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Multimodal Approach to the Surgical Removal of Gliomas in Eloquent Brain Regions

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1. Introduction

Supratentorial glial neoplasms are the most common primary brain tumor in adults and one of the leading causes of cancer-related death in the general population. Glioblastomas carry the worst prognosis, while low-grade gliomas have the best chance for survival. It has been demonstrated, however, that low-grade gliomas represent a precancerous state, as they have the potential to evolve into higher-grade malignancies. Although management algorithms vary among different types of tumors, surgery remains the mainstay of treatment for several reasons. Surgical resection allows the opportunity to obtain a sufficient amount of tumor for histological identification. This point is of utmost importance, as the best predictors of survival are the World Health Organization (WHO) grade and other immunohistological characteristics of the tumor. Additionally, it has been demonstrated that radical or subtotal resection correlates positively with prolongation of survival and longer time to progression. Given this information, neurosurgeons aim to achieve maximal surgical resection of these tumors whenever feasible. Unfortunately, gliomas are often located in regions of the brain defined as "eloquent" or "critical," meaning that physical damage to these areas can create permanent neurological deficits. A careful evaluation of surgical strategy is mandatory in light of this fact, with the goal being to maximize tumor resection while respecting the highly functional cortical and subcortical regions of the brain.

Different techniques are available that allow the neurosurgeon to study the brain function topography both preoperatively and intraoperatively. These methods of preoperative and intraoperative brain mapping are used to gain essential information about functional and topographic organization in a specific patient. Functional magnetic resonance imaging (fMR) is the most commonly used tool for preoperative visualization of the motor, sensory, language, and visual functional organization of a patient's brain. Since gliomas typically invade white matter, the extent of resection is additionally limited by the degree of infiltration, particularly when critical bundles are involved (e.g., the pyramidal tract). As with the eloquent cortical areas, the relationship of the tumor to the subcortical pathways should be defined in order to avoid permanent deficits. Diffusion tensor imaging (DTI), the

latest MR imaging advancement, allows reconstruction of the anatomy of the main white matter tracts. Using this imaging modality, further information can be gathered on the status of these tracts (e.g., infiltration, displacement, interruption).

It is crucial that contemporary neurosurgeons understand how to properly use these technological advancements to improve postoperative neurological results. It is also vital that critical analysis and discussion of the limits and appropriate use of these devices is part of the neurosurgical routine.

In this chapter, we will focus on some fundamental aspects of brain mapping, particularly regarding the surgical resection of gliomas. First, we will review the concept of eloquent brain regions and the evolution of the concept of critical areas. Then, we will deal with state-of-the-art functional imaging and diffusion tensor imaging, underlining their conceptual and technical limitations and explaining how to use them in surgical planning. Direct brain mapping by CSES will also be examined from a practical point of view, focusing on basic technique, anesthesia, equipment, patient selection, limitations, and future directions. Finally, we will discuss how to integrate these different mapping modalities while highlighting clinical evidence from our experience and that of other authors.

We hope that this chapter will help those who are approaching brain mapping in a clinical and neurosurgical setting not only by showing mechanisms and usefulness but also in posing questions and criticisms.

2. The evolution of the concept of eloquent brain regions

When dealing with brain functions it is quite strange to consider a part of the brain "eloquent" and some other part not, since the brain as a whole is considered the most eloquent organ of the body. Actually, in the routine practice of a neurosurgeon this riddle very often arises, particularly when a tumor is located in an area usually considered "eloquent" (i.e. central region, Broca's area, Wernicke's area). The concept of brain function organization into well defined and localized areas is the legacy of pioneering studies of the 19th and 20th centuries (D'Aubigné 1980; Mohr 2004). The basic method of these revolutionary inquiries rested on the connection between neurological deficits and post-mortem anatomical observations. Consequently, every area of the brain cortex was associated with a specific neurological function and a lesion in that region would have led to a well-defined neurological impairment. This anatomo-functional correlation gave rise to the assertion that some cortical gyri were "eloquent," for example, the triangular gyrus of the frontal operculum (Broca's area), the supramarginal gyrus (Wernicke's area), the angular gyrus, the precentral gyrus (motor area), and so on, while others were not. This tight coupling between anatomy and function has deeply influenced the practice of neurosurgery, making some patients with brain tumors in specific areas aprioristically not suitable for surgery. Even today in clinical practice, neurosurgeons very often rely mainly on standard anatomical cortical references as the initial basis for which resection of a tumor is considered potentially critical or at high risk of causing neurological damage. The excellent anatomical definition produced by MR imaging has made the process of investigation of the cerebral gyri even easier. The Rolandic region, for example, has been extensively portrayed as a model of cerebral landmarks for specific functions (sensory-motor area), but there has also been evidence that reliability is not always absolute. Intrinsic neuroanatomical variability accounts for a distinct challenge to strict anatomo-functional coupling. There are multiple factors that affect neuroanatomical variability, including sex, handedness, aging, and

neurological diseases (Annet 1992; Thompson et al. 1998; Toga et al. 2001; Ballmaier et al. 2004; Luders et al. 2005; Narr et al. 2007). In the complex relationship between neuroanatomy and function, the significance of neuroanatomical variability is evidenced by its association with and probable contribution to distinct patterns of functional organization. For example, interhemispheric anatomical asymmetries (especially with respect to the planum temporale) have repeatedly been shown to be related to language lateralization (Josse et al. 2003; Steinmets et al. 1991). A trustworthy functional representation of a defined anatomical landmark is typically feasible for the hand motor area, showing as a correlate a characteristic dorsally oriented convexity in the precentral gyrus (the so-called "hand-knob") (Yousry et al. 1997; Boling et al. 2008). However, motor activity can also be detected outside of the typical landmarks, and the pattern of motor cortex activation is modulated by different physiological factors (Yousry et al. 2001; Mattay & Weinberger 1999). The discrepancy between anatomical references and functions becomes even more complex when dealing with higher cognitive functions, such as language, which have multiple and extensively distributed epicenters. It is nowadays accepted that the classical language model (Lichtheim 1885; Geschwind 1971) is not sufficient to reflect the complexity of cortical language representations (Gabrieli et al. 1998; Grabowski 2000; Bookheimer 2002). The view that there are no well-defined language areas is strongly supported by many fMR studies, as well as cortical and subcortical electrical stimulation (CSES) studies, that have identified widespread and overlapping networks for phonological, semantic, orthographic, and syntactic processing (Ojeman et al. 1989; Herolz et al. 1996; Tzourio-Mazoyer et al. 2004). In an extensive analysis performed on more than 200 patients operated on for intrinsic brain tumor through an awake craniotomy and CSES, Berger et al. (Sanai et al. 2008) showed that sites associated with speech function are variably located along the cortex and can go well beyond the classic anatomical boundaries.

In the neurosurgical population, additional inter-patient anatomical variability arises from the presence of intracranial pathology. Brain tumors can alter the understanding of neuroanatomy and function localization through two mechanisms. The first is related to the deformity created by the space-occupying lesion on adjacent sulci such that normal anatomical and imaging landmarks are more difficult or impossible to identify. The second is related to the reorganization and redistribution that occur in the cortical functional maps as a consequence of the presence of the brain tumor. Post-lesional recovery and the pattern of brain reorganization involved in functional compensations have been well documented in stroke patients (Rijntes & Weiller 2002; Rossini et al. 2003; Ward 2004). These studies have elucidated the concept of cerebral plasticity: the natural capacity of the brain to remodel itself as a consequence of learning and developmental strategy. Cerebral plasticity defines a continuous process that allows reshaping of the neuronosynaptic maps to optimize the functioning of brain networks. It is also the way to recover from lesions of different origin. Gliomas, especially low-grade gliomas, have in the very recent years increasingly attracted researchers because of their tendency to reach large volumes in eloquent areas, frequently without causing neurological symptoms. Functional MR studies have shown how these slow growing tumors can induce functional reshaping by displacing critical epicenters either around the tumor or even to the contralateral hemisphere (Mueller et al., 1996; Carpentier et al. 2001; Baciu et al. 2003). Moreover, several authors have reported series of patients who have undergone awake craniotomy and CSES in whom tumors in critical areas were safely and efficiently removed without permanent morbidity. In these series authors have documented different types and mechanisms of tumor-induced functional

reorganization (Duffau 2005; Duffau 2006). In addition, in some cases functional tissue is located within the tumor nidus, and it is now understood that the standard surgical principle of debulking tumor from within to avoid neurological deficits is not always safe (Duffau et al. 2005; Berger et al. 2010; Spena et al. 2010).

The concept of the eloquent area is not limited to cortical functional maps. It is also applied to the bundles of axons connecting a cortical area to secondary neurons and to other areas of a specific cortical network. Hence, the most thorough examination of a tumor requires a careful consideration of its relationship with subcortical white matter. In particular, gliomas are well known to invade white matter tracts through which they can reach the contralateral hemisphere. Accumulating evidence has demonstrated that postsurgical or post-stroke damage to subcortical critical pathways can result in irreversible deficits. There is no documented plasticity in the white matter, and recovery after interruption of a subcortical functional bundle is difficult. Hence, presurgical planning should determine whether tumor invades or simply displaces subcortical pathways. In the very recent years a new application of MR diffusion sequences imaging called Diffusion Tensor Imaging (DTI) has created the opportunity to reconstruct the anatomy of the main white matter tracts. A virtual in vivo dissection of white matter, very similar to those coming from cadaver studies, has been produced, adding new insights into the relationship between tumors and white matter bundles (Catani 2002, Ozawa 2009, Nimsky 2007). The availability of this new tool marks a period in which neuroscientists have given great resonance to connectionism to explain brain functions and neurosurgeons have focused their efforts on gaining preoperative information about subcortical pathways.

This brief overview of advances in understanding of the brain function has given us the opportunity to point out that the modern-era neurosurgeon should be able to preoperatively collect a large amount of information on the distinctive functional and anatomical organization of each patient's brain in order to individualize surgical strategy.

3. Preoperative brain mapping

3.1 Functional MR

Functional MRI is a non-invasive technique that visualizes brain activity indirectly by detection of local hemodynamic changes in cortical capillaries and draining veins (Frahm et al. 1994; Menon et al. 1995). This blood-oxygen level-dependent (BOLD) technique makes use of blood as an intrinsic contrast agent (Ogawa et al. 1993). A BOLD signal is based upon the increase of oxygen consumption by neuronal cells inducing a relative increase in the local perfusion (Heeger 2002; Toronov 2003). The activation spots have been shown to reflect actual neuronal activity with high spatial accuracy (typically between 1 and 5 mm) (Logothetis 2003; Logothetis & Pfeuffer 2004; Logothetis & Wandell 2004). Functional MR imaging maps reflect task-related local changes in the vascular response of brain tissue, and they are therefore an indirect measure of neural activity. Temporal resolution is generally lower than EEG (Gevins, Leong et al. 1995) or MEG (Hämäläinen M 1993) because the hemodynamic BOLD response lags behind the neural response by several seconds. There are other imaging tools that indirectly detect brain activity, such as positron emission tomography (PET) (Fox et al. 1986) (Mazziotta et al. 1982; Raichle 1983) and single-photon emission computer tomography (SPECT) (Holman and Devous 1992), but their description is beyond the scope of this chapter, except to note that they have lower spatial/temporal resolution and are less available for use in clinical scanning. At present, functional magnetic

resonance imaging (fMRI) is the most widely used method of functional neuroimaging in both the clinical and research environments. For the latter purpose, and unlike more invasive mapping methods, fMR allows for the study of subjects who are free from neurological illness and enables the modeling of brain processes and of individual differences in brain organization. These are the principal factors that account for the enormous advancements brought by fMR to the understanding brain functional organization.

The two predominant diagnostic aims of presurgical fMR are the localization of eloquent brain areas and their relationships with the tumor, and the determination of the dominant hemisphere for language. As a clinical research tool, fMR can be performed longitudinally pre- and postoperatively to identify neuroplastic changes in brain activity.

Any clinical application of fMRI involves a "paradigm," a defined functional measurement including stimulation, and a task that is presumed to activate the cortical area to be studied. For motor function, the patient is scanned while performing an active blocked motor task. The task consists of 12 seconds of foot plantarflexion/dorsiflexion, hand opening/closing, or tongue movement, with a frequency of 0.5 Hz, followed by 12 seconds of rest for a total acquisition time of 5 minutes. The sensory cortex test is similar, with an active condition of 0.5-Hz brushing of the foot or hand. Language is investigated as follows: in the active condition, the patient listens to a list of nouns and generates associated verbs for 21 seconds; in the rest condition, the patient counts from 1 to 10 for 15 seconds. These paradigms are those usually performed in our routine. For further technical details refer to the bibliography (Moritz & Haughton 2003; Gaillard 2004).

Due to its good spatial resolution and direct correlation to surface anatomy BOLD-fMRI has been used since shortly after its first description (Bandettini et al. 1992) (Kwong et al. 1992; Ogawa et al. 1992) for presurgical localization of the primary sensorimotor cortex in patients with rolandic brain tumors (Jack et al. 1994), for determination of the language dominant hemisphere in patients with left frontal or temporo-parietal tumors (Desmond 1995), and for the localization of Broca and Wernicke language areas (FitzGerald et al. 1997; Stippich et al. 2003; Stippich et al. 2007).

The most relevant concern in presurgical visualization of eloquent areas is the reliability of the spatial position and the extent of the spot of activation as depicted on the fMR. It is important to clarify that the spots of activation are strictly related to the statistical threshold chosen for data evaluation. Even with the use of one or more fixed statistical thresholds, BOLD signal intensities and cluster sizes differ significantly from one patient to another and between different paradigms (e.g. foot movement, hand movement), even when examinations are carried out in a standardized way. This has a direct impact on the planning of the neurosurgeons, who may, based on an fMR map, consider a determined eloquent area to be wider or narrower than it actually is. To address this matter, comparisons of presurgical fMRI data with a reference procedure such as CSES have been performed. In patients with lesions around the central sulcus (Dymarkowski et al. 1998; Achten et al. 1999; Roux et al. 1999), many studies have reported highly concordant data of presurgical fMRI and CSES, with correlation ranging from 83% to 92% (Majos et al. 2005; Lehericy et al. 2000; Spena et al. 2010). However, for language areas, the utility of fMRI to predict the presence of language epicenters in or around the tumor surface is diminished. This is seen in our results (42.8%) as well as in previous works that have indicated variable sensitivities and specificities ranging from 59% to 100% and from 0% to 97%, respectively

(Petrovich et al. 2005, Rutten et al. 2002). Aside from methodological issues, language areas are organized in a large-scale network that is widely variable. Functional MRI maps the entire cortical network involved in a specific task, and it is normally not able to differentiate between essential and substitutable epicenters. These studies mainly addressed the reliability of the position of the focus of an activation spot but no data were produced regarding the extent of those spots (Fig. 1). Furthermore, since a BOLD signal is generated by an increase in blood flow, the presence of infiltration by vascularized tumor can completely alter the local microvascular organization and potentially hamper the reliability of the BOLD signal (Holodny et al. 1999; Ulmer et al. 2004). Therefore, the use of presurgical BOLD activations on fMR to predict resection margins and surgical risks of neurological damage is not routinely indicated. The data available to quantify a safe distance between functional activation and resection borders (Hall et al. 2005; Krishnan et al. 2004) with respect to surgically induced neurological deficits are still very limited and do not justify any general conclusion or recommendation. Moreover, since fMR imaging is only intended to visualize cortical activity, no information is gained about subcortical white matter bundles and connections.
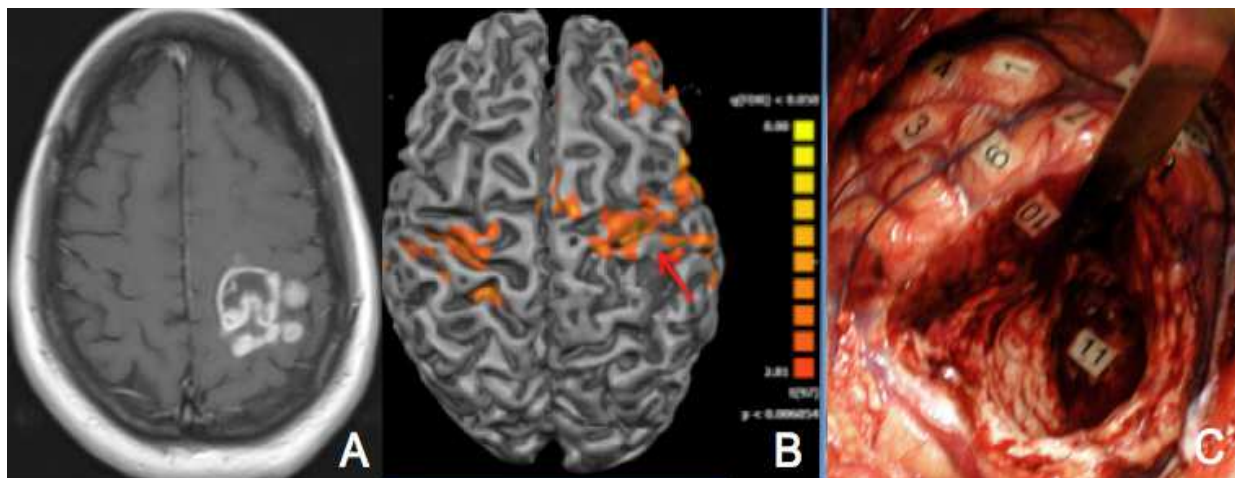

Fig. 1. (A) Preoperative MR showing a retrocentral glioblastoma invading the central gyri. (B). Preoperative fMR showing that the area of the hand seems to be infiltrated by the tumor, and the activation spot seems to be interrupted (red arrow; q< 0.05 FDR corrected, minimum cluster size K>5 voxels in the native resolution). (C) Intraoperative stimulation demonstrated that the infiltrated postcentral gyrus was still functional (hand sensibility: 6, 7, 10) and so was not removed.

Nonetheless, functional MRI is still an important source of non-invasive diagnostic information that can reduce the number of invasive diagnostic procedures, such as the Wada test. We use fMRI in preoperative planning mainly to understand the activation pattern, the location of the pre- or postcentral gyrus, and the approximate distance to the tumor. If the distance from the activation spot is greater than one gyrus or the subcortical infiltration is minimal, we may even choose not to perform an awake surgery with CSES. For tumors in language areas, we calculate the lateralization index that, together with neuropsychological testing, gives an indication about the dominant hemisphere. We strongly recommend precise intraoperative control of functional structures in every situation where there is suspected tumor invasion of an eloquent area.

3.2 Diffusion tensor imaging and fiber tracking

The "eloquence" of a brain region is not only determined by importance of neuron functions. In order to maintain correct functioning of a neural network it is crucial that all the groups of neurons are connected. Consequently, neurosurgeons must try to spare subcortical functional bundles (at least the largest and more essential), otherwise connections between cortical epicenters will be damaged. The seminal works by Kringler, through post-mortem dissections (Agrawal et al. 2011), demonstrated the complex organization of the white matter into bundles of different length and thickness that connect either one gyrus to another or to very distant parts of the brain. Unfortunately these observations are hardly applicable during surgery, when white matter appears as a uniform tissue that can be infiltrated by the tumor. In recent years a new, non-invasive pre-operative technique of white matter signal analysis has been introduced: diffusion tensor imaging (DTI). This is a modification of diffusion weighted imaging (DWI) that is sensitive to the preferential diffusion of brain water along white matter fibers and can detect subtle changes in white matter tracts in disease (Nucifora et al. 2007). 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 can 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.

DTI has been applied to patients with brain tumors for different purposes. First, measures of mean diffusivity and fractional anisotropy have been used to differentiate normal white matter, edematous brain, and enhancing tumor margins (Sinha 2002, Lu 2003). Anisotropy is reduced in cerebral lesions due to the loss of structural organization (Wieshmann et al. 1999; Mascalchi et al. 2005). It seems that the abnormalities on DTI are more significant than those seen on T2-weighted images in high grade gliomas, but not in metastatic tumors (Beppu et al. 2003; Price et al. 2003). Second, DTI may distinguish if the white matter fibers are displaced (Wieshmann et al. 2000; Gossl et al. 2002), infiltrated, or disrupted by the tumor (Wittwer et al. 2002). Finally, the most fascinating application of DTI is the fiber-tracking technique (DTI-FT) that is able to identify and reconstruct the main white matter connections. This information is very useful for presurgical planning, delineating the spatial relationships of eloquent structures and tumors in order to preserve the functional pathways intraoperatively (Holodny et al. 2002; Tummala et al. 2003; Henry et al. 2004). Since the images generated by DTI-fiber tracking are the result of complex mathematical modeling aimed at resolving the hypercomplex structure of white matter, several authors have worked to answer some practical problems. For instance, what degree of correspondence do the images have to the actual anatomy of the bundles? What is the relationship of the bundle(s) to the tumor (displaced, infiltrated, interrupted)? And, most importantly, what is the function of the bundle(s)? Must it be spared or can it be sacrificed? DTI-FT is currently intended to virtually reconstruct white matter tracts, but it is not able to investigate the function related to a tract. CSES is the gold standard to map subcortical pathways, and DTI-FT findings can be integrated with intraoperative CSES with or without the implementation of intraoperative navigation devices (Henry et al. 2004; Kinoshita et al. 2005; Bello et al. 2008; Ozawa et al. 2009, Leclercq et al. 2010; Spena et al. 2010). The fundamental observation that preoperative DTI-FT cannot itself account for the determination of the presence or absence of functional subcortical tracts in or in the vicinity

of the tumor is clearly demonstrated by cases of cystic tumors in which, because of the absence of infiltration and edema, the white matter tract reconstructions are very reliable (fig. 2). DTI-FT underestimates the presence of functional tracts in the context of the tumor, as demonstrated by our finding of 60.4% of infiltrated functional white matter predicted by
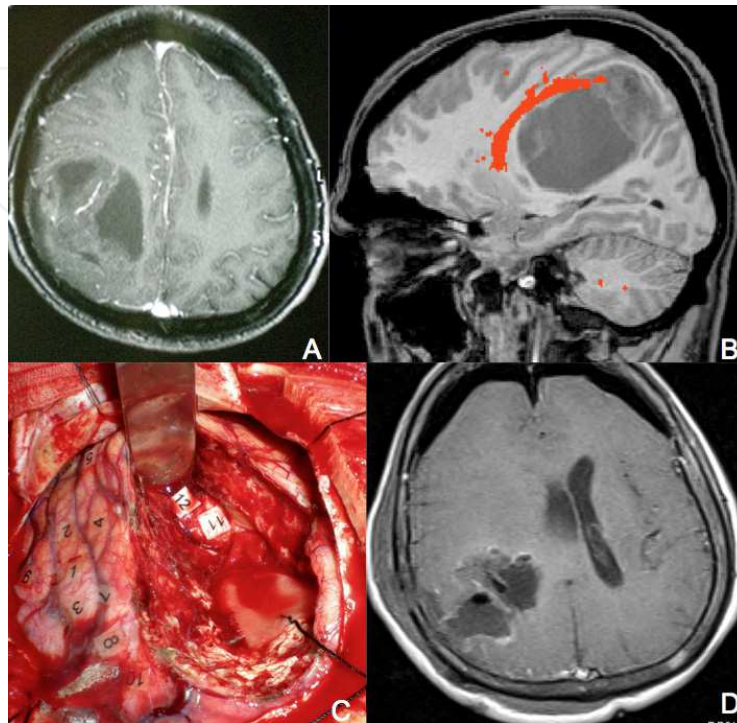

Fig. 2. (A) Male, 43 years old. Preoperative MR showing a large and partly cystic oligodendroglioma (WHO III) in the central area. (B) DTI-FT demonstrates the displacement of the pyramidal tract anteriorly and the close contact to the cystic portion of the tumor. (C) Intraoperative image demonstrating the presence of talamo-cortical fibers at the subcortical level in the anterior aspect of the surgical cavity (11, 12 paraesthesia of the shoulder and neck). (D) On immediate postoperative MRI there was no residual tumor and the patient had no postoperative deficit confirming the DTI-ft hypothesis that the tract was neither damaged nor infiltrated.

DTI compared to the postoperative MRI and intraoperative stimulation results (fig. 3). A typical image featured a white matter bundle in close vicinity to the tumor without any information on how much of the pathway or pathway function was invaded. 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 to begin fiber tracking. 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) with the target ROI in the cerebral peduncle (Schomberg et al. 2006; Smits et al. 2007; Staempfli et al. 2007). Also notable is that in language areas, DTI might emphasize the presence of white matter tracts when subcortical stimulation did not show a zone of positive response, favoring an unnecessarily conservative surgery, whereas direct stimulation would have indicated removal of the entire portion of non-eloquent tissue. More recent advances in

calculation and characterization of fractional anisotropy have allowed for a more precise reconstruction of the white matter bundles by depicting complex distributions of intravoxel fiber orientation. This new algorithm, called diffusion spectrum imaging (DSI), is a very promising technological advancement (Kuo et al. 2008; Wedeen et al. 2008, Canales-Rodríguez et al. 2010), but unfortunately these methods require very long sessions (up to 60 minutes) of MR scanning that are sometimes unsuitable for patients.
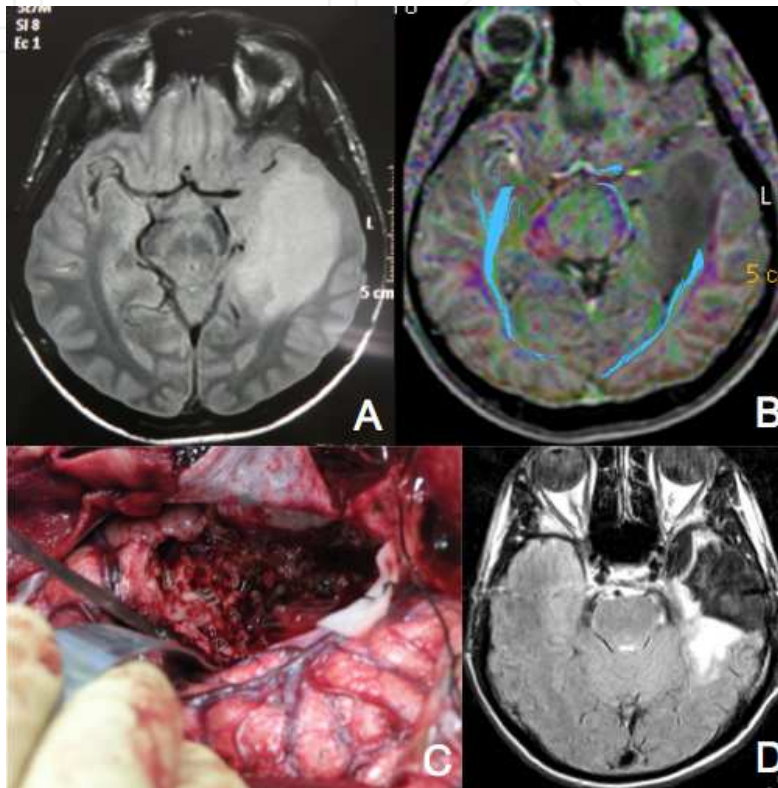
Fig. 3. Man, 42 years old. Three episodes of absence. A) On preoperative MR a temporal mass is demonstrated. B) DTI showed a fascicle just beside the mass that seemed interrupted. No other tract was visualized inside the tumor. By looking at the position and direction, this bundle was referred to the inferior longitudinal fasciculus (ILF). C) CSES confirmed at the subcortical level of naming disturbances (8, 9, 10, 11); consequently resection was arrested, and no language deficit was diagnosed at follow-up. (D) Postoperative MRI confirmed the subtotal resection as well as the functionality of the infiltrated white matter although DTI-FT showed absence of fibers.

4. Intraoperative brain mapping: Awake surgery and cortical and subcortical electrical stimulation (CSES)

4.1 Introduction and indications

Direct electrical stimulation of the brain surface is a technique that has regained greater interest worldwide in the past decade than it has had since its introduction by Foerster, Penfield and Rasmussen in 1930 (Foerster 1931, Penfield & Boldrey 1937, Penfield & Erickson 1941, Penfield & Rasmussen 1950). More recently Berger introduced the technique of subcortical stimulation to spare functional white matter bundles that are very often infiltrated by gliomas (Berger 1994). Indeed, refinement of technical equipment and, mostly, the

availability of ultra-short acting anesthetics and new analgesics, have given a strong impetus to the revival of awake surgery and CSES. The goal of CSES is to detect the areas of the brain that are necessary to a given function. The stimulation of neurons provokes either a positive effect (i.e. movement on contralateral muscles or dysaesthesias) or a suppressive effect (speech arrest, anomia, anarthria). In both cases the aim is to define the effect of the resection of that part of brain in order to avoid deficits. The main use of CSES is for intrinsic brain tumors because cortical and mostly subcortical boundaries are very often impossible to define. Moreover, it has been demonstrated that gliomas are frequently located in eloquent areas, thus they are sometimes treated with only a biopsy or a very limited resection. The availability of the direct control of functional topography during surgical tumor resection not only gives the opportunity to avoid permanent neurological impairment, it can also facilitate a larger extirpation. During resection of a tumor, the surgeon does not have to follow anatomical limits, but will follow functional boundaries (Fig. 4). CSES makes it possible to continuously check the integrity of a circuitry at both the cortical and the subcortical level. The ability to maximize resection while preserving a satisfying functional outcome is of particular interest in brain gliomas for two reasons: first, gliomas mostly affect young adults in full social and working activity, so functional outcome is of the utmost relevance. Second, many different studies (Berger 1994; Keles et al. 2001; Sanai & Berger 2009; Stendel 2009) have by now demonstrated that total or subtotal resection has a clear impact on survival and, for LGG (low grade glioma), on malignant transformation, and that the extent of resection is strongly affected by eloquence of the tumor location (Chang et al. 2008).
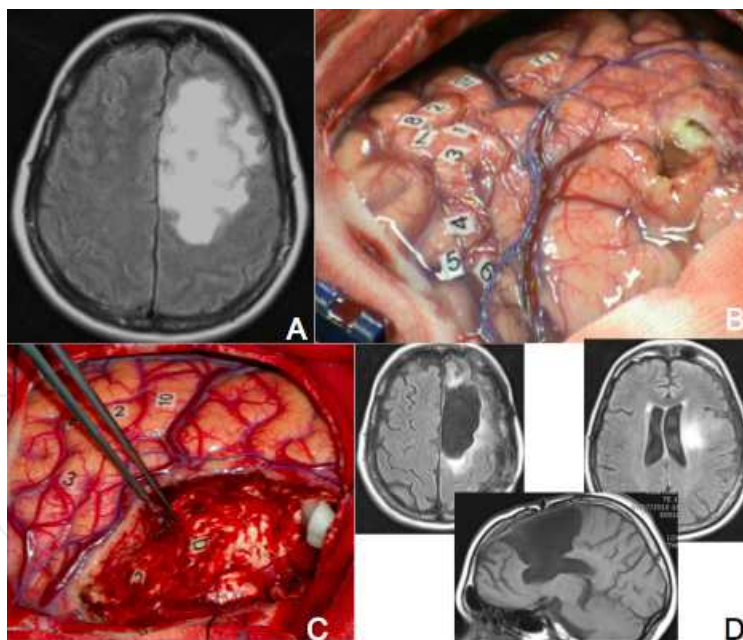

Fig. 4. Female, 38 years old suffering from seizures. (A) Preoperative FLAIR MR showing a left large premotor low grade glioma invading also the supplementary motor area. B) Intraoperative picture: the blue line surrounds the tumor cortical margins. 1, 2, 3, 7, 8: motor area of the face; 10: anartria with face contraction; 4, 5, 6: motor area of the hand. 11: speech arrest). No functional site (neither motor nor language) was detected on the surface of the tumor. C) At subcortical level, resection was stopped when descending motor pathway were stimulated (D and C). D) Postoperative MR showing a residue of tumor on the posterior part of the cavity infiltrating descending motor pathways.
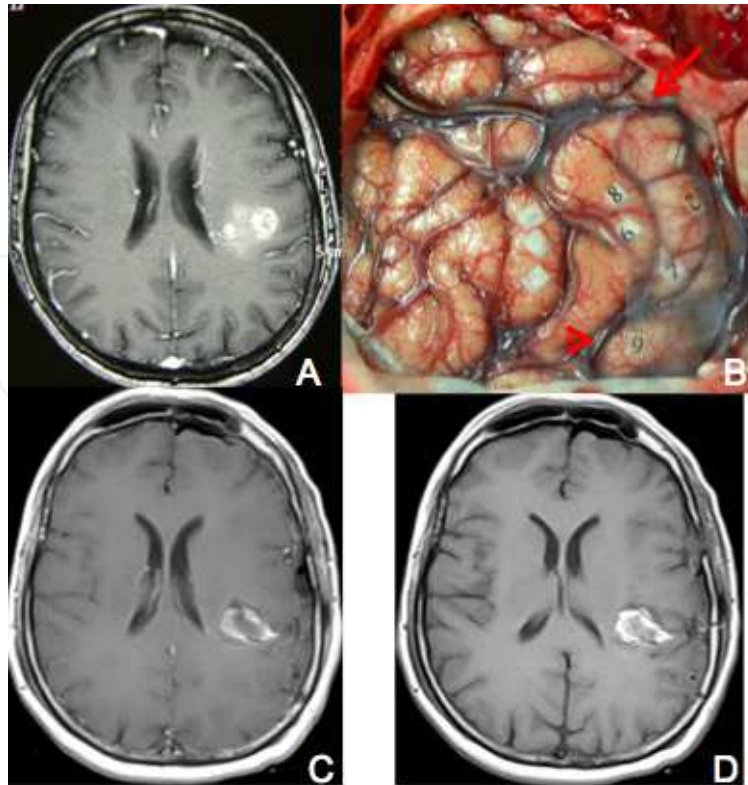
Fig. 5. 63 y.o. woman, transient speech disturbance. A) Preoperative contrast enhanced MR showing an inhomogeneous mass in the white matter of the left fronto-parietal passage. B) Intraoperative picture after cortical mapping (1, 2 speech arrest; 7 anartria; 6 motor area of the mouth; 8, 9 anartria). *Red arrow*: sylvian fissure; *red arrow-head*: central sulcus. The white tags show an area of negative mapping that was chosen to reach the subcortical tumor. Postoperative MR (C with gadolinium and D without) showing complete removal of the tumor. The patient did not present speech disturbance.

In some cases, CSES can also guide in the detection of the safest route for removing purely subcortical tumors. In these circumstances, the surgeon will choose a non-responsive cortical area to perform cortectomy and then will follow a subcortical corridor by alternating stimulation and dissection until the tumor is exposed. Then resection continues, together with the stimulation and monitoring of neurological function of the patient even during stages of non-stimulation (see fig. 5).

From a practical point of view, indication for an awake surgery and CSES is primarily based on the localization of the tumor on an anatomical MR followed by confirmation of the activation pattern on fMR. Typical regions that should be considered for intraoperative mapping are the central regions (sensory-motor areas) on both the dominant and non-dominant hemispheres. Preoperative neurological evaluation is fundamental to detect any sensory, coordination or muscles strength disturbance. For non-dominant hemisphere tumors in the occipito-temporo-parietal junction we also perform a global neuropsychological evaluation of the visuo-spatial abilities (Rey's tangled figures test, copying, spontaneous drawing, clock drawing test, apraxia tasks, line cancellation test, line bisection test, Diller's letter cancellation test, line completion test). It has been established that awake surgery is mandatory since the patient will experience subjective dysaesthesias and will interact with the surgeon, for motor areas there is still debate. In many centers

worldwide, neurosurgeons prefer not to operate on awake patients for tumors in motor areas. They argue that the motor responses such as the contraction of muscles do not require a conscious patient. For motor stimulation in an anesthetized patient either the motor evoked potentials (MEPs) method (Kombos et al. 2001; Fujiki et al. 2006; Yoshikawa et al. 2006) or CSES can be chosen. For the former it must be noted that only the action potentials of selected muscles can be controlled, which may hamper both the detection and the avoidance of motor deficits in non-monitored muscles. Furthermore, no information is obtained on the function of cortex adjacent to the central region, and intraoperative evoked potentials presently cannot be used to perform mapping of language or other higher functions. Concerning CSES and the sleeping patient, higher currents are normally required for stimulation, leading to a higher number of intraoperative seizures that can reduce the reliability of mapping. In our experience (Spena et al. 2010) mapping of the motor cortex in an awake patient guarantees more precise cortical and subcortical mapping with a very low risk of intraoperative seizures.

When the tumor is located in the so-called "language areas" (dominant perisylvian, posterior part of F1 and F2, premotor cortex, inferior parietal, posterior temporal, and insular lobes) the first step is to document the hemispheric dominance. A neuropsychological assessment (handedness tests by Edinburgh inventory) and the fMR are sufficient to establish dominance (Stippich et al. 2007). In addition, a detailed and extensive language assessment (Aachen Aphasia Test; WAISS) is necessary to highlight possible subclinical language deficit and to prepare the patients for the intraoperative tests (reading, pictures naming, famous faces naming, counting). At our institution patients with severe motor deficit or language impairments that do not improve after one week of steroid therapy are not considered for awake surgery. This is particularly true for high grade gliomas (HGG) in eloquent areas that more often present with some kind of clinical symptom. These cases merit special consideration because of their natural history and very low survival. In these patients we prefer not to attempt extirpation in cases of low performance status (<70 KPS or >3 Rankin score) unresponsive to steroid drugs; however, we may decide to perform a biopsy. Operating on delicate brain regions often produces a transient deterioration in postoperative status related mostly to manipulation and inflammation, and the presence of rapidly evolving tumors can further impede recovery. Therefore, we can anticipate that a more careful selection of patients with high-grade gliomas located in very delicate regions is the best way to prevent unsatisfying results.

Neurological and neuropsychological tests have a prominent role when treating eloquent area tumor because of different reasons. In general, accumulating information about preoperative neurological and neuropsychological status of the patient gives a great opportunity not only to better document the clinical course and improvements, but also to study the biological behavior of the tumor. In fact, the relapse of a tumor or the passage to a higher grade of malignancies is sometimes predicted by even subtle changes in neuropsychological performance. Moreover, it's fundamental to correlate intraoperative findings with postoperative tests in order to create robust outcome measurements and to document that the resection of a "negative" site has no actual negative effect. That's why tests must be repeated in the early postoperative period (7-10 days) and at least after 3 and 6 months.

Once the surgeon has established the indication for awake surgery, it is very important to consider the patient's general status as well as the psychological profile. In Table 1, some

general and anaesthesiological factors that can contraindicate awake surgery are summarized. The idea of undergoing an awake surgery is a source of anxiety for psychologically intact patients. It is essential that a thorough and clear relationship between medical staff and the patient is established and that the patient is correctly informed about every event that he or she is going to experience. Different authors have demonstrated that good preoperative communication is even more effective in alleviating anxiety than preoperative sedative drugs (Egbert 1963; Aglio 2001).

Severe cardio-pulmonary dysfunction (>ASA 3)
Factors predicting difficult intubation
Prior difficult intubation
Claustrophobia
Generalized anxiety disease
Severe obesity
Sleep apnea

Table 1. General and anesthesiology factors contraindicating awake surgery.

4.2 Anesthesia and surgical techniques

The goal of anesthesia is to obtain an easily reversible sedation while maintaining spontaneous respiration. We do not use tracheal masks or other intubation devices. Two large bore venous accesses are sufficient and intra-arterial pressure monitoring is required. Positioning on the operating table is very important and the patient must feel comfortable in order to avoid pain or the need to continuously move. We usually prefer lateral decubitus with the contralateral arm and leg free from drapes so that reaction during stimulation can be easily detected. In men, a urethral catheter is avoided and a condom-like urine reservoir ("Texas catheter") is applied instead. Scalp anesthesia is achieved through nerve block by infiltration of levobupivacaine (0.75%) and mepivacaine (1%). During craniotomy, we sedate spontaneously breathing patients with intravenous remifentanil (0.01 to 0.08 mg/Kg/min) and propofol (0.3 to 1 mg/Kg/h), continuously throughout the procedure. Lidocaine filled cotton paddies are used to locally anesthetize the dura. Before opening the dura, drugs are arrested and the patient is completely awakened. At this time a rapid check of responsiveness and collaboration as well as control of comfort and pain is very important. In case of pain and depending on the site of pain, local anesthetics or intravenous low dose remifentanil is administered.

The craniotomy is targeted to expose the area of the tumor and the motor and/or sensory strips upon which current intensity will be determined by establishing the minimum current required to generate a movement or a dysaesthesia. If the tumor is not visible at the cortical surface, it is important to delineate the superficial projection of its boundaries by using a neuronavigation system or an ultrasound. A bipolar fork, measuring 6 mm in distance between the electrodes (Nimbus, Newmedic, Labege, France), is used to deliver a non-deleterious, biphasic square-wave current in 4-second trains at 60 Hz. We start stimulation at 1 mA and increase by increments of 0.30 mA until the initiation of contralateral face or upper limb movements and paresthesias. Normally no more than 4 mA are necessary to have a positive response. In our experience, factors necessitating higher current intensity are large or deep-seated tumors and the presence of edema. Every positive site is restimulated

to confirm reproducibility of the response. Once the proper current intensity is set, the entire surface of the tumor is thoroughly examined in order to exclude the presence of functional sites. 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, anarthria, anomia, or reading errors). These same tests are administered the day before surgery in order to detect baseline errors or hesitations that could be misinterpreted during intraoperative stimulation. Intraoperatively, 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 area, the patient rests for a while, then spontaneous speech and slide reading are tested, and stimulation starts again. Every time a positive response is encountered, a numbered tag is left in place and the function associated to the stimulation of that point is recorded. If the tumor is separated from a functional gyrus by a sulcus, maximal attention is paid in order to respect the arachnoid plane and the vasculature of the sulcus. If the tumor invades functional gyri or subcortical functional tracts, the resection must to be very careful since no anatomical limit is present between the infiltrated parenchyma and the normal functioning cortex. In these situations as well as for subcortical tumors, we test language or motor function throughout the resection even when no stimulation is applied, stopping whenever anomalies appear. Many authors have for a long time postulated a need to maintain a safe distance of at least 1 cm from a functional site (Haglund et al. 1994; Carrabba et al. 2007; Sanai & Berger 2008). More recently, this concept has been evolving because accumulated experiences have clearly demonstrated that continuous cortical and subcortical stimulations can enable the surgeon to identify and preserve eloquent cortex and the white matter bundles. Abandoning the idea of leaving a "safe margin" in favor of reaching functional boundaries yields an increase of the extent of resection, and thus, it is believed, has an increased impact on the natural history of the tumor. This more aggressive strategy is related to a higher percentage of transient postoperative neurological deficits, but it has also led to very satisfying long-term neurological outcomes (Gil-Robles & Duffau 2010).

In order to collect the largest amount of information about the unique functional organization of each individual patient, it is very important to record all the possible data from pre-, intra- and postoperative observations, including intraoperative photographs or films and, in cases of language area tumors, recordings of patients' voices. It also is important to register parameters such as current intensity, reproducibility of stimuli, and seizure occurrence, as well as the degree of pain control (at minimum a visual analog scale should be checked) and other anesthesiology concerns, such as nausea, vomiting, and need for respiratory support or for switching to general anesthesia.

5. Brain mapping in neurosurgery: Criticisms and future perspectives

Ideally, neurosurgeons could detect and locate the exact position of brain functions before performing tumor resection, allowing them to recommend 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 yet available, but major advances have been made since the days when neurosurgeons performed brain surgery only via anatomical references.

Undoubtedly, CSES has gained a prominent role in neurosurgery above all because a large number of studies worldwide have shown a clear advantage in terms of usefulness, safety, and neurological and oncological outcomes (Berger 1994; Duffau et al. 2005; Duffau 2006; Kim et al. 2009; Sanai & Berger 2009; De Benedictis et al. 2010; Spena et al. 2010). The spatial accuracy and the ability to perform functional resection (that is, a resection in which limits are represented by spared functions) have met the approval of many neurosurgeons, who now use CSES routinely. However, there are some technical and methodological drawbacks of CSES that have yet to be addressed. First, the application of an electric current on the brain can have effects that are more complex than anticipated. For example, the excitation of the stimulated cortex can diffuse to near or far cortex by short or long-range white matter tracts. Consequently, the observed effect of the stimulation may not be related (or not only) to that portion of a gyrus. In this case the tumor resection might be prematurely arrested. At the same time, at which point is the surgeon sure that a functional area is essential and cannot be substituted by other epicenters? The concept of plasticity can explain recovery after various brain injuries, but the stimulation of a functional site intraoperatively cannot give information about the brain's potential to substitute that site. Another highly debated issue in CSES is the technique of negative stimulation, which means pursuing resection where no positive site is detected. Although results of such strategy have been encouraging (Sanai & Berger 2008; Kim et al. 2009), the question arises concerning the possibility of missing a positive site because of a false negative result during the intraoperative tests. This is especially true for cognitive functions, given that an awake patient has a limited time span for testing before fatigue arrives (normally no more than 90 minutes in our experience). Further, intraoperative cognitive tests (language, calculation, writing, visuo-spatial abilities) are limited to very simple tasks that cannot account for more complex functions. From this point of view, fMR allows a more comprehensive analysis of brain function because all the epicenters involved during a specific task are visualized and a real-time mapping is generated. If this represents a limitation of the spatial accuracy of fMR for surgical planning, at the same time it offers a means to non-invasively study a patient pre- and postoperatively, which is undoubtedly a unique opportunity to gain precious insights into functional organization and post-lesional adaptation at the individual level.

Direct mapping methods such as CSES are, at the moment, the safest procedures to achieve the most extensive resections with controllable risks. 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 to safely guide maximal resection and to guarantee a satisfying neurological outcome. It is unlikely that the study of functional connectivity and the longitudinal modification of brain maps will leave behind the integration of repeated fMR. This multimodal approach is more aggressive, leads to better outcomes, and should be used routinely for resection of lesions in eloquent brain regions.

It is probably no longer necessary to compare different methods of brain mapping because of their intrinsically different functioning; rather, we propose that now it would be most desirable to share preoperative (fMR, DTI, and neuropsychology) and postoperative protocols in order to accumulate a major cohort of patients in multicenter studies. At the same time, results of intraoperative stimulations should be well documented and standardized to create a common comprehensive database of intraoperative brain mapping results.

6. References

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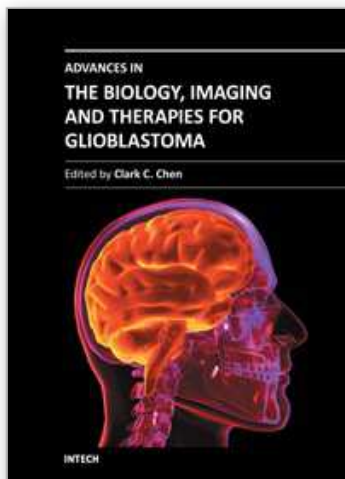
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