels were recorded from surface electrodes positioned over the right and left forearm extensors (extensor digitorum communis, extensor carpi radialis), with each pair of electrodes located ~15 cm apart (distal tendon reference). The high-pass filter for EMG was set to 30 Hz.

The EEG data were analysed using two different approaches: (i) task-related power (TRPow) and event-related desynchronization (ERD) to assess regional activation and its time course and (ii) task-related coherence (TRCoh) to assess interregional coupling.

For analysis of TRPow, EEG signals were digitally filtered off-line (1–50 Hz, slope 24 dB/octave) and, for each experimental condition separately, segmented into non-overlapping epochs (= disjoint sections; cf. Amjad *et al.*, 1997) of 1024 ms (allowing a frequency resolution of 1 Hz). After removal of slow drifts by linear trend correction and baseline correction (using the entire window from 0 to 1024 ms), the single sweeps were visually inspected, and trials with artifacts were rejected. On average, in the patient group 431 artifact-free trials (median) were obtained for the rest condition, 415 trials for the movement condition. In the control group, 458 artifact-free trials were obtained during rest, 447 during movement. Each single sweep was Hamming windowed to minimize spectral leakage. For spectral power analysis, a discrete Fourier transform was computed for each 1024 ms epoch and all electrodes. Spectral power (Pow) was calculated for 4 standard frequency bands: low alpha (8–10 Hz), high alpha (11–13 Hz), low beta (16–20 Hz) and high beta (22–26 Hz). In order to reduce the effect of inter-subject and inter-electrode variability of absolute spectral power values, task-related relative power at an electrode x ($TRPow_x$) was obtained by computing a ratio of rest ($Pow_{x\ rest}$) and corresponding activation conditions ($Pow_{x\ activation}$), according to the following

Table 1 Clinical data

Patient	Age (years)	Gender	Initial symptoms	Years after stroke	Residual symptoms	Localization of ischaemic lesions*						
						Left hemisphere						Right hemisphere
						ICP	GP	PUT	TH	CR	WML	
1	76	M	Right-hand side weakness, unable to walk, dysarthria	2.3	Slight right-hand clumsiness (MRC = 4), spasticity of leg, facial weakness	x	x	x			x	
2	73	F	Severe right hemiparesis, no other symptoms	7.0	Right-hand clumsiness, no weakness (MRC = 5)	x				x	x	
3	59	M	Right-arm paralysis, severe leg; hemiparesis, dysarthria	2.0	Moderate right-hand clumsiness; (MRC = 4), moderate spasticity	x	x	x		x	x	
4	60	M	Right-hand side weakness, unable to walk, dysarthria	2.5	Slight right-hand clumsiness (MRC = 4) Mild spasticity, facial weakness	x	x					PUT
5	73	F	Right-hand side hemiplegia, right visual field defect	7.2	Slight right arm paresis (MRC = 4) moderate spasticity	x	x	x		x	x	
6	61	M	Right-hand side hemiparesis (severe)	2.0	Mild spasticity right arm and hand (MRC = 4)	x						PUT
7	81	M	Right-hand side hemiparesis	4.1	Moderate right-hand weakness (MRC = 4-)	x						
8	50	M	Right-hand side hemiplegia, dysarthria	0.9	Moderate right-hand clumsiness, No weakness (MRC = 5)	x	x		x		x	
9	70	M	Right-hand side hemiparesis, dysarthria	3.6	Moderate right-hand clumsiness, limited use of right hand (MRC = 4-)	x	x	x			x	TH, ICP
10	75	M	Right-hand side hemiplegia, inability to speak	2.3	Moderate right-hand clumsiness, slight right-hand weakness (MRC = 4)	x		x	x		x	TH, ICP
11	66	M	Right-hand side hemiparesis, milder weakness of lower extremity	9.0	Slight right-hand clumsiness and weakness (MRC = 4)	x	x	x	x			PUT

*Lesions other than in the posterior limb of the left internal capsule (ICP) were lacunar and asymptomatic according to clinical history and neurological examination.
GP = globus pallidus; PUT = putamen; TH = thalamus; CR = corona radiata; WML =white matter lesions.

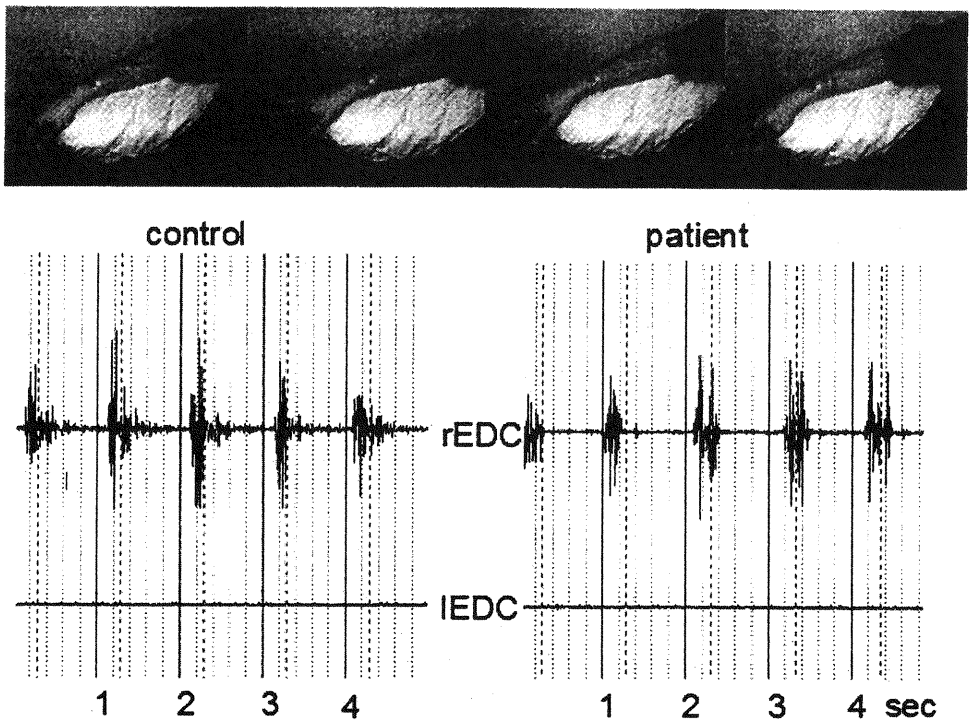

Fig. 2 Experimental paradigm. Top = the motor task consisted in brisk finger extensions at a rate of 1 per second. Bottom = EMG of bilateral forearm extensors (left and right extensor digitorum communis muscles, lEDC and rEDC) was monitored throughout all imaging procedures. Two representative traces are shown. Left = control subject, right = stroke patient. Absence of mirror activity in the hand at rest was required for all trials that entered the final analysis (PET, EEG).

equation.

$$\frac{\mathrm{Pow}_{x\ \mathrm{rest}} - \mathrm{Pow}_{x\ \mathrm{activation}}}{\mathrm{Pow}_{x\ \mathrm{rest}}} \times 100. \quad (1)$$

This approach and its statistical evaluation (including logarithmic, *log*, transformation to stabilize the variance) has been described elsewhere in detail (Pfurtscheller and Aranibar, 1977; Sailer *et al.*, 2000). Relative TRPow decreases ('activation') are expressed in per cent and as positive values. In topographic maps, 'activation' is coded by red colour. To assess the temporal evolution of spectral power changes, the technique of ERD was employed as described elsewhere in detail (Pfurtscheller and Andrew, 1999; Pfurtscheller *et al.*, 2003). This analysis was added in order to get supplementary information on the nature of the contralesional activation in the central region. If the nature of this activation would be linked to reafferent feedback or reflex-like activation of the contralesional motor system as has been proposed previously (Verleger *et al.*, 2003), it should occur only after movement onset; if it is related to movement preparation and execution, it needs to be present before and during movement. For ERD calculation, the raw EEG signal is band-pass filtered for the frequency range of interest (here, 16–20 Hz), rectified and averaged after epoching. The time course of spectral power changes is then plotted in relation to a baseline value (here, mean power during rest) as a function of time. As this type of baseline correction is used and spectral power during baseline (= rest) is typically higher than during activation (= movement), ERD ('activation') is represented as negative values. For the sake of comparability, topographic ERD maps were plotted like the maps for TRPow, i.e. 'activation' is coded in red.

Coherence is computed in the frequency domain and is a normalized measure of the coupling between two signals at any given frequency (Shaw, 1984; Classen *et al.*, 1998). For TRCoh analysis, EEG signals were filtered, segmented, trend and baseline corrected, inspected for artefacts, Hamming windowed and Fourier transformed as described for TRPow. The coherence values (Coh) were calculated for each frequency bin λ according to the following equation (commercial software by Neuroscan, Inc., El Paso, TX, USA).

$$\mathrm{Coh}_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) f_{yy}(\lambda)} \quad (2)$$

The mathematical details as well as the statistical procedures for significance testing (including inverse hyperbolic tangent transformation, $\tanh^{-1}$, to stabilize the variance) have been reported elsewhere (Classen *et al.*, 1998; Andres *et al.*, 1999; Hummel and Gerloff, 2005). In order to reduce the effect of inter-subject and inter-electrode-pair variability of absolute coh, task-related relative coherence (TRCoh_{xy}) was obtained by subtracting rest ($\mathrm{Coh}_{xy\ \mathrm{rest}}$) from corresponding activation conditions ($\mathrm{Coh}_{xy\ \mathrm{activation}}$). Coherence magnitude increments ('coupling') are expressed as positive values, and coherence decrements are expressed as negative values. Coherence increments or decrements between baseline and movement conditions for each pair of electrodes were displayed as color-coded 'link' plots, which permit the inspection of the magnitude and spatial patterns of TRCoh. The subtractive approach also minimizes the bias in the absolute coherence introduced by volume conduction or the reference electrodes (Classen *et al.*, 1998; Fein *et al.*, 1988; Rappelsberger and Petsche, 1988). Broadband coherence was calculated for the same frequency bands as TRPow.

For statistical analysis, factorial ANOVA designs with contrast analyses were used on log-transformed TRPow or $\tanh^{-1}$ transformed TRCoh data (Gerloff *et al.*, 1998, 2003). For TRlogPow,

factors were group (patients, control) and region. For TRtanh^{-1}Coh, factors were group (patients, control) and connection. We have described the definition of regions and connections in a similar study on normal subjects in previous papers in detail (Gerloff *et al.*, 1998; Andres *et al.*, 1999). For TRPow analysis, nine electrodes of interest (EOI) were grouped into three regions each represented by three electrodes: 'left central' (FC3, C3, CP3), 'right central' (FC4, C4, CP4) and 'mesial frontocentral' (Fz, FCz, Cz). For TRCoh analysis, the total number of links between the EOIs was 27 (27 pairs of interest, POI), which were grouped into three major connections: 'left central to right central' (FC3–FC4, FC3–C4, FC3–CP4, C3–FC4, C3–C4, C3–CP4, CP3–FC4, CP3–C4, CP3–CP4), 'left central to mesial frontocentral' (FC3–Fz, FC3–FCz, FC3–Cz, C3–Fz, C3–FCz, C3–Cz, CP3–Fz, CP3–FCz, CP3–Cz) and 'right central to mesial frontocentral' (FC4–Fz, FC4–FCz, FC4–Cz, C4–Fz, C4–FCz, C4–Cz, CP4–Fz, CP4–FCz, CP4–Cz). Significance levels obtained from multiple tests on the same data pool were Bonferroni-corrected. Results were considered significant if $P < 0.05$ after correction.

$H_2{}^{15}O$ PET

PET scanning was performed during the same conditions as EEG, (i) metronome-paced extensions of fingers II–V at a rate of 1 per second with the right hand (MOVE) and (ii) listening to the metronome beats at 1 per second without moving (REST). Scans were obtained in 3D mode using a GE Advance PET tomograph (Waukesha, WI, USA) with an axial field of view of 15.3 cm, covering the whole brain. Task performance began 30 s before bolus infusion of 10 mCi of $H_2{}^{15}O$ (half life, 2.1 min) via a left cubital vein catheter. Scanning was started when a rising brain radioactivity count was first detected (20–30 s after radioisotope injection) and continued for 60 s thereafter. Arterial blood was not sampled and the radioactive counts were therefore used as a measure of relative rCBF (Herscovitch *et al.*, 1983). Five scans were obtained for each REST and MOVE conditions. Interscan interval was 10 min. A transmission scan was obtained prior to each session and used to correct for radioactivity attenuation. Head movement was minimized by using a thermoplastic mask molded to each subject's head and attached to the scanner bed. Attenuation-corrected scans were reconstructed into 35 transaxial planes, 4.25 mm apart, with an in-plane center resolution of 6.5 mm full width at half maximum (FWHM) in each direction. SPM99 software (http://www.fil.ion.ucl.ac.uk/spm) was used for realignment, normalization to a standard stereotactic space (Montreal Neurological Institute brain template) and smoothing with an isotropic Gaussian filter of 12 mm to accommodate individual variability in gyral anatomy.

After correcting for variations in global blood flow (normalized to 50 ml/100 cm^{-3}/min) using ANCOVA (analysis of covariance), differences between experimental conditions (using the contrast MOVE minus REST) were statistically tested for each voxel (search volume was from $z = -50$ to $z = 80$) with SPM99. The resulting whole-brain statistical parametric maps (SPMs) based on the *t*-statistic (transformed to normalized *Z*-scores) had a final spatial resolution of $x = 10.4$, $y = 11.8$, $z = 13.4$ mm (FWHM). We used a two-step random-effects method to determine between-group differences (Friston *et al.*, 1999; Woods, 1996). We applied a statistical significance threshold of peak activity at $Z > 3.09$ and used $P < 0.05$ with small volume correction of for prespecified regions in known motor areas (Poline *et al.*, 1997).

During PET scanning, EMG was monitored from bilateral forearm extensors and flexors with a Dantec Counterpoint unit (*A/D* rate, 5 kHz, band-pass filter 5 Hz–1.5 kHz; DANTEC Counterpoint electromyograph, DANTEC Medical A/S, Skovlunde, Denmark). Two subjects had to be excluded from PET analysis because their motor performance in the scanner did not match the performance of the nine other patients (different movement rate, different type of movement; non-compliance with the instructions in supine position).

Transcranial magnetic stimulation

TMS was performed using a magnetic stimulator (Cadwell Laboratories, Inc., Kennewick, WA) equipped with a focal 2 × 70 mm 'figure-of-eight' coil, and an EMG unit (*A/D* rate, 5 kHz, band-pass filter 5 Hz–1.5 kHz; DANTEC Counterpoint electromyograph, DANTEC Medical A/S, Skovlunde, Denmark). Motor evoked potentials (MEPs) were recorded simultaneously from both forearms using surface EMG electrodes attached over the patients' finger extensor muscles (extensor digitorum communis, EDC), 5 cm apart, or, in two patients, abductor pollicis brevis (APB) muscles, with the active electrode placed on the muscle belly and the inactive electrode over the base of the metacarpophalangeal joint of the thumb. MEPs can be facilitated by voluntary pre-contraction of the target muscles. With this technique, ipsilateral responses can be elicited even in some healthy adults (Wassermann *et al.*, 1994; Ziemann *et al.*, 1999). Thus, for the main part of the TMS experiment we opted to stimulate with the target muscles at rest. Only moderate pre-contraction (~5–10% maximum) was then used in a second run in order to test with higher sensitivity for ipsilateral responses. Continuous acoustic feedback of EMG activity in both forearms was provided during the entire examination. Both hemispheres were searched for stimulation points eliciting contra- or ipsilateral MEPs, and the optimal points (OP; defined as the scalp position where a reproducible muscle response was elicited with the lowest stimulation intensity) as well as their resting motor thresholds (MT; defined as the minimum stimulation intensity that produced at least 5 MEPs exceeding 50 μV in 10 trials) were determined separately. After detection of the OP and determination of MT, the cortical representation of the target muscle was mapped. For quantitative evaluation, the number of active positions (NAP) was computed. 'Active' was defined using a strict (a) and less conservative (b) cutoff. The cutoff for (a) was >50% of the amplitude when stimulated over OP, for (b) >25% of this amplitude. Topographical location was assessed further by calculation of the center of gravity (COG) of each map, according to following equation, i.e. the sum of the vectors of site position weighted individually by MEP amplitudes divided by the sum of all MEP amplitudes (Liepert *et al.*, 1999; Ziemann *et al.*, 1999).

$$\frac{\sum(\text{MEP} \times \text{site})}{\sum \text{MEP}} \quad (3)$$

The COG *x*- and *y*-coordinates are given relative to the vertex (=Cz position of the international 10/20 system of electrode placement). Negative *x*-values correspond to left-hemispheric positions, negative *y*-coordinates denote positions anterior to the vertex.

The absence of ipsilateral responses from the healthy hemisphere was documented by stimulation with 200% MT or 100% stimulator output (whatever was reached first) at the OP for contralateral responses, and at positions 1 and 2 cm anteriorly, posteriorly, laterally and medially.

MT, NAP and the coordinates of the COG were compared between DAM-H and CON-H using the Wilcoxon matched pairs test. The significance level was set at $P < 0.05$.

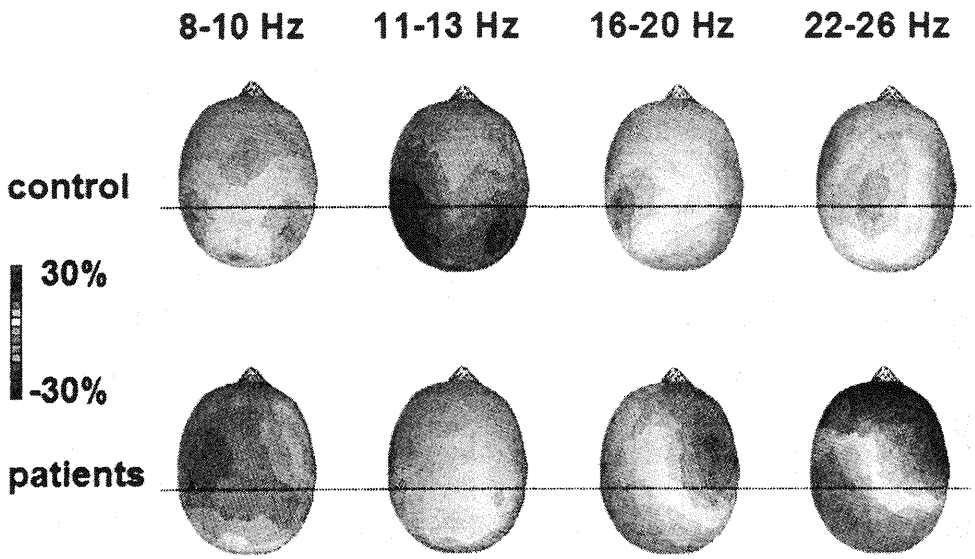

Fig. 3 Results of EEG spectral power analysis (TRPow). Grand average. Cortical activation (TRPow decreases, given in per cent with positive sign) is colour-coded in red. Top = control group, Bottom = stroke patients. The beta frequency band (16–20 and 22–26 Hz) is known to be particularly sensitive to variation of motor parameters in sensorimotor tasks. In this band, the main result was enhancement of activity in the CON-H of stroke patients, extending from the central region (dotted horizontal line) into the frontal and prefrontal cortex. In the alpha band, the results were more variable and only the global decrease of activation in the 11–13 Hz band was statistically significant. At 8–10 Hz, no significant differences were found. Right-hand side of each map = right-hand side of the brain.

Results

Spectral power and coherence analysis of the EEG

The amplitude of activation (TRPow) and the topographic pattern of activation were different for patients and controls (ANOVA, main effect group, $P = 0.0001$; interaction group x region, $P = 0.0001$). Figure 3 illustrates the topographic maps of cortical activation related to right-hand movements in both groups. Distinct patterns were found in normal controls in four frequency ranges (8–10 Hz, 11–13 Hz, 16–20 Hz, 22–26 Hz), in line with a previous EEG study on aged healthy subjects (Sailer *et al.*, 2000). The differences between patients and controls were significant in the high alpha band (11–13 Hz), and in the low and high beta band (16–20 Hz, 22–26 Hz). TRPow decreases (activation) in the (right) CON-H were larger in patients (ANOVA, contrast analysis, $P < 0.01$). In these frequency bands, TRPow decreases in the DAM-H (i.e. activation) were reduced in patients compared with the control group (ANOVA, contrast analysis, $P < 0.01$). In the low alpha band (8–10 Hz) there was a trend towards greater TRPow decreases in patients which, however, did not reach significance because of inter-subject variability.

The most pronounced enhancement of central region activity in the CON-H of patients occurred in the beta frequency range (16–20 Hz). Time-course analysis (16–20 Hz ERD) demonstrated that this enhanced activity in the right central region occurred both in the pre-movement phase and during movement execution (Fig. 4). Together with the known sensitivity of this frequency range to variation of motor parameters rather than somatosensory aspects of a task (Conway *et al.*, 1995; Pfurtscheller *et al.*, 1997; Mima *et al.*, 2000), the time-course data substantiate the notion that this contralesional overactivation is related to actual motor processing including preparation of the recovered movement.

The pattern of inter-regional functional coupling (TRCoh) between left and right central regions and between lateral central and frontomesial areas (including the region of the supplementary motor area, SMA) was also different in patients. TRCoh was generally lower after stroke (high alpha, low and high beta band; ANOVA, main effect group, $P < 0.0001$). In addition, TRCoh showed a relative, focal increase between right central and frontomesial cortex in patients (all frequencies; ANOVA, contrast analysis, $P < 0.05$), i.e. between the motor and premotor areas of the CON-H and the mesial premotor structures (like SMA). In addition to the marked convergence of coherence links to the right central region, the ipsilesional (left) central region (e.g. electrode C3, DAM-H) also showed links to mesial and contralateral premotor and sensorimotor areas (low beta band). The topographic coherence maps are displayed in Fig. 5.

Statistical parametric mapping of rCBF ($H_2{}^{15}O$-PET)

Movements were associated with activation of known sensorimotor structures such as left primary motor and primary somatosensory cortex (BA 4 and BA 3), left SMA (BA 6), left PMd (BA 6), left insula (BA 13), basal ganglia (claustrum, thalamus) and cerebellum. Details are given in Table 2.

On direct comparison with the control group, right-hand movements in patients were associated with increased activation of several areas in both the DAM-H (left) and CON-H

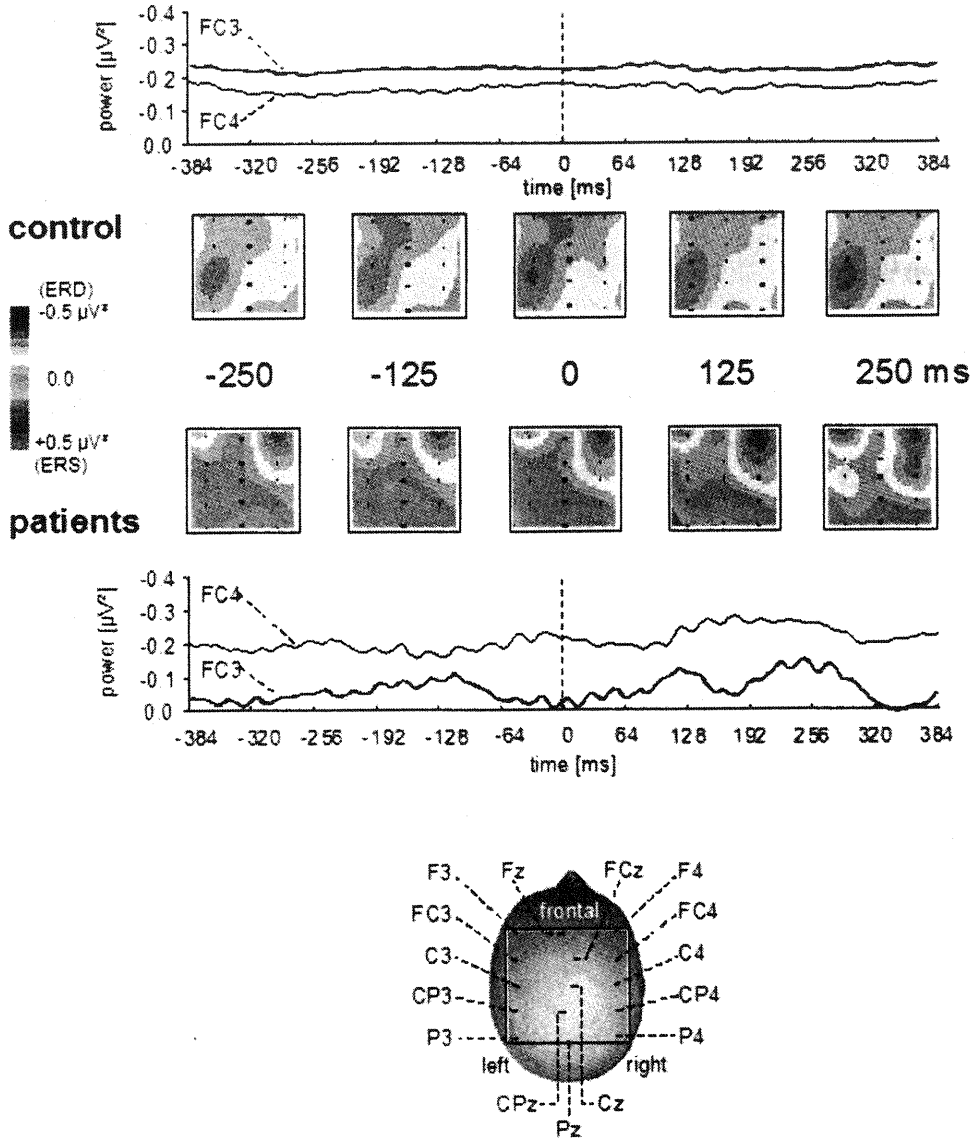

Fig. 4 Time-course analysis of spectral power in the beta band (16–20 Hz) in controls (*top row*) and stroke patients (*bottom*) (ERD). Grand average (n = 11 for each group). The curves depict the temporal evolution of ERD from 384 ms before to 384 ms after EMG onset in the central region of the lesioned (FC3) and the contralesional (FC4) central region. In normal subjects, a clear dominance of activation in the left central region (FC3 > FC4) is seen throughout the movement. In patients, the dominant activation occurs in the contralesional central region (FC4 > FC3). The topographic maps (activation coded in red) illustrate for five time points how ERD evolves in the central region (right in the map corresponds to right in the patient's brain). Note that activation of the contralesional central region in patients occurs already in the preparation phase before movement and increases slightly during movement execution. The duration of a typical EMG burst was between 200 and 350 ms. The power values on the y-axis are given relative to baseline (rest). Bottom = map orientation and electrode specifications.

(right). In the DAM-H, increased rCBF was found in the premotor cortex (BA 6) and medial frontal gyrus in the vicinity of the inferior frontal sulcus (BA 6). In the CON-H, increased rCBF was maximal in the PMd, (BA 6) and extended into the M1 (BA 4). Further, the right superior parietal lobule (SPL; BA 5, to a lesser extent BA 7) was more activated in patients. Finally, left cerebellar activity was higher in patients than in controls. The statistical results are given in Table 3. The topographic distribution of unequivocally enhanced activation loci in stroke patients is displayed in Fig. 6, thresholded at $Z > 3.09$. Figure 7 illustrates the details of BA 6 and BA 4 activation in the CON-H and provides an anatomical schematic on the transition between these two areas, i.e. between PMd and the corresponding parts of the M1. It is noteworthy that, the transition between these two structures varies considerably between subjects and depends on the lateral position along the central sulcus (Braak, 1979; White *et al.*, 1997; Geyer *et al.*, 2000). More medially, the M1 covers posterior aspects of the crown of the precentral gyrus, more laterally M1 tends to submerge inside the central sulcus. The co-registration plots of PET activation are given with a colour-coded scale and are thresholded at $Z > 3.09$ and

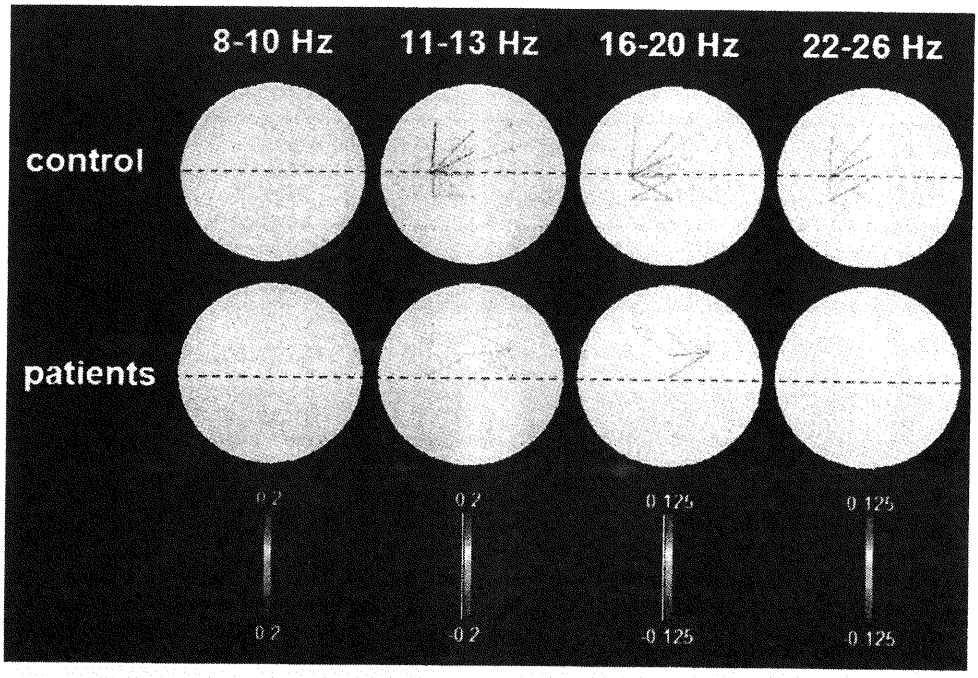

Fig. 5 Summary of functional connectivity analysis (EEG, TRCoh). Grand average (n = 11 for each group). Coherence is coded in colored links with red indicating high TRCoh increases ('enhanced synchrony') during movement. Top = in control subjects maximal functional coupling regularly occurred between the left central region and the left frontal and mesial frontocentral cortex as well as between left central and right central electrodes (11–13, 16–20, 22–26 Hz). Bottom = in patients the main difference to the normal coherence pattern was a convergence of functional links over the contralesional (right) central region. This was most prominent in the beta frequency range (16–20 Hz), indicating functional integration of the contralesional central region in the reorganized cortical network subserving motor control of the recovered hand. The dotted line indicates the anterior–posterior position of the electrodes T4, C4, Cz, C3, T3. Right-hand side of each map = right-hand side of the brain.

Table 2 Brain regions activated during right-hand movement in both patients and controls

Cerebral regions and Brodmann areas (n = 18 subjects).	Talairach-MNI coordinates (x, y, z)	t-statistic	P-value
Left central sulcus, primary motor and primary somatosensory cortex (BA 4 and BA 3)	−38, −34, 64	14.42	<0.0001
Left SMA (BA 6)	−12, 0, 66	11.39	<0.0001
Left M1 (BA 4) and left dorsal premotor cortex (BA 6)	−26, −20, 70	10.44	<0.0001
Left insula (BA 13) and basal ganglia (claustrum)	−34, −6, 8	8.25	0.001
	−32, −4, 16	7.56	0.002
Left thalamus	−12, −20, 4	7.17	0.003
	−8, −24, 10	6.56	0.010
Right anterior and posterior cerebellum	16, −56, −20	11.77	<0.0001
	40, −46, −34	7.93	<0.0001
	4, −66, −42	6.21	0.023
Left anterior and posterior cerebellum	−30, −60, −30	7.87	0.001
	−2, −72, −32	6.20	0.023
	−6, −56, −24	5.95	0.041

$Z > 2.46$. The extension of the activated area from PMd into M1 is seen at both thresholds, but more clearly in the less conservative $Z > 2.46$ map. This information has been added here because it might be important for the interpretation of diverging previous results of imaging studies with inconsistent findings regarding BA 4 (iM1) (Cramer *et al.*, 1997; Seitz *et al.*, 1998). It was noted that, the overactivation in patients inside BA 6 and BA 4 of the CON-H extended more ventrally than in the DAM-H. Also, the y- and z-coordinates of these maxima suggest that the main increase of rCBF in patients covered portions of the precentral gyrus medially adjacent to the hand knob rather than the hand knob itself.

Motor thresholds and cortical maps (TMS)

MT for the M1 of the DAM-H was significantly increased compared with the M1 of the CON-H (67.3 ± 16.8% left

Table 3 Brain regions showing significantly higher activation during right-hand movement in patients compared with control subjects

Cerebral regions and Brodmann areas	Talairach-MNI coordinates (*x*, *y*, *z*)	*t*-Statistic	*P*-value
Left premotor cortex (BA 6)	−16, −16, 76	5.16	<0.0001
Medial frontal gyrus (BA 6)	−26, 8, 30	5.03	<0.0001
Right premotor cortex (BA 6), posteriorly extending into M1 (BA 4)	14, −14, 74	4.57	<0.0001
Right SPL (precuneus, BA 5 and BA 7)	2, −40, 68	4.64	<0.0001
Left anterior cerebellum	−10, −66, −28	3.89	0.001

x, *y*, *z*-Talairach coordinates of voxels with maximal difference. *P*-value uncorrected for multiple comparisons.

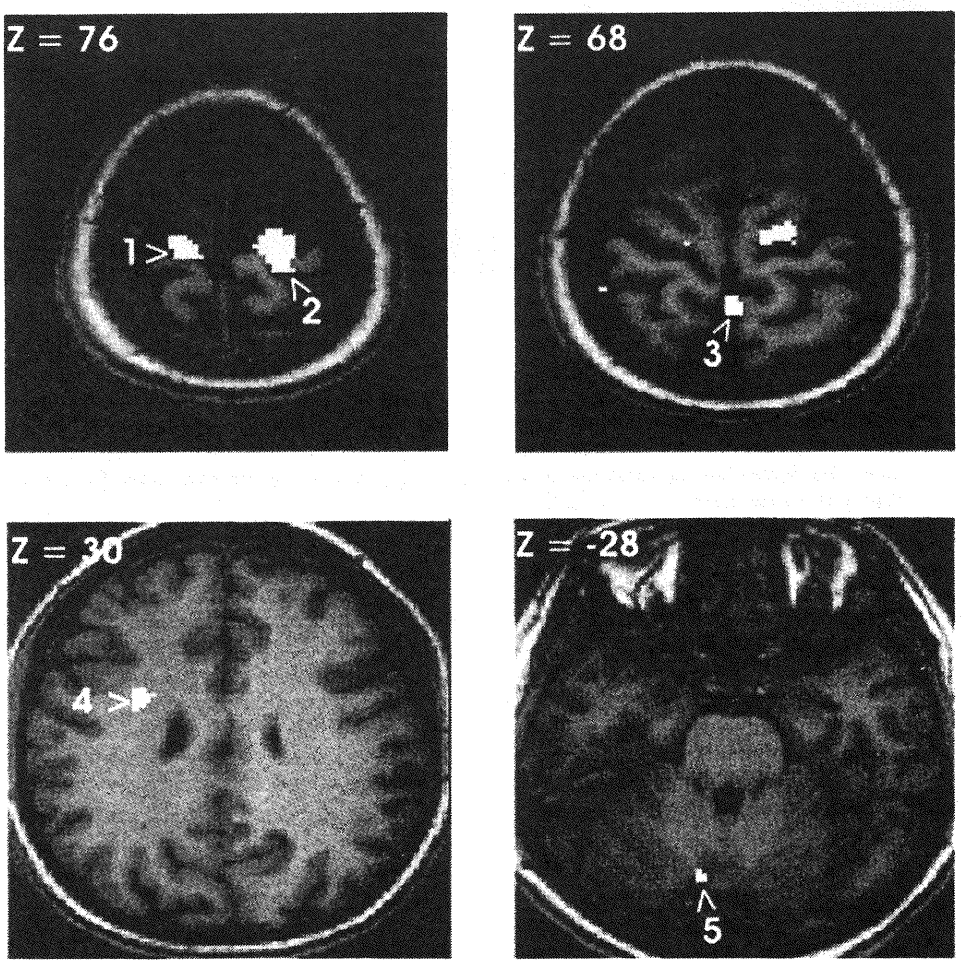

Fig. 6 Illustration of $H_2{}^{15}O$-PET results. Illustrated are the regions in which patients showed signficantly greater rCBF during right (recovered) hand movement than controls (n = 9 for each group). The regions were premotor cortex (no. 1) and medial frontal gyrus (BA 6) (#4) of the stroke hemisphere (left), premotor and M1 (no. 2) (BA 6 and BA 4) of the CON-H, SPL (no. 3) (BA 7, also BA 5) of the CON-H and left cerebellum (no. 5). *z*-Coordinates are given at the top left of each overlay. Images thresholded at $Z > 3.09$. Note that the location of maximum no. 4 is relatively deep, most likely at the bottom of the inferior frontal sulcus. The apparent location in the white matter in this figure is likely to be due to overlaying the group difference data on a standard anatomical brain.

versus 56.6 ± 9.4% right, Wilcoxon matched pairs test, $P < 0.05$). The results are illustrated in Fig. 8.

The *x*/*y* coordinates of the COG in the DAM-H were −5.1 ± 0.6/0.8 ± 1.3 cm, the corresponding values for the CON-H (right) were 4.8 ± 1.2/0.4 ± 1.7 cm (Wilcoxon matched pairs test, n.s.). This suggests that for MEPs elicited from the DAM-H, there was no relevant change in cortical topography of the M1 hand representation compared with the CON-H.

The NAP at the >25% level was 7.8 ± 6.7 for the DAM-H, and 7.8 ± 5.7 for the CON-H (Wilcoxon matched pairs test, n.s.). At the >50% level, the corresponding values were 4.8 ± 4.4 positions for the DAM-H, and 3.7 ± 1.8 positions for the CON-H. Although, with the strict criterion (>50%

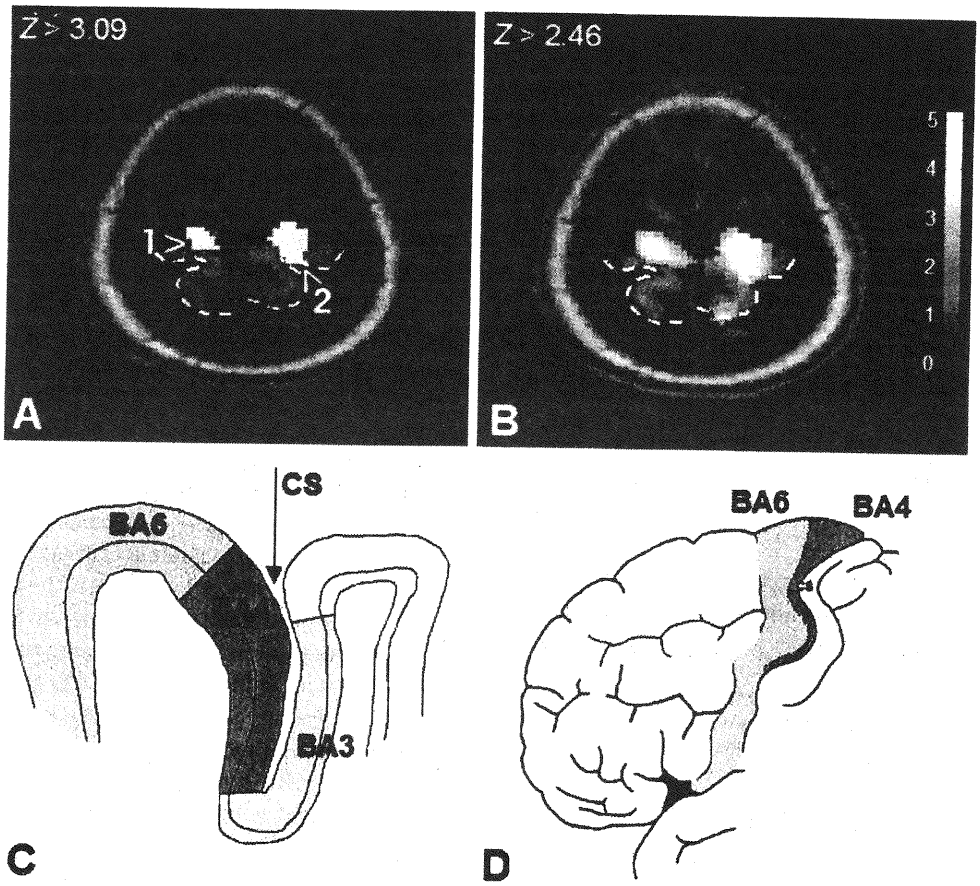

Fig. 7 Detailed illustration of enhanced rCBF during right (recovered) hand movements in stroke patients (n = 9) compared with age-matched controls (n = 9) in the contralesional central region. (**A**) image thresholded at $Z > 3.09$ (as in Fig. 6), (**B**) same image thresholded at $Z > 2.46$. Z-score colour scale is given on the right. The central sulcus is marked with a dashed white line. Note that independent of the threshold used, BA 6 activation extends into BA 4 of the CON-H. (**C**) schematic of the transition between BA 4 and BA 6. As a rule, this transition is close to the posterior limit of the precentral gyrus but varies according to the lateral position along the central sulcus (CS). This latter aspect is depicted in (**D**). The vicinity of BA 6 and BA 4 as well as the variability of the transition between the two of them might contribute to some of the inconsistencies regarding presence or absence of contralesional BA 4 activation in previous studies.

amplitude) the map size therefore tended to be slightly larger in the DAM-H, this did not reach significance because of inter-subject variability (Wilcoxon matched pairs test, P = 0.12, n.s.). In summary, there was no relevant increase or decrease of the cortical representation of hand muscles in the M1 of the DAM-H.

Most importantly, in no instance were we able to elicit MEPs in the recovered (right) hand by stimulating iM1 (at rest and with pre-contraction of the right-hand muscles).

Discussion

This study combines clinical, structural, metabolic and electrophysiological measures in a group of stroke patients with very similar subcortical lesions, clinical outcome and handedness. All patients were tested in the chronic phase after stroke, had small lesions of the posterior limb of the left internal capsule and had recovered well enough so that they could use the formerly paralysed hand for daily life activities. During all functional imaging procedures involving voluntary movement of the recovered hand, EMG was monitored bilaterally to control for mirror movements or covert involuntary co-contractions of the healthy hand. In our opinion, this is an important prerequisite for any attempt to interpret enhanced activation in the CON-H as a surrogate marker of plastic reorganization.

Although some of the data are corroborative, this study fulfils two requirements, (i) it combines a comprehensive spectrum of imaging and electrophysiological techniques in the same patients and (ii) it includes only patients with focal lesions of the posterior limb of the internal capsule in the left (dominant) hemisphere. Thereby, the present results gain additional validity as to the conclusions drawn with respect to pattern and potential functional implications of reorganization in subcortical capsular stroke.

Localization of ischaemic lesions

In all patients, the ischaemic lesion affected the posterior limb of the left internal capsule. As documented in Table 1, all but

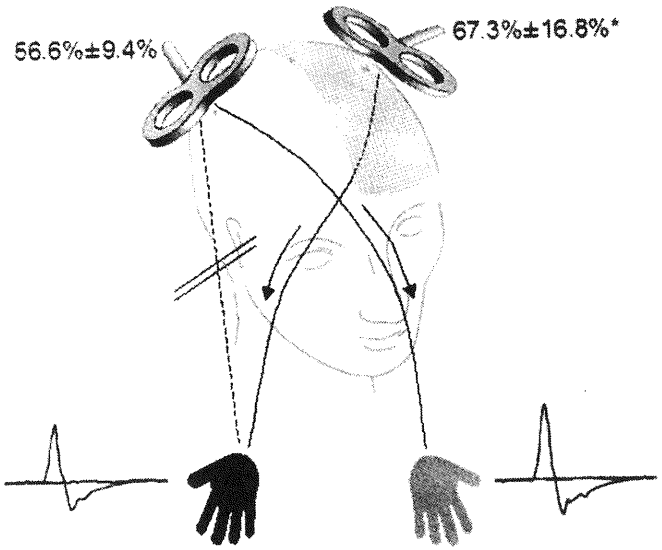

Fig. 8 Illustration of TMS data in the patient group. The stroke hemisphere is marked in yellow. The only significant difference between hand motor representations in the DAM-H and CON-H was a significantly increased MT in the affected side (*$P < 0.05$). Of note, no ipsilateral ('uncrossed') responses could be elicited in any of the patients (dashed line). Bottom right and left, two examples of MEPs.

one patient had minor additional T_1 and/or T_2 signal abnormalities which probably represented clinically inapparent ischaemic lesions in this population. These occurred mostly in the globus pallidus ($n = 7$) white matter ($n = 7$), or putamen ($n = 6$) of the left (stroke) hemisphere. None of our patients had any cortical or infra-tentorial lesions, and none had experienced previous clinical strokes or transient neurological symptoms.

Activation patterns in the CON-H (intact)

One of the major objectives of this study was to evaluate the role of the iM1, in reorganization after stroke. In our experiments, evidence for involvement of iM1 came from EEG spectral power analysis showing that the right central region was more active in patients than in controls. This result was most pronounced in the beta frequency range which is particularly sensitive to variation of motor parameters (rather than somatosensory) (Andres *et al.*, 1999; Mima *et al.*, 2001*a*; Chen *et al.*, 2003). Moreover, the time course of spectral power evolution verified that activation of the contralesional central region was present during movement preparation as well as execution. This precludes the possibility that the contralesional activation seen here was caused by altered feedback processing or reflex-like activation of the contralesional motor system by the movement as proposed previously (Verleger *et al.*, 2003). As the topographical resolution of a 28-channel surface EEG is only in the centimeter range, $H_2{}^{15}O$-PET data were obtained for assessment of metabolic changes. In line with the EEG results in the high alpha and beta bands (11–13, 16–20, 22–26 Hz), rCBF was enhanced in the frontocentral region of the CON-H. Specifically, contralesional BA 6 and BA 4 showed enhanced PET activation. In addition, the SPL including BA 5 and BA 7 exhibited higher rCBF values in patients than in the control group. This confirms that BA 4 (iM1) is reorganized during recovery from capsular stroke and is generally in line with the PET data of Nelles *et al.* (1999) and an fMRI study by Fujii and Nakada (2003). As in the EEG results which showed a more anterior distribution of the activation maxima in the CON-H than in the DAM-H, the increased rCBF in patients had its maximum in the PMd (BA 6) and extended into BA 4, as well as ventrally. As mentioned above (results section), one reason for inconsistencies regarding BA 4 activation in capsular stroke patients across multiple studies could be a different interpretation of active voxels in the vicinity of the posterior aspect of the precentral gyrus. According to several anatomical studies, M1 reaches the surface in more medial parts of the central sulcus, but submerges laterally (Braak, 1979; White *et al.*, 1997; Geyer *et al.*, 2000). In our data, the enhanced activation in this area was at the medial end of the presumed hand and arm representation in the precentral gyrus and thus certainly covered BA 4 in addition to BA 6. The greater rCBF values in the left cerebellum in our patients are in agreement with recent data of Johansen-Berg *et al.* (2002*a*), who have demonstrated with fMRI that improvements in hand function after stroke correlated with increases in activity in superior posterior regions of the cerebellar hemispheres. Thus, it appears that the CON-H and its crossed cerebellar connections can be reorganized and upregulated as a unit after capsular stroke.

The contralesional SPL also showed increased movement-related rCBF in stroke patients. This area of interest appears to be involved in the implementation of complex sensorimotor tasks, e.g. the selection of movement based on the integration of visual and somatosensory information (Tanaka *et al.*, 1996; Wexler *et al.*, 1997; Caminiti *et al.*, 1998; Catalan *et al.*, 1998). From our results, it is tempting to speculate that the SPL serves as a multimodal integration area monitoring and controlling activation of additional resources after brain lesions.

Activation patterns in the lesioned (stroke) hemisphere

Inside the DAM-H, increased (PET) activation was present in the premotor cortex (BA 6). Most previous studies have found activation in BA 6 of the DAM-H, but to varying degrees. In subcortical stroke, enhanced bilateral BA 6 activation was observed by Weiller *et al.* (1992) (10 patients) and by Calautti *et al.* (2001) (5 patients). In patients with a mixture of cortical and subcortical lesions, both bilateral (6 and 7 patients, respectively) (Chollet *et al.*, 1991; Seitz *et al.*, 1998) and only ipsilesional (8 patients) (Pariente *et al.*, 2001) overactivation of the premotor cortex was reported. In some studies, premotor activation in the DAM-H was absent (10 patients) (Cramer *et al.*, 1997) or only present in 1out of 8 patients (Weiller *et al.*, 1993). The reason for these inconsistencies remains unclear. It needs to be noted,

that also in our patients the rCBF changes in the DAM-H were less consistent with the electrophysiological data than in the CON-H. EEG showed a global reduction of activity in the central region of the stroke hemisphere. Similarly, TMS proved higher MTs in the DAM-H, confirming the observations of other authors (Thompson *et al.*, 1995; Werhahn *et al.*, 2003). As the results of PET, EEG and TMS in the CON-H were very consistent, it is unlikely that the discrepancies in the DAM-H can be attributed to the different control groups or technical issues. The increase of rCBF in patients in the DAM-H (BA 6) did not extend ventrally like in the CON-H. This difference between hemispheres might contribute to the relative shift of EEG activation patterns from DAM-H to CON-H, but it cannot explain the absolute reduction of EEG activity in the central region of the stroke hemisphere. One possibility is that PET, EEG and TMS represent activity or excitability in different, although most likely overlapping, subsets of neurons. Another explanation is that vascular autoregulation and neurovascular coupling in the DAM-H are altered after ischaemic stroke (Sette *et al.*, 1989; Dettmers *et al.*, 1993; Pineiro *et al.*, 2002).

Cortico–cortical connectivity

Inter-regional cortico–cortical connectivity was assessed by coherence analysis of the EEG data. There was a clear shift of connectivity towards the CON-H. While 29% of the 10% highest coherence links (beta frequency range, 16–20 Hz) were centered on the left hemisphere in healthy subjects, only 18% were centered over this hemisphere in stroke patients. Instead, 70% of the top 10% coherence links in patients converged over the CON-H. This strongly suggests that the CON-H is functionally integrated in the reorganized cortical network subserving right (recovered) hand movements after stroke.

The anatomical substrate of this shift could be the corpus callosum. The iM1 is connected with its homologue via transcallosal fibers (Gould *et al.*, 1986; Rouiller *et al.*, 1994), as is the premotor cortex, and there are numerous somatotopic connections between M1 and BA 6 (Wise, 1985; Wise *et al.*, 1997). Therefore, mere shifts in synaptic weights according to Hebbian rules (Hebb, 1949; Wang *et al.*, 1995) would be sufficient to account for the observed reorganization with increased activation in the sensorimotor structures of the CON-H. True structural changes (e.g. axonal sprouting) do not have to be part of this type of reorganization. This explanation is supported by experiments in healthy subjects (Plewnia *et al.*, 2003) and studies in stroke patients (Liepert *et al.*, 2000; Shimizu *et al.*, 2002; Butefisch *et al.*, 2003) showing that reduced excitability in the M1 of one hemisphere is associated with disinhibition and enhanced excitability of the homologous M1, that this effect can occur immediately (Plewnia *et al.*, 2003), and that when it takes place in the intact M1 of stroke patients performance improvements are documented in the paretic hand (Mansur *et al.*, 2005).

The functional significance of coherence measures in the beta and alpha band of surface EEG or magnetoencephalography (MEG) has been well established (Classen *et al.*, 1998; Miltner *et al.*, 1999; Mima *et al.*, 2001*a*; Hummel and Gerloff, 2005). In the context of our comparative PET and TMS data and taking into account behavioural studies by others (Johansen-Berg *et al.*, 2002*a*), the present coherence results are likely to indicate that the observed activity of sensorimotor and premotor structures in the CON-H of stroke patients signifies integration into a functioning network, despite differences in impairment levels between our patients and those reported by Johansen-Berg.

Corticospinal connectivity

When stimulated with TMS, the M1 generates monosynaptic corticospinal commands, resulting in activation of alpha-motoneurons and finally in muscle responses (Asanuma, 1989; Goldring and Ratcheson, 1972). If the functional role of the (homologous area) iM1 were truly 'homologous', it should share this characteristic feature, i.e. stimulation of the iM1 (right hemisphere = CON-H) should result in MEPs in the recovered (right) hand. In none of the 11 patients, ipsilateral MEPs could be elicited. In contrast, stimulating the M1 of the DAM-H induced MEPs in the paretic hand. The only robust abnormality was an increased MT for M1 stimulation in the DAM-H indicating a persistent reduction in connectivity of the lesioned corticospinal tract. This result is in line with the recent observation of Werhahn *et al.* (2003) who demonstrated that single pulses of TMS given at 100 ms after the visual cue in a reaction time task were more effective in interfering with performance in stroke patients when applied to the M1 of the DAM-H than to the M1 of the CON-H.

Just because there are no ipsilateral MEPs, it cannot be concluded that the iM1 does not contribute to recovery. The functional role of uncrossed corticospinal pathways could become only 'unmasked' during voluntary action. Corticospinal connectivity during voluntary action can be assessed by computation of cortico–muscular coherence from EEG or MEG data. Mima *et al.* (2001*a*) have done this experiment in a group of stroke patients, and found no evidence for cortico–muscular coupling between CON-H and recovered hand during an isometric contraction task.

These physiological data are in line with anatomical studies performed by Kuypers and Lawrence showing that the uncrossed PT subserves only proximal and axial muscles—at least in the adult monkey (e.g. Lawrence and Kuypers, 1965; Kuypers, 1981).

Thus, if iM1 does not relay direct corticomotoneuronal connections, what role could it play in the recovery of function? A function such as mediating a simple reaction time movement is unlikely (Werhahn *et al.*, 2003). However, there is converging evidence that the M1 can process higher-order sensorimotor information such as direction selectivity, movement preparation, static or dynamic load effects (Alexander and Crutcher, 1990) or patterning of multijoint

activity (Ghez *et al.*, 1991; Martin and Ghez, 1993). Hocherman and Wise (1990, 1991) found a large population of trajectory-specific cells in the M1. Zhang *et al.* (1997) suggested that the M1 belongs to a distributed network such that its neuronal activity reflects the underlying network dynamics that translate a stimulus representation into a response representation. Results of two studies in which M1 was temporarily inactivated with repetitive TMS during motor sequence performance showed that both the contralateral and iM1 participate in coding of motor sequence complexity (Chen *et al.*, 1997; Gerloff *et al.*, 1998). Polysynaptic uncrossed (or double-crossed) connections from the iM1 to spinal alpha-motoneurons cannot be excluded on the basis of the available data, because the sensitivity of TMS and cortico–muscular coherence to those pathways has not been studied systematically.

The EEG coherence results may be taken as supportive evidence for the involvement of the ipsilateral BA 6 and BA 4 in higher-order motor processing, as they show enhanced connectivity of the contralesional central region with other motor and premotor areas in our patients. Similar enhancement of interregional coherences has been documented in healthy subjects in the initial phase of bimanual coordination learning (Andres *et al.*, 1999) and with increasing complexity of motor sequences (Manganotti *et al.*, 1998). That this can be seen in stroke patients during simple finger movement may be related to the fact that a simple movement carried out with a formerly paretic hand is more difficult. The relevance of the coherence data in this regard is further strengthened by the fact that M1 of the DAM-H in the patients appears less well connected to the other motor and premotor areas than in the control group. In an experiment on 11 patients with ischaemic lesions of various locations, Johansen-Berg *et al.* (2002*a*) applied single-pulse TMS to a point 2 cm anterior to the OP (approximately representing the contralesional PMd) and to another point 1 cm posterior to the OP, closer to the contralesional M1, in order to interfere with a finger movement. TMS applied to PMd early (100 ms) after the visual cue to move slowed reaction time by 12% compared with controls in patients with more prominent impairment. Stimulation 1-cm posterior to the OP produced no effect. This is in line with our findings suggesting the maximum of contralesional activation in BA 6 and the absence of a direct corticospinal projection from the contralesional M1. The functional relevance of the activation that we found in BA 6 of the DAM-H is supported by a recent paper of Fridman *et al.* (2004) who showed that TMS to this area was particularly effective in inducing delays in reaction time in the recovered hand of stroke patients with little impairment.

Concluding remarks and physiological considerations

The present data and recent behavioural experiments (Johansen-Berg *et al.*, 2002*a*; Werhahn *et al.*, 2003; Fridman *et al.*, 2004) indicate that both hemispheres contribute to recovery of function after capsular stroke, perhaps involved in differentiated aspects of motor planning and execution in patients with different degrees of impairment. It is very likely that restitution of near normal circuitry is the best basis for excellent recovery (Cramer, 2004). If perilesional, or in a wider sense, ipsilesional reorganization provides sufficient neural resources to compensate loss of function, good outcome seems to be most probable (Baron *et al.*, 2004). For these patients, also the notion that activity in the CON-H increases temporarily after the stroke but returns to baseline in the course of effective recovery (Ward *et al.*, 2003) is likely true. However, in many patients purely perilesional or ipsilesional reorganization might not be sufficient, and task-related increases of activity in the CON-H also persist in the chronic stage, as in our patients. On the basis of EMG monitoring during PET scanning and EEG recordings, it can be ruled out that activation of iM1 and premotor cortex of the CON-H is merely due to involuntary co-contractions of the healthy hand. Also, there was no evidence for bilateral proximal upper extremity synkinesias in our patients, and no comparable overactivation occurred in the M1 in the DAM-H, rendering this explanation unlikely. The relative importance of ipsilesional and contralesional BA 6 and BA 4 as well as of parietal areas, however, might differ substantially depending on the individual lesion pattern and other patient characteristics (Ward *et al.*, 2003; Luft *et al.*, 2004), and it would be consistent with our results and those of others that some aspects of activity in the CON-H interact with the DAM-H through interhemispheric inhibitory interactions (Murase *et al.*, 2004; Ward and Cohen, 2004).

The M1 and premotor cortex as well as the SPL of the CON-H showed increased activity after recovery from capsular infarction. Because all patients in our study had good recovery, it seems reasonable to propose that these contralesional structures, together with structures of the DAM-H such as the premotor cortex, are functioning parts of a reorganized cortical network and subserve motor recovery. This conclusion is supported by the cortico–cortical connectivity pattern as revealed by EEG coherence measurements and by the additional left cerebellar activation on PET. Considering our TMS and previous EEG–EMG coherence data (Mima *et al.*, 2001*b*), it is highly unlikely that in capsular stroke the contribution of the ipsilateral BA 4 (iM1) consists in the generation of an ipsilateral (uncrossed) monosynaptic corticospinal pathway. Thus, we favour the interpretation that the areas identified here are involved in higher-order motor processing such as selection, preparation, temporal or spatial organization of movement. This concept finds additional support in the EEG time-course data documenting that enhanced ipsilateral activity is present already before EMG onset.

In physiological terms, the present data are compatible with two interpretations: (i) effective recovery after stroke is based on repair mechanisms such as axonal sprouting with formation of new synapses and subsequently enhanced activation in novel parts of a neuronal network (for review see Chen *et al.*, 2001) or (ii) effective recovery can be achieved by enhanced

recruitment of pre-existing network elements, similar to the situation with complex movements compared to simple movements in the healthy brain (Sadato *et al.*, 1996; Manganotti *et al.*, 1998; Catalan *et al.*, 1999; Hummel *et al.*, 2003). The latter would mean that for stroke patients even the simplest movement is 'complex' and requires an extended network of premotor and sensorimotor structures. Both explanations are possible and, in our opinion, not mutually exclusive. Training-related structural changes in dendritic spine density and axonal connectivity have been shown in adult animals (Yuste and Bonhoeffer, 2001; Leuner *et al.*, 2003), and dynamic reorganization in the course of learning a complex motor task is also a well-documented phenomenon (Karni *et al.*, 1995; Andres *et al.*, 1999). Hence, it is likely that in the course of recovery, a post-stroke brain undergoes some structural change. For example, neuronal excitability and long-term potentiation are enhanced after experimental brain lesions (Hagemann *et al.*, 1998) and provide a basis for functional and structural adaptive changes. In this connection, it is worth noting that in some stroke patients the M1 of the CON-H is disinhibited (Liepert *et al.*, 2000). Given the link between enhanced excitability and plasticity (Ziemann *et al.*, 2001; Stefan *et al.*, 2002; Plewnia *et al.*, 2004), this might allow for a more effective adaptation. Clinical experience suggests that for the majority of recovered stroke patients any movement with the formerly paretic limb is more challenging than before the stroke. This aspect would then correspond to the upregulation of activity in pre-existing parts of the motor network such as contralesional BA 6 and BA 4, SPL and corresponding aspects of the cerebellum (Baron *et al.*, 2004). If upregulation were the only mechanism, we would expect concomitant upregulation of all corresponding areas in the DAM-H as well. As this is not the case (the overall activation pattern changes), a combination of 'true' plastic changes and recruitment of pre-existing resources appears to be more likely. Although there seems to be a plethora of ways for cortical assemblies to compute a movement and use alternative routes to generate corticospinal control (Dobkin, 2003), an effective and lasting recruitment of uncrossed corticospinal tract fibres as seen with very early lesions, e.g. perinatal periventricular lesions (Staudt *et al.*, 2002; Gerloff *et al.*, 2005) does not appear to be a relevant mechanism of recovery in adult stroke patients. On the contrary, converging evidence points to a crucial contribution of non-primary motor areas of both hemispheres, in particular BA 6 (Johansen-Berg *et al.*, 2002*b*; Fridman *et al.*, 2004), but according to our PET data also the SPL. Finally, our data in well-recovered patients do not preclude a more active role of ipsilateral projections from the intact M1 early after a stroke (Marshall *et al.*, 2000; Ward *et al.*, 2003) or in patients with larger lesions, greater neurological deficit and less successful recovery (Turton *et al.*, 1996; Carey *et al.*, 2002; Butefisch *et al.*, 2003). Effective recovery may be associated with a dynamic change from initially excessive activation in the CON-H toward a more lateralized pattern in the chronic stage, more similar to healthy subjects (Cramer, 2004; Rossini *et al.*, 2003; Traversa *et al.*, 2000; Ward *et al.*, 2003). Of note, there is some persistent enhancement of activation in contralesional motor areas which is likely to be involved in the control of recovered hand function.

With respect to therapeutic interventions geared at modulating cortical activity in order to facilitate recovery after stroke or reading out meaningful neuronal signals for improving motor functions by neuroprosthetic devices, the present data suggest that enhancing activity in BA 4 of the DAM-H (Hummel *et al.*, 2005) and also BA 6 and SPL of the CON-H are interesting targets. Also decreasing activity in the intact M1 (CON-H) appears to contribute to motor improvements in the paretic hand. Neurostimulation or electrode placement in areas of the CON-H has the obvious advantage that excitatory electrical currents or mechanical irritations are not applied directly to damaged or perilesional tissue. Also with respect to potential side effects (e.g. seizure induction), manipulation of non-primary motor areas is likely to be safer than targeting M1 directly.

Acknowledgements

We are grateful to Ms S. Thomas, laboratory technician, for technical support, and to D.G. Schoenberg, MSc, for skillful editing. The study was supported by NIH intramural, C.G. and A.S. by grants of the Deutsche Forschungsgemeinschaft (Ge 844, SFB 307/B12, SFB 550/C5).

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ORIGINAL RESEARCH

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Optic Nerve Hyperintensity on T2-Weighted Images among Patients with Pituitary Macroadenoma: Correlation with Visual Impairment

PURPOSE: Visual acuity (VA) disturbance other than field defect is important in evaluating patients with pituitary macroadenoma. The purpose of this study was to evaluate MR imaging appearances of optic nerves in patients with pituitary macroadenoma and to ascertain whether visual impairment was correlated with abnormality in optic nerve signal intensity.

PATIENTS AND METHODS: Twenty-seven patients with pituitary macroadenoma were examined. Optic nerves were evaluated on T2-weighted images and correlations of signal intensity abnormality with VA disturbance, visual field disturbance, degree of optic chiasm compression, pathologic findings of surgical specimen, and disease duration were statistically analyzed. Correlations between recovery of VA after treatment and the above-mentioned factors were also determined.

RESULTS: Coronal T2-weighted images demonstrated unilateral optic nerve hyperintensity lesions in 9 patients. Bilateral signal intensity abnormality of the optic nerve was seen in 5 patients. Signal intensity abnormality of the optic nerve was seen at the site of compression and in the ventral side of the tumor. These patients did not demonstrate signal intensity abnormality posterior to the tumor. Presence of such signal intensity abnormalities was correlated with the degree of optic chiasmal compression and with VA disturbance. Recovery of VA after treatment was correlated with disease duration.

CONCLUSION: Hyperintensity of the optic nerves ventral to the pituitary macroadenoma was associated with VA impairment. Recovery of VA after treatment was correlated with disease duration. MR imaging of the optic nerves can provide valuable information for management of pituitary macroadenoma.

In some patients with pituitary macroadenoma, visual acuity (VA) diminishes despite the existence of no field defect other than bitemporal hemianopia. This clinical information is very important in patient management; however, no published reports have analyzed the relationship between VA disturbance and MR imaging findings of the optic nerves of the patients with the pituitary macroadenoma. In this study, the authors used T2-weighted MR imaging to investigate signal intensity abnormality of the optic nerves and statistically analyzed the relationship between this and factors including the degree of optic chiasm compression, disease duration, degree of VA disturbance, and tumor histopathology.

Hyperintensity of the optic nerves was frequently detected among patients with diminished VA. Among those with long disease duration and prolonged signal intensity abnormality, improvements in VA disturbance tended to be poor, which suggests the possibility of degeneration of optic nerves caused not only by compression-induced edema, but also by compression of the arteries, veins, and capillary networks in the optic chiasm.

Patients and Methods

We reviewed pre- and postoperative MR images from 27 consecutive patients with pituitary macroadenoma, 24 of whom were treated surgically at the National Defense Medical College between April 1999 and November 2003. All MR examinations were performed by using a 1.5T system. We used fast spin-echo sequences for T2-weighted (3500/110/2) and T1-weighted (500/15/1) images. Three-millimeter-thick sections were obtained in the coronal and sagittal planes with a 256 × 512 acquisition matrix. All images were blindly reviewed by 2 radiologists, focusing on the presence of abnormal signal intensity in the optic nerves ventral to the tumor, at the site of compression, and dorsal to the tumor. We also classified degree of optic chiasm compression into 3 grades as follows: (−) no compression; (+) compression of less than half of the optic chiasm; and (++) compression with severe thinning. Signal intensity abnormality of the optic nerve was defined as abnormality involving not only the area around the optic nerve, but also the septum (+). In patients with (+) or (++) compression, we also evaluated the location of the tumor in relation to the optic nerve and optic chiasm. Cephalocaudal diameter of each tumor was also measured

Visual signs (visual field defect and VA) were evaluated by an ophthalmologist. Twenty-four patients underwent surgical procedures, and histologic confirmation of the diagnosis was obtained in each case.

A Mann-Whitney *U* test was used for statistical analysis of the relationships between signal intensity abnormality and tumor size, degree of chiasm compression, histology, VA disturbance, and disease duration. Correlations between recovery of VA after treatment and the above-mentioned factors were also ascertained.

Results

Patient clinical data are summarized in Table 1. The results are shown in Figs 1–4.

Received August 1, 2004; accepted after revision July 23, 2005.

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