Localisation of motor areas in brain tumour patients: a comparison of preoperative [18F]FDG-PET and intraoperative cortical electrostimulation

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Received 25 February and in revised form 20 May 2001 / Published online: 31 July 2001

Abstract. Assessment of the exact spatial relation between tumour and adjacent functionally relevant brain areas is a primary tool in the presurgical planning in brain tumour patients. The purpose of this study was to compare a preoperative fluorine-18 fluorodeoxyglucose positron emission tomography ([18F]FDG PET) activation protocol in patients with tumours near the central area with the results of intraoperative direct cortical electrostimulation, and to determine whether non-invasive preoperative PET imaging can provide results equivalent to those achieved with the invasive neurosurgical "gold standard". In this prospective study, we examined 20 patients with various tumours of the central area, performing two PET scans (each 30 min after i.v. injection of 134–341 MBq [18F]FDG) in each patient: (1) a resting baseline scan and (2) an activation scan using a standardised motor task (finger tapping, foot stretching). Following PET/MRI realignment and normalisation to the whole brain counts, parametric images of the activation versus the rest study were calculated and pixels above categorical threshold values were projected to the individual MRI for bimodal assessment of morphology and function (PET/MRI overlay). Intraoperative direct cortical electrostimulation was performed using a Viking IV probe (5 pulses, each of 100 µs) and documented using a dedicated neuro navigation system. Results were compared with the preoperative PET findings. PET revealed significant activation of the contralateral primary motor cortex in 95% (19/20) of the brain tumour patients (hand activation 13/13, foot activation 6/7), showing a mean increase in normalised [18F]FDG uptake of 20.5%±5.2% (hand activation task) and 17.2%±2.5% (foot activation task). Additionally detected activation of the ipsilateral primary motor cortex was interpreted as a metabolic indication for interhemispheric compensational processes. Evaluation of the PET findings by cortical stimulation yielded a 94% sensitivity and a 95% specificity for identification of motor-associated brain areas. In conclusion, the findings indicate that a relatively simple and clinically available [18F]FDG PET activation protocol enables a sufficiently precise assessment of the local relation between the intracranial tumour and the adjacent motor cortex areas and may facilitate the presurgical planning of tumour resection.

Keywords: [18F]FDG PET – Motor activation – Brain tumour – Cortical electrostimulation

Eur J Nucl Med (2001) 28:1394–1403
DOI 10.1007/s002590100582

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Introduction

An important aspect of presurgical planning in patients with intracranial tumours is the exact estimation of the spatial relation of the tumour to the eloquent brain areas. Owing to individual variations in the functional anatomy, however, estimation exclusively based on anatomical landmarks is not advisable. Electrophysiological stimulation trials on the exposed brain [1] and PET activation studies [2] have shown a clear interindividual variability in the localisation and spatial extension of eloquent cortical areas. Without knowledge of the exact spatial relation between the tumour and the eloquent brain areas, undertaking a radical, prognostically vital tumour excision always carries the risk of permanent damage to functionally relevant cortical areas. Furthermore, it is not known to what extent eloquent cortical areas reorganise

themselves (neuronal plasticity) in the case of slowly growing tumours, such as low-grade gliomas or meningiomas [3]. A neuronal reorganisation due to different types of cerebral lesion has been described for motor function by several authors [4, 5, 6, 7, 8]. It is important for each individual tumour excision to know whether homologous contralateral areas are activated (interhemispheric compensation) or whether there is an increased ipsilateral activation of the remaining or neighbouring areas of the respective systems (specific or global intrahemispheric compensation).

In the last 10 years, oxygen-15 labelled water ($[^{15}O]H_2O$) has become the tracer of choice for cerebral PET activation studies since its short half-life permits numerous repeat scans with multimodal activation designs. On the other hand, owing to its slow intracerebral uptake kinetics, fluorine-18 fluorodeoxyglucose [^{18}F]FDG) as a marker for glucose metabolism has played only a minor role in cerebral activation studies, despite the fact that cerebral blood flow and glucose metabolism correlate positively in neuronal processes of healthy brain tissue.

The few studies so far published on preoperative PET activation [9, 10, 11, 12, 13, 14, 15, 16, 17] have only examined a small number of patients. These studies exclusively used $[^{15}O]H_2O$ and did not consistently conduct a systematic comparison with intraoperative cortical electrostimulation, which is still considered the neurosurgical "gold standard" for brain mapping.

The suitability of functional MRI (fMRI) for preoperative brain mapping has also been investigated by several authors [4, 10, 18], including single studies which have compared the fMRI findings with intraoperative cortical stimulation in small patient populations [19, 20]. Even though fMRI is an established modality for cerebral activation studies, a special problem in brain tumour patients (who frequently suffer from central paresis of various degrees) is the high sensitivity of fMRI to motion artefacts. For this neurosurgical patient group it is desirable to have a simple and robust approach for preoperative brain mapping.

We therefore sought to determine the clinical validity of preoperative [^{18}F]FDG activation PET using a larger number of patients with histologically different intracranial tumours. Depending on tumour location and the neurological symptoms, we employed a motor activation of the hand or the foot (a) to determine the exact spatial relation of the tumour to the motor area and (b) to compare the PET findings with neuro navigation-controlled direct cortical electrostimulation.

Materials and methods

This study included 20 patients (8 males, 12 females) with an age range of 21–72 years (mean 48.7±15.8 years), all of whom had intracranial tumours.

Inclusion criteria were: (1) tumour in or near the central area; (2) surgery planned shortly after the PET examination; and (3) sufficiently clear consciousness to permit cooperation with our team. The study protocol was approved by the ethics committee of the Aachen University of Technology and the study was performed in accordance with the Declaration of Helsinki. Patients were informed about the radiation exposure associated with the PET examinations and the expected individual benefit and gave written informed consent.

MRI. Following i.v. injection of 10–15 ml gadolinium-DTPA, each patient was imaged using a cranial T1-weighted 3D-flash sequence on a 1.5-T magnetic resonance tomograph (Magnetom 1.5 T, Siemens, Erlangen) with a circular polarised Helmholtz head coil (TE 5 ms, TR 40 ms, 256 matrix, 127 slices, interslice distance 1.56 mm).

PET. PET examinations (rest and activation) were performed on an ECAT Exact tomograph (Siemens/CTI, Erlangen/Knoxville, Germany/USA). Depending on the clinical urgency of the neurosurgical operation, the 20 patients were examined using either a 1-day (n=7) or a 2-day (n=13) protocol (Fig. 1). All patients fasted

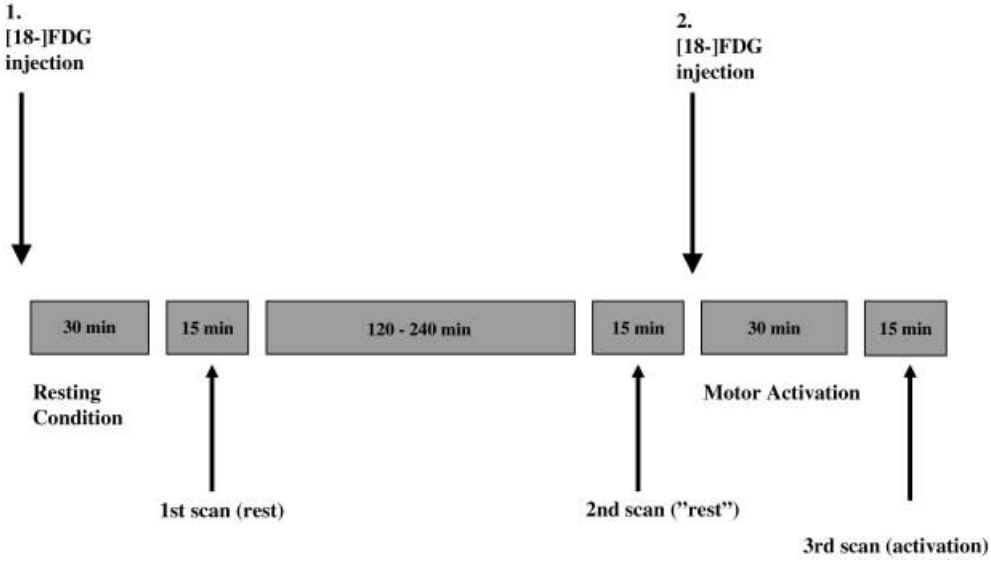


Fig. 1. Schematic description of the time course in 1-day activation protocols. The 1-day protocols require a second resting scan immediately before the second [^{18}F]FDG injection for correction of resting activity (see "Image analysis")

for a minimum of 10 h before the study. After injection of 134–341 MBq (mean 184±59) [^{18}F]FDG, patients were instructed to lie in the supine position in a darkened room with their eyes closed and with minimal background noises. Thirty minutes after the injection, the patient was placed in the PET scanner and the head fixed with an elastic latex strip. A 2D emission scan was acquired for 15 min. For 1-day protocols, a new resting acquisition was performed immediately prior to the second [^{18}F]FDG injection. Attenuation correction was then performed using a computerised threshold limit routine to define an isodensity contour for the maximum cerebral activity/pixel. The exact position of these isodensity contours was controlled visually slice by slice and eventually corrected manually. Next, 47 transversal slices (slice thickness 3.375 mm) were reconstructed using a Hanning filter (cut-off frequency 0.5). Transaxial FWHM (full-width at half-maximum) was 6.0 mm.

Activation tasks. This study employed motor activation tasks of the hand or the foot depending primarily on the tumour location on MRI as well as the clinical symptoms. The activation tasks were started simultaneously with the second [^{18}F]FDG injection and lasted 30 min.

Upper extremity activation was achieved by finger tapping, where the patient was asked to perform sequential same-hand digit oppositions (thumb to the other four fingers), while lower extremity activation was achieved by flexion or rotation of the foot. The patients were asked to execute these motion sequences as quickly as possible for a maximum metabolic signal level.

Image analysis. Following AC/PC (anterior/posterior commissure) alignment of the MRI data set, the PET data sets were realigned to fit the MRI data using special multimodal image processing software (MPI Tool [21]) under isodensity contour definition in the PET data sets. Next, the two PET examinations were normalised to each other as a proportional scaling after the global cerebral activities at rest and under activation had been calculated using an automatic, threshold value-based segmentation.

For patients examined under a 1-day protocol, data from the first resting examination were decay corrected and subtracted from the activation task to eliminate the radioactivity which might have remained from the first examination (Fig. 1). This correction for decay hinges on the (simplified) assumption that, over the space of several hours, there is a homogeneous (primarily decay-dependent) decrease in radioactivity without a significant intracerebral redistribution of [^{18}F]FDG. In order to test this assumption, the total counts of the first resting examination were compared with the decay-corrected total counts of the second resting examination: there was a maximum deviation of about 3%, which agrees with our starting hypothesis of a mainly decay-dependent decrease in cerebral radioactivity. In order to further test this, we calculated a parametric division image of resting scan 2 ÷ resting scan 1 (Fig. 2). Remarkably, despite only minor deviation of the decay-corrected whole brain counts (resting scan 2 vs resting scan 1, see above), we found a very inhomogeneous regional radioactivity distribution, with locally increased uptake especially in the visual cortex and bilaterally in the central region. This inhomogeneous intracerebral distribution pattern might be caused by a regional "redistribution" of [^{18}F]FDG due to non-specific visual and motor stimulation between the first and the second resting examination (120–240 min), during which the patient was allowed to move about freely. This could indicate re-uptake of circulating [^{18}F]FDG in those brain areas which are non-specifically stimulated between the two scans.

These experimental results do not support the starting hypothesis of a mainly decay-dependent decrease in cerebral radioactivity, so that in all 1-day protocols, data from the second resting examination had to be decay corrected and subtracted from the activation task that immediately followed. Next, parametric division (activation ÷ rest) and subtraction images (activation–rest) were calculated and the resultant activated areas projected into the MRI data set (PET/MRI overlay) according to empirical threshold values: brain voxels were considered as significantly activated if the ratio of regional normalised counts of the activation study to regional normalised counts of the resting study was ≥1.1. This categorical threshold value of 10% was set according to increases in blood flow and glucose metabolism which are characteristic for motor tasks, as evident from data of our own and from the literature [22, 23, 24].

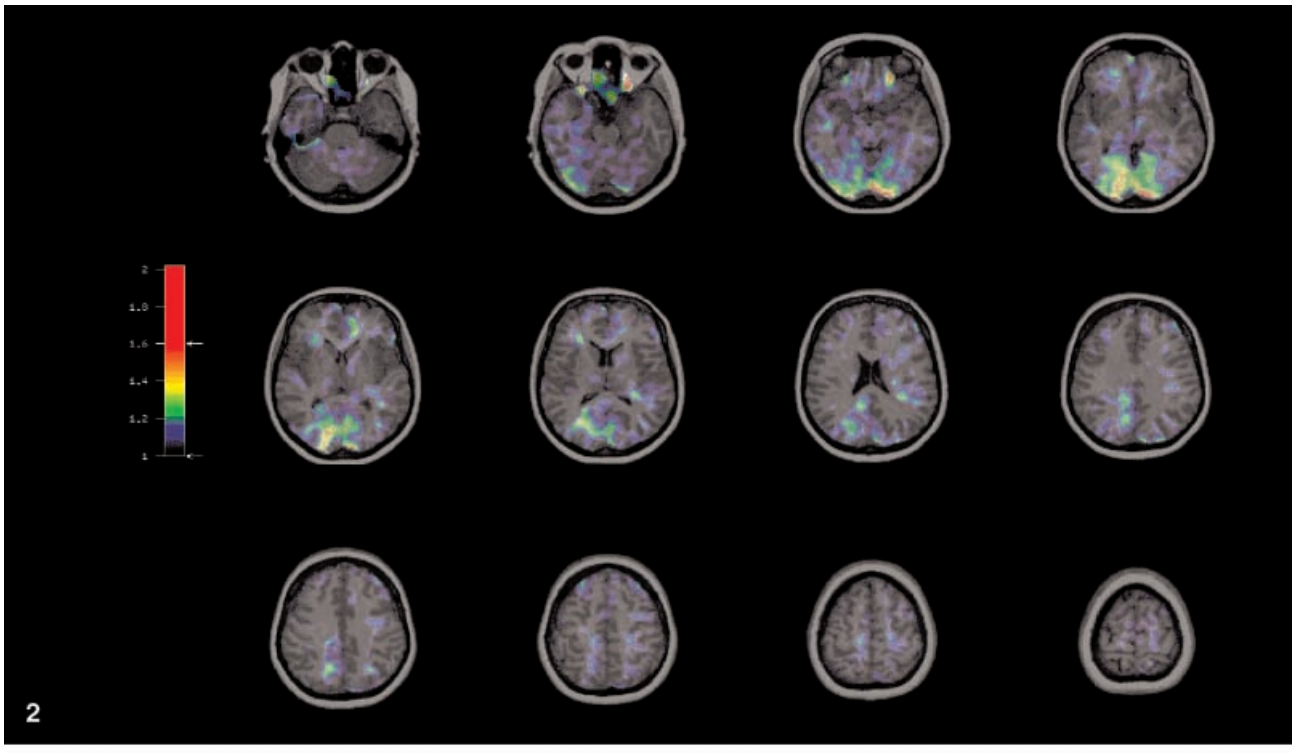
Intraoperative direct cortical stimulation. Electrostimulation of the intraoperatively exposed cortex was performed using a 10-mm-diameter monopolar electrode (Nicolet stainless steel disc electrode) which was placed on the exposed cortex. For electromyographic (EMG) (Nicolet Viking IV-P) detection of the peripheral stimulus, the patient's musculature was not pharmacologically relaxed during the operation. For cortical stimulation, five repeated electrical impulses of 0.1–0.2 ms duration were administered between periods of 1.8–1.9 ms at a frequency of 500 Hz. The intensity of the individual stimuli was increased in increments of about 2 mA from 0 mA to 25 mA. The EMG electrodes were placed in the following muscles contralateral to the stimulated hemisphere:

- 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.

At each successful stimulation, the exact position of the stimulating electrode was documented using the dedicated neuro navigation system EasyGuideNeuro (Philips Medical Systems, the Netherlands) in all three section planes (transversal, coronal, sagittal).

Comparison between PET findings and cortical electrostimulation. The data from the preoperative PET activation studies were compared with the intraoperative stimulation results after PET/MRI realignment using the fusion images and the data of the neuro navigation system. Three experienced investigators (one nuclear medicine physician, one neurosurgeon, one neuroradiologist) compared the bimodal results in all three planes (transversal, coronal, sagittal). A PET/electrostimulation match was defined as a spatial concordance of the activation signal and the probe localisation within the spatial resolution of the probe (10 mm). A bipolar probe with higher spatial resolution for cortical stimulation was not used by the neurosurgeons because of the higher current density and the possibility of heat damage to the brain tissue. The results of the PET/electrostimulation comparison were classified into four categories:

I. Positive PET signal/positive electrostimulation signal: PET true positive
II. Positive PET signal/negative electrostimulation signal: PET false positive



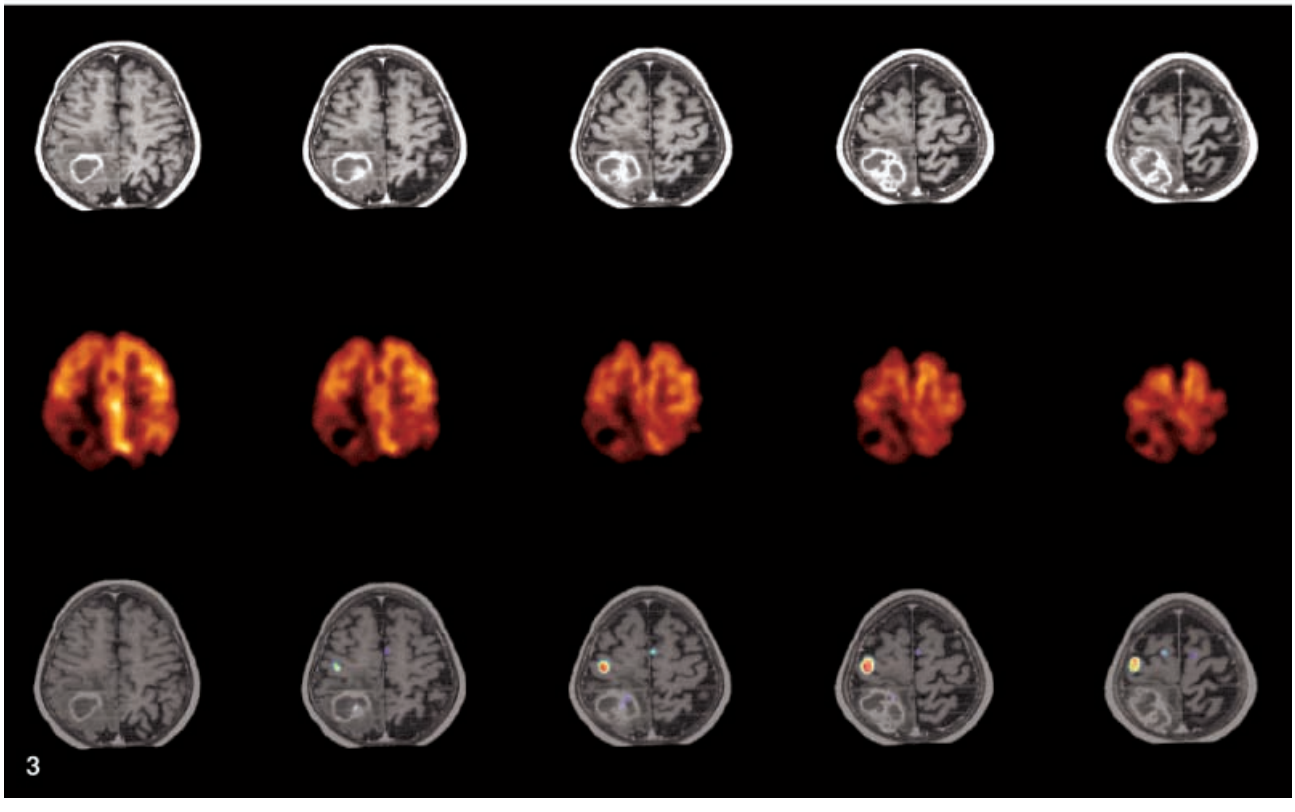


Fig. 2. Parametric division image of resting scans (decay corrected resting scan2 ÷ resting scan1) overlaid onto the individual MRI. The time interval between the resting scans was 204 min. Note the locally increased radiopharmaceutical activity in the bilateral visual cortex (up to 50% higher in the second resting scan as compared with the first resting scan, see *colour bar on the left side*)

Fig. 3. A 66-year-old patient with a right parietal glioblastoma multiforme (*top row*) and slight left-sided hemiparesis. On resting PET (*middle row*), the tumour showed a glucose metabolism lower than that of the normal cortex. The *bottom row* (PET/MRT overlay) shows the brain areas activated by a motor task of the left hand (finger tapping): the primary motor area is clearly located anterior to the tumour without any direct proximity. There is an additional activation in the bilateral supplementary motor area

III. Negative PET signal /negative electrostimulation signal: PET true negative
IV. Negative PET signal/positive electrostimulation signal: PET false negative

Statistical data analysis. For the comparison of the frequency of detected activation signals between 1-day and 2-day protocols we used the χ^2 test. The difference in signal increases in 1-day and 2-day protocols was investigated using the non-parametric Mann-Whitney U test.

Technical note. In the following text, the term *ipsilateral* brain area activation means ipsilateral to the side of the motor-activated hand or foot.

Table 1. Relative frequency of tumour by histopathology

Histology	No.
Chondroma	1
Metastasis	1
Meningioma WHO grade II	2
Anaplastic meningioma WHO grade II	1
Astrocytoma WHO grade III	1
Oligoastrocytoma WHO grade II	2
Oligoastrocytoma WHO grade III	2
Oligodendroglioma WHO grade II	1
Oligodendroglioma WHO grade III	1
Glioblastoma WHO grade IV	7
Others	1
Total	20

Results

The distribution of tumour entities identified by the postoperative histopathological examination of the removed tumour tissue is shown in Table 1. Glioblastomas represented the largest tumour group (n=7), followed by semi-malignant (WHO grade III, n=4) and semi-benign (WHO grade II, n=3) gliomas.

PET activation

Motor activation of 20 investigated brain tumour patients (13 of whom performed hand activations, and seven, foot activations) yielded significant activation signals (as defined by an increase in normalised regional counts by >10% of resting counts) in brain areas described in Table 2 (hand activation task) and Table 3 (foot activation task).

Overall, it was possible to unequivocally identify the corresponding primary motor cortex (contralateral precentral area) in 95% (19/20) of the patients (hand activation 13/13, foot activation 6/7). The mean increase in normalised [^{18}F]FDG uptake in the primary motor cortex was 20.5%±5.2% and 17.2%±2.5% for hand and foot activation tasks, respectively.

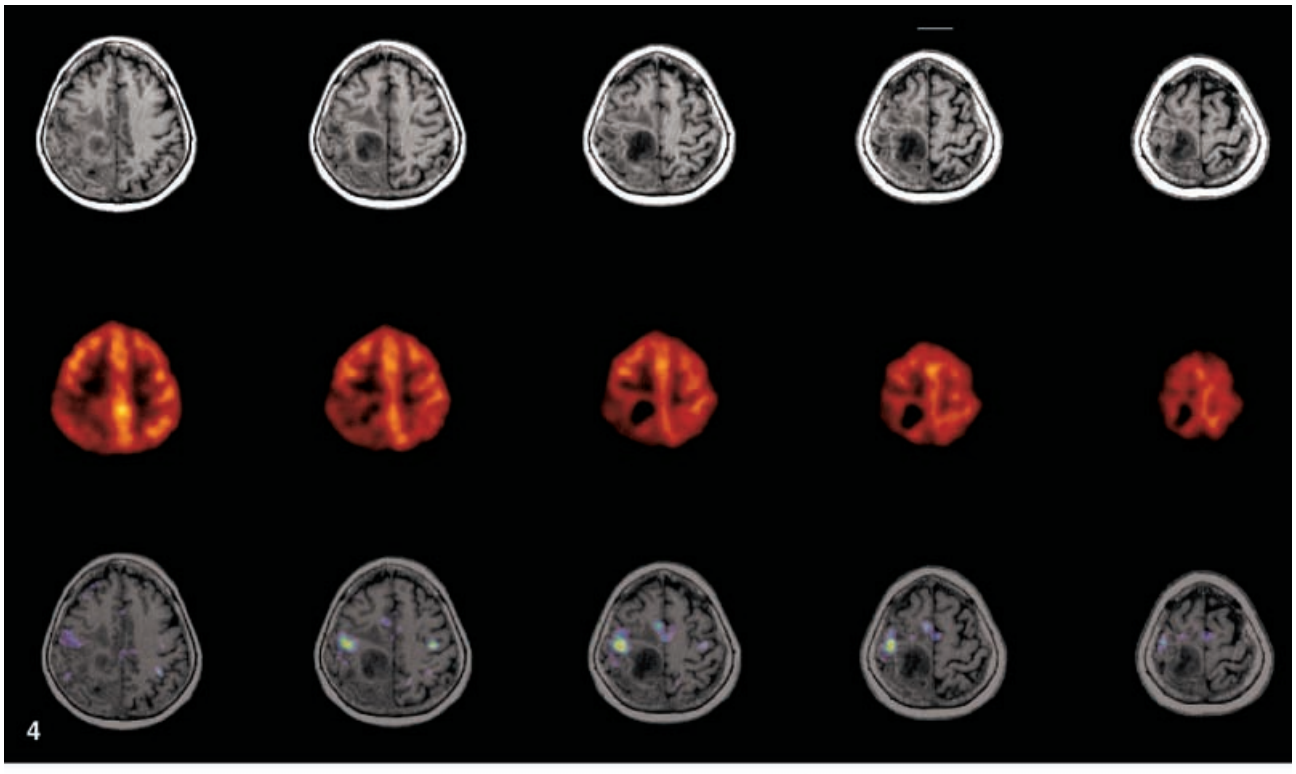
Remarkably, even though the patients moved only one hand or one foot, we also found activation of the ipsilateral primary motor cortex in 6/13 patients who performed the hand activation task) and in 3/7 who performed the foot activation task. One patient suffering

Table 2. Motor activation of the hand (13 patients); frequency of regional activation signals and average maximum activation increase in the corresponding brain region

Region	Frequency of significant activation signals	Average activation signal increase (%)
Contralateral precentral area	100% (n=13)	20.5±5.2
Ipsilateral precentral area	46% (n=6)	16.8±3.0
Contralateral SMA	54% (n=7)	17.1±3.6
Ipsilateral SMA	39% (n=5)	20.6±4.6
Contralateral premotor area	23% (n=3)	16.7±1.3
Ipsilateral premotor area	23% (n=3)	22.3±2.1
Contralateral cerebellum	46% (n=6)	19.0±2.2
Ipsilateral cerebellum	85% (n=11)	23.0±4.4

Table 3. Motor activation of the foot (seven patients); frequency of regional activation signals and average activation increase in the corresponding brain region

Region	Frequency of significant activation signals	Average activation signal increase (%)
Contralateral precentral area	86% (n=6)	17.2±2.5
Ipsilateral precentral area	43% (n=3)	18.3±5.3
Contralateral SMA	57% (n=4)	14.5±1.5
Ipsilateral SMA	14% (n=1)	15.0
Contralateral premotor area	29% (n=2)	20.5±2.5
Ipsilateral premotor area	14% (n=1)	20.0
Contralateral cerebellum	71% (n=5)	16.0±5.0
Ipsilateral cerebellum	86% (n=6)	18.0±5.5



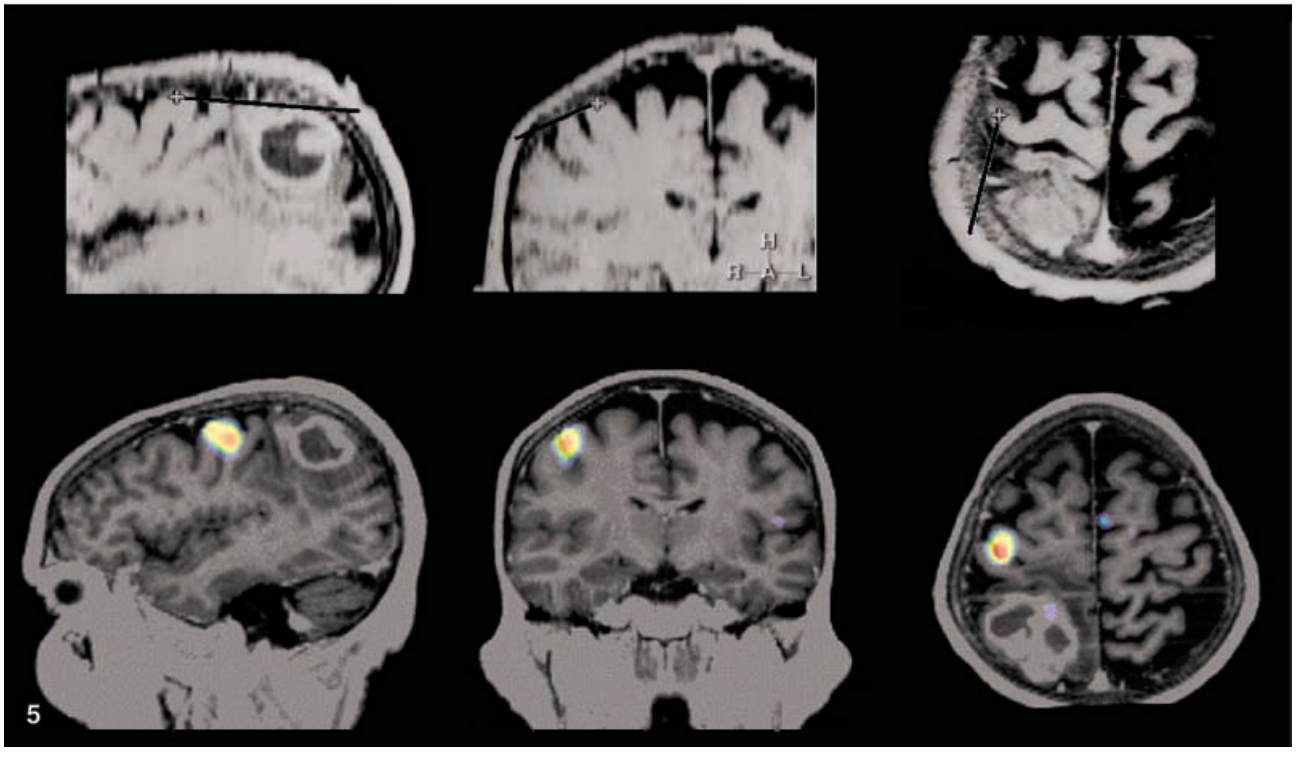


Fig. 4. A 65-year-old patient with a right frontoparietal glioblastoma multiforme (*top row*) and moderate left-sided hemiparesis. On resting PET (*middle row*), tumour and the adjacent brain tissue showed a reduced glucose metabolism compared with normal grey matter but an increased metabolism in the tumour parts which are located within the centrum semiovale. PET/MRI overlay shows the activated cortical areas during finger tapping of the left hand: the corresponding primary motor cortex is slightly shifted to the lateral and anterior direction, and there is a clear activation signal in the SMA and in the left precentral area

Fig. 5. Same patient as shown in Fig. 3. The *upper row* shows the localisation of the intraoperative stimulation electrode (*white cross, black line*), as documented by the neuronavigation system. The *bottom row* (PET/MRT overlay; left hand finger tapping) shows activation signal at the same position where the cortical electrostimulation yielded a motor response of the left forearm muscles

from a glioblastoma did not show a significant activation signal in the motor cortex but within the hypermetabolic tumour region. This activation "signal" was classified as an artefact by the observers, and intraoperatively, the cortical electrostimulation could not induce motor activation potentials from this area.

In addition to the primary motor cortex, preoperative [^{18}F]FDG PET activation enabled the identification of other motor-associated cortical areas: activation signals were regularly found in the ipsilateral and contralateral supplementary motor areas and in the ipsilateral and contralateral premotor cortex. Activation of the cerebellum (via hemisphere-crossing cortico-cerebellar projections) could be detected in the ipsilateral cerebellum (17/20 patients: 85%) and in the contralateral cerebellum (11/20 patients: 55%).

The activation signals in the motor-associated brain regions shown as an increase in regional glucose metabolism from the resting studies varied from 16.7%±1.3% (contralateral premotor area) to 23.0%±4.4% (ipsilateral cerebellum) in hand activations and from 12.0% (ipsilateral postcentral area) to 20.5%±2.5% (contralateral premotor area) in foot activations.

Figure 3 shows a PET/MRI overlay of a motor left-hand activation in a female patient with a right parietal glioblastoma. The primary motor area projects anterior to the tumour without immediate proximity to the contrast agent-absorbing tumour regions. There is an additional activation in the supplementary motor area. Figure 4 shows the PET and MRI data of a patient with a right frontoparietal glioblastoma and moderate left-sided hemiparesis. The corresponding right primary motor cortex is slightly shifted to the lateral and anterior direction. There is an additional activation signal in the supplementary motor area (SMA) and in the left primary motor cortex.

Comparison of 1-day and 2-day protocols

For the clinical acceptance of preoperative activation PET by neurosurgeons, it is mandatory to offer 1-day PET examination protocols, especially for clinically urgent patients showing a progressive neurological worsening. In order to investigate whether 1-day and 2-day activation protocols provide equivalent results, frequency and increase of detected activation signals were compared. This comparison revealed no statistically significant differences in the frequency of detected activation signals ($P>0.05$ for all regions, χ^2 test), whereas the signal increase was significantly higher (20.8% vs 14.6%) in the ipsilateral primary motor area of 1-day protocol patients ($P<0.05$, Mann-Whitney U test) (Table 4). The other motor-associated brain regions did not show significant differences between the two protocols, even though there was a trend towards higher values in most of the regions in 1-day protocol patients.

Table 4. Average activation signal increase (%) in the 1-day (n=7) and 2-day (n=13) protocols

Region	One-day protocol	Two-day protocol
Contralateral precentral area	20.2±3.6	19.2±5.5
Ipsilateral precentral area	20.8±3.0*	14.6±2.8*
Contralateral SMA	17.0±2.7	15.8±4.1
Ipsilateral SMA	21.0±4.6	17.0±7.1
Contralateral premotor area	23.0	17.0±1.4
Ipsilateral premotor area	21.0±1.4	22.5±3.5
Contralateral cerebellum	20.3±5.7	17.0±3.5
Ipsilateral cerebellum	21.0±4.4	21.1±6.1

*$P<0.05$

Table 5. Evaluation of preoperative [^{18}F]FDG activation PET by intraoperative direct cortical electrostimulation in 20 patients

Category I (PET true positive)	94% (16/17)
Category II (PET false positive)	5% (1/20)
Category III (PET true negative)	95% (19/20)
Category IV (PET false negative)	6% (1/17)

Intraoperative direct cortical electrostimulation

Direct cortical electrostimulation was performed intraoperatively on all of the 20 motor-stimulated patients during the tumour resection. Owing to the small trepanation approach of modern "key-hole" neurosurgery, it was not possible to intraoperatively stimulate all cortical regions which showed a positive PET finding (including contra- and ipsilateral activation signals). Therefore, the cortical electrostimulation was performed to identify the contralateral primary motor cortex in all of the patients.

Overall, a positive motor signal in the corresponding muscles after stimulation of the intraoperatively exposed cortical area was found in 17/20 (85%) patients. In 16/17 (94%) patients, comparison of the preoperative PET results with those of direct cortical stimulation (Table 5) revealed concordant findings for the detection of primary motor cortex, showing a positive stimulus response which conformed exactly with the PET activation signal (category I: PET true positive). One patient (1/20: 5%) showed PET motor activation signals which electrostimulation of this area could not reproduce (category II: PET false positive). In 19/20 (95%) patients, cortical areas with no significant PET activation signal were concordantly electrophysiologically mute (category III: PET true negative). One patient (1/17: 6%) with a positive electrostimulation signal showed no corresponding PET signal in this cortical area (category IV: PET false negative) when using a categorical threshold of 10% for signal detection. Retrospective analysis of this case with a lower threshold of 8% yielded a signal corresponding to the electrostimulation finding.

Calculation of sensitivity and specificity of preoperative [18F]FDG activation PET showed a sensitivity of 94% and a specificity of 95% for the identification of motor-associated brain areas compared with the invasive gold standard, direct cortical electrostimulation.

Figure 5 demonstrates the corresponding results of cortex electrostimulation and PET in the same patient as shown in Fig. 3.

Discussion

The aim of this study was to compare [18F]FDG PET with direct cortical stimulation in order to assess its value as a preoperative diagnostic tool for intracranial tumours related to the central area. Knowledge of the exact spatial relation between the tumour and functionally relevant brain areas (primary motor area) is of decisive importance for planning both access and extent of the excision; for neither of these tasks are exclusively morphologically oriented imaging methods completely adequate.

All previous studies on PET-based preoperative brain mapping either relied on case reports [9, 13, 24] or included only a small number of patients [10, 11, 12, 14, 15, 16, 17]. Preoperative PET was compared with the neurosurgical gold standard intraoperative electrostimulation in only a few cases [25]. These studies employed almost exclusively [15O]H_2O as the radiotracer, while [18F]FDG was used to measure tumour glucose metabolism. In these studies using freely diffusing tracers such as [15O]H_2O or 15O-butanol, the authors referred to the advantages of performing multimodal activations with a better temporal resolution of 10–30 s. [18F]FDG has a resolution of 20–30 min, which can make a significant difference in more complex cognitive activation studies. However, more recent studies [26] have shown the suitability of [18F]FDG for assessing cognitive-linguistic performance, where [18F]FDG has the advantage of higher spatial resolution due to the lower positron energy (18F: 0.64 MeV, medium range 0.2 mm; 15O: 1.72 MeV, medium range 1.5 mm), as well as an improved signal-to-noise ratio [27].

Since the present study dealt with patients suffering from tumours related to the central region, we chose motor activation of the hand or the foot, depending on the tumour location and the neurological status. The clinical value of preoperative [18F]FDG activation for operative planning was clearly demonstrated in this comparative study (performed in the largest patient sample to date), the technique having a sensitivity of 94% and a specificity of 95% as assessed by comparison with intraoperative electrostimulation.

The primary advantage of [18F]FDG PET compared with presurgical fMRI brain mapping is the lower sensitivity to motion artefacts and the considerably more robust activation signal, which is 5–10× higher than the fMRI signal in motor tasks [28, 29]. These factors may be particularly relevant for the examination of brain tumour patients, who are often unable to perform the activation task as precisely as healthy volunteers.

Unlike activations with blood flow tracers, [18F]FDG PET usually comprises only two scans, thereby necessarily limiting the study to a single specific task. There is an advantage in using blood flow tracers since these allow multimodal activations, as when assessing extensive tumours. When using only one resting and one activation scan, as we did in this study, statistical significance of the activation signals cannot be given, and specific activations can therefore be filtered out from the statistical "background noise" only empirically. It is for this reason that we chose the categorical threshold values for motor activation of 10% of the resting normalised counts [23, 24]. The use of categorical thresholds depending on empirical values of glucose metabolism increase seems to be a clear disadvantage of [18F]FDG PET as compared with [15O]H_2O PET, but the results of this study indicate that, at least for the assessment of motor areas, the application of categorical thresholds can provide valid results. We consistently found activation signals which agreed with general neurophysiological experience and with results reported by other authors using comparable tasks for motor activation, e.g. with regard to the contralateral and the ipsilateral precentral area, the SMA, the premotor cortex and the bilateral cerebellum. The average maximum increase in activation ranged from 12.0% (ipsilateral postcentral area) to 23.0% (ipsilateral cerebellum).

The comparison of 1-day and 2-day activation protocols revealed no significant differences in the detection of motor-relevant cortical areas when an adequate correction of the persistent activity of the first PET scan was performed. This correction requires a second resting scan immediately before the second [18F]FDG injection for the activation study. The option of 1-day [18F]FDG activation protocols seems very appropriate for the examination of neurology patients with rapid deterioration who are not candidates for prolonged preoperative diagnostic procedures.

Even though the very good agreement between the PET data and the cortical electrostimulation would seem to indicate the validity of the signal increases at a threshold value of 10%, we could only detect activation signals of the grey matter. Task-induced metabolic changes in the eloquent white matter disappeared in the background noise, and remained a domain of the intraoperative electrostimulation [25].

It was a remarkable finding that one patient with a hypermetabolic tumour yielded an "activation signal" within the tumour region which was considered by the observers as artificial due to varying tumour glucose metabolism between the resting and activation scans. Hypermetabolic tumours may be a diagnostic problem in certain cases since functional cortical tissue can be found within glioma-infiltrated tissue [30, 31]. In such cases showing an equivocal PET finding, intraoperative stimulation is still mandatory for clear differentiation.

In this study, we found bilateral activations of the primary motor area in 46% (hand activation) and 43% (foot activation) of the patients. These activation signals may represent the metabolic correlate of interhemispheric compensation due to neuronal plasticity. The main hypothesis on ipsilateral activation of primary motor cortex suggests a compensatory recruitment of the non-crossing parts of the pyramidal tract because of contralateral lesions [5, 7]. In this study, we found that low-grade tumour patients with bilateral activation of the primary motor cortex showed no central paresis, whereas each high-grade tumour patient with bilateral motor activation signals yielded a paresis. This finding is most likely explained by the different progress of tumour growth, since connatal or slowly growing tumours may enable a complete compensation of neuronal functions. In contrast, incomplete compensatory mechanisms were mostly found in patients with fast-growing tumours, where the tumour size seems to have a minor influence on the degree of paresis [5].

However, the frequent finding of bilateral brain motor activation by a unilateral task in these patients indicates a clear advantage of activation PET over intraoperative cortical stimulation. PET enables the examination of the whole brain, detecting an ipsi- and/or contralateral neuronal reorganisation which may influence the extent of the tumour removal, whereas cortical electrostimulation via a small trepanation hole enables the examination of only a relatively small area of the cortex. Furthermore, the PET activation results can be preoperatively available for an exact operation planning.

One advantage of [^{18}F]FDG over blood flow tracers in preoperative diagnosis is the possibility of additional assessment of tumour glucose metabolism as a prognostically significant grading parameter. Various approaches have been reported in the literature for the assessment of glioma grade with [^{18}F]FDG. While absolute quantification of tumour metabolism is generally not recommended for routine clinical examination because of the significant rate constant differences relative to healthy brain tissue, several relative quantification methods have been reported which employ quotients with homologous contralateral brain regions [32, 33, 34, 35]. Recent investigations comparing different quantification methods using receiver operator curve analysis could show that a simple visual grading scale represents a clinically suitable method with high correlation to region of interest-based quantitative grading procedures [36].

In conclusion, compared with the neurosurgical "gold standard", direct cortical electrostimulation, preoperative [^{18}F]FDG PET using a robust and relatively simple activation protocol shows a high validity with a good signal-to-noise ratio for the detection of motor cortex. The data demonstrate that the relatively low temporal resolution of [^{18}F]FDG does not play a relevant role in preoperative diagnosis for the assessment of motor areas. The findings indicate that routine preoperative motor activation using [^{18}F]FDG PET could contribute in reducing the risk of intraoperative damage to functionally relevant brain areas and that the technique has some advantages over the exclusive application of intraoperative cortex electrostimulation. The only clinically relevant limitation is the restricted number of scans, enabling only unimodal activation tasks (hand *or* foot activation). On the other hand, in addition to the advantage of also measuring tumour metabolism, [^{18}F]FDG-PET has a lower incidence of motion artefacts (because unlike ^{15}O-labelled blood flow tracers or fMRI, task-dependent head movements by the patient are of no consequence since the acquisition scan only begins after the activation task has been completed).

The use of [^{18}F]FDG activation PET may enable improved neurosurgical preoperative planning and optimise evaluation of whether tumoural lesions localised in eloquent areas can be treated with an acceptable surgical risk.

Acknowledgements. The authors wish to thank Professor A. Thron (Head, Department of Neuroradiology, Aachen University of Technology) for performing some of the 3-D MR scans for PET/MRI overlay and Dr. A. Rodon and Mrs. J. Neverve for editorial services.

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