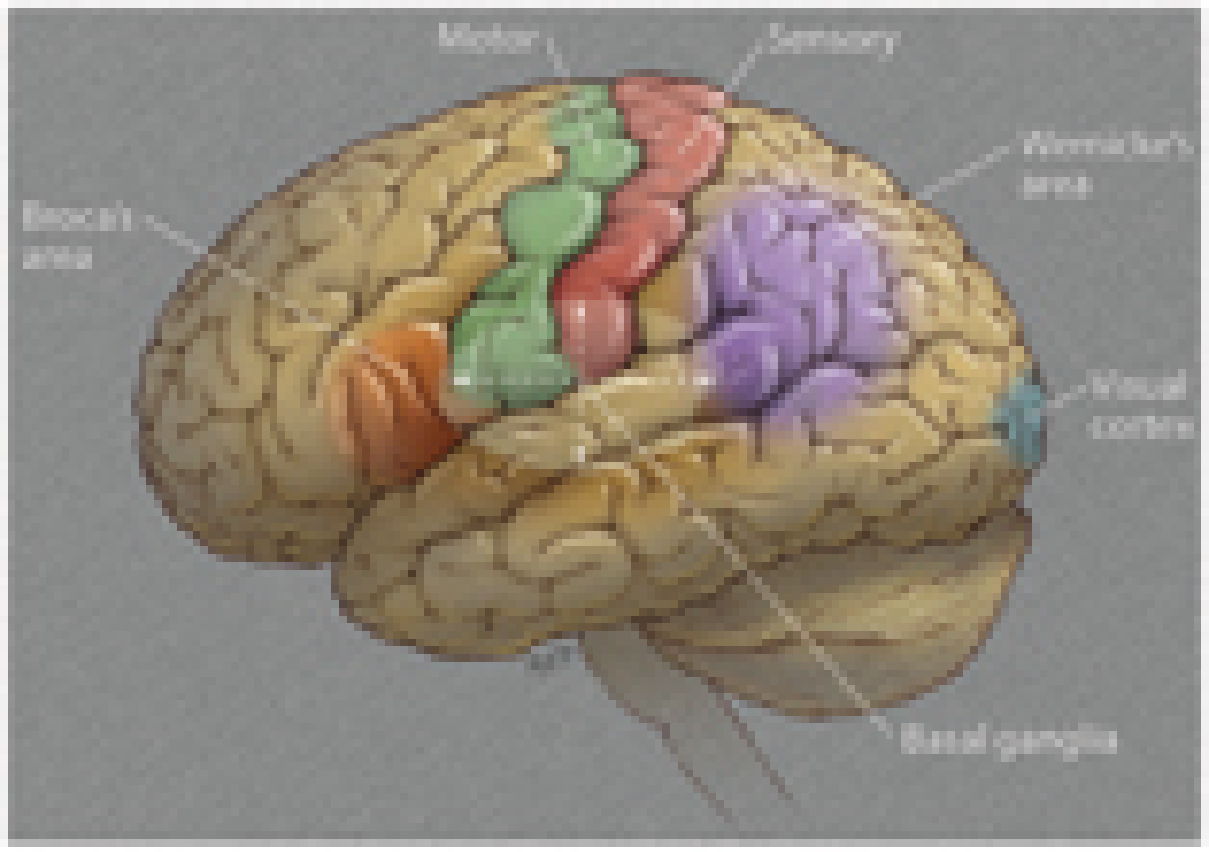
Motor
Sensory
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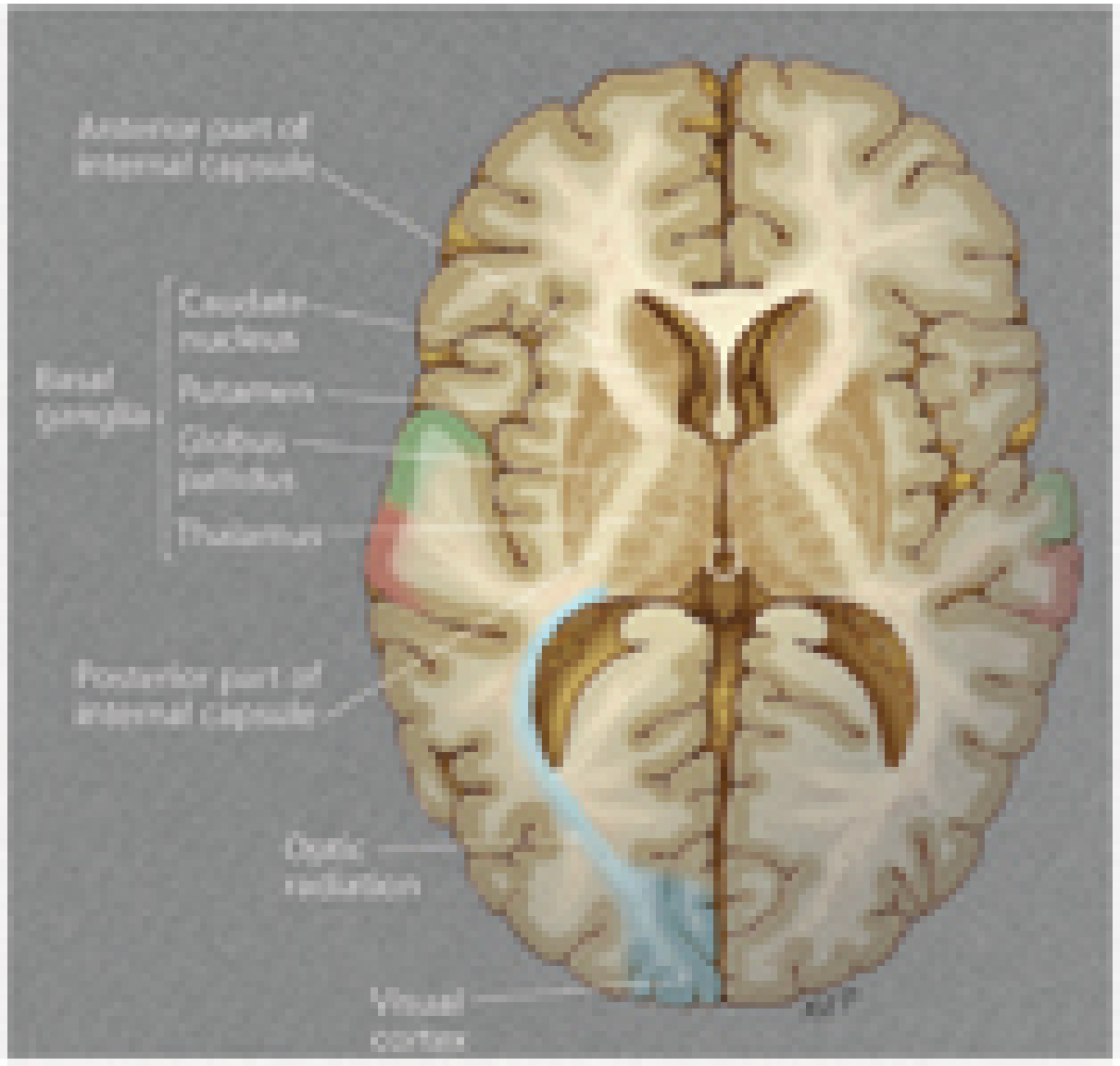
Broca's area
Visual cortex
Basal ganglia


Anterior part of internal capsule
Basal ganglia
Caudate nucleus
Putamen
Globus pallidus
Thalamus
Posterior part of internal capsule
Optic radiation
Visual cortex

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Introduction. Surgery of gliomas in eloquent areas: from brain hodotopy and plasticity to functional neurooncology

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In this issue of *Neurosurgical Focus*, the dilemma of the surgery for glial tumors in eloquent areas—with the goal to maximize the extent of resection while preserving or even improving the cerebral function—is covered from different aspects. Although the surgery has been a matter of debate for a long time, recent series have shown the significant impact of surgery on the natural history of low-grade[7] and high-grade gliomas.[8]

An in-depth knowledge of the anatomy of the CNS is crucial with regard to cortical (gyri and sulci) and subcortical (especially white matter pathways) structures. Nevertheless, because of the major interindividual anatomofunctional variability, relying solely on neuroanatomy is not sufficient to predict eloquence and thus to avoid the risks of postoperative permanent deficits. Recent advances in brain mapping methods have enabled a better understanding of brain processing in allowing us to identify the unique variations in patients. Functional neuroimaging and fiber tractography may help to identify eloquent areas before surgery, and they can be integrated into a multimodal neuronavigational system during resection. However, it is worth noting that these techniques are not yet reliable enough, especially methodologically regarding the selection of tasks, choice of biomathematical model, and in cases of glioma, neurovascular decoupling. Thus, intraoperative electrophysiological techniques (monitoring and electrostimulation mapping, particularly in awake patients) are still the gold standard for surgery of gliomas in eloquent structures. These techniques allow the detection of functional cortical areas as well as subcortical connectivity, on the condition that a rigorous methodology is applied. Therefore, it is possible to tailor the tumor resection according to individual functional boundaries to optimize the benefit/risk ratio of the surgery, namely to extend the surgical indications within regions usually considered inoperable (such as the Broca area, the central area, or the insula) and to increase the extent of resection by avoiding leaving a margin around the crucial areas while decreasing the rate of permanent deficit (< 2% in the recent literature) and even improving the quality of life of patients (particularly regarding seizure relief).[5]

In addition, a combination of these various techniques of pre-, intra-, and postoperative mapping is able to provide new insights into the anatomofunctional organization of the brain. It opens the door to the concept of brain "hodotopy" and plasticity, that is, a dynamic organization of the CNS constituted by parallel distributed networks that are interconnected and able to compensate themselves.[1,2] This plastic potential, which implies that the subcortical connectivity must be preserved, now makes it possible to consider a multistage surgical approach in tumors involving eloquent areas, especially in slow-growing lesions such as low-grade gliomas. The principle is to perform a second (or even a third) surgery after glioma regrowth in cases in which the first resection was incomplete for functional reasons. Indeed, it is possible the second time to improve the extent of tumor removal thanks to functional remapping over time. This reshaping can be induced by the first surgery itself, the tumor regrowth, and also partly by adapted programs of rehabilitation following the first operation.[6] Finally, from a fundamental point of view, such methodological and conceptual developments also participate in the better understanding of the neural foundations underlying cerebral processing. Nonetheless, ethical aspects of invasive human brain mapping must not be forgotten, given that the first goal of surgery is to be beneficial for the patient. To this end, longitudinal neuropsychological assessments, before and after each surgery, should be performed more systematically.[4]

In summary, neurosurgeons must now consider both the median survival and the quality of life to move toward a functional neurooncology.[3]

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Intraoperative stimulation techniques for functional pathway preservation and glioma resection

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Although a primary tenet of neurosurgical oncology is that survival can improve with greater tumor resection, this principle must be tempered by the potential for functional loss following a radical removal. Preoperative planning with functional and physiological imaging paradigms, combined with intraoperative strategies such as cortical and subcortical stimulation mapping, can effectively reduce the risks associated with operating in eloquent territory. In addition to identifying critical motor pathways, these techniques can be adapted to identify language function reliably. The authors review the technical nuances of intraoperative mapping for low- and high-grade gliomas, demonstrating their efficacy in optimizing resection even in patients with negative mapping data. Collectively, these surgical strategies represent the cornerstone for operating on gliomas in and around functional pathways. *(DOI: 10.3171/2009.12.FOCUS09266)*

Key Words • **language mapping** • **motor tract** • **cortical stimulation** • **extent of resection**

Central nervous system tumors are a major cause of morbidity and death, with ~ 18,000 new cases of primary intracranial tumors diagnosed each year in the US. This represents ~ 2% of all tumors found in adults in this country. More than half of these are HGGs. These lesions are extremely aggressive and the vast majority of patients invariably have tumor recurrence, with the median survival time ranging from 1 to 3 years after initial diagnosis. Despite facing a better prognosis when compared with higher-grade glial tumors, 50–75% of patients harboring LGGs eventually die of their disease. Median survival times have been reported to range between 5 and 10 years, and estimates of 10-year survival rates range from 5 to 50%.

Although a primary tenet of neurosurgical oncology is that survival can improve with greater tumor resection, this principle must be tempered by the potential for functional loss following a radical removal. Current neurosurgical innovations aim to improve our anatomical, physiological, and functional understanding of the surgical region of interest to prevent potential neurological morbidity during resection. Emerging imaging technologies, as well as state-of-the-art intraoperative techniques, can facilitate a greater extent of resection while minimizing the associated morbidity profile. Specifically, the value of mapping motor and language pathways is well established for the safe resection of intrinsic tumors.

Interestingly, controversy persists regarding prognostic factors and treatment options for both low- and high-grade hemispheric gliomas. Among the various tumor- and treatment-related parameters—including tumor volume, neurological status, timing of surgical intervention, and the use of adjuvant therapy—patient age and tumor histological characteristics have been identified as primary predictors of patient prognosis. However, location of the tumor in an eloquent area (Fig. 1) has recently emerged as another critical factor affecting outcome, particularly as it relates to tumor extent of resection.[10] Importantly, despite significant advances in operative technique and preoperative planning, the effect of glioma extent of resection in prolonging tumor-free progression and/or survival remains unclear. Although the value of glioma resection in obtaining tissue diagnosis and decompressing mass effect are unquestionable, a lack of Class I evidence prevents similar certainty in assessing the influence of extent of resection. Even though LGGs and HGGs are distinct in their biological features, clinical behaviors, and outcomes, understanding the effect of surgery remains equally important for both. This is also true for lesions in areas of eloquence, where the proximity of critical pathways, often related to language and motor function, can present a significant challenge to standard operative strategies.

Abbreviations used in this paper: CS = cortical stimulation; DT = diffusion tensor; fMR = functional MR; HGG = high-grade glioma; LGG = low-grade glioma.

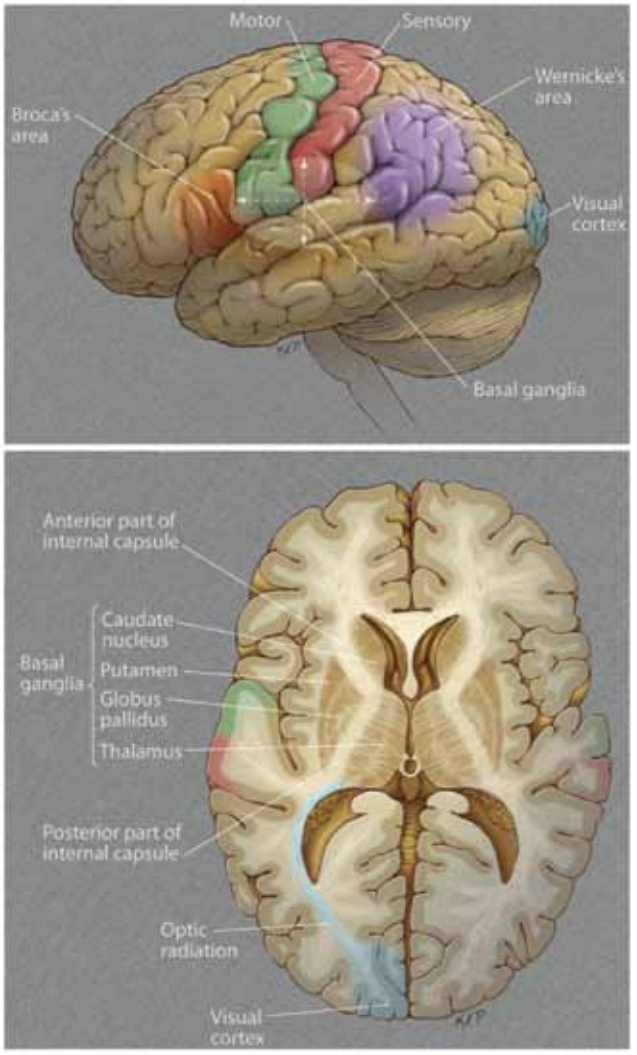

Fig. 1. Illustration of eloquent cortical and subcortical sites in the supratentorial compartment. (Reprinted by permission. Originally published in Chang et al.: Preoperative prognostic classification system for hemispheric low-grade gliomas in adults. **J Neurosurg 109:**817–824, 2008.)

Evolution of Cortical Mapping Strategies

Direct CS has been used in neurosurgery since 1930, first by Foerster,[26] and then later by Penfield and colleagues.[72–74] In recent years, the technique of intraoperative CS has been adopted for the identification and preservation of language function and motor pathways. Stimulation depolarizes a very focal area of cortex, which in turn evokes certain responses. Although the mechanism of stimulation effects on language are poorly understood, the principle is based on the depolarization of local neurons and also of passing pathways, inducing local excitation or inhibition, as well as possible diffusion to more distant areas by way of orthodromic or antidromic propagation.[85] Studies in which optical imaging of bipolar CS was used in monkey and human cortex have shown precise local changes, within 2–3 mm, after the activation of cortical tissue.[30,31] With the advent of the bipolar probe, avoidance of local diffusion and more precise mapping have been enabled with an accuracy estimated to be ~ 5 mm.[30]

Language mapping techniques were historically developed in the context of epilepsy surgery, in which large craniotomies exposed the brain well beyond the region of surgical interest to localize multiple cortical regions containing stimulation-induced language and motor function (that is, "positive" sites) prior to resection. Until recently, it has been thought that such positive site controls must be established during language mapping before any other cortical area could be safely resected. Using this tactic, awake craniotomies traditionally identify positive language sites in 95–100% of the operative exposures. Brain tumor surgery, however, is now evolving toward a different standard of language mapping, in which smaller, tailored craniotomies often expose no positive sites, and tumor resection is therefore directed by the localization of cortical regions that when tested contained no stimulation-induced language or motor function (that is, "negative" sites). This "negative mapping" strategy represents a paradigm shift in language mapping technique by eliminating the neurosurgeon's reliance on the positive site control in the operative exposure, thereby allowing for minimal cortical exposure overlying the tumor, less extensive intraoperative mapping, and a more time-efficient neurosurgical procedure.

Variability in Cortical Language Localization

Prediction of cortical language sites based on classic anatomical criteria is inadequate in light of the significant individual variability of cortical organization,[35,64,66,70] the distortion of cerebral topography from tumor mass effect, and the possibility of functional reorganization through plasticity mechanisms.[71,95,121] A consistent finding of language stimulation studies has been the identification of significant individual variability among patients.[64] Speech arrest is variably located and can go well beyond the classic anatomical boundaries of the Broca area for motor speech. It typically involves an area contiguous with the face-motor cortex, and yet in some cases is seen several centimeters from the sylvian fissure. This variability has also been suggested by studies designed to predict the location of speech arrest preoperatively, based on the type of frontal opercular anatomy[83] or by using functional neuroimaging.[15,43,94,105,111–113] Similarly, for temporal lobe language sites, one study of temporal lobe resections assisted by subdural grids demonstrated that the distance from the temporal pole to the area of language function varied from 3 to 9 cm.[14] Functional imaging studies have also corroborated such variability.[25] Furthermore, because functional tissue can be located within the tumor nidus,[102] the standard surgical principle of debulking tumor from within to avoid neurological deficits is not always safe. Consequently, the use of intraoperative cortical and subcortical stimulation to detect functional regions and pathways accurately is essential for safely removing dominant-hemisphere gliomas to the greatest extent possible.

Preservation of Functional Pathways by Using Intraoperative Stimulation Mapping

Intraoperative CS has yielded critical data regarding essential language sites, which seem to be organized in discrete mosaics that occupy a much smaller area of cortex than described by traditional language maps.[65,67,69] Interestingly, the majority of these language sites are surrounded by cortex that, when stimulated, produce no language errors.[68] In the temporal lobe, identification of speech areas within the superior and middle temporal gyri has been documented within 3 cm of the temporal lobe tip.[64] In this region, the distance of the resection margin from the nearest language site is the most important variable in predicting the improvement of preoperative language deficits. Accordingly, if the distance to the resection margin from the nearest language site is > 1 cm, significantly fewer permanent language deficits occur.[29] Strict adherence to this principle when operating in any region of the dominant hemisphere can substantially reduce the risk of inadvertently resecting functional tissue.

The Role of Functional Imaging for Eloquent Tissue Localization

Because the need to preserve cortical language function must be balanced with the goal of maximal tumor resection, intraoperative language mapping is advocated by some as the rule, rather than the exception.[108] The greatest risk of tumor recurrence is located within 2 cm of the contrast-enhancing rim on imaging studies,[37,117] supporting the concept that the resection should ideally go beyond the gross tumor margin apparent on preoperative imaging. However, because of the infiltrating nature of gliomas, it is more than likely that a portion of the mass will occupy, or be continuous with, functional tissue. Again, this emphasizes the need for CS mapping to avoid injuring these critical areas, particularly language pathways. Although it was classically thought that patients who were neurologically intact or minimally affected preoperatively had their functional pathways either displaced or obliterated by infiltrative tumors, we now know that normally functioning language, motor, or sensory tissue can blend with tumor.[102] Therefore, it is not only patients with tumors located within the frontal operculum who benefit from intraoperative language mapping, but also those with lesions in proximity to this region, because there is significant variability in this region's anatomical and functional organization.[23,83]

Functional imaging has advanced considerably in both technology and availability, raising the question of whether it may supplant intraoperative CS mapping. Devices such as fMR imaging, PET, and magnetoencephalography units may aid in the preoperative planning of the resection strategy, but these techniques remain too imprecise for complex functions such as language mapping: their sensitivity (PET, 75%; fMR imaging, 81%) and specificity (PET, 81%; fMR imaging, 53%) are suboptimal.[25,34] These modalities highlight language-associated areas of indeterminate significance,[7] and they do not offer real-time information intraoperatively. To this end, MR neuronavigational techniques not only facilitate greater resection, but embedding of DT imaging–based tractography can prevent inadvertent resection of adjacent subcortical pathways.[107,120] In a recent study of 238 patients with glioma who were randomized to DT imaging–based imaging versus traditional MR neuronavigation with DT imaging, postoperative motor deterioration occurred in 32.8% of control cases, whereas it occurred in only 15.3% of the study cases. Although the use of DT imaging–based tractography has not been shown to impact patient survival directly, the literature highlights the utility of this technology in maximizing tumor resection while minimizing morbidity. Nevertheless, for the identification of functional language pathways and guidance of safe tumor removal, these diagnostic imaging tools are still only supplements, not substitutes, for direct intraoperative stimulation mapping.

Current Intraoperative Language and Motor Mapping Techniques

In general, a limited craniotomy should expose the tumor and up to 2 cm of surrounding brain. Using bipolar electrodes, cortical mapping is started at a low stimulus (1.5 mA) and increased to a maximum of 6 mA, if necessary. A constant-current generator delivers biphasic square wave pulses (each phase, 1.25 msec) in 4-second trains at 60 Hz across 1-mm bipolar electrodes separated by 5 mm. Stimulation sites (~ 10–20 per patient) can be marked with sterile numbered tickets. Throughout motor and language mapping, continuous electrocorticography should be used to monitor afterdischarge potentials, and therefore eliminate the chance that speech or naming errors are caused by subclinical seizure activity.

Awake CS and Impact of Language Mapping

Speech arrest is based on blocking number counting without simultaneous motor response in the mouth or pharynx. Dysarthria can be distinguished from speech arrest by the absence of perceived or visible involuntary muscle contraction affecting speech. For naming or reading sites, CS is applied for 3 seconds at sequential cortical sites during a slide presentation of line drawings or words, respectively. All tested language sites should be repeatedly stimulated at least 3 times. A positive essential site can be defined as an inability to name objects or read words in 66% or more of the testing per site. In all cases, a 1-cm margin of tissue should be measured and preserved around each positive language site to protect functional tissue from the resection.[49] The extent of resection is directed by targeting contrast-enhancing regions for high-grade lesions and T2-hyperintense areas for low-grade lesions. Some groups advocate the use of language mapping along subcortical white matter pathways as well.[19,21]

Despite the considerable evidence supporting the use of intraoperative CS mapping of language function, the efficacy of this technique in preserving functional outcome following aggressive glioma resection remains poorly understood. Nevertheless, it is important to define the long-term neurological effects after using this tech-

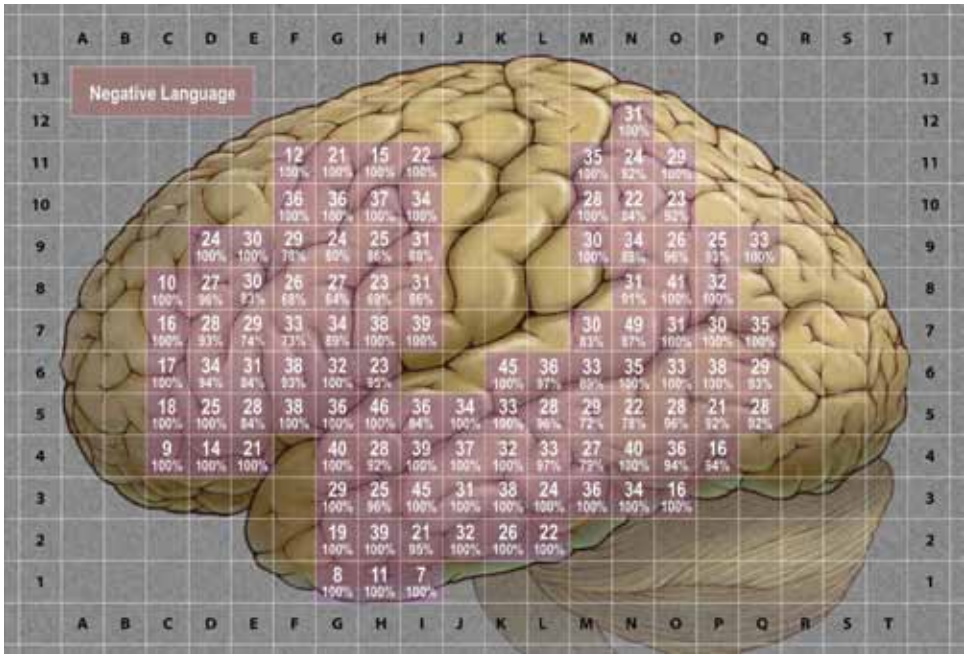

Fig. 2. Negative language map indicating the percentage of negative stimulations per square centimeter of the dominant cerebral hemisphere. (Reprinted by permission. Adapted with permission from Fig. 2 in Sanai et al.: Functional outcome after language mapping for glioma resection. **N Engl J Med 358:**18–27, 2008. Copyright © 2008, Massachusetts Medical Society. All rights reserved.)

nique for large, dominant-hemisphere gliomas to advocate its use accurately.[88]

Our experience with 250 consecutive patients with dominant-hemisphere glioma (WHO Grades II–IV) suggests that functional language outcome following awake mapping can be favorable, even in the case of an aggressive resection.[89] Overall, 159 of these 250 patients (63.6%) had intact speech preoperatively. At 1 week postoperatively, 194 (77.6%) remained at their baseline language function, whereas 21 (8.4%) worsened and 35 (14.0%) had new speech deficits. However, by 6 months, 52 (92.8%) of 56 patients with new or worsened language deficits returned to baseline or better, and the remaining 4 (7.1%) were left with a permanent deficit. Interestingly, among these patients, any additional language deficit incurred as a result of the surgery had either improved by 3 months or not all (Fig. 1). Thus, using language mapping, only 1.6% (4 of 243 survivors) of all glioma patients develop a permanent postoperative language deficit. One explanation for this favorable postoperative language profile may be our strict adherence to the "one-centimeter rule," first described by Haglund et al.,[29] which demonstrated that, for temporal lobe tumors, a resection margin of 1 cm or more from a language site significantly reduces postoperative language deficits.

Cortical and Subcortical Motor Mapping Techniques

For patients with gliomas that are located within or adjacent to the rolandic cortex, and thus the descending motor tracts, stimulation mapping of cortical and subcortical motor pathways enables the surgeon to identify these descending motor pathways during tumor removal and to achieve an acceptable rate of permanent morbidity in these high-risk functional areas.[8,20,47] In a recent study, new immediate postoperative motor deficits were documented in 59.3% of patients in whom a subcortical motor tract was identified intraoperatively and in 10.9% of those in whom subcortical tracts were not observed. However, permanent deficits were observed in 6.5% and 3.5%, respectively.[8] In another study of subcortical motor pathways in 294 patients who underwent surgery for hemispheric gliomas, 14 patients (4.8%) had a persistent motor deficit after 3 months. Interestingly, patients whose subcortical pathways were identified intraoperatively were more prone to develop an additional transient or permanent motor deficit (27.5 vs 13.1%).[47] In another study with an 87% gross- or subtotal resection rate, the overall neurological morbidity was 5% after using cortical motor mapping.[20] Thus, collectively the recent literature suggests that intraoperative cortical and subcortical motor mapping can safely identify corridors for resection, as well as define the limits of tumor resection.

Tailored Craniotomies and the Value of Negative Mapping

In contrast to the classic mapping principles practiced in epilepsy surgery, where 95–100% of operative fields contain a positive language site, a paradigm shift is emerging in brain tumor language mapping, where positive language sites are not always found prior to resection (Fig. 2). In our practice, because of our use of tailored cortical exposures, < 58% of patients have essential language sites localized within the operative field. Our experience suggests that it is safe to use a minimal exposure of the tumor and resect based on a negative language map, rather

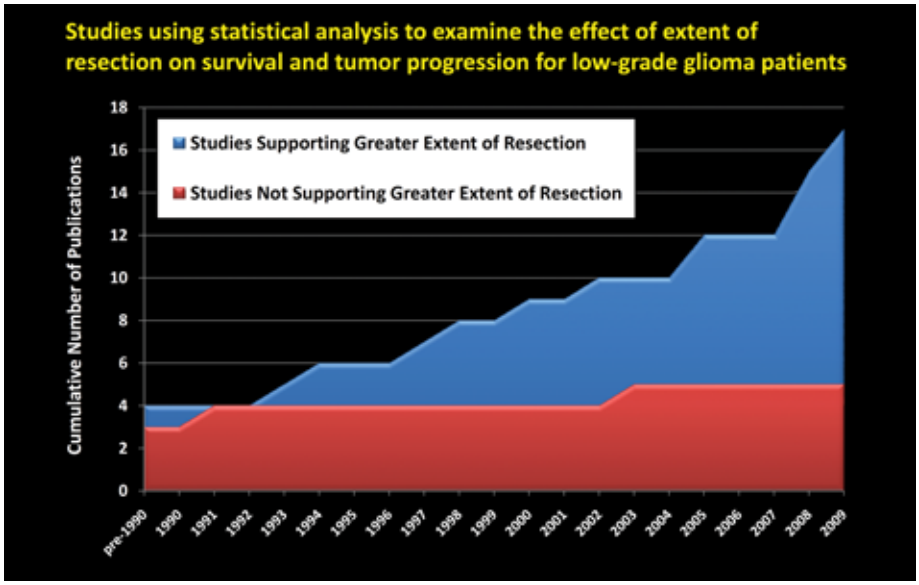

Fig. 3. Chart showing absolute number of LGG studies in the neurosurgical literature from 1990 to 2009 that statistically examined the effect of extent of resection on patient survival.

than rely on a wide craniotomy to find positive language sites well beyond the lesion. However, language mapping techniques such as this are generally more successful and safer at high-volume neurosurgical centers.

Negative language mapping, however, does not necessarily guarantee the absence of eloquent sites (Fig. 2). Despite negative brain mapping, permanent postoperative neurological deficits have been reported.[108] In our experience with 250 consecutive patients with dominant-hemisphere glioma, all 4 of our patients with permanent postoperative neurological deficits had no positive sites detected prior to their resections. Other cases of unexpected postoperative deficits have also been attributed to progressive tumor infiltration into functional areas.[3] Furthermore, both intraoperative stimulation and functional imaging techniques have provided evidence for redistribution of functional neural networks in cases of stroke,[11,95,118] congenital malformations,[54,56] brain injury,[27] and tumor progression.[24,95,121] Not surprisingly, it has been hypothesized that brain infiltration by gliomas leads to reshaping or local reorganization of functional networks as well as neosynaptogenesis.[18,109] This would explain the frequent lack of clinical deficit despite glioma growth into eloquent brain areas,[17,24,95] as well as the transient nature of many postoperative deficits. In the case of language function located in the dominant insula, the brain's capacity for compensation of functional loss has also been associated with recruitment of the left superior temporal gyrus and left putamen.[17]

Assessing the Value of Glioma Extent of Resection

Microsurgical resection remains a critical therapeutic modality for all gliomas.[4,28,45,122] However, there remains no general consensus in the literature regarding the efficacy of extent of resection in improving patient outcome.[32,36,60,78,81,87,92] With the exception of WHO Grade I tumors, gliomas are difficult to cure with surgery alone, and the majority of patients will experience some form of tumor recurrence. Patients with glioblastomas have median survival rates of 12.2–18.2 months,[33] whereas those with anaplastic astrocytomas can expect to survive 41 months, on average.[46] Low-grade gliomas carry a better prognosis, although the vast majority of patients eventually die of their disease and 5-year survival percentages range from 42 to 92% in the literature.[51,52,59,76,84,96,97,123]

For all gliomas, the identification of universally applicable prognostic factors and treatment options remains a great challenge. Among the many tumor- and treatment-related parameters, only patient age and tumor histological characteristics have been identified as reliable predictors of patient prognosis, although tumor location in an eloquent area and a patient's functional status can also be statistically significant. Surprisingly, despite significant advances in brain tumor imaging and intraoperative technology during the last 15 years, the effect of glioma resection in extending tumor-free progression and patient survival remains unknown.

Although LGGs and HGGs are distinct in their biology, clinical behavior, and outcome, understanding the efficacy of surgery remains equally important for each. With this in mind, an examination of the modern neurosurgical literature (1990 to present) reveals clues as to the role of extent of resection in outcome for glioma patients (Fig. 3).

Extent of Resection Studies for LGG

In the last 2 decades, mounting evidence in the literature suggests that a more extensive resection of an LGG is associated with a more favorable life expectancy (Fig. 3). In addition to providing longer overall survival, more aggressive resections for LGG can also influence the risk of malignant transformation, raising the possibility that a surgical intervention can alter the natural history of the

disease.[87] These associations are evident not only within the population with general hemispheric LGGs,[9,103] but also for those with specific LGGs limited to specific eloquent subregions, such as insular LGGs.[90,100] An overall review of the modern neurosurgical literature reveals 23 studies[2,12,40,42,44,52,55,57,59,61,63,75,76,84,86,90,93,96,98,103,115,119,123] since 1990 that have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression among patients with LGG. Six of these studies included volumetric analysis of extent of resection.[12,44,90,98,103,115] Of the nonvolumetric studies, 14 demonstrated evidence supporting extent of resection as a statistically significant predictor of either 5-year survival or 5-year progression-free survival. These studies were published between 1990 and 2009, and most commonly used a combination of multivariate and univariate analyses to determine statistical significance. Interestingly, of the 3 nonvolumetric studies that did not support extent of resection as a predictor of patient outcome, none of these reports evaluated progression-free survival, but instead focused solely on 5-year survival.

Extent of Resection Studies for HGG

Twenty-nine studies[1,5,6,13,16,22,38,39,41,45,46,48–50,53,58,62,77,79,80,82,91,99,101,104,106,110,114,116] since 1990 have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression among patients with HGG. Four of these studies included volumetric analysis of extent of resection.[45,46,49,79] Of the nonvolumetric studies, 16 demonstrated evidence supporting extent of resection as a statistically significant predictor of either time to tumor progression or overall survival. Although some of these reports showed extent of resection to have a significant effect on both tumor progression and overall survival, every study showed a survival benefit. Ten studies, however, demonstrated no significant benefit based on extent of resection. Notably, the distribution of adjuvant chemotherapy and radiation treatment was comparable among all extent of resection studies for HGG. Echoing the nonvolumetric study results, half of all HGG volumetric studies showed a significant survival advantage with greater extent of resection.

Conclusions

Intraoperative stimulation for cortical and subcortical mapping is a reliable, robust method to maximize resection and minimize morbidity, even when removing gliomas within or near adjacent functional pathways. Unlike motor function, speech and language are variably distributed and widely represented, thus emphasizing the utility of language mapping in this particular patient population. Gliomas located in eloquent territories can displace predicted fiber pathways in unpredictable conformations. The combination of advanced imaging paradigms, such as neuronavigational DT imaging–based tractography, with intraoperative mapping techniques can best assure preservation of critical function. Using this approach, and in conjunction with standardized neuroanesthesia and neuromonitoring, the postoperative motor and language resolution profiles following glioma resection may be predictable. Specifically, in our experience, any additional language deficit incurred as a result of the surgery will improve by 3 months or not all. Our experience also emphasizes the value of negative language mapping in a patient with a tailored cortical exposure. Although the value of extent of resection remains less clear, the available literature for both low-grade and high-grade hemispheric gliomas demonstrates mounting evidence that a more extensive resection is associated with a more favorable life expectancy for patients with both LGG and HGG. This objective should be cautiously pursued for all gliomas, even those in an eloquent location.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: N Sanai, MS Berger. Drafting the article: N Sanai, MS Berger.

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The cerebral sulci and gyri

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The aim of this study was to describe in detail the microanatomy of the cerebral sulci and gyri, clarifying the nomenclature for microneurosurgical purposes. An extensive review of the literature regarding the historical, evolutionary, embryological, and anatomical aspects pertinent to human cerebral sulci and gyri was conducted, with a special focus on microneuroanatomy issues in the field of neurosurgery. An intimate knowledge of the cerebral sulci and gyri is needed to understand neuroimaging studies, as well as to plan and execute current microneurosurgical procedures. *(DOI: 10.3171/2009.11.FOCUS09245)*

Key Words • **brain gyrus** • **brain mapping** • **brain sulcus** • **cerebral cortex** • **cerebral lobe**

Although there is no strict relationship between brain structure and function, current knowledge shows that the two are closely interrelated. The brain is divided into regions and subdivided into more specific zones, although there is increasing evidence that the borders between those zones are much blurrier than was previously thought.[35] Therefore, it is essential that neurosurgeons have an intimate knowledge of brain microanatomy, not only to improve their understanding of neuroimaging studies, but also to allow them to plan and perform neurosurgical procedures while considering particular brain functions.

In the relatively new field of microneurosurgery, the development and use of the transcisternal, transfissural, and transsulcal approaches[80,84,85] have established the sulci as fundamental landmarks on the brain surface. The well-known variability in cortical function[1,2,17,47,53,75] calls for the aid of cortical mapping techniques to precisely identify specific sites related to cortical function. Nevertheless, detailed knowledge of the structure and form of the cerebral sulci and gyri continues to be mandatory for neuroimaging as well as intraoperative guidance. Once identified, the cerebral sulci can be used by the neurosurgeon either as microneurosurgical corridors or simply as cortical landmarks.[61,62]

A review of the literature regarding the historical, evolutionary, embryological, and anatomical aspects of the cerebral sulci and gyri was conducted to establish detailed descriptions of these structures, as well as their groupings in the brain lobes, for microneurosurgical purposes.

Historical Aspects

Interest in the human brain dates back to antiquity, and cranial trephination is probably the oldest systematized surgical procedure.[23] As early as ~ 10,000 years ago, cranial trephination was performed "successfully" (that is, with new bone formation after the procedure) in the neolithic cultures of Europe, and there are findings dating to 2000 years ago in South America, where the practice was particularly common in the pre-Incan and Incan cultures of Peru.[26] Despite this historical context, knowledge of the anatomy of the brain in general and of its surface in particular is quite recent.[23,26,38]

The first significant contributions to neuroanatomy were made during the Golden Age of Greek civilization. Hippocrates (460–370 BC), who is considered the father of medicine, posited that the brain was responsible for mental activities and convulsions, whereas some important Greek philosophers, such as Aristotle (384–322 BC), believed that the heart was the seat of intellectual, perceptual, and related functions.[23]

In Alexandria, Egypt, then a Greek city that was particularly advanced in cultural terms, human dissections, which had until then been forbidden in Greek society, began to be performed in ~ 300 BC. There, Herophilus (ca. 335–280 BC), a follower of Hippocrates and considered the father of anatomy, studied the brain and its ventricles as well as the cerebellum, distinguished the motor nerves from sensory nerves, and described the confluence of the cranial venous sinuses, whose name was originally derived from his own name ("torcular herophili"). One of his contemporaries and compatriots, Erasistratus (ca. 310–250 BC) studied the comparative anatomy of the brain surface and had already hypothesized that there was a relationship between intellect and gyral complexity.[23]

Despite the importance of the Greek contribution, the most widely known anatomical descriptions of classical antiquity are those of Galen (130–199 AD), who studied

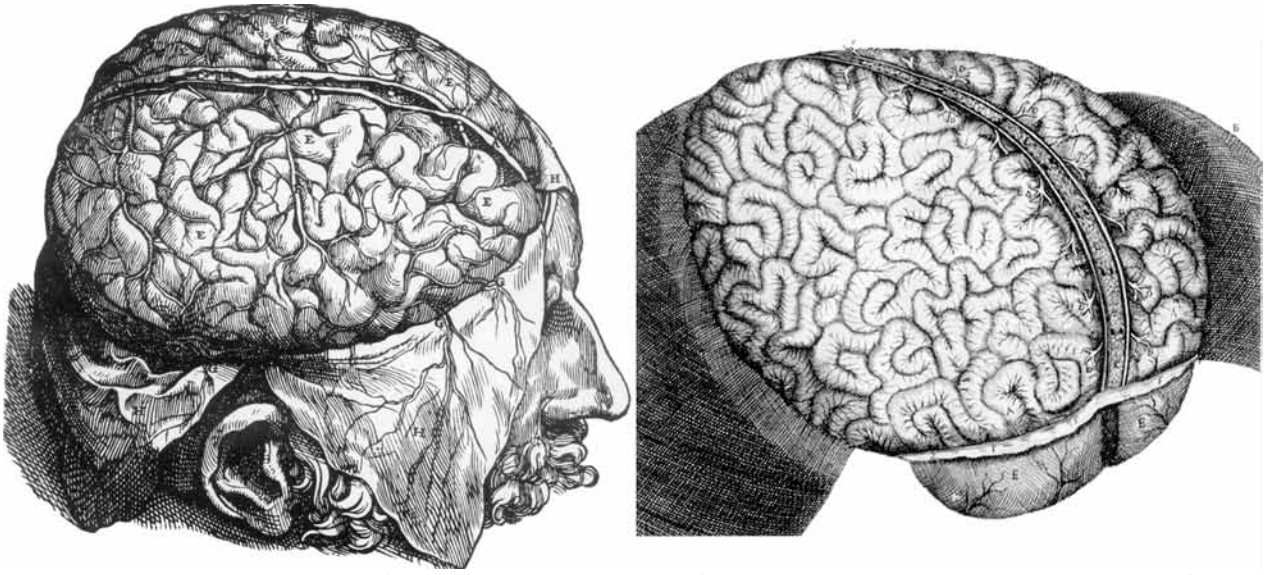

Fig. 1. Renaissance illustrations of the brain sulci and gyri with a configuration that resembles the small bowel disposal. **Left:** By Andreas Vesalius, 1543.[65] **Right:** By Raymond Vieussens, 1684. Reprinted from Vieussens R: **Nevrographia Universalis.** Frankfurt: Georgium Wilmelmum Künnium, 1690.

anatomy in Alexandria, returned to Greece, and finally settled in Rome, where he was surgeon to the gladiators and performed dissections, primarily on animals.[38]

The Middle Ages, roughly from the 4th to the 14th century, is well known to have been poor in terms of scientific developments in general. Although there were some contributions from individuals in certain regions—in the Arabic world, from Avicenna (980–1037 AD), who some authors credit with the first representation of the brain, made in ~ 1000 AD;[69] and in Europe, from Mundino dei Luzzi,[69] who, in 1316, performed the first human dissections reported in Europe—anatomical studies were quite limited, principally because of the prohibition against the dissection of human cadavers. During the Renaissance, this prohibition was finally lifted, which led to the progressive development of all anatomical knowledge. The most preeminent figure in this field was undoubtedly Andreas Vesalius (1514–1564), professor of anatomy and surgery at the University of Padua, who published the textbook *De Humanis Corporis Fabrica*,[65] in which he pointed out the many errors made by Galen, outlined the distinctions between white matter and gray matter, and described various other aspects of brain anatomy.[23,38,69]

Although Vesalius provided intricate anatomical descriptions, especially of the ventricular cavities and their related deep neural structures, illustrations of the brain convolutions, including those of Vesalius, continued to show them in a chaotic arrangement. Among other notable Renaissance authors were the great Leonardo da Vinci (1472–1519), who, in addition to his elegant descriptions of the brain ventricles, created beautiful illustrations of the brain surface,[12] and Julius Casserius (ca. 1545–1616), who depicted the brain convolutions, which were at that time understood to resemble the small bowel (Fig. 1).[69]

In 1663 Franciscus de la Böe (1614–1672), also known as Dr. Sylvius, described the lateral cerebral sulcus, which therefore came to be known as the *sylvian fissure*.[23]

In 1664 Thomas Willis (1621–1675) published his highly regarded *Cerebri Anatome*, which featured illustrations by the renowned architect Christopher Wren (1632–1723). In addition to describing the group of arteries surrounding the base of the brain (now known as the *circle of Willis*), Willis introduced a variety of terms, including *neurology*, *hemisphere*, *lobe*, *corpus striatum*, *peduncle*, and *pyramid*, and showed a relationship between the cerebral gyri and memory.[23]

Raymond Vieussens (1644–1716) published the famous *Neurographia Universalis* in 1690,[76] describing in detail the "centrum semiovale" and other cerebral structures but still illustrating the brain surface similarly to the small bowel.[23,69] Godefroid Bidloo clearly displayed the central sulcus in his atlas and textbook published in 1685,[69] and subsequently Félix Vicq d'Azyr (1748–1794), famous for describing the mamillothalamic tract, also described the precentral and postcentral convolutions and coined the term *uncus*.[69] Later, Johann Christian Reil (1759–1813) provided a comprehensive description of the insula, which had been identified by Bartholin in 1641.[23,69] In 1827 Herbert Mayo, student of the renowned anatomist and surgeon Charles Bell (1774–1842), published illustrations of the corona radiata and the internal capsule as well as other important tracts.[74] In 1829, the Italian anatomist Luigi Rolando (1773–1831) published his text *Della Strutura degli Emisferi Cerebrali*,[63] becoming the first author to accurately portray the cerebral sulci and convolutions, including the central sulcus, which later received his name and is still occasionally referred to as the *fissure of Rolando*.[23,74]

It was the German physiologist Friedrich Arnold (1803–1890) who first used the terms *frontal*, *parietal*, and *occipital* to describe the cranial bones. In a text published in 1851,[5] Arnold recognized only the sylvian fissure and the parietooccipital sulcus (then known as the *internal perpendicular fissure*) as anatomically constant sulci. He did not recognize any organized arrangement among the cerebral gyri, and he described the temporal region as an anterior extension of the occipital region.

TABLE 1: Mammalian cortical development*

Primitive Cortex: Allocortex (3 layers)	Medial Cortical Ring: Mesocortex (6 layers)	Lateral Cortical Ring: Isocortex (6 organized layers)
limbic structures	paralimbic structures & insula	parainsular & other neocortical structures
archicortex	neocortex	
amygdala	parahippocampal gyrus	motor cortex
hippocampus	cingulate gyrus	sensory cortex
paleocortex		visual cortex
olfactory or piriform cortex	insula	auditory cortex
		language cortices (humans)
		rest of neocortex, associative areas

* Adapted from Sarnet and Netsky.

The French anatomist Louis Pierre Gratiolet (1815–1865) provided the first accurate descriptions of the cerebral lobes and cerebral fissures.[6,72,74] In addition to his well-known description of the optic radiation, Gratiolet also distinguished between primary and secondary sulci based on their phylogenetic appearance and adopted the terms initially proposed by Arnold to divide each cerebral hemisphere into 5 lobes (*frontal*, *parietal*, *occipital*, *temporal*, and *insular*). Gratiolet coined the elegant term *plis de passage* to describe the connections between adjacent gyri. He was the first anatomist to understand and describe the fact that despite individual variations, the cerebral sulci and gyri are organized in accordance with a general arrangement.[27,74] It is notable that despite the intense interest that humankind has always had in relation to the brain, it was only in the middle of the 19th century that the anatomical organization of the cerebral sulci and gyri was perceived and described.

The work of Gratiolet laid the foundation for the important studies later conducted by the French anatomist, anthropologist, and surgeon Paul Broca (1824–1880), who examined the cerebral sulci and fissures. Broca was the first to describe the craniocerebral topographical relationships[6,7] and to outline the motor speech area of the brain.[4] In 1861 Broca introduced the concept of cerebral localization.[7,36] Using as a basis the correlations he found between cranial points and the brain surface,[3,5] Broca became a pioneer of modern neurosurgery, establishing original guiding anatomical landmarks.[3]

In 1869 Alexander Ecker accurately described all of the cerebral sulci and gyri, introducing the designations *orbital*, *precentral*, *parietooccipital*, and *transverse occipital* to describe the various sulci.[69] William Turner (1832–1916) also studied the cerebral sulci in detail, and *Turner's sulcus* became an eponym for the *intraparietal sulcus*.[36]

Brodmann in 1909[9] and Von Economo in 1925[77] studied the cerebral sulci and gyri in greater detail, describing the cytoarchitectonic features of the gyri.

Evolutionary Aspects

According to evolutionary theory, the primitive fishes left the oceans ~ 350 million years ago.[24] The transition from fish to amphibian to reptile involved profound physical transformations, one of which was related to the CNS, which then consisted of a spinal cord segment with an incipient brainstem, hypothalamus, and striatum. The CNS evolved to include the olfactory lobes needed to perceive the new world, as well as the hippocampus and amygdala, which, in conjunction with the hypothalamus, would allow them to analyze their new perceptions and direct their behavior.[10,41,64,67] Since these new structures surrounded the top of the primitive CNS, they were called *limbic*, from *limbus*, the Latin word for *ring*.[22] To create different input and output connections, their cells were organized in a laminar arrangement, characterizing then the most primitive cortices, denominated the *archicortex* (amygdala and hippocampus) and *paleocortex*, the latter also known as the *olfactory (piriform) cortex*.[10,64] The development of the cerebral hemispheres and their cortical surfaces, in particular, began soon after the appearance of these primitive structures. The neocortex first appeared in the brains of early mammals (~ 230 million years ago) and became more complex throughout the evolution of the primates, culminating ~ 50,000 years ago with the emergence of modern humans.[10,24,25]

According to Sarnat and Netsky,[64] cytoarchitectonic evidence suggests that the 6-layered neocortex of primitive mammals evolved simultaneously from the archicortex and paleocortex. Initially, the archicortex and paleocortex respectively formed the medial and lateral sides of the cerebral hemisphere. It is likely that the 2 first gave rise to a cortex whose architecture was intermediate in complexity between the 3-layered design of the primitive cortex of origin and the "standard" 6-layered cortex. A second zone of more highly differentiated neocortex then formed as an additional concentric ring in the parahippocampal region, including the cingulate gyrus on the medial side and the insular cortex laterally. Subsequently, a third ring of well-differentiated neocortex appeared, comprising the paralimbic and parainsular cortices, which became sites of specialized sensory and motor functions. A visual cortex developed in the paralimbic zone, and part of the parainsular region became an auditory center (Table 1).

Morphologically, this marked development of the mammalian cortex occurred through an extensive infolding process, which increased its surface area significantly without a proportional enlargement of its outer dimensions or total volume. The current human cortical pattern

is characterized by fissures, sulci, and their delimited gyral convolutions—with fissures being the most prominent and anatomically constant sulci.[6,7] If one also considers the interhemispheric fissure, this invagination process led to the burial of approximately two-thirds of the human cortical surface into the depths of the sulci and fissures.[79]

Phylogenetically, the first hemispheric sulcus to appear was the hippocampal sulcus, which separates the archicortex (dentate gyri of the hippocampus) from its surrounding structures, including the parahippocampal subiculum, which arises during the phylogenetic and embryological caudal migration of the original supracallosal hippocampus.[64] The second hemispheric sulcus was the rhinal sulcus, which demarcates the border between the paleocortex and neocortex. The rhinal sulcus appeared after the ventral displacement of the piriform cortex, caused by the development of the neocortex.[64] In humans, the rhinal sulcus separates the parahippocampal uncus from the rest of the neocortical temporal lobe. The hippocampal sulcus and rhinal sulcus were both already present in early mammals.[64]

The sylvian fissure resulted from the growth of the infolding opercula of the surrounding lobes, overlapping onto the insula,[82] and became narrow only in humans, in whom the frontoparietal operculum is particularly developed (although underdeveloped in even the highest anthropoid apes).[64,67] The most notable development was that of the pars triangularis and pars opercularis of the inferior frontal gyrus, which, in the dominant hemisphere of the human brain, correspond to the Broca area.[4]

Embryological Considerations

Embryologically, the sulci develop according to a sequence that reflects their phylogeny and a hierarchy that exists among them. Their formation begins with the appearance of the fissures, followed by sulci related to eloquent areas of the brain, and finally the secondary and tertiary cortical area sulci.[5,11,46]

Very early during embryogenesis, the forebrain vesicle (or prosencephalic vesicle, the most superior of the 3 primary brain vesicles originating from the neural tube) divides into the endbrain (telencephalic) and interbrain (diencephalic) vesicles.[67] By approximately the 10th week of gestation, a superior midline depression of the endbrain gives rise to the interhemispheric fissure, and the transverse fissure of the brain appears between the endbrain and interbrain vesicles.[11]

Between the 8th and 10th weeks of gestation, transitory furrows that are not precursors of the permanent sulci appear in the cerebral hemispheric surfaces. These furrows persist until the 5th month, when the brain surfaces become smooth and the insular area is the only evident depression.[50,79]

During the 4th and 5th months of gestation, the first identifiable sulci (olfactory, calcarine, parietooccipital, cingulate, and central) begin to appear, followed by additional secondary and tertiary furrows (Table 2), some of which develop only after birth.[11,50]

The process of sulcal development and its relatively variable final result are in great part determined by genetics.[67] However, the sulci evolve through an infolding process while the entire developing brain undergoes a process of circular curvature, effectively wrapping the thalami in its morphological center. Therefore, it is noteworthy that in their final presentation, the sulci of the superolateral and inferior surfaces of the cerebral hemisphere are directed toward the most proximal portion of the lateral ventricle. The development of the sulcal pattern of the medial surfaces seems to be particularly influenced by the development of the corpus callosum, since its congenital absence is linked to the absence of an arched cingulate gyrus and a radial pattern of the medial surface sulci.[50]

The fissures correspond to the more well-developed and anatomically constant sulci, and the gyri or convolutions that have a more rounded or quadrangular shape are usually referred to as *lobules*.[5–7,27,79]

TABLE 2: Prenatal cerebral sulci development

Characteristic	Chi et al., 1977	Nishikuni, 2006
no. of fetuses	207	107
gestational age in wks	10–44	12–40
longitudinal cerebral fissure	10	12
superolat surface		
lat sulcus	14	17
circular insular sulcus	18	17
central insular sulcus		29
central sulcus	20	21
precentral sulcus	24	26
superior frontal sulcus	25	25
inferior frontal sulcus	28	30
postcentral sulcus	25	29
intraparietal sulcus	26	29
transverse occipital sulcus		30
lunate sulcus		24
superior temporal sulcus	23	26
inferior temporal sulcus	30	31
transverse temporal sulcus	31	33
inferior surface		
olfactory sulcus	16	17
orbital sulcus		22
hippocampal sulcus	10	12
rhinal sulcus		25
collateral sulcus	23	29
occipitotemporal sulcus	30	33
medial surface		
callosal sulcus	14	12
cingulate sulcus	18	19
marginal ramus		33
paracentral sulcus		30
paraolfactory sulcus		29
subparietal sulcus		30
calcarine sulcus	16	17
parietooccipital sulcus	16	19
secondary sulcus	40	38

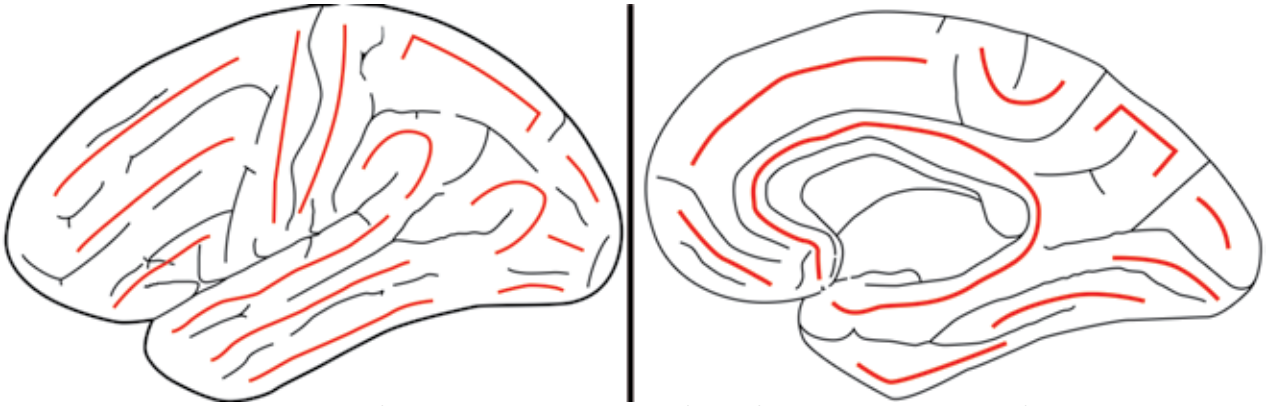

Fig. 2. Basic organization of the brain gyri: superolateral surface **(left)** and medial and basal surfaces **(right)**. *Red lines* indicate the constant arrangement of the brain gyri.

General Anatomical Features

Given their phylogenetic and embryological development, especially the fact that it is based on an infolding process,[64] the fissures and sulci are natural extensions of the subarachnoid space and delimit the gyri on the brain surface, with approximate depths ranging from 1 to 3 cm, and harbor smaller opposing gyri within their sulcal spaces. These smaller gyri are collectively known as the *transverse gyri*. Their wavelike surfaces are interlocked like cogwheels, and their arrangement cannot be estimated from observations of the brain surface.[82] The furrows that separate the intrasulcal transverse gyri are variable in depth and length, and when they reach the superficial margins of the gyri, they are visible as incisures or notches, although furrow-like impressions can also result from indentation by arteries.[50]

On the brain surface, the sulci can be long or short as well as continuous (sylvian fissure, callosal, calcarine, parietooccipital, collateral, and generally the central sulcus) or interrupted. Ono et al.[50] have described 4 main types of sulci: large primary sulci (for example, central, precentral, postcentral, and continuous sulci); short primary sulci (for example, rhinal, olfactory, lateral, and occipital sulci); short sulci composed of several branches (for example, orbital and subparietal sulci); and short, free supplementary sulci (for example, medial frontal and lunate sulci). Frequently, the sulci are composed of side branches that can be unconnected or connected (with end-to-side, end-to-end, or side-to-side connections that can also join 2 neighboring parallel sulci).

Since connections between sulci are common, the nomenclature varies widely, with different authors providing different interpretations.[14,50,72] Bear in mind that the sulci can vary in size and shape from person to person. In addition, the cerebral gyri constitute a real continuum in that the surface presents a serpentine configuration because of the connections across the sulcal extremities and interruptions, and are continuous throughout the sulcal depths.[82] The gyral separation is only superficial and is defined by the continuity and depth of the adjacent sulci. Therefore, each gyrus should be understood as a region and not as a well-defined structure.

Because they result from an infolding process, the sulci of the superolateral and inferior surfaces of the brain are usually oriented toward the nearest ventricular cavity, although this feature does not apply to the medial surface of the cerebral hemisphere, where the sulci are particularly dependent on the development of the corpus callosum.[50] The single most common identifiable surface feature is the sylvian fissure, given its particular mechanism of development.[79]

Their variations and irregularities give the sulci and gyri of the human brain a labyrinthine appearance. Nevertheless, they are arrayed in a particular configuration. In fixed anatomical specimens from which the arachnoid and vessels have been removed, an observer with knowledge of the principal features of the sulci can generally recognize that configuration from an initial identification of the sulci that are the most characteristic and constant.

In rough terms, the human brain is organized as follows: the frontal and temporal regions of each hemisphere are each composed of 3 horizontal gyri; the central area is composed of 2 slightly oblique gyri; the parietal region is composed of 2 lobules, with a quadrangular superior lobule and an inferior lobule consisting of 2 semicircular gyri; the occipital region is composed of 3 irregular, less well-defined, predominantly longitudinal gyri that converge toward the occipital pole, the superior being vertical and the middle and inferior being horizontal; and the insula is composed of 4–5 diagonal gyri (Figs. 2 left and 3).

Medially, the external lateral gyri and lobules extend along the superior and inferolateral borders of each hemisphere. Together, these gyri constitute an outer medial ring surrounding a well-defined, C-shaped inner ring primarily composed of 2 continuous gyri. Inferiorly, the base of each hemisphere consists of 2 horizontal gyri longitudinally oriented between the lateral extended gyri (along the inferolateral and inferomedial borders) and the medial continuous gyri (of the inner ring; Figs. 2 right and 4).

Among all of these features, the prominent sylvian fissure appears as a particularly distinctive structure in the superolateral aspect of the brain, as do the uniquely oblique precentral and postcentral gyri, with their related sulci.

The Cerebral Lobes

Since the initial proposal made by Gratiolet[6,74] in

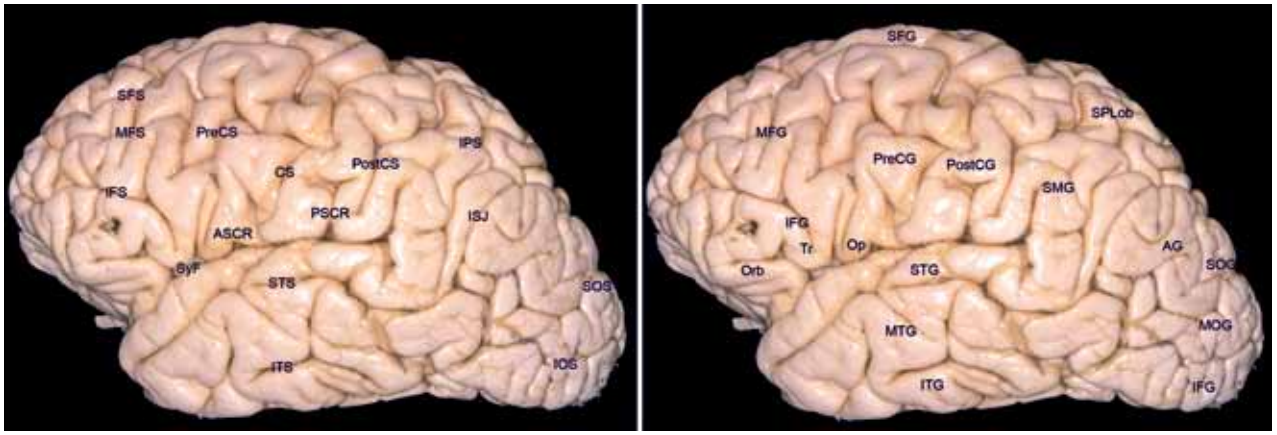

Fig. 3. The main sulci **(left)** and gyri **(right)** of the superolateral surface of the brain. AG = angular gyrus; ASCR = anterior subcentral ramus of sylvian fissure; CS = central sulcus; IFG = inferior frontal gyrus; IFS = inferior frontal sulcus; IOS = inferior occipital sulcus; IPS = intraparietal sulcus; ISJ = intermediary sulcus of Jensen; ITG = inferior temporal gyrus; ITS = inferior temporal sulcus; MFG = middle frontal gyrus; MFS = middle frontal sulcus; MOG = middle occipital gyrus; MTG = middle temporal gyrus; Op = opercular part of inferior frontal gyrus; Orb = orbital part of inferior frontal gyrus; PostCG = postcentral gyrus; PostCS = postcentral sulcus; PreCG = precentral gyrus; PreCS = precentral sulcus; PSCR = posterior subcentral ramus of sylvian fissure; SFG = superior frontal gyrus; SFS = superior frontal sulcus; SMG = supramarginal gyrus; SOG = superior occipital gyrus; SOS = superior occipital sulcus; SPLob = superior parietal lobe; STG = superior temporal gyrus; STS = superior temporal sulcus; SyF = sylvian fissure; Tr = triangular part of inferior frontal gyrus.

the 19th century—to relate the cortical areas of the brain with the overlying skull bones previously identified by Arnold[6,36]—the arbitrary division of the cerebral hemispheres into lobes has always been based particularly on anatomical aspects. The objective was to establish a system of categorization that would inform medical practice, particularly in the fields of neurology, neurosurgery, and neuroradiology.

The evolution of the official anatomical terminology, including the official description of the nomenclature related to the cerebral lobes, can be seen in successive editions of the *Nomina Anatomica*, which was recently superseded by the *Terminologia Anatomica*.[21]

In an initial meeting held in Basel in 1888, the International Federation of Associations of Anatomists began to systematize the anatomical nomenclature in Latin, and the first edition of the *Nomina Anatomica* was published in 1895.[34] In this work, which came to be known as the

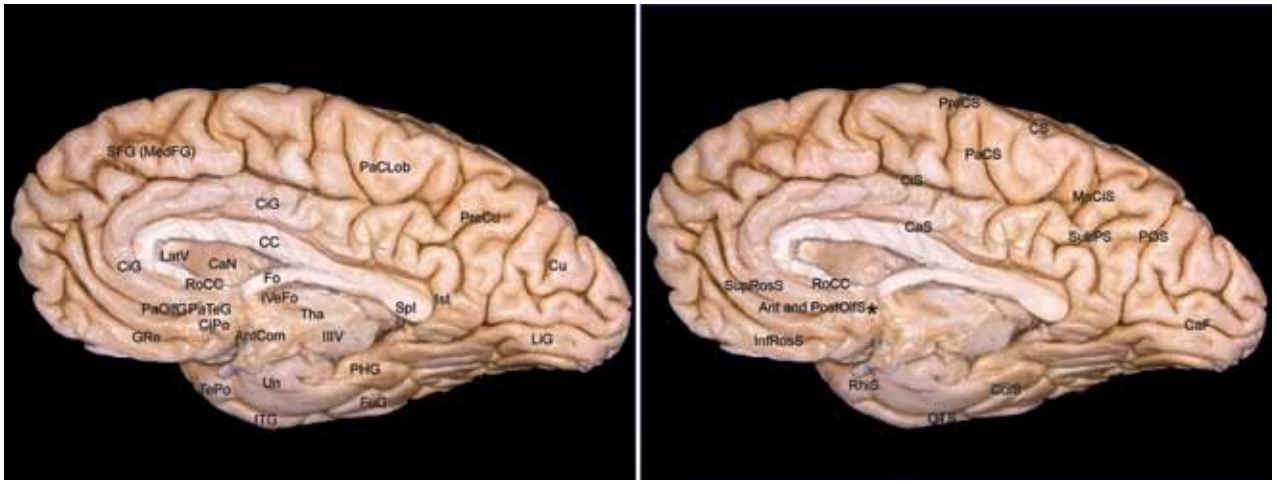

Fig. 4. The main sulci **(left)** and gyri **(right)** of the medial and basal temporooccipital surfaces. AntCom = anterior commissure; Ant and PostOlfS = anterior and posterior paraolfactory sulcus; CaF = calcarine fissure; CaN = caudate nucleus; CaS = callosal sulcus; CC = corpus callosum; CiG = cingulate gyrus; CiPo = cingulate pole; CiS = cingulate sulcus; ColS = collateral sulcus; CS = central sulcus; Cu = cuneus; Fo = fornix; FuG = fusiform gyrus; GRe = gyrus rectus; IIIV = third ventricle; InfRosS = inferior rostral sulcus; Ist = isthmus of cingulate gyrus; ITG = inferior temporal gyrus; IVeFo = interventricular foramen of Monro; LatV = lateral ventricle; LiG = lingual gyrus; MaCiS = marginal ramus of the cingulate sulcus; MedFG = medial frontal gyrus; OTS = occipitotemporal sulcus; PaCLob = paracentral lobule; PaCS = paracentral sulcus; PaOlfG = paraolfactory gyri; PaTeG = paraterminal gyrus; PHG = parahippocampal gyri; POS = parietooccipital sulcus; PreCS = precentral sulcus; PreCu = precuneus; RhiS = rhinal sulcus; RoCC = rostrum of the corpus callosum; SFG = superior frontal gyrus; Spl = splenium of corpus callosum; SubPS = subparietal sulcus; SupRosS = superior rostral sulcus; TePo = temporal pole; Tha = thalamus; Un = uncus.

Basle Nomina Anatomica, each hemisphere of the brain was divided into frontal, parietal, occipital, and temporal lobes, and the insula was considered a separate addendum but not a lobe.

The second edition of the *Nomina Anatomica*, published in 1935, became known as the *Jena Nomina Anatomica*[68] and maintained the same cerebral subdivisions, as did subsequent quinquennial editions. In 1955 the *Parisiensia Nomina Anatomica*[20] was published. That edition also presented no alterations in the terms of the cerebral subdivisions. The *Nomina Anatomica* then came to be considered an international anatomical reference.

Just after the Tenth International Congress of Anatomists, held in Tokyo in 1975, the fourth edition of the original *Parisiensia Nomina Anatomica* was published.[18] In that edition, the insula was designated a brain lobe. The fifth edition,[19] approved at a subsequent meeting held in Mexico City in 1980, presented no further modifications regarding the cerebral lobes.

At the Federative World Congress of Anatomy, held in Rio de Janeiro in 1989, a Federative Committee on Anatomical Terminology (FCAT) was elected. In several meetings over the next 8 years, the committee "reviewed and revised the anatomical Latin terminology with the addition of a list of English terms in common usage" and published the *Terminologia Anatomica* in 1998.[21] The *Terminologia Anatomica* contains the contemporary official international anatomical terminology and designates the limbic lobe as another cerebral subdivision. Therefore, according to the current official anatomical nomenclature, the brain is divided into 6 lobes: frontal, parietal, occipital, temporal, insular, and limbic.

The development of and advances in microneurosurgery during the latter part of the 20th century, guided in particular by the contributions of Yaşargil,[80] led initially to the transcisternal approaches,[81,85] which gave rise to the transfissural (for extrinsic lesions) and transsulcal approach (for intrinsic lesions).[28,52,82,83,84] The consequent microsurgical possibilities naturally required anatomical and topographic descriptions that were more accurate and detailed. In 1990 Ono et al.[50] studied the details of the main cerebral sulci. More recently, Yaşargil provided a complete and didactic description of the cerebral sulci and gyri, dividing each cerebral hemisphere into 7 lobes—frontal, central, parietal, occipital, temporal, insular, and limbic[82]—and that division is adopted in the present article. The concept of a central lobe composed of the precentral and postcentral gyri is justified, since they compose a single morphological and functional unit, as has been suggested by Penfield and Rasmussen[51] and Rasmussen alone.[54–56]

The Sulci, Gyri, and Cerebral Lobes

Given the visual evidence of the lateral cerebral sulcus, or sylvian fissure, together with the distinct, slightly oblique arrangement of the precentral and postcentral gyri as well as of the sulci that delineate them at approximately the center of the external brain surface, the character of the remaining gyri of the superolateral surface of each cerebral hemisphere can be more easily understood if we take as our starting point and basis those sulcal spaces and cerebral gyri. The macroscopic study of the sulci and gyri of each cerebral hemisphere should therefore begin with the identification of the sylvian fissure, which clearly separates the superolateral surfaces of the frontal, central, and parietal lobes from the temporal lobe, and should be followed by the identification of the precentral and postcentral gyri, which divide the portion of this surface that is superior and posterior to the sylvian fissure into its anterior and posterior halves. Adopting this approach, we will describe the 7 lobes of each cerebral hemisphere as follows: frontal, central, parietal, occipital, temporal, insular, and limbic.[82] Since the connections of the limbic lobe are particularly complex, the text related to that lobe also addresses the adjacent and correlated areas.

The Frontal Lobe

The frontal lobe constitutes the largest, most anterior part of each hemisphere. Within the scheme adopted in this article, the frontal lobe is delineated posteriorly by the oblique precentral sulcus and is composed of the superior, middle, and inferior frontal gyri, which are oriented longitudinally and separated by the superior and inferior frontal sulci, also longitudinally oriented (Fig. 3). These gyri are often referred to as F1, F2, and F3, respectively.

On the cerebral surface posteriorly, the superior frontal gyrus is connected to the precentral gyrus by at least 1 fold, which more commonly lies medially along the interhemispheric fissure. Anteriorly, the superior frontal gyrus might be connected to the middle frontal gyrus, with the orbital gyri and the gyrus rectus. In general terms, the superior frontal gyrus is subdivided into 2 longitudinal portions by the so-called medial frontal sulcus, and its medial portion is at times designated the *medial frontal gyrus*.[50] Along the most medial portion of the superior frontal gyrus and immediately facing the precentral gyrus is the important region known as the *supplementary motor area*, which varies from person to person and has poorly defined borders.[8,79]

The middle frontal gyrus is typically the largest of the frontal gyri and often has a sulcus that is shallower than that of the other frontal gyri, usually running along its anterior two-thirds and known as the *middle* or *intermediate frontal sulcus*.[50] In most human brains, the middle frontal gyrus is superficially connected to the precentral gyrus by a prominent root that lies between the extremities of a marked interruption in the precentral sulcus. The frequent interruptions in the inferior frontal sulcus are attributable to connections between the middle and inferior frontal gyri.

The inferior frontal gyrus is irregular, crisscrossed by various small branches of the inferior frontal sulcus, which typically superiorly delineate the gyrus in an interrupted manner. Inferiorly, this gyrus is delineated and crisscrossed by rami of the sylvian fissure. Anteriorly, the inferior frontal gyrus terminates, merging with the anterior portion of the middle frontal gyrus. Posteriorly, it is connected to the precentral gyrus. The inferior frontal gyrus is composed of, from anterior to posterior, its orbital, triangular, and opercular parts.

The emergence of the horizontal and ascending ante-

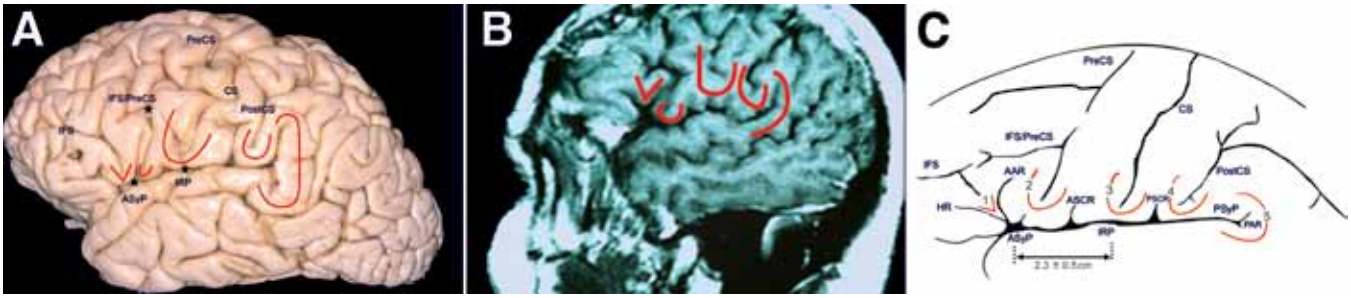

Fig. 5. The frontoparietal operculum: cadaveric specimen **(A)**, MR image **(B)**, and sketch of sulcal and gyri morphology **(C)**. The frontoparietal operculum is characterized by a V-shaped convolution consisting of the triangular part of the inferior frontal gyrus (IFG) (1), located just superiorly to the anterior sylvian point (ASyP), and usually containing a descending branch of the inferior frontal sulcus (IFS); the 3 following U-shaped convolutions respectively composed by the opercular part of the IFG (2), which is always intersected by the inferior part of the precentral sulcus; the subcentral gyrus or rolandic operculum (3), composed of the inferior connection of the pre- and postcentral gyri enclosing the inferior part of the central sulcus (CS); the connection arm between the postcentral and supramarginal gyri (4) that contains the inferior part of the postcentral sulcus; and finally the C-shaped convolution (5) constituted by the connection of the supramarginal and superior temporal gyri that encircles the posterior end of the sylvian fissure. The bottoms of the U-shaped convolutions and their related sulcal extremities can be situated either superior to the fissure or inside its cleft. *Stars* designate the areas labeled. AAR = anterior ascending ramus of the sylvian fissure; ASCR = anterior subcentral ramus of sylvian fissure; HR = horizontal ramus of sylvian fissure; IFS/PreCS = IFS and precentral sulcus; IRP = inferior rolandic point, projection of the central sulcus in the sylvan fissure; PAR = posterior ascending ramus of sylvian fissure; PostCS = postcentral sulcus; PreCS = precentral sulcus; PSCR = posterior subcentral ramus of sylvian fissure; PSyP = posterior sylvian point.

rior rami from the same point in the sylvian fissure characterizes the triangular part of the inferior frontal gyrus, which is typically more retracted than the other 2 parts (Figs. 5 and 6). The orbital part is the most prominent of the 3, and the opercular part is consistently U-shaped. Given the usual retraction of the triangular part, the horizontal and ascending anterior branches of the sylvian fissure typically emerge from a small widening of the subarachnoid space, designated the *anterior sylvian point*.[61,86] Therefore, the anterior sylvian point is situated inferior to the triangular part and anterior to the base of the opercular portion. The point, which is typically visible to the naked eye, divides the sylvian fissure into its anterior and posterior branches.[61,86]

The triangular part is quite often divided superiorly by a small descending branch of the inferior frontal sulcus, and the inferiormost portion of the precentral sulcus is always harbored within the U of the opercular part.[61] Inferiorly and anteriorly delineated by the anterior sylvian point and posteriorly delineated by the anterior subcentral branch of the sylvian fissure, the posterior half of the U that characterizes the opercular part corresponds to the important connective fold that is always situated between this portion of the inferior frontal gyrus and the precentral gyrus. In some cases, the anterior basal portion of the opercular part is more developed and is divided by another branch of the sylvian fissure. That branch runs from front to back and is called the *diagonal sulcus of*

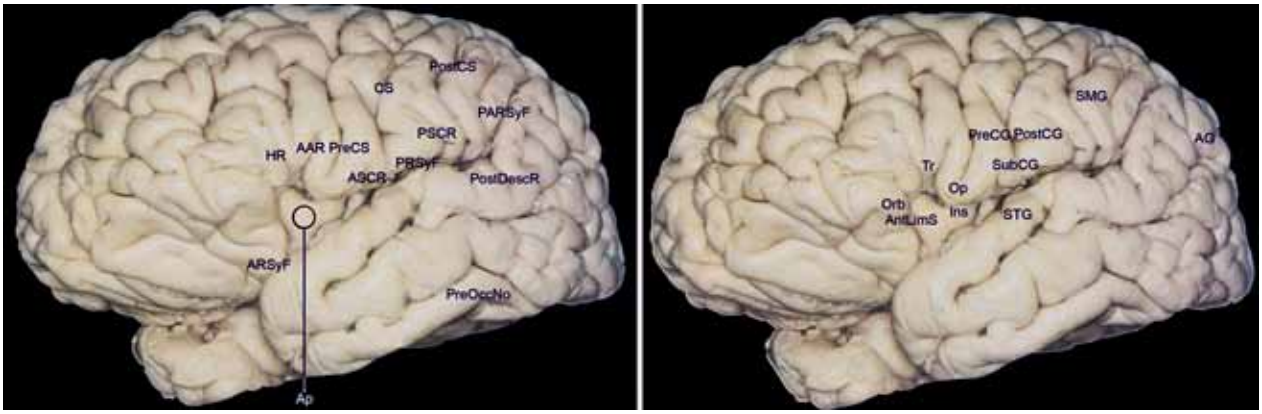

Fig. 6. Sulci **(left)** and gyri (**right)** of the frontoorbital, frontoparietal, and temporal operculi. AAR = anterior ascending ramus of the sylvian fissure; AG = angular gyrus; AntLimS = anterior limiting sulcus of the insula; Ap = insular apex; ARSyF = anterior ramus of sylvian fissure; ASCR = anterior subcentral ramus of sylvian fissure; CS = central sulcus; HR = horizontal ramus of sylvian fissure; Ins = insula; Op = opercular part of inferior frontal gyrus; Orb = orbital part of inferior frongal gyrus; PARSyF = posterior ramus of sylvian fissure; PostCG = postcentral gyrus; PostCS = postcentral sulcus; PostDescR = posterior descending ramus of sylvian fissure; PreCG = precentral gyrus; PreCS = precentral sulcus; PreOccNo = preoccipital notch; PRSyF = posterior ramus of sylvian fissure; PSCR = posterior subcentral ramus of sylvian fissure; SMG = supramarginal gyrus; STG = superior temporal gyrus; SubCG = subcentral gyrus; Tr = triangular part of inferior frontal gyrus.

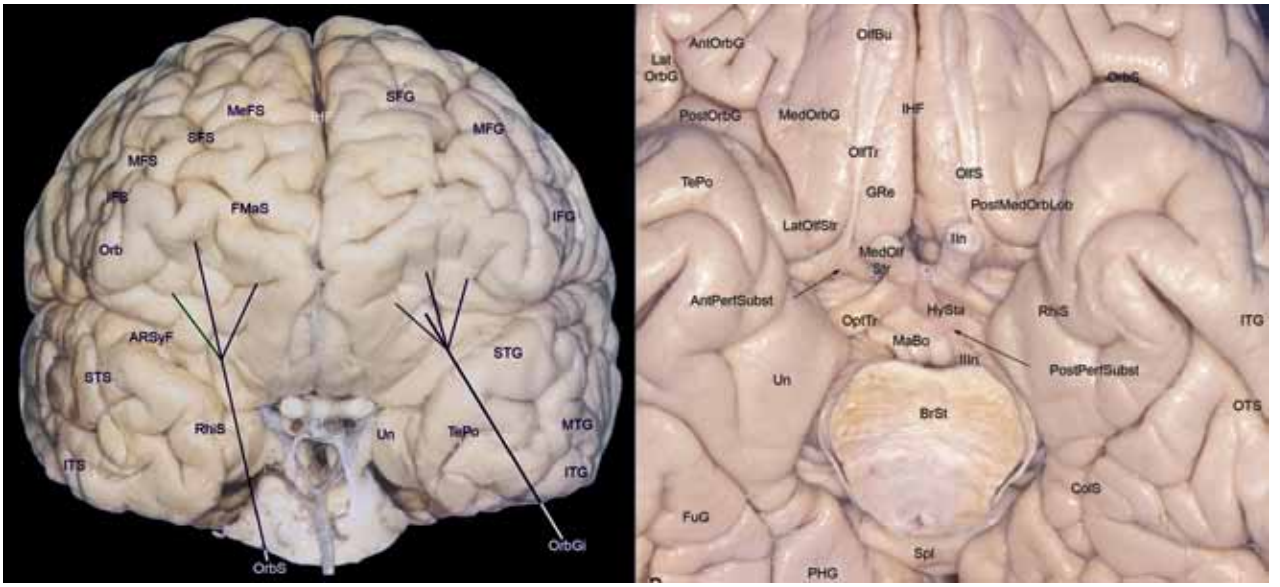

Fig. 7. Anterior view of cerebral hemispheres **(left)** and view of the basal frontotemporal surface **(right)**. AntOrbG = anterior orbital gyrus; AntPerfSubst = anterior perforated substance; ARSyF = anterior ramus of sylvian fissure; BrSt = brainstem (pons); ColS = collateral sulcus; FMaS = frontomarginal sulcus; FuG = fusiform gyrus; GRe = gyrus rectus; HySta = hypophyseal stalk; IFG = inferior frontal gyrus; IFS = inferior frontal sulcus; IHF = interhemispheric fissure; Ist = isthmus of cingulate gyrus; ITG = inferior temporal gyrus; ITS = inferior temporal sulcus; LatOlfStr = lateral olfactory striae; LatOrbG = lateral orbital gyrus; MaBo = mamillary body; MedOlfStr = medial olfactory striae; MedOrbG = medial orbital gyrus; MeFS = medial frontal sulcus; MFG = middle frontal gyrus; MFS = middle frontal sulcus; MTG = middle temporal gyrus; OlfBu = olfactory bulb; OlfS = olfactory sulcus; OlfTr = olfactory tract; OptTr = optic tract; Orb = orbital part of inferior frontal gyrus; OrbGi = orbital gyri; OrbS = orbital sulcus; OTS = occipitotemporal sulcus; PHG = parahippocampal gyri; PostMedOrbLob = posteromedial orbital lobule; PostOrbG = posterior orbital gyrus; PostPerfSubst = posterior perforated substance; RhiS = rhinal sulcus; SFG = superior frontal gyrus; SFS = superior frontal sulcus; Spl = splenium of corpus callosum; STG = superior temporal gyrus; STS = superior temporal sulcus; TePo = temporal pole; Un = uncus; IIn = optical nerve; IIIn = oculomotor nerve.

Eberstaller. When the diagonal sulcus of Eberstaller is present, it divides the anterior portion of the opercular part into 2 triangular portions that are positioned inversely to each other.

In the dominant hemisphere, the opercular and triangular parts of the inferior gyrus correspond to the Broca area, which is responsible for the production of spoken language.[4,8,29,53,79]

Inferiorly, although the orbital part continues with the lateral orbital gyrus, at times passing under a shallow sulcus known as the *frontoorbital sulcus*, the triangular part is always superior to the sylvian fissure, and the base of the opercular part can be located either superiorly or within that same fissure.[50,60]

The triangular and opercular parts together with the subcentral gyrus, which connects the precentral and postcentral gyri, and the anteroinferior portion of the supramarginal gyrus cover the superior aspect of the insular surface and constitute the frontoparietal operculum (Figs. 5 and 6). Therefore, the frontoparietal operculum is situated between the horizontal and posterior ascending branches of the sylvian fissure.[61,79]

Anteriorly, the frontal gyri are delineated by the appropriately named *frontomarginal sulcus*, which lies superior and parallel to the supraciliary margin, separating the superolateral and orbital frontal surfaces.[50,82]

On the frontobasal, or orbital, surface of each frontal lobe, the deep olfactory sulcus, which harbors the olfactory bulb and olfactory tract, is very deep and lies longitudinally in a paramedian position (Fig. 7). Posteriorly, the olfactory tract is divided into the medial and lateral striae, which delineate the anteriormost aspect of the anterior perforated substance.

Medial to the olfactory sulcus is the long and narrow gyrus rectus, considered the most anatomically constant of the cerebral gyri, which is continuous with the superior frontal gyrus along the medial surface of the hemisphere (Fig. 4).

Lateral to the olfactory sulcus are the orbital gyri, which account for the greatest proportion of the frontobasal surface (Fig. 7). The H-shaped orbital sulcus (cruciform sulcus of Rolando) delineates the anterior, posterior, medial, and lateral orbital gyri. The posterior orbital gyrus is situated anterior to the anterior perforated substance and typically presents a configuration similar to a tricorner or "Napoleon" hat, which can facilitate its identification in anatomical specimens in which the H-shaped orbital sulcus presents variations.

The posterior orbital gyrus is connected medially to the medial orbital gyrus, characterizing the posteromedial orbital lobule situated posterior and along the olfactory tract and the lateral olfactory striae, which is in turn connected to the anterior portion of the insula via the transverse insular gyrus. The remaining orbital gyri are connected to the superior, middle, and inferior frontal gyri, along the frontal pole.

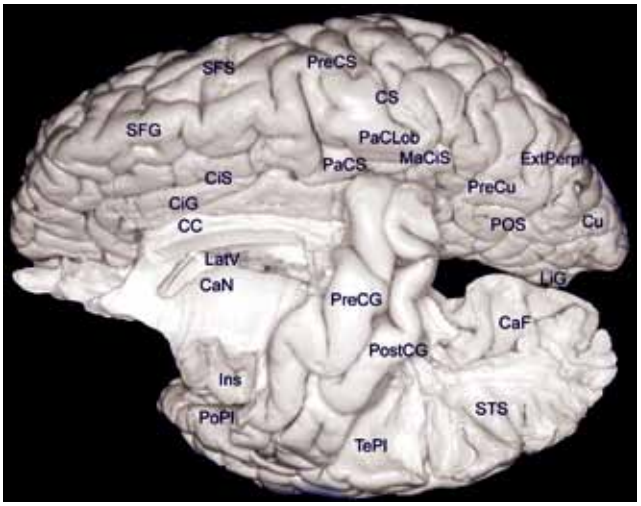

Fig. 8. The central lobe and medial contralateral surface. CaF = calcarine fissure; CaN = caudate nucleus; CC = corpus callosum; CiG = cingulate gyrus; CiS = cingulate sulcus; CS = central sulcus; Cu = cuneus; ExtPerpF = external perpendicular fissure; Ins = insula; LatV = lateral ventricle; LiG = lingual gyrus; MaCiS = marginal ramus of the cingulate sulcus; PaCLob = paracentral lobule; PaCS = paracentral sulcus; PoPl = polar plane of the opercular temporal surface; POS = parietooccipital sulcus; PostCG = postcentral gyrus; PreCG = precentral gyrus; PreCS = precentral sulcus; PreCu = precuneus; SFG = superior frontal gyrus; SFS = superior frontal sulcus; STS = superior temporal sulcus; TePl = temporal plane.

The Central Lobe

The central lobe consists of the precentral (motor gyrus) and postcentral gyri (sensitive gyrus; Fig. 8), which are oriented obliquely on the superolateral surface and are separated by the central sulcus, by their inferior (subcentral gyrus) and superior connections (paracentral gyrus, or lobule, located on the medial surface) and by the other related sulci.[82]

Morphologically, the central lobe is situated obliquely over the sylvian fissure corresponding approximately to the median portion of the cerebral hemisphere.

On the superolateral surface, the central lobe is delineated anteriorly by the precentral and anterior subcentral sulci, and posteriorly by the postcentral and posterior subcentral sulci (Figs. 3, 5, and 6). On the medial surface of the cerebral hemisphere (Fig. 4), the paracentral lobule is delineated anteriorly by the paracentral sulcus, and inferiorly and posteriorly by the ascending and distal part of the cingulate sulcus, which is known as the *marginal ramus of the cingulate sulcus*.[50]

The precentral and postcentral gyri are situated obliquely in relation to the interhemispheric fissure, being less serpiginous than the other gyri of the cerebral convexity, and are connected to adjacent gyri via the usual interruptions in the precentral and postcentral sulci.

The precentral and postcentral gyri are consistently united inferiorly by the subcentral gyrus (Broca's inferior frontoparietal *pli de passage*, or rolandic operculum) and superiorly by the paracentral lobule (Broca's superior frontoparietal *pli de passage*), which is located on the medial surface of each hemisphere. The precentral and postcentral gyri together resemble an elongated ellipse that is furrowed by the central sulcus, which is usually continuous, and are respectively delineated anteriorly and posteriorly by the precentral and postcentral sulci, which are typically discontinuous. This morphological unit, together with the functional interaction between motricity and sensitivity, justifies the characterization of these gyri as constituting a single lobe.

Inferiorly, the subcentral gyrus is delineated anteriorly and posteriorly by the anterior and posterior subcentral rami of the sylvian fissure, respectively. It can be situated either completely over the sylvian fissure or in part internal to the fissure, giving the false impression that the central sulcus is a branch of the sylvian fissure.[60,61] The portion of the subcentral gyrus that corresponds to the base of the postcentral gyrus consistently lies over the transverse gyrus of Heschl, which is situated on the opercular surface of the temporal lobe.[78]

Superiorly, and situated in the interhemispheric fissure, the paracentral lobule is delineated anteriorly by the paracentral sulcus and posteriorly by distal part of the cingulate sulcus, that is, the ascending marginal ramus of the cingulate sulcus.

The precentral gyrus typically presents 3 prominences known as *knees*: the superior and inferior knees are characterized by anterior convexities, and the middle knee is characterized by a posterior convexity. The precentral gyrus, in addition to its superior and inferior connections with the postcentral gyrus via the superior (paracentral lobule) and inferior frontoparietal fold (subcentral gyrus, or rolandic operculum), is usually also connected to the postcentral gyrus via a transverse gyrus that lies along the bottom of the central sulcus and constitutes the so-called Broca's medial frontoparietal *pli de passage*.[2,72] This fold is situated at the level of the middle knee of the precentral gyrus, which is itself normally situated at the level of the superior frontal sulcus, corresponding to the portion of the gyrus that functionally harbors the motor representation of the contralateral hand. Therefore, the superior frontal sulcus tends to point the way to the medial frontoparietal *pli de passage*, as well as to the middle knee of the precentral gyrus, with its respective motor representation of the hand.[2] On axial MR images, this part of the precentral gyrus frequently presents a configuration that resembles the Greek letter ω.[2]

Since they are disposed obliquely, the superior portions of the precentral and postcentral gyri that constitute the paracentral lobule on the medial surface of the cerebral hemisphere are topographically related to the ventricular atrium, which is situated posteriorly to the thalamus (Fig. 8). In contrast, the inferior portions cover the posterior half of the insula and are topographically related to the body of the lateral ventricle, which is situated superior to the thalamus.

The Parietal Lobe

The parietal lobe anatomy is more complex in the sense that it is composed of gyri structurally less well defined and particularly serpiginous and curved. These gyri are also referred to as *lobules*.

On the superolateral surface, the parietal lobe is de-

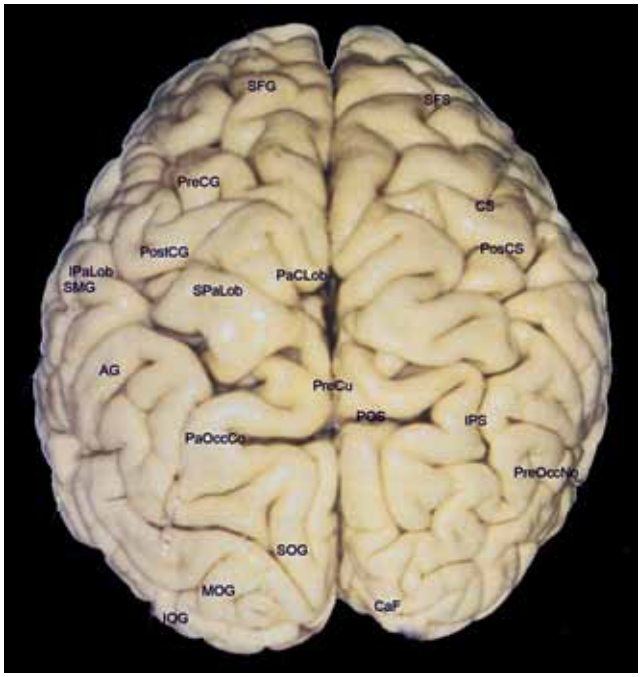

Fig. 9. Superior view of the cerebral hemispheres. AG = angular gyrus; CaF = calcarine fissure; CS = central sulcus; IOG = inferior occipital gyrus; IPaLob = inferior parietal lobule; IPS = intraparietal sulcus; MOG = middle occipital gyrus; PaCLob = paracentral lobule; PaOccCo = parietooccipital arch; POS = parietooccipital sulcus; PosCS = postcentral sulcus; PostCG = postcentral gyrus; PreCG = precentral gyrus; PreCu = precuneus; PreOccNo = preoccipital notch; SFG = superior frontal gyrus; SFS = superior frontal sulcus; SMG = supramarginal gyrus; SOG = superior occipital gyrus; SPaLob = superior parietal lobe.

lineated anteriorly by the postcentral sulcus and posteriorly by the imaginary line running from the point from which the parietooccipital sulcus emerges (on the superomedial border) to the preoccipital notch, which is situated on the inferolateral border, ~ 5 cm anterior to the occipital pole.[79] The intraparietal sulcus, which originates from around the midpoint of the postcentral sulcus, is prominent along the parietal superolateral surface, in general runs almost parallel to the interhemispheric fissure, and posteriorly penetrates into the occipital lobe. The intraparietal sulcus divides the superolateral parietal surface into the superior and inferior parietal lobules (Fig. 9).

The superior parietal lobule is quadrangular and typically connected to the postcentral gyrus via a connection that transects the most superior portion of the postcentral sulcus and, occasionally, via another fold that more inferiorly interrupts the postcentral sulcus. The superior parietal lobule is delineated laterally by the intraparietal sulcus; medially, it is continuous with the precuneus gyrus along the superomedial border (Fig. 4); and, posteriorly, it continues to the superior occipital gyrus via the prominent and arched superior parietooccipital fold that surrounds the external perpndicular fissure, which represents the depth of the parietooccipital sulcus over the superolateral cerebral surface (Fig. 9). In some brains, there is also a small sulcus, designated the *superior parietal sulcus*, emerging from the interhemispheric fissure, between the postcentral sulcus and the external perpendicular fissure, over the superior parietal lobule.[50]

The inferior parietal lobule consists of, anteriorly, the supramarginal gyrus, which is a curved gyrus surrounding the distal portion of the sylvian fissure, and, posteriorly, the angular gyrus, which encircles the horizontal distal portion of the superior temporal sulcus. The supramarginal and angular gyri characterize the cranial parietal tuberosity, or bossa. Those 2 gyri are separated by the intermediate sulcus[77] (of Jensen), which is an inferior vertical branch of the intraparietal sulcus or a distal and superior vertical branch of the superior temporal sulcus or both (Fig. 3).

Anteriorly, the supramarginal gyrus is connected to the postcentral gyrus via a fold that lies around the inferior portion of the postcentral sulcus; inferiorly, it consistently encircles the terminal portion of the sylvian fissure and continues to the superior temporal gyrus; and posteriorly, it occasionally rounds the inferior border of the intermediate sulcus, connecting to the angular gyrus (Figs. 3 and 5). In turn, the angular gyrus typically curves anteriorly around a distal horizontal branch of the superior temporal sulcus, also known as the *angular sulcus*,[50] continuing to the middle temporal gyrus and giving rise to a posterior fold that connects it to the middle occipital gyrus. (Broca, basing his ideas on the work of Gratiolet, considered the supramarginal and angular gyri to be folds connecting the parietal lobe with the temporal lobe. From Broca's perspective, the supramarginal gyrus, which wraps around the distal portion of the sylvian fissure, corresponded to Gratiolet's superior marginal fold, and the angular gyrus, which wraps around the distal portion of the superior temporal sulcus, corresponded to the inferior marginal fold, or curved fold.[71,72])

Therefore, the intraparietal sulcus delineates superiorly the supramarginal and angular gyri with a slightly arciform and inferiorly concave course, and, anteriorly, it typically continues to the inferior portion of the postcentral sulcus. Posteriorly, the continuation of the intraparietal sulcus becomes the intraoccipital sulcus,[14,44] also known as the *superior occipital sulcus*[71] or *transverse occipital sulcus*,[50] which separates the (more vertical) superior occipital gyrus from its (more horizontal) middle counterpart.[14,50,71,72] Along its length, the intraparietal sulcus typically gives rise to 2 vertical folds: a smaller, superior fold located anterior to the external perpendicular fissure, known as the *transverse parietal sulcus of Brissaud*, and another inferior, more developed fold that constitutes the previously mentioned intermediate sulcus of Jensen, which separates the supramarginal gyrus from the angular gyrus.[71,72,77] The superior parietal lobule, supramarginal gyrus, and angular gyrus are also known as P1, P2, and P3, respectively.

On the medial surface of each hemisphere, the precuneus gyrus is a medial extension of the superior parietal lobule along the superomedial border of the brain and corresponds to to the medial portion of the parietal lobe (Fig. 4). The precuneus is also quadrangular, delineated anteriorly by the marginal branch of the cingulate sulcus, posteriorly by the parietooccipital sulcus, and inferiorly by the subparietal sulcus. Inferiorly to the subparietal

sulcus, the precuneus is connected to the isthmus of the cingulate gyrus and the parahippocampal gyrus.

The Occipital Lobe

On the superolateral cerebral surface, the occipital lobe is situated posterior to the imaginary line that connects the point of emergence of the parietooccipital sulcus (on the superomedial border of the cerebral hemisphere) with the preoccipital notch. The sulci and gyri of the occipital lobe have greater anatomical variation as compared with other lobes. Despite being less well defined and less anatomically constant than gyri in other dorsal cortical areas, the occipital gyri of the superolateral cerebral surface tend to consist of 3 gyri that are, for the most part, arrayed longitudinally in relation to the interhemispheric fissure and converge posteriorly to form the occipital pole of each hemisphere. As is the case for the frontal and temporal lobes, the occipital gyri of the superolateral surface are usually designated superior, middle, and inferior,[14,71] or O1, O2, and O3, respectively. While the superior occipital gyrus is arranged more vertically along the interhemispheric fissure, the middle and inferior occipital gyri are arranged more horizontally and parallel to the inferior cerebral margin (Fig. 9).

On the medial surface, the occipital lobe is particularly well defined anatomically. It is separated from the parietal lobe by the parietooccipital sulcus and is composed of the cuneal and lingual gyri, which are separated by the calcarine fissure (Fig. 4). The basal, or inferior, surface of the occipital lobe, in turn, is contiguous with the basal surface of the temporal lobe (Fig. 10).

On the superolateral surface, whereas the superior and middle occipital gyri are separated by the intraoccipital sulcus,[14,44,71] which is the continuation of the intraparietal sulcus and is also known as the *superior occipital sulcus*[14,71] and *transverse occipital sulcus*,[50] the middle and inferior occipital gyri are separated by the less well-defined inferior occipital sulcus,[14,71] also known as the *lateral occipital sulcus*.[50] When present, the so-called lunate sulcus is typically oriented vertically, immediately facing the occipital pole.[14,50] Given the shallow depth and discontinuity as well as the (often) multiple branches of the 2 principal occipital sulci, the occipital gyri are not always well defined and are typically joined by various anastomotic folds, and thus constitute a cortical surface that is difficult to characterize morphologically. (According to the description given by Gratiolet, the parietal and temporal lobe connections with the occipital lobe are made via 4 folds [2 parietooccipital and 2 temporooccipital]: 1) the first and more superior parietooccipital fold, which surrounds the external perpendicular occipital fissure and connects the superior parietal lobule with the superior occipital gyrus; 2) the second and more inferior parietooccipital fold, composed of a posterior extension of the angular gyrus, which converges with the middle occipital gyrus and also occasionally with the superior occipital gyrus; 3) the first temporooccipital fold, characterized by the union of the middle temporal gyrus and the inferior occipital gyrus; and 4) the second temporooccipital fold, characterized by the union of the inferior temporal gyrus and the inferior occipital gyrus.[71,72])

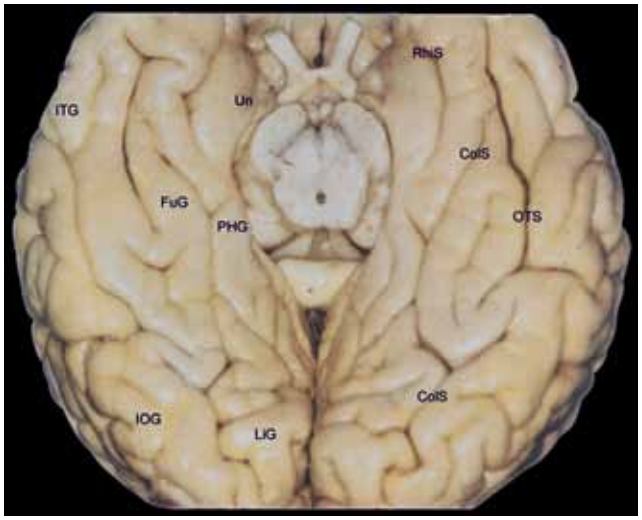

Fig. 10. The basal temporooccipital surface. ColS = collateral sulcus; FuG = fusiform gyrus; IOG = inferior occipital gyrus; ITG = inferior temporal gyrus; LiG = lingual gyrus; OTS = occipitotemporal sulcus; PHG = parahippocampal gyri; RhiS = rhinal sulcus; Un = uncus.

Superiorly, the superior occipital gyrus extends along the superior border of the cerebral hemisphere, thus continuing along the medial surface to the cuneal gyrus. Inferiorly, the inferior occipital gyrus extends along the inferolateral margin, and its basal surface is lateral to the medial temporooccipital gyrus, also known as the *lingual gyrus*, as well as to the collateral sulcus that separates the two.

On the medial surface of the cerebral hemisphere, as previously mentioned, the occipital lobe is delineated and characterized by its well-defined and anatomically constant sulci and gyri. Its principal sulcus is the calcarine fissure, which is located just above the inferomedial margin of the cerebral hemisphere. The calcarine fissure starts over the splenium of the corpus callosum, delineating inferiorly the isthmus of the cingulate gyrus from the parahippocampal gyrus, and continues posteriorly as a gentle and superior convex curvature from whose apex emerges, superiorly, the parietooccipital sulcus, which in turn delineates anteriorly the occipital lobe on the medial surface of the cerebral hemisphere. Posteriorly, the calcarine fissure occasionally crosses the superomedial margin and extends along the occipital pole to the superolateral surface of the cerebral hemisphere.

The point of emergence of the parietooccipital sulcus divides the calcarine fissure into its proximal and distal parts. Superior to the proximal portion of the calcarine fissure and anterior to the parietooccipital sulcus is the precuneal gyrus, which is part of the parietal lobe. Superior to its distal part and posterior to the parietooccipital sulcus is the cuneus, or cuneal gyrus, so designated because of its wedge shape.

Inferiorly and along the entire length of the calcarine fissure is the medial temporooccipital gyrus, or lingual gyrus, which anteriorly continues to the parahippocampal gyrus and constitutes the mediobasal portion of the occipital lobe, which is supported on the cerebellar tentorium.

The lingual gyrus is therefore delineated superiorly by the calcarine fissure and inferiorly by the collateral sulcus, which is a deep and generally continuous sulcus situated at the cerebral base, extending from the occipital pole to the temporal lobe and running parallel to the calcarine fissure.

The parietooccipital sulcus and calcarine fissure appear continuous on the surface. However, when their borders are retracted, it is obvious that they are separated by one or more small gyri. These gyri are composed of extensions of the cuneus and are known as the *cuneolingual gyri*.

The proximal part of the calcarine fissure is classified as a complete sulcus because its depth creates a rise in the medial wall of the occipital horn of the lateral ventricle, designated the *calcar avis*, and the distal part is considered an axial sulcus given that its axis runs along the visual cortex. Only the distal part includes the primary visual cortical areas, which are located on its superior (cuneal) and inferior (lingual) surfaces.

On the basal surface of the cerebral hemisphere, lateral to the lingual gyrus, is the medial temporooccipital gyrus or fusiform gyrus, situated between the collateral sulcus and the temporooccipital sulcus. The temporooccipital sulcus lies lateral and parallel to the collateral sulcus, rarely extends to the occipital pole, and in general is interrupted and divided into 2 or more parts. Anteriorly, the temporooccipital sulcus often bends medially and joins the collateral sulcus. The fusiform gyrus, in turn, extends to the basal surface of the temporal lobe, and lateral to its posterior portion lies the inferior occipital gyrus, whose lateral aspect constitutes the inferiormost portion of the lateral surface of the occipital lobe.

The Temporal Lobe

The temporal lobe is situated inferior to the sylvian fissure and delineated posteriorly by the imaginary line running from the superomedial portion of the parietooccipital sulcus to the preoccipital notch. Its lateral surface is composed of the superior, middle, and inferior temporal gyri—also respectively known as T1, T2, and T3—which are separated by the superior and inferior temporal sulci, parallel to the lateral or sylvian fissure (Fig. 3). Anteriorly, the middle temporal gyrus is generally shorter, causing the superior and inferior temporal gyri to come together, and thereby forming the temporal pole.

The superior temporal sulcus is always a very well defined and deep sulcus and often presents as a continuous sulcus because of its parallelism with the sylvian fissure. In fact, in the past it was called the *parallel sulcus*. The inferior temporal sulcus is usually discontinuous and composed of various parts. Both of the temporal sulci start at the proximal portion of the temporal pole and end posterior to its borders. Whereas the posterior portion of the sylvian fissure typically terminates as an ascending curve that penetrates the supramarginal gyrus, the superior temporal sulcus always terminates at a point posterior to the end of the sylvian fissure (posterior sylvian point). In general, the superior temporal sulcus then bifurcates into an ascending sulcal segment, which separates the supramarginal gyrus from the angular gyrus,

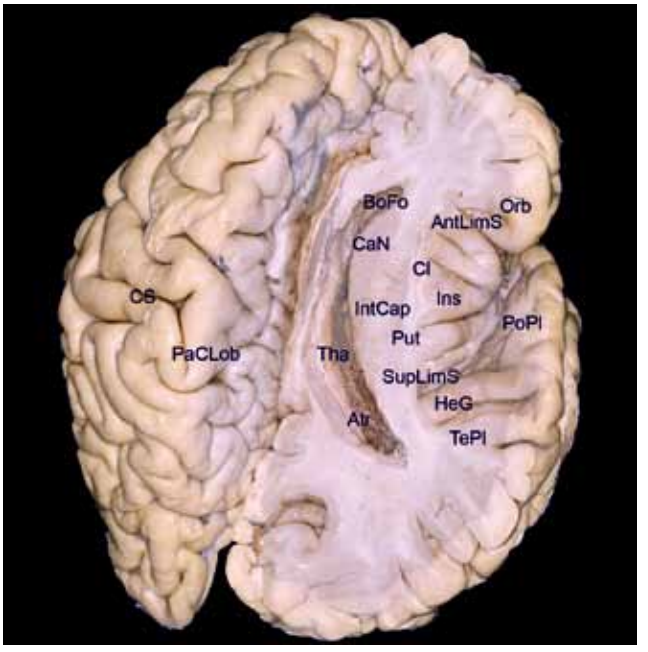

Fig. 11. The temporal opercular surface, the insula, and the central core of the brain. AntLimS = anterior limiting sulcus; Atr = atrium of lateral ventricle; BoFo = body of fornix; CaN = caudate nucleus; Cl = claustrum; CS = central sulcus; HeG = Heschl gyrus; Ins = insula; IntCap = internal capsule; Orb = orbital part of inferior frontal gyrus; PaCLob = paracentral lobule; PoPl = polar plane of the opercular temporal surface; Put = putamen; SupLimS = superior limiting sulcus of insula; TePl = temporal plane; Tha = thalamus.

and corresponds to the intermediate sulcus of Jensen, and a distal and horizontal segment that penetrates the angular gyrus.[50,60,62] Given this configuration of the sulci, the superior temporal gyrus always continues posteriorly to the supramarginal gyrus, encircling the terminal portion of the sylvian fissure. The middle temporal gyrus is often partially connected to the angular gyrus beneath the distal and horizontal portion of the superior temporal sulcus that penetrates the angular gyrus proper and inferiorly is often connected to the inferior occipital gyrus. In turn, the inferior temporal gyrus continues to the inferior occipital gyrus, over the preoccipital notch that posteriorly delineates the temporal lobe. Inferiorly, the inferior temporal gyrus extends along the inferolateral margin of the cerebral hemisphere. Medially, its basal surface lies along the lateral temporooccipital gyrus, or fusiform gyrus, and along the temporooccipital sulcus that separates the 2 gyri (Fig. 10).

The superior temporal gyrus constitutes the temporal operculum and covers the inferior aspect of the insular surface, and its superior, or opercular, surface (Fig. 11), which is within the sylvian fissure, is composed of various transverse gyri that emerge from the superior temporal gyrus and are directed obliquely toward the inferior part of the circular insular sulcus.[73,78]

Chief among these temporal gyri of the operculum is a much more voluminous transverse gyrus that originates in the posteriormost portions of the superior temporal gyrus and is oriented diagonally toward the posterior vertex of

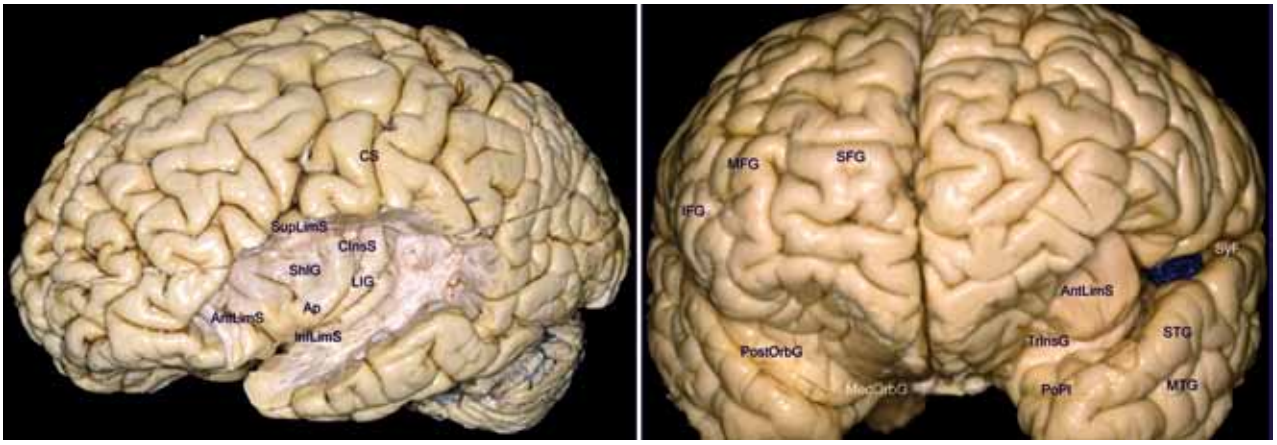

Fig. 12. The lateral **(left)** and anterior **(right)** surfaces of the insula. AntLimS = anterior limiting sulcus; Ap = insular apex; CInsS = central insular sulcus; CS = central sulcus; IFG = inferior frontal gyrus; InfLimS = inferior limiting sulcus; ITG = inferior temporal gyrus; LIG = long insular gyri; MedOrbG = medial orbital gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; PoPl = polar plane of the opercular temporal surface; PostOrbG = posterior orbital gyrus; SyF = sylvian fissure; SFG = superior frontal gyrus; ShIG = short insular gyri; STG = superior temporal gyrus; SupLimS = superior limiting sulcus of insula; TrInsG = transverse insular gyrus.

the floor of the sylvian fissure and toward the ventricular atrium. This gyrus is designated the *transverse gyrus of Heschl*. In some brains, 1 or 2 sulci divide this gyrus; and in such cases, 2 or 3 gyri are also featured. Together with the posteriormost aspect of the superior temporal gyrus, the most anterior transverse gyrus of Heschl constitutes the primary auditory cortical area.[73,79] This gyrus has particular topographical importance because it underlies the opercular surface of the postcentral gyrus, its longest axis is oriented toward the ventricular atrium, and it divides the temporal opercular surface into 2 planes: an anterior plane called the *polar plane* and a posterior plane known as the *temporal plane* (Fig. 11).[78]

The floor of the polar plane is composed of short transverse gyri at oblique angles, and the lower border of the plane is defined by the inferior portion of the circular insular sulcus that runs along the bottom of the sylvian fissure. The temporal plane is triangular with an internal vertex that exactly corresponds to the posterior vertex at the bottom of the sylvian fissure, where the superior part of the circular insular sulcus comes into contact with its inferior part. The temporal plane is oriented horizontally and faces the inferior surface of the supramarginal gyrus as if supporting its anteriormost portion. Whereas the sylvian fissure appears oblique in coronal slices taken in the polar plane, it appears horizontal in those taken in the temporal plane.

The basal surface of the temporal lobe is continuous with the basal surface of the occipital lobe and is situated over the floor of the middle cranial fossa, anterior to the petrous portion of the temporal bone, whereas the basal occipital surface lies over the superior surface of the cerebellar tentorium.

The temporal lobe is composed laterally of the inferior surface of the inferior temporal gyrus and the anterior portion of the lateral temporooccipital gyrus, or fusiform gyrus, and medially of the inferior surface of the parahippocampal gyrus. The fusiform gyrus is situated lateral to the parahippocampal and lingual gyri, between the collateral and temporooccipital sulci. Its temporal portion presents a slight basal prominence due to its adaptation to the concavity of the middle cranial fossa. Its anterior aspect is typically curved or pointed, because the anteriormost portion of the temporooccipital sulcus frequently presents a medial curvature toward the collateral sulcus (Fig. 10). The anterior border of the fusiform gyrus, in general, corresponds medially to the level of the mesencephalic peduncle; as a whole, it constitutes the floor of both the atrium and the inferior horn of the lateral ventricle.

The parahippocampal gyrus and the anterior portion of the collateral sulcus have been described as limbic lobe structures.

The Insular Lobe

On the publication of the fourth edition of the Paris *Nomina Anatomica* in 1975,[18] the insula came to be considered a cerebral lobe. The insular surface is composed of the so-called mesocortex, which is anatomically situated between the allocortex, which is older and topographically more medial (comprising the amygdala and hippocampus), and the isocortex, which is phylogenetically younger and topographically more lateral (comprising the neocortex of the cerebral hemispheres).

Embedded between the frontal and temporal lobes of each cerebral hemisphere and constituting the base of each sylvian cistern, the insula has an anterior surface and a lateral surface (Fig. 12) that are encased in their respective opercular convolutions,[73] which correspond to the regions of the cerebral hemispheres that have lately become more fully developed. The anterior surface of the insula is covered by the frontoorbital operculum (comprising the posterior portion of the posterior orbital gyrus and the orbital part of the inferior frontal gyrus), whereas its lateral surface is covered superiorly by the frontoparietal operculum (triangular and opercular parts of the inferior frontal gyrus, subcentral gyrus, and anterior and basal part of the supramarginal gyrus) and inferiorly by

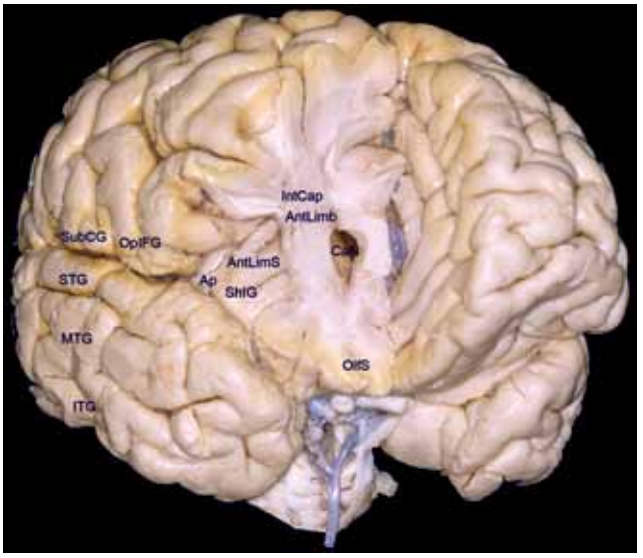

Fig. 13. The anterior surface of the insula and the anterior horn of the lateral ventricle. AntLimb = anterior limb of the internal capsule; AntLimS = anterior limiting sulcus; Ap = insular apex; CaN = caudate nucleus; IntCap = internal capsule; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; OlfS = olfactory sulcus; OpIFG = opercular part of the inferior frontal gyrus; ShIG = short insular gyri; STG = superior temporal gyrus; SubCG = subcentral gyrus.

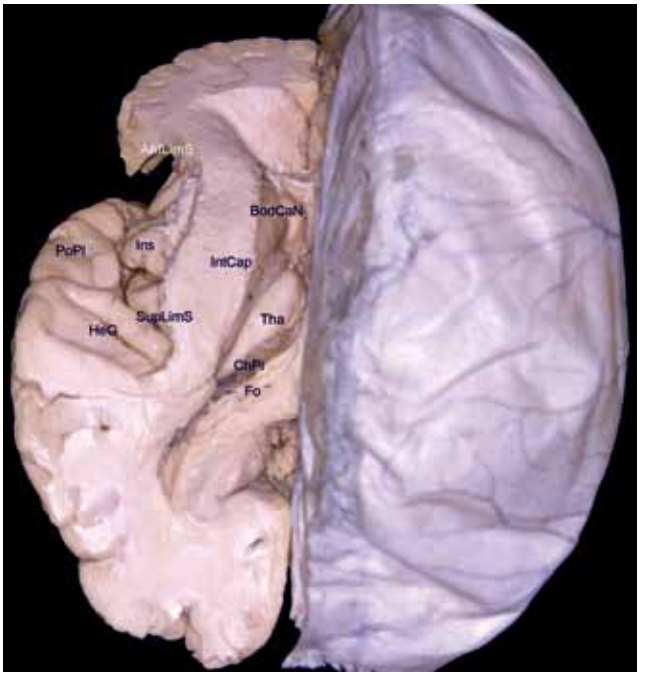

Fig. 14. The insular lateral surface corresponds to an external shield of the central core of the brain. AntLimS = anterior limiting sulcus of insula; BodCaN = body of the caudate nucleus; ChPl = choriodal plexus; Fo = fornix; HeG = Heschl gyrus; Ins = insula; IntCap = internal capsule; PoPl = polar plane of the opercular temporal surface; SupLimS = superior limiting sulcus of insula; Tha = thalamus.

the temporal operculum (superior temporal gyrus; Figs. 5 and 6).[73,79,87]

The lateral surface of the insula is characterized as a pyramid with a triangular base, whose anteroinferior vertex constitutes the limen insulae, and is divided by the oblique central sulcus of the insula into an anterior portion and a posterior portion, with the former having a larger area. The anterior portion is typically composed of 3 short gyri that originate at the apex of the insula, which corresponds to the most prominent aspect of the insular pyramid, with the anteriormost aspect extending over the anterior surface of the insula; and the posterior portion, in general, is composed of 2 long gyri not originating at the apex but oriented obliquely and in parallel. The transverse and accessory insular gyri, which together constitute the insular pole, also originate from the apex of the insula.[73,74] The transverse insular gyrus, which is situated more inferiorly, runs along the limen insulae and is connected to the posteromedial orbital lobule, which is composed of the posterior portion of the medial orbital gyrus and the medial portion of the posterior orbital gyrus[73,81] and is located anterior and along the lateral olfactory stria.

The insular surface is delineated peripherally by the circular sulcus of Reil,[14,70] or periinsular sulcus,[72,73] which is interrupted by the previously mentioned transverse insular gyrus. Given the triangular shape of the insula, its circular, or periinsular, sulcus is usually divided into 3 parts, that is, the anterior, superior, and inferior periinsular sulci,[73] also designated the *anterior*, *superior*, and *inferior limiting sulci of the insula*.[57]

To understand the periinsular spaces more fully, one should remember that the insula has a lateral surface and an anterior surface. The superior and inferior limiting sulci are morphologically categorized as true sulci that delineate the respective transitions and deflections occurring among the lateral insular surface and the frontoparietal operculum, and the lateral insular surface and the temporal operculum. The so-called anterior limiting sulcus of the insula, on the other hand, is considerably deeper and morphologically characteristic of a true fissure or space that separates the anterior surface of the insula from the posterior surface of the posterior orbital gyrus.

The upper half of the fundus of the anterior limiting sulcus is separated from a true anterior ventricular recess at the head of the caudate nucleus only by the fibers of the thin anterior limb of the internal capsule, whereas the fundus of the lower half continues to the ventral striatopallidal region (Fig. 13).

From a morphological and topographical perspective, the surface of the insula clearly represents the external shield of a true central core of the brain,[57] quite well defined anatomically. This central core of the brain comprises, in each cerebral hemisphere, the insula proper, the basal nuclei, the thalamus, and the internal capsule (Fig. 14). The anterior half of the lateral surface of the insula corresponds internally to the head of the caudate nucleus, whereas the posterior half corresponds to the thalamus and the body of the caudate nucleus. Each central core of each cerebral hemisphere, composed of all the structures mentioned above, is incorporated into the corresponding half of the mesencephalon, morphologically characterizing a brainstem with 2 heads that correspond to the 2 central cores (Fig. 15).

Under the insular cortex and its respective subcorti-

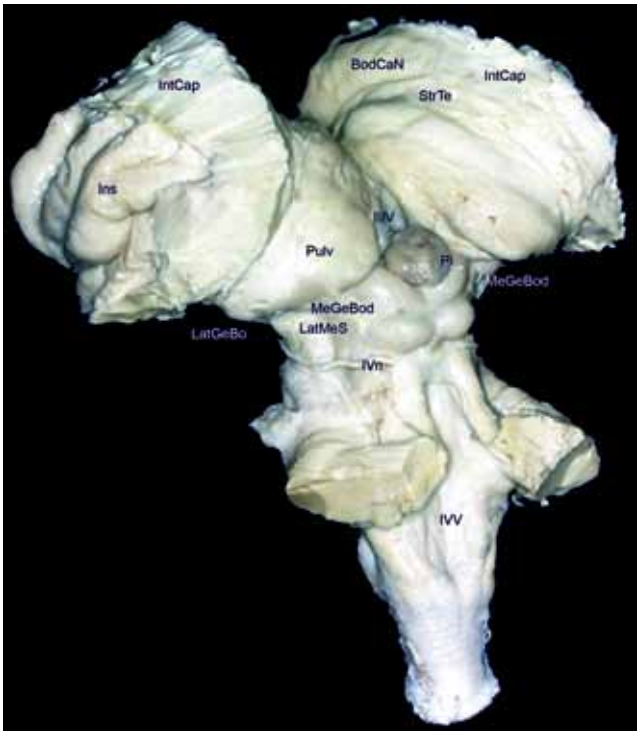

Fig. 15. Each central core of the brain corresponds to a head of each half of the brainstem. BodCaN = body of the caudate nucleus; Ins = insula; IntCap = internal capsule; LatGeBo = lateral geniculate body; LatMeS = lateral mesencephalic sulcus; MeGeBod = medial geniculate body; Pi = pineal gland; Pulv = pulvinar of thalamus; StrTe = stria terminalis; IIIV = third ventricle; IVn = trochlear nerve; IVV = fourth ventricle.

cal white matter, also known as the *extreme capsule*, is the fine lamina of gray matter that constitutes the claustrum. Underneath that is the putamen, enclosed within its external and internal capsules. The thin external capsule is composed of fibers that cover only the lateral portion of the putamen and are bereft of major functional importance, whereas the internal capsule consists of important projection fibers that originate from, and are directed toward, the cerebral cortex as a whole. Since the area of the putamen is slightly smaller than that of the lateral surface of the insula,[73] and given the shape of the internal capsule, the recesses of the anterior, superior, and inferior limiting sulci are practically adjacent to the fibers of the internal capsule.

The Limbic Lobe and Correlated Areas

The Limbic Lobe. The publication entitled *International Anatomical Terminology,* published in 1998[21,66] and replacing the previous *Nomina Anatomica,* introduced the limbic lobe as another of the cerebral lobes and described it as comprising the cingulate and parahippocampal gyri.

The term *limbic* was first used in the 19th century by Broca,[5] who observed that certain cerebral structures constituted a continuum arranged in the shape of a C surrounding the diencephalic region. Since then the term *limbic*—meaning border, ring, or surround[22]—came to be definitively established in the neuroanatomical literature.

TABLE 3: Principal limbic cortical structures

cingulate gyrus
parahippocampal gyrus
hippocampal formation
hippocampus (Ammon's horn)
subiculum
dentate gyrus
prehippocampal rudiment/indusium griseum
frontal mediobasal cortical area
paraterminal gyrus
paraolfactory gyri or subcallosal area
olfactory cortical areas

Subsequent studies introduced the notion that the limbic system is composed of telencephalic and diencephalic structures that, despite their anatomical and functional diversity, are particularly responsible for the physiology of emotions, memory, and learning.[29,33,58,59,79]

The limbic system, in its entirety, is composed of cortical, subcortical, and nuclear structures that are interconnected and have connections with other areas of the CNS via a complex network of tracts (Table 3). However, the principal elements of the limbic system are the hippocampal formation and the amygdala, which participate in distinct circuits with the rest of the brain. The hippocampal formation is principally related to telencephalic and diencephalic structures via circuits whose basic purpose is to convert short-term memory into long-term memory, whereas the circuits that include the amygdala are more strictly related to the emotions and ultimately influence the effector systems (autonomic, neuroendocrine, and motor), primarily via the hypothalamus.

Within the medial surface of each cerebral hemisphere, one prominent feature is the cingulate gyrus, which wraps around the corpus callosum and continues posteriorly and inferiorly to the parahippocampal gyrus, forming the shape of a C around the diencephalon (Fig. 4). Broca originally described the cingulate and parahippocampal gyri as contiguous, jointly dubbing them the *greater limbic lobe*. He also considered the cingulate, subparietal, and collateral sulci to be segments of the sulcus he referred to as the *limbic sulcus*.[5,29,30]

The cingulate gyrus is situated above the callosal sulcus and below the cingulate sulcus. It starts below the rostrum of the corpus callosum, and as it ascends around the knee of the corpus callosum, it typically presents a connection with the medial (or medial aspect of the superior) frontal gyrus. Under the trunk of the corpus callosum it is connected to the paracentral lobule, and more posteriorly it is connected to the precuneus. These connections, which vary in number, are arrayed from front to back and from bottom to top and are particularly visible after removing the cingulate gyrus's most cortical aspect.

Posterior to the splenium of the corpus callosum

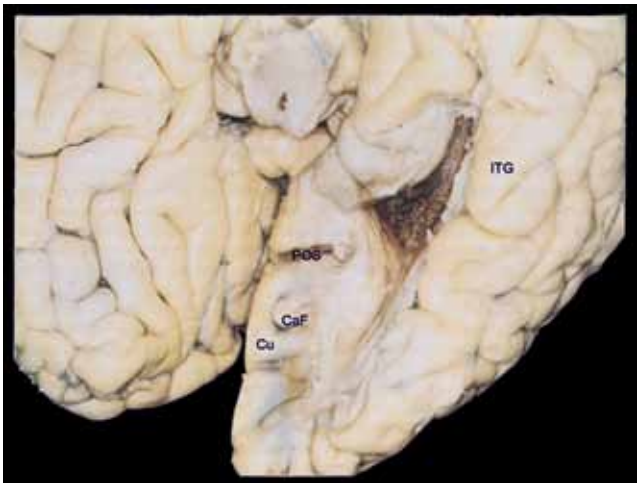

Fig. 16. Basal view of the parahippocampal gyrus and the atrium after removing the fusiform and lingual gyri. CaF = calcarine fissure; Cu = cuneus; ITG = inferior temporal gyrus; POS = parietooccipital sulcus.

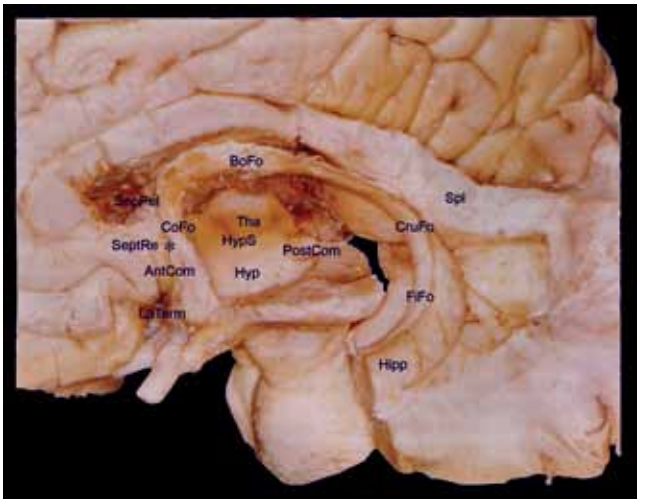

Fig. 17. The corpus callosum, fornix, septal area, and septum pellucidum. AntCom = anterior commissure; BoFo = body of fornix; CoFo = column or pillar of the fornix; CruFo = crura of fornix; FiFo = fimbria of the fornix; Hipp = hippocampus; Hyp = hypothalamus; HypS = hypothalamic sulcus; LaTerm = lamina terminalis; PostCom = posterior commissure; SepPel = septum pellucidum; SeptRe = paraterminal gyrus/septal region; Spl = splenium of corpus callosum; Tha = thalamus.

the cingulate gyrus consistently becomes narrower, at which point it is referred to as the *isthmus of the cingulate gyrus*, and continues to the parahippocampal gyrus. The site of transition between these 2 gyri is identified by the emergence of the anterior branch of the calcarine fissure, which originates beneath the isthmus of the cingulate gyrus.

As already mentioned, the terminal ascending branch of the cingulate sulcus delineates posteriorly the paracentral lobule and anteriorly the precuneus, whereas the subparietal sulcus is located inferior to the precuneus, separating it from the cingulate gyrus and appearing to be a posterior continuation of the cingulate sulcus after a short interruption of the latter. The connections between the cingulate and the precuneus gyri are anterior and posterior to the subparietal sulcus.

The parahippocampal gyrus forms the lower half of the C that wraps around the diencephalic region. Posteriorly, it comprises the isthmus of the cingulate gyrus and is also the anterior continuation of the lingual gyrus, which lies under the calcarine fissure. The parahippocampal gyrus is situated lateral to the cerebral peduncle. Anteriorly, it folds back on itself medially, assuming the shape of a hook and constituting the uncus of the parahippocampal gyrus situated anterolateral to the cerebral peduncle, and harbors the uncal sulcus.

Medially, the parahippocampal surface curves superiorly and laterally, constituting the subiculum, characterized as a flat, superior surface running along the anteroposterior axis of the parahippocampal gyrus and under the pulvinar of the thalamus, so that these 2 surfaces constitute the portion of the transverse fissure of the brain that harbors the so-called wing of the ambient cistern. The hippocampus is situated lateral to the subiculum.

The hippocampus consists of Ammon's horn, which is characterized as an intraventricular prominence (Fig. 16), and the small dentate gyri, which lie laterally along Ammon's horn. The small dentate gyri are separated from the subiculum by the hippocampal sulcus, which anteriorly terminates within the uncus. Given the greater magnitude of Ammon's horn, the term *hippocampus* is commonly used in reference to this structure. Within the ventricular cavity, Ammon's horn, or the hippocampus, is covered by the alveus, a thin layer of fibers that gives rise to the fimbria of fornix, the principal bundle of efferent fibers of the hippocampus (Fig. 17). These structures are collectively known as the *hippocampal formation*. Between the dentate gyri and the fimbria of fornix is the fimbriodentate sulcus, which lies lateral and parallel to the hippocampal sulcus.[15,78]

The uncus of the parahippocampal gyrus is triangular with a medial vertex, such that its anteromedial surface faces the carotid cistern and its posteromedial surface faces and encircles the mesencephalic peduncle (Fig. 7). Two small prominences known as the *semilunar gyrus* and *ambient gyrus*, which are separated by the semiannular sulcus, are evident in the anterior portion of the surface of the uncus. The ambient gyrus, which is more inferior, often presents with a depression caused by the pressure of the free edge of the tentorium cerebelli. The anterior half of the uncus includes the amygdala, whereas its posterior half includes the head of the hippocampus.[78] Superiorly, the amygdala runs toward the base of the globus pallidus so that, in a coronal slice, the base of the lentiform nucleus and the amygdala form a figure-eight or an hourglass shape.[74,78,79]

Along the cerebral base, the parahippocampal gyrus is laterally delineated by the collateral sulcus, which separates it from the fusiform gyrus, and by the rhinal sulcus, which is occasionally continuous with the collateral sulcus. The rhinal sulcus, which is not always readily identifiable, is consistently the sulcus that separates the uncus from the rest of the temporal pole (Figs. 7 and 10).

Some authors consider the indusium griseum and its connections as also belonging to the hippocampal formation.[15,79] The indusium griseum is composed of a thin

layer of gray matter situated over the corpus callosum. On each side, the indusium griseum is characterized by medial and lateral striae that run within the callosal sulcus and constitute the remains of the vestigial indusium. Because it lies laterally within the callosal sulcus, it can be confused with the cortex of the cingulate gyrus of each side. Anteriorly, the indusium griseum is connected to the paraterminal gyrus via the prehippocampal rudiment. Posteriorly, it circles the splenium of the corpus callosum and on each side runs along the fasciolar gyri (fasciola cinerea, gyrus of Andreas Retzius, and retrosplenial gyri), a thin layer of gray matter that reaches to the posterior portion of the dentate gyrus.

To ease understanding of the anatomical features, it is interesting to remember that, phylogenetically, the hippocampus is supracallosal in origin, subsequently migrating posteriorly and inferiorly and finally presenting as a structure that runs along the floor of the inferior horn of the lateral ventricle.[64] Considering these observations, the indusium griseum can be understood as a remnant of the supracallosal hippocampus, and the fornix as its tail that was left behind during its inferior migration.

The Temporal Stem. Laterally, the parahippocampal gyrus is contiguous with the fusiform gyrus and the remainder of the basal surface of the brain. Posteriorly, it continues along the cingulate gyrus. Medially, it runs under the thalamus along the natural space comprising the choroidal fissure. Anteriorly, its uncal portion is superiorly incorporated into the lateralmost aspect of the frontobasal region via a well-defined neural peduncle anterior to the inferior horn of the lateral ventricle.

Anteriorly and externally, this true temporal peduncle is composed of the cortex of the transverse insular gyrus, which crosses the limen insulae, connecting to the posteromedial orbital lobule.[82] Internally, it consists of the uncinate fascicle, which joins the frontal and temporal lobes;[16] fibers of the frontooccipital fascicle, which are arrayed immediately posterior to the uncinate fascicle; amygdalofugal fibers, which are composed of the ventral extensions of the amygdala—that project to the septothalamohypothalamic region[79] and the nucleus of the stria terminalis, situated under the head of the caudate nucleus[29,30,40]—and fibers of the anterior commissure. Medially, it includes the superior extension of the amygdala, which superiorly extends medially to the putamen and toward the globus pallidus.[78]

In the literature, this set of structures has been given the generic and controversial name of *temporal stem*, equivalent to the *temporal axis*. According to Duvernoy,[14] "the temporal stem consists of only a thin layer of white matter situated between the ventricular cavity and the fundus of the superior temporal sulcus." In contrast, Wen et al.[78] stated that the term refers "only to the connections between the temporal lobe and the insula, excluding the superior extension of the amygdala in the direction of the globus pallidus and the limen insulae." Türe et al.[73] defined the temporal stem as "the portion of white matter that penetrates the temporal lobe between the anterior border of the insula and the inferior horn, . . . composed of the fronto-occipital fascicle and the anterior thalamic peduncle," and therefore being the portion anterior to the sagittal stratum, which in the present text is designated the *temporal stem* and can be understood as the *peduncular portion of the temporal stem*.

Posterolaterally, the temporal stem is contiguous with the layers of fibers called the *sagittal strata*,[37,74] which cover the inferior horn and ventricular atrium. All of these structures collectively join the temporal lobe to the remainder of the cerebral hemisphere beneath the insula. The so-called sagittal stratum consists of the frontooccipital fascicle, the inferior thalamic peduncle, or radiation—which encompasses the auditory and optic radiations—and the fibers that compose the anterior commissure and tapetum. The layer of callosal fibers known as the *tapetum* lies under the optic radiation and then constitutes the most inferior layer of the sagittal stratum. The sagittal stratum is situated inferiorly to the inferior limiting sulcus of the insula, forming the roof and lateral wall of the inferior horn and consituting the lateral wall of the ventricular atrium. Superficial to the sagittal stratum is the subcortical white matter of the entire neocortical portion of the temporal lobe.

From a topographical perspective, it is notable that the sagittal stratum corresponds to the set of fibers that cover the inferior horn and atrium of the ventricle, inferiorly and posteriorly to the insula, whereas the temporal stem is situated anterior to the inferior horn, connecting the anteromedial temporal portion to the basolateral frontal portion of the brain.

The Basal Forebrain and Ventral Striatopallidal Region. The mediobasal frontal cortical area of each cerebral hemisphere, composed of the paraterminal gyrus and the paraolfactory gyri, is also considered a limbic cortical area. The paraterminal gyrus is situated on the medial wall of each cerebral hemisphere, immediately facing and quasi-continuous with the lamina terminalis, and is delineated anteriorly by a short, vertical sulcus known as the posterior olfactory sulcus. The small anterior curvature of the paraterminal gyrus is called the prehippocampal rudiment and extends superiorly, along the previously described indusium griseum. Inferiorly, the paraterminal gyrus extends along the diagonal band of Broca and the lateral olfactory stria.

The posterior and anterior paraolfactory gyri, which are also vertical and separated by the anterior paraolfactory sulcus (the latter not always identifiable), are located anterior to the paraterminal gyrus. This area of the paraolfactory gyri is also known as the *subcallosal area*. Anterior to the subcallosal area is a fold that connects the basalmost portion of the cingulate gyrus with the gyrus rectus, encircles the posteriormost part of the superior rostral sulcus, and is called the *cingulate pole*.[82]

The paraterminal gyri harbor the septal nuclei[79] and constitute the septal area, which corresponds to the so-called paraolfactory area of Broca.[36] Therefore, the septal region is situated on the medial surface of the cerebral hemisphere, immediately facing the anterior commissure. This region is also known as the *septum verum* ("true septum"), or *precommissural septum*,[8,29,79] in counterpoint to the septum pellucidum, which does not contain neuronal

cells and is situated posterior and superior to the anterior commissure, morphologically constituting the medial walls of the anterior horns and the ventricular bodies. (The septal nuclei receive afferents principally from the hippocampus and subiculum of the parahippocampal gyrus via the indusium griseum as well as from the precommissural fornix. The efferents of the septal nuclei project to the area surrounding the hippocampus via the fornix itself and to the hypothalamus, the mesencephalon [via the medial prosencephalic fasciculus], and the habenula [via the stria medullaris thalami], which in turn projects to the mesencephalon.[8,29,39,79] Functionally, the septal nuclei are responsible for connecting limbic structures with the hypothalamus and the brainstem, principally via the hippocampal formation. The so-called septal syndrome is clinically characterized by exaggerated reactions to environmental stimuli and the consequent behavioral alterations, principally related to eating and drinking habits, as well as by episodes of rage and disorders in the sexual sphere.)

The generic term *olfactory cortical areas* refers to the olfactory nerves, bulb, tract, trigone, and striae as well as the anterior perforated substance, the diagonal band of Broca, and the piriform lobe, in each cerebral hemisphere. The piriform lobe comprises the following: 1) the prepiriform cortical area; 2) the lateral olfactory stria, which extends to the gyrus semilunaris; 3) the uncus of the parahippocampal gyrus and the small gyri of which it consists (uncinate gyrus, caudal portion of the dentate gyrus or band of Giacomini, and intralimbic gyrus); and 4) the entorhinal area (rostralmost area of the parahippocampal gyrus, easily recognized by its speckled, superficial aspect, attributed to the discontinuity of its most superficial cell layer, characterized by islands of large, multipolar neurons).

The area known as the *anterior perforated substance* constitutes a particularly important topographical region of the basal forebrain (Fig. 7 right). Macroscopically, this area is delineated anteriorly by the olfactory trigone and the lateral and medial olfactory striae, whereas it is delineated posteriorly by the edges of the optic tracts, medially by the interhemispheric fissure, and laterally by the uncus of the parahippocampal gyrus and the limen insulae. Topographically, the anterior perforated substance is situated just above the bifurcation of the internal carotid artery, and thus forming the roof of the space that harbors the distal portion of the artery and the proximal segments of the anterior and middle cerebral arteries. The perforating branches that emerge from those arterial segments constitute the lenticulostriate arteries, and it is from the surface of the anterior perforated substance that they penetrate the frontobasal parenchyma. In fixed anatomical specimens from which the arachnoid and blood vessels have been removed, its surface is easily identified by its multiple orifices. Laterally, the anterior perforated substance continues to the limen insulae, where it extends along the prepiriforme cortex (the cortical area that lies lateral to the lateral olfactory stria and is also occasionally referred to as the *lateral olfactory gyrus*). More posteriorly, it extends to the periamygdaloid area (the semilunar gyrus, where the lateral olfactory stria terminates

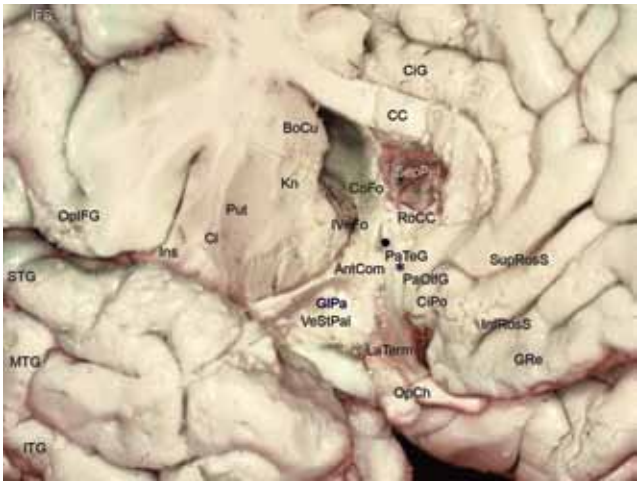

Fig. 18. The subinsular central core structures and the ventral striatopallidal and septal region. AntCom = anterior commissure; BoCu = body of caudate nucleus; CC = corpus callosum; CiG = cingulate gyrus; CiPo = cingulate pole; Cl = claustrum; CoFo = column or pillar of the fornix; GlPa = globus pallidus; GRe = gyrus rectus; IFS = inferior frontal sulcus; InfRosS = inferior rostral sulcus; Ins = insula; ITG = inferior temporal gyrus; IVeFo = interventricular foramen of Monro; Kn = knee of corpus callosum; LaTerm = lamina terminalis; MTG = middle temporal gyrus; OpCh = optic chiasm; OpIFG = opercular part of the inferior frontal gyrus; PaOlfG = paraolfactory gyri; PaTeG = paraterminal gyrus; Put = putamen; RoCC = rostrum of the corpus callosum; SepPel = septum pellucidum; STG = superior temporal gyrus; SupRosS = superior rostral sulcus; VeStPal = ventral striatopallidal region.

and which harbors the cortical amygdaloid nuclei of the amygdaloid complex). The posteriormost portion of the anterior perforated substance is traversed by the diagonal band of Broca, a particularly smooth bundle of fibers immediately facing the optic tract.

Posteriorly, the anterior perforated substance extends along the cell aggregates and nerve fibers that compose the so-called ventral striatum region, which harbors the ventral striatopallidal system structures and is currently considered an important site in relation to the limbic system. From a functional point of view, one of the basic principles of the concept of the limbic system is that its structures project to the hypothalamus—not to the basal ganglia, as occurs in the remainder of the cerebral cortex.[29,30,33] However, it has been shown that the portion most anterior and basal to the striatum (nucleus accumbens and striatal areas of the olfactory tubercle) receives projections not only from the olfactory cortex, hippocampus, entorhinal cortices, cingulate gyrus, and temporal pole, but also from the orbitomedial and insular cortices. In addition, the nucleus accumbens projects to the anteriormost portions of the globus pallidus, which in turn gives rise to anterior thalamocortical projections. These findings prompted Heimer and colleagues[31,32] to include within the concept of the "greater limbic lobe" the posterior regions of the orbital cortex and the insula. Various authors came to view the ventral striatum and ventral pallidum as regions of the basal ganglia that include the ventral corticostriatopallidal system, which is distinct from the classical dorsal corticostriatopallidal system related to motor activities, and with particular

neuropsychiatric implications.[30,31,33,42] Functionally, the caudal, or dorsal, system is composed of certain cortical surface connections (neocortex—dorsal striatum—dorsal pallidum—ventrolateral thalamic nuclei—motor cortex), whereas the ventral system is composed of the allocortex and mesocortex connections (greater limbic lobe—ventral striatum—ventral pallidum—dorsomedial thalamic nuclei—prefrontal cortex/cortex of the anterior part of the cingulate gyrus).[29]

The brain region currently known as the *ventral striatopallidal system*,[29,32] or more simply the *ventral striatum* (Fig. 18), corresponds in part to the substantia innominata, a name taken from the historical literature in German, and can be confused with the concept of the basal forebrain in current English literature. (Note that the substantia innominata of Reichert corresponds most closely to the ventropallidal region.[30,36]) The ventral striatum refers to the basal forebrain region situated between the anterior perforated substance and the anterior commissure of each cerebral hemisphere. Superiorly, it is closely related to the most anterobasal portion of the anterior limb of the internal capsule, whereas laterally it is contiguous with the peduncle of the temporal stem, and medially it is particularly related to the septal region and the hypothalamus. The ventral striatopallidal region includes the nucleus accumbens, which corresponds to a basal connection of the head of the caudate nucleus with the most anterior and inferior portion of the putamen (hence the name *ventral striatum*), the globus pallidus, the magnocellular nucleus of the basal forebrain (nucleus basalis of Meynert), and the fibers that constitute the ventral extension of the amygdala and are directed toward the septal region, the hypothalamus, the thalamus, and the bed nucleus of the stria terminalis, located under the head of the caudate nucleus. Because of its topography, the ventral striatum is crisscrossed by the perforating lenticulostriate arteries. Functionally, the ventral striatum is closely correlated with neuropsychiatric functions.[30,31,33,59]

Superiorly, the ventral striatum and pallidum are covered by the anterior limb of the internal capsule, which harbors the fibers that carry their projections to the prefrontal and anterior cingulate cortices.[32,40] Medial to the ventral striatum and ventral pallidum is the portion of the hypothalamus that forms the inferior part of the ipsilateral wall of the third ventricle and, more anteriorly, the septal region.

Topographical Aspects of the Limbic Structures. It is interesting to note that the mediobasal frontal cortical areas (paraterminal gyrus and subcallosal area), the olfactory cortical areas (anterior perforated substance and components of the piriform lobe), and the ventral pallidal-striatum region (with its subjacent nuclei) constitute a corticosubcortical continuum running along the ventral surface of the brain from the medial portion of the temporal pole to the posterior mediobasal portion of the frontal lobe, with its posterior border being delineated by the anterior commissure.

These structures extend along the anterior and medial surface of the cerebral hemisphere via the cingulate gyrus and along the basal surface via the parahippocampal gyrus; these 2 gyri are posteriorly continuous (Fig. 19). Therefore, the limbic lobe looks like a slightly tilted circle. In relation to the midsagittal plane, in which the diencephalic structures are located, the superior portion of the limbic lobe is more medial, whereas its inferior portion is more lateral. The ventral striatopallidal region, which encompasses the substantia innominata, is then situated under the anterior base of the limbic lobe. Topographically, it is posterior to the anterior perforated substance, anterior to the anterior commissure, and inferior to the fibers of the anterior limb of the internal capsule. Laterally, the ventral striatum is contiguous with the temporal stem and the amygdaloid complex, whereas medially it is contiguous with the septal region.

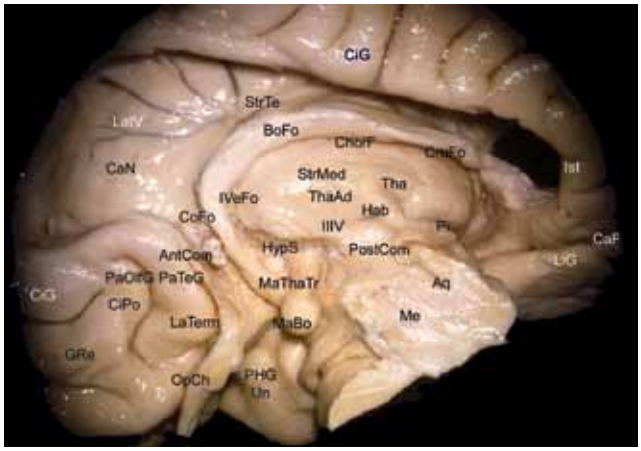

Fig. 19. The medial deep cerebral structures after removal of the corpus callosum. AntCom = anterior commissure; Aq = cerebral aqueduct; BoFo = body of fornix; CaF = calcarine fissure; CaN = caudate nucleus; ChorF = choroidal fissure; CiG = cingulate gyrus; CiPo = cingulate pole; CoFo = column or pillar of the fornix; CruFo = crura of fornix; GRe = gyrus rectus; Hab = habenula; HypS = hypothalamic sulcus; Ist = isthmus of cingulate gyrus; IVeFo = interventricular foramen of Monro; LaTerm = lamina terminalis; LatV = lateral ventricle; LiG = lingual gyrus; MaBo = mamillary body; MaThaTr = mamillothalamic tract; Me = mesencephalon; OpCh = optic chiasm; PaOlfG = paraolfactory gyri; PaTeG = paraterminal gyrus; PHG = parahippocampal gyri; Pi = pineal gland; PostCom = posterior commissure; StrMe = stria medullaris of thalamus; StrTe = stria terminalis; Tha = thalamus; ThaAd = interthalamic adhesion; Un = uncus; IIIV = third ventricle.

In parallel with these observations, Mesulam[43] proposed that because of their particularly superficial presentation, the most medial portions of the amygdaloid complex, the substantia innominata (within the ventral striatopallidal region), and the septal nuclei (within in the paraterminal gyri), which together constitute the basal forebrain, should be considered constituents of the cerebral mantle.

In conclusion, it should be emphasized that although the cortical areas mentioned compose the cortical portion of the limbic lobe, the concept of the limbic system as a functional unit also involves the participation of deep structures and is controversial in terms of its conception and composition.[29–31,59] From a morphological perspective, however, the structures that make up the limbic system present as a series of C-shaped curves centered around the thalamus and hypothalamus in each cerebral hemisphere. Nieuwenhuys et al.[45] characterized the orga-

nization (medial to lateral) of 5 of these curves: 1) stria medullaris thalami, habenular nuclei, and habenulointerpeduncular tract; 2) amygdala, posterior extension of the amygdala (stria terminalis), and anterior extension of the amygdala, which project to the nucleus of the stria terminalis, located below the head of the caudate nucleus, and together constitute the so-called extended amygdala;[48,49] 3) fimbria, crura, body, and column of fornix, which connect the hippocampus to the mammillary body; 4) hippocampus and longitudinal striae (indusium griseum), which connect the hippocampus with the paraterminal gyrus; and 5) cingulate gyrus and parahippocampal gyrus.

Discussion

Given their phylogenetic and embryological development, especially the process of invagination of the surface of the brain, which effectively increases the cortical area without proportionally increasing the volume of the brain,[64,79] the cerebral sulci, which delineate the respective gyri, can be considered natural extensions of the subarachnoid space. When they are deep and anatomically constant, they are referred to as *fissures*.[6,7] The principal sulci have approximate depths ranging from 1 to 3 cm, and their walls harbor small gyri that face, adapt to, and connect with each other. Those gyri are generically designated the *transverse gyri*. The sulci that separate the transverse intrasulcal gyri vary in length and depth. At the surface of the brain, they become visible as incisures. The indentations caused by cortical arteries can have an appearance similar to that of the incisures.

To understand and correctly identify the sulci, and consequently the cerebral gyri, it is fundamental to consider the notion that the characterization of a given sulcus does not necessarily imply that it is composed of a single continuous space. A sulcus can consist of one or more parts, which in some cases can be oriented in different directions. Those parts can be long or short and can be isolated or connected to other sulci.[50]

It is noteworthy that the timing of their embryological development and their degree of variability define[11,46] a true morphological hierarchy, at the top of which are the fissures and principal sulci (Table 2). It is equally notable that this structural hierarchy is directly correlated with the functional importance of the areas to which the sulci are related, the more anatomically constant sulci being those that are topographically related to areas that are more specialized.

Typically, the sulci are divided into 4 types: limiting, axial, opercular, and complete.[79] Albeit complex, this system of classification is useful for demonstrating the heterogeneity of the cerebral sulci. The axial sulci develop along the axis of a functionally homogeneous area, as in the case of the posterior portion of the calcarine fissure, which is actually a fold situated in the center of the striate visual cortex. In any given gyrus, the invaginations made by the axial sulci result in the formation of subgyri, whose white matter can be designated *subgyral sectors of the principal gyrus*. The limiting sulci are situated between functionally different cortical areas. One example is the central sulcus, which separates the motor area from the sensory area. The opercular sulci are also situated between cortical areas that are structurally and functionally different. However, unlike the separations defined by the limiting sulci, those created by the opercular sulci exist only along their edges and not in their fundi. One example of an opercular sulcus is the lunate sulcus, which, when present, is oriented vertically, separating the striate and peristriate areas of the cortical surface and including the submerged parastriate area within its walls.

The sulci referred to as *complete sulci* are those whose fundi produce rises in the walls of the lateral ventricles. For example, the collateral sulcus creates the collateral eminence on the floor of the inferior horn, and the calcarine fissure causes the calcar avis in the medial wall of the posterior horn.[79] This phenomenon has no functional significance and is only of morphological importance.

As some other authors have observed, the sylvian fissure and parietooccipital sulcus are the only sulci that do not fall into 1 of the 4 categories and therefore must be understood on the basis of their own development.[50,79] The slower expansion of the insular cortex leads to its consequent submersion by the adjacent areas, and the convergence of those areas delineates the sylvian fissure, or lateral cerebral sulcus. The sylvian fissure is composed of a deep anterior and a posterior branch that harbor the sylvian cistern. The frontoparietal and temporal opercular surfaces constitute the walls of the sylvian fissure, and the insular surface is its floor.

The parietooccipital sulcus as well as the external perpendicular fissure that constitutes its extension over the superolateral surface is formed as a consequence of the development of the corpus callosum. Interhemispheric fibers originating in the occipital and temporal lobes are then carried by the posteriormost portion of the corpus callosum, which results in the invagination of the medial surface and the consequent creation of the parietooccipital sulcus. This process also leads to the development and grouping of smaller axial and limiting sulci that are located together in the intrasulcal walls of the parietooccipital sulcus.

From a more objective and practical standpoint and as proposed by Ono et al.,[50] the cerebral sulci can be characterized as follows: interrupted or continuous (sylvian fissure, calcarine fissure, callosal sulcus, parietooccipital sulcus, collateral sulcus, and central sulcus); and long or short. These authors divided the sulci into the following categories: long principal sulci (central, precentral, and postcentral sulci together with those listed above as continuous); short principal sulci (rhinal, olfactory, intraparietal, and intraoccipital, or occipital superior, sulci); short sulci composed of multiple branches (orbital and subparietal sulci); and free supplementary sulci (frontal medial and lunate sulci).[50] Often the sulci are also composed of branches to which they are not connected or to which they are connected in an end-to-end, side-to-side, or end-to-side manner, and such connections can even join 2 parallel sulci. Because of the frequency of such connections, there are discrepancies in the literature regarding the nomenclature and definitions of the sulci.[14,50,72] To fully understand the cerebral sulci and gyri, one must realize that even the principal sulci can vary in form and size from

person to person and that the surface of the brain constitutes a true continuum, presenting a serpentine configuration given its various forms of connections surrounding the sulcal extremities and running under the fundus of the sulci.[82] The separation between neighboring and adjacent gyri is therefore only superficial and is structurally defined by the continuity and the fundi of the sulci that surround them. The interruption of a sulcus or the presence of a free sulcal extremity necessarily indicates the presence of a fold that connects different gyri or different sectors of the same gyrus. Each cerebral gyrus should therefore be understood as a region of the brain surface and not as an individual, anatomically well-defined neural structure. In terms of nomenclature, the gyri that are more rounded or quadrangular are usually referred to as *lobules*.

For microneurosurgical applications, is also notable that given the mechanism of invagination of the surface of the brain throughout its evolution and embryological development,[64] the sulci of the superolateral and inferior surfaces of the brain are consistently oriented toward the nearest ventricular cavity, which is especially evident in coronal slices of MR imaging studies. This disposition of the sulci is not seen on the medial surface of the hemispheres because the development of the sulci on this surface is directly related to that of the corpus callosum, and these sulci therefore tend to be arranged in parallel with this commissure.[50]

Considering that the cerebral gyri constitute a continuum via their multiple and, in part, variable superficial and deep connections, it is important to understand that the gyri are actually composed of arbitrarily circumscribed regions on the surface of the brain and that they are delineated by the cerebral sulci, which correspond to extensions of the subarachnoid space and are equally arbitrary in terms of their extensions and interruptions throughout the cerebral surface.

Conclusions

The brain fissures and sulci constitute the fundamental anatomical delimiting landmarks of the cerebral gyri and the main surgical corridors of modern microneurosurgery. Despite their variability, both cerebral sulci and gyri are organized according to a basic configuration that permits their identification.

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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The reliability of neuroanatomy as a predictor of eloquence: a review

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The adjacency of intracranial pathology to canonical regions of eloquence has long been considered a significant source of potential morbidity in the neurosurgical care of patients. Yet, several reports exist of patients who undergo resection of gliomas or other intracranial pathology in eloquent regions without adverse effects. This raises the question of whether anatomical and intracranial location can or should be used as a means of estimating eloquence. In this review, the authors systematically evaluate the factors that are known to affect anatomical-functional relationships, including anatomical, functional, pathology-related, and modality-specific sources of variability. This review highlights the unpredictability of functional eloquence based on anatomical features alone and the fact that patients should not be considered ineligible for surgical intervention based on anatomical considerations alone. Rather, neurosurgeons need to take advantage of modern technology and mapping techniques to create individualized maps and management plans. An individualized approach allows one to expand the number of patients who are considered for and who potentially may benefit from surgical intervention. Perhaps most importantly, an individualized approach to mapping patients with brain tumors ensures that the risk of iatrogenic functional injury is minimized while maximizing the extent of resection. *(DOI: 10.3171/2009.11.FOCUS09239)*

Key Words • brain mapping • cortical stimulation • eloquence • functional magnetic resonance imaging

The adjacency of intracranial pathology to canonical regions of eloquence has long been considered a significant source of potential morbidity in the neurosurgical care of patients.[52] Yet, several reports exist of patients who undergo resection of gliomas or other intracranial pathology in eloquent regions without adverse effects.[37,39] For example, Plaza and colleagues[37] recently reported on a patient who underwent resection of a posteroinferior left frontal glioma. The patient's speech was grossly intact even after resection of the Broca area. Such reports not only highlight the "efficiency of brain plasticity," but also call into question whether anatomical and intracranial location can or should be used as a means of estimating eloquence. It is increasingly apparent from the scientific and clinical literature that the relationship between anatomy and function is not as clearly coupled as once believed and that this relationship is even more complicated in patients with intracranial pathology.[9]

The sources of variability of functional localization, including anatomical, functional, pathology-related, and modality-specific sources, are systematically reviewed in this manuscript, highlighting the unpredictability of functional eloquence based on anatomical features alone. We argue that patients should not be considered ineligible for surgical intervention based on anatomical considerations alone. Rather, neurosurgeons need to take advantage of modern technology and mapping techniques to create individualized maps and management plans for each patient.

Abbreviations used in this paper: AVM = arteriovenous malformation; ECoG = electrocorticography; ESM = electrocortical stimulation mapping; LGG = low-grade glioma.

Anatomical Variability

Across patients, the human brain has a stereotypical pattern of gyri and sulci that forms the basis of neuroanatomical teaching. In patients without intracranial mass lesions, the consistent patterns of sulci and gyri enable clinicians and researchers to use neuroimaging studies to reliably identify neuroanatomical structures. For example, Kido and colleagues[25] identified a constant relationship between the posterior end of the superior frontal sulcus and the precentral sulcus to aid in the localization of the precentral gyrus. Similarly, Yousry and colleagues[60] suggested the precentral gyrus (even more specifically, the hand region of the motor strip) can be identified by the presence of a "knob-like" structure that is shaped like the Greek letters omega or epsilon on axial imaging. These common features across patients at least partially justify the development of neuroanatomical atlases such

as those of Talairach and Tournoux, and Schaltenbrand and Wahren, and the common practice in neuroscientific research to refer to specific cerebral areas by coordinates (for example, in the Talairach coordinate system, the inferior frontal gyrus corresponds to –56, +12, +32).[46,54]

Despite these common features and neurosurgery's historical reliance on atlases, there is tremendous interpatient neuroanatomical variability. Single-patient atlases, such as that of Schaltenbrand and Wahren, cannot account for normal variability across patients, let alone more complex variability introduced by aging, disease, and other unanticipated factors. Technological advances and increased availability of neuroimaging have made it easier to recognize this variability across patients. For example, Caulo and colleagues[13] reassessed the "knob-like" region of the motor strip in 257 patients and found 5 variants of the regions, 3 of which were previously undescribed. Likewise, Ebeling and colleagues[19] characterized the inferior precentral sulcus anatomy and identified 4 major anatomical variants. Anatomical variability is perhaps best highlighted by average intensity volumetric atlases, such as the MNI 305 and ICBM 452, which use multiparameter transformations and high-order polynomial warping to align brains of multiple patients, but still contain indistinct representations of both cortical and subcortical structures (Fig. 1).[47] Because of this, Shattuck and colleagues[47] constructed a probabilistic atlas in which they provided a voxel-by-voxel probability of finding a specific cortical structure at a given location, demonstrating a high degree of variability in the spatial localization of each cortical landmark. Similar probabilistic anatomical maps have been generated for subcortical structures.[1] Neuroanatomical studies have identified multiple factors that affect anatomical variability, including but not limited to sex, handedness, aging, and neurological and psychiatric diseases such as depression, psychosis, and dementia.[2,3,30,33,56,57]

In the neurosurgical population, additional interpatient anatomical variability arises from the presence of intracranial pathology. Space-occupying lesions can efface adjacent sulci such that normal anatomical and imaging landmarks are more difficult or impossible to identify.[42,59] Moreover, slow-growing low-grade tumors can infiltrate (and widen) neighboring gyri in such a way as to obliterate normal anatomical landmarks but retain function within the limits of the tumor.[49]

Interpreting the relationship between anatomy and function and the significance of neuroanatomical variability is further complicated by the fact that anatomical variability is associated with and may itself contribute 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 (see Josse and Tzourio-Mazoyer[24] for review).[23,53] These studies unambiguously demonstrate that anatomical variability and functional organization are intimately related in multiple dimensions, in ways that are difficult to account for on an individual basis.

Given current technology and paradigms, the potential factors that can affect neuroanatomical variability, particularly the unpredictable effect of intracranial mass lesions on neighboring brain, are likely too numerous to account for and make it difficult to use neuroanatomical landmarks to predict eloquence when evaluating an individual's brain.

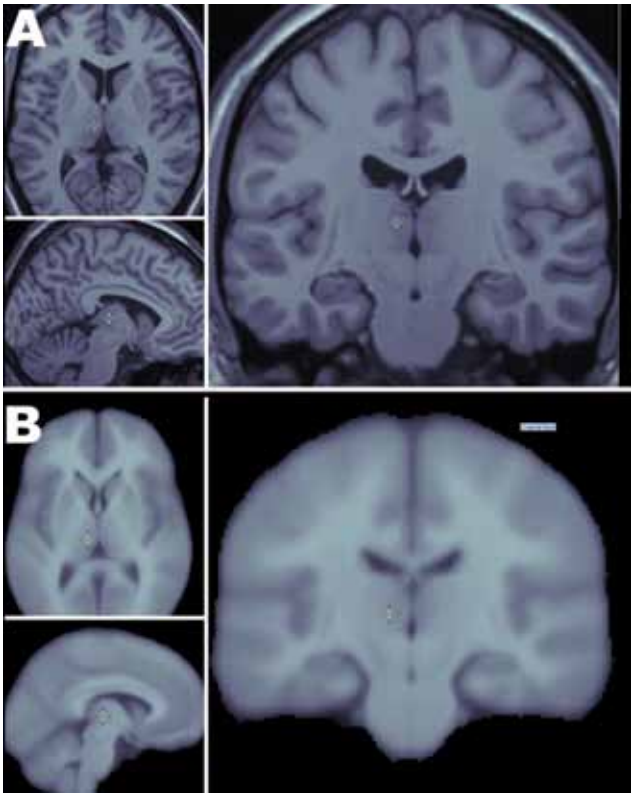

Fig. 1. Anatomical variability of cerebral anatomy across 452 patients (ICBM 452 Atlas). **A:** Axial, sagittal, and coronal views of a T1-weighted MR image of a single patient's brain, demonstrating the high degree of precision with which a single patient's cerebral anatomy can be imaged. **B:** Axial, sagittal, and coronal views of the average brain of 452 patients who were imaged using the same imaging protocol as that in **A**. In this "average brain," patients' brains were linearly transformed into a common space using a 12-parameter affine transformation.

Intrinsic Functional Variability

Early reports of functional organization suggested that function is tightly coupled to anatomy and that anatomical and imaging landmarks can be reliably used to predict the functional organization of the brain.[4,25] For example, in the report described above by Kido and colleagues,[25] the authors suggest that the knob-like landmark of the precentral gyrus was highly predictive of the primary motor cortex dedicated to control of the hand. The assumption of tight and specific functional-anatomical coupling emerged in part from Penfield's depiction of the homunculus, which was intended as a pictorial simplification of his original findings.

Over time, it has become increasingly apparent that even with anatomical constraints to account for structural variability, functional localization is highly variable.[7,20,48,55] For example, the concept of the precentral knob representing the primary motor area of the hand has

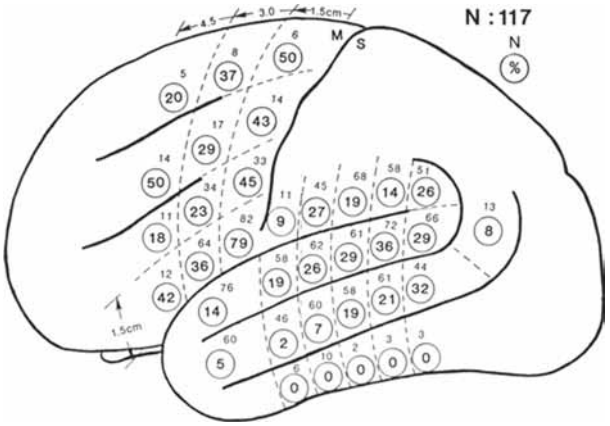

Fig. 2. Image demonstrating the variability in language localization in 117 patients. Electrocortical stimulation maps from 117 patients were plotted in a common space, based on major anatomical landmarks. The upper number in each area is the number of patients who had language testing performed in that cortical region and the lower number (in the circle) represents the percentage of all patients tested in that cortical region in whom cortical stimulation evoked significant naming errors (essential language sites). M = motor cortex; S = sensory cortex. From Ojemann et al.: Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. **J Neurosurg 71:**316–326, 1989.

been called into question with a recent report suggesting that depending on the patient, the "knob" can either represent primary motor or premotor cortex.[48] Others have reported variability in the functional organization of the primary sensorimotor cortices as well. For example, within the precentral gyrus, stimulation of individual cortical sites has been shown to recruit both sensory and motor phenomenon and in other cases stimulation has been shown to recruit motor movements in more than 1 motor group.[7,20,45] Variability in essential language cortices has also been described. For example, even after accounting for the anatomical variability of the posterior inferior frontal area, the University of California San Francisco group reported > 4 cm of variability in the localization of speech arrest sites in that region.[42]

Although the University of California San Francisco group studied the variability of language function within anatomical constraints, the representation and variability of language cortices is generally more widespread, involving multiple cortical regions throughout the frontal, parietal, and temporal lobes.[17,34,44] In fact, the distribution of language sites is so vast that it is easier to predict where language will not be (for example, the inferior temporal gyrus) than where it is likely to be.[34] Not all areas, however, are equally likely to be essential for language function. For example, Ojemann and colleagues[34] reported that the posterior inferior frontal region is essential in 79% of patients, whereas the anterior middle temporal gyrus is essential in only 5% of patients (Fig. 2). The variability of speech arrest sites in the frontal lobe (the Broca area) is generally greater than that of the parietotemporal regions (the Wernicke area). Despite the widespread distribution at a population level, essential language sites in an individual are usually discreet and occupy a smaller surface area than traditional descriptions of the Broca and Wernicke areas.[34] These ESM studies of functional variability have important limitations. Although intrinsic functional variability likely contributes significantly to the reported results, the effect of intracranial pathology (such as epilepsy and tumor) on the reported functional variability cannot be excluded or separated (discussed below). Also, these studies divide the brain into parcels based on predetermined metric distances (1 or 3 cm) rather than anatomical landmarks and therefore do not and cannot wholly account for the contribution of anatomical variability or intracranial mass lesions to the final results.

Disease-Related Functional Variability

The anatomical and functional variability described above are complex enough to make it unlikely to predict eloquence with a high level of precision and accuracy even in healthy patients. These intrinsic sources of variability, which are present in every individual, are compounded by the presence of intracranial pathology. Besides changes in cerebral anatomy (discussed above), intracranial pathology can introduce at least 3 additional sources of potential variability.

First, the presence of intracranial lesions, especially congenital lesions such as AVMs, may result in distinct patterns of functional acquisition. For example, several studies have noted a greater preponderance of right-sided language lateralization in patients with cerebrovascular malformations.[28,58] By comparing these patients with those with adult-onset left hemisphere brain injury, who retain a normal distribution of language lateralization, Vikingstad and colleagues[58] suggested that the congenital nature of vascular malformations contributes to the atypical patterns of functional acquisition. Likewise, in patients with left temporal lobe epilepsy, earlier age of onset has been associated with a greater likelihood of atypical language lateralization, suggesting that the presence of intracranial pathology may affect acquisition (or consolidation) patterns.[8,22] Whether these case series represent differential acquisition as opposed to reorganization is not entirely clear and is subject of great debate. However, for the purposes of the current discussion, the definitive cause for atypical organization is not necessarily important. What these and other studies show is that functional organization patterns (especially that of language) are different in patients with intracranial pathology and healthy patients.

As noted, intracranial pathology may not only affect acquisition patterns, but can also induce functional reorganization, in which functional representations shift to adjacent or remote (contralateral) regions due to insult to or progressive enlargement or involvement of eloquent structures, such as may be the case with LGGs. For example, Lucas and colleagues[29] compared language maps in patients with adult-acquired neurological injury (including glioma, subarachnoid hemorrhage, and traumatic brain injury) with age-matched controls and found that patients with neurological injuries have a greater proportion of frontal lobe language areas than controls, suggesting functional reorganization of language representations in these patients. The degree of functional reorganization and compensation, both neurophysiologically and

behaviorally, is likely related to the time course of the disease, a topic reviewed extensively by Desmurget and colleagues.[16] This relationship is perhaps best exemplified by the fact that patients with LGG rarely present with neurological deficits.[36] Moreover, mapping studies in patients with LGG demonstrate multiple patterns of reorganization and compensation, including identifying function persisting within the tumor or redistributed immediately around the tumor, throughout the ipsilateral hemisphere, or into the contralateral hemisphere.[16] In all cases, patients seemingly have no deficit. This result is in stark contrast to outcomes in patients with acute stroke, who do not compensate or recover as well as patients with LGG of the same size and in the same location.[16] Studies of serial intraoperative mapping in patients with repeated surgeries for gliomas unambiguously demonstrated that the functional organization of the brain is dynamic and is subject to acute changes in the local environment. For example, Robles and colleagues[43] reported on 2 patients in whom maps of eloquent language cortices changed between surgeries spaced by several years, allowing a multistaged surgical approach for resection of LGGs in eloquent cortices. Duffau and colleagues[18] have also similarly reported acute patterns of reorganization during the same surgery, again reinforcing the concept that short- and long-term changes in the intracranial environment can lead to reorganization or unmasking of eloquent functions that would be impossible to predict based on anatomical localization alone.

Besides influencing the functional organization of the brain, intracranial disease can also cause disease-related imaging artifacts. Although this characteristic does not specifically affect the relationship between anatomy and function, it introduces yet another level of uncertainty in assessing eloquence. For example, some argue that functional MR imaging cannot be used to map eloquent cortices adjacent to AVMs because AVMs may alter the perfusion-dependent response that functional MR imaging relies on or because AVMs cause susceptibility artifacts that can interfere with detection of the blood oxygen level–dependent functional MR imaging response. These potentially disease-specific preoperative mapping limitations suggest that it is important to verify the reliability and accuracy of different mapping modalities in each disease population. For example, we specifically tested the accuracy and reliability of blood oxygen level–dependent functional MR imaging mapping in patients with vascular malformations and found that functional MR imaging is highly sensitive and specific for determining language localization in patients with vascular malformations, even directly adjacent to these lesions.[39]

Mapping-Related Sources of Variability in Functional Localization

The myriad of preoperative and intraoperative functional brain mapping techniques raise yet another layer of complexity. Although all mapping modalities measure functional changes that are related to underlying neuronal activity, the maps generated by various mapping techniques may not be directly comparable because the precise signal measured with each technique differs. Moreover, despite extensive research, the precise significance and relationship between various mapping signals is not necessarily well understood. Broadly speaking, functional brain mapping techniques localize brain function by measuring either electrophysiological or perfusion-related signals. Electrophysiological maps can be generated using single unit recordings, ECoG and local field potentials, and electroencephalographic or magnetoencephalographic techniques. On the other hand, PET, functional MR imaging, and optical imaging generate maps based on perfusion-related signals that are coupled to neuronal activity (to support local metabolism). Cortical stimulation mapping and transcranial magnetic stimulation are in a class of their own because maps are generated by inducing temporary lesions to disrupt function rather than measuring activity-related signals.

While all mapping techniques will (or should) produce similar maps, intermodality variation exists due to differences in techniques and underlying assumptions. The relationships between these various mapping techniques have been the subject of numerous studies, including comparisons between ESM and PET,[6] ESM with functional MR imaging,[39] ECoG and ESM,[10] ECoG with functional MR imaging,[26,32] optical imaging and functional MR imaging,[11,38,41] electroencephalography with functional MR imaging,[31] and functional MR imaging with single units and local field potentials.[32,35] Ultimately, for clinical relevance and implementation, each technique will have to be evaluated relative to patient outcomes. In the meantime, the most important comparisons from a clinical perspective are those between each technique and ESM. Whereas most mapping techniques identify all areas that are recruited by a specific task (detecting all activity-related signals), ESM only identifies essential areas, or areas without which the task cannot be executed. Consequently, in most such comparisons, techniques that map nonessential cortices are considered to be very sensitive but not very specific. With current technologies and implementation, preoperative and intraoperative mapping techniques besides ESM at best provide a framework within which to map the exposed brain but cannot replace ESM.[10,39] Further discussion of studies comparing the various mapping signals is beyond the scope of this review but are critical for gaining insight into the physiological basis of and the relationship between the different modalities. The salient point is that while all signals are related, there are inherent differences in modality-specific maps that must be considered.

In addition to intermodality variability, one must also consider trial-to-trial variability of mapping signals (which can result in distinct functional maps) and variability of functional maps related to differences in technique and analysis.[15,40] For most mapping modalities, post hoc analysis of acquired data are as important, if not more important, than the original acquisition parameters. The sources of variability can be center-specific and therefore may change the reliability, accuracy, or clinical relevance of one mapping technique from one medical center to another.

Conclusions

Despite a tradition in neurosurgery of relying on standardized atlases and anatomically defined regions of eloquence to guide surgical decision making, we must instead rely on individualized data and maps that can account for much (but not all) of the variability discussed. Moreover, we must rely on mapping techniques that have been validated relative to patient outcomes, rather than relative to a surrogate marker. Because we are practicing in an era in which neuroimaging, functional imaging, and intraoperative brain mapping are more accessible than ever, it is imperative that lesions in or near eloquent regions are managed using an individualized approach. An individualized approach allows us to make informed clinical and operative recommendations for each patient[12] and expands the number of patients who are considered for and who potentially may benefit from surgical intervention.

Given the probability that more extensive resection of gliomas is associated with improved outcomes,[21,50] all patients with gliomas should be given serious consideration for resective surgery. Resectability is affected by multiple factors, including size, diffuse borders, insular or temporal lobe involvement, and presumed eloquent location.[14] When eloquent location is one of the primary factors limiting consideration for resection, further preoperative functional evaluation is mandatory. Neurosurgeons practicing in facilities that do not have means for preoperative brain mapping (functional MR imaging) or intraoperative stimulation mapping should refer such patients to centers that can offer these services. There is no "gold standard' for preoperative mapping and evaluation because no preoperative brain mapping technique has been validated with respect to outcomes. Nonetheless, based on our experience, preoperative evaluation should include functional MR imaging at a minimum. Evaluation of resectability may be augmented with addition of diffusion tensor imaging to visualize the position and integrity of white matter tracts deep to and around the lesion.[5,27] Alternative approaches that have been advocated and could be considered include PET and magnetoencephalography/magnetic source imaging, depending on the experience, expertise, and availability of technology at a particular center.[5,51] Regardless of technique used, preoperative maps should be evaluated by a neurosurgeon who is experienced in interpreting these maps to determine the best surgical approach. In patients in whom resection is attempted, intraoperative stimulation mapping is mandatory because it is the only technique with validated outcome measures.[34,44]

An individualized approach to mapping patients with brain tumors such as the one described in this paper will ensure that the risk of iatrogenic functional injury is minimized while maximizing the extent of resection.[43]

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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The role of functional magnetic resonance imaging in brain surgery

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New functional neuroimaging techniques are changing our understanding of the human brain, and there is now convincing evidence to move away from the classic and clinical static concepts of functional topography. In a modern neurocognitive view, functions are thought to be represented in dynamic large-scale networks. The authors review the current (limited) role of functional MR imaging in brain surgery and the possibilities of new functional MR imaging techniques for research and neurosurgical practice. A critique of current clinical gold standard techniques (electrocortical stimulation and the Wada test) is given. *(DOI: 10.3171/2009.12.FOCUS09251)*

Key Words • **functional magnetic resonance imaging** • **neurosurgery** • **review** • **neuroscience** • **oncology**

Functional MR imaging can map the living brain in space and time. Because of its noninvasive nature and widespread availability, it has helped in revolutionizing cognitive neuroscience, and it has shed new light on the cerebral representation of functions.[56,58,96] In a modern neuroscientific view, cognitive and behavioral functions are thought to be dynamically represented in large-scale networks that are hierarchically organized around cortical epicenters.[3,56] Mesulam[56] stated, "At least five large-scale networks can be identified in the human brain," namely for spatial attention, language, memory-emotion, executive function, and face-and-object recognition. Such a network view largely opposes the dogmatic and static neurological models that are still used in clinical decision making. Key elements of these models are the almost invariant relationship between anatomy and function, and the strict subdivision of the brain either into eloquent areas (in which damage can to lead to permanent neurological deficit, for example, the Broca area) or noneloquent areas (in which damage is not expected to have any neurological implications, for example, right prefrontal cortex).

There is now abundant evidence that contradicts this more classic view; important findings are the substantial variation in anatomical and functional topography that is already present in healthy individuals, and the fact that the neural representation of brain functions is constantly changing on microscopic and macroscopic levels.[55] This plasticity is in fact a fundamental property of the brain, which permits normal physiological processes such as learning and memory. Under pathological conditions, the brain probably uses similar mechanisms to recover from functional loss whenever its networks are damaged. This explains why in some patients a brain tumor can grow to a considerable size without causing any obvious neurological deficits, or why children who had undergone a left hemispherectomy are able to walk and talk. In these cases, functions seem to have reorganized to perilesional or contralesional brain areas.[17,95]

Because fMR imaging has good spatial resolution and can easily be integrated with anatomical images, it is frequently used for presurgical planning or as an adjunct to existing techniques for this purpose, such as the amobarbital test and ESM. In experienced hands, it is already able to replace these techniques in some patients. However, the technique and methodology of fMR imaging are complex. Studies that have compared fMR imaging brain maps with the results of the amobarbital test and ESM have found an incomplete match between these modalities. From this incongruity, it is usually concluded that fMR imaging cannot yet replace the existing techniques and that further research and refinement are needed to obtain that goal. However, it is very likely that fMR im-

Abbreviations used in this paper: BOLD = blood oxygen level–dependent; DT = diffusion tensor; ESM = electrocortical stimulation mapping; fMR = functional MR; LI = lateralization index; MEG = magnetoencephalography; SMA = supplementary motor area.

aging findings will never completely agree with those from the amobarbital test and ESM because of fundamental differences in methods and outcome measures. More importantly, the techniques that are currently considered gold standards suffer from drawbacks and methodological flaws and need to be reevaluated for their purpose.

In the first part of this paper, we will review the pros and cons of fMR imaging and ESM as tools for localization of functional brain areas and as predictors of postoperative neurological function. We will conclude that the use of these techniques does indeed decrease the risk of postoperative neurological deficits as they are reliable predictors of immediate neurological outcome after surgery. However, they are not very sensitive tools to predict postoperative recovery or long-term functional outcome. Another drawback of current clinical techniques is that assessment of higher cognitive functions such as emotion or attention is very difficult or even impossible. In the second part of the paper, we will look at how new functional neuroimaging techniques are now beginning to elucidate the complex cortical and subcortical networks that sustain brain functions and their behavior under normal and pathological conditions. Arguments for a new network view of functional brain topography will be given, as well as clinical relevancy. Ultimately, functional neuroimaging techniques should become reliable clinical tools to model the long-term behavioral and cognitive effects of surgery in the individual patient. This will permit better presurgical risk assessment, will increase the efficacy of surgery, and can guide rehabilitation therapy.

Functional MR Imaging: a Short Introduction to Its Principles and Methods

Several articles and books are available that extensively review the technical, methodological, and practical aspects of clinical fMR imaging.[58,76] We will therefore only briefly touch on the most relevant aspects here from a clinical point of view.

Functional MR imaging rests on the assumption that there is a relationship between brain function and cerebral blood dynamics. There are several fMR imaging methods available, but the one most widely used employs the effect of deoxyhemoglobin on MR imaging signals (the BOLD effect).[60] 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. The BOLD changes seem most closely related to changes in afferent input.[49,63] Spatial resolution is high (typically between 1 and 5 mm), and submillimeter resolution of voxels is possible. There is a possible mismatch between the location of the BOLD signal and the actual site of neural activity that can be reduced to a maximum error of 3–6 mm with dedicated MR imaging and postprocessing techniques.[82,84] Temporal resolution is generally low, as the hemodynamic BOLD response lags behind the neural response by several seconds. There are methods to increase temporal resolution to tens of milliseconds.[54]

The foremost advantage of fMR imaging is that any sensorimotor or cognitive function of interest can in principle be studied once appropriate experimental conditions are devised. It is therefore not limited to the regions of the brain that have been damaged or to the function that is disturbed. Another advantage is that individuals without neurological impairments can be studied, which allows modeling of brain processes in a population that is free from the effects of pathology and potential reorganization

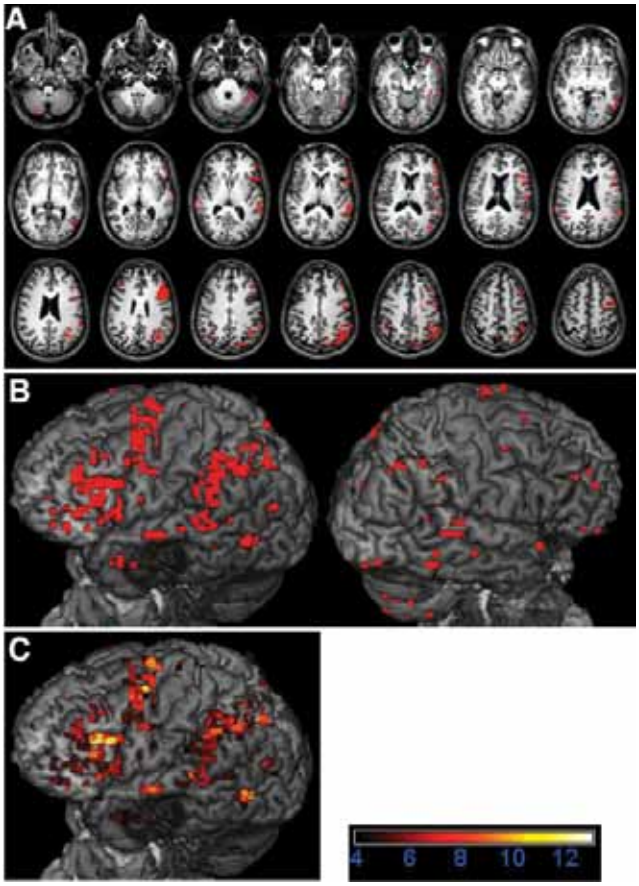

Fig. 1. Images obtained in a 35-year-old man with a low-grade glioma in the left middle and inferior temporal gyri. Results of a verb generation task *(red)* are superimposed on anatomical T1-weighted images. The task is block-designed and consists of visual presentation of nouns (5 epochs of 9 nouns) alternated with a simple control task (looking at abstract symbols). The imaging time is 5 minutes, in which a total of 486 volume images are acquired (PRESTO, Philips Achieva 3T). **A:** Axial images showing clear left-sided dominant activation. Note that all the different responses that the patient gave to the set of 45 different stimuli eventually condense into a single brain activation map. **B:** In a rendered view, the relationship among language areas, normal anatomy, and tumor is better appreciated. During surgery one can easily localize fMR imaging areas via cortical topography (in our experience this is more precise than with navigation, as there are no effects of brain shift). **C:** Activation patterns strongly depend on statistical threshold. The color-coded bar shows T values. Higher T values represent a more stringent threshold; this eliminates false-positive results but at the same time also decreases detection power. In this case there were 2 strong areas of fMR imaging activation in the immediate vicinity of the tumor (both in the superior temporal gyrus); these areas were confirmed using ESM. The weaker anterior temporal lobe activation was not confirmed with ESM and was included in the resection. Postoperatively, the patient had subtle new language deficits that disappeared after a few days.

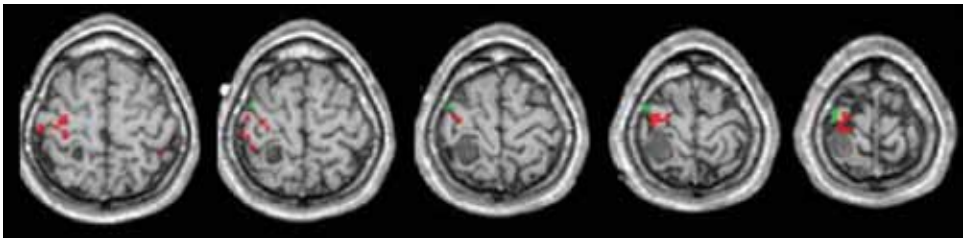

Fig. 2. Images obtained in a patient with a right parietal low-grade glioma without neurological deficits. The results of a left-handed finger tapping fMR imaging experiment are shown in *red*. Two clusters of fMR imaging activation are seen, in the precentral and the postcentral gyri. *Green dots* denote sites of electrical stimulation evoked motor responses. The anterior cluster of activation thus proved to be primary motor cortex. The posterior cluster probably represents sensory activation due to tactile feedback during the finger tapping experiment.

of function; this also permits study of individual differences in brain organization.

An fMR imaging experiment is conducted to test the investigator's hypothesis of a particular brain function. This requires a task design that can extract the function of interest and has adequate detection power. Most fMR imaging experiments follow a block design in which 2 or more conditions are alternated over the course of the image. An fMR image can best be described as a series of MR images that are acquired like a movie (Fig. 1). Every few seconds, an image of the brain is acquired. During the procedure, the individual performs a carefully designed computerized task in which specific brain functions are invoked and alternated with periods of rest or a control task (see below). The movie of the brain images is analyzed as a time series, and each spatial element (volume element, or voxel) is assessed for a correlation with the alternating task. Only voxels in brain areas that are involved in the task—and are switched on and off according to the task design—will correlate with the task. These are assessed for significance of the correlation and are then displayed as colored regions on top of an anatomical image acquired before or after the fMR imaging procedure.[72]

Repeated stimuli are necessary to increase the contrast-to-noise ratio (that is, the ability to detect brain activity) and obtain statistically sound activation maps; the number of stimuli depends on experimental design and hardware. Ideally, one condition contains the function of interest, while another (control) condition involves a similar set of functions except for the one of interest. Experiments that use substraction of conditions are fairly simple to implement, are robust, and have high statistical power. For these reasons they are most often used in clinical practice.[1] However, subtraction of conditions relies on assumptions that are not always valid. One is the idea of pure insertion, where it is thought that a cognitive process can be added to a set of existing cognitive processes without affecting them.[25] More complex task designs have been developed to target such methodological pitfalls or to analyze individual hemodynamic responses to stimuli; these designs involve multiple levels of task complexity (parametric design), measurements of single stimulus-related BOLD responses (event-related design), or multiple task-control conditions (for example, conjunction analyses).[70,73]

Most MR imaging units today have software for real-time automatic analysis and display results during, or immediately after, imaging. The fMR imaging maps can be implemented in neuronavigational systems for intraoperative use.[80] The fact that these automated software programs are available (either commercially or as freeware) does not imply that the resulting maps are always a reliable roadmap for surgery or that expert knowledge is no longer needed. Contrary to the suggestion that is sometimes made in the literature or in commercial advertisements, there are currently no standardized and user-independent fMR imaging protocols that can be easily and reliably used for surgical purposes, or even for simpler tasks such as localization of primary motor function.

The main reason for the lack of these protocols is the fact that interpretation of fMR imaging maps is not straightforward. It is very difficult to construct a task protocol that can extract only the function of interest and thereby differentiate between brain areas indispensable for that specific function and brain areas that are involved in task performance but are not truly indispensable. As an example, consider identification of primary hand motor cortex (M1), a common presurgical question. Constructing a task for this purpose seems not very difficult, as various simple motor tasks (for example, finger tapping or hand clenching) have shown reliable activation of M1.[76,103] If the brain activation map shows a relatively large cluster of fMR imaging activation in the central region, this cluster is, in our experience, always located within the central sulcus and/or the posterior part of the precentral gyrus. In this case identification of M1 is straightforward. The problem is that there are usually several other activated areas, often in neighboring gyri, and this makes a priori identification of M1 with fMR imaging difficult. For an example of this, see Fig. 2, where 2 clusters of fMR imaging activation were found near a centrally located tumor. The challenge is to disentangle the M1 activation from activation in secondary motor or nonmotor areas. There are currently no fMR imaging protocols that can selectively activate only primary motor cortex, so additional information is needed from other modalities to increase reliability. What is often done in practice, as a first step, is to compare the location of fMR imaging activity with the expected location of M1 according to anatomical landmarks such as the handknob.[103] Note that this is again a fallback to a static view of functional topography; in this classic view, control over different body parts is strictly somatotopically organized along the precentral gyrus,

which is also considered a synonym for the primary motor cortex area.[66] As with any model, by definition, it is only a simplified reduction of reality. In the original stimulation studies by Penfield and Rasmussen[66] (from which the model of the sensory and motor homunculus was created) it had been found that motor responses could not only be obtained from the precentral gyrus (80%) but also quite frequently from the postcentral gyrus (20%). A minor representation of somatic sensation was also found in the precentral gyrus (in 25% of stimulations that elicited sensory responses; the remainder were obtained from the postcentral gyrus). Animal studies with intracortical microstimulation and, more recently, human fMR imaging studies have yielded further arguments for a more complex view of primary sensorimotor representation, where the controlling neural populations for different fingers show considerable overlap in M1 and are represented in a more widespread cortical area than usually assumed. Studies have also shown that at least part of the primary motor cortex seems to code for movement rather than for a specific muscle or body part, with several sites, instead of one, for each functional representation.[86] In addition, M1 has been postulated to participate not only in the executive but also the preparative motor phase.[12,39] Additionally, pathological lesions may influence functional topography and lead to functional reshaping of motor areas, even on the level of M1.[9,19,87] This all implies that unexpected activation on fMR imaging maps needs to be cautiously interpreted, whereby it is easily forgotten that we are often biased in our anatomically guided expectations. Abnormal fMR imaging activation can of course be truly false positive because of movement artifacts or a low statistical threshold, but it can also represent variations in normal anatomy (double precentral sulcus) and physiology (multiple representations) or reflect brain plasticity. Of course, things get even more complex when one is asked for the localization of cognitive functions such as working memory or language.

Another reason it is difficult to create standardized clinical fMR imaging protocols is that the parameters that are mostly used to interpret and judge fMR imaging maps (that is, the extent and the number of activated areas) are not a very reproducible measure of brain activation.[52,81] When a patient undergoes imaging twice with the same protocol using the same imaging unit, the activation maps will not be exactly the same.[83] Some of the factors that contribute to this variability are known, such as field-strength or imaging unit type and artifacts due to movements (for example, respiration and cardiovascular pulsation); these factors can to some extent be controlled in data analysis. Part of the test-retest variation is, however, caused by yet unknown factors. For clinical use of fMR imaging, there are some strategies to increase the reliability and detection power of brain activation maps.[26,81,83]

Absence of activation is another important issue to consider. Failure to detect activity can be caused by several factors, some of which are difficult or impossible to control. They should at least be known so that fMR imaging maps are properly interpreted and possible false-negative results can be verified with other functional techniques. A tumor or vascular malformation can distort the brain or cause blood flow abnormalities that may alter or diminish the BOLD signal.[33,34,46,87] Under these circumstances, absence of fMR imaging activation does not necessarily imply absence of relevant neural activity. On the other hand, fMR imaging activity within tumor borders is not necessarily false positive and can be functionally relevant, as was confirmed with ESM.[47,79]

Other confounding factors can be experimentally controlled for, but this requires radiological personnel and clinicians who are familiar with all stages of the fMR imaging experiment, as errors often go unnoticed in inexperienced hands; it also requires a continuous feedback from surgical practice so that fMR imaging protocols can be validated and optimized. A factor that needs to be controlled is task performance. We think that optimal task performance requires a practice session prior to the imaging session in which the patient is acquainted with the setting and the stimulus presentation. Patients with a paresis or cognitive impairments may suffer from a limited attention span or early fatigue; in these cases task design should be adapted. If task performance is not monitored, the investigator is left with uncertainty about the cause of poor results, that is, is brain function impaired or did the patient fail to perform the task as required? The effects of impaired performance due to brain damage on brain activation maps are a known problem that is very difficult to solve with task-driven fMR imaging. Examples are studies in patients with poststroke aphasia in whom baseline measures are obviously not available. New MR imaging techniques (notably resting state functional connectivity mapping) eliminate the effects of impaired task performance on activation maps but are not yet reliable on an individual level.[13]

In conclusion, all stages of an fMR imaging experiment are tightly interwoven and slight changes in MR hardware, task design, task performance, or data analysis can significantly change the resulting brain activation maps. As of today there are no fMR imaging protocols that are invariant to such changes and that provide the surgeon with a roadmap that unambiguously shows only "go" and "no-go" areas. This variability can also account for the significant differences that are often reported between different studies or institutions. This hinders validation of fMR imaging results (as it is difficult to pool and compare data across different institutions) and development of user-independent clinical protocols. We think, therefore, that every institution that uses fMR imaging for neurosurgical planning should have clinicians who are trained for this purpose. The fMR imaging maps should be used as an adjunct to existing clinical techniques and be compared with ESM and, in particular, with patient outcome for continuous optimization of fMR imaging protocols.

A Critique of Clinical Gold Standard Techniques

Electrocortical Stimulation Mapping

Electrocortical stimulation mapping remains the gold standard for localization of eloquent brain areas. Electrocortical stimulation mapping has a good track record in

neurosurgery, and most surgeons consider it a valuable technique to safely maximize tumor resection.[20,30] Electrocortical stimulation mapping relies on the principle that a particular brain area can be functionally disabled for several seconds during electrical stimulation. At first glance, the technique seems very intuitive and valid. When a particular area is stimulated and the patient has difficulty performing a task, there must be a close and essential relationship between that brain area and the disturbed function. Consequently, areas in which ESM is positive are considered to be indispensable for normal function and are not included in the resection. However, such a straightforward inference is not justified. For example, when the posterior part of the SMA proper is electrically stimulated, this will often elicit involuntary motor responses in a patient. As expected, resection results in immediate postoperative neurological deficits (hemiparesis, akinesia, and mutism). However, these deficits typically resolve in several weeks or months. Thus, the fact that an area is tested positively with ESM does not necessarily imply that it this indispensable (that is, eloquent) for that particular function (note that in this case an eloquent area is defined as an area that when damaged leads to permanent deficits). This finding calls into question the clinical usefulness and even the validity of ESM for its purpose, as ESM seems unable to account for functional reorganization after surgery. Stated otherwise, ESM is not predictive of permanent loss of function. What probably happened in the patients with SMA resections is that contralateral secondary motor areas partially compensated for the loss of function. Indeed, such unmasking of new motor areas has been demonstrated when fMR imaging activation patterns were compared before and after surgery.[41]

It is very likely that such a redundancy of positive ESM sites is not only present in the motor domain but also holds for other (cognitive) functions. There is indirect evidence for this in the language domain. For instance, several authors have claimed that a nontailored left anterior temporal lobectomy without the use of ESM does not worsen language functions.[14,31] This conflicts with the results of ESM studies in similar groups of patients with epilepsy where, in approximately 20% of patients, language areas are found in the dominant anterior temporal lobe.[63] Similar conflicting observations have been made for the basal temporal language area.[51] Although no randomized studies have been performed to resolve these issues (for obvious reasons), it seems that with ESM some areas are more equal than others.[64] Again, long-term functional compensation could account for this redundancy. Another explanation would be that stimulation of anterior or basal temporal areas indirectly interferes with more distant critical areas via subcortical connections (this is a more likely explanation in those patients who have no short-term postoperative language deficits).

Besides these fundamental limitations of ESM, there are methodological concerns. Little is known about local or possible distant current spread.[59] There are no studies that have systematically investigated reproducibility across surgical sessions (for obvious reasons). There is some information from reoperations in patients with brain tumors, but in these cases mapping results are confounded by tumor growth and functional reshaping. Some authors have advocated maximizing the stimulation current at each cortical site to optimize the detection power for all critical areas, whereas others have used a single current to map the brain.[18,69] Lastly, the relatively short duration of stimulation (maximum ± 6 seconds) and the restricted setting in the operating room limit the functions that can be investigated intraoperatively. This might lead to false-negative information if the correct function were not tested for the appropriate area and probably explains in part the discrepancies that are found with fMR imaging results. Also, assessment of higher-order cognitive functions such as emotion or discourse is currently not possible.

In conclusion, ESM seems a reliable technique to assess the immediate functional consequences of removal of part of the brain and is currently the best technique available for this purpose. It cannot, however, predict whether perilesional or distant neural networks are able to compensate for any loss of function after operation (that is, there is a risk of false-positive results). It also has limited potential to test different or more complex cognitive functions. For this, new techniques need to be developed. To do so, as a first step theories need to be further developed to explain and model the new concepts of functional topography.

The Amobarbital (or Wada) Test

The amobarbital test (or Wada test, named after its inventor Juhn Wada) is widely used in epilepsy surgery and occasionally in tumor surgery to probe whether a single hemisphere is capable of normal language (and memory) function.[97] It uses an ultra–short acting barbiturate that is injected into an internal carotid artery, effectively disabling a large part of that hemisphere for approximately 5 minutes. During this period, the contralateral hemisphere is examined for language and other functional capacities. While the patient is asked to perform a series of language tasks (object-naming, reading, picture-describing, and so on), he or she is monitored for aphasic errors. Validity of the test is based on 2 assumptions. First, the injected amobarbital can reach and anesthetize all brain areas in the ipsilateral hemisphere that are involved in language function. Second, during the testing period (that is, the time that the amobarbital is effective) there is no substitution of language function by nonanesthetized ipsilateral or contralateral brain areas.

There are several factors that may confound interpretation of the Wada test.[53] At times, agitation or somnolence make determination of language dominance problematic. Inadequate anesthetization of brain regions may also lead to false-negative results on laterality of function. For instance, as the temporoparietal region receives blood from the middle and/or the posterior cerebral artery, the amobarbital that is injected via the carotid system may not always adequately deactivate some of the temporoparietal areas involved in speech comprehension. Another possible confounder is that the amobarbital may cross over to the other hemisphere via variations in vasculature; this can be monitored with angiography.

Among different clinical centers, there is no standardized set of parameters in terms of which language functions are evaluated during the test. This accounts for at least some of the considerable variability in the reported incidences of typical (that is, left-sided) and nontypical (that is, right-sided or bilateral) language dominance. Most groups use naming or responses to verbal commands, but others have predominantly relied on the duration of speech arrest as an important parameter for hemispheric language dominance.[4,97] There is some concern that the Wada test underestimates the incidence of bilateral language dominance, as inconsistencies have been reported with clinical outcome or the findings of ESM.[36,101] These arguments favor the notion that the Wada test may not be a highly independent measure of language dominance.

The Current Role of fMR Imaging in Brain Surgery

Brain mapping in neurosurgery is predominantly performed for planning surgery of motor and language areas. The main questions are the location of primary sensorimotor areas (occasionally also the location of the motor part of the SMA), assessment of the language-dominant hemisphere, and location of language areas. Other cognitive functions are seldom asked for and are only occasionally mapped by neurosurgeons with a special interest in functional mapping. Examples are calculation, writing, spatial attention, and working memory.[62,78,93] This is probably for 2 reasons. First, it is common neurosurgical opinion that these functions are not easily damaged after surgery and that they are therefore not as localized and vulnerable as motor and language functions. However, more recent studies have clearly shown that when patients are tested with dedicated neuropsychological tests, cognitive deficits are far more common than previously assumed on the basis of clinical impression and observation, both before and after surgery.[28,92] Second, in the classic studies of lesions, a firm anatomical basis for most cognitive functions was never established, with the incorrect exception of language functions. We now know that the static neurological models that resulted from these postmortem studies of patients with brain lesions, first formulated at the end of the 19th century by Wernicke and Lichtheim,[10] have several severe shortcomings that make them unsuitable for use in the individual neurosurgical patient. More recent alternative models have proposed a more dynamic network view, where multiple regions are interconnected and serve specific functions. Given the inherent interindividual and pathology-driven variability of these areas and interconnections, functional mapping techniques are necessary to identify each individual's critical epicenters to optimize surgical treatment. To do so, techniques other than fMR imaging are additionally required to visualize critical subcortical connections. A review of the advantages and limitations of these techniques (notably DT imaging) is beyond the scope of this paper.[11,38]

Localization of Primary Motor Areas

In the absence of anatomical variations or functional reorganization, it is probably safe to assume that the primary motor cortex (M1) is located in the precentral gyrus. Various anatomical landmarks have been described that help to identify the central sulcus and the precentral gyrus. On MR images, there are at least 6 of these landmarks, the handknob being the most robust one. In fact, this landmark was discovered because of consequent fMR imaging activation within this area.[103] These landmarks are obviously less reliable under pathological conditions in which a lesion can distort or destroy anatomical and functional topography. Lehéricy et al.[47] found that in 8 of 60 patients with a centrally located brain tumor, it was not possible to reliably identify the precentral gyrus using only anatomical landmarks. With help of fMR imaging or ESM, identification was 100%. According to their study, "There was a good agreement between fMR imaging and intraoperative mappings," with 92% of ESM areas located at the margins of the fMR imaging area; the remaining ESM sites were within 15 mm of fMR imaging areas. Bizzi et al.[7] reported sensitivity and specificity of 88 and 87%, respectively, when hand motor function on fMR imaging was compared with ESM (both modalities were considered to match if fMR imaging activation was present within 1 cm of a positive ESM site). With similar criteria, Roessler et al.[75] found 100% agreement in 17 patients with low- or high-grade gliomas. They were able to detect fMR imaging activation in the handknob region in all patients. As this significantly exceeds the detection power for fMR imaging activation in other studies, Roessler et al. speculated that this might be related to the use of high-field fMR imaging (3 T) in their study. Various other studies have shown good but suboptimal agreement between fMR imaging and ESM; unfortunately, many studies have methodological flaws and/or judged the correlation in a qualitative manner or in small patient series.[68,102]

Studies have also tried to establish the surgical relevance of fMR imaging activation patterns by looking at the distance between the resection border and fMR imaging activation.[29] Not surprisingly, this distance was found to be inversely related to the occurrence of postoperative motor deficits; a safe margin of 1–2 cm was mentioned in these studies.[43] However, many other factors can contribute to the presence or absence of postoperative deficits, and these factors are generally not accounted for in the few studies that compared fMR imaging with functional outcome. An important confounder is proximity to the corticospinal tract. Despite these limitations, displacement of brain activation or an asymmetrical activation pattern often reliably reflects the anatomical and functional impact of a lesion (Fig. 3).[87]

Other previously discussed confounders are disturbance of the neurovascular coupling due to brain lesions and impaired task performance due to sensorimotor deficits or cognitive problems. The latter can have a profound influence on the resulting brain activation maps. In a series of 110 patients with centrally located brain tumors, Krings et al.[42] found that, with an increasing degree of paresis, activation decreased in the primary motor area, whereas activation increased in secondary motor areas. Although these findings suggest brain plasticity, one needs to be cautious; as with task-driven fMR imaging,

these changes may also be related to an increase in effort and reflect the result (rather than the cause) of impaired performance.

In conclusion, there is general consensus in the literature that fMR imaging is a valuable tool for localization of the primary motor cortex and assessment of presurgical risks. However, several methodological and practical questions remain to be answered, and there is currently no standardized protocol for surgical use of motor fMR imaging.

Our strategy for clinical use of motor fMR imaging is as follows. First, the hand motor area on the primary motor cortex is determined according to anatomical and fMR imaging results. Then, the following margins are determined: the distance between the primary motor cortex and the cortical tumor border, and the distance between the corticospinal tract and the subcortical tumor border. The corticospinal tract is visualized using DT imaging fiber tracking. We advise using ESM if the cortical margin is less than 1 gyrus or the subcortical margin is less than 15 mm. In these cases, fMR imaging results are implemented in the surgical navigation system to guide ESM. We believe that this increases the efficiency and safety of our procedure.[57] Note that we use fMR imaging protocols that have been validated with ESM at our own institutions. We are currently assessing the exact accuracy of DT imaging fiber tracks compared with subcortical neurosurgical stimulation in awake patients for use in the neuronavigation system during surgery.

Localization of Secondary Motor Areas

Krainik et al.[41] published an important paper in which they were able to show that resection of fMR imaging activation in the posterior part of the SMA (the SMA proper) predicted an SMA syndrome. Patients in their series had a low-grade glioma in or near the SMA. In a follow-up paper, the authors showed that, in these patients, there was already preoperative reorganization in ipsilateral and contralateral premotor cortex activations (including SMA). Although this reorganization could not prevent the temporary deficits, postoperative recovery was faster and was associated with increased activity in secondary motor areas in the healthy hemisphere. There are no other studies that have systematically validated motor-related fMR imaging activation in medial or lateral premotor areas with ESM or patient outcome.

Assessment of the Language-Dominant Hemisphere

To begin, there is no unique definition of language, and there is no definite neurobiological substrate for its various functions. Lack of anatomical and functional definitions makes development of clinical fMR imaging protocols and comparison with existing techniques very difficult as there is no agreement on outcome measures. Historically, neurosurgeons use a rather restrictive but practical definition of language based on clinical assessment. This means that subtler language functions or potential right-hemisphere language functions are normally not tested.

From a clinical perspective, most people are considered left-hemisphere dominant for language, as lesions that cause aphasia are usually located in the left hemisphere. Language dominance is considered a discrete variable, that is, language is either present or absent in a hemisphere. Aphasia develops in 20–30% of left-handed individuals after right-hemisphere damage (in right-handed individuals the incidence is < 2%), illustrating that most individuals (whether right- or left-handed) are therefore left-hemisphere dominant for language. These data are comparable to results in Wada-tested patients and fMR imaging studies in healthy volunteers.[71,89] Atypical language organization (right-sided or bilateral) is more often found in patients with structural or functional damage to the left hemisphere. In these cases, the right hemisphere has partially taken over.[44,91] In general, recovery is more successful if the injury has slowly evolved.[15,94]

The clinical gold standard for assessment of language dominance remains the amobarbital test, although this technique can be disputed on methodological and practical grounds. Several fMR imaging (and PET) studies have tried to match outcome of the amobarbital test. To do this, most studies have calculated an LI to quantify the proportion of activation in both hemispheres; this LI varies from –100 (all activation in the right hemisphere) to 100 (all activation in the left hemisphere). A cutoff value of the LI is then chosen to determine whether patients have typical or atypical language dominance. Unfortunately, the variability in the reported LIs across fMR imaging studies is

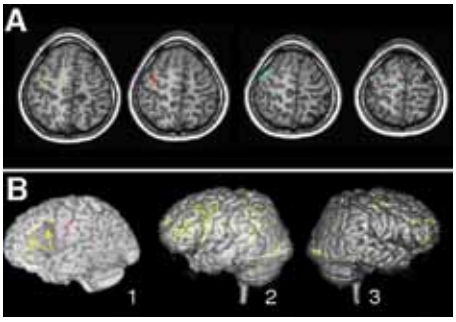

Fig. 3. Examples of functional reorganization due to brain lesions. **A:** Images obtained in an 11-year-old girl with a right-sided hemiplegia due to extensive perinatal left hemispheric stroke. She had limited hand function but was able to walk and use her arms almost normally. Functional MR imaging revealed that nonparetic and paretic hand function predominantly activated the right precentral gyrus (*blue* and *red voxels*, respectively; *yellow* denotes an area of overlap). Transcranial magnetic stimulation over the right central area yielded responses in both hands; no responses were obtained with stimulation over the left hemisphere. Subsequent functional hemispherectomy induced no new sensorimotor deficits. (Reprinted with permission from Rutten GJ et al: Interhemispheric reorganization of motor hand function to the primary motor cortex predicted with functional magnetic resonance imaging and transcranial magnetic stimulation. **J Child Neurol 17:**292–297, 2002, with permission from SAGE.) **B:** Perilesional reorganization of language functions in a patient with a low-grade glioma involving the classic language area of Broca (B1). Frontal fMR imaging activation (from 3 different language tasks) is projected on the cortical surface for use during surgery *(yellow dots)*. The *red line* denotes the central sulcus. The areas were confirmed with ESM (performed by N.F.R.). The cortical part of the glioma was resected without permanent language deficits. For comparison, typical results in a right-handed healthy volunteer are shown (B2 and B3).

so large that every study has defined its own criteria for assessment of language dominance; there is no consensus about an optimal fMR imaging protocol or cutoff values for the LI. In general, a good correlation has been reported in the literature between fMR imaging and the amobarbital test, but no protocol has been able to obtain complete agreement between the methods. Combining multiple fMR imaging language tasks is currently the best strategy and yields reproducible and reliable results. Use of only a single task is less reliable in particular for identification of the one atypical patient among the majority of typical patients.[26,81] When atypical language dominance is suspected, activation maps should be inspected for possible mixed dominance, as frontal and temporoparietal areas can be located in different hemispheres.[37,81] Only a few studies have compared fMR imaging and the amobarbital test to the true gold standard: patient outcome. Sabsevitz et al.[85] showed that preoperative fMR imaging predicted naming decline after left anterior temporal lobectomy. Somewhat paradoxically, in this study ESM was used to tailor the extent of the resection.

There are several fundamental issues that need to be resolved and that hinder straightforward interpretation of any currently available monitoring technique for language. First, since neuropsychological studies began to study language functions in greater detail, it is realized that the so-called nondominant right hemisphere also has an important language contribution, in particular for functions such as prosody, kinesics, and understanding of nonliteral content (for example, jokes or metaphors).[27,77,99] This explains at least part of the activation that is usually seen in the nondominant hemisphere with fMR imaging. Second, some authors have found evidence for a continuous distribution of language functions across hemispheres. For instance Springer et al.[89] observed a gaussian-like distribution of fMR imaging–derived LI values in healthy volunteers and patients with epilepsy. This could implicate a degree of equipotentiality between hemispheres with respect to language processing that is also supported by some of the amobarbital studies.[6,74] Third, discrepancies among ESM, the amobarbital test, and patient outcome have been reported and need to be clarified. Hunter et al.[36] reported on a patient with a 6-month postoperative aphasia after left-sided temporal lobectomy where the amobarbital test showed right-hemisphere language dominance. Wyllie et al.[101] found language areas in the left hemisphere with ESM in 2 of 9 patients in whom the amobarbital test had previously found right-hemisphere dominance. Kho et al.[40] found a discrepancy between the amobarbital test (right) and ESM (left); in this case, fMR imaging yielded bilateral frontal language areas. We agree with the conclusion of Wyllie et al. that when right-hemisphere dominance is found with the amobarbital test, these results need to be validated by other techniques.

In our assessment, we perform a combined analysis of 3 fMR imaging tasks for language.[73,81] If brain activation is strongly left lateralized, surgery in the right hemisphere is considered safe with regard to language problems, and additional invasive testing is not deemed necessary. From previous studies we calculated a cutoff value of the LI of 75 (note that these values are protocol and hardware specific). If the LI is less than 75, there is possible involvement of the right hemisphere in language. In these cases we rely on ESM when language areas are judged to be close to the surgical area of interest.

Localization of Language Areas

From historical lesion studies, the phrenological view was that language processing is performed in the areas of Broca and Wernicke in the left hemisphere. Contemporary neurological textbooks still often show a cartoon of 2 relatively large areas that are connected by the arcuate fasciculus, despite abundant evidence that language processing depends on a network of many other subcortical and cortical areas (Fig. 3B). Contrary to the general clinical assumption, there are no clear functional or anatomical definitions of the areas of Broca and Wernicke.[61,100] Although the Broca area is generally denoted as the posterior part of the left inferior frontal gyrus, damage to this area alone yields only a transient decrease of speech output and not Broca aphasia.[12] The Wernicke area is often defined as "the region which causes Wernicke's aphasia when damaged."[56] The view that there are no well-defined language areas is strongly supported by the many functional neuroimaging studies that have identified widespread and overlapping networks for phonological, semantic, orthographic, and syntactic processing.[23,96] Recent MR imaging–based analyses of dysphasic patients with brain lesions confirm a wide area of potential language cortex in the left hemisphere with different frontal and temporal epicenters than classically formulated.[3] The ESM and fMR imaging studies show that these critical language epicenters are smaller than generally thought (< 1–2 cm^2) with multiple representations in frontal and temporoparietal areas.[61]

Only a few studies have meticulously compared fMR imaging and ESM for the purpose of language localization.[22,79,82] General findings from these studies are as follows: 1) Functional MR imaging is able to identify most of the language areas that are found with ESM. To achieve optimal detection power, the results from multiple fMR imaging tasks need to be combined (a minimum of 3 tasks seems necessary). In practice, this means that fMR imaging can very reliably predict the absence of positive ESM sites (that is, fMR imaging has a very high negative predictive value). 2) Functional MR imaging finds more areas than ESM (up to 50%), and consequently the positive predictive value is limited. 3) There is a significant variability of fMR imaging data across patients, tasks, and statistical methods, and this makes generalization of results or development of a standard protocol currently impossible.

There are several possible explanations for the observed discrepancies between fMR imaging and ESM. One explanation for the observed differences in the language maps is the fundamental differences in methodology between the techniques. Functional MR imaging potentially shows all areas that are involved in language processing, including various supportive functions such as attention or verbal memory. The main difficulty is to design an fMR imaging protocol that can selectively

identify only the critical language sites. Although different cognitive functions may be easily separated on theoretical grounds, this is not the case in practice, and it is questionable whether brain mapping techniques will ever be able to show only critical language areas.

Most surgical teams that use intraoperative ESM use a single language task, most often visual object naming. This task is chosen because naming errors are common to most aphasic syndromes, the task is simple to apply, and it yields good correlation with postoperative language outcome. However, by performing only a single language task, one implicitly assumes that any critical language area is involved in all aspects of language processing. A more likely view is that different language functions are in part supported by different critical areas. This is strongly supported by results from both fMR imaging and ESM studies.[22,50,79,82] This would also imply that the match between the two modalities can be further optimized when multiple tasks are used during ESM. There are, of course, practical problems and constraints in doing this intraoperatively. Language can operate in different modalities (reading, writing, speaking, and gesturing), and many patients do speak more than one language. Should all these modalities be monitored to ensure safe surgery, and in what detail? Even if one were to consider this clinically relevant (and there is currently not much evidence for this), it would take too much time during surgery as patient cooperation during surgery is time limited.

In our practice, we use fMR imaging intraoperatively as guidance for ESM. We do not plan surgery solely on the basis of fMR imaging results when language areas are judged to be close to the surgical area of interest.

In conclusion, much more data are required to answer these questions. The multiple-task approach can be addressed in patients who have temporarily implanted grid electrodes and in whom extraoperative ESM is possible. Questions regarding the sensitivity and validity of the various brain mapping techniques can only be investigated when information in large patient series is collected and when results are compared with patient outcome (the true gold standard). This can only be achieved in multicenter studies.

New Concepts of Functional Topography

There is convincing evidence to move away from the classic concept of a static brain with fixed functional areas and to adapt the new and dynamic view in which functions are thought to be represented in large-scale networks that are organized around cortical epicenters.[56] The advent of functional neuroimaging and its ability to visualize brain functions has been a profound contribution to the advance of an ongoing paradigm shift that is, however, yet to be accepted in general clinical practice.

These new insights in functional topography are grounded in animal studies where it has been found that information processing for a given modality (for example, vision) is performed in a highly distributed and hierarchically organized system of different brain areas.[35] In the macaque monkey, 32 cortical areas were found that relate to visual processing, and 305 connections have been reported between the different areas.[21] Motor and language systems operate in similarly distributed networks. Such a network model explains the existence of selective neurological impairments such as prosopagnosia, akinetopsia, or transcortical motor aphasia. Because of the parallel design and the numerous reciprocally connected areas, it is practically impossible to exactly localize a function. So in effect, when a neurosurgeon wants to know whether a brain area is functionally relevant, he or she in fact wants to know whether the particular area is crucial for normal functioning of the network. To answer this question, the behavior of the modified network (that is, the network minus the planned area of resection) should be known.

The one important factor that was never accounted for in the older clinical models is time and the concept of a plastic functional brain topography. Continuous modifications in neuronal networks are a sine qua non for the brain to store and update information, to acquire new skills, to optimize and automate information processing, and to adapt to structural changes (for example, aging or a brain tumor). This automatically implies interindividual variability. One of the big advantages of fMR imaging is that it can provide information about both the spatial and temporal aspects of neural activity. The spatial extent of activation ranges from millimeters (firing patterns of groups of neurons) to centimeters (interaction between cortical regions). In a similar manner, temporal processes can be represented on a scale from milliseconds (firing patterns of groups of neurons, synchronization, and cognitive processes) to weeks and months (for example, recovery from loss of brain function due to stroke or surgery) and to years (for example, functional reshaping due to growth of a low-grade glioma). We will give several examples to illustrate the potential relevance for neurosurgery and the abilities of current fMR imaging techniques to assess these processes.

Although there is a time lag of several seconds between the onset of the neural event and the BOLD response, the relative timing between the onset of the hemodynamic responses in different brain areas seems to be preserved. This can be used to study the temporal order of activation within a network. For example, Lee et al.[45] tracked the temporal activation of primary and secondary motor areas in an event-related motor task. Within the SMA, temporal profiles were different for the anterior and posterior parts. These differences in latencies can be used to monitor and characterize networks, and possibly differentiate normal from pathological behavior. However, this method has significant practical limitations as differences in timing can only be detected with fMR imaging when areas are activated in a sequential manner. When areas behave as coupled high-frequency oscillators, they will appear as 2 parallel activated areas with fMR imaging. Interestingly, even when the brain is at "rest" there is a vast amount of spontaneous neuronal activity that is coupled between different regions that form a functional network. This temporal synchronization between brain areas defines the concept of functional connectivity[24] and is currently investigated with fMR imaging, electroencephalography, and MEG. Resting-state fMR imaging

has already proven to yield maps of networks without requiring individuals to perform a task (see below).

Several different frequencies have been described in the brain, which are related to particular regions or pathological conditions. For instance, alpha waves (8–12 Hz) are measured over the posterior regions of the brain and are attenuated with closure of the eyes or relaxation. Similar low-frequency waves can be measured over sensorimotor areas (mu waves), and these are influenced by movement of, for instance, the hand or fingers. This leads to so-called event-related desynchronization, and this is considered an electrophysiological correlate of activated or excited cortical neurons.[67] Higher frequencies (> 30 Hz, gamma waves) are a particularly promising index of cortical activation. In a study using electrocorticography, Sinai et al.[88] found reasonable agreement between areas with language-related changes in the gamma band and positive sites found with ESM. Recently, Hirata et al.[32] used MEG and event-related desynchronization to map language areas for use in neurosurgery. Although these are still experimental studies, it seems a promising new way to look at localized brain function.

Temporal correlations in activity can also be used to study the interaction between different cortical regions.[90] With MEG, significant differences in functional connectivity were found between patients with brain tumors and healthy controls, and an association with cognitive functions was reported.[2,8,65] Somewhat paradoxically, functional connectivity can also be studied using fMR imaging but only at very low frequencies (0.01–0.1 Hz). With data obtained from individuals in a resting state, several of the known networks have been identified.[13] A recent exploratory study reported that the motor regions that were localized based on the correlation of spontaneous fMR imaging measurement were quite similar to the regions that were defined with actual movements and with cortical stimulation in these patients.[48] The main advantage of this functional connectivity MR imaging is that the resulting brain maps are independent of the actual sensorimotor and cognitive status of the patient. This means that a neurological deficit does not confound the brain maps because of impaired performance. Another advantage is that multiple brain systems can be determined with a single resting-state image.

Functional MR imaging has been used to study recovery from acute lesions (most often stroke). There is a large amount of data showing evidence for functional reorganization to brain areas close to or distant from the lesion. With acute lesions, recovery is often incomplete, and task-related brain activation studies such as fMR imaging are confounded by this impaired performance and by a lack of baseline measurements. It is unclear whether for instance (unmasked) activation that is seen in contralateral homolog areas is truly related to language processing. Techniques such as transcranial magnetic stimulation may help clarify these issues.[98] Krainik et al.[41] performed one of the few studies that compared fMR imaging maps before and after surgery. They demonstrated that recovery from a motor SMA syndrome correlated with increased postoperative activity in the healthy hemisphere. In patients with slow-growing lesions, such as a low-grade glioma, functional compensation can be impressive, and deficits are generally less severe than in patients with acute-onset lesions.[15,17] Despite large lesions most of these patients with low-grade gliomas have a normal social and professional life. Benzagmout et al.[5] demonstrated that in patients without aphasia, a low-grade glioma in the classic area of Broca can be resected without permanent language or cognitive deficits, and even with improvement in the quality of life. Patterns of reorganization appear to differ between patients.[16] As of yet, these patterns have not been mapped out comprehensively, but the increasing use of fMR imaging, coupled with functional outcome, may prove particularly informative in the coming years. To do so, multicenter studies need to increase patient numbers. This is one of the motivations of the European Low Grade Glioma Network, a platform for clinical and scientific collaboration (refer to http://www.braintumours.eu/).

Conclusions

It is clear that new functional neuroimaging techniques are changing our understanding of the human brain. New insights into networks that serve brain functions, notably language and motor systems, improve our understanding of effects of both pathology and surgical lesions on behavior. However, these have had little impact yet on most of the surgical procedures that are still often based on the classic static view of functional organization. As insight into the mechanisms of brain functions is still evolving, the effects on current neurosurgical practice are understandably limited.

This warrants several new strategies. We think fMR imaging and DT imaging should be used routinely as presurgical functional localization techniques, and that there should be a bolder approach toward resection of lesions in so-called eloquent cortex. To prove that the effects of brain plasticity can have major influence on surgical decision making, multicenter studies are needed in which brain lesions, surgical therapy, and functional outcome are studied. In these studies, outcome should be thoroughly assessed with dedicated behavioral and neuropsychological test batteries. Multicenter studies should also be started to develop evidence-based standard fMR imaging and DT imaging protocols. Longitudinal studies are important to study network behavior and monitor the effects of brain plasticity.

Ultimately, long-term effects of surgery should be predicted with functional neuroimaging techniques prior to surgery to optimize survival and quality of life for each patient.

We envision that several other areas of research will benefit surgical practice in the near future, for instance development of techniques to promote reorganization of brain function away from the surgical area of interest, or patient-specific rehabilitation therapy. Overall, neurosurgery not only benefits but can also make vital contributions to the advancing field of brain function research.

Disclosure

The authors report no conflict of interest concerning the mate-

rials or methods used in this study or the findings specified in this paper.

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Multimodal navigation in the functional microsurgical resection of intrinsic brain tumors located in eloquent motor areas: role of tractography

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Object. Nowadays the role of microsurgical management of intrinsic brain tumors is to maximize the volumetric resection of the tumoral tissue, minimizing the postoperative morbidity. The purpose of this paper was to study the benefits of an original protocol developed for the microsurgical treatment of tumors located in eloquent motor areas where the navigation and electrical stimulation of motor subcortical pathways have been implemented.

Methods. A total of 17 patients who underwent resection of cortical or subcortical tumors in motor areas have been included in the series. The preoperative planning for multimodal navigation was done by integrating anatomical studies, motor functional MR (fMR) imaging, and subcortical pathway volumes generated by diffusion tensor (DT) imaging. Intraoperative neuromonitoring included motor mapping by direct cortical stimulation (CS) and subcortical stimulation (sCS), and localization of the central sulcus by using cortical multipolar electrodes and the N20 wave inversion technique. The location of all cortically and subcortically stimulated points with positive motor response was stored in the navigator and correlated with the cortical and subcortical motor functional structures defined preoperatively.

Results. The mean tumoral volumetric resection was 89.1 ± 14.2% of the preoperative volume, with a total resection (≥ 100%) in 8 patients. Preoperatively a total of 58.8% of the patients had some kind of motor neurological deficit, increasing 24 hours after surgery to 70.6% and decreasing to 47.1% at 1 month later. There was a great correlation between anatomical and functional data, both cortically and subcortically. A total of 52 cortical points submitted to CS had positive motor response, with a positive correlation of 83.7%. Also, a total of 55 subcortical points had positive motor response; in these cases the mean distance from the stimulated point to the subcortical tract was 7.3 ± 3.1 mm.

Conclusions. The integration of anatomical and functional studies allows a safe functional resection of the brain tumors located in eloquent areas. Multimodal navigation allows integration and correlation among preoperative and intraoperative anatomical and functional data. Cortical motor functional areas are anatomically and functionally located preoperatively thanks to MR and fMR imaging and subcortical motor pathways with DT imaging and tractography. Intraoperative confirmation is done with CS and N20 inversion wave for cortical structures and with sCS for subcortical pathways. With this protocol the authors achieved a good volumetric resection in cortical and subcortical tumors located in eloquent motor areas, with an increase in the incidence of neurological deficits in the immediate postoperative period that significantly decreased 1 month later. Ongoing studies must define the safe limits for functional resection, taking into account the intraoperative brain shift. Finally, it must be demonstrated whether this protocol has any long-term benefit for patients by prolonging the disease-free interval, the time to recurrence, or the survival time. *(DOI: 10.3171/2009.11.FOCUS09234)*

Key Words • brain tumor surgery • cortical mapping • subcortical mapping • intraoperative stimulation mapping • intrinsic brain tumor • tractography navigation

The role of radical surgery in the management of glial-type brain tumors is still controversial. In fact, there is no scientific evidence that a greater extent of resection is associated with a better prognosis.[2,19,20,31,35,37] It does seem clear that the infiltrative growth pattern of the neuropil by glial tumors is the reason for surgical treatment not being curative,[7] and therefore the majority of patients will suffer a relapse or local progression of the disease after surgery. The known molecular mechanisms that drive this pattern of cellular migration have

Abbreviations used in this paper: CS = cortical stimulation; DT = diffusion tensor; fMR = functional MR; sCS = subcortical stimulation; SSEP = somatosensory evoked potential.

also not allowed for the development of really effective treatments.[11–13,16]

Until new treatments for glial tumors are developed, the cytoreductive treatment provided by surgery will maintain its value, because it provides material for diagnosis and research, alleviates both the focal and clinical symptoms of intracranial hypertension, and contributes to a greater efficacy of oncological treatments. Following this line of reasoning, there is a large number of modern papers supporting the idea of resecting the largest possible volume of tumor.[11,25,26,35] The price to pay for radical resection may be an increase in morbidity. In this sense, a great number of imaging, neurophysiological, neurochemical, and even surgical techniques have recently been developed and incorporated into the management of these tumors, with the ultimate objective being to optimize the resection limits; to extend them to the maximum while minimizing the eventual associated morbidity.[32,33,38,39] The final objective of this approach is to resect the lesion identified as tumoral based on the imaging techniques, as well as the neighboring brain tissue that is normal in appearance during the surgery, but that is suspected of already being invaded by the tumor cells, or with cells already affected by the molecular disorder that would convert them into tumor cells. In this way, the "tumoral resection limit" would be taken to the point where there may be deterioration of any neurological function considered important ("functional resection limit").

The motor and sensory cortex, as well as their corticospinal and associated projections, are probably some of the most eloquent brain structures. For this reason, these are the most anatomically and functionally well-defined areas, but it is also true that they often become distorted by the tumor that is located in the area and is the reason for the surgical treatment.[4,29,30]

The objective of this work was to study the value of the new anatomical and functional pre- and intraoperative techniques in defining the functional resection limits in a series of tumors located in eloquent motor areas and undergoing microsurgical treatment. In accordance with this goal, a pre- and intraoperative study protocol has been designed that combines cortical anatomical localization techniques (CT scanning and different sequences of MR imaging) and functional localization techniques (fMR imaging and direct CS) as well as subcortical anatomical (DT imaging) and functional localization techniques (direct sCS). These techniques are intraoperatively integrated and correlated with the aid of the navigation system. The ultimate objective of the study was to define an ideal protocol for the most radical and safest microsurgical management of tumors in eloquent motor areas, by studying the role of subcortical localization techniques.

Methods

The study was performed in a series of patients who underwent surgery for cortical or subcortical intrinsic brain tumors located within or close to eloquent motor areas. The following have been anatomically considered as eloquent motor areas. 1) In the frontal lobe, the precentral or vertical gyrus (primary motor area—Brodmann area 4), the posterior region of the frontal superior gyrus (premotor area—Brodmann area 6), the mesial region of the frontal superior gyrus (supplementary motor area—Brodmann area 8), and the inferoposterior part of the pars opercularis or frontal operculum (primary motor area and Broca area—Brodmann areas 44, 6, and 4). 2) In the parietal lobe, an important role is played by the postcentral gyrus (somatosensory area—Brodmann areas 3, 2, and 1) in the control of movement. 3) In the insula, the insular cortex is considered an important region in motor planning and motor speech (Brodmann area 13). 4) Finally, the bundle of somatosensory and associated motor tracts that form the internal capsule in the layer of the corona radiata is considered to be an eloquent area.[3,34]

All cases were studied prospectively, following the same basic clinical study protocol for imaging, surgical procedure, and postoperative controls. In all cases, informed consent was obtained from the patients for the different study, monitoring, and treatment techniques. This study has been approved by the ethics committee of the Hospital Clínico Universitario of Valencia, with a specific informed consent having been drawn up for inclusion in the study.

Preoperative Study

The clinical variables collected included age, sex, clinical history, symptoms and signs on diagnosis, and response to treatment at the time of surgery. The imaging studies for the initial diagnosis included a cranial CT scan without contrast, followed by an MR imaging study with an original protocol for tumor and morphological characterization. This protocol includes the following sequences: axial 3D T1-weighted, sagittal 3D magnetization-prepared rapid acquisition gradient echo, axial and coronal T2-weighted, axial FLAIR, perfusion, diffusion, spectroscopy, and axial T1-weighted imaging obtained with Gd contrast.

After the suspicion of a tumor was raised by the imaging study, a 3D volumetric reconstruction of the lesion was undertaken on a Medtronic Stealth planning station with the aid of the StealthViz software package, for which axial T1-weighted images with Gd were used in the lesions with enhancement, and axial FLAIR images were used in the lesions without evident contrast enhancement. The reconstruction had two objectives; the first was to determine the tumor volume, and the second was to confirm the location of the lesion in an eloquent motor area. For the second objective, the central sulcus was used as the anatomical reference, identified directly or with the aid of the ascending cingulate sulcus visible in the midline sagittal image, defining from this point the postcentral gyrus, precentral gyrus, superior frontal gyrus (anterior and posterior), insula, and frontal operculi.[3,6,9,34] After the identification of these anatomical areas, the degree of eloquence was determined using the classification proposed by Sawaya et al.,[36] which classifies the lesions on the basis of their location relative to brain function as follows: Grade I, lesion in a noneloquent area; Grade II, lesion close to an eloquent area; and Grade III, lesion in an eloquent area. With the aim of preoperatively validating the real functional responsibility of these cortical anatomical areas considered as eloquent, an fMR imaging study was

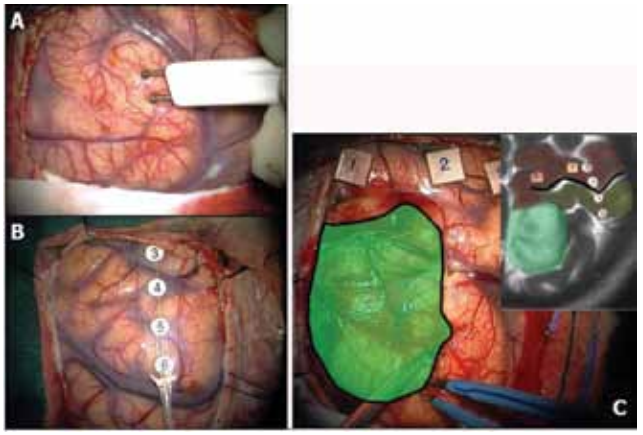

Fig. 1. Intraoperative views obtained during multimodal cortical navigation. View through the operating microscope after dura mater opening during mapping with CS **(A)** and placement of a flat electrode grid for localization of central sulcus **(B)**. View through the operating microscope after opening of dura mater **(C)** and T2-weighted MR image **(inset)** in navigator; *green* area contours the tumor, and the position of the central sulcus is marked by a *black line*.

performed with study paradigms of motor function (foot, hand, and tongue), superimposed over an anatomical MR imaging study.[1,3,14,17,21,27]

The preoperative evaluation was completed with a DT MR imaging study, and a tractography study of the tracts involved in each case was undertaken, especially the corticospinal pathway and superior longitudinal fasciculus.[9] Thanks to a series of freely available software tools (MRIcro, dTV.II SR Volume One, MedINRIA, and Image J) the chosen tract was converted into volumes, which were superimposed over the 3D magnetization-prepared rapid acquisition gradient echo anatomical study, according to the pattern of uptake. The volumetric transformation of these tracts and their fusion with the anatomical studies was achieved in all cases, with a specific pattern of shades of gray to avoid confusion with the rest of the structures in the studies over which they were fused.

All the MR imaging studies were performed at the installations of Exploraciones Radiológicas Especiales SA in the Hospital Clínico Universitario of Valencia, and using the Siemens MAGNETOM Trio 3-T system and Signa Excite 3-T system (General Electric Healthcare).

Fusion and Preoperative Planning

Thanks to a network connection between the MR systems, the planning station, and the intraoperative navigator unit, all the imaging studies mentioned were sent directly from the study equipment to the aforementioned planning station situated in the Neurosurgery Department, where the fusion and posterior planning were completed. Depending on the pattern of enhancement, the 3D T1-weighted study with Gd contrast or the FLAIR study was chosen as the base for the fusion, over which the fMR imaging study and the volumes of the tracts generated from the tractography were fused. After the fusion, the preoperative planning was performed, and sent via the hospital's intranet directly to the navigator unit situated in the Department of Neurosurgery's operating room.

Navigation and Intraoperative Neurophysiological Monitoring

With the brain cortex exposed after craniotomy, the cortical projection of the lesion was located and the anatomical structures were identified with the navigator's probe by using the electromagnetic module. The routine neurophysiological monitoring was composed of 3 techniques. Immediately after the craniotomy and the anatomical localization of the structures with the navigator, cortical mapping was performed with CS (Nihon Kohden Neuropack equipment and Integra NeuroSciences Ojemann Cortical Stimulator [OCS-2]), identifying the cortical areas with a motor response, which were identified in the surgical field with marks (CS enabled mapping of the cortical motor area via direct bipolar stimulation and electromyographic recording) (Figs. 1 and 2).

In case of lesions around the central sulcus, this was identified with a 6-contact flat electrode and the N20 wave inversion technique (mapping of the central sulcus with SSEPs from the contralateral median nerve). To identify the central sulcus, we used the following registration and stimulation parameters: sensibility, 20–50 μV; sweeping time, 5 msec/division; filters, 1.5 kHz–5 Hz; pulse rate, 0.2 msec; square wave, 5.8 Hz; and intensity between 20 and 25 mA.

Finally, after the volumetric resection of the lesion based on the position of the subcortical tracts (volumes generated by the tractography), direct stimulation of the subcortical tracts was performed (sCS enabled subcortical motor mapping via direct bipolar stimulation and electromyographic recording). For CS and sCS we used the same stimulation parameters, which were a 60-Hz square wave, 0.5- to 1-msec pulse duration, during at least 2- to 4-second stimuli, and an ascendent intensity from 2 to 10 mA, depending on the response.

As a control, transcranial stimulation of the ipsi- and contralateral motor cortex was performed with electromyographic recording of ipsi- and contralateral cortical SSEPs (Digitimer D185 Stimulator and Neuropack equipment). For this registration we used 4–7 pulse trains with stimuli duration of 50 μsec, 150–200 V intensity, and a stimulus-free interval of 4 msec.

The combination of the anatomical information provided by navigation and the functional information provided by cortical mapping with CS allowed for the design of the transsulcal approach or, if applicable, the corticectomy. The anatomical information on the calculated volumetric resection provided by the navigator, along with the result (if applicable) from the mapping of the white matter with sCS, marked the resection limit. In both situations, however, the final decision on accepting the result of the planning or, in case of conflict, the pertinent modifications, was the ultimate responsibility of the surgeon in charge of the procedure.

The position of all the points where a positive CS or sCS motor response was obtained were marked with the probe, with the aim of analyzing the correlation between the stimulation, cortical and sulcal anatomical references, anatomical tract, and functional cortical area identified on the fMR imaging studies. In the sCS, the stimulation parameters (potential, intensity, and duration of stimulus)

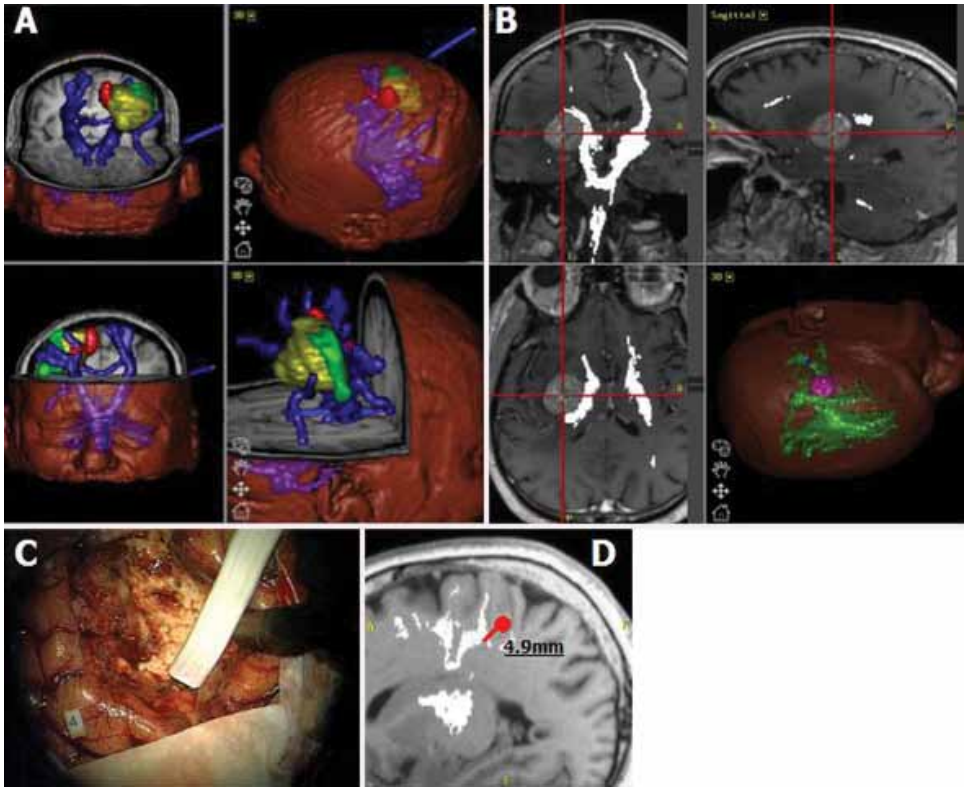

Fig. 2. Intraoperative multimodal subcortical navigation. **A:** A 3D display of tumor *(yellow)*, hand *(green)*, and foot *(red)* motor fMR imaging activity and pyramidal tracts *(blue)* superimposed on a T1 MR imaging anatomical study. **B:** Pyramidal tracts superimposed on a Gd-enhanced T1-weighted MR imaging study in a patient with a deep-seated metastasis. **C:** Intraoperative photograph showing an sCS after microsurgical resection of a cortico-subcortical tumor. **D:** Real-time navigation of a point subjected to sCS with positive motor response *(red dot and line)*, and the measurement of the distance to the nearest corticospinal tract.

were recorded in each case, and the distance between the point of response to the stimulation and the stimulated anatomical tract was calculated on the navigator. We considered it a good correlation if motor responses were obtained when stimulating the cortical or subcortical areas with suspected motor function, and the distances to the navigated corticospinal tract were related between 3.0 and 11.0 mm, according to previous studies[4] and our own experience.

Surgical Procedure and Follow-Up Data

All patients underwent surgery after induction of general anesthesia and in the absence of neuromuscular relaxation to allow for intraoperative neurophysiological monitoring. Wide craniotomies were designed, centered on the lesion that had been located with the navigator, including also the eloquent cortical area defined based on intraoperative study. The lesion was resected with the aid of a surgical microscope (Pentero), via a transsulcal approach, and according to standard microsurgical techniques, including the use of an ultrasonic aspirator. We used fluorescence techniques after administration of 5-aminolevulinic acid in the 8 cases we investigated in which important contrast enhancement and the suspicion of high-grade behavior occurred. The objective of the surgery was the complete resection of the lesion defined in the planning as tumor, with the widest possible margin of tissue removal without causing any new neurological deficits (so-called functional resection). The anesthesia was reversed in the operating room itself or in the recovery room in the first 6 hours after the surgery. Apart from the routine neurological progress evaluations, a neurological assessment was performed according to the protocol at 24 hours and at 30 days after surgery, and any new neurological deficits and the evolution of the previous ones were recorded. Apart from the routine postoperative CT scans obtained for follow-up evaluation of the surgery, an MR imaging session was performed within 72 hours for resection assessment, with the following: axial T1-weighted sequences with Gd contrast, axial FLAIR, and DT images. Using these studies, after a new volumetric analysis, a calculation was made of the extent of tumor resection, and 4 groups were defined: total (100%); subtotal (90–99%); partial (50–89%); and suboptimal resection (< 50%), according to the classification proposed by Berger et al.[2] Finally, the data provided by the anatomopathological study were collected.

Results

In this study, a total of 17 patients were included who underwent surgery for tumors in eloquent motor ar-

TABLE 1: Preoperative motor deficit, results of sCS and postsurgical focality, and distance between sCS points with a positive response and involved fasciculi on DT imaging navigation in 17 patients who underwent functional microsurgical resection of brain tumors*

Case No.†	Preop Motor Deficit	Positive sCS on Nav DT Imaging	Postop Focality		No. DsCS+/Distance Btwn DsCS & Nav DT Imaging
			6–24 Hrs	30 Days	
1	lt hemiparesis	anterior tibial; rostral tumor limit	monoplegia, lt leg	NA	3/9.7
3	none	abductor pollicis brevis & bilat abductor hallucis; caudal & lateral tumor limit	monoparesis, lt arm	NA	2/12.3
4	rt hemiparesis	orbicularis oris & quadriceps; rostral & inferior tumor limit	rt hemiparesis	hemianopia & monoparesis, rt leg	3/8.3
5	none	deltoids & hemiface; medial tumor limit	motor dysphasia & phasic seizures	phasic seizures (lower frequency)	5/6.7
7	lt hemiparesis	quadriceps & abductor hallucis; medial & caudal tumor limit	monoplegia, lt leg & monoparesis, lt hand	deficit in lt foot, dorsal flexion	4/10.1
8	rt monoparesis	quadriceps, anterior tibial, & abductor of little finger; pyramidal pathway medial to tumor	rt hemiplegia & aphasia	monoparesis, rt arm	7/3.2
9	none	NA	hemiparesis & ideomotor apraxia	ideomotor apraxia	NA
10	none	short abductor of thumb, deltoids, & common extensor of fingers; lateral-medial & caudal tumor limit	NA	NA	5/8.4
11	rt hemiparesis	positive response in deltoids & orbicularis oris; caudal & dorsal tumor limit	rt hemiparesis & motor dysphasia	motor dysphasia	6/5.5
12	none	positive response in deltoids, abductor of little finger, anterior tibial, gastrocnemius, & abductor hallucis; lateral-medial & caudal tumor limit	monoparesis, rt leg	NA	5/4.0
13	none	positive response in deltoids & abductor pollicis brevis; rostral, medial, & caudal tumor limit	lt hemiplegia	mono-hypesthesia, lt leg	3/6.9
14	rt hemiparesis	positive response in quadriceps & gastrocnemius; pyramidal pathway medial to tumor	rt hemiparesis	NA	4/11.2
15	lt hemiparesis	positive response in deltoids; pyramidal pathway lateral to tumor	lt hemiplegia	monoparesis, lt arm	2/7.9
16	none	positive response in orbicularis oris & short abductor of thumb; caudal & lateral tumor limit	monoplegia, rt arm & monoparesis, rt leg	deficit in supination & extension of fingers of rt hand	6/8.5

* DsCS+ = positive direct sCS; NA = not applicable; Nav = navigated.

† Cases 2, 6, and 17 were omitted because there was no positive response after sCS.

eas between June 2008 and April 2009 at the Neurosurgery Department of the Hospital Clínico Universitario of Valencia. The series was composed of 7 women and 10 men (1:1.4) with a mean age (± SD) of 54 ± 9.5 years. The principal clinical presentation was irritative in 11 patients (64.7%), with contralateral deficit (Table 1) in 5 patients (29.4%), and in the remaining patient (5.9%) the presenting symptom was headache refractory to analgesic treatment. All patients received symptomatic, antiepileptic, or corticosteroid treatment before the intervention, with control or improvement of the symptoms. After neurological examination performed preoperatively, a total of 58.8% of patients had some kind of motor neurological deficit. Two patients had undergone previous surgery for Grade II oligodendroglioma, presenting now with a local recurrence.

In the CT scan obtained without contrast, the lesions were identified in all cases except one as hypointense masses. Hyperintense areas were found in 3 studies, corresponding to calcifications in 2 cases and intratumoral bleeding in the remaining one. The lesion was identified on all the MR imaging studies, with a pattern of hypointensity in the T1-weighted sequences and of hyperintensity in the T2-weighted sequences and FLAIR, with uptake of Gd in 8 cases and areas suggestive of necrosis in 3 patients. The perfusion and spectroscopy studies showed patterns of high-grade tumor in 10 patients (58.8%) and of low-grade tumor in the remaining 7 cases. The mean tumor volume was 27.2 ± 21 cm^3 (range 3.4–72.7 cm^3). Assessing the anatomical location of the lesions, the tumor was cortical in 12 patients (70.6%; 3 in the postcentral gyrus, 4 in the precentral gyrus, 2 in the posterior part of the superior frontal gyrus, 1 in the anterior part of the superior frontal gyrus, and 2 in the frontal operculum), and the lesions were subcortical in the 5 remaining cases (29.4%; 3 in the corona radiata displacing the internal capsule and 2 in the insular white matter). The dis-

tribution of the lesions according to the classification of Sawaya et al.[36] was as follows: 7 Grade II lesions (41.2%) and 10 Grade III lesions (58.8%). Functional MR imaging was performed in 11 patients, and showed areas of activation over the contralateral precentral area. Positive areas of activation were obtained superimposed over the lesion in 3 cases, all of them low-grade gliomas in the precentral area. The DT MR imaging studies were completed in all cases. Tractography was performed without any difficulties, with segmentation and individualization of the corticospinal pathway in 16 studies and of the superior longitudinal fasciculus in 6.

The fusion of the anatomical and diagnostic studies, of fMR imaging and tractography, was achieved in all cases with high precision (estimated error < 1.5 mm), in 15 cases (88.2%) automatically and in the 2 remaining ones by using points to achieve the same level of precision.

Clinical and Imaging Results

All the lesions were located during surgery and were anatomopathologically confirmed. There was no intra- or postoperative death or morbidity related to the study methods or monitoring. The anatomopathological study showed the following lesions: low-grade astrocytoma (3 cases), anaplastic astrocytoma (3), oligoastrocytoma (2), low-grade oligodendroglioma (2), glioblastoma multiforme (4), and metastasis (3).

Twenty-four hours after surgery, there was deficit or irritative neurological focality in 12 patients (70.6%). One month after the surgery, deficits were substantially reduced, both quantitatively (8 patients, 47.1%) and qualitatively, and daily activities were affected in only 1 patient.

The postoperative volumetric analysis showed an extent of tumor resection of 89.1 ± 14.2% of the tumor volume calculated in the preoperative studies, with total resection in 8 patients (47.1%), subtotal resection in 3 patients (17.6%), and partial resection in the 6 remaining patients (35.3%). The average resection was higher in the tumors located in the frontal operculum, superior frontal gyrus, and corona radiata, but it was lower in the insular regions and pre- and postcentral gyri. Regarding the correlation between the percentage of resection and the Sawaya grades, we found that in the Grade II tumors the extent of resection was 91.9%, whereas in the Grade III tumors the mean extent of resection was 87.1%. According to the nature of the lesion, the maximum grade of resection was found in metastases and oligodendrogliomas, was lower in anaplastic astrocytomas and glioblastomas, and even lower in low-grade astrocytomas.

Operative Anatomofunctional Correlation Between the Motor Cortex and the Corticospinal Pathway

Using anatomical references, the central sulcus and the precentral gyrus were located with certainty in 11 studies (64.7%), whereas in the 6 remaining cases, definition of the central sulcus was impossible because of the distortion due to the mass effect of the tumor. Functional MR imaging always showed activation over the anatomically located precentral gyrus, although in many cases the precision was poor due to activity over the tumor, and in many other cases there were regions of dispersed activation in front of or behind the precentral gyrus. In all cases in which the corticospinal pathway was defined using tractography, there was complete correlation with the location defined in the anatomical imaging studies, namely the precentral gyrus where this tract originates, including the 6 cases in which the lesions had displaced the normal anatomy more or less grossly, which was extremely useful to confirm the anatomical localization of the central sulcus and precentral gyrus. There was also a good correlation with the areas of activation in the fMR imaging in the majority of cases when both studies were fused.

Intraoperative Anatomofunctional Correlation: Electrical Stimulation and Mapping

In the tumors located in the postcentral, precentral, and superior frontal gyri, a total of 52 direct cortical stimulations were performed in which a positive motor response identifying the primary motor area occurred. We got a positive correlation in 83.7% between these points recorded in the navigator and the corresponding functional areas identified in the fMR imaging. In 4 cases of tumors adjacent to the central sulcus, it was necessary to use the N20 wave inversion technique to locate the lesion due to the anatomical distortion produced by the tumor, which made it impossible to recognize with navigation. In 3 of these cases, the location of the central sulcus was consistent with the volumes of corticospinal tract identified with DT imaging. In the remaining case, the central sulcus located with wave inversion was 4 mm behind the anatomical sulcus identified according to the navigated tractography. Navigating the images obtained by tractography was really useful when resecting lesions close to the corticospinal pathway. After the volumetric resection, we stimulated the tumor bed to identify the subcortical motor tracts and, in 13 patients, a total of 55 sCS procedures were performed, with positive motor response that identified corticospinal tracts coming from the primary motor area (Table 1). In these cases, the average distance between points of response and the location of the tracts in the navigator was 7.3 ± 3.1 mm (range 1.8–13.4 mm). Given that the CS and sCS parameters have an influence on the response obtained, stimuli of 0.5- to 1-msec duration were used with intensities between 2 and 10 mA. The SSEPs were only altered in one case of deep lesion adjacent to the pyramidal pathway in the layer of the corona radiata.

On analyzing the relationship between the neurological focality at 30 days and the distance between the last point with a positive response to subcortical or corticospinal tract stimulation, an inverse relationship can be seen between them both, with an empirical safety margin of 8–10 mm (Fig. 3).

Between 1 and 3 days after the surgery, a functional mobility study was performed in all the patients included in this work. After this first evaluation, an initial functional rehabilitation based on passive movements was performed in 12 of the patients, continuing, when pos-

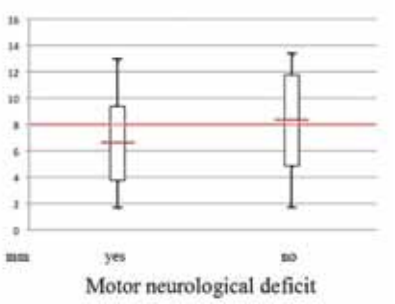

FIG. 3. Boxplot showing the relationship between the presence of focal motor neurological deficits 30 days after surgery and the distance between the point of sCS and the navigated pyramidal tract *(short red line)*.

sible, with active movements to avoid muscle atrophy and improve strength during the first postoperative stage. When the improvement seemed to have peaked, the functional rehabilitation continued with occupational therapy, based on the development of daily activities.

Discussion

The current recommendation for the treatment of intrinsic brain tumors is radical microsurgical resection of the lesion while maintaining the integrity of neurological function, followed by observation using neuroimaging, or oncological treatment. Given that glial tumors show infiltrating growth regardless of their grade, considering a volumetric resection beyond the limits of the tumor determined by the imaging techniques is necessary. However, this so-called tumor resection limit should only extend to the point where, as a consequence of the tissue resection, deterioration of the neurological function may appear (the functional resection limit).

One of the most critical and eloquent functional activities is motor activity, due to which microsurgical treatment of tumors in this region is particularly interesting. The cortical part of the motor and associated motor areas is composed of the postcentral gyrus, central sulcus, precentral gyrus, superior frontal gyrus, and frontal operculi, and should also include the short subcortical connections between the neighboring gyri (U-shaped fasciculi) and the long subcortical connections, such as the superior longitudinal fasciculus and particularly the effector corticospinal pathway.[3,9,30,34] In clinical practice, there is a large number of techniques that can be used to delimit these structures anatomically and functionally and to make surgery on tumors located in these areas safer.[1,5,8,15,17,21,23,24,28,29]

Preoperative and Intraoperative Protocol

In our study, the cortical areas were anatomically determined with imaging techniques, specifically with 3D reconstructions of MR images. This anatomical identification is usually safe, and although it may be distorted by the underlying pathological entity itself, it is determined preoperatively and checked intraoperatively with navigation, correlating it with the microsurgical field. Functional MR imaging allows a particular function to be preoperatively assigned to a cortical region that is activated as a consequence of the development of an eloquent activity. We have studied motor activity, again with a good anatomical correlation, but also with examinations with contradictory results as a consequence of diffuse activation or activation over the tumor itself. The fMR imaging fusion in the anatomical studies allows this information to be integrated into the intraoperative navigation.[1,10,14,21,27] However, there are still doubtful or contradictory cases when making decisions during surgery. In this circumstance, we added neurophysiological monitoring with two techniques in the motor area. First we performed anatomical localization of the central sulcus by using the N20 wave inversion technique, and then we delivered CS with a bipolar electrode.[5,8,18,23,27] This protocol has led to a great advance in the microsurgical treatment of tumors in motor areas, but only provides information on the cortex, with no data on the anatomical arrangement of the subcortical tracts or on their functional integrity.

Until now, sCS of the resection margins allowed the surgeon to discover the functional integrity of the stimulated fibers,[5,8,27] but without having a clear idea of the 3D location of the tract in relation to the stimulated point. The possibility of locating the subcortical tracts preoperatively by using DT imaging and tractography has led to a new advance in understanding the anatomical relationships between the lesions and these pathways, because they allow the arrangement of tracts in the white matter to be studied three-dimensionally, voxel by voxel, throughout the entire human brain.[3] This has been the reason for our interest in incorporating DT imaging into the navigation system, thus discovering preoperatively the anatomical location of the points subjected to sCS, to make decisions on whether to continue with the tissue resection.

Role of Tractography and sCS

In our experience, adding DT images into the Medtronic StealthStation navigation system has been possible in a simple but very laborious fashion. The preoperative surgery planning work has increased significantly, to get a better anatomical understanding of the subcortical anatomical pathways and of the lesion itself. Formerly, our protocol for preoperative planning and intraoperative monitoring focused on the identification of the lesion, the sulci, the gyri, and specific cortical vascular structures for anatomical reference, and on knowledge of the functionality of eloquent cortical areas. The incorporation of DT imaging and sCS has allowed us to understand the anatomical location of the white matter tracts and to study them functionally, above and beyond the intuition and imagination of the surgeon.

However, the objective of all this effort in terms of human and economic resources is to maximize the resection of lesions in the region and to minimize morbidity. The impression gained after undertaking this work is that the integration of DT imaging into the navigation protocol has substantially increased the extent of tumor resection in motor areas, and that more neurological deficits are produced. In fact, the volumetric analysis of tumor resection is found to be 90%, with total resections in almost half of the series, and at the same time, in the immediate postoperative period nearly all patients have experienced new

neurological deficits or worsening of preexisting deficits. However, the neurological deficits are totally or partially reversible in the majority of patients, and within 30 days only one patient had presented with problems that made it difficult to conduct daily activities. The literature gives us an awareness of the presence of high rates of neurological focality in the early postoperative period for lesions in eloquent areas, and its subsequent resolution.[5,8,10,15] This has been related to the fact that anatomical and functional monitoring allows us to work very close to the eloquent areas, in which the inevitable phenomena of traction, heat due to bipolar thermocoagulation, cytotoxic edema, or phenomena of microvascular reorganization would have greater functional repercussions during the immediate postoperative period.

It has already been stated that the processing of DT imaging and its conversion into DICOM and/or Analyze format (which allow for fusion in the navigator with the anatomical and fMR images) consumes a significant amount of time during preoperative planning. However, the information provided by DT imaging allows us to shorten the time spent in the intraoperative process of cortical functional localization with CS and N20 wave inversion to define the sulci for the approach to the tumor and for corticectomy. Also, once the volumetric tumor resection has been undertaken, the anatomical knowledge and the ability to visualize the cortical pathways, and especially the corticospinal pathway by using navigation, reduce the number of sCSs needed to locate the pathways and improve the interpretation of the information obtained to maximize the resection. In this sense, as a consequence of our initial results, a safe distance of 8–10 mm (Fig. 3) has been established between the point of stimulation at the functional resection limit and the corticospinal tract, which turns out to be similar to that which has been proposed by other authors.[4,5,29]

Limitations of DT Imaging and Tractography

The wide safety distance established between the point of sCS and the tract may seem excessive after the entire preoperative calculation process. This may be an important point of criticism of the study protocol we used, and may be due to several reasons. The process of obtaining the DT images and subsequent reconstructions to generate 3D images implies a huge number of matrix calculations that may accumulate errors. An important aspect is that the mechanism used to generate the eigenvector (that is, the main direction of the tract included in the seeding area) from the tensor is a user-defined procedure and, consequently, subject to interindividual differences.[22] The number of fibers that will be included in the tract depends on the anatomical location chosen to generate the tract in question, on the fractional anisotropy values chosen, on the algorithm used, and on the user-defined area. Also, consideration has to be given intraoperatively to the error introduced into the navigation data by the shifting of brain structures after the tumor resection, which includes the phenomenon of expansion generated by the recovery of space lost due to the growth of the tumor, edema due to manipulation, and relative pressure changes. The consequence is that the reexpansion makes the white matter move closer to the center of the resection cavity generated, shortening the distances between the point of sCS and the real location of the stimulated eloquent tract.

After analyzing our results during the sCS, the conclusion we reached is congruent with the results obtained by other authors. The distance between the motor response–stimulated point and the navigated corticospinal fascicle implicated on the transmission of that movement has always been positive in our series (+1.8 to +13.4 mm). This fact means that we have positive responses in tissue localized closer to the center of the resection cavity than to the "real fascicle." If we had only analyzed this fact, we could have concluded that we were leaving some tumor tissue surrounding the corticospinal tract and achieving lower extents of resection. However, when we analyzed the postoperative MR imaging studies, the extent of resection was nearly 90% of the tumor volume, a fact that leads us to affirm that the shifting of these brain structures was always directed to the center of the resection cavity. This phenomenon of tissue reexpansion during tumor resection has been extensively studied by Archip et al.[1] and Nimsky and colleagues,[29,30] who demonstrated using intraoperative MR imaging and DT imaging with tractography of the corticospinal pathway, that while the resection cavity was filled with neighboring parenchyma due to the phenomenon of reexpansion, the tracts of the pyramidal pathway moved closer to the center of the cavity. After our experience, we think it could be really interesting to assess the phenomenon of "growth" of the subcortical pathways affected by surrounding tumors during the surgical decompression, and to analyze the possible responses with the aid of sCS at lower intensities and at some distance away from the fascicles.

In the absence of this sophisticated method of intraoperative control, the combination of the data provided by preoperative DT imaging and intraoperative sCS can be correctly interpreted by introducing a correction factor to compensate for the shift. Thus, Nimsky et al.[29] propose adding a safety margin to the volume generated by each tract that, based on their own experience, they calculate to be between 5 and 7 mm. This can be determined preoperatively by using fractional anisotropy values < 0.2, or simply by adding a fictitious volume to that generated after the primary calculation.

Conclusions

The integration of pre- and intraoperative anatomical and functional studies allows for functional resection that significantly widens the extent of resection in lesions in relevant eloquent areas. Navigation allows us to integrate and understand the correlation between the preoperative data and the intraoperative findings. The cortical functional motor areas are anatomically and functionally defined in the preoperative period by using MR and fMR imaging studies, and the subcortical functional motor areas are defined with DT imaging and the generation of tractography from the DT images, whereas intraoperative confirmation is achieved using CS and the N20 wave inversion study for the cortical areas and sCS for the subcortical areas. Microsurgical treatment guided by navigation

and with the aid of the studies described allows for mean tumor resections of 90% in lesions located in cortical and subcortical eloquent motor areas, with high neurological morbidity in the immediate postoperative period, which is significantly reduced both quantitatively and qualitatively within 4 weeks. The ongoing studies should define safety margins for functional resection that take the brain shift into consideration. Finally, the benefit of these protocols for disease-free interval, recurrence, or ultimate patient survival remains to be defined.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: JM González-Darder. Acquisition of data: V Cortés. Analysis and interpretation of data: P González-López, F Talamantes, V Quilis, G García-March, P Roldán.

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Intraoperative use of diffusion tensor imaging fiber tractography and subcortical mapping for resection of gliomas: technical considerations

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Resection of lesions involving motor or language areas or pathways requires the intraoperative identification of functional cortical and subcortical sites for effectively and safe guidance. Diffusion tensor (DT) imaging and fiber tractography are MR imaging techniques based on the concept of anisotropic water diffusion in myelinated fibers, which enable 3D reconstruction and visualization of white matter tracts and provide information about the relationship of these tracts to the tumor mass. The authors routinely used DT imaging fiber tractography to reconstruct various tracts involved in the motor and/or language system in a large series of patients with lesions involving the motor and/or language areas or pathways. The DT imaging fiber tractography data were loaded into the neuronavigational system and combined intraoperatively with those obtained from direct electrical stimulation applied at the subcortical level. In this paper the authors report the results of their experience, describing the findings for each tract and discussing technical aspects of the combined use as well as the pitfalls. *(DOI: 10.3171/2009.12.FOCUS09240)*

Key Words • intraoperative mapping • glioma • diffusion tensor imaging fiber tractography • motor and language subcortical sites

Surgical removal of lesions located in or within functional areas requires the intraoperative identification of functional sites at both cortical and subcortical levels to safely resect the tumor and at the same time preserve functional integrity for the patient.[10,16,49] Commonly referred to as brain mapping, this identification process involves a number of surgical, neurophysiological, and neuropsychological adjuncts, which work together to provide the functional results.[3,9,15] Neuroradiological techniques, such as fMR imaging and DT imaging–FT, respectively, offer the opportunity to identify preoperatively the location of functional sites at a cortical level and the course or modification of subcortical tracts.[6,18,27,46–48] These techniques are particularly useful because they can help the surgeon in surgical planning and, when the data are loaded into the neuronavigational system[45] and available intraoperatively, may provide intraoperative guidance as well.[6,13,17,32] Specifically, DT imaging and FT are MR imaging techniques that allow the visualization of the amount and orientation of water diffusion along myelinated fibers and enable 3D reconstruction and visualization of white matter tracts.[1,2,11,14,35,44,52,60] In addition, DT imaging–FT depicts the relationship of subcortical tracts with the tumor mass and the surrounding brain edema.[12,20,34,50] A tract can be depicted as unchanged (when its course is not modified by the tumor or edema), dislocated, or infiltrated and/or interrupted (when the tract is in strict relationship with the mass or interrupted by it).[25,57] These results are influenced by some technical factors,[30,51] such as the fractional anisotropy threshold used for start and stop tracking,[33,35,59] or by characteristics of the tumor, such as histology, edema, and location.[19,22,50,53,56]

Abbreviations used in this paper: CST = corticospinal tract; DES = direct electrical stimulation; DICOM = Digital Imaging and Communications in Medicine; DT = diffusion tensor; ECoG = electrocorticography; EEG = electroencephalography; EMG = electromyography; fMR = functional MR; FOV = field of view; FT = fiber tractography; IFO = inferior frontooccipital fasciculus; ILF = inferior longitudinal fasciculus; MEP = motor evoked potential; ROI = region of interest; SENSE = sensitivity encoding; SLF = superior longitudinal fasciculus; UNC = uncinate fasciculus.

We have previously described our experience with the use of DT imaging–FT during the surgical removal of gliomas located in eloquent areas, reporting the correlation between DT imaging–FT data and those obtained with DES applied at the subcortical level.[5] In that preliminary experience, based on a limited group of patients with low- and high-grade gliomas, we showed that the location and course of the tract was dependent on tumor histological type and degree of infiltration; the tracts were usually at the tumor periphery in high-grade gliomas, or inside the tumor mass and highly infiltrated in low-grade gliomas. In addition, we also reported the percentage of correlation between some of the tracts, involved either in the motor or language function, as depicted by DT imaging–FT and DES findings. We concluded that the combination of DT imaging–FT and DES allowed accurate identification of eloquent fiber tracts and enhanced surgical performance and safety, maintaining a high rate of functional preservation. Furthermore, it decreased the duration of surgery, patient fatigue, and risk of intraoperative seizures. Since then, we have routinely used DT imaging–FT for reconstruction of subcortical tracts, involved either in the motor and language system, and correlate these data with those obtained intraoperatively by the aid of neurophysiology. This work describes such an experience, reporting the results in a larger group of patients, providing data pertaining to additional tracts involved in language, and discussing the advantage and pitfalls of our protocol.

For reasons of simplicity, we will focus on the correlation with neurophysiological data obtained with 60-Hz stimulation, which is the most widely used in the clinical setting.

Methods

Patient Population

Between November 2005 and August 2009, 230 patients with gliomas in or within motor and/or language areas or pathways were admitted in our institutions. Age, sex, clinical history, and symptoms, as well as neurological status at admission, were registered. Preoperatively, all patients underwent a neuropsychological evaluation, baseline and volumetric MR imaging studies, fMR imaging, and DT imaging–FT. Surgery was performed in all patients with the aid of intraoperative cortical and subcortical mapping for motor and/or language functions. Volumetric scan analysis was used for establishing the exact tumor location and topography as well as the volume of the lesion.[4]

Tumor volume was calculated via a computerized system, using 3D axial FLAIR images (see below) for low-grade gliomas and contrast-enhanced T1-weighted MR images for high-grade gliomas. Histological type was classified according to the WHO brain tumor classification. Extent of resection was measured on postoperative volumetric FLAIR images (for low-grade gliomas) or post-contrast volumetric MR images (for high-grade gliomas) immediately after surgery or at 3 months and classified as previously reported.[4,16,29]

Surgical Procedures Including Cortical and Subcortical Mapping

Surgery was performed with the patient in a state of general (asleep) anesthesia when only the motor function was to be registered and monitored; alternatively, when language or visuospatial function also had to be monitored and tested, asleep-awake anesthesia was used. In these cases, a craniotomy exposing the cortex corresponding to the tumor area and a limited amount of the surrounding cortex was performed during the initial period of surgery, with the patient in a state of general anesthesia. Afterward, the dura was opened, the patient awakened, and cortical mapping performed. Multimodal electrophysiological monitoring was used throughout the entire duration of surgery. It included continuous EEG and ECoG recording along with a multichannel polygraphic recording of EMG responses (Comet system, Grass Technologies).

Electroencephalographic activity was recorded bilaterally by means of 4 subdermal needle electrodes, providing 4 bipolar leads. Electroencephalography was used to monitor brain activity when ECoG was not available, for example at the beginning and the end of surgery, and also to assess brain activity at sites distant from the operating field, such as in the contralateral hemisphere.

Electrocorticographic activity from a cortical region adjacent the area being stimulated was recorded by subdural strip electrodes (Cortical Strip Electrode, Integra LifeScience), in a monopolar array, referred to a midfrontal electrode. Cerebral activity was recorded with a bandpass of 1.6–320 Hz, and displayed with a sensitivity of 50–100 μm/cm for EEG and 200–400 μm/cm for ECoG. Continuous electrocorticographic recording (Comet system, Grass Technologies) was used during the entire duration of the procedure to monitor the brain basal electrical activity, to define the working current (as that immediately below that which induced an afterdischarge), to monitor for the occurrence of afterdischarges, to monitor and adjust the level of anesthesia, or to detect seizures during resection.

For continuous monitoring of motor function, MEP recording was also performed. The train-of-5 technique, being introduced for surgery in anesthetized patients, has been described as sensitive to detect imminent lesions of the motor cortex and the pyramidal pathways.[9] A strip electrode containing 4–8 electrodes was placed over the precentral gyrus. In awake patients a single stimulus or a double pulse stimulus (individual pulse width 0.3–0.5 msec, anodal constant current stimulation; interstimulus interval 4 msec, stimulation close to motor threshold) was usually delivered. The muscle MEPs were recorded with either needle or—more convenient in awake patients—surface EMG electrodes. The MEP recording was usually alternated with direct cortical and subcortical motor mapping.

Cortical and subcortical mapping was performed with the use of an Orisis stimulator (Inomed), delivering biphasic square wave pulses, each phase lasting 1 msec, at 60 Hz in trains lasting 1 second for cortical mapping and 1–2 seconds for subcortical mapping. Subcortical mapping was alternated with resection. Subcortical mapping

was performed by using the same current threshold applied for cortical mapping. Surgery was performed with the aid of a neuronavigation system (BrainLAB).

Motor mapping was performed with the aid of a continuous multichannel EMG recording, which was used throughout the entire procedure. Several separate muscles belonging to agonist or antagonist groups were monitored on either the contralateral or the ipsilateral side. Motor responses were collected via pairs of subdermal hooked needle electrodes inserted into contralateral muscles from face to foot. Each pair of electrodes recorded activity from 2 different muscles in the same body segment (for example, a flexor and an extensor muscle in the forearm) in order to sample as many muscles as possible. On average, 16 channels were used for each procedure. Most often, the muscles used included muscles from the face (upper and lower face), neck, arm, forearm, hand, upper leg, and lower leg. A computerized video image system was continuously coupled with the EMG recordings (Comet system, Grass Technologies) to monitor and record the motor activity. Motor activity was also evaluated clinically. In addition, in cases involving patients with a lesion in the dominant hemisphere, language mapping was performed. In such cases, patients underwent extensive preoperative language testing composed of a battery of tests aimed at evaluation of oral language production and comprehension together with repetition.[4]

Language dominance was evaluated by means of the Edinburgh Inventory Questionnaire and fMR imaging. The following tasks were performed: spontaneous speech; oral controlled association by phonemic cue; famous face naming; object picture naming; action picture naming; word comprehension; sentence comprehension; and transcoding tasks. In addition the token test, the digit span test, and counting were performed. Ideomotor apraxia and face apraxia were also assessed. The majority of the tests we used have been standardized on the normal population. Language was also evaluated during the entire duration of the surgical procedure by testing spontaneous speech.

Neuroradiological Evaluation

Magnetic resonance imaging was performed preoperatively on a Philips Intera 3.0-T system with a maximum field gradient strength of 80 mT/m. Patients underwent standard MR imaging evaluation for morphological characterization of the lesions: conventional imaging consisted of an axial turbo spin echo T2-weighted sequence (TR 3800 msec, TE 85 msec, FOV 230 mm, 22 slices, section thickness 5 mm with a 1-mm gap, matrix 512 × 512, SENSE reduction factor 1.5), a 3D axial FLAIR sequence (TR 10,000 msec, TE 110 msec, FOV 230 mm, 120 slices, section thickness 1.5 mm with no gap, matrix 224 × 256, SENSE reduction factor 2), and a postcontrast inversion recovery T1-weighted sequence (TR 2000 msec, TE 10 msec, FOV 230 mm, 22 slices, section thickness 5 mm with a 1-mm gap, matrix 400 × 512, SENSE reduction factor 1.5).

Diffusion Tensor Imaging Data Acquisition and FT Processing

Diffusion tensor imaging data were obtained at 3 T[21,37,41] using a single-shot echo planar imaging sequence (TR 8986 msec, TE 80 msec) with parallel imaging (SENSE reduction factor 2.5).[23] Diffusion gradients were applied along 32 axes, using b values of 0 and 1000 mm^2/second. An FOV of 240 × 240 mm and a data matrix of 96 × 96 were used, resulting in isotropic voxel dimensions of 2.5 × 2.5 × 2.5 mm. The data were interpolated in plane to a matrix of 256 × 256 leading to a voxel size of 0.94 × 0.94 × 2.5 mm. Fifty-six slices were obtained, with a thickness of 2.5 mm and no gap. The sequence was repeated twice and data were averaged offline to increase the signal-to-noise ratio; thus, total time for DT MR imaging was 10 minutes and 46 seconds. Three-dimensional fast field echo T1-weighted sequences (TR 8 msec, TE 4 msec, image resolution equal to DT imaging) were obtained for anatomical guidance.

Diffusion tensor imaging data sets were realigned offline on a PC workstation using the AIR (Automatic Image Registration) software to correct for artifacts due to rigid body movement during scan acquisition.[58]

Deterministic tractography was performed in all patients with the aid of DTI Studio v2.4.01 software (H. Jiang and S. Mori, Department of Radiology, Johns Hopkins University), obtaining main eigenvector and fractional anisotropy maps.[43] Subcortical connections were reconstructed using the "fiber assignment by continuous tracking" (FACT) method.[33,36,59] A fractional anisotropy threshold of 0.1 and a turning angle > 55° were used as criteria to start and stop tracking. Seeding ROIs for tractography were defined around areas of white matter that represent the brain regions that all the fibers of each tract must pass through to reach their cortical or subcortical end points. The ROIs were chosen, on the basis of previous anatomical knowledge, in sections perpendicular to the main course of the tracts.[54]

To reconstruct the CST, an ROI was placed on an axial section at the level of the subcortical white matter of the precentral gyri. For the IFO, ILF, and UNC, an ROI was placed on a coronal section at the level of the anterior part of the external capsule at the junction of the frontal and temporal lobes, where the 2 tracts run in contiguity.

To reconstruct the SLF, a first ROI was placed on a coronal section at the level of a high-anisotropy region lateral to the central part of the lateral ventricle; a second ROI was placed in a peritrigonal site at the level of the descending branch of the fascicle.

For all the tracts reconstructed, contaminating fibers were removed.

Volumetric precontrast T1-weighted or FLAIR images were coregistered to the mean of all diffusion weighted images using SPM2 software to obtain the superimposition of the white matter tracts on T1-weighted anatomical images. This allowed us to compare the trajectories of the tracts in the involved hemisphere with those of the contralateral (unaffected) hemisphere, and to evaluate the anatomical relationship between the tract and the tumor mass as well as the effect exerted by the tumor on the tract of interest. The DT imaging–FT data were saved in

a compatible format (DICOM) to be transferred to the neuronavigational system using MEDx Software (Medical Numerics, Inc.).

Correlation Between DT Imaging–FT Data and Perioperative Subcortical Motor and Language Findings

As previously reported, the correlation between DT imaging–FT data and subcortical sites identified during perioperative DES was assessed at the time of surgery and postoperatively. At the time of surgery, the location of each subcortical site was recorded during the various phases of resection by the use of neuronavigation system into which the DT imaging–FT data fused with preoperative MR images were loaded. The distance between the point of response to DES and the tract border was measured on axial navigation images, and relationship between the two was graded as correspondent (at the tract border or within the tract), close (within 1 cm), or distant (> 1 cm). In addition, each subcortical site identified during subcortical mapping was marked with a sterile numbered tag and a digital picture of the surgical cavity was taken at the end of the resection. On the immediate postoperative MR images we evaluated the anatomical location of the subcortical pathways (the periphery of the surgical cavity, where the resection was stopped according to the functional responses elicited by intraoperative stimulation).[16] This was accomplished by transferring immediate postoperative MR images obtained in each patient to a BrainLAB workstation and fusing them with preoperative MR images with which DT imaging–FT results for each fascicle had been merged. The existence of a correspondence between the location of a subcortical site identified by DES and that of the tract in DT imaging–FT images was considered only when the distance between the location of the subcortical site evoked by DES and identified intraoperatively by the use of neuronavigation system was graded as correspondent to the tract in axial neuronavigation images. In all the other cases, the correspondence was considered null.

Statistical Analysis

Data were analyzed by the use of Prism 4 for Macintosh (GraphPad Software, Inc).

Differences in the duration of resection expressed as means and SDs were evaluated with the Student t-test. Differences in percentages of patients with clinical and electrical evidence of seizure activity and differences in patient fatigue were studied with the Fisher exact test. Sensitivity and specificity of DT imaging–FT for the identification of subcortical tracts were calculated as previously reported.[5]

Results and Discussion

Patient Population

Two hundred and thirty patients were included. Of these, 176 had low-grade gliomas (oligodendrogliomas and astrocytomas) and 54 had high-grade gliomas (glioblastomas or anaplastic astrocytomas and oligodendrogliomas). As for location, 71 tumors were in the precentral lobe, 71 were rolandic, 18 parietal, 46 temporal, and 24 within the insula. In all patients we were able to reconstruct subcortical tracts. Depending on the location of the tumor and language dominance, various language tracts were reconstructed.

Results will be presented hereafter according to tumor histological type and motor and language tracts.

Tumor Histological Type

The analysis of the course of the tracts according to tumor histological type confirmed the results obtained in our previous work based on a smaller group of patients. In patients with high-grade gliomas, most of the tracts were located at the tumor periphery and were depicted as dislocated or infiltrated. No tract was found inside a tumor mass. Subcortical mapping demonstrated functional subcortical areas in the same location, specifically at the tumor border. In addition, when the tract was found to be infiltrated and/or interrupted, no responses were evoked by DES in the same areas. In patients with low-grade gliomas, DT imaging–FT showed that the tracts were mostly infiltrated and interrupted or dislocated by the tumor mass. In addition, in many patients large portions of the tracts were shown to be inside the tumor mass, in the same places where DES identified motor or language responses. Furthermore, when tracts were found interrupted inside the tumor mass, in some cases DES documented the presence of functional areas in the same areas. Globally considered, these data indicate that DT imaging and FT reconstruction are particularly useful in low-grade glioma surgery, where most of the tracts are inside the tumor mass.[5,9,24] This is the reason why we preferentially performed DT imaging–FT in patients in whom preoperative MR images suggested a low-grade glioma; it was used in only selected cases in which preoperative images indicated a high-grade glioma.

Motor Tracts

Per our routine protocol, the CST was reconstructed in all 230 patients and tested intraoperatively by DES due to its close relationship with the tumor in 180 cases. In selected patients, additional tracts running in the premotor areas were also reconstructed, mainly for research purposes; these findings are not included in this work. As an exception, the course of the motor fibers belonging to the premotor facial areas were also reconstructed. These findings are reported under *Language Tract*.

In all the cases of precentral tumors, the CST was depicted either as unchanged (66% of cases) or as dislocated posteriorly (34% of tumors, all large lesions) (Table 1). In both conditions, subcortical stimulation located the tract at the posterior border of the tumor mass. Motor responses appeared as focal (few muscles) when the tract was stimulated in close vicinity to the surface, whereas responses to deep stimulation involved multiple muscle groups. The cortical or near-cortical stimulation always induced evident movements, while subcortical stimulation frequently induced muscle activation that was only detected by magnified EMG in the early stages of resection, when approaching the subcortical tracts, and that

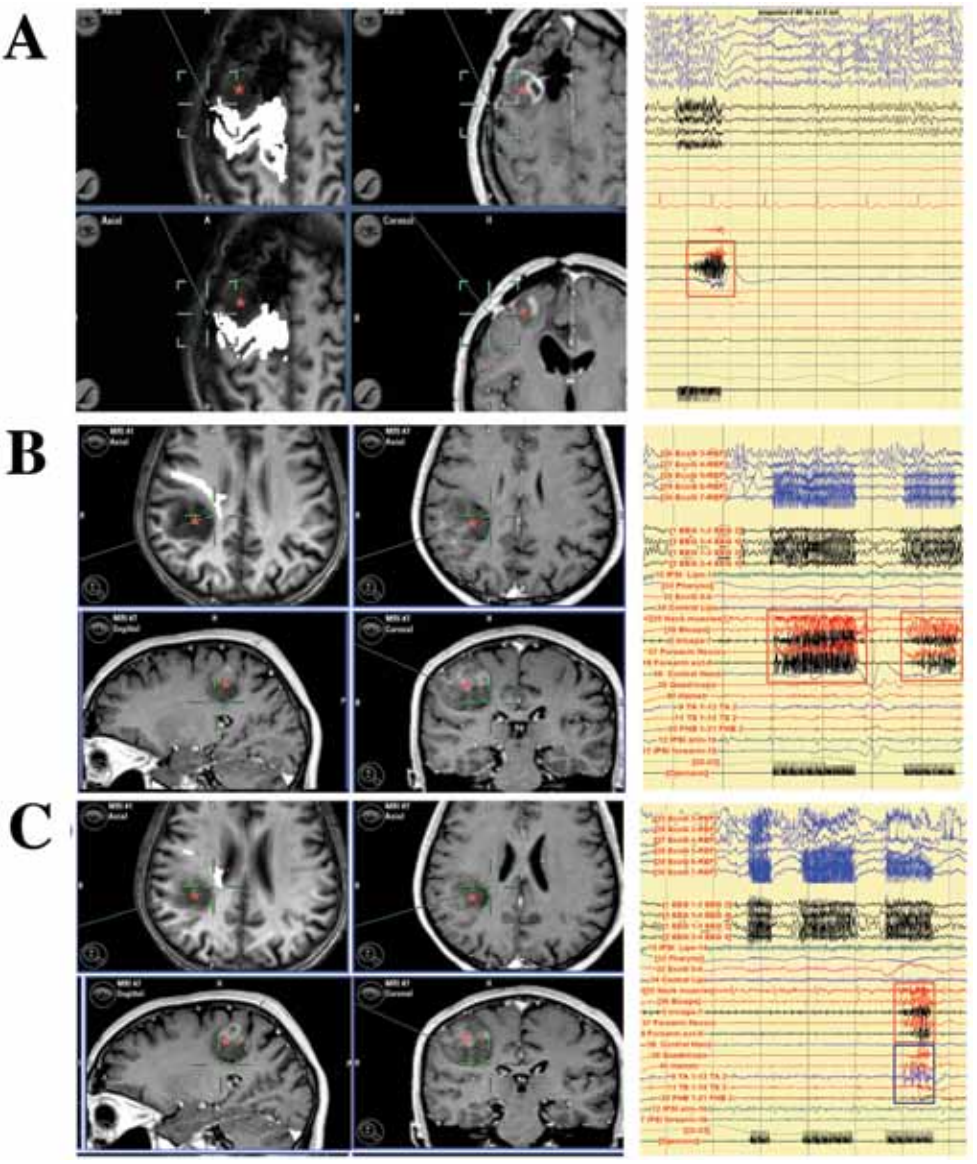

Fig. 1. Diffusion tensor imaging–FT and DES data for the CST obtained in patients with rolandic tumors. The **left panels** show intraoperative screen shots taken where DES located motor responses. The **right panels** show EMG responses evoked during subcortical stimulation. In cases of rolandic tumors *(red asterisks)*, DT imaging reconstructed the CST *(bright white tract)* inside the tumor mass. Motor responses to DES appeared as focal (forearm muscles grouped in the *red rectangle* **[A]**) when the tract was stimulated in close vicinity to the surface and progressively affected multiple muscle groups with stimulation of the deeper portion of the tract (hand and arm **[B]**; arm and leg **[C]**, grouped in the *red* and *blue rectangles,* respectively). For all shown cases, the stimulation point is indicated by the center of the *green cursor.*

became overt movements when the CST was reached. In all cases, subcortical DES located the CST where it was shown by DT imaging–FT, and therefore, the results were graded as correspondent.

In cases of rolandic tumors, DT imaging reconstructed the CST mainly inside the tumor mass (98% of cases). In the majority of bulky tumors (92%), the tract was displaced either anteriorly (22%), or more frequently posteriorly (78%), and highly infiltrated by the tumor mass (Fig. 1, Table 1). Less frequently, and in cases of highly infiltrating and diffuse low-grade gliomas, the tract was depicted inside the tumor mass and as highly infiltrated. In the first group of tumors, subcortical DES located the tract in the same position where it was depicted by DT imaging–FT (Fig. 1). Some discrepancies were observed in the superior portion of the tract, close to the cortical surface, where DT imaging–FT failed to reconstruct fibers and instead DES located motor responses. As we previously reported, even the placement of additional ROIs in those regions did not improve the fiber reconstruction. More problematic are the cases of highly diffuse low-grade gliomas, where DT imaging–FT usually reconstructed the tract as highly infiltrated and inside the tumor mass (Fig. 2). Particularly in those cases with a long history of seizures, and at the beginning of the resection, when 60-Hz stimulation was applied over the regions of the tumor where DT

TABLE 1: Corticospinal tract: preoperative DT imaging–FT findings, correspondence with intraoperative subcortical mapping, and postoperative deficits*

Tumor Location & Preop DTI-FT Findings†	No. of Cases	No. of Cases w/ Intraop Mapping ‡	Correspondence§		Deficits¶	
			Yes	No	Early	Late
rolandic (71 cases)						
unchanged	8	8	8	0	0	0
dislocated	13	13	13	0	11	0
infiltrated	50	50	50 (12)**	0	50	0
precentral (71 cases)						
unchanged	47	24††	24	0	0	0
dislocated	24	24	24	0	23	0
infiltrated	0	—	—	—	—	—
insular (24 cases)						
unchanged	14	0	—	—	—	—
dislocated	10	10	10	0	10	0
infiltrated	0	—	—	—	—	—
parietal (18 cases)						
unchanged	3	3	3	0	0	0
dislocated	7	7	7	0	6	0
infiltrated	8	8	8	0	8	0
temporal (46 cases)						
unchanged	28	0	—	—	—	—
dislocated	18	10	10	0	1	0
infiltrated	0	—	—	—	—	—

* Values represent numbers of cases. Abbreviation: — = not applicable.

† The DT imaging–FT findings represent the modification of the tract in relationship to the tumor.

‡ The number of cases in which DT imaging–FT depicted the tract as adjacent to or inside the tumor mass and it was possible to directly test the correspondence between DT imaging–FT and intraoperative subcortical mapping.

§ Correspondence between DT imaging and subcortical mapping with respect to the location of the tract.

¶ Early = 3 days after surgery; late = 1 month after surgery.

** Includes 12 cases of highly diffuse low-grade gliomas in which the CST was depicted by DT imaging–FT as inside the tumor mass and highly infiltrated and in which a good correspondence was reached by the combined use of monopolar and bipolar stimulation.

†† The number of precentral tumors in which the CST was depicted close to the posterior border of the tumor and therefore found during surgery by DES.

imaging–FT depicted the location of the upper portion of the tract, it usually failed to locate overt motor responses. When the current intensity was progressively increased to induce responses, it usually resulted in seizures, without overt movements. In these cases, the electrical identification of the CST required the use of different modalities of stimulation, such as the monopolar stimulation, or alternatively, the initial resection could be performed under DT imaging–FT guidance. However, as in the previous cases, DT imaging–FT failed to show fibers close to the more lateral portion of the homunculus, probably due to the presence of crossing fibers that cannot be depicted by the simple tensor model here used for tractography,[26,55] where DES (generally with monopolar stimulation) induced laryngeal or upper or lower face responses. When a portion of the tumor was removed, and the CST partially decompressed, the 60-Hz stimulation again started to produce motor responses, usually in the same location where DT imaging–FT reconstructed the deeper portion of the CST.

In the cases of parietal tumors, DT imaging–FT usually located the CST at the anterior border of the tumor, and depicted either as unchanged when the tumor volume was small (16.7% of cases), or dislocated anteriorly when the tumor was larger (83.3%, Table 1). Direct electrical stimulation located the tract in a similar position.

In cases of insular or temporal tumors, the CST was located at the medial and posterior border of the tumor, and depicted either as unchanged or dislocated (Table 1). The concordance was tested in a subgroup of patients in which the tract was depicted as close to the border of the tumor, where DES during surgery produced motor responses.

Considered together, these data indicate that there is usually a very high concordance between DT imaging–FT data for CST and subcortical mapping, with the CST

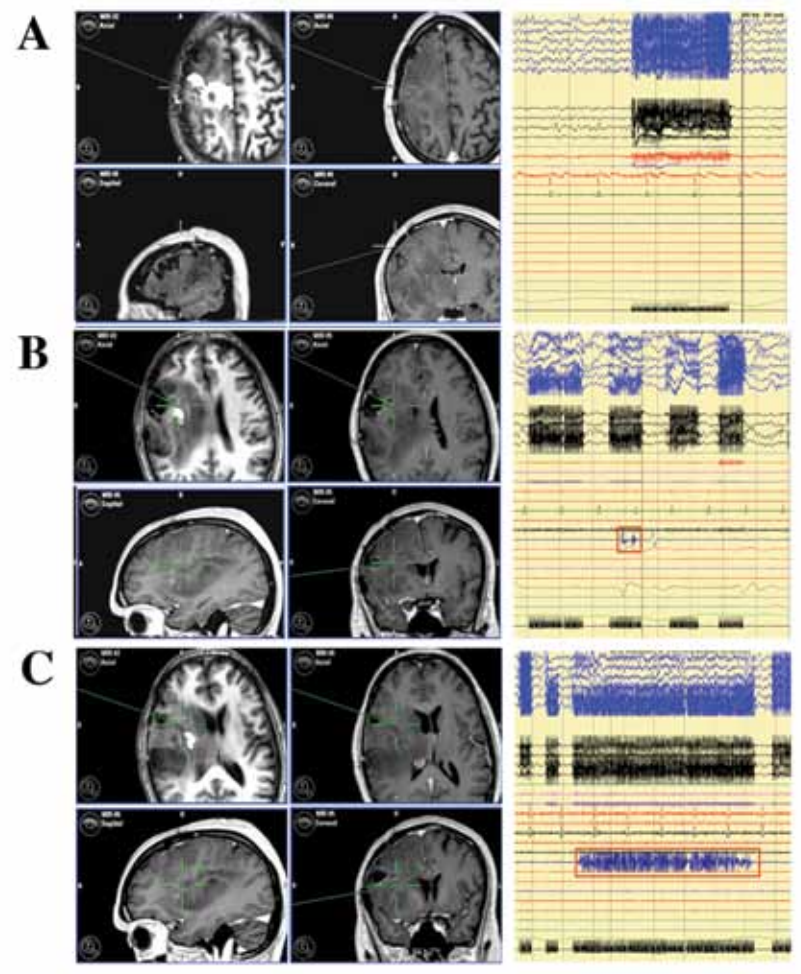

Fig. 2. Diffusion tensor imaging–FT and DES data for the CST in a case of diffuse low-grade glioma. The **left panels** show intraoperative screen shots taken where DES identified motor responses. The **right panels** show EMG responses evoked during subcortical stimulation. In this patient, DT imaging–FT reconstructed the tract as highly infiltrated and inside the tumor mass. In the upper portion of the tract, the 60-Hz stimulation failed to induce overt motor responses, as shown in **A**. When a portion of the tumor was removed and the CST partially decompressed, the 60-Hz stimulation started again to produce motor responses with stimulation in the same location where DT imaging–FT reconstructed the deeper portion of the CST, as shown in the *red rectangles* in **B** and **C**.

being located in the same position where it was depicted by DT imaging–FT. Some pitfalls may occur in a limited subgroup of highly diffuse low-grade gliomas located in the rolandic areas (12 cases in this study), in which DT imaging–FT may fail in reconstructing portions of CST, particularly in areas of extensive infiltration. In addition, in these particular cases, the electrical identification of the CST may be problematic and require the use of alternative stimulation modalities.

Language Tracts

We will initially present the results for the SLF and the IFO and then we will analyze the results for additional language tracts, such as UNC and ILF, separately.

The SLF and IFO were reconstructed in all patients with either temporal or frontal dominant tumors, given that these 2 tracts are essential for the preservation of language function.

The SLF is a large tract,[31] running from the parietal to the frontal lobe, mediating the phonemic component of language. It was depicted by DT imaging–FT as dislocated or infiltrated by the tumor, generally depending on histological type, size, and location of the tumor mass (Fig. 3, Table 2). The tract was usually unchanged or dislocated in patients with high-grade tumors, and infiltrated in those with low-grade gliomas. Large tumors dislocated or infiltrated the tract; smaller ones were more likely to leave the tract unchanged. When the SLF was found during surgery and stimulated with a 60-Hz current, phonemic paraphasias were induced by stimulation in the same places where the tract was located by DT imaging–FT. As previously reported, the anatomical distribution of this tract is usually quite a bit larger than the functional distribution as identified by subcortical mapping. Therefore, a large part of the tract can be safely resected because it is not functional in terms of language. This is particularly true in patients with frontal and temporal tumors. In

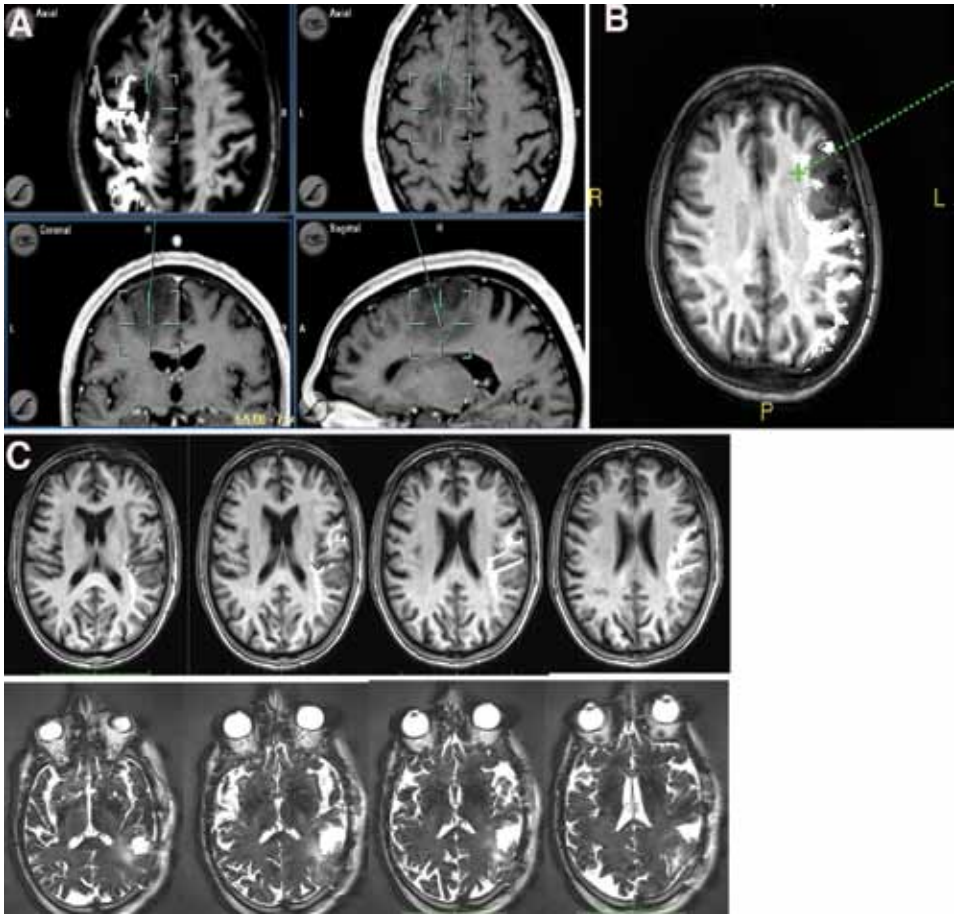

Fig. 3. Diffusion tensor imaging–FT reconstruction of the SLF. **A:** A case of a left frontal F1, F2 Grade II oligodendroglioma. Diffusion tensor imaging–FT reconstructions of the SLF, highlighted as a *bright white ROI*, were fused with T1-weighted MR images. The tract constituted the lateral border of the tumor. Resection was performed with the aid of subcortical language mapping, which was continuously alternated with the tumor resection. Resection was stopped when language responses (phonemic paraphasias) were encountered. The intraoperative screen shots were taken where DES, performed in the site indicated by the center of the *green cursors*, identified such a response. **B:** A case of an F3 low-grade glioma. Diffusion tensor imaging–FT reconstruction of the SLF was fused with T1-weighted MR images. To visualize the portion of the tract located at the anterior and medial border of the tumor, an additional ROI was placed in the subcortical region of F3. Intraoperative DES induced phonemic paraphasias. The location of this site *(green cross)* was registered into the neuronavigation system at the time of surgery, as visualized by the intraoperative screen shot. **C:** A case of left temporal oligodendroglioma. Diffusion tensor imaging–FT reconstruction of the SLF was merged with T1-weighted MR images **(upper panels)**. Postoperative T2-weighted MR images showed that the resection margins coincided with the location of the SLF **(lower panels)**.

addition, in cases of low-grade gliomas involving the F3 gyrus, an additional ROI should be placed in the subcortical area of F3 to visualize the portion of the SLF tract that produces phonemic paraphasia in response to stimulation. This portion usually constituted the anterior and superior border of the tumor in our patients.

The IFO is a discrete tract, running from the occipital to the frontal lobe, and mediating the semantic component of language. The relationship between the tract and the tumor depends on the tumor's location, size, and histological type. The tract was depicted as unchanged or dislocated in cases of high-grade tumors, or as dislocated and/or infiltrated in cases of low-grade gliomas. Again, large tumors dislocated or infiltrated the tract; small tumors were more likely to leave the tract unchanged. It is to be stressed that the anatomical distribution of this tract is small and usually corresponds to the functional one depicted by subcortical mapping (Fig. 4, Table 3). In fact, DES evoked no language disturbances in areas lacking fibers when the tract was depicted as interrupted inside the tumor mass. In only a few cases of frontal low-grade gliomas (9 of 76), where the tract was located inside the more anterior portion of the tumor mass and depicted as highly dislocated and infiltrated, a limited portion of the tract could be safely removed because it was not functional. In addition, some problems may occur for F3 low-grade gliomas in which DT imaging–FT may fail in reconstructing the more superior part of the tract at the inferior border of the tumor, when the tumor infiltration in this area is quite extensive.

These data indicate that the reconstruction of the IFO by DT imaging–FT is of particular use, because the results correlate closely with the results of functional mapping by DES. In contrast, the anatomical distribution of

TABLE 2: Superior longitudinal fasciculus in dominant-hemisphere tumors: preoperative DT imaging–FT findings, correspondence with intraoperative subcortical mapping, and postoperative deficits

Tumor Location & Preop DTI-FT Findings	No. of Cases	No. of Cases w/ Intraop Mapping	Correspondence		Deficits	
			Yes	No	Early	Late
rolandic (30 cases)*						
unchanged	3	3	3	0	0	0
dislocated	6	6	6	0	6	0
infiltrated	21	21	21	0	21	0
precentral (40 cases)*						
unchanged	8	8	8	0	0	0
dislocated	5	5	5	0	4	0
infiltrated	27	27	27	0	26	0
insular (18 cases)*						
unchanged	1	0	—	—	—	—
dislocated	6	6	6	0	6	0
infiltrated	11	11	11	0	11	0
parietal (14 cases)*						
unchanged	0	—	—	—	—	—
dislocated	4	4	4	0	2	0
infiltrated	10	10	10	0	6	0
temporal (40 cases)*						
unchanged	0	—	—	—	—	—
dislocated	18	18	18	0	14	0
infiltrated	22	22	22	0	22	0

* Number of patients with a left-hemisphere tumor in whom the tract was reconstructed.

SLF by DT imaging–FT is quite large, and particularly inside the tumor mass, a large part of the tract can be safely resected.

The UF was reconstructed in cases of insular tumors or frontal tumors, and in cases of temporal tumors. In insular tumors, the UF ran at the anterior border of the tumor mass and was depicted usually as dislocated and infiltrated in low-grade gliomas or anteriorly dislocated in high-grade tumors. When the UF was found during subcortical stimulation, phonemic paraphasia followed by speech arrest resulted from stimulation in the same areas where the tract was depicted by DT imaging–FT. In frontal tumors that extended posteriorly toward the anterior portion of the insula, the tract ran along the posterior inferior border, and it was dislocated posteriorly in 84% of cases. In cases of temporal tumors, the UNC was located in the medial anterior portion of the lobe, running rostrally. The identification of the tract both in DT imaging–FT maps and during surgery depended on tumor size. The tract could be easily identified as a separate fascicle in cases of small or medium-sized tumors, in which it usually runs anteriorly, medially, and inferiorly to the IFO. In cases of large tumors, DT imaging–FT showed that the tract was intermingled with the IFO, and during surgery it could not be identified, as it was "masked" by the IFO.

The ILF is a discrete fascicle running in the anterior and lateral portion of the temporal lobe, laterally and superiorly to the IFO, close to the ventricle. The tract can be depicted as unchanged or dislocated or infiltrated depending on the size and histological type of the tumor. High-grade gliomas usually dislocated the tract, whereas low-grade gliomas infiltrated it. The ILF was identified as a separate fascicle in cases of small- or medium-sized tumors (Fig. 5). In large tumors, it was depicted as intermingled mainly along its posterior part with the IFO, from which it could not be functionally separated at the time of surgery. Functional results by others[15,17,18] as well as by our group have shown that the tract can be safely resected during surgery, resulting in a transient speech disturbance that resolved in less than 2 weeks.

In cases of F3 or F2 frontal or insular tumors, we found it useful to reconstruct the course of the face premotor fibers. These are fibers running from the dorsal premotor cortex toward the Broca area, and their stimulation during surgery induced anarthria. As with the IFO and SLF, the maintenance of these fibers is essential for the preservation of language. Diffusion tensor imaging–FT depicted the course of these fibers at the posterior border of F3, F2, or insular tumors, where they were identified by DES (Fig. 6).

Clinical Significance of the Combined Use of DT Imaging–FT and Subcortical DES

Our experience with a large number of patients

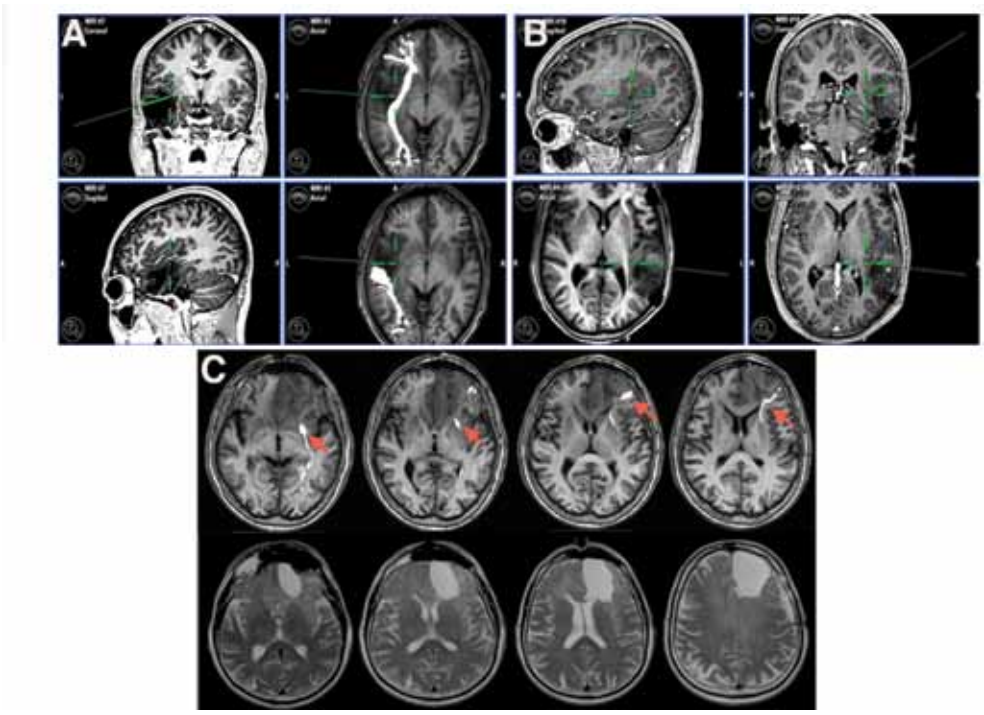

Fig. 4. Diffusion tensor imaging–FT reconstruction of the IFO. **A and B:** Cases of low-grade temporal oligodendrogliomas. Diffusion tensor imaging–FT reconstruction of the IFO was fused with postcontrast T1-weighted MR images and loaded into the neuronavigation system. The IFO, shown as a *highlighted bright white ROI,* was located at the superior medial border of the tumor, where DES evoked semantic paraphasias (DES sites were located at the center of the *green cursors*). **C:** A case of a left frontal oligodendroglioma. Diffusion tensor imaging–FT reconstruction of the IFO, which was merged with postcontrast T1-weighted MR images, showed that the tract was located at the posterior border of the tumor (**upper panels**, *arrows*). Postoperative T2-weighted MR images showed that the resection margins coincided posteriorly with the location of the IFO as shown by DT imaging–FT **(lower panels)**.

showed that the combined use of DT imaging–FT and DES is a feasible approach that can be effectively and safely applied in routine clinical practice. Diffusion tensor imaging–FT, when used with a neuronavigation system, can help reduce the time required for surgery by helping the surgeon design the surgical approach as well as helping—at the time of the resection—to locate the tract where subcortical stimulation should be initiated. This may result in a reduction in the number of stimulations needed to safely identify a tract as well as a decrease in seizures and in patient fatigue. As already reported in limited cases, such as in diffuse low-grade gliomas, this combined approach may help at the beginning of the resection when the use of a 60-Hz current may be problematic. In addition, in our experience it has also helped in a few cases in which surgery was performed under awake anesthesia, when at the end of a long procedure the patient's cooperation became suboptimal, rendering direct language guidance no longer useful. In these few cases, we were able to continue resection under the guidance of DT imaging–FT images until the position of subcortical tracts was encountered and to maintain the patients' functional integrity.

In our patient population, the combined use of DT imaging–FT and DES for identification of subcortical tracts during surgery was associated with immediate postoperative deficits in 72.2 and 84% of patients with lesions involving motor or language pathways, respectively, and these deficits lasted 1 week on average (Tables 1–3). Deficits were most likely to develop in those cases in which preoperative DT imaging showed the tracts as dislocated or infiltrated. At 1-month follow-up, 94% of patients with a motor lesion had normal findings on motor function examination, and 96.8% of those with lesions involving speech areas or pathways had normal language function.

Neuronavigation, Brain Shift, and Technical Performance of Surgery

It is important to remember that DT imaging–FT provides anatomical information, whereas subcortical motor or language mapping provides functional information. This distinction affects the concordance between DT imaging–FT images and functional information obtained with subcortical mapping. This is of some importance for CST but is of particular relevance for language tracts, in which the anatomical distribution of the tract as depicted by DT imaging can be larger than the functional ones obtained with mapping. Therefore, portions of some tracts as depicted by DT imaging–FT can be removed because they are not involved in the function tested at that time.

As a whole, the data presented in the previous section indicate that the reconstruction by DT imaging–FT of specific tracts, such as the CST, IFO, SLF and face premotor fibers, and its availability at the time of surgery are of particular help, especially for resection of low-grade

TABLE 3: Inferior frontoccipital fasciculus in left-hemisphere tumors: preoperative DT imaging–FT findings, correspondence with intraoperative subcortical mapping, and postoperative deficits

Tumor Location & Preop DTI-FT Findings	No. of Cases	No. of Cases w/ Intraop Mapping	Correspondence		Deficits	
			Yes	No	Early	Late
rolandic (40 cases)*						
unchanged	28	0	—	—	—	—
dislocated	12	12	12	0	10	0
infiltrated	0	—	—	—	—	—
precentral (40 cases)*						
unchanged	3	1	1	0	1	0
dislocated	12	12	12	0	11	0
infiltrated	25	25	25 (9)†	0	25	0
insular (14 cases)*						
unchanged	2	2	2	0	1	0
dislocated	8	8	8	0	8	0
infiltrated	4	4	4	0	4	0
parietal (12 cases)*						
unchanged	3	0	—	—	—	—
dislocated	6	6	6	0	3	0
infiltrated	3	3	3	0	3	0
temporal (40 cases)*						
unchanged	0	—	—	—	—	—
dislocated	22	22	22	0	22	0
infiltrated	18	18	18	0	18	0

* Number of cases of left-hemisphere tumors in which the tract was reconstructed.

† Includes 9 cases of left precentral tumors (low-grade gliomas) in which it was possible to safely resect the anterior portion of a highly infiltrated IFO which was determined to be not functional by intraoperative subcortical mapping.

gliomas. Apart from the cases in which DT imaging–FT data can be obtained intraoperatively by the use of an intraoperative MR imaging system,[38–40] in the majority of settings DT imaging–FT data are usually loaded into the neuronavigation system and fused with preoperative MR images. For a correct use of DT imaging–FT data in this setting, 2 points appear as critical: the transfer of the data to the neuronavigation system, and the use of technical adjustments during surgery to maintain global accuracy of the information.[7,8,28,42]

With respect to the first point, in our center DT imaging–FT data are saved in a compatible format (DICOM) by using MEDx Software (Medical Numerics, Inc.); this allows the images to be transferred and loaded into the neuronavigation system. The BrainLAB neuronavigation system performed an automatic coregistration between DT imaging–FT datasets and the preoperative MR images acquired with skull fiducials by means of a voxel-by-voxel intensity-matching nonlinear algorithm. As an estimate of the clinical navigation accuracy, the target registration error localizing a separate fiducial, which was not used for registration, was also determined; this target registration error was less than 2 mm. Furthermore, repeated landmark checks were performed during surgery to ensure overall ongoing clinical navigation accuracy.

With respect to the second point, the maximal accuracy of the neuronavigation system should be maintained to reduce the problem of brain shift: 1) Repeated landmark checks should be performed during surgery to ensure overall ongoing clinical navigation accuracy. 2) Craniotomy size should be limited to the minimum necessary to expose the tumor area and a limited portion of the surrounding brain. 3) Resection should be performed in a manner that ensures maintenance of maximal accuracy of the information. In cases of frontal tumors located in the proximity of the CST, resection was started from the posterior border of the tumor, where the CST was located, and after its identification the tract was followed inside the tumor mass. Afterward the remaining anterior part of the tumor was removed. Similarly, in cases of parietal tumors, resection was started from the anterior border following the same principle. In any case, during resection of temporal or insular tumors, or at the end of the resection of large tumors, even when these suggestions were carefully followed, the amount of brain shift can become substantial, and the accuracy of the information provided by the neuronavigation system may be limited.[38–40]

Conclusions

Globally considered, our data indicate the usefulness

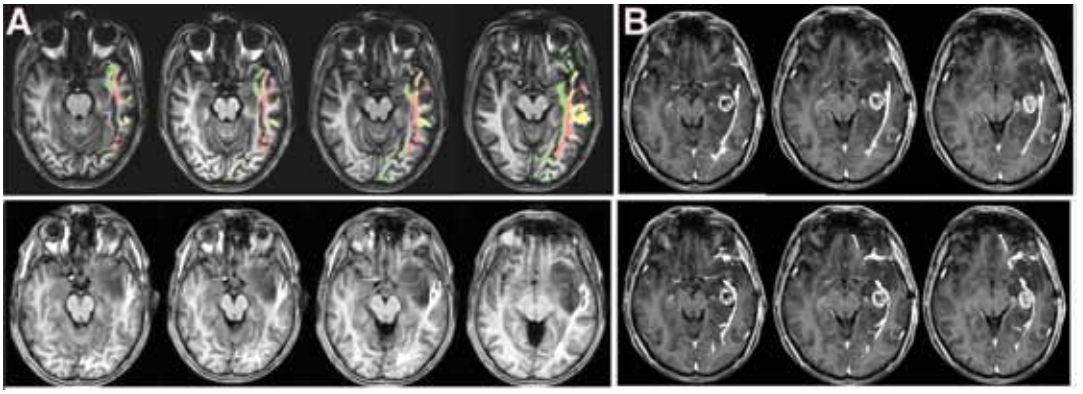

Fig. 5. Diffusion tensor imaging–FT reconstruction of the ILF. **A:** A case of a low-grade temporal oligodendroglioma. Diffusion tensor imaging–FT reconstructions of the IFO *(green ROIs)*, ILF *(red ROIs)*, and SLF *(yellow ROIs)* were merged with T1-weighted MR images (results shown in **upper panels**). Images with only the DT imaging–FT reconstruction of the ILF *(white ROIs)* were fused with T1-weighted MR images (results show in **lower panels**). Both sets of images show that the tracts were inside the tumor mass and can be depicted as separate fascicles. **B:** A case of a large left temporal high-grade glioma. The DT imaging–FT reconstruction of the ILF is shown in the **upper panels** and that of the IFO in the **lower panels.** The ILF and IFO (*white ROIs,* **upper and lower panels**, respectively) were fused with postcontrast T1-weighted MR images. In this case, the ILF was intermingled with the IFO, and they could not be functionally separated during surgery.

of the routine combined use of DT imaging–FT and subcortical mapping, particularly in patients with low-grade gliomas. These tumors display an infiltrative modality of growth, along short and long connecting fibers, and visualizing the trajectory of the tracts is important for planning and performing surgery. When used in combination with subcortical mapping, DT imaging–FT offers the opportunity to quickly find the fibers associated with motor or language functions during surgery. The clinical relevance of this combined approach comes from the

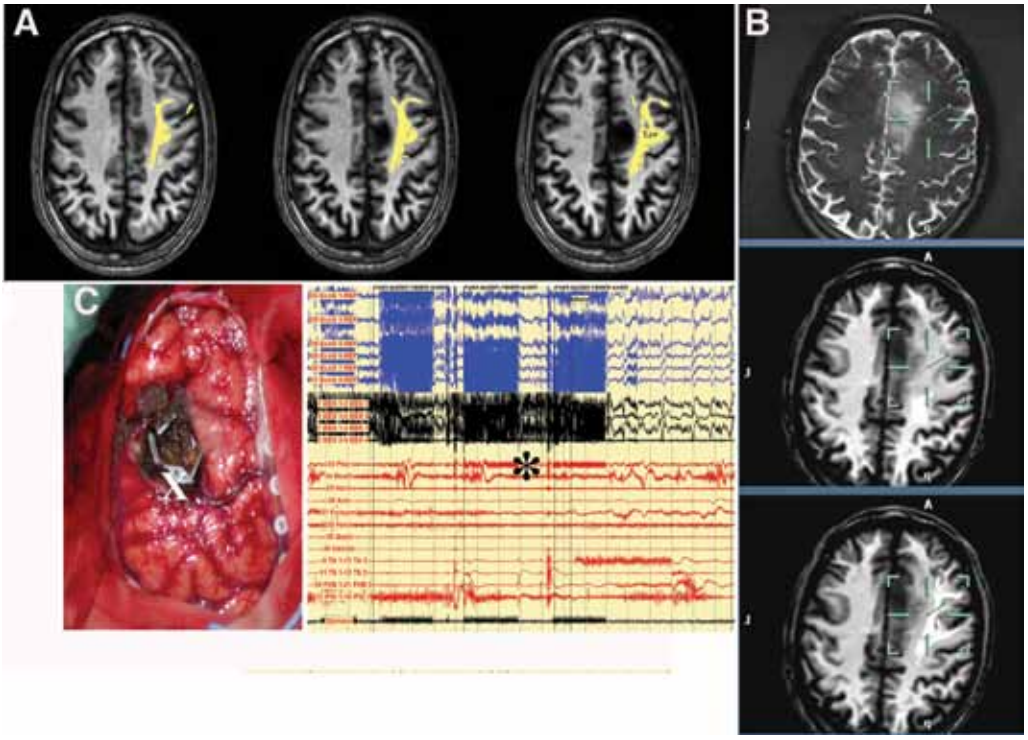

Fig. 6. Diffusion tensor imaging–FT reconstruction of the face premotor fibers. **A:** A case of a left-hemisphere oligodendroglioma in which DT imaging–FT reconstruction of the face premotor fibers *(yellow ROIs)* was merged with T1-weighted MR images. The fibers were located at the lateral border of the tumor. **B:** A similar case of a left-hemisphere oligodendroglioma, in which DES, performed at the center of the *green cursors*, located the fibers intraoperatively, in the same position as depicted by DT imaging–FT as *white ROIs* **(lower panel**). The **middle panel** shows the DT imaging–FT reconstruction of the CST. **C:** The **left panel** is an intraoperative picture of the surgical field. The *white X* indicates the position of the fibers at the posterior border of the surgical cavity. The **right panel** reports the EMG findings. The *black asterisk* indicates the activation of the upper and lower lips, which resulted in speech arrest (anarthria).

fact that it further enhances surgical safety, maintaining a high rate of functional preservation. Careful use requires the knowledge of its limitations, mainly the occurrence of brain shift.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: L Bello, A Falini. Acquisition of data: L Bello, A Castellano, E Fava, G Casaceli, M Riva, A Falini. Analysis and interpretation of data: L Bello, A Castellano, G Casaceli, M Riva, SM Gaini. Drafting the article: L Bello, E Fava. Critically revising the article: L Bello, A Castellano, G Casaceli, G Scotti, A Falini. Reviewed final version of the manuscript and approved it for submission: L Bello, G Scotti, A Falini.

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Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice

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There is increasing evidence that the extent of tumor removal in low-grade glioma surgery is related to patient survival time. Thus, the goal of resecting the largest amount of tumor possible without leading to permanent neurological sequelae is a challenge for the neurosurgeon. Electrical stimulation of the brain to detect cortical and axonal areas involved in motor, language, and cognitive function and located within the tumor or along its boundaries has become an essential tool in combination with awake craniotomy. Based on a literature review, discussions within the European Low-Grade Glioma Group, and illustrative clinical experience, the authors of this paper provide an overview for neurosurgeons, neurophysiologists, linguists, and anesthesiologists as well as those new to the field about the stimulation techniques currently being used for mapping sensorimotor, language, and cognitive function in awake surgery for low-grade glioma. The paper is intended to help the understanding of these techniques and facilitate a comparison of results between users. *(DOI: 10.3171/2009.12.FOCUS09237)*

Key Words • awake craniotomy • direct cortical stimulation • low-grade glioma surgery • brain mapping

The direct intraoperative application of electric current onto the human cortex for localizing and activating function dates back to the 1930s.[10,20,37] Its definite impact on preserving function in the resection of low-grade gliomas has been reported.[6–8,13,18,36] Nevertheless, methodological rigor and the meticulous performance of mapping procedures are indispensable to avoid any false-positive or false-negative stimulation results, which could lead to inadequate tumor resection or cause permanent neurological deficits. If all the technical rules are not respected faithfully, inaccurate results will create a false sense of security, which could lead to undesired surgical results and permanent neurological sequelae. Based on published material, personal experience, and discussions with members of the European Low-Grade Glioma Group who are dedicated to the intraoperative stimulation procedure, the most important aspects of brain mapping during surgeries in awake patients are presented and reviewed.

The purpose of the mapping procedure is to reliably identify cortical areas and subcortical pathways involved in motor, sensory, language, and cognitive function. Although similar techniques are utilized, the application of mapping at different centers involves a diversity of approaches.

Electrical Stimulation

The technical aspects of electrical stimulation include the stimulator device; the stimulation parameters consisting of the individual pulse type, pulse width, frequency of stimulation, and applied intensity; and the stimulation probe being used to deliver the electric current.

Stimulator Device

For brain mapping purposes, constant-current stimulators are considered safer and more reliable because they deliver the preset current independently from the imped-

Abbreviations used in this paper: CUSA = Cavitron ultrasonic aspirator; DT = diffusion tensor; ECoG = electrocorticography; EMG = electromyography; MEP = motor evoked potential.

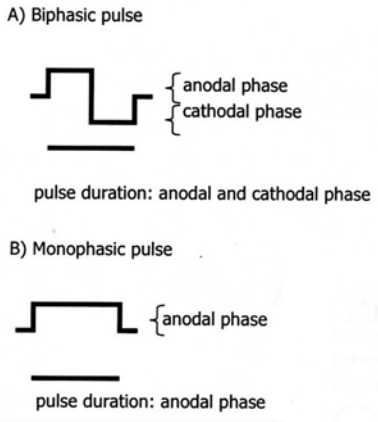

Fig. 1. Schematic of monophasic and biphasic pulse forms.

ance of the cortical or subcortical surface. Conversely, in constant-voltage stimulators, the delivered current also depends on the impedance. Hence, if impedance decreases, the amount of current delivered can dramatically increase and compromise the safety of the procedures. An extensive discussion of the differences between constant-current and constant-voltage stimulators is beyond the scope of this review.

Stimulation Parameters

For brain mapping, a low frequency paradigm has been established, consisting of the application of short pulse trains with frequencies of 25–60 Hz. The most commonly applied frequencies are 50 Hz (Europe) or 60 Hz (North America).

The individual pulse is rectangular and either monophasic or biphasic (Fig. 1). As described in the first experiments, cortical stimulation is more effective with anodal current; that is, a lower stimulation intensity is needed to see a stimulation effect.[21,23] Thus, the first phase of the pulse should be anodal. If a monophasic pulse is used, it should be anodal (or positive); if a biphasic pulse is used, it should be in an anodal/cathodal mode. The anodal phase duration can vary between 0.2 and 0.5 msec. In applying a biphasic current, the duration of the pulse includes both the positive and negative phases. Therefore, only half of the pulse duration is anodal and effective for stimulation—meaning that a monophasic pulse of 0.5 msec delivers the same anodal current as a biphasic pulse of 1 msec. However, as the charge is dependent on pulse duration (charge [Asec] = pulse duration [sec] × intensity [A]), the charge applied to the brain using a biphasic pulse is twice that applied using the same current but with a monophasic pulse. For safety considerations, the maximum stimulation intensity should not exceed 40 $\mu C/cm^2$/phase and is commonly limited to 20 mA.[1] For a detailed physical background regarding monopolar versus bipolar stimulation techniques see the study by Kombos and Süss.[28]

Historically, at times when only uncoupled stimulators were available, a biphasic pulse was seen to be less neurotoxic as the reversed pulse could minimize those effects.[40] With the utilization of coupled stimulators and limited application times during surgical procedures, neurotoxic effects have not been described.[2,22,31,40,41]

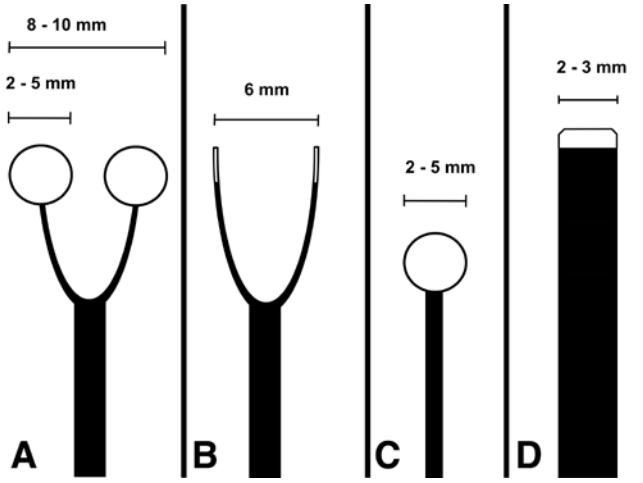

Fig. 2. Schematic of probes used for bipolar stimulation with ball tips **(A)** or straight tips **(B)** and for monopolar stimulations with a ball tip **(C)** or straight tip **(D)**.

Stimulation Probe

The use of a bipolar probe with 2 tips separated by 6–10 mm has become standard (Fig. 2). An interelectrode distance > 10 mm seems to favor the elicitation of large pyramidal tract neurons.[25] Alternatively, a monopolar probe with a frontal reference electrode can be used. The distribution of the electric field differs between monopolar and bipolar probes. Given the same stimulation intensities, a monopolar probe provides a homogeneous radiant spreading electric field, which leads to lower current densities in the area surrounding the reference electrode but has the benefit of more spacious stimulation effects. With this probe the probability of stimulating nervous tissue at a more distant site increases. In contrast, stimulation with a bipolar probe creates an electric field in which the current density is more homogeneous and the electric field lines between both poles are close to parallel (Fig. 3).[32,38] If monopolar and bipolar electrodes have the same shape, the current density close to the stimulating electrodes is the same and the greatest.

Documentation of Stimulation's Effect

Observation of the Patient

The most simple and most complex task for the examiner is observing the patient's reaction to stimulation. Movement can be observed and categorized by its complexity. Clonic movement relates to stimulation of the primary motor area, whereas tonic movement is more related to stimulation of the premotor area (Area 6). Furthermore, the absence of any induced movement should be tested for negative motor phenomena (see *Mapping of Motor Function*).

Recording Electrodes

Small movements or movements at distant sites can go unrecognized. Simultaneous brain mapping and monitoring of muscle activity by continuous EMG recording (either surface electrodes or needle electrodes) can be

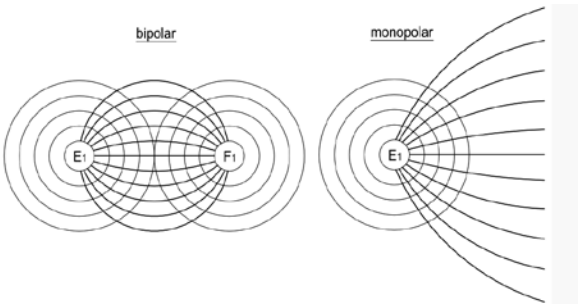

Fig. 3. Schematic of electric field distribution in bipolar **(left)** and monopolar **(right)** stimulations.

helpful.[50] Electromyography—complementary to ECoG—also allows for early detection of the spreading of muscle activation over a limb as a sign of seizure. These data can be stored and used for offline analysis and for the purpose of documentation. To record EMG activity, subdermal needle electrodes are used and are surprisingly well tolerated even during awake procedures. Alternatively, surface EMG electrodes placed in the belly-tendon fashion can be used.

Mapping in Awake Patients

As stimulation-induced movements are easy to observe, it is typically recommended to start with the mapping of motor function. The presence of a speech therapist, neuropsychologist, or neurologist is very important for observation and judgment, especially for language and cognitive function. It is highly recommended to introduce members of the surgical team to the patient and to explain the intraoperative procedure as well as the testing to the patient at least a day prior to surgery. The patient might feel uncomfortable experiencing involuntary movement or the inhibition of voluntary movement and language, which could lead to feelings of fear and angst and might be accompanied by an alteration of vital and vegetative signs such as nausea, hypertonia, and tachycardia. Moreover, patients might conclude from positive testing that the tumor has invaded important cortical structures and thus that the tumor surgery might not be successful. Some patients experience overwhelming fear, which could interfere with further testing and even the whole surgical procedure. In such patients, ECoG is helpful for ruling out nonconvulsive but focal temporal seizures. The patient's guidance is very important, and therefore each step of the testing and stimulation procedure should be announced. Patients should be carefully examined and asked about any sensation, feelings, or movements, especially the contraction of pharyngeal muscles, which might not be observed by the examiner.

Mapping of Motor Function

While performing direct cortical stimulation, the stimulation intensity should be increased stepwise by 1 mA until a movement or EMG response is observed. This stimulation intensity should be used for further mapping of sensorimotor, language, and cognitive function. One to 2 msec duration of stimulation is sufficient to induce

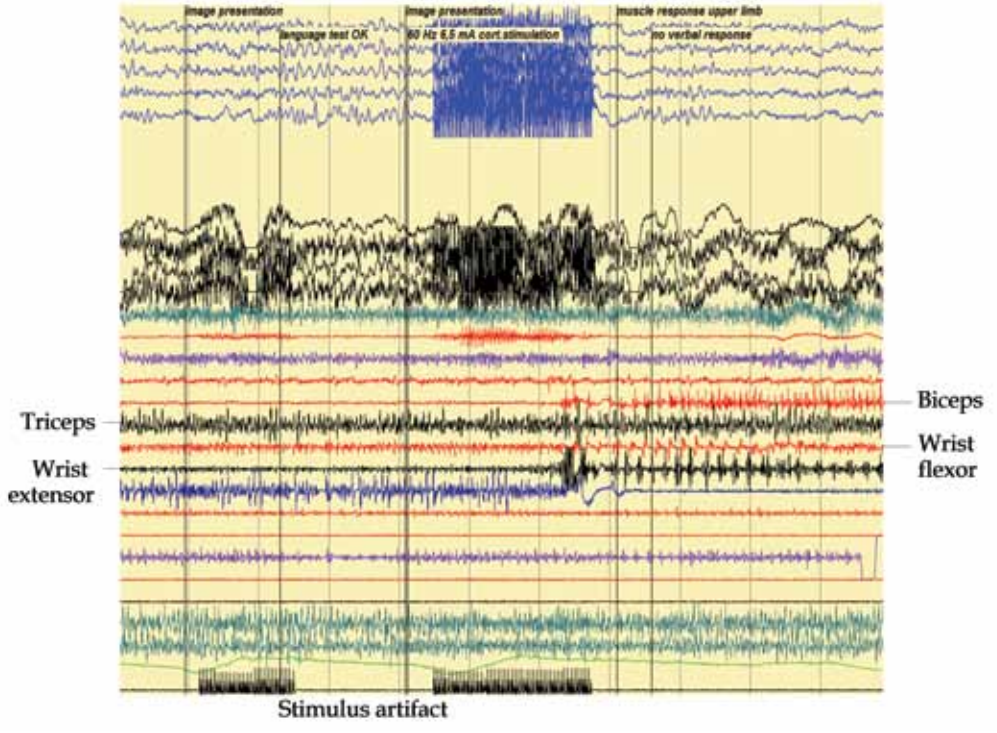

Fig. 4. Awake surgery ECoG (Traces 1–4), surface electroencephalography (Traces 6–9), and EMG traces (remaining traces) showing 60-Hz stimulations (6.5 mA) of the premotor cortex. During stimulation for language testing, a speech arrest was induced, followed by clonic jerks in the right upper limb muscles.

TABLE 1: Practical stimulation guide

stimulation	stimulate entire exposed cortical area every 5 mm^2 (according to probe spacing) stimulate every site at least 3 times never stimulate same cortical area twice successively always perform checking test w/o stimulation btwn 2 stimulations
mapping	start w/ motor mapping: movement is easy to observe for cognitive & language tasks, stimulation should be started before presentation of the item for subcortical mapping, imagine path of the white matter tract stimulated & raise the intensity by 2 mA, repeating the stimulation very regularly while mapping the path tract
documentation	mark positive areas w/ small paper tag document anatomical relations *special advice:* *1) do not stop mapping after identifying only 1 eloquent site, but search for possible redundancies; a negative mapping does not protect, but creates the problem of questionable stimulation reliability* *2) an area invaded by a tumor has an increased impedance, which could justify an increase in the intensity of stimulation parameters relative to neighboring healthy tissue, especially in cases in which gliomas infiltrate functional areas*
side effect: seizure	irrigate w/ cold Ringer solution or isotonic NaCl; do not restimulate immediately afterwards special advice: stimulation intensity should be decreased during control stimulations in areas of decompressed brain tissues to limit the risk of inducing a seizure; no-response sites at beginning of surgery should always be retested after decompression intraop ECoG can be useful in detecting afterdischarges

movement if the primary motor cortex is stimulated. Longer durations of stimulus (2–4 msec) are required to induce motor responses from secondary motor areas. Electromyography can be used to record motor phenomena, showing even low-amplitude muscle responses and the onset of clonic muscle activity (Fig. 4).[50] Mapping of motor function can be performed in both awake and anesthetized patients. In awake patients, both muscle activation and muscle inhibition should be investigated, following a protocol related to the site of surgery. The absence of movement might be explained by a stimulation-induced inhibition of movement. In such cases, the testing of negative motor phenomena is helpful for identifying associative motor areas;[30] that is, the patient is asked to perform a continuous movement—for example, alternating extension and flexion of the wrist—which is inhibited by the stimulation. Once a movement is observed, the whole of the exposed cortical area is systematically mapped every 5 mm^2 (according to the probe spacing). The placement of sterile tags with numbers or letters on stimulation-positive spots is helpful for visualizing the cortical areas involved in motor, cognitive, or language function.[14,37] A meticulous drawing of the anatomy or a photograph and notes describing the evoked phenomena document the testing as well as help with further surgical planning and intraoperative reference.

Mapping of Language and Cognitive Function

For the mapping of language and cognitive function, the patient's compliance is very important, as is the close cooperation among members of the participating medical team. For stimulation-induced interference with speech, language, and cognition, the duration of the stimulus must be longer than that for motor mapping. The duration of stimulation is commonly set to 3–4 seconds. To exclude occasional noncompliance or temporary impairment related to a nonconvulsive seizure, every stimulation should start after presentation of the material has started and the patient has said an introductory sentence.[24] As repetitive stimulation can trigger seizures (see *Side Effects*), one could use an alternating testing mode; that is, one in which the patient continuously performs tasks, and each task with stimulation is followed by a task with sham stimulation (Table 1).

During resection of the tumor, continuous assessment of function as well as the potential risk of injury is necessary to maximize the extent of resection and prevent iatrogenic injury. Continuous clinical assessment during the resection is alternated with cortical and subcortical mapping and specific testing of the function anatomically closest to the resection site. As subcortical pathways might be involved within the tumor and at risk during resection, intermittent subcortical stimulation and testing has been shown to be effective at successfully preventing iatrogenic injury.[5,13,15,16,26,29]

Motor Function

For continuous monitoring of motor function in addition to periodical cortical/subcortical mapping, intentional movement of the patient can be continuously assessed. However, because this process can be exhausting for the patient and fatigue can mimic paresis, the only way to truly continuously assess the functional integrity of the motor pathways is to perform MEP monitoring.

For this purpose, continuous direct cortical stimulation of the precentral gyrus can be performed with a modified train-of-five technique. This technique, introduced for surgery in anesthetized patients, has been described as sensitive in detecting dysfunction of the motor cortex and the corticospinal tract.[33–35,46–48] A strip electrode containing 4–8 electrodes must be placed over the precentral gyrus. In awake patients a single stimulus or a short train consisting of 2–4 pulses (individual pulse width 0.3–0.5 msec, anodal constant-current stimulation; interstimulus interval 4 msec, stimulation close to motor threshold) is usually sufficient to elicit muscle

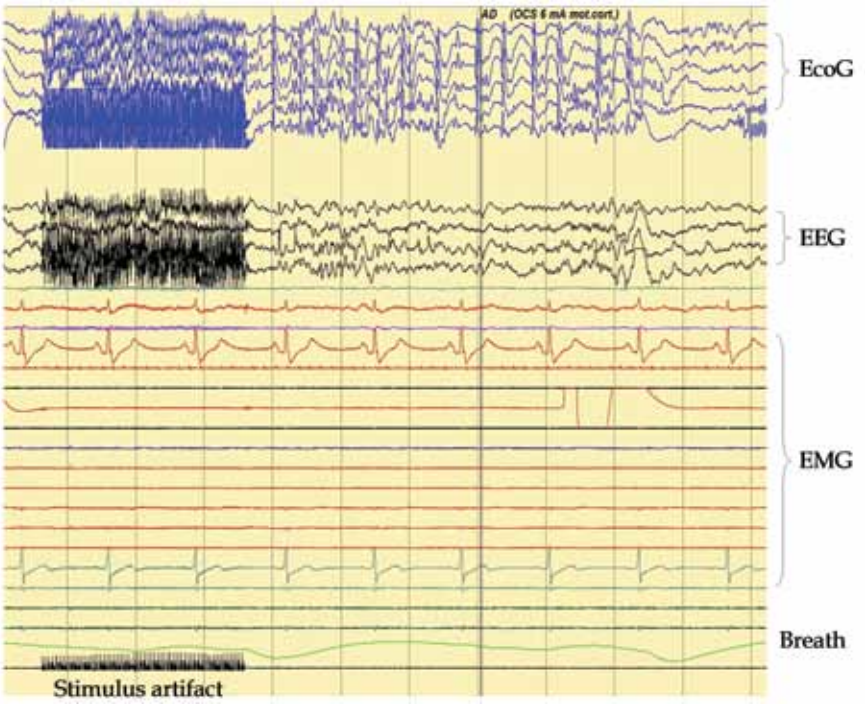

Fig. 5. Asleep surgery ECoG (Traces 1–6), surface electroencephalography (Traces 7–10), and EMG traces (remaining traces) obtained during 60-Hz stimulations (6 mA) of the primary motor cortex, showing nonconvulsive seizure activity.

MEPs. Motor evoked potentials must be recorded either with needle electrodes, preferably the same in use for continuous EMG assessment, or—if believed more convenient in awake patients—with surface EMG electrodes. The method's advantage lies in the independence of a patient's compliance and the ability to distinguish between lesions of the supplementary and those of the primary motor area.[51] Moreover, MEPs are useful for preventing vascular injury in insular and/or deep temporal regions, where critical arteries are at risk during tumor resection.[34] Test clamping can even be performed. The intraoperative use of direct cortical stimulation via a strip electrode to elicit MEPs can be performed repeatedly. As simultaneous cortical and subcortical stimulation can lead to false results, one must ensure that none of the methods is applied simultaneously.

Note that the same stimulation parameters (short-train technique with interstimulus interval of 4 msec) used for continuous MEP monitoring from a strip electrode can be used for cortical (anodal stimulation) and subcortical (cathodal stimulation) mapping from a hand-held monopolar probe. This option represents a valid alternative to the classic 60-Hz technique with the advantage of a lower risk of intraoperative seizures (see *Side Effects*). Nevertheless, the widespread use of the short-train technique during awake surgery is just starting and has recently been reported as a possibility for language testing in awake patients.[3]

Cognitive and Language Function

For cognitive and language tasks, either spontaneous speech or the continuous completion of standardized tasks can be performed. It is beyond the scope of this paper to provide a detailed description and philosophy of the tests being utilized at different centers.

Side Effects

Long-lasting side effects due to intraoperative brain stimulation have not been reported.[22] Seizures are the most common side effects and can be harmful to the patient, although there have been no reports of serious injury due to intraoperative seizures. Interestingly, seizures are easily terminated with the direct application of iced Ringer lactate onto the cortex.[44] Longer stimulus durations can induce seizures and are related to the occurrence of after-discharges at low stimulation intensities. Although preoperative epilepsy is expected to be related to an increased occurrence of intraoperative seizures, there are no data supporting this assumption.[45] Intraoperative seizures most frequently develop in patients with lesions involving the rolandic and prerolandic areas. Furthermore, they are more frequent with 50–60 Hz of stimulation than with the train-of-five technique.[45] The neurosurgeon should consider changing the stimulation modality in patients who are prone to have seizures during mapping.

The resection procedure and instruments, such as the bipolar coagulation probe or the CUSA, can mimic nonconvulsive seizure-related transient disturbance of a patient's performance. Reportedly, the use of the CUSA can interfere with motor and language mapping, inducing a transient masking of active sites.[9] Therefore, the simultaneous use of CUSA and bipolar coagulation and stimulation should be avoided.

Controversies in Mapping

Size of Craniotomy

A recent publication described a tailored craniotomy with sole exposure of the tumor region, language mapping of the exposed area, and guidance by positive and negative stimulation results,[42] with excellent effects. Note that this procedure has been established by a team with vast experience in cortical mapping and thus should only be relied on if the cortical stimulation technique is well established within the mapping team.

Electrocorticography Recording

The simultaneous recording of ECoG is used to determine spontaneous or stimulation-induced epileptic discharges, so-called afterdischarges that can occur after electrical stimulation of the cortical areas to detect nonconvulsive seizures (Fig. 5). As a rule, current used for cortical mapping should not exceed certain thresholds to avoid the possibility of misleading false-positive mapping results. Unfortunately, afterdischarge thresholds vary across the cortex.[49] For certain cortical sites, mapping may be successful only at currents above the afterdischarge thresholds.[39] Therefore, although ECoG is recommended by most to improve the reliability of mapping and to prevent intraoperative seizures, it also has some limitations that should be remembered during mapping. Still other authors have reported vast experience with successful mapping in a large group of patients without the use of ECoG.[17] To compromise between the efficacy of mapping and the afterdischarge thresholds, different stimulus durations and/or repetition rates may have to be used.

Focality of Stimulation

From studies of transcranial magnetic stimulation and direct cortical stimulation in tumor surgery, it is known that the excitation of cortical motor areas other than the primary motor cortex (M1) requires higher intensities.[27] Nevertheless, in intraoperative practice, the most practical and sufficient way is to determine the motor threshold and use this stimulation intensity for further mapping.[11,14]

Effectiveness of Monitoring and Mapping

A recent meta-analysis has underlined the growing evidence of the positive relation among the extent of tumor removal, the tumor progression–free interval, and the 5-year survival rate.[43] Despite the lack of Class 1 evidence, the effect of confounding factors, such as tumor histology and the intraoperative utilization of neurophysiological methods, has not been investigated in the studies included in the meta-analysis. Subcortical mapping has been proven useful in several studies;[4,12,13,17,19,26] thus, the deduction that it can help in maximizing the extent of tumor resection may be obvious.

Utilization of DT Imaging

As the extent of tumor removal seems to be important for a patient's overall survival, preoperative imaging for planning the resection becomes more and more important. Authors have analyzed relations between subcortical mapping and DT imaging.[5,29] A positive correlation has been found between a stimulation intensity of 8–12 mA and a < 6-mm distance between the stimulation site and visualized tracts. Nevertheless, the estimated distance between DT imaging and the location of stimulation is influenced by the inaccuracies of DT imaging, the invasiveness of the tumor, intraoperative brain shift affecting navigation accuracy, and the various stimulation parameters and probe types used. Up to now, only subcortical stimulation allows for the in situ real-time assessment of subcortical tracks.

Conclusions

The 50- or 60-Hz stimulation performed with a biphasic pulse and a bipolar stimulation probe is the most widely applied technique for mapping motor and cognitive function during awake surgery. The additional application of the MEP short-train technique broadens the stimulation strategies being used, especially in patients who are not fully compliant or those suffering preexisting partial neurological and developing partial deficits, which can impair intraoperative testing. The main advantage of this technique is the possibility of performing both mapping and continuous MEP monitoring while minimizing the risk of intraoperative seizures. The utilization of those short-train stimulation parameters for cognitive mapping is in its infancy. The relatively short duration of the stimulus has to be timely presented to interfere with the function being tested. Close clinical observation and guidance of the patient combined with recording of EMG activity allows for the best documentation of the mapping procedure.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Surgical management of World Health Organization Grade II gliomas in eloquent areas: the necessity of preserving a margin around functional structures

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Object. Recent surgical studies have demonstrated that the extent of resection is significantly correlated with median survival in WHO Grade II gliomas. Consequently, thanks to advances in intraoperative functional mapping, the authors questioned whether it is actually necessary to leave a "security" margin around eloquent structures.

Methods. The authors first reviewed the classic literature, especially that based on epilepsy surgery and functional neuroimaging techniques, which led them to propose the rule of a security margin. Second, they detailed new developments in the field of intrasurgical electrical mapping, especially with regard to subcortical stimulation of the projection and long-distance association pathways. On the basis of these advances, the removal of gliomas according to functional boundaries has recently been suggested, with no margin around eloquent structures.

Results. Comparative results showed that the rate of permanent deficit was similar with or without a security margin, that is, < 2%. However, a higher rate of transient neurological worsening in the immediate postsurgical period was associated with the absence of a margin, with recovery following adapted rehabilitation. On the other hand, the extent of resection was in essence improved with no margin.

Conclusions. This no-margin technique, based on the subpial dissection, and the repetition of both cortical and subcortical stimulation to preserve eloquent cortex as well as the white matter tracts (U-fibers, projection pathways, and long-distance connectivity) allow optimization of the extent of resection while preserving the quality of life (despite transitory impairment) thanks to mechanisms of brain plasticity. *(DOI: 10.3171/2009.12.FOCUS09236)*

Key Words • **awake surgery** • **direct electrical stimulation** • **intraoperative functional mapping** • **low-grade glioma** • **eloquent area**

During the past decade, the surgical management of WHO GIIGs has dramatically changed. The modification in strategies focused mainly on 2 points: 1) oncological considerations, with an optimization of the EOR to increase overall patient survival; and 2) functional considerations, with a minimization of postoperative morbidity and preservation of the quality of life.

Indeed, on the basis of objective control MR imaging of the glioma removal, recent surgical studies have demonstrated that the EOR was significantly correlated with overall survival.[4,10,20,47,66,70] As a consequence, surgery is the first therapeutic option in GIIGs.[13]

This more aggressive surgical attitude should nonetheless avoid permanent functional worsening. Usually, GIIGs are diagnosed after a seizure in young patients with no or only mild neurological deficits,[23,58,59] despite the frequent involvement of so-called eloquent areas and progressive diffusion along functional subcortical pathways.[24] Such functional compensation is attributable to brain plasticity mechanisms made possible by the slow growth of GIIGs, with the recruitment of perilesional and/or remote (ipsi- or contralateral) areas.[11] Therefore, the identification and preservation of these compensatory areas throughout the resection is crucial.

For these reasons, intraoperative electrostimulation mapping is increasingly used by neurosurgeons to optimize the benefit/risk ratio of surgery.[1–6,8,14,17,20,25,69] This technique has progressively evolved since the pioneers[55–58] who first applied it in epilepsy surgery. Over decades, several authors have contributed to its development, especially Ojemann and colleagues[49–53] and Berger and associates,[4,5] who began to use direct corticosubcortical stimulations in oncology in the early 1990s. At that

Abbreviations used in this paper: DT = diffusion tensor; EOR = extent of resection; fMR = functional MR; GIIG = Grade II glioma; MEG = magnetoencephalography.

time, they proposed that a "security" margin should be maintained around positive stimulation sites, especially language sites, to minimize the risk of a permanent deficit.[33] Moreover, advances in preoperative functional neuroimaging techniques and the incorporation of these data into a neuronavigational system (so-called functional neuronavigation) have widely contributed to the concept of this security margin around "activated areas."[35,42,69,73]

Interestingly, although white matter pathways have received less interest for a long time, subcortical connectivity has recently been studied by a growing number of investigative teams. This attitude is in part attributable to the newly developed method of tractography with DT imaging, which allows noninvasive visualization of the main bundles in vivo.[9] A revival of the fiber dissection technique on cadavers has also occurred to foster a better understanding of the anatomy of the white matter pathways and to validate DT imaging.[28,45,61] In this context, some authors have proposed the regular use of intraoperative electrostimulation during glioma surgery to map not only the cortex but also the subcortical tracts.[1,2,6,8,14,17,23] The goal was to study the function of the different (somatosensory, motor, visuospatial, and language) pathways to continue the resection until these bundles are encountered.[23] Indeed, it has been shown that the preservation of subcortical connectivity is crucial to allow for the efficiency of brain plasticity mechanisms: in cases of white matter injury, the risk of inducing a permanent deficit with no functional recovery is very high.[12] Thus, online detection of these tracts by using subcortical electrostimulation mapping at the end of glioma removal is essential to preserve normal brain processing. On the other hand, to improve the EOR, tumor removal should not be interrupted before contact with these pathways.[14]

On the basis of these new oncological and functional insights into GIIG surgery, the aim of our review was to raise the question of whether it is actually necessary to leave a security margin around eloquent structures.

The Principle of a Security Margin

It is now widely accepted that one cannot localize functional areas, especially language sites, by solely relying on anatomical landmarks. Since the seminal works of Ojemann et al.[49] using cortical electrostimulation, it has been shown that language networks are underlain by a mosaic of distributed epicenters with great intersubject variability. Therefore, a maximal resection with minimal risks requires individual extra- or intraoperative brain mapping, a technique initially developed mainly for epilepsy surgery.[49,51] Extraoperatively, cortical stimulations were performed using subdural grids, generally with contacts spaced 10 mm apart. As a consequence, a margin of ~ 1 cm was typically preserved around functional sites. Intraoperatively, Ojemann and colleagues described putting sterile tags on the brain surface, spaced ~ 1 cm apart, before performing electrical mapping, which consisted of testing each site marked by a tag. When they applied this method to tumor surgery, these same authors recommended preserving an equivalent margin of ~ 7 to 10 mm around the positive stimulations sites.[33,65,67] Since this study, the principle of a security margin has been integrated by many teams into the surgical technique of brain mapping for tumor surgery.[8,65,67,68]

The progressive development of noninvasive functional neuroimaging techniques of cortical mapping, such as fMR imaging and MEG, also had an important role in reinforcing the principle of a security margin.[32,37,60] Indeed, it was demonstrated that functional neuroimaging—as opposed to direct corticosubcortical stimulations—was not accurate enough, with modifications in the spatial location of activations when repeated acquisitions were performed in the same patients over time.[34] Moreover, many teams have compared fMR imaging with intraoperative electrophysiology[27,29,40,63] and have shown that the reliability of functional neuroimaging was only between 60 and 90%,[63] especially for language functions using both naming and verbal tasks, and thus alone is insufficient to rely on for brain surgery. In addition, these data can be integrated into a neuronavigational system[35,48,64,73] but with the risk of brain shift throughout the resection. Taking into account these numerous limitations, all authors have agreed to keep a security margin of at least 5–10 mm around the activation sites provided by presurgical functional neuroimaging to safely achieve lesion removal. Furthermore, it has been proposed that a significant predictor of new neurological deficits is a lesion-to-activation site distance of < 5 mm.[38]

Finally, fMR imaging and MEG do not provide any information about the white matter pathways, although it is currently understood that subcortical damage is associated with a high risk of severe and permanent neurological deficits.[15] To overcome this drawback, the new technique of fiber tracking with DT imaging has been widely integrated into presurgical planning in the past few years. Indeed, DT imaging noninvasively provides anatomical information about the white bundles and their relationships to the tumor.[9] Nonetheless, recent studies have shown that this method is not yet reliable enough, with different results of tracking provided according to the biomathematical model and software used.[7] Therefore, as reported at the cortical level with regard to fMR imaging and MEG, the correlations between DT imaging and intraoperative electrophysiology at the subcortical level have shown that the fiber tracking technique should be improved before it can be considered as a standard in defining the boundaries of a tumor resection.[39] As a consequence, several authors have again suggested keeping a margin around the pathways identified using DT imaging and incorporated into a neuronavigational system.[35]

In summary, on the basis of converging evidence provided by both (extra- and intraoperative) electrophysiological and neuroimaging techniques, the principle of a security margin became actual dogma. In this paper, we question whether this rule applies in tumor surgery, especially surgeries concerning infiltrating WHO GIIGs.

Resection With No Margin According to Intrasurgical Cortical and Subcortical Functional Boundaries

With the aim of improving the EOR, for many years

TABLE 1: Clinical, radiological, and surgical characteristics in 162 patients who underwent surgery for a WHO GIIG in the left dominant hemisphere*

Glioma Location (no. of patients)	Preop Examination (no. of patients)	Preop KPS Score (no. of patients)	Rate of Immediate Postsurgical Deficit	Delayed Postop Examination >3 Mos (no. of patients)	Postop KPS Score (no. of patients)	Extent of Resection
frontal (85)	normal (78)	100 (48)	96	normal (83)	100 (39)	32 T
F1 (41)	language deficits (7)	90 (30)		language deficit (2)†	90 (44)	41 ST
F2 (23)		80 (7)			80 (2)	12 P
F3 (21)						
temporal (25)	normal (22)	100 (12)	89	normal (24)	100 (11)	10 T
	language deficits (3)	90 (10)		language deficit (1)†	90 (13)	13 ST
		80 (3)			80 (1)	2 P
paralimbic (27)	normal (23)	100 (13)	60	normal (24)	100 (14)	6 T
	language deficits (4)	90 (10)		language deficit (3)	90 (8)	12 ST
		80 (4)		new deficits (2)‡	80 (3)	9 P
					70 (2)	
POTJ (10)	normal (9)	100 (5)	90	normal (10)	100 (4)	4 T
	language deficit (1)	90 (4)			90 (6)	5 ST
		80 (1)				1 P
parietal (15)	normal (12)	100 (9)	95	normal (15)	100 (9)	6 T
P1 (8)	language deficit (1)	90 (5)			90 (6)	6 ST
P2 (7)	hypesthesia (2)	80 (1)				3 P

* F1 = superior frontal gyrus; F2 = middle frontal gyrus; F3 = inferior frontal gyrus; KPS = Karnofsky Performance Scale; P = partial; POTJ = parietooccipitotemporal junction; ST = subtotal; T = total.

† From the patients with preoperative deficits.

‡ New deficits occurred in 2 of the 3 patients with language deficits.

we have proposed the resection of GIIGs in functional areas[14] without leaving any margin around the positive stimulation sites intraoperatively identified using both cortical and subcortical electrical mapping. Summarized in Table 1 are the clinical and radiological characteristics of 162 patients who underwent surgery and corticosubcortical stimulations for WHO GIIGs in the dominant hemisphere without any margin. This surgical strategy is based on several principles.

Cortical Subpial Dissection

In all cases, independent of preoperative data provided by functional neuroimaging methods—used mainly as a baseline to study the mechanisms of plasticity on an individual scale rather than as a technique for delineating resection boundaries[19,62]—we performed intraoperative cortical electrostimulation mapping before any tumor removal. This method, including the electrical parameters and intraoperative clinical tasks, has been described in detail elsewhere.[42] Briefly, a bipolar electrode with tips spaced 5 mm apart and delivering a biphasic current (pulse frequency 60 Hz, single pulse phase duration 1 msec, and amplitude 2–8 mA under local anesthesia and 2–16 mA under general anesthesia exclusively for motor mapping near the pyramidal structures in the nondominant hemisphere) was applied to the brain. When this surface mapping revealed crucial site(s) immediately near a sulcus, the other side of the sulcus was used to perform a subpial dissection in direct contact with the eloquent area(s). It means that no margin was left, except the sole protection represented by the 2 layers of pia and the vessels preserved within the depth of the sulcus—so minimizing the risk of ischemia within the eloquent structures even if they constituted the edge of the surgical cavity, because they were covered by the pia mater. It is worth noting, however, that the cortex buried within the nonfunctional side of the sulcus as well as the U-fibers coming from this cortex should be mapped online throughout the resection before removing it. Interestingly, such mapping cannot be performed if only extraoperative mapping using cortical grids has been decided on or if the resection is based on fMR imaging studies alone, which is unable to differentiate activated areas on the surface cortex from those buried within the sulcus by using the blood oxygen level–dependent (BOLD) effect. Therefore, this technique of subpial dissection with online cortical and subcortical (U-fibers) mapping provides more accurate functional data than the methods typically described in the literature (Figs. 1 and 2).

Intragyral Resection With Mapping of the Subcortical Projection Fibers

After cortical surface mapping, when there is no sulcal limit between the positive stimulation site(s) and the tumor, the resection is pursued within the gyrus in contact with the crucial zone(s). Such resection with no security margin is made possible thanks to 2 intraoperative techniques. First, at the cortical level, we used a probe and not grids, meaning that we can perform multiple stimulations by slightly moving the probe from 1 to 2 mm and/

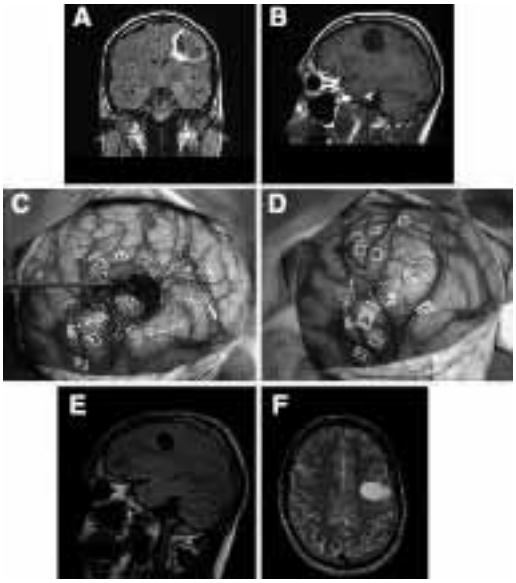

Fig. 1. Preoperative coronal FLAIR **(A)** and sagittal T1-weighted **(B)** MR images showing a left precentral glioma involving the middle frontal gyrus. Intraoperative photographs **(C and D)** of cortical mapping: tags A, B, and C are tumor boundaries, as shown by intraoperative ultrasonography. Numbers 1, 2, and 3 indicate the primary motor area of the hand; 4, speech arrest with facial movements; and 5 and 6, speech arrest in the ventral premotor cortex. Subcortical mapping **(D)** showing the resection cavity with no margin between function and tumor, thanks to a subpial dissection along the precentral sulcus (spatula). The subcortical functional boundaries were the pyramidal fibers tract of the hand at the bottom of the sulcus (Number 37) and fibers coming from ventral premotor cortex inducing anarthria (Number 36)—both constituting the so-called projection fibers vertical connectivity—as well as phonemic paraphasia elicited by stimulation over the arcuate fasciculus, that is, long-distance association pathways or deep connectivity, or horizontal connectivity (Number 34). Postoperative coronal T2-weighted MR image **(E)** demonstrating the surgical cavity, which is directly in contact with the precentral sulcus where the subpial dissection was performed, with no residual tumor at this level and no margin. Sagittal FLAIR MR image **(F)** showing the inferior limit of the surgical cavity directly in contact with the arcuate fasciculus, which lies just above the insula.

or by changing its orientation (parallel or perpendicular to the main axis of the gyrus). As a consequence, even if the space between the electrodes is fixed (5 mm), it is nevertheless possible to increase the spatial resolution of the functional mapping ~ 1 mm—that is, the size of each electrode. Interestingly, we did not put a priori sterile tags on the cortex every 5–10 mm, as described by Ojemann et al.,[49] but we did mark a cortical zone if reproducible transient disturbances were elicited by repeated stimulations. Thus, once again, this method allowed better accuracy by identifying the exact spatial delineations of each eloquent area and not its epicenter exclusively. In addition, throughout the resection, we continued to perform repeated stimulations, not only at the cortical level but also at the subcortical level. Indeed, we have shown that real-time converging information between functional mapping of the cortex and its subcortical projection fibers enables us to perform glioma removal until the functional boundaries have been encountered, with no margin.[23] Thanks to

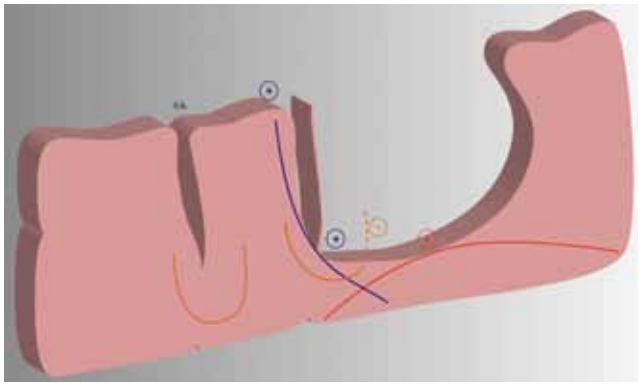

Fig. 2. Schematic showing removal of a precentral tumor without leaving any margin and using subcortical functional boundaries. Using a subpial dissection along a functional sulcus (for example, the precentral sulcus), fibers coming from the cortex are found at the bottom of it (the projection fibers, that is, vertical connectivity, *blue line* and *plus sign*), where the resection is stopped. In addition, U-fibers are mapped throughout the resection (*orange lines* and *minus sign*). The horizontal connectivity, namely the long-distance association fibers, are the other subcortical functional boundaries in the depth, for example, arcuate fasciculus (*red line* and *plus sign*) at the bottom of the cavity.

online feedback provided by awake patients performing adapted tasks controlled by a speech therapist during the entire resection, language as well as somatosensory and visuospatial functions can be tested (Figs. 3 and 4).[14]

Subcortical Stimulation: Mapping of the Deep Connectivity and Long-Distance Association Pathways

We also applied the same principle of online electrical mapping with regard to the deep connectivity—that is, functional identification, throughout the glioma removal, of the long-distance white matter association pathways (so-called horizontal connectivity)[15] as well as the gray nuclei.[31] For instance, we showed that real-time anatomofunctional correlations allow for the reliable detection and preservation of the superior longitudinal fasciculus in the dominant hemisphere, eliciting reproducible phonemic paraphasia when stimulated;[24] the lateral part of the left superior longitudinal fasciculus, inducing speech apraxia during stimulation;[22] the left occipitofrontal fasciculus, generating semantic paraphasia when stimuated;[21] the posterior part of the left inferior longitudinal fasciculus, eliciting visual paraphasia during stimulation;[41] the right superior longitudinal fasciculus, generating hemineglect during stimulation;[72] or even the left deep gray nuclei, eliciting preservation (caudate) and anarthria (putamen) when stimulated.[31] Interestingly, such an extensive resection until subcortical functional limits have been encountered also means that there is no rationale for maintaining a cortical security margin. Indeed, if a tumor removal is subcortically pursued in direct contact with the eloquent pathways, even if a cortical margin is preserved around the functional cortex, the projection fibers arising from this cortical security margin will in essence be cut underneath, because they will not respond to stimulation. Thus, all the infiltrated cortical tissue preserved as a security margin will be completely disconnected and without any possibility of

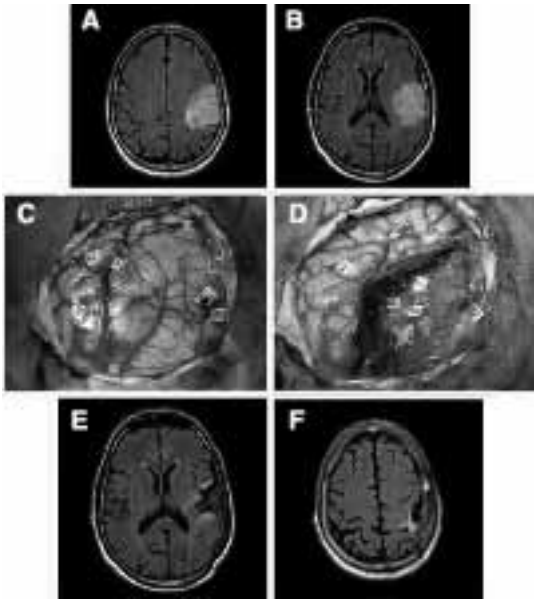

Fig. 3. Preoperative axial FLAIR MR images **(A and B)** showing a low-grade glioma involving the left inferior parietal lobule as well as the retrocentral gyrus. Intraoperative photograph **(C)** of cortical mapping: letters show the tumor limits as indicated by ultrasonography. Moreover, electrostimulation identified the primary motor cortex of the face inducing facial movements (Number 46) as well as the region eliciting speech arrest (ventral premotor cortex, Number 8). Anomia was also generated by stimulation over the posterior third of the superior temporal gyrus (Wernicke Area, Number 47). Intraoperative photograph **(D)** of the surgical cavity, with no margin around the eloquent regions, showing the subpial dissection all along the central sulcus and the sylvian fissure (anteroinferior margin). Thus, we removed the retrocentral gyrus that did not respond to stimulation. In addition, the subcortical functional boundaries, pyramidal fibers of the face (projection fibers, Number 48), arcuate fasciculus generating phonemic paraphasias (Number 49), and the frontoparietal articulatory loop generating dysarthria (Number 50)—both constituting the long-distance association pathways or deep connectivity—represented the subcortical functional boundaries of the resection. Postoperative axial FLAIR MR images **(E and F)** showing removal of the retrocentral gyrus and inferior parietal lobule. The surgical cavity came in contact with the central sulcus without any margin (subpial dissection) as well as with the arcuate fascicle.

participating in cerebral processing. Therefore, its preservation is not justified, because it would be functionally useless (Figs. 3 and 4).

Results With and Without Preservation of a Security Margin

A comparison of results between studies utilizing the margin rule and those not is difficult because of their heterogeneity. Nonetheless, some differences can be pointed out (Table 1).

Oncological Considerations

We have reported that GIIGs can be considered as ellipsoids, and thus that it is possible to calculate the approximate volume of the tumor by applying the formula $4/3\pi^3$, that is, the product of the 3 main diameters divided by 2.[43,44] We also showed that in our extensive and homogeneous series of GIIGs, the mean lesion volume after diagnosis and before surgery was around 60 ml.[14,20] Interestingly, by using the formula described above, the mean diameter for a volume of 60 ml is ~ 4.9 cm. If a security margin of 1 cm is preserved during surgery, the estimated residual volume would be $60–3.9^3/2 = 30$ ml. In other words, in the classic literature, it was usual to speak in terms of distance rather than volume, and thus, there was an underestimation of the postoperative residual tumor. Indeed, leaving a 10-mm margin for a tumor measuring 60 ml means that only half of the lesion would actually be removed. As a consequence and on the basis of a recent oncological series demonstrating a significant correlation between the EOR of the GIIG and overall survival (see above), our proposal to perform resection with no security margin allows clear improvement in the EOR and thus its impact on the natural history of a GIIG.

Functional Results

Postoperative Permanent Deficit. When comparing the rate of permanent neurological deficits between studies in which patients underwent surgery with cortical and subcortical functional boundaries but without a margin, and those in which a margin was preserved, no differences were observed: 1.7% without a margin[14] and 1–2.5% with a margin.[33,67] These similar results confirm that surgery performed without a security margin is a safe technique that does not increase the rate of long-term morbidity. The data also support the fact that surgery for GIIGs in eloquent areas performed under direct electrostimulation to preserve function, with or without a margin, represents a reliable tool for minimizing the risks of permanent deficits.

Postoperative Transient Deficit. We must acknowledge that the rates of transient deficits in the immediate postoperative period are very different. Data from recent surgical series of GIIGs in eloquent areas with no preservation of a security margin showed transitory worsening following resection in almost all patients.[14] Nonetheless, it is worth noting that at 3 months postsurgery, after an intensive speech and motor reeducation program, all patients recovered except 1.7%, who still experienced a functional deficit. In contrast, in a surgical series of GIIGs in which a 10-mm margin was preserved, only 22[67] to 60%[33] of patients had an immediate postoperative language deficit. These same results have been reported for motor function.[36] For instance, Carrabba et al.[8] recently used cortical and subcortical mapping for tumors of the rolandic region in 146 patients. These authors indicated that when motor tracts were identified subcortically, new postoperative deficits were evident in 59.3% of patients, while they were observed in only 14.5% when motor pathways were not detected intraoperatively. Interestingly, these deficits were permanent in only 6.5% of the patients, leading the authors to conclude that they were due to transient edema and not an actual brain injury. Indeed, the higher rate of impairment with the no-margin technique is a clear consequence of the technique itself—meaning that the price one pays for a more extensive resection is an immediate postsurgical worsening lasting several weeks in almost all patients. Of course, this point should be extensively

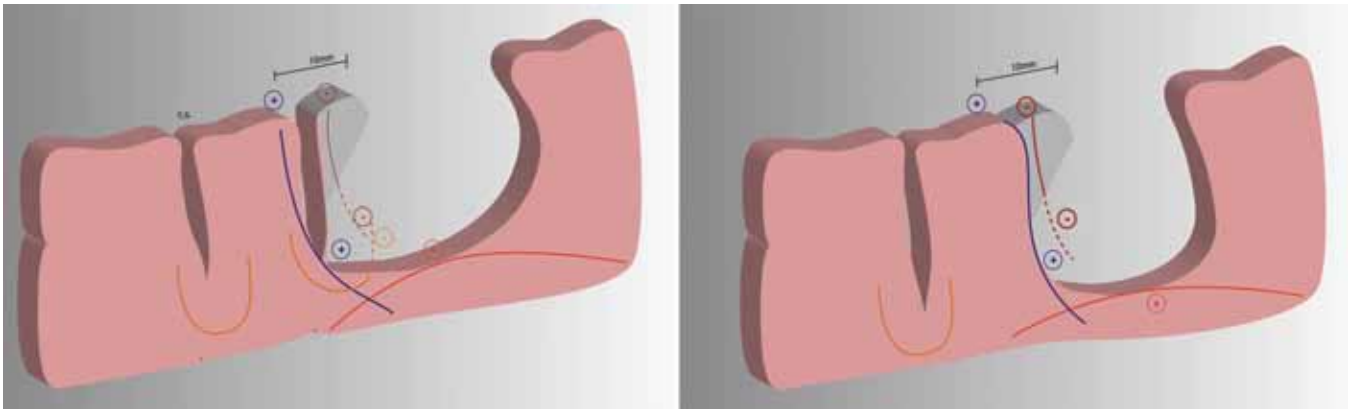

Fig. 4. Schematic showing 2 examples of a resection with a margin. First, a tumor coming into contact with a sulcus **(left)** removed by leaving a 10-mm security margin from the positive cortical stimulation site (that is, with no subpial dissection; *blue line* and *plus sign*). If subcortical stimulation is performed, the projection fibers' vertical connectivity will be identified at the bottom of the sulcus (for example, pyramidal tracts; *blue line* and *plus sign*). The U-fibers coming from the other side of the sulcus will also be tested throughout the resection (*orange lines* and *minus sign*). At the bottom of the cavity, the horizontal connectivity or long-distance association fibers (for example, the arcuate fasciculus) will represent the deep functional subcortical boundary (*red line* and *plus sign*). Interestingly, the cortex invaded by the tumor *(gray)* is functionally useless, since the resection has been pursued until the subcortical pathways have been encountered (*blue* and *red lines* and *plus signs*). Thus, the fibers arising from this cortex have been disrupted, as they do not respond to stimulation (*brown line* and *minus sign*). As a consequence, this cortex was disconnected and can therefore be removed with no functional risk. Schematic **(right)** showing the same example in the case of an intragyral dissection, without a sulcus.

discussed with the patient and his or her family before any surgery. Moreover, we suggest that an intensive functional reeducation program represents a valuable adjunct for allowing complete recovery, by guiding cerebral plasticity.[19,71]

Brain Plasticity: an Explanation of Recovery After Resection Without a Margin

To explain this transient worsening followed by functional recovery, we have proposed the principle of a dynamic (not fixed) anatomofunctional organization of the CNS, in large-scale parallel corticosubcortical distributed networks (not in discrete areas)—that is, the concept of a hodological and plastic brain.[15,16] This type of organization offers the brain the possibility of recruiting perilesional and/or remote (ipsi- and/or contralesional) regions enabling functional compensation, at least when no essential structures detected by intraoperative stimulation are damaged.[17] This plasticity can occur "online" during surgery[26] or can take longer, as regularly observed during reoperations in patients with a recurrent GIIG after an incomplete tumor resection for functional reasons: a reshaping was frequently found when comparing 2 mappings spaced by several years.[46] The slow-growing slope of GIIGs (4 mm/year, on average),[44] in contrast to acute brain lesions such as stroke or high-grade glioma, can induce this kind of progressive cerebral redistribution in which there is no time for the functional network to compensate for the deficit.[11] Moreover, this long-term remapping can be studied pre- and postoperatively through repeated noninvasive fMR imaging performed over time during the patient follow-up. Such a strategy opens the door to a multistage surgical approach, optimizing the benefit/risk ratio of the radical resection of GIIGs within eloquent areas.[31] We must nevertheless insist that when dealing with higher-grade gliomas invading functional areas, one should be more cautious in preserving the quality of life, because the plastic potential of the brain is lower given the rapid growth of the tumor.[11] Furthermore, because of the shorter median survival, it seems more questionable to generate even a transient deficit lasting several weeks, and thus, it is more questionable not to leave a security margin—in contrast to GIIG.

Interestingly, beyond GIIG, a dynamic view of cerebral organization has also been reported by other authors in epilepsy surgery.[54] When asking awake patients to perform verb-generation tasks involving novel versus practiced lists during direct brain stimulation, such authors have noted that cortical areas that responded to stimulation in both cases were not concordant. They hypothesized that the cortical regions devoted to a particular task had decreased involvement as the task was learned. The authors concluded that the learning process may explain this modification of the language network. Thus, intensive language rehabilitation after surgery could be underlain by quite similar pathophysiological mechanisms of brain reshaping as compared with those subserving the learning process.[18] In addition, Ojemann and colleagues[54] also stated that when comparing the results of language mapping during object-naming versus verb-generation tasks, both functions showed a spatial dissociation in their respective cortical representations, but usually in the range of 10 mm. These findings may constitute another explanation for the higher rate of transient language impairment when no margin is maintained, depending on the functional tasks performed before, during, and after surgery as well the kind of rehabilitation, which should be adapted to each patient.[30,71]

Conclusions

Surgical removal of GIIGs in eloquent areas can be safely accomplished with no security margin around the functional structures and without increasing the rate of permanent deficits thanks to the use of intraoperative mapping in awake patients. This no-margin technique—based on the subpial dissection and the repetition of both cortical and subcortical stimulations to preserve eloquent cortex as well as the white matter tracts (U-fibers, projection fibers, and long-distance connectivity)—allows optimization of the EOR, and thus an increased impact on the natural history of the tumor, while preserving and even improving the quality of life.

Nevertheless, this method implies a higher rate of immediate postoperative worsening, even if patients completely recover within the 3 months following surgery thanks to an intensive and adapted functional (especially speech) rehabilitation program. It is also worth noting that if cerebral plasticity is induced by the slow-growing curve of GIIGs and thus explains the postsurgical functional recovery after a resection with no margin, caution must be recommended because the brain's plastic potential is reduced—and the chances of (rapidly) recovering after a radical resection with no security margin in eloquent regions is clearly decreased.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: S Gil-Robles, H Duffau. Acquisition of data: S Gil-Robles, H Duffau. Analysis and interpretation of data: S Gil-Robles, H Duffau. Drafting the article: S Gil-Robles, H Duffau. Critically revising the article: S Gil-Robles, H Duffau. Reviewed final version of manuscript and approved it for submission: S Gil-Robles, H Duffau. Study supervision: H Duffau.

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Musical hallucinations following insular glioma resection

Case report

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Hallucinations can be auditory, visual, tactile, gustatory, or olfactory, and can be caused by psychiatric (such as schizophrenia and depression), neurological (such as cerebrovascular accidents, neoplasia, and infection), or endocrine and metabolic disorders. Musical hallucinations related to neurological disorders are rare. The authors present a case of a patient with a right insular glioma who developed transient musical hallucinations after microsurgical resection of the tumor. *(DOI: 10.3171/2009.12.FOCUSFOCUS09243)*

Key Words • insula • musical hallucination • glioma

Hallucinations are perception disorders characterized by the sensation of an external stimulus without the presence of such a stimulus. The term hallucination was introduced in the psychiatric literature in 1837 by Esquirol.[23] Hallucinations can be auditory, visual, tactile, gustatory, or olfactory, and can be caused by psychiatric (such as schizophrenia and depression), neurological (such as cerebrovascular accidents, neoplasia, and infection), or endocrine and metabolic disturbances.[1–4,6,11–15,17–20]

Music and neuroscience have been related for a long time. In 1977, Critchley and Henson published the book *Music and the Brain*. Despite countless advances in this field during the last 30 years, *Music and the Brain* remains one of the main books on this topic.[23] Auditory hallucinations in which music is perceived are rare and occur mainly in cases of deafness or psychiatric disorders.[1] A small number of cases are related to neurological disorders, generally due to alterations of the primary auditory area.[3,4,17,18]

Insular gliomas are usually slow-growing tumors of low-grade malignancy.[25–27] They may grow large before a diagnosis is made.[25–27] The main symptoms of these tumors are complex partial seizures with or without secondary generalization.[25–27] Due to the deep localization and the close relationship with the MCA, tumor resection in insular topography is considered a highly complex surgical procedure.

Abbreviations used in this paper: MCA = middle cerebral artery.

In this paper we report the case of a patient who underwent microsurgical resection of a large right insular tumor and who developed musical hallucinations of limited duration during the early postoperative period. As far as we know, this is the first report of a patient with musical hallucinations after insular tumor resection.

Case Report

History and Presentation. This right-handed 34-year-old man was first seen at our institution due to new onset of episodic intense headaches and 1 episode of complex partial seizures. The neurological examination was unremarkable. A CT scan and 1.5-T MR imaging with Gd (T1-weighted, T2-weighted, FLAIR, perfusion, and tractography) disclosed a nonenhanced intraaxial tumor in the right insula, extending to the superior temporal gyrus and enveloping the planum polare and planum temporale (Fig. 1).

Operation and Postoperative Course. The patient underwent resection of the tumor (> 90%) using microsurgical techniques, and underwent monitoring for somatosensory evoked potentials and transcranial electric motor evoked potentials. Pathological examination of the tumor specimen revealed a WHO Grade II glioma (Fig. 2). The surgical approach was conducted via a right frontotemporal craniotomy, using an interfacial dissection of the temporal fascia and microdissection of the sylvian fissure (transsylvian approach).[16] The tumor was aspirated

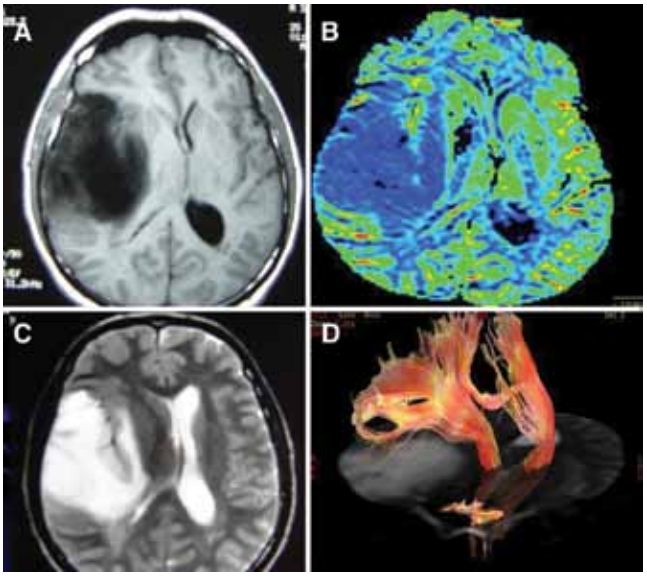

Fig. 1. Preoperative MR images of the patient. **A:** Contrast-enhanced T1-weighted image showing a nonenhanced lesion in the right insula causing midline deviation. **B:** Perfusion-weighted image showing the lesion. **C:** Contrast-enhanced T2-weighted image showing the absence of an important vasogenic edema. **D:** Diffusion imaging tractography showing the relation of the corticospinal tract to the tumor.

between the M_2 and M_3 segments of the MCA. The tumor portion extending to the planum polare and planum temporale was resected through the inferior circular sulcus of the insula, and a transopercular approach was used at the superior temporal gyrus, which was necessary to resect tumor in the lateral part of the Heschl gyrus. Deep resection of the tumor close to the internal capsule was stopped when there was an alteration in the intraoperative motor evoked potential.

The patient did not develop any neurological deficit as a result of the surgery. Diphenylhydantoin was initiated in the immediate preoperative period as prophylaxis for seizures. After 1 month, and while still receiving 100 mg of diphenylhydantoin three times a day, the patient began to have musical hallucinations. These hallucinations were characterized by a song that was very familiar to the patient although he was not able to identify it. The hallucinations occurred several times during the day, lasted several seconds, and were not associated with alterations of consciousness. This phenomenon occurred daily for approximately 2 months, and then disappeared. An electroencephalogram obtained at this time revealed discharges in the right centroparietal region and in the temporal regions of the right hemisphere. The patient has been asymptomatic for 1 year after surgery.

Discussion

Musical hallucinations can be observed to occur in association with otologic, psychiatric, and neurological causes, or their combination. Sporadic cases have been reported in patients with psychiatric, otorhinolaryngologic, or neurological problems.[1–4,6,11–15,17–20] It has been assumed that the upper portion of the temporal lobe is

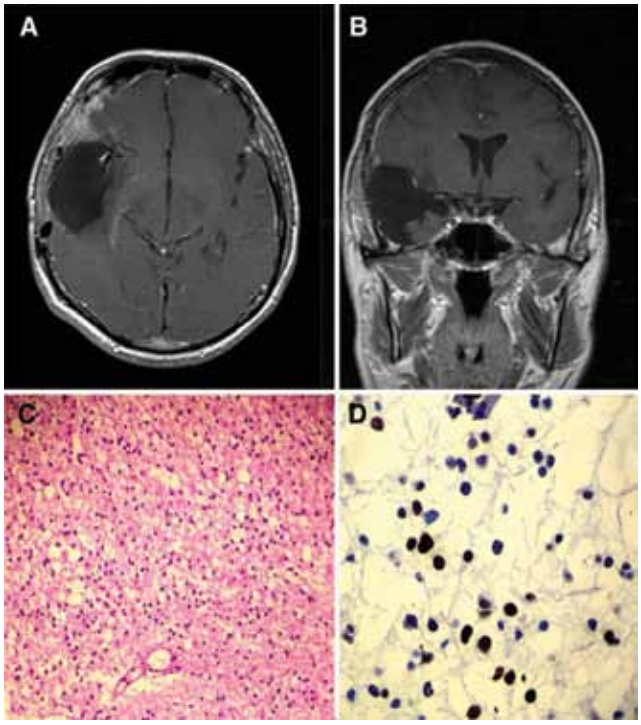

Fig. 2. Postoperative contrast-enhanced MR images **(A and B)** and photomicrographs **(C and D)**. **A:** Axial T1-weighted image obtained 3 months after surgery showing tumor resection (> 90%) with a small remaining tumor in the posterosuperior region of the tumor cavity. **B:** Coronal T1-weighted image showing the tumor resection. **C:** Tumor specimen showing features of a WHO Grade II astrocytic neoplasm. H & E. Original magnification × 100. **D:** Immunohistochemical specimen showing < 2% staining for Ki 67 (MIB-1). Original magnification × 400.

the etiopathogenic substrate of this phenomenon. The functional imaging studies using the paradigm "listen to music" result in a bilateral activation of the brain.[21,23] On the other hand, studies of patients with acquired amusia suggest that the structures involved in this activity are the superior temporal cortex, the insula, and the frontal lobe of the nondominant cerebral hemisphere.[23] Although less common, lesions in the dominant cerebral hemisphere can also cause deficits in musical perception. For the latter aspect, however, we should consider the bias that patients with lesions in the left hemisphere generally present with aphasia, which makes it more difficult to perform nonlinguistic ability tests.[23]

Musical hallucinations can involve 3 large groups of alterations: otologic, psychiatric, and less commonly, neurological alterations. Regarding this last group, our case is the first report of musical hallucinations involving resection of a tumor in the insula topography.

Musical hallucinations associated with deafness have an estimated prevalence of approximately 2.5% in older patients.[6] Usually patients state that they hear familiar sounds, such as popular music.[13,24] Sometimes a humming sound precedes the musical hallucination. Hearing musical instruments and voices is a common phenomenon. Based on the humming that developed into musical hallucinations, Gordon[12] proposed that the etiological basis of the phenomenon is in the cochlea, although it is impos-

sible to confirm that the mechanism has been explained based only on this premise. The release hallucinations concept is based on West's perceptive theory, whose main hypothesis is that blindness and deafness interrupt external sensorial stimuli necessary to inhibit brain memory evocation.[5,7,22,23] This phenomenon will release previously stored perceptions and visual or auditory memories.[3,4] Release musical hallucinations occur mainly in the elderly with hearing deficiencies, mainly while awakening. The atypical antipsychotic drug quetiapine improved these symptoms in some patients.[7] A similar phenomenon could be the reason for the transient symptoms experienced by our patient; the surgical procedure may have been responsible for the transitory release of the primary auditory area. Musical hallucinations associated with psychiatric disease are less common than verbal auditory hallucinations observed in schizophrenic, depressed, obsessive-compulsive, and alcoholic patients. Musical hallucinations are generally considered rare in psychiatric patients.[3] Fukunishi et al.[11] identified only 6 patients with musical hallucinations (3 of whom were deaf) in a population of 3578 psychiatric patients. However, this estimate may not be accurate, because Hermesh et al.[14] identified 20% of 190 psychiatric patients (mainly patients with obsessive-compulsive problems) who developed musical hallucinations at some period in their life.

Musical hallucinations associated with neurological diseases are less frequent than in the 2 former groups. In case reports, they are usually associated with abnormalities of the right nondominant cerebral hemisphere. Although quite rare, there are reports of musical hallucinations associated with dementia, meningioma,[19] gliomas,[9] subarachnoid hemorrhage,[20] cerebral ischemia,[2] and pontine hemorrhage.[18] To the best of our knowledge, there are no previous reports of hallucinations associated with insular gliomas.

On the other hand, the auditory aura is a rare phenomenon. In the series of 8000 patients of Florindo et al.[10] the auditory aura was present in only 121 cases. The role of laterality in epilepsy, where aura musical hallucinations occur, is a mechanism that must still be elucidated. The clinical characteristics of the case reported, in association with the electroencephalographic findings and the resection of the tumor tissue at the level of the planum temporale (more specifically, the anterior transverse temporal gyrus [Heschl gyrus]), lead us to believe the hypothesis that the postoperative musical hallucinations experienced by our patient could be a simple partial seizure due to surgical manipulation of the planum temporale or a release phenomenon.

Insular gliomas are tumors that become very large in many patients before they become symptomatic.[25–27] Sometimes these tumors are a casual finding observed during MR imaging. The cortex of the insula is an interface between the allocortex and the neocortex and constitutes part of the paralimbic system. It is related to motor, sensorial, language, auditory-vestibular, and cognitive functions.[8] The surgical treatment of these lesions is technically challenging because of their proximity to the internal capsule and the close anatomical relationship with the segments of the MCA and its branches.[25–27] The MR imaging tractography performed in this case illustrates the close proximity of the deep tumor portion to the corticospinal tract.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: GR Isolan. Acquisition of data: GR Isolan, JA Bragatti, C Torres. Analysis and interpretation of data: GR Isolan, MM Bianchin. Drafting the article: GR Isolan, MM Bianchin. Critically revising the article: MM Bianchin, G Schwartsmann. Reviewed final version of the manuscript and approved it for submission: G Schwartsmann.

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