Preoperative motor system brain mapping using positron emission tomography and statistical parametric mapping: hints on cortical reorganisation

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Objectives: This study investigated the applicability of statistical parametric mapping (SPM) for analysing individual preoperative brain mapping studies in patients with cerebral mass lesions for neurosurgical planning. The study further investigated if hints on functional reorganisation processes can be found.

Methods: Nine adult patients with cerebral mass lesions underwent activation [^{15}O]water-PET under stimulation by finger ($n=9$) and foot ($n=4$) movement. Individual SPM- t -maps were computed without anatomical normalisation and coregistered to the individual magnetic resonance imaging. Relative cerebral blood flow change maps were calculated for comparison.

Results: The spatial relation between the sensorimotor cortex and the lesion could be determined in all cases. Additional activations covered the ipsilateral sensorimotor cortex and the bilateral cerebellum, premotor cortices and supplementary motor areas. Patients with motor symptoms of the stimulated hand (paresis, focal seizures) activated the ipsilateral premotor cortices and contralateral cerebellum more often than patients without motor symptoms. The SPM results for $p<0.005$ and cerebral blood flow change maps showed considerably overlapping motor area activations. For $p<0.001$, SPM missed three sensorimotor cortex activations depicted by cerebral blood flow change maps and by SPM for $p<0.005$ in typical localisation. SPM analyses showed less activations probably unrelated to task performance.

Conclusion: It is concluded that SPM provides an efficient method for analysing individual preoperative PET activation studies. Activations of the ipsilateral premotor cortices and contralateral cerebellum may indicate an enhanced recruitment of ipsilateral motor pathways evoked by functional reorganisation processes. However, this changed activation pattern was not necessarily associated with a better neurological status.

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Several groups have used functional imaging methods such as positron emission tomography (PET)^{1–10} and functional magnetic resonance imaging (fMRI)^{2–11} for a preoperative brain mapping of eloquent brain areas in patients undergoing neurosurgery. The rationale behind determining the spatial relation between the lesion and surrounding eloquent brain areas is to identify the least traumatic neurosurgical approach, and to evaluate the extent of possible resection. In some cases of cerebral mass lesions, the identification of morphological landmarks is complicated by the disturbance of the normal gyral pattern. Furthermore, functional reorganisation processes may have taken place, leading to a reorganisation of motor functions in cortical areas ipsilateral and contralateral to the affected functional areas.^{7, 12–21}

Cerebral blood flow PET (CBF-PET) has been extensively used for preoperative activation studies. A variety of methods have been suggested for the detection of task related CBF changes in these single subject studies. While some groups used task minus baseline subtraction images^{3–5} or volume/region of interest based methods⁹, others used more sophisticated voxel based statistical analysis methods,^{1, 2, 4, 6, 7} namely the change distribution analysis (CDA)²² and Worsley's method.²³ This substantially complicates the comparison of results reported by different groups.

The computation of relative CBF change maps (task scan divided by baseline scan) has been successfully used for preoperative brain mapping at our institution. In preoperative ¹⁸FDG-PET activation studies, this method has been shown to be highly reliable in comparison with direct electrical cortical

stimulation.¹⁰ However, the use of relative CBF change maps is problematic as reliable criteria to scale these maps are missing. Therefore, a scaling of these maps to define areas of task related CBF changes is always biased because it depends on certain a priori assumptions regarding the expected activation pattern. This could lead to false negative results, especially in presence of unexpected reorganisation processes.

The voxel based statistical analysis method statistical parametric mapping (SPM)^{24–25} has been extensively used to access significant regional CBF changes in multi-subject activation studies after stereotactic normalisation of individual scans into a standard anatomical space. SPM can also be applied to single subject studies, if multiple PET scans for each condition are acquired. Furthermore, in single subject studies, SPM analyses can be performed without spatial normalisation to preserve the individual brain anatomy. Compared with CBF change maps, SPM offers the advantage of relative observer independence and comparability across laboratories. Nevertheless, to our knowledge, SPM in conjunction with CBF-PET has not been used for an individual preoperative brain mapping in patients with cerebral mass lesions.

Abbreviations: SPM, statistical parametric mapping; PET, positron emission tomography; SMC, sensorimotor cortex; CBF, cerebral blood flow; PMC, premotor cortices; SMA, supplementary motor area; DCS, direct electrical cortical stimulation; CMAP, compound muscle action potential

We investigated the feasibility of SPM in conjunction with CBF-PET to assess task related regional CBF changes in cortical motor areas of individual patients with cerebral mass lesions. As to our knowledge SPM has not been evaluated for this clinical purpose before, we additionally calculated relative CBF change maps used at our institution to ensure a high diagnostic accuracy. We investigated whether the SPM analyses lead to a clinically relevant loss or gain of information compared with the currently used approach. Furthermore, we investigated whether abnormal patterns of motor cortex activation can be detected by the SPM analyses, which might reflect functional reorganisation processes of cortical motor functions in response to the mass lesion.

METHODS

Patients

Nine consecutive patients with supratentorial mass lesions were enrolled (six women; mean age (SD) 38 (17.5) years; see table 1). Eight patients underwent first time lesion resection. One patient presented a malignant relapse of a low grade astrocytoma resected three years earlier. In another patient, two years earlier a craniotomy was performed to remove a haematoma caused by bleeding of a cavernoma. Neurological examinations were carried out by a board certified neurosurgeon. Patients underwent surgery within 13 days after PET scanning (mean 4.7 days). All patients gave informed consent. All procedures were approved by the local ethics commission.

Magnetic resonance imaging

A high resolution three dimensional T₁ weighted FLASH MRI dataset (Gyrosan Intera, Philips, Eindhoven, Netherlands) was acquired for MRI-PET image overlay in each patient within three days of PET scanning (TE=4.6 ms, TR=30 ms, flip angle=30°, matrix=256×256, voxel size=1×1×1 mm³).

Positron emission tomography

All PET scans were obtained on a dedicated PET scanner (ECAT Exact, Siemens-CTI, Knoxville, TN, USA) in three dimensional mode. Patients laid supine with their head immobilised by an elastic ribbon in canthomeatal orientation in a light dimmed room at reduced ambient noise. Attenuation correction was done by Ge-68/Ga-68-transmission scanning (12 minutes) before emission scanning. Emission scans were started at the presumed tracer arrival in the brain—that is, 20 seconds after intravenous bolus injection of 500 MBq (13.5 mCi) [¹⁵O]-water. Integrated counts over 60 seconds were used as an index of regional CBF. Forty seven fully corrected transaxial planes (3.38 mm thickness) were reconstructed in a 128×128 matrix (pixel size=1.72×1.72 mm²) using the PROMIS re-projection algorithm and Hanning filtering (cut off=0.5 Ny).

Activation tasks

The first activation task consisted of a sequential finger opposition movement (thumb to each other finger)^{26,27} of the hand contralateral to the lesion. Depending on the lesion location and the patient's condition, a second activation task was added (in four patients), consisting of flexion-extension movements of the contralateral foot. Before scanning the patients exercised the tasks until they were able to perform the tasks sufficiently well in a continuous fashion. We did not use fixed external pacing but asked the patients to perform the tasks continuously at a comfortable rate. This led to a slightly variable movement rate (about 1–2/s and 0.5–1/s for finger opposition and flexion-extension of the foot, respectively). Rest served as control. Each condition was scanned four times in randomised order with an interscan interval of 10 minutes. The patients were carefully monitored to exclude movements of the other extremities.

Single subject analyses

The MRI datasets were manually realigned into anterior/posterior commissural (AC-PC)-orientation using a multi-modality imaging tool (MPI-Tool, ATV, Erftstadt, Germany²⁸). All PET scans of one patient were averaged to generate a PET dataset with a high signal to noise ratio, which was subsequently realigned to fit the re-sliced MRI. Finally, the averaged PET dataset was used as a template for an automatic coregistration of all single PET scans.

SPM analysis

The realigned PET scans were used for the SPM analysis (SPM99, Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK). A transformation of the individual scans into a standard anatomical space was not performed to conserve the individual pathological anatomy. All scans were smoothed with an isotropic Gaussian filter with a kernel of 12 mm FWHM. The effect of the different tasks on the regional CBF was estimated according to the general linear model by Friston *et al.*²⁵ After proportional scaling of all PET scans to a mean global CBF of 50 ml/min/100ml, *t* statistical parametric maps (SPM(*t*)) were calculated. These SPM(*t*) were thresholded with respect to the size of the resulting activation clusters and their *t* statistics. The cluster size threshold was empirically chosen to be 30 voxels (0.3 cm³). Furthermore, all voxels had to exceed a *t* score of 5.21 and 4.30 for 6 and 9 degrees of freedom (depending on the total scan number—that is, 8 or 12) (corresponding to *p*<0.001), respectively. To avoid a too conservative testing that might potentially harm the patients' neurological intactness, we further lowered the *t* threshold to 3.71 and 3.25 (corresponding to *p*<0.005), respectively. We did not apply a correction for multiple comparisons to avoid too conservative testing. To substantially reduce the number of comparisons and thus the likelihood of a type I error, we a priori restricted our investigations to brain areas, which are well known to be involved in motor system activities under physiological^{26,27} and pathological^{7,12–16} conditions, including bilaterally the primary sensorimotor cortex (BA 1–BA 4 (SMC)), secondary motor areas (premotor cortex (PMC) and supplementary motor area (SMA)—that is, lateral and mesial BA 6) and the cerebellum.

Relative CBF change map

The method used to calculate the relative CBF change maps was originally designed to analyse preoperative ¹⁸F-DG-PET activation studies. It proved to be highly reliable in comparison with direct electrical cortical stimulation¹⁰ and also applicable to CBF-PET activation studies. In brief, all realigned scans of the same condition were summed. The relative CBF change was then calculated on voxel level by dividing the summed activation scans by the summed rest scans (activation+rest = CBF change (%) + 1). Three preprocessing steps were performed: firstly, the global count rates of the summed images were linearly normalised by their global mean count rates to account for total count rate differences. All voxels with count rates less than 35% of the maximum count rate of the two scans were excluded. This threshold empirically proved to exclude virtually all parts of the scan volume outside the brain and volumes with very low count rates (that is, ventricles, adjacent white matter). Finally, the results were smoothed with a Gaussian filter (kernel = 3×3×3 voxels = 5.16×5.16×10.14 mm³).

The agreement of both methods regarding the localisation of the SMC contralateral to the stimulated extremity was judged by two investigators. The Euclidean distance between the peak CBF increase and the peak *t* value was determined. As the areas of activation indicated by both analyses showed an extensive overlap (especially in the SMC and cerebellum), we thresholded the relative CBF change maps to appear

Figure 1 Patient number 7 stimulated by right hand sequential finger movement (upper row) and right foot movement (lower row; PET-MRI overlay). Left: relative CBF change map (individually scaled to show CBF changes in motor areas most clearly, all CBF increases $>15\%$). Middle: SPM analysis, $p<0.005$ Right: SPM analysis, $p<0.001$. Upper row: note that a clear activation of the left SMC and the left SMA (dorsally displaced by a low grade astrocytoma) is shown by all approaches. A right sided SMA activation is only detected by the relative CBF change map and the SPM analysis for $p<0.005$. The last two analyses also show additional activations of the right BA 4 (not in the plane shown for the SPM analysis) and weak responses of the left PMC. Lower row: an activation of the left SMC is shown by all methods. The relative CBF change map also depicts activations of the right BA 4/6 and the left SMA. Note the more rostral extension of the activation cluster into BA 6 in the SPM analysis for $p<0.005$ compared with $p<0.001$.

spatially most similar to the results of the SPM analyses for $p<0.001$ and $p<0.005$, respectively. This enabled us to approximate the minimum CBF increase within the areas detected by SPM at a given level of significance. As will be discussed, the CBF change thresholds determined by this approach were lower (especially for $p<0.005$) than thresholds usually set with the aim to display areas of presumed CBF increases most clearly (in our experience about $\geq 15\%$).

By means of a two tailed Fisher exact test we investigated if the neurological symptoms of the patients were related to the occurrence of specific activations in the SPM analyses.

Multi-subject SPM analysis

We retrospectively performed a multi-subject SPM group analysis of the largest patient subgroup (seven patients with left sided lesions, sequential finger movement of the right hand). In contrast with the individual analyses, a spatial transformation of the individual scans into the standard anatomical SPM space²⁴ was performed, after the voxel size was interpolated to $2\times 2\times 2\text{ mm}^3$. The algorithm converged in all cases. Visual inspection confirmed the high quality of all spatial transformations. Subsequently, all scans were smoothed by an isotropic Gaussian filter (12 mm FWHM). SPM(t) were calculated and thresholded at a cluster size of 30 voxel and a t value of 3.27 (omnibus $p<0.001$). All activation clusters reported exceeded a level of significance of $p<0.05$ ($t=5.12$) after correction for multiple comparisons using Random Field Theory.²³ As the results of this group analysis were of no direct consequence for the patients' surgical treatment, we applied a correction for multiple comparisons in this instance to establish a more conservative estimate of the cortical areas involved in task execution (especially of the unaffected hemisphere).

Direct electrical cortical stimulation

In five patients, intraoperative direct electrical cortical stimulation (DCS) was carried out with a monopolar disc electrode (10 mm diameter) under EMG recording of compound muscle

Figure 2 Patient number 5 (upper row) stimulated by right hand and patient number 2 (lower row) stimulated by left hand sequential finger movement (PET-MRI overlay). Left: relative CBF change map. Right: SPM analysis for $p<0.001$. Upper row: activation of the left SMC (adjacent to a cavernoma) and the left SMA is depicted by both methods (CBF change map scaled individually, all CBF increases $>17\%$). Both analyses also show activations of the dorsolateral BA 6, although not identical. Lower row: both methods show activations of the right SMC and SMA, while the activations of the left SMC and PMC are not spatially fully concordant (relative CBF change map scaled individually, all CBF increases $>14\%$). Note that the relative CBF change map shows an additional weak activation of the left SMA. The patient presented a thrombosed giant aneurysm located below this plane.

action potentials (CMAP) of the contralateral, not relaxed extremities (arm: M deltoideus, M biceps brachii, M extensor digitorum, M abductor pollicis brevis; leg: M vastus lateralis, M vastus medialis, M tibialis anterior, M abductor hallucis) via subcutaneous needle electrodes (Nicolet Viking IV-P; Nicolet Biomedical Instruments, Madison, WI, USA; filter setting: 30–3000 Hz, sensitivity: 10–50 $\mu\text{V}/\text{division}$). Five repeated electrical impulses of 0.1–0.2 ms duration were administered (frequency = 500 Hz). The stimulus intensity was increased in 2 mA increments to maximal 25 mA until CMAPs were elicited. The localisation of cortical areas with the largest CMAPs were documented by a neuro-navigation system (EasyGuideNeuro, Philips Medical Systems, Eindhoven, Netherlands) in all three cross sectional planes and qualitatively compared with the localisation of the SMC of the respective extremity shown by the SPM analyses. In our experience, a monopolar disc electrode enables a more reproducible and reliable DCS with less current spread compared with a bipolar electrode.

RESULTS

Individual analyses

Mapping of the SMC: SPM, DCS, relative CBF change map

The SPM analyses resulted in somatotopically organised foci of significant CBF increase corresponding to the SMC of the affected hemisphere in every case. Thus the spatial relation between the lesion and the SMC could be determined in every patient. In 10 activation studies, this goal was achieved at a significance level of $p<0.001$ ($n=7$ finger movement task, $n=3$ foot movement task). In three cases, a clearly defined activation focus corresponding to the presumed SMC representation area was only detected for $p<0.005$ ($n=2$ finger movement task (patients 1 and 4), $n=1$ foot movement task (patient 8)).

In two patients (numbers 5 and 7), DCS elicited maximal CMAPs of the hand and foot muscles in cortical areas shown to be involved in motor task execution by the respective SPM

Table 1 Summary of the patient characteristics

Patient	Age (y)/sex	Histology	Tumour localisation	Largest diameter	Preoperative symptoms	Postoperative symptoms	Activation tasks
1	22.2/f	Astrocytoma WHO Grade III	left frontal lobe, extending into the corpus callosum	6.5 cm	mild right sided hemiparesis, arm > leg, mild aphasia	unchanged	right finger movement
2	30.5/f	Giant aneurysm	right posterior end of the sylvian fissure	2 cm	mild hemihypesthesia, especially left upper extremity	resolved	left finger movement
3	70.1/f	Metastasis (adenocarcinoma)	left parietal lobe, close to the postcentral gyrus	3 cm	complex partial seizure (right sided arm movements)	no deficits	right finger movement
4	42.0 /f	Astrocytoma WHO Grade III	left superior / middle frontal gyrus	4 cm	mild disturbance of word finding	unchanged	right finger movement
5	20.8/f	Cavernoma (recent bleeding)	left central region	3.5 cm	mild paresis of the right leg	unchanged	right finger/foot movement
6	62.0/m	Metastasis (squamous cell carcinoma)	left sulcus precentralis	2.5 cm	mild right sided hemiparesis, arm > leg	resolved	right finger movement
7	32.6/f	Astrocytoma WHO Grade II	left superior frontal gyrus, precentral gyrus	5.5 cm	complex partial seizure (right sided leg movements)	no deficits	right finger/foot movement
8	37.5/m	Astrocytoma WHO Grade III	left frontal lobe, extending into the corpus callosum	6 cm	mild right sided hemiparesis and hemihypesthesia	mild dysarthria, unchanged	right finger/foot movement
9	24.4/m	Cavernoma	right parietal lobe, close to the postcentral gyrus	2.5 cm	complex partial seizure (left sided arm movements)	no deficits	left finger/foot movement

analyses (all $p < 0.001$). In an additional patient (number 1), DCS elicited maximal CMAPs of the forearm muscles in an cortical area found to be activated by finger movement in the SPM analysis for $p < 0.005$ but not for $p < 0.001$. In these patients and in two patients (numbers 6 and 9), in whom the SMC was not accessible via the trepanation, DCS could not elicit CMAPs in cortical regions, where SPM also showed no activation foci.

Compared with the SPM results for $p < 0.005$ and $p < 0.001$, the respectively adjusted relative CBF change maps showed considerably overlapping areas of CBF increase in the SMC in all but one patient. Figure 1 and figure 2 show representative examples. In one patient (number 1), the SMC activations detected by both analyses overlapped only in a small area (confirmed by DCS). In this case the Euclidean distance between the peak CBF increase and peak t value was the largest (19.2 mm) of all studies. The mean (SD) distance between the two maximums in all studies was 5.4 (4.5) mm (range

1.4–19.2 mm; after exclusion of patient number 1: 4.2 (1.8) mm). The mean (SD) maximal CBF increase in the contralateral SMC was 27.2 (6.5) % (range 19%–40%), with no apparent difference between finger (26.9 (5.7)%) and foot (27.8 (9.0)%) movements. Again, patient number 1 showed the smallest maximal CBF increase (19%). Relative CBF changes exceeding a mean (SD) of 12.0 (1.8)% and 14.0 (1.7)% spatially fitted the SPM results for $p < 0.005$ and $p < 0.001$ most appropriately.

Other cortical areas engaged in task execution as shown by SPM

In addition to the SMC contralateral to the limb moved, the ipsilateral SMC and the bilateral SMA and PMC (particularly during sequential finger movements) were frequently activated (see table 2). Compared with activations of the contralateral SMC, activations of the ipsilateral SMC were located more anteriorly, in most cases anteriorly to the central sulcus in the

Table 2 Summarised results of the individual SPM analyses: sequential finger and foot movement tasks (total $n = 9$ patients)

Area	Number (SPM, $p < 0.005$)	Number (SPM, $p < 0.001$)	Mean (SD)* Z maximum
Sequential finger movement			
SMC cl	9	7	4.79 (0.54)
SMC il	6	2	3.77 (0.47)
PM cl	6	2	4.39
PM il	6	4	3.74 (0.29)
SMA cl	7	5	3.50 (0.51)
SMA il	8	5	3.64 (0.35)
Cerebellum cl	6	5	4.48 (0.70)
Cerebellum il	9	7	4.12 (0.52)
Foot movement			
SMC cl	4	3	4.36 (0.38)
SMC il	2	0	4.64
PM cl	0	0	–
PM il	2	0	3.90
SMA cl	3	1	3.90
SMA il	2	1	3.60
Cerebellum cl	0	0	–
Cerebellum il	1	0	3.47

SMC, sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; cl/il, contralateral/ipsilateral to the moved extremity; mean Z maximum, mean of the local Z maximums of the SPM cluster; *standard deviations (SD) were only determined if the number of identifiable Z (sub-)maximums was ≥ 4 .

Table 3 Result of the SPM group analysis in seven patients with left sided lesions stimulated by sequential finger movement of the right hand (clusters of increased CBF, all $p < 0.05_{\text{corrected}}$)

Cluster	Cluster size (voxel)	Local maximums	Area (Brodmann area)	Max <i>t</i> value	Max <i>Z</i> value	Mean mm	x mm	y mm	z mm
1	3322	1.1	left SMC (BA 3/4)	14.07	∞	-44	-17	54	
		1.2	left inf. parietal / SII (BA 40)*	7.66	6.16	-50	-30	25	
2	5114	2.1	right cerebellum	12.49	∞	20	-55	-14	
		2.2	left cerebellum*	8.44	6.58	-4	-63	-10	
3	1482	3.1	right PMC (dorsolateral BA 6)*	8.09	6.39	26	-5	61	
		3.2	right SMC (BA 4)	7.57	6.11	40	-11	58	
		3.3	right SMA (mesial BA 6)*	7.30	5.96	8	4	48	
		3.4	right cingulate gyrus (BA 24)	6.94	5.75	2	12	36	
4	147	4.1	right PMC (ventrolateral BA 6)	7.88	6.28	63	7	27	
5	56	5.1	left cerebellum	6.29	5.35	-22	-37	-37	
6	64	6.1	left PMC (junction BA 6/BA 44)	5.86	5.07	-52	4	11	
7	62	7.1	right cerebellum*	5.82	5.04	55	-58	-29	

Max *t* value/max *Z* value, maximal *t* / *Z* values; x/y/z, coordinates of the Talairach-Tournoux standard anatomical atlas (converted out of the MNI coordinates provided by SPM99); inf, inferior; SMC, sensorimotor cortex; SMA, supplementary motor area; PMC, premotor cortex; SII, presumed secondary somatosensory cortex; *region showed multiple submaximums.

primary motor area. SMA activations occurred as separated activation clusters in hand activation studies, while they occasionally fused with the SMC activation in foot activation studies. Frequently, PMC activations were represented by an anterior extension of a large activation cluster covering the central region. In 6 of 14 PMC activations, no separate PMC submaximum was revealed by the SPM analysis (three local maximums assessed per cluster). Because of the limited resolution of [¹⁵O]-water PET, bilateral SMA activations could not be clearly separated, although the SPM analyses frequently showed separate submaximums for each side. The activation cluster of the SMA often extended into the anterior cingulate gyrus.

Cortical activations outside the SMC showed a looser spatial relation between the SPM analyses and the relative CBF change maps than the more robust activations of the SMC and cerebellum (fig 1 and fig 2). In addition to the constantly activated anterior superior part of the ipsilateral cerebellum, the contralateral cerebellum was frequently activated.

Overall agreement between SPM and the relative CBF change map

In two cases, no single activation could be detected by SPM for $p < 0.001$ ($n=1$ finger movement task (patient 4), $n=1$ foot movement task (patient 8)). If only patients were considered in which SPM showed activation areas for

$p < 0.005$ and $p < 0.001$, a total number of 70 activations of the SMC, PMC, SMA, and cerebellum were detected by at least one of the two analysis methods using the lower threshold. Sixty five (92.9%) of these activations were detected by SPM for $p < 0.005$ and 67 (95.7%) by the respectively adjusted CBF change map. For $p < 0.001$, the SPM analysis resulted in a total number of 44 (62.9%) activations, while the respectively adjusted CBF change map still revealed 60 (85.7%) activations. Among the activation that were not shown by the SPM analysis for $p < 0.001$ were three SMC activations detected in typical localisations by the SPM analyses for $p < 0.005$ and by the relative CBF change map (confirmed by DCS in $n=1$). Considering all studies, the SPM analyses exclusively revealed three activations (all SMA), while the CBF change maps exclusively revealed 10 activations areas (three SMA, three PMC, three cerebellum, one ipsilateral SMC), that were not shown by the other method. CBF increases in areas beyond the areas to which we a priori restricted our investigation were shown more often by the relative CBF change map than by the SPM analyses (especially for $p < 0.001$). Most of these activations were well defined and occurred in typical localisations (for example, insulae, parietal lobes, basal ganglia, thalami, visual cortices). The relative CBF change maps displayed several additional CBF increases of uncertain origin probably reflecting artefacts, most of which were ill shaped, rather small, and followed no anatomical structure.

Figure 3 Result of the SPM group study (rendered SPM illustration). Analysis of seven patients with left sided lesions, stimulated by right hand sequential finger movement (all $p < 0.05_{\text{corrected}}$). Upper row, left: left lateral view, activations of the SMC including parts of the dorsolateral PMC and BA 40 (presumed SII), frontal operculum at the junction of BA 44/BA 6. Upper row, middle: view from above. Upper row, right: right lateral view, activations of BA 4, dorsolateral PMC, ventrolateral PMC. Lower row: left (left image) and right (right image) mesial view, bilateral activations of the SMA, cingulate gyrus and cerebellum.

Individual activation patterns shown by SPM compared with clinical findings

The frequently detected activations of ipsilateral motor areas and the contralateral cerebellum during the finger movement task were somewhat unexpected. When we grouped the patients according to their symptoms in patients with (group 1: patients numbers 1, 3, 6, 8, and 9) and without (group 2: patients numbers 2, 4, 5, and 7) symptoms involving the central motor system of the arm (paresis or focal seizures), patients of group 1 did not show a higher frequency of activations of the ipsilateral SMC than patients of group 2 (3 of 5 v 3 of 4; $p=1$). However, patients of group 1 showed significantly more often activations of the ipsilateral PMC (5 of 5 v 1 of 4; $p<0.05$) and of the contralateral cerebellum (5 of 5 v 1 of 4; $p<0.05$). (We did not contemplate SMA activations because of the uncertainty regarding the side of origin.)

SPM group analysis

The group analysis (seven patients with left sided lesions, right hand sequential finger movement; fig 3) revealed a large area of increased CBF extending laterally from the precentral gyrus over the dorsolateral PMC to the SMA and the anterior cingulate gyrus in the unaffected right hemisphere. Furthermore, there was a significant activation of the ipsilateral ventrolateral PMC. Activations of the SMA, the cingulate gyrus and the cerebellum occurred bilaterally, although more prominent on the right side. As will be discussed, the result of the group analysis regarding the affected left hemisphere are of restricted validity (tabulated in table 3 for reasons of completeness). All results are summarised in table 3.

DISCUSSION

Methodological aspects

The first goal of this study was to investigate the applicability of SPM for the analysis of individual preoperative CBF-PET activation studies. To our knowledge this has not been done before. This preliminary study shows that SPM provides an efficient alternative analysis approach for this purpose.

In comparison with the relative CBF change maps that have been successfully used for this purpose at our institution so far, the SPM analysis resulted in no loss of clinically relevant information when the t maps were thresholded at $p<0.005$. Five patients underwent DCS. All SMC activations accessible were confirmed by DCS ($n=3$ hand area, $n=2$ foot area), while DCS could not elicit positive EMG responses in cortical regions, where SPM also showed no activation foci. The areas of activation shown by SPM and the relative CBF change map were spatially very similar for robust activations like SMC and cerebellum while they were less for less frequent and weaker activations. This might be explained by the fact that both methods assess different, although not totally independent measures: foci with high relative count rate increases but also high local variance can be missed by SPM, while they are detected by the relative CBF change map, and vice versa. Depending on the local heterogeneity, both methods may therefore detect different sub-foci. This (beside differences in filtering) probably contributed to the mean spatial separation of the peak of CBF increase and the peak t value of 5.4 mm within the same SMC area.

Because of missing objective and theoretically justified criteria, the thresholding of relative CBF change maps is always biased by a priori assumptions of the expected activation pattern. In our experience, a scaling of relative CBF change maps with the aim to display presumed activations most clearly while suppressing the background requires CBF increased thresholds in the magnitude of about 15% (see fig 1 and fig 2). This is close to the mean threshold of 14% that we used to adjust the CBF change maps to the SPM results for $p<0.001$. However, because of this scaling about 10% of the motor area activations detected by the less restrictively scaled CBF change

maps (adjustment to SPM $p<0.005$: mean threshold 12%) and the SPM analysis for $p<0.005$ were missed. The less restrictively scaled CBF change maps showed an activation pattern virtually identical to the SPM result for $p<0.005$ in regard of cortical motor areas, but it displayed considerably more areas of increased CBF most probably unrelated to task performance (artefacts) and thus lower specificity.

As we used comparatively low statistical thresholds in the single subject analyses ($p<0.005$), it might be suggested that some activations (especially ipsilateral motor areas) may represent false positive results, although the high frequency of detection and the systematic pattern argues against this. To establish a statistically more conservative estimate of ipsilateral areas involved in the finger movement task in our patients, we retrospectively performed a SPM group analysis using stereotactic normalisation and a correction for multiple comparisons ($p<0.05$). As the transformation algorithm is not designed to transform brains with macroscopical structural alterations, we emphasise that the results of the group analysis concerning the affected left hemisphere have to be interpreted cautiously, while they should be sufficiently accurate for the unaffected right hemisphere. No major mass effect was present in any of the seven cases. Visual inspection confirmed the goodness of the spatial normalisation in every case. Within its limitations, the group analysis confirmed the results of the single subject analyses. That is a prominent involvement of ipsilateral primary and secondary motor areas and the bilateral cerebellum in the task execution.

The fact that SPM for $p<0.005$ showed considerably more motor area activations than it did for $p<0.001$ (65 v 44, including three activations of the contralateral SMC) relates to the important question how statistical significance is related to neurological significance. Bittar *et al*⁶ showed that SMC areas with CBF increases at a t statistical level of $t>4.75$ (Worsley's method) were associated with positive DCS response, while areas with $t<3.2$ were not. Analogous values have to be defined for approaches using SPM. Consequently, at this stage, the SPM results are used in conjunction with the relative CBF change maps for preoperative planning at our institution. The definition of the resection borders with the aim of most extensive tumour resection depends on the neurosurgeons judgment relying on conventional criteria.

The fact that a fairly heterogeneous population of mass lesions was examined without compromising the results underscores the stability of the SPM analyses. However, large mass occupying tumours accompanied by oedema might hinder the detection of SMC activations for $p<0.001$ as in the three high grade tumour patients with the largest tumour diameters.

The basis for the calculation of statistical parametric maps is a voxel-wise t test. A violation of the underlying assumption of a normal distribution cannot be excluded if only a limited number of scans are available in single subject studies. Grabowski *et al*²⁹ compared different pixel based statistical methods for the analysis of multi-subject PET activations studies: especially for small sample sizes, methods depending on local variance estimates (like SPM and an enrolled non-parametric model) were shown to be less powerful than the CDA and Worsley's method, which are based on pooled variance estimates. In single subject studies, however, the performance of SPM should be improved in comparison with the other methods because the local variance estimates should be particularly improved by removing inter-subject variability. It has also been claimed, that pooled variances represent a simplification in the presence of non-uniform regional variances.^{29, 30} To increase the statistical power it would be useful to use shorter interscan intervals as suggested by Chmielewska *et al*.³⁰ An interscan interval of six minutes for instance would allow up to 18 instead of 12 scans within acceptable time (<2 hours) and radiation exposure limits. Furthermore, a data acquisition in multiple frames per scan

with a subsequent analysis of variance with blocking across frames might be used to increase the sensitivity of single subject analyses.³¹

The use of a smaller smoothing filter kernel than the one used in this study (12 mm FWHM) might be more appropriate in single case SPM analyses where one is not confronted by group variability. In this preliminary study we did not systematically seek to optimise filtering. Optimal processing parameters need to be defined.

Activation pattern

Investigating a sequential finger movement task (right hand; metronome paced, 1.5/s) in normal volunteers by CBF-PET, Colebatch *et al*²⁶ found significant CBF increases in the contralateral SMC and in the bilateral SMA, cingulate gyri, and PMC (ipsilateral < contralateral; among others). Remy *et al*³² reported that a more complex self paced one finger movement in contrast with a simple self paced fist making significantly increased the regional CBF in the ipsilateral SMC and SMA, although less intense than contralateral. The PMC was not activated. Similarly, Shibasaki *et al*³³ reported that in comparison with a simple sequential finger opposition task like ours, a more complex sequential finger opposition task (both self paced, 2/s) caused an additional significant mean CBF increase in the ipsilateral SMC and cerebellum and in the contralateral PMC and SMA. None of the tasks activated the ipsilateral PMC. Using four sequential finger movement tasks of varying complexities (the simplest being equivalent to ours; metronome paced, 2/s), Sadato *et al*²⁷ observed significant CBF increases in the SMC bilaterally, the ipsilateral cerebellum and the contralateral PMC and SMA, regardless of complexity. The regional CBF of the ipsilateral PMC was linearly related to task complexity, but resulted in an additional activation focus only in the comparison of the most complex task versus rest.²⁷

Thus an activation of the ipsilateral SMC seems to be physiological during sequential finger movements, although the associated CBF increase might not reach significance. However, activations of the ipsilateral PMC and the contralateral cerebellum during simple sequential finger movements are unexpected. It might be argued that this could be attributable to a motor function impairment of the patients, which might have exaggerated the complexity of this simple task for handicapped patients and thus enforced ipsilateral PMC activation. Assuming that the task complexity is influenced by its performance rate, we instructed the patients to perform the task at a comfortable rate to keep the complexity of the task roughly constant across all patients with variable degrees of impairment. Nevertheless, the performance rates in our patient group remained in a narrow range (1–2/s), comparable with the studies cited above. Jenkins *et al*³⁴ showed that the CBF increase in bilateral PMC (among others) was positively correlated to the rate of freely selected joystick movements in a frequency range of 0.2–1/s, tending to reach a plateau at about 1/s. Despite different tasks, this does not support the notion that activations of the ipsilateral PMC in our study may be caused by a higher performance rate, especially when it is considered that PMC activations occurred more often in handicapped patients.

A possible influence of cueing on PMC activations has to be considered: Jenkins *et al*³⁵ found bilateral activations of the PMC during self initiated finger movements. In contrast, when unpredictably externally cued, PMC activations were absent. It is questionable if this observation can be transferred to our study, as Jenkins *et al* requested their subjects to repeatedly self initiate a one finger movement at a variable rate (once every 2–7 s), while we asked our patients to perform the same pre-learned sequential finger oppositions continuously. In fact, the same group found bilateral activations of the PMC during learning of a novel finger movement sequence guided by auditory cues.³⁶ During an auditory paced performance of a

comparable pre-learned sequence, there was only an (significantly smaller) activation of the contralateral PMC. These studies suggest a role of the PMC in the decision what movement to make rather than in the decision when to move.

The activations of the ipsilateral PMC and contralateral cerebellum are very well compatible with activation studies in stroke patients, where these activations were associated with functional recovery: Chollet *et al*¹² and Weiller *et al*^{13, 14} found significantly stronger activations of the ipsilateral SMC (partially associated with mirror movements) and PMC and of the bilateral SMA, cerebellum and insula/frontal operculum (among others) during sequential finger movements in patients recovered from poststroke arm paresis compared with healthy controls and to the movement of the unaffected hand. The PMC, striatum, insula, BA 40, and the cerebellum showed correlated CBF changes bilaterally and thus might serve as a higher order motor network with a greater compensatory capacity.¹³ Other PET studies in patients recovered from paresis caused by cortical¹⁶ and subcortical infarctions¹⁵ also claimed a compensatory role of ipsilateral, non-primary motor areas. An enhanced recruitment of ipsilateral motor pathways was also demonstrated by transcranial magnetic stimulation,^{17, 18, 37} although not associated with a more beneficial outcome.^{17, 37}

Although this study is preliminary, we found that activations of the ipsilateral PMC and the contralateral cerebellum occurred significantly more often in patients with motor symptoms of the respective arm. As in stroke patients, this might reflect a compensatory recruitment of ipsilateral motor pathways.

Caramia *et al*²¹ were able to elicit ipsilateral motor evoked potentials in glioma patients by transcranial magnetic stimulation over the PMC of the unaffected hemisphere that were absent in healthy controls. In a series of preoperative brain mapping studies using PET, Bittar *et al*⁷ observed that movements of the hand contralateral to a lesion compared with movements of the ipsilateral hand may evoke additional activations of the bilateral SMA and opercula, the contralateral insula and superior parietal lobule, and the ipsilateral SMC. Two fMRI studies^{38, 39} also reported an enhanced recruitment of ipsilateral primary and secondary motor areas, particularly in patients with paresis.³⁸ Seitz *et al*¹⁹ and Wunderlich *et al*²⁰ using PET activation found that the hand representation was shifted into the neighbouring SMC, PMC, and parietal lobe, if the primary motor region of the hand was compromised by tumour growth. Such intra-hemispheric compensatory mechanisms have also been proposed by other groups investigating neoplastic³⁹ and ischaemic lesions.^{14, 40} A lesion dependent disinhibition of cortical motor areas in the affected^{41–43} and in the unaffected hemisphere^{44, 45} shown in animal and human studies might act as a trigger for the compensatory use of unaffected primary and secondary motor areas and uncrossed corticospinal projections may be recruited.^{12, 17, 18, 21}

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