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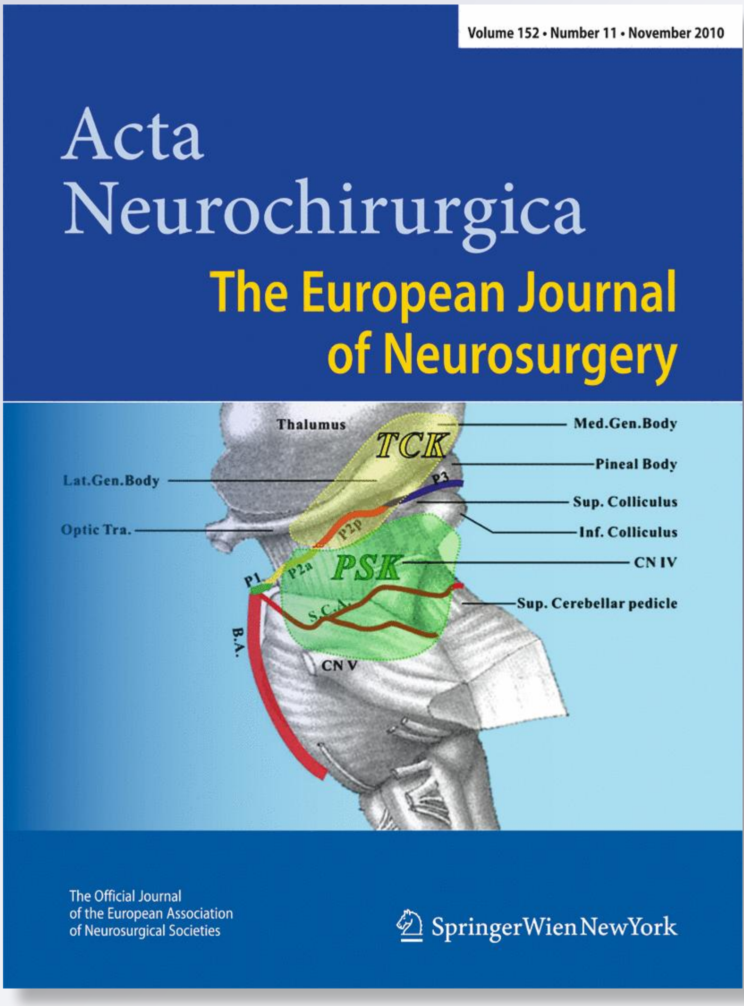

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CLINICAL ARTICLE

Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes

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Abstract
Background Localization of brain function is a fundamental requisite for the resection of eloquent-area brain tumors. Preoperative functional neuroimaging and diffusion tensor imaging can display cortical functional organization and subcortical anatomy of major white matter bundles. Direct cortical and subcortical stimulation is widely used in routine practice, however, because of its ability to reveal tissue function in eloquent regions. The role and integration of these techniques is still a matter of debate. The objective of this study was to assess surgical and functional neurological outputs of awake surgery and intraoperative cortical and subcortical electrical stimulation (CSES) and to use CSES to examine the reliability of preoperative functional magnetic resonance (fMRI) and diffusion tensor imaging fiber tracking (DTI-FT) for surgical planning.
Patients and methods We prospectively studied 27 patients with eloquent-area tumors who were selected to undergo awake surgery and direct brain mapping. All subjects underwent preoperative sensorimotor and language fMRI and DTI tractography of major white matter bundles. Intra- and postoperative complications, stimulation effects, extent of resection, and neurological outcome were determined. We topographically correlated intraoperatively identified sites (cortical and subcortical) with areas of fMRI activation and DTI tractography.
Results Total plus subtotal resection reached 88.8%. Twenty-one patients (77.7%) suffered transient postoperative worsening, but at 6 months follow-up only three (11.1%) patients had persistent neurological impairment. Sensorimotor cortex direct mapping correlated 92.3% with fMRI activation, while direct mapping of language cortex correlated 42.8%. DTI fiber tracking underestimated the presence of functional fibers surrounding or inside the tumor.
Conclusion Preoperative brain mapping is useful when planning awake surgery to estimate the relationship between the tumor and functional brain regions. However, these techniques cannot directly lead the surgeon during resection. Intraoperative brain mapping is necessary for safe and maximal resection and to guarantee a satisfying neurological outcome. This multimodal approach is more aggressive, leads to better outcomes, and should be used routinely for resection of lesions in eloquent brain regions.

Keywords Brain tumors · Eloquent areas · Direct brain mapping · fMRI · DTI fiber tracking

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Abbreviations

fMRI Functional Magnetic Resonance

DTI-FT Diffusion Tensor Imaging Fiber Tracking

Introduction

Operating on patients suffering from brain tumors in eloquent areas poses two main challenges: removing an oncologically adequate amount of tumor, while respecting neurological function and quality of life. For years, neurosurgeons have been relying on standard functional maps to treat brain lesions. With the evolution of functional neuroimaging and its wider clinical applications, especially in stroke patients, a huge amount of data has demonstrated clear interindividual variability in eloquent area location and the existence of plasticity phenomena [6, 26, 53, 54]. Furthermore, in recent years the advent of diffusion tensor imaging (DTI) has permitted reconstruction of the principal long-range association fibers, adding to our understanding of the connectivity of brain networks. These insights have shown that standard anatomical references are insufficient and changed the approach to eloquent-area tumors. Direct cortical and subcortical electrical stimulation (\) has regained a prominent role in neurosurgery and is now the most reliable method to directly acquire brain functional topography and achieve safe surgical resection while avoiding permanent neurological deficits [3, 12, 16, 29]. The advantages of direct cortical and subcortical stimulation are particularly true for intrinsic brain tumors where subtotal or total resection has been demonstrated to impact malignant progression and survival [14, 28, 46]. However, surgery cannot cure the majority of intrinsic tumors, so maintaining or improving quality of life also is important. Unfortunately, many tumors arise inside or in the proximity of critical areas [57], and the first goal of a surgeon is to localize those functions. Interindividual variability, cortical plasticity, and distortion due to mass effect make purely anatomical references insufficient [1, 4, 7, 13, 15, 31, 41, 45]. The integration of preoperative and intraoperative brain mapping is an important advance in neurosurgery and allows the treatment of complex brain tumors while preserving quality of life. Yet, debate still exists about the surgical use of preoperative mapping and its effective integration in the operating room.

The objective of this study was to assess surgical and functional neurological outputs of awake surgery with CSES and use CSES to examine the reliability of preoperative functional magnetic resonance (fMRI) and diffusion tensor imaging fiber tracking (DTI-FT) for routine surgical planning. We discuss our findings focusing on technical and methodological issues, usefulness, and clinical results.

Methods

This is a prospective study of 27 patients with tumors in eloquent brain regions that were selected to undergo awake surgery and CSES between September 2007 and October 2009. All patients underwent preoperative functional MRI and DTI-FT imaging (see below for details on methodology). Preoperative evaluation comprised a neurological examination and an evaluation of the degree of disability (modified Rankin score). A neuropsychologist (P.A., B.M.) evaluated neurocognitive function; language was assessed by the Aachener Aphasia Test. Handedness was measured using a standardized questionnaire (Edinburgh inventory). Postoperative clinical and neuropsychological evaluation was performed at 1 week, at 3 and 6 months, and then yearly. A postoperative MRI with gadolinium was performed in all patients at 24 h postoperative. Complete resection was defined as the disappearance of contrast enhancement in T1 (for high-grade tumors) or hyperintensity on FLAIR (for low-grade gliomas). Subtotal resection was defined as a residue of tumor of less than 10 cc, measured using a previously described method [3].

fMRI and DTI

We gathered BOLD data on a 1.5 Tesla INTERA™ scanner (Philips Medical Systems) with a SENSE high-field, high-resolution (MRIDC) head coil optimized for functional imaging. Resting state functional T2-weighted images were acquired using echo-planar (EPI) sequences, with a repetition time (TR) of 3000 ms, an echo time (TE) of 50 ms, and a 90° flip angle. The acquisition matrix was 64×64, and the field of view (FoV) was 200 mm. A total of 100 volumes were acquired; each volume consisted of 25 axial slices, parallel to the anterior–posterior (AC–PC) commissural line and slice thickness was 4 mm with a 0.5-mm gap. Two scans were added at the beginning of the functional scanning session. For motor function, the subject was scanned while performing an active blocked motor task. The task consisted of 12 s of foot (plantarflexion/dorsiflexion), hand (opening/closing), or tongue movement with a frequency of 0.5 Hz, followed by 12 s of rest for a total acquisition time of 5 min. The sensory cortex test was similar, with an active condition of 0.5-Hz brushing of the foot or hand. Language was investigated as follows: in the active condition, the subject listened to a list of nouns and generated associated verbs for 21 s; in the rest condition, the subject counted from 1 to 10 for 15 s. The total acquisition time was 5.65 min. BrainVoyager QX was used for image processing and analyses (Brain Innovation, The Netherlands). The first two volumes of each run were discarded to ensure a steady state. Functional volumes then were spatially aligned to the first volume by a trilinear interpolation algorithm. Temporal smoothing with a 2.8-s FWHM Gaussian kernel was applied to improve the signal-to-noise ratio by removing high-frequency fluctuations. Data series were submitted to single-subject analysis for blocked designs using the general linear model. Conditions were modeled by boxcar waveforms and convolved with the hemodynamic response function. Baseline was defined as the average activity during periods of no stimulus presentation. A fixed statistical threshold of $p<0.05$, Bonferroni corrected for multiple comparisons, was used to display results and activation maps with a cluster size of $K>5$ contiguous voxels. 3D images were created projecting the 2D map onto the 3D rendered brain volume with the BrainVoyager QX 2.0 3D image tool.

DTI data were acquired axially using a dual-spin echo, a single shot, a pulsed gradient, and an echo-planar imaging (EPI) sequence (TR=6.6 s, TE=70 ms, 70 slices, voxel size=2×2×2 mm, 0-mm skip, FOV=240 mm, b value=800 s/mm^2). Diffusion was measured along 16 directions. In the same session, a set of three-dimensional, high-resolution T1-weighted structural images was acquired for each participant. This data set was acquired using a Fast Field Echo sequence, with a repetition time (TR) of 25 ms, an ultra-short echo time (TE), and a 30° flip angle. The acquisition matrix was 256×256, and the field of view (FoV) was 256 mm. The set consisted of 160 contiguous sagittal images throughout the whole brain. The in-plane resolution was 1×1 mm, and the slice thickness was 1 mm (1×1×1-mm voxels).Tracking was performed using the FiberTrack Specialist tool of the Philips Intera 1.5 T with a multi-ROI approach, an FA threshold of 0.25, and a direction threshold of 0.85. Seed points for fiber tracking were selected in two locations along each white matter tract of interest in the target FA maps, as described by Catani et al. [8].

Cortical and subcortical mapping

Local anesthesia of the scalp is achieved through nerve block by infiltration of levobupivacaine (0.75%) and mepivacaine (1%). During the craniotomy, we sedate spontaneously breathing patients with intravenous remifentanyl (0.01 to 0.08 mg/Kg/min) and propofol (0.3 to 1 mg/Kg/h), continuously throughout the procedure. Lidocaine-filled cotton pledgets are used to locally anesthetize the dura.

The craniotomy is targeted to expose the area of the tumor (as depicted on the neuronavigation system) as well as the motor and/or sensory strips upon which current intensity is set. A bipolar fork, measuring 6 mm in distance between the electrodes (Nimbus, Newmedic, Labege, France), delivers a non-deleterious, biphasic square-wave current in 4-s trains at 60 Hz. We start stimulation at 1 mA and increase by 0.30 mA until generation of contralateral face or upper limb movement and paraesthesias. Every positive site is restimulated to confirm reproducibility of stimuli.

When tumors are located in language areas, a neuropsychologist administers tests on a laptop screen (a series of slides with black and white pictures preceded by the words "this is a….") and describes the type of language disturbance observed (speech arrest, anartria, anomia, or reading errors). The patient is unaware of the timing of stimulation, and the current is delivered just before presentation of the slide. After disruption of a language error, the patient rests for a while, then the spontaneous speech and slide reading are tested, and stimulation starts again. For subcortical tumors, we test language or motor areas throughout the subcortical resection, stopping whenever anomalies appear. The entire procedure is filmed, and the patient's voice is recorded.

Parameters such as current intensity, reproducibility of stimuli, and seizure occurrence are observed and registered.

Topographical correlation

To assess the reliability of preoperative fMRI in detecting sensorimotor and language sites, we visually compared the site of maximal activation area on a 3D rendering of the subject's brain (i.e., precentral gyrus, triangular operculum, supramarginal gyrus, etc.) with intraoperative cortical positive sites. The maximal distance to consider that the correlations were positive was no more than 5 mm between the center of the activation spot and the center of the positive stimulation site. Similarly, the position of subcortical white bundles on a preoperative DTI-FT was compared with subcortical positive sites during surgery and on postresection MRI. Moreover, DTI-FT's ability to identify white matter tracts within tumors was tested by comparing tumor residue on postoperative MRI with preoperative DTI-FT images (see Fig. 1). The maximal distance to consider a positive correlation was no more than 5 mm between the point of stimulation and the presence of fibers bundles on DTI. Our rationale for using visual inspection instead of merging of images in a neuronavigation device is explained in the discussion.

Results

Table 1 describes preoperative demographic and clinical characteristics. We prefer performing awake procedures for

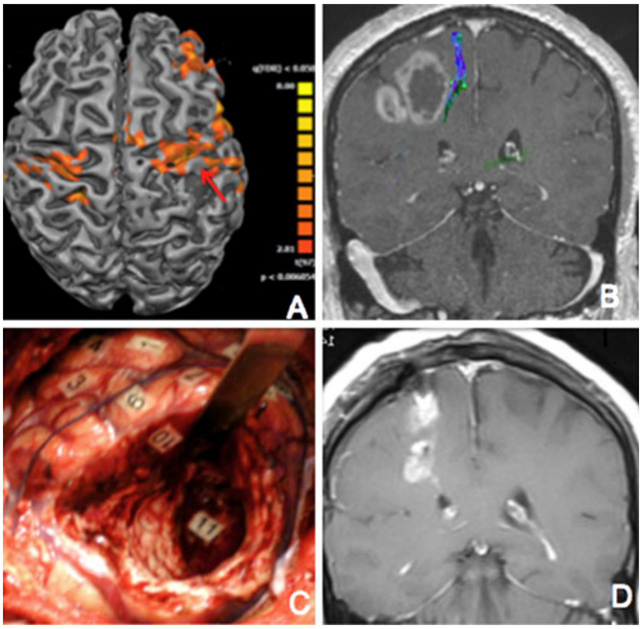

Fig. 1 (**a**) Preoperative fMRI showing a retrocentral GBM invading the sensory strip. The area of the hand seems to be infiltrated by the tumor, and the activation spot seems to be interrupted (*red arrow*; $q<0.05$ FDR corrected, minimum cluster size $K>5$ voxels in the native resolution).(**b**) Corticospinal tract as reconstructed on DTI-FT. Note that this bundle seems to be in close contact with the tumor. (**c**) Intraoperative stimulation confirmed that the infiltrated postcentral gyrus was still functional (hand sensibility: 6, 7, 10) and so was not removed. At the subcortical level, the invaded white matter was also still functional (paresthesias of the shoulder, 11). (**d**) Postoperative post-cotrast MR Iconfirmed residue of tumor in an area where DTI failed to demonstrate the descending pathways

Table 1 Demographic, clinical, and neuroradiological characteristics of patients

Age	
Mean	45 (range 12–62)
Sex (male/female)	17/10
Clinical onset	
Asymptomatic	4 (14.8%)
Seizures	12 (44.4%)
Sensorimotor deficits	11 (40.7%)
Language deficits	7 (25.9%)
Tumor location	
Sensory area	8 (30.7%)
Motor area	5 (18.5%)
Left parietal	3 (11.1%)
Left temporal	8 (30.7%)
Left frontal	3 (11.1%)
Handedness	
Right	24 (85.1%)
Left	3 (11.1%)

lesions located in or around motor areas because we have found that sleeping patients need higher current intensity and 100% experience intraoperative seizures. We have found that such operations also result in less precise mapping, especially at the subcortical level (five-patient unpublished series).

All patients tolerated the procedure well; there was no need to arrest the surgery or convert to general anesthesia in any patient. Two patients suffered a momentary decrease of consciousness, dropping their blood oxygen saturation for a few minutes without consequence. Pain control was excellent, as demonstrated by a postoperative visual analog scale (range 2 to 4 points on a 0 to 10 scale).

During surgery, there were cortical stimulation-related seizures in 4 cases (14.8%), which were successfully treated through irrigation with cold Ringer's solution, as described [41]. Three patients presented with nausea. Postoperative mortality was 0%. There were no complications related to the surgical approach, i.e., postoperative hematoma, infarction, surgical site infection, or CSF leaks. Two patients experienced seizures in the early postoperative course, but these disappeared with the temporary intensification of anticonvulsants.

Twenty-one patients (77.7%) suffered worsened neurological impairments postoperatively. At 8 months follow-up, only three patients (two with a preoperative score of 1 and postoperative of 3 and 4, another with a preoperative score of 2 and postoperative score of 4) had persistent neurological impairment; all of these patients were symptomatic preoperatively and had high-grade gliomas that eventually progressed despite maximal adjuvant therapy. The other 24 patients (88.8%) regained preoperative neurological status. Table 2 compares preoperative and definitive (at 6 months follow-up) postoperative modified Rankin scores. Histological results are shown in Table 3. Of those patients that presented seizures preoperatively, eight (30.7%) did not experience any seizures after surgery, while three patients showed a reduction in frequency.

In eight subjects (30.7%), the radiological resection was total. Sixteen patients (59.2%) had a subtotal resection, and in three patients (11.1%), a partial resection was obtained.

Table 2 Comparison between pre- and postoperative modified Rankin score

Rankin score	Preoperative	Postoperative
0	9 (33.3%)	9 (33.3%)
1	16 (59.2%)	14 (51.8%)
2	2 (7.4%)	1 (3.7%)
3	0%	1 (3.7%)
4	0%	2 (7.4%)

Table 3 Pathological findings

Type of tumor	Nr
Anaplastic astrocytoma	7
Grade II glioma	9
Glioblastoma	5
Metastasis	4
Infantile desmoplastic ganglioglioma	2

Electrical stimulation

CSES produced motor, sensory, or language responses in all subjects. Current intensity ranged from 1.5 to 4.5 mA with a mean of 2.4 mA. Mapping sensorimotor strips in patients harboring tumors in this region generally required less current (1.5 to 2.8 mA). Deep-spreading high-grade tumors (often associated with edema and mass effect) necessitated higher current intensities (2.4 to 4.5 mA) to generate responses.

Concerning language mapping, a discrete distribution of epicenters was detected. Speech arrest sites were predominantly found on the pars triangularis and pars opercularis of the inferior frontal gyrus. Some positive sites were also encountered on the inferior parietal lobule and superior temporal gyrus. Anomia was clearly reproducible during stimulation of the dorsal premotor cortex (posterior part of the middle frontal gyrus) and the posterior portion of middle and inferior temporal gyrus. Difficulties in speech production with contraction of mouth and tongue (anartria) were detected with stimulation of the ventral premotor cortex (inferior and anterior part of the precentral gyrus). Phonemic errors (truncation of words or substitution of parts of words) were detected after stimulation of the supramarginal gyrus and posterior–inferior parietal region. Three left-handed patients with tumors in the left temporal lobes (n=2) and supramarginal gyrus (n=1) showed bilateral activation for language on fMRI. During surgery, CSES confirmed the presence of language sites in the presumed non-dominant hemisphere.

Overall, in 19 (70.3%) patients, cortical and subcortical mapping revealed functional areas invaded by the tumor, resulting in termination of the resection to avoid permanent postoperative deficits. In the remaining patients, CSES helped detect the vicinity of the tumor to eloquent areas or plasticity phenomena (Fig. 2).

In cases of tumor-infiltrated cortex, function persisted in 46.1% of cases (12 cases with seven central area tumors and five language area tumors). Similarly, subcortical stimulation documented pyramidal tract invasion in seven cases (25.9%), while language white matter tracts were infiltrated in nine patients (34.6%). In five language area cases, no language disturbances were detected (one left unco-hippocampal tumor, two left superior frontal, and two anterior temporal). This condition did not provoke postoperative permanent deficits. Table 4 shows the effects of subcortical stimulation and correlation with DTI-FT.

fMRI and DTI-FT and topographical correlation

The motor area of the hand was found predominantly over the “knob” of the precentral gyrus although the extent of activation varied. The sensory area of the hand was located on the postcentral gyrus but the position, as well as the extent of activation, was even more variable than that seen in motor areas. In some cases, small areas of activation in the contralateral central region were detected. When performing a motor task or a sensory task alone, a degree of overlap was observed between the sensory and motor activation areas. The activation of SMA regions was inconsistent and some activation was also observed in prefrontal regions and the precentral sulcus. The number of activated areas, other than primary sensorimotor, varied depending on the individual. During language tasks, activation areas were broadly distributed and the main epicenters were located predominantly on the frontal and temporal opercula. In four patients, the distribution of activated areas was only on the dominant hemisphere. Supramarginal and angular gyri in the dominant hemisphere were less active, perhaps because of the high frequency of tumors in the parieto–temporal area in this series. In two of these patients, activation was detected on the surface of the tumor. The three left-handed patients always exhibited bilateral representation, especially in the temporal area.

In all but one of the central region tumors (13 cases), there was topographical visual correlation between at least one activation area (motor or sensory) on fMRI and the intraoperative cortical stimulation findings. Therefore, fMRI showed the position of sensorimotor strips in 92.3% of cases. For language function, fMRI predicted the presence of language epicenters involved in production (speech arrest and anartria sites) or comprehension (anomia or alexia sites), but a spot-by-spot visual correlation was found in only six patients (6/14 patients, 42.8%). Moreover, in these cases we noted differences between the extent of activation on fMR and the intraoperative positive site. Concerning DTI-FT, this study produced faithful anatomical reconstructions of the pyramidal tracts (particularly regarding position and direction) and long-range association fibers (arcuate, inferior fronto-occipital, inferior longitudinal). The majority of white matter bundles in close contact with the tumor were preoperatively defined as displaced and in four cases they appeared interrupted. Based on tumor residue on postoperative MRI and

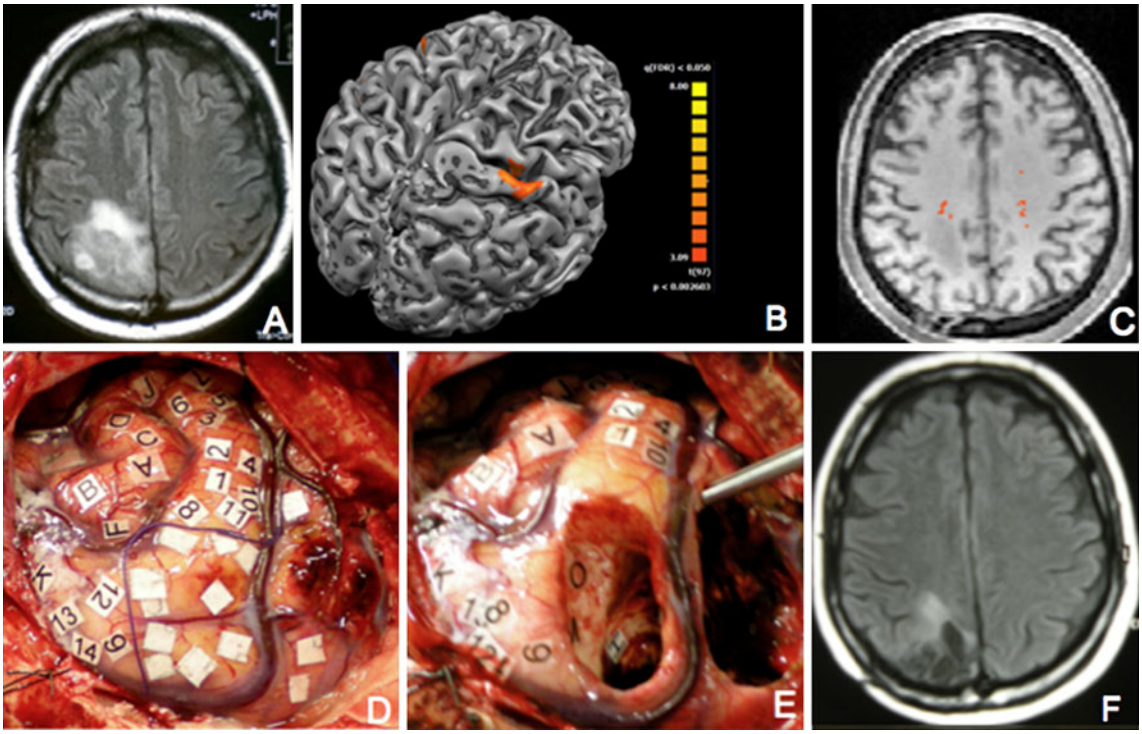

Fig. 2 (**a**) A 33-year-old man with partial seizures was diagnosed with a right retrocentral, low-grade astrocytoma invading the sensorimotor strip. (**b**) fMRI activations during the tasks of index brushing and fingers movement in the middle part of the retrocentral gyrus ($q<0.05$ FDR corrected, minimum cluster size $K>5$ voxels in the native resolution). (**c**) DTI shows a cluster of fibers just in front of the anterior pole of the tumor. (**d**) CSES confirmed the presence of the sensory area of the fingers (2, 3, 4, 5 ,6) in the lower part of the retrocentral gyrus. Letter tags indicate the motor area of the hand and biceps, triceps, and deltoid (9, 12, 13, 14, *K* sensory area of the foot, ankle, leg, and tibia). The area of the gyrus covered with white tags was unresponsive to CSES, likely as a consequence of tumor infiltration. The absence of preoperative and postoperative sensory deficits is a demonstration of functional reorganization. (**e**) During subcortical resection, CSES demonstrated thalamocortical projection of the foot (M), leg (O), and calf (H). (**f**) Postoperative MRI confirmed residue of tumor in an area where DTI failed to demonstrate the descending pathways

subcortical stimulation, DTI-FT underestimated the presence of functional fibers in the wall of the mass for the whole subgroup (15 patients; Fig. 3). We found maximum visual correlation of DTI-FT in only one voluminous retrocentral tumor with a cystic component that displaced the thalamocortical projection. In this case, the wall of the cyst represented the interface between the tumor and the white matter. Therefore, a faithful comparison between the reconstruction of the pyramidal tract and the intra-operative finding was possible because of the absence of tumor infiltration (Fig. 4).

Table 4 Effects of subcortcial stimulation in language areas

Site	Effect of subcortical stimulation	Fasciculus on DTI
Left pITG	Anomia (3 pts)	ILF
Left pMTG	Phonetic disturbances (2 pts)	ARC
Left IPL	Phonetic disturbances (3 pts)	ARC

The site indicates the underlying white matter

In the third column is reported the nearest fasciculs as depicted on DTI

pITG posterior inferior temporal gyrus' *pMTG* posterior middle temporal gyrus, *IPL* inferior parietal lobule, *ILF* inferior longitudinal fasciculus, *ARC* arcuate fasciculus

Discussion

Ideally, neurosurgeons could detect and locate the exact position of brain functions before performing tumor resection, allowing them to suggest surgery only in those patients with the prospect of radical or grossly subtotal resection. Moreover, technological support would serve as a guide during surgery in order to spare critical areas. Such complete and reliable technology is not currently available, but major advances have been made since the days when neurosurgeons performed brain surgery only via anatomical references. One such reference is the precentral gyrus, long considered the anatomical correlate of the primary motor cortex as well as the "knob" or "omega" for localization of the motor area of the hand. However, the problem with using sulci and gyri patterns as reliable references is the interindividual variability of organization and the presence of multiple variants [11, 17]. The situation is even more

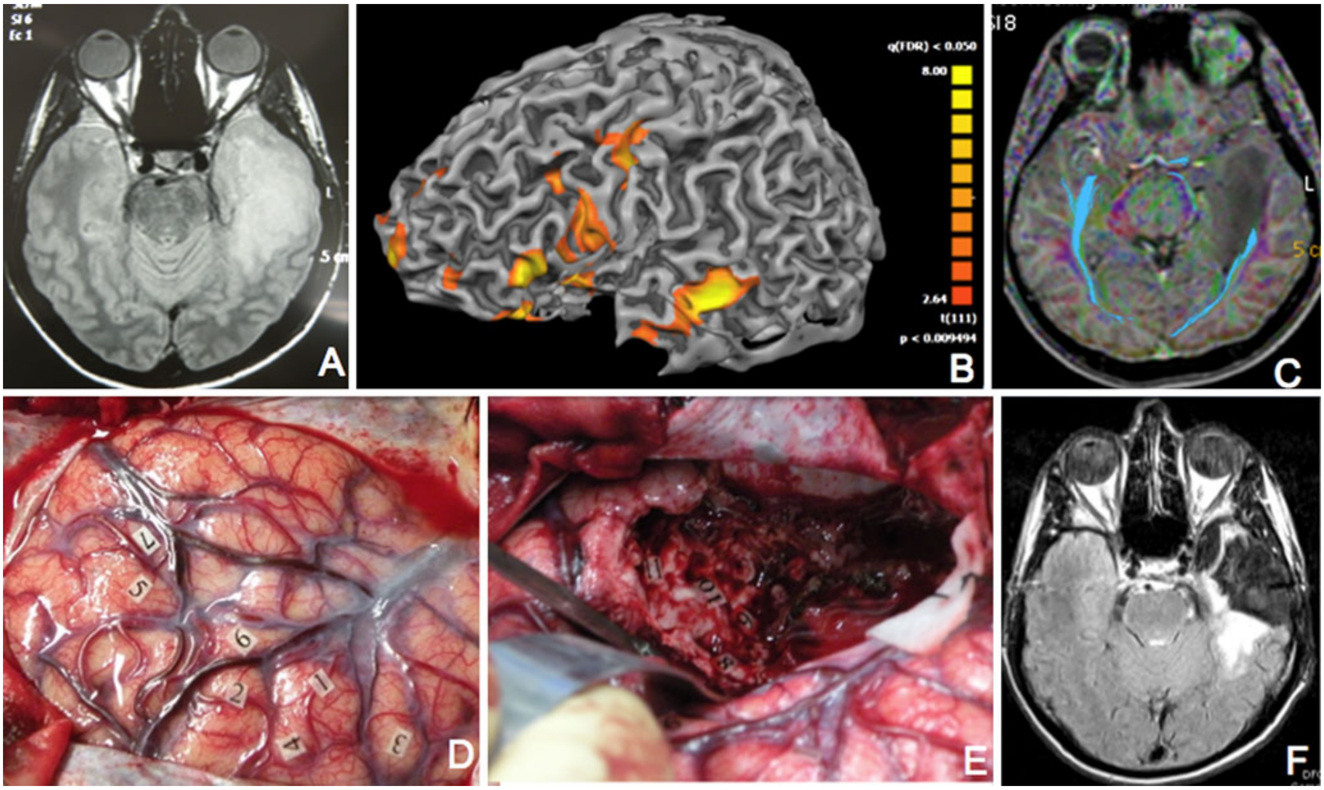

Fig. 3 (**a**) A 39-year-old man suffering absence seizures received a brain MRI that showed a large, low-grade astrocytoma in the left temporal lobe. (**b**) During a verb generation task, fMRI demonstrated activations in the frontal operculum, in the foot of the central area, in the temporal operculum, and on the middle temporal gyrus ($q<0.05$ FDR corrected, minimum cluster size $K>5$ voxels in the native resolution). (**c**) DTI showed a fascicle just beside the mass that seemed interrupted. No other tract was visualized inside the tumor. By looking at the position and direction, this bundle was referred to the inferior longitudinal fasciculus (ILF). (**d**) CSES confirmed the presence of speech arrest sites (tags 1, 3, 4, and 6) in the lower third of precentral gyrus, in the dorsal premotor cortex and in the posterior part of the superior temporal gyrus. Naming sites were found on the middle temporal gyrus (tags 7, 5). (**e**) At the subcortical level, stimulation provoked naming disturbances (8, 9, 10, 11); consequently resection was arrested, and no language deficit was diagnosed at follow-up. (**f**) Postoperative MRI confirmed the subtotal resection as well as the functionality of the residue of tumor, although DTI-FT showed absence of fibers

complex when dealing with higher cognitive functions, such as language, which have multiple and extremely distributed epicenters. Moreover, there have been numerous scientific and clinical studies demonstrating that the relationship between anatomy and function is not as clearly coupled as once believed and is complicated in patients with intracranial pathology [5, 36]. Neurosurgeons have documented these difficulties reporting high rates of neurological impairment following resection of tumors in critical areas [18, 43, 51]. The advent of functional imaging has advanced our understanding of brain function organization, and has changed the clinical management of brain tumors in critical areas [37, 40, 48, 52]. In particular, this innovative imaging tool allows the surgeon to abandon an a priori conception of brain function organization, favoring a more individual and pathology-based approach. However, questions remain regarding the effective reliability and spatial precision during surgery. CSES has gained acceptance in routine practice because of its capacity to directly disclose the effect of removing brain sections. Clinical studies evaluating the effect of direct cortical and subcortical stimulation on neurological outcome have also contributed to their wide use. Some authors that have used CSES to validate the reliability of fMRI imaging in detecting sensorimotor areas have found that sensitivity ranges from 82% to 100% [19, 33, 39]. Our findings confirm this; in nearly all of our patients, the position of sensory or motor activation areas identified by fMRI was confirmed during CSES. With language areas, the utility of fMRI during surgery is diminished, however. This is seen in our results (42.8%) as well as previous work indicating variable sensitivity and specificity ranging from 59% to 100% and from 0% to 97%, respectively [35, 38, 40]. Recently, Giussani et al. reviewed studies comparing language fMRI with CSES of language areas and found contradictory results due to differences in pre- and intraoperative tasks, correlation methods, and tumor types [21]. Apart from methodological issues, language areas are

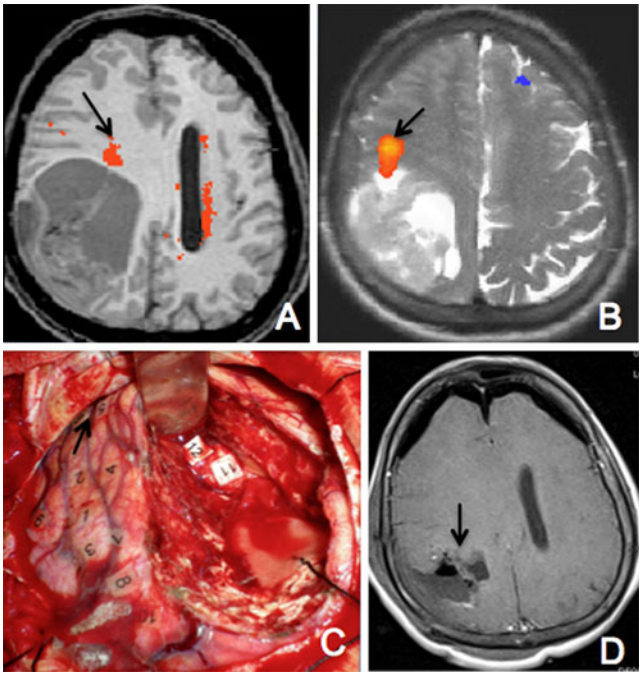

Fig. 4 Male, 43 years old. A mild head trauma was the occasion to diagnose a large and partly cystic oligodendroglioma in the central area. (**a**) Preoperative DTI-FT demonstrates the displacement of the **pyramidal tract** anteriorly and the close contact to the cystic portion of the tumor (*arrow*). (**b**) fMRI also shows deformation of the central area with the sensory area of left index (*arrow*; $q<0.05$ FDR corrected, minimum cluster size $K>5$ voxels in the native resolution). (**c**) Intraoperative image demonstrating good visual correlation between fMRI and cortical stimulation (5, paraesthesia of the index). At the subcortical level (11, 12 paraesthesia of the shoulder and neck), there is also a comparable finding to the DTI reconstruction with the **pyramidal tract** in the antero–medial part of the surgical cavity. *Arrow*: central sulcus. (**d**) Immediate postoperative MRI (*arrow*: position of thalamocortical tract). After 1 month, the patient returned to his work

organized in a large-scale network that is widely variable. fMRI maps the entire cortical network implicated in a specific task, and normally it is unable to differentiate between essential and substitutable epicenters. Conversely, intraoperative language tasks are designed to detect predominantly essential epicenters, i.e., anomia or speech arrest sites. Moreover, the neurovascular and metabolic coupling that produces the blood oxygen-level dependent (BOLD) signal on fMRI can be misleadingly altered in an infiltrated cortex, allowing underestimation of the quantity of functional cortex involved [27, 50]. For instance, in the current study, 46.1% of active infiltrated cortex was revealed during direct stimulation and subsequently spared, avoiding permanent morbidity. Yet, we cannot draw conclusions about the capacity of fMRI in identifying activation in an invaded cortex since BOLD activity is related to the tasks during fMRI acquisition. When a tumor invades the precentral gyrus, for instance, it is impossible to know if that part of the gyrus is devoted to movement of the shoulder rather than the forearm. Likewise, it is inconceivable to map the entire corresponding hemibody during an fMRI session. Thus, fMRI only affords an estimation of motor area position. Another limitation of fMRI in surgical planning is a lack of information about the white matter that is often infiltrated by tumors (60.4% of cases in our series). DTI is a recently developed MRI technique that can measure macroscopic axonal organization in nervous system tissues. The random, diffusion-driven displacements in diffusion magnetic resonance imaging allow microscopic-scale resolution of tissue structure. As diffusion is a three-dimensional process, molecular mobility in tissues may be anisotropic, as in brain white matter. With DTI diffusion, anisotropy effects can be fully extracted, characterized, and exploited, providing even more exquisite detail of tissue microstructure. The most advanced application is that of fiber tracking in the brain, which, in combination with functional MRI, has revealed much about brain connectivity. This technique allows dissection of subcortical pathways and adds new insights into brain connectivity [8–10, 22, 24]. Although several authors have tried to validate DTI-FT through correlation with intraoperative CSES [2, 25, 34], some intrinsic drawbacks still exist. The tracking of fibers in the vicinity of or within lesions is complicated due to changes in diseased tissue, such as elevated water content (edema), tissue compression, and degeneration. These changes deform the architecture of the white matter, and, in some cases, prevent selection of the seed region of interest (ROI) from which fiber tracking begins. To overcome this problem, some investigators have suggested posing a seed ROI in the white matter area subjacent to the maximal fMRI activity (i.e., for the pyramidal tract, in the precentral cortex) and the target ROI in the cerebral peduncle [44, 47, 49]. According to our data, DTI-FT underestimates the presence of functional tracts in the context of the tumor, as demonstrated by the assessment of 60.4% of infiltrated functional white matter compared to the postoperative MRI. A typical image featured a white matter bundle in close vicinity of the tumor without any information on how much of the pathway or pathway function was invaded. In language areas, when subcortical stimulation did not show a zone of positive response, DTI could have emphasized the presence of white matter tracts, favoring an unnecessarily conservative surgery, whereas direct stimulation would have indicated removal of the entire non-eloquent tissue. One criticism to our topographical correlation could be a lack of spatial precision. In other words, visual comparison does not permit centimeter-by-centimeter verification of the cortical activation sites as well as subcortical pathways. The use of a stereotactic frame to acquire and merge the preoperative fMRI and DTI-FT would be inapplicable and expensive, so neuronavigation also is not a sufficient methodology. Although navigation is feasible in the cortex immediately after opening the dura, once the tumor has been removed and brain relaxation is maximal, the anatomy is completely deformed. This makes it impossible to acquire useful data about the position of white matter tracts as depicted on DTI-FT. Moreover, our topographical method allows us to focus on infiltrated portions of cortex and white matter that are still functioning.

Beginning an awake surgery practice is demanding for the entire operating team, but the learning curve can be quite rapid. Once the procedure is well established, the surgeon can continuously check the impact of his/her work on brain functions. As such, surgical resection becomes functional and not merely anatomical. The absence of intraoperative and perioperative major complications in the current series affirms that this technique is safe and applicable to routine practice in even very young patients (12 and 13 years old). CSES demonstrated high sensitivity, as the stimulation detected eloquent sites in all patients. Moreover, the spatial resolution and ability to map the entire exposed cortical region allowed identification of the functional organization, and plastic reorganization, of surrounding areas of the brain. This is particularly useful when dealing with cognitive areas. Overall, awake surgery and CSES widened surgical indications, allowing us to treat patients who were previously deemed unsuitable for surgery. The high incidence of postoperative deterioration (77.7%) and the 88.4% rate of definitive conservation of neurological status suggest two important points. First, tumor location was critical in all subjects (confirmed by a rate of 46.1% of still functioning cortex). The total plus subtotal resection of 88.3% also demonstrates the ability of CSES to guide resection by following functional boundaries. Second, CSES provides an excellent prognosis; in our study, removal of negative cortical and subcortical areas did not lead to permanent neurological impairment. Recently, Kim et al., analyzing a large population of patients operated on for tumors in eloquent brain regions by direct electrical mapping, confirmed that a safe resection is feasible when only negative stimulation sites are found [30]. Determining a surgical course in patients with high-grade gliomas in critical areas that are already symptomatic is a delicate process. Although some authors believe that these tumors preferentially displace white matter bundles rather than infiltrate them [23, 25], we did not observe this. Operating on delicate brain regions often produces a transient deterioration in postoperative status related mostly to manipulation and inflammation (69.2% in the current series) [42]. Thus, the presence of rapidly evolving tumors could impede recovery. We can thus argue that a more careful selection of patients (i.e., by screening completely asymptomatic subjects) with high-grade gliomas located in very delicate regions, is the best way to prevent unsatisfying results.

Although CSES has been used for the resection of intrinsic brain tumors, as well as epilepsy foci, we agree [55] that it also is useful in the resection of subcortical metastasis. In fact, even though this kind of tumor is cleavable from brain parenchyma, CSES can help in defining the safest point at which to penetrate cortex when dealing with highly functional regions.

For motor and sensory functions, intraoperative evoked potentials are still preferred in some centers. Although this method is reliable [20, 32, 56], there are some limitations. First, only the action potentials of selected muscles can be controlled, hampering both the detection and avoidance of motor deficits in non-monitored muscles. Second, no information is obtained on the function of cortex adjacent to the central region. Finally, intraoperative evoked potentials cannot currently be used to perform mapping of language or other higher functions.

Although CSES is, today, considered the gold standard for direct localization of brain functions, some technical drawbacks should be noted. The number of cognitive tasks that a conscious patient is able to perform is limited by physical and psychological fatigue. This might lead to false-negatives if the correct function was not tested for the appropriate area; this may, in part, explain the discrepancies found with fMRI. Furthermore, the presence of an expanding lesion and related reorganization phenomena could alter the mechanisms underlying some cognitive functions. This could make it difficult to apply evidence from intraoperative mapping to the neurophysiology of a “normal” brain.

Conclusions

Although the path toward perfecting a system to treat brain tumors in critical regions without morbidity has been long, the widespread adoption of presurgical and intraoperative mapping presents a unique opportunity to obtain information about a patient's brain in order to individualize surgical planning. Preoperative fMRI and DTI-FT aid in planning awake surgery by displaying cortical and subcortical functional and anatomical organization in an individual patient. fMRI imaging and DT imaging should be used routinely during presurgical functional localization techniques in order to aggressively resection lesions in the eloquent cortex. At the same time, our data confirm that these devices cannot provide information directly in the operating room or guide a critical surgical strategy. CSES is still a very safe, effective, and useful technique that improves the quality of surgical resection and the outcome in patients with eloquent area tumors. More extensive longitudinal and multicentric studies comparing the effects of preoperative and intraoperative brain mapping are needed. In doing so, we could obtain further insight into the plastic potential of the brain and refine our methods of patient selection for surgery. To achieve this goal, shared protocols of fMRI, DTI, and intraoperative mapping are required and a continuous and reciprocal exchange of knowledge between neurologists, neuropsychologists, neuroradiologists, and neurosurgeons should be encouraged.

Conflicts of interest None.

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Comment

The authors have prospectively studied 27 patients who underwent surgery for a lesion located within eloquent brain areas. Functional mapping was performed by combining preoperative fMRI and DTI as well as intrasurgical electrostimulation in awake patients. The authors conclude that, although preoperative functional neuroimaging is useful, intraoperative mapping is still necessary for safe and maximal resection of lesions in eloquent areas.

This is a very interesting article, for several reasons (1) it is a prospective series (even if the number of patients is small); (2) correlations have been made between fMRI and cortical stimulation as well as between DTI and subcortical stimulation, concerning both sensorimotor and language functions: they demonstrate that functional neuroimaging is not reliable enough, and that intrasurgical mapping is still mandatory for the detection of both eloquent cortex and functional white matter pathways; (3) the authors show a tumoral invasion of cortical areas still functional in 46.1% of cases and a tumoral invasion of subcortical structures still functional up to 34.6% of cases for language, which is a very important result supporting the necessity of performing brain mapping in glioma surgery.

However, the authors must be careful before they write that "a safe resection is feasible when only negative stimulation sites are found", because the rate of permanent deficit in their series is still of 11.1%. Indeed, the authors insisted on "learning curve" with regard to awake mapping. In this state of mind, it is important for neurosurgeons who begin this activity to remind that a perfect methodology of electrostimulation is crucial, especially to avoid false negative which could lead to permanent deficit. A positive mapping is thus highly recommended in order to have well-understood the individual anatomo-functional organization before to remove a cerebral tumor, and to tailor the resection according to these reliable boundaries which are very variable from one patient to another.

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