PAPER

Evaluation of preoperative high magnetic field motor functional MRI (3 Tesla) in glioma patients by navigated electrocortical stimulation and postoperative outcome

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Objectives: The validity of 3 Tesla motor functional magnetic resonance imaging (fMRI) in patients with gliomas involving the primary motor cortex was investigated by intraoperative navigated motor cortex stimulation (MCS).

Methods: Twenty two patients (10 males, 12 females, mean age 39 years, range 10–65 years) underwent preoperative fMRI studies, performing motor tasks including hand, foot, and mouth movements. A recently developed high field clinical fMRI technique was used to generate pre-surgical maps of functional high risk areas defining a motor focus. Motor foci were tested for validity by intraoperative motor cortex stimulation (MCS) employing image fusion and neuronavigation. Clinical outcome was assessed using the Modified Rankin Scale.

Results: FMRI motor foci were successfully detected in all patients preoperatively. In 17 of 22 patients (77.3%), a successful stimulation of the primary motor cortex was possible. All 17 correlated patients showed 100% agreement on MCS and fMRI motor focus within 10 mm. Technical problems during stimulation occurred in three patients (13.6%), no motor response was elicited in two (9.1%), and MCS induced seizures occurred in three (13.6%). Combined fMRI and MCS mapping results allowed large resections in 20 patients (91%) (gross total in nine (41%), subtotal in 11 (50%)) and biopsy in two patients (9%). Pathology revealed seven low grade and 15 high grade gliomas. Mild to moderate transient neurological deterioration occurred in six patients, and a severe hemiparesis in one. All patients recovered within 3 months (31.8% transient, 0% permanent morbidity).

Conclusions: The validation of clinically optimised high magnetic field motor fMRI confirms high reliability as a preoperative and intraoperative adjunct in glioma patients selected for surgery within or adjacent to the motor cortex.

Cerebral glioma surgery seems beneficial for patient survival of low and high grade glioma, especially in cases where a gross total resection can be achieved.[1–10] However, the ultimate neurosurgical goal in patients with cerebral gliomas in highly eloquent areas such as the motor cortex is to preserve function and quality of life.[11] Progress in computer science introduced neuronavigation systems in the mid 1980s to neurosurgical intraoperative techniques, which allowed the transformation of image structures of all imaging modalities onto the brain surface during surgery for definition of anatomical resection borders.[12 13] Intraoperative electrocortical stimulation has proven to be the gold standard in glioma surgery since the 1930s for the avoidance of postoperative neurological deterioration.[14–16] However, such stimulation introduces the risk of triggering intraoperative seizures, which may jeopardise the reliability of further stimulation mapping.[17]

Preoperative functional magnetic resonance imaging (fMRI) enables the definition of cortical motor areas and their association to tumour tissue, and can provide global preoperative information about the resectability of the tumor without causing neurological deterioration.[18–25] Up to now, validation of fMRI topography by intraoperative electrocortical stimulation studies has shown variable failure rates,[24 26–28] with up to 20% disagreements when 1.5 T clinical MRI systems were tested.[29] Application of higher field strengths has the advantages of improved signal to noise ratio and enhanced blood oxygenation level dependent (BOLD) effect;[30 31] however, clinical data on the validity and postoperative outcomes in patients with higher field strength (3 T) fMRI do not as yet exist.

Thus, this is to our knowledge the first study testing clinical outcome and correlation between fMRI and navigated MCS with preoperative high field (3 T) motor fMRI. These data should clarify whether 3 T fMRI results could safely be used preoperatively and intraoperatively to identify and spare motor areas during glioma surgery.

PATIENTS AND METHODS

Patient population

For the study, 22 patients (mean age 39 years, range 10 to 65) with gliomas close to or involving the motor cortex were recruited. Clinical, radiological, and histological (according to the recent WHO classification[32]) findings and extent of resection (gross total >99%, subtotal between 90 and 99% radiological amount) as defined by an immediate postoperative MRI scan are summarised in table 1. Six patients had one previous surgery and one patient had two (previous histology in brackets). Preoperative neurological function and postoperative outcome 1 week and 3 months after surgery were assessed using the MRS[33] (table 2).

Abbreviations: BOLD, blood oxygenation level dependent; fMRI, functional magnetic resonance imaging; MCS, motor cortex stimulation

Table 1 Patient characteristics

No.	Age	Tumour site	Size (cm)	Pre-op neurology	FMRI paradigm	Extent of surgery	Histology	MRS pre-op	MRS 1 week post-op	MRS 3 months post-op	Results MCS localisation of:	Correspondence of fMRI/MCS in:
1	36	Fronto-precentral right	4.5	GM	H/F left motor	GT	Astro II	0	0	0	Foot, lower leg, thigh, forearm, hand	Foot extension, finger flexion,
2	33	Central right	3.0	GM, JE	H/F left motor	ST	GBM/ (GBM/ GBM)	0	0	0	Hand, forearm	Finger flexion, FISIS
3	56	Precentral right	5.0	JE A left	H/F left motor	GT	Oligo I	0	5*	0	Hand, forearm	Finger flexion, FISIS
4	32	Central right	3.0	CPS	H left M motor	GT	Astro III	0	0	0	Hand, finger, face	Finger flexion/ extension
5	64	Centro-paracentral left	5.0	JE AF right	H/F left motor, F motor	B	GBM	2	2	2	Foot, lower leg	Foot extension
6	49	Precentral right	4.0	GM	H/F left M	ST	Astro III	0	2*	0	Hand	Finger flexion
7	38	Postcentral left	6.0	HH, Cogn.	H/ right M	GT	GBM	1	1	1	Hand, forearm	Finger movements
8	41	Central left	5.0	Aphasia	FA flex right	ST	GBM/ (Astro III)	2	2	2	Excluded	NR
9	33	Fronto-central left	4.5	CPS	H/F right motor	ST	Astro II	0	2*	0	Hand,	Finger flexion
10	56	Central left	2.5	JE A right	H right motor	ST	GBM	0	2*	0	Hand, forearm	Finger flexion
11	29	Centro-postcentral right	2.5	JE AF left,GM	H left motor/ sensory	GT	Oligo I	0	0	0	Hand, forearm, shoulder	Finger flexion, FISIS
12	45	Postcentral left	4.0	CPS	H right motor/ sensory	GT	AstroIII / (astro II)	0	0	0	Excluded	Technical problem
13	13	Centro-temporal right	2.0	CPS, JE	H left M motor	ST	Ganglio-glioma II/ (I)	0	2*	0	Face, tongue	Face contraction, tongue movement
14	31	Central left	3.0	JA face/HP right	H right M motor	B	GBM/ astroII	2	2	2	Hand, forearm	Finger flexion
15	40	Centro-insular right	3.0	HP left	H left M motor	ST	GBM/ (astro II)I	3	4*	3	Hand, forearm	Finger flexion, extension
16	44	Postcentral left	5.0	CSD	H right motor/ sensory	GT	Oligoastro III, (astro II)	1	2*	1	Excluded	Technical problem
17	29	Precentral right	4.0	JE face A left	H left M motor	GT	GBM	0	0	0	Hand, forearm	Finger flexion
18	41	Fronto-central/ paracentral	3.0	GM	H/F left motor	ST	Oligoastro III, (astro II)	0	0	0	Foot, lower leg, thigh, hip	Foot extension
19	14	Centro-paracentral right	6.0	Hhyp left	H left motor/ sensory	GT	GBM	1	1	1	Hand, forearm	Finger flexion
20	10	Postcentral left	6.0	GM	H/F right motor	ST	Astro I, pilocytic	0	0	0	Foot, lower leg	Foot extension
21	65	Precentral right	4.5	HP left	H left motor	ST	GBM	2	2	2	Excluded	Technical problem
22	55	Precentral left	4.0	GM	H/F right M motor	ST	OligoII	0	0	0	Excluded	NR

Transient neurological worsening. CSD, cognitive and speech disturbance; CPS, complex partial seizures; GM, generalised seizures; HH, hemihanopia, HP, hemiparesis; H, hand; F, foot; M, mouth; GT, gross total; ST, subtotal; B, biopsy; astro, astrocytoma; GBM, glioblastoma multiforme; oligo, oligodendroglioma; oligoastro, oligoastrocytoma; fMRI, functional MRI; MCS, motor cortex stimulation; MRS, Modified Rankin Scale level; pre-op, preoperative; post-op, postoperative; FISIS, focal intraoperative stimulation induced seizures; NMR; no motor responseSPS, simple patrial seizures;.

Magnetic resonance imaging studies

Preoperatively, all patients underwent morphological and fMRI imaging in a 3 Tesla high field MR tomograph (BRUKER Medspec 30/80, BRUKER BioSpin, Ettlingen, Germany) with a phase corrected blipped GE, single shot, EPI sequence (repetition time 4000 ms; echo time 5.5 ms; flip angle 90°, 128×128matrix, 230×230 field of view, 25 axial slices, slice thickness 3 mm, no interslice gap, sinc pulse excitation), using an fMRI techniqueemploying motor paradigms as described previously [34–36 52] (table 1). Individually constructed plaster cast helmets for each patient were used for head fixation.[37] A common anatomical reference system was defined using the Talairach approach.[38]

Prior to further analysis, all volumes of every subject were realigned using dedicated software (AIR 3.08 [39]) with a rigid six parameter (three transformation and three rotation parameters) model. Motor risk maps,[34 36 52] which avoid localisation errors caused by functional smoothing procedures[40 41] were then generated. Voxel reliability was determined by evaluating the number of runs a voxel surpassed a certain correlation threshold. At various correlation thresholds, reliability values were colour coded and mapped as follows: yellow = 75–100% of runs active; orange = 50–75% of runs active; red = 25–50% of runs active (figs 1 and 2). The largest correlation threshold that yielded voxel clusters with voxels of a reliability >75% was then determined. The most reliable voxel cluster was defined as the motor centre. To avoid localisation errors due to EPI distortions, motor centres were individually transferred from distorted EPI images to non-distorted anatomical images by a neuroanatomical

Table 2 Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

expert in a semiautomatic fashion.[52] The resulting anatomical functional dataset was used for MCS.

Imaging data transfer and surgical planning

Anatomical MRI and fMRI datasets were uploaded to the neuronavigation systems. Image correlation was carried out by mechanical data transformation in the neuronavigation system via a magneto-optical disc or, for the last 10 cases, automatically with recently available commercial software (Medtronic, Minneapolis, Minnesota, USA). The fMRI image information was transformed into digital imaging and comminications in medicine (DICOM) format and split into anatomical and functional information. The anatomical 3 T MRI was consecutively fused with the 1.5 T navigation image, and exchanged with the functional image content. This procedure led to a spatially correct transformation of the fMRI images for intraoperative navigation. Preplanning of surgery and navigation was performed in the planning station of the navigation systems outside the operating theatre the day before surgery. Image registration was carried out in the operating theatre, using an established protocol, to avoid registration inaccuracies and to minimise brain shift associated inaccuracies at the beginning of stimulation mapping.[42–44]

Intraoperative neuronavigation and motor cortex stimulation

The patient's head was fixed in a standard head rest (Mayfield clamp, Germany). Three different navigation systems were used for spatial correlations of fMRI data with intraoperative motor cortex mapping. For registration of image data onto the patient's head, the infrared pointer navigation system EGN (Philips, Best, The Netherlands) was used in five patients, the infrared pointer and robotic microscope navigation system MKM (Zeiss, Oberkochen, Germany) in seven, and the infrared pointer and microscope navigation system StealthStation TREON (Medtronic, Minneapolis, Minnesota, USA) for the last 10 patients. Correlation of image data and brain structures was achieved as described earlier.[42–44] When the registration procedure demonstrated a registration error (deviation of image structures and corresponding patient structures after registration) >2 mm, the registration was cancelled and the procedure was repeated. Spatial correlation between fMRI data and cortical mapping results was performed immediately after opening the dura to avoid the effect of brain shift. Motor fMRI data were outlined with the navigation system as preoperatively defined, and were stimulated along with the

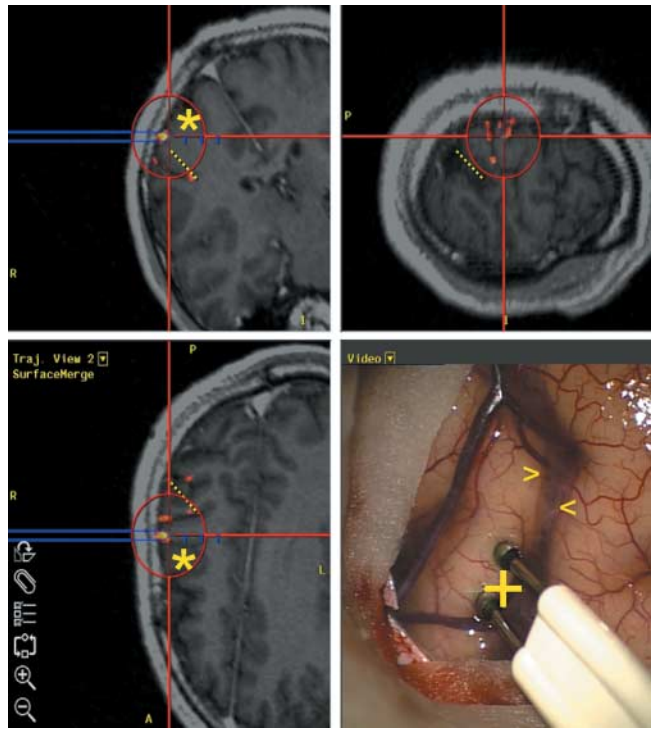

Figure 2 Intraoperative correlative stimulation mapping using neuronavigation. Intraoperative neuronavigation: fMRI was fused to structural contrast enhanced 1.5 T MRI and registered to the patient's head. A correlation analysis of anatomical details on the images and corresponding cerebral structures is possible. Electrocortical stimulation on the fMRI finger flexion extension paradigm activation area was performed with the Ojemann stimulator. Finger flexion occurs during stimulation of the cortical area, which showed the FMRI activation. *fMRI activation signal, +, corresponding cortical area identified by neuronavigation; >< , central sulcus.

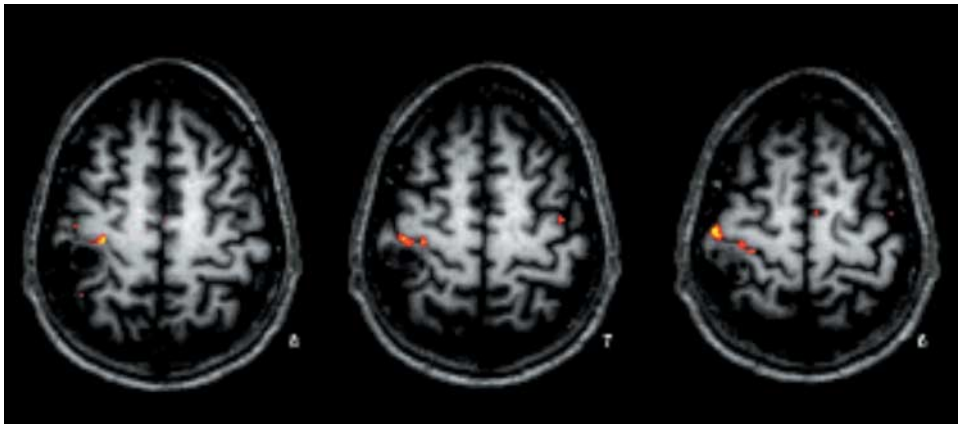

Figure 1 An fMRI risk map. Case 11: 29 year old male, presenting with focal sensible Jackson's epilepsy on the left hand and left forearm. Neuroradiological examinations revealed a hypointense, partially calcified lesion within the postcentral gyrus, next to the central sulcus and precentral knob on the right. The fMRI activation areas are visualised as yellow and red areas after performing a finger flexion extension paradigm within the 3 T MRI using a plaster cast helmet and repeated measurements and correlation data analysis (risk map technique[35 51]).

surrounding tissue using a bipolar stimulation electrode and electrical stimulator (Ojemann cortical stimulator OCS-1; Radionics, Germany). The current was increased stepwise from 2 mA to a maximum of 25 mA, and trains of square wave pulses of 2–4 ms duration at 50 Hz were used. The effect of cortical stimulation was observed and documented by a member of the neurosurgeryl (or neuroanesthesiology) team. Tonic actication of contralateral limb or facial muscles was classified as positive motor response and further increase of stimulus intensity was stopped. As the main goal of this study was the investigation of the functional significance of the preoperatively defined fMRI motor focus, the motor focus and a surrounding area of about 1 cm was primarily mapped. Depending on the topographic relationship between tumour tissue and fMRI activation sites, areas with less reliable or no fMRI activation were additionally stimulated). Anatomical sites of stimulation responses were marked using sterile paper plates numbered with consecutive Arabic numerals and documented by photographs.

All patients were kept under total intravenous anaesthesia during the whole surgery and stimulation mapping procedure, using propofol (6–12 mg/kg/h) as a sedative and remifentanyl (0.05–2 μg/kg/min) as an analgesic drug. No muscle relaxants were used except for the induction of general anaesthesia. In three patients, focal motor seizures developed, which were easily abolished by rinsing the cortex with cold Ringer's solution[17] and administering an additional bolus of 10–20 mg propofol.

RESULTS

In the study, all 22 patients (100%) successfully demonstrated cortical activation from a finger flexion/extension paradigm in the fMRI within the precentral knob, nine patients additionally from a foot flexion/extension paradigm in the region of the motor part of the paracentral lobule, and six patients from a mouth opening/closing paradigm in the opercular part of the precentral gyrus. Motor foci representing most reliable activations at the highest possible correlation thresholds comprised only few voxels (fig 1). In 17 of the 17 patients in whom a motor response could be elicited, motor cortex stimulation at the fMRI motor focus or within an area of 1 cm around the focus resulted in a motor response, somatotopically corresponding to the MRI paradigm (table 1, fig 1). For safe tumour resection, mapping of tissue not activated with our fMRI paradigm was also performed. Results showed motor responses, but these were qualitatively different from the target movement (table 1). In two patients (9.1%), no motor response could be elicited by stimulating the exposed cortex, in three patients (13.6%), technical problems occurred during stimulation. These five patients had to be excluded from the evaluation of fMRI MCS correlation. MCS induced seizures occurred in three patients (table 1).

A gross total resection was achieved in nine patients (41%), a subtotal resection in 11 (50%), and two (9.1%) had a biopsy as a consequence of motor responses within the tumour areas (table 1, fig 2). Transient mild or moderate neurological deterioration occurred in seven patients (31.8%), but all patients recovered within 3 months, resulting in 0% permanent morbidity (MRS pre-operatively, 1 week and 3 months postoperatively; table 1).

DISCUSSION

Despite the controversy surrounding the prognostic significance of the extent of resection in the treatment of hemispheric gliomas, growing evidence exists that surgical resection of gliomas is beneficial for long term patient survival of high and low grade gliomas.[1–10] In highly eloquent areas, such as the motor cortex, high morbidity rates are reported for resective surgery, and in most cases only biopsy or subtotal resection is advisable.[45–48] Employing motor cortex stimulation, image fusion, and intraoperative neuronavigation, complications may be reduced and resection optimised.[14 16 42–44 49 50]

The role of preoperative functional MRI and its validity in glioma surgery for sparing eloquent cortex areas are still under debate.[18–25] Therefore, we investigated the validity of a recently developed clinical high field motor fMRI protocol by navigated motor cortex stimulation intraoperatively, and evaluated the postoperative neurological outcome. This technique combines optimised head fixation,[36] high spatial functional resolution, and evaluation of voxel reliability in high magnetic field with improved signal to noise ratio, enhanced BOLD effect (functional contrast), and reduced artefacts, as described previously.[31 34 36 52 53]

Preoperative fMRI motor mapping was successfully performed in all patients. A success rate superior to results using conventional lower field fMRI was achieved.[53] Eloquent tissue was always detected as highly focal in the sense of voxels representing the largest probability for true positive activation within the experimental context (table 1). In 5 of 22 patients, technical problems with MCS prevented correlation of fMRI findings with stimulation results (MCS failure rate of 22.7%), which seems high, compared with literature.[17 49 50] Subclinical seizure activity and repeatedly experienced problems with the technical performance of the stimulation might be the reason.

In all 17 patients, where correlation mapping was successful, a good spatial correlation of fMRI activation site and motor response similar to the activation task in fMRI was noted, indicating 100% reliability of the preoperatively detected fMRI risk areas. Compared with literature results, where best correlation mapping using image guidance with a considerable number of patients showed failure rates of up to 20%,[27–29] our results support the clinical applicability of the achieved technical refinements. Considering the 5 mm distance of the two poles of the stimulation probe, accuracy was guaranteed for a distance of about 10 mm around the motor focus, discussed as the critical distance from response site to resection margin for inducing permanent neurological deficits,[16 49 50] which we respected in every patient. In comparison, the correlation reported for magnetic source imaging for somatosensory and motor mapping ranges was within a distance of 19 mm, with the disadvantage that magnetoencephalography units are rarely available.[51]

Despite the unfavourable localisation of the cerebral gliomas in the investigated patients, clinical outcome resulted in 31.8% transient morbidity. Nevertheless, this seems unacceptably high, underlining the problem with using imaging instead of biopsy for radical glioma surgery in and around the motor cortex.[3 9] Recent reports on comparably eloquent tumour surgery within eloquent areas and with comparable amounts of resection report up to 71% transient postoperative morbidity and 5–10% permanent neurological deficits, despite application of electrocortical mapping and neuronavigation.[45–47] In contrast, in our study, all patients who experienced deterioration recovered to the original preoperative MRS level, resulting in no permanent neurological morbidity.

A significant problem with preoperative fMRI as used here is that in complex clinical situations more extended mapping of primary motor cortex may be desirable. Repeated preoperative fMRI investigations with more complex motor tasks[34 40] need to be perfomed. This, of course, would demand extended preoperative preparation time and data analysis work. In contrast, extended motor mapping using electrical stimulation probes takes much less time. Another problem using our improved technique is the time consuming patient

preparation, with a total data acquisition and integration time for navigated surgery of about 24 hours, which is not acceptable in space occupying gliomas presenting with acute signs of increased intracranial pressure or in children.[52] However there are no such restrictions for patients with low grade gliomas, and the 100% concordance of preoperative fMRI activation with intraoperative cortical mapping favours this method as a preoperative planning and intraoperative navigation assistance whenever feasible.

In summary, high field fMRI combined with specifically developed clinical fMRI technique has been demonstrated to be safe and highly reliable for motor tasks in preoperative investigation of glioma patients. Intraoperative neuronavigation guided electrocortical mapping and correlation with fMRI motor foci showed agreement within about 10 mm spatial resolution. This technique may add benefit in reducing postoperative morbidity when used as an adjunct to all affordable technical adjuncts for the planning of glioma surgery in motor areas.

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