Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity

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Surgical treatment of low-grade gliomas (LGGs) aims to maximise the amount of tumour tissue resected, while minimising the risk of functional sequelae. In this review I address the issue of how to reconcile these two conflicting goals. First, I review the natural history of LGG—growth, invasion, and anaplastic transformation. Second, I discuss the contribution of new techniques, such as functional mapping, to our understanding of brain reorganisation in response to progressive growth of LGG. Third, I consider the clinical implications of interactions between tumour progression and brain plasticity. In particular, I show how longitudinal studies (preoperative, intraoperative, and postoperative) could allow us to optimise the surgical risk-to-benefit ratios. I will also discuss controversial issues such as defining surgical indications for LGGs, predicting the risk of postoperative deficit, aspects of operative surgical neuro-oncology (eg, preoperative planning and preservation of functional areas and tracts), and postoperative functional recovery.

Introduction

The traditional approach to cerebral tumour surgery was to remove the neoplasm located within a "static" brain while preserving the crucial structures such as rolandic, Broca's, and Wernicke's areas. This approach assumes that the brain has a fixed functional organisation that is similar in all patients. Recent advances in functional brain imaging in healthy volunteers has questioned this canonical view by showing that there is a large interindividual variability in the functional organisation of the brain.[1] These advances have also proved the existence of great plasticity within the CNS. In particular, short-term and long-term redistributions of functional maps have been described for individual people, especially in learning or memory; [2] this is called "natural plasticity". The capacity for the brain to reorganise itself is critical for the process of functional recovery in patients who present with acute cerebral lesion—such as traumatic brain injury or stroke;[3] this is often called "postlesional plasticity". Interestingly, more progressive lesions such as slow growing tumours—in particular low-grade gliomas (LGGs)—induce a large functional reshaping.[4] Reorganisation is thought to explain why slow infiltrative LGGs within the so-called "eloquent" areas often do not induce detectable neurological deficits.

As a consequence, a new approach to brain-tumour surgery should take into account dynamic interactions between the natural history of the tumour and the reactive process of cerebral adaptation. Such an approach, applied to each patient and each tumour, should allow specific selection of surgical indications that maximise the quality of glioma resection while minimising the risk of irreversible postoperative deficits.

The goal of this review is to review recent advances in neuro-oncology and functional mapping. Three issues will be addressed: the biological and kinetic behaviour of each tumour, the potential of functional modification within the brain in response to slow-growing LGG for each patient (plasticity), and how we can apply the two previous points to optimise the benefit-to-risk ratio of glioma surgery.

Behaviour of gliomas

Natural history

Understanding the natural history of a tumour is essential for the optimal selection of a therapeutic strategy, especially in the context of surgical indications. This includes not only determining the histological grade of the neoplasm and its potential for invasion, but also its ability to progress from a benign to malignant subtype. LGG (gliomas WHO grade II[5]) can manifest and progress by means of: local growth, invasion, or anaplastic transformation. Recent studies have found that before any anaplastic transformation, LGG shows a continuous, constant growth, with a mean tumour diameter growing on average about 4 mm per year.[6] LGG invade the main white-matter pathways within the lesional hemisphere and spread controlaterally via the corpus callosum.[7] Furthermore LGGs systematically change and evolve towards high-grade gliomas, with a median of around 7–8 years for anaplastic transformation. This change is invariably fatal (median survival around 10 years).[8,9] Because determining the risk factors of spontaneous evolution of LGG for each patient by use of classic clinical and radiological parameters is difficult,[10,11] the addition of individual data obtained from non-invasive metabolic neuroimaging studies is useful and allows actual "tumour mapping".[12–22] These data from non-invasive metabolic neuroimaging complement other information gained from molecular biology[23] and biomathematical models.[24,25]

In summary, it would be highly desirable to adapt therapeutic strategies to the "dynamic" behaviour of LGG and thus prevent the progression of LGG to a malignant and eventually fatal form. Recent data show that the progression of LGG triggers a large functional reorganisation within cerebral structures. This brain plasticity may allow a functional compensation (ie, the absence of deficit).

Dynamic organisation of functional networks: the plastic brain

Despite the early description of several cases of postlesional recovery, the dogma of a static functional organisation of the brain was dominant in the 20th century. This idea was rooted in anatomofunctional associations identified in acute lesion studies. These associations led to the idea that the brain was segmented into so-called "eloquent" and "silent" regions. Damage in eloquent areas was thought to induce major neurological deficit, whereas lesions in the silent (non-functional) structures had no clinical consequence. However, the publication of reports showing major functional improvements after injuries of "eloquent" corticosubcortical structures called this static model into question. During the past few decades, many studies were carried out to investigate this question. Initial data was obtained in vitro and in animals. More recently, the development of functional mapping methods enabled the study of postlesional functional reorganisation in humans (ie, cerebral plasticity).

Cerebral plasticity is a continuous process allowing short-term, middle-term, and long-term remodelling of the neuronosynaptic maps, the purpose of which is to optimise the functioning of brain networks. Cerebral plasticity has a critical role during ontogeny, learning, and recovery from lesions in the peripheral nervous system and CNS. Several hypotheses have been proposed to explain the pathophysiological mechanisms underlying cerebral plasticity. At a microscopic level, modulations of synaptic efficiency,[26] unmasking of latent connections,[27] phenotypic modifications,[28] and neurogenesis[29] have been identified. At a macroscopic level, diaschisis,[30] functional redundancies,[31] cross-modal plasticity with sensory substitution (ie, compensatory recruitment of areas not initially dedicated to the function damaged),[32] and morphological changes[33] have been described. The behavioural consequences of these cerebral changes have been investigated recently in humans, both at the physiological (ontogeny and learning)[2] and pathological level.[34] However, postlesional recovery and the pattern of brain reorganisation involved in functional compensations have been mostly documented in stroke patients.[3,35]

Advances in functional brain imaging methods

Non-invasive functional neuroimaging

Preoperative non-invasive techniques, including PET, functional MRI (fMRI), electroencephalography, and magnetoencephalography enable accurate functional mapping of the whole brain (grey matter). This mapping gives a precise estimation of the location of the functional areas in relation to a tumour, therefore, decreasing surgical risk. The first studies of preoperative mapping in tumours were PET studies of sensorimotor, language, and visual areas.[36,37] During the past decade, fMRI, a widely available technique using the blood oxygenation level-dependent (BOLD) effect, has been extensively used before surgery.[38,39] Due to the improvement of the stimulation paradigms, particularly for language mapping, fMRI can be routinely used with high specificity and high sensitivity (figure 1).[40,41] Unfortunately, the BOLD response in the vicinity of a tumour does not reflect the neuronal signal as accurately as in healthy tissue, such that sensitivity decreases (66% for language).[42,43] Although poorly understood, this degraded sensitivity does not seem to result from reduced neuronal activity but rather from a change in neurovascular and metabolic coupling.[44,45]

Recently, magnetoencephalography and electro-encephalography have also become available for planning and guiding tumour surgery.[46] The former has been used mainly for sensorimotor, language, auditory, and visual mapping.[47,48] Furthermore, magneto-encephalography may also help measure tumour infiltration. Delta and theta activity have been recorded close to the lesion, whereas gamma activity was observed contralaterally.[49] In addition, association between high signal powers in the delta band and the aggressivity of the tumour has been described.[50] Transcranial magnetic stimulation (TMS) may also be useful in a more

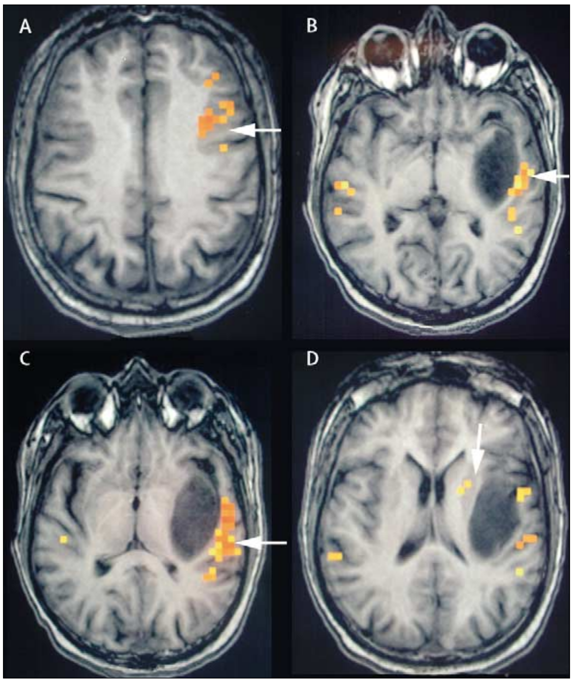

Figure 1: **Preoperative fMRI during a language task in a patient with a left dominant insular LGG and slight dysphasia**
There was no activation within the insula, but a perilesional redistribution of language sites in the frontal (A) and temporal (B, C) operculae, and within the left putamen (D). This functional reshaping allowed glioma removal without postoperative sequelae and the patient's language improved after resection. Reproduced with permission from Lippincott Williams and Wilkins.[41]

marginal way for presurgical mapping, especially for tumours near the rolandic cortex.[51]

In summary, there are different complementary techniques available for brain mapping before surgery. The best approach would be to combine all these different neurofunctional imaging methods during preoperative assessment.[52]

Individual data defining the spatial relation between the lesion and its surrounding eloquent areas are obviously useful for the selection of surgical indications, in particular for determining the feasibility of tumour resection.[53] Once the decision to operate has been made, these techniques are very important for the planning of surgery. These techniques provide significant information for determining three factors of the operation: (1) surgical technique, and more specifically, which patients should have an awake craniotomy (this awake procedure should be used, for instance, if the tumour is located within the dominant hemisphere as determined using preoperative neurofunctional imaging);[54] (2) the least traumatic approach using functional neurosurgical simulation,[55] and (3) the limits of resection such that functional structures are preserved. This last point, however, is still open to discussion; preoperative techniques cannot be used to differentiate the structures essential for the function (which should be surgically preserved) from the "modulatory" areas, which can be functionally compensated (and hence resected without permanent deficit).[4]

Preoperative diffusion tensor imaging

Functional neuroimaging is sensitive to changes in the grey matter, but it cannot map white matter.[56] Because surgical interruption of subcortical tracts can lead to major sequelae, the use of diffusion tensor imaging (DTI), a new preoperative non-invasive technique of fibre tracking, has been advocated.[56] This technique is a modification of diffusion weighted imaging and is sensitive to the preferential diffusion of brain water along subcortical fibres—ie, "diffusion anisotropy". DTI can detect subtle changes in white-matter tracts in the brain.[57]

In brain tumours, DTI can be used to differentiate normal white matter, oedematous brain tissue, and enhancing tumour margins.[58] Diffusion anisotropy is reduced in cerebral lesions due to the loss of structural organisation.[59] The measurement of fractional anisotropy allows prediction of histological characteristics such as cellularity, vascularity, or fibre structure in gliomas.[60] In addition, DTI may help determine if the fibres are displaced, infiltrated, or disrupted by the tumour.[61] Such knowledge could contribute to the selection of surgical indications. Finally, DTI can help identify the subcortical connections. Results from DTI can be combined with functional neuroimaging methods[62] to allow mapping of individual anatomofunctional connectivity. This information is useful for surgical planning by delineating the spatial associations of the eloquent structures and lesions. However, beyond its potential promises, DTI still needs to be validated before it can be used routinely in neurosurgery.[63] Furthermore, DTI is able to give only anatomical but not functional data about the subcortical pathways.

Intraoperative functional brain mapping

Functional neuronavigation

Anatomical neuronavigation is based on the co-registration of the physical space of the head of the patient in the operating room to the virtual space of an MRI or CT image set. This procedure is widely applied in brain surgery. Recently, neuronavigation progressed from the anatomic to functional level by integrating PET,[64] fMRI,[65] magnetoencephalography,[66] DTI,[67] magnetic resonance spectroscopy[68] (or even multimodal imaging)[69] into frameless stereotactic surgery—this is referred to as "functional neuronavigation".[70] It is tempting to use this new tool before surgery for determining functional networks in a single patient; however, relying solely on this input for deciding which area to resect might be misleading. Despite the relative accuracy of the technique (about 4 mm),[71] there is a risk of intraoperative brain shift due to surgical retraction, mass effect, gravity, extent of resection, or CSF leakage.[72] If this shift is not taken into account it can lead to major functional damage, especially at the end of the resection (within in the subcortical pathways).[67] Several technical improvements have been proposed to minimise the influence of this displacement: the combination of neuronavigation and intraoperative ultrasound to produce real-time imaging;[73] the use of mathematical models;[74] and the development of intraoperative MRI to generate high-quality imaging during surgery[70,75] and optimise the accuracy of glioma removal.[76] Furthermore, intraoperative fMRI[77] and intraoperative fibre tracking with DTI[78] are now possible.

Invasive electrophysiological mapping

Preoperative functional neuroimaging still has major limitations despite its recent development. As a consequence, invasive electrophysiological investigations currently remain the "gold-standard" when operating on tumours in eloquent corticosubcortical structures.[79]

During the past decades, somatosensory and motor evoked potentials were widely used for intraoperative identification of the sensorimotor region.[80,81] However, the reliability of this approach is not ideal; 6–9% of localisations of the central sulcus are inaccurate.[82,83] This inaccuracy may explain why evoked potentials have been associated with a large prevalence of definitive postoperative deficit (20%), mainly due to resection of subcortical lesions near the pyramidal tract.[82] Another limitation of this technique is that evoked potentials cannot be used to map language, memory, or other higher functions.

Subdural grids might be used when making extraoperative electrophysiological recordings to increase the time available for extensive and reliable cortical mapping.[84,85] This method consists of surgically putting electrodes directly onto the brain surface, thus enabling invasive electrocorticographic recordings and direct cortical stimulation at the same time. With this approach, the patient is placed in optimal conditions; he or she stays in his room and does the relevant tasks with a minimal amount of stress—particularly important in children.[86] However, extraoperative mapping typically involves grids with electrodes 1 cm apart, which is not a sufficient level of accuracy. Moreover, subcortical mapping is not possible. In addition, two surgical procedures are needed, one to implant the grids and one to resect the tumour. Finally, there is a notable risk of infection resulting from the presence of the implanted grid during several days of assessments.[87]

The advantages and limitations of the different mapping techniques can be most effectively complemented by the use of intraoperative direct electrical stimulation during surgery of tumours in eloquent areas (figure 2),[79,88–93] which can be done under general or local anaesthetic. Direct electrical stimulation allows the mapping of motor function, possibly under general anaesthetic, by inducing involuntary movement if a motor site is stimulated. For patients who are conscious during the procedure, somatosensory function (by eliciting dysaesthesia described by the patient) and cognitive functions, such as language (spontaneous speech, object naming, comprehension, etc), calculation, memory, reading, or writing, can be investigated. The idea is to generate transient disturbances by applying direct electrical stimulation to the cerebral tissue at the level of a functional "epicenter".[94]

Furthermore, direct electrical stimulation also allows the study of the functional connectivity of the brain throughout the resection when directly stimulating the white-matter tracts (figure 2).[79,88,93,95–98] A speech therapist must be present in order to accurately interpret the kind of disorders induced by the cortical and subcortical stimulations—eg, speech arrest, anarthria, speech apraxia, phonological disturbances, semantic paraphasia, perseveration, and anomia.[99] These intraoperative anatomofunctional correlations represent a unique opportunity to study individual connectivity, as has been shown for motor pathways and their somatotopy from the corona radiata to the internal capsule and the mesencephalic peduncles,[95,96,100] thalamocortical somatosensory pathways,[96] subcortical visual pathways,[101] and language pathways. The functional mapping of language pathways was done at several levels: the locoregional connectivity (ie, short-distance association pathways); the corticocortical connections, including the phonological loop;[102] the striatocortical loop, such as the subcallosal medialis fasciculus; the long-distance association language bundles including the arcuate fasciculus;[93] or the inferior fronto-occipital fasciculus involved in semantic connectivity.[103]

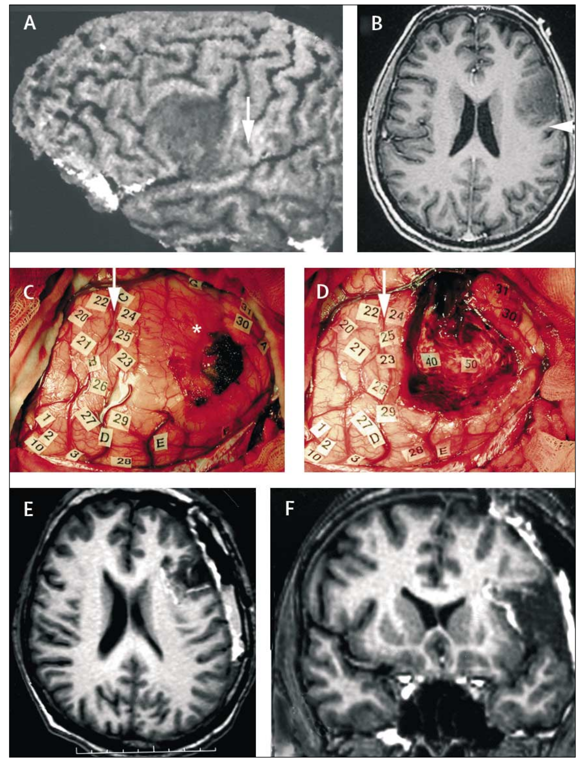

Figure 2: **Preoperative, intraoperative, and postoperative views of eloquent areas**
Preoperative anatomical MRI showing a left LGG involving Broca's area (A), in front of the rolandic operculum (B; the arrow marks the central sulcus). Reproduced with permission Oxford University Press.[93] Intraoperative views (left=posterior) before (C) and after (D) resection of the tumour (star), which is delineated by letter tags. Electrical mapping shows a reshaping of the eloquent maps, with a recruitment of perilesional language sites—ie, the ventral premotor cortex (tags 23–25), dorsolateral prefrontal cortex (tag 29), and pars orbitaris of the inferior frontal gyrus (tags 30 and 31). This language remapping induced by the slow-growing glioma has allowed the compensation of Broca's area, which can therefore be removed. The resection was continued up to the contact of the language pathways, in particular the insulofrontal connections and the anterior part of the arcuate fasciculus (tags 40 and 50). The arrow shows the lateral part of the central sulcus. Postsurgical control MRI (E and F) showing a complete glioma removal.

These observations show that direct electrical stimulation is an accurate, reliable, and safe technique for online detection of the cortical and subcortical regions, which are essential for a given function, at each place and each moment of the resection. It follows that any functional disturbance repeatedly induced by direct electrical stimulation must lead to the immediate termination of the resection, both at the cortical and subcortical level. The removal of the tumour is then done according to functional boundaries. This strategy allows optimal resection while minimising the risk of permanent postoperative deficit.[96]

However, there are limitations to this approach. In particular, direct electrical stimulation allows only locoregional mapping, and it is not possible to map the whole brain. In addition, direct subcortical (but not cortical) stimulation may induce a functional (motor) response, even if the pyramidal pathways are still damaged by the resection. As a consequence, regular cortical direct electrical stimulation should be done to check the anatomofunctional integrity of the white fibres.[93] However, the procedure is time consuming and the number of tasks that can be done to the awake patient during surgery is restricted. Consequently, direct electrical stimulation should be used in combination with other functional mapping methods previously described, especially preoperative neuroimaging.

Dynamic interactions between the glioma and the brain

Functional reorganisation induced by the glioma

Preoperative plasticity

Most patients with LGG present with seizures and have no neurological deficit. This is puzzling considering the frequent invasion of eloquent structures.[104] The most likely explanation is that slow growing lesions have induced progressive functional reshaping of brain networks. Preoperative neurofunctional imaging supports this claim.[105] The patterns of reorganisation may differ among patients. This needs to be taken into account when considering surgical intervention (indication and planning).[106] Theoretically, three kinds of preoperative functional redistribution are possible in patients without deficit. First, function can still persist within the tumour.[107] In this case the opportunities to perform a total resection without postoperative sequelae are very limited. Second, eloquent areas can be redistributed around the tumour (figure 1).[108] Thus, the chances of a near total resection may be possible; transient deficit is likely just after the surgery, but with secondary recovery within some weeks or months. Third, preoperative compensation exists. This compensation can rely on some remote areas within the same hemisphere as the tumour[109] or in parts of the contralateral hemisphere homologous to the structures invaded.[36,105,110,111] In this case, a total resection is likely and postoperative deficits are likely to be minor and transient.

These observations suggest that mechanisms for plasticity are based on a hierarchically organised model involving three levels recruited successively; first, an intrinsic reorganisation within injured areas (index of favourable outcome);[112] second, the recruitment of other regions implicated in the original functional network in the ipsilateral hemisphere but remote to the damaged area; and third, the solicitation of the homologuous regions in the contralateral hemisphere.

Intraoperative plasticity

Direct electrical stimulation before any resection supports the existence of brain functional reshaping in response to the development of LGG. This reshaping has been identified for both the sensorimotor[113] and language networks (figure 2).

Interestingly, acute functional reorganisation does also occur during resection. This is likely to be due to the surgery itself. The resection can generate a locoregional hyperexcitability.[114] For instance, in several patients presenting with a frontal LGG, only a few of cortical sites showed induced motor activity in response to direct electrical stimulation before the resection. Immediately after the surgery, however, some sites that were initially silent started to induce clear motor responses, revealing an acute unmasking of redundant motor sites within the damaged precentral gyrus.[114] Acute unmasking of redundant somatosensory sites was also observed within the retrocentral gyrus during resection of parietal LGG.[115] A redistribution within a larger network involving the whole rolandic region was also detected using direct electrical stimulation—ie, with the existence of redundant precentral and postcentral motor areas for the same movement. The precentral redundancy has been unmasked after removal of a central lesion, although they were silent before the resection.[31] Finally, direct electrical stimulation also has a predictive value regarding the postoperative recovery.[116]

Postoperative plasticity

The reshaping induced by surgical resection has also been studied directly with postoperative neuroimaging after complete functional recovery (ie, the performance of the patient reached their preoperative level). In particular, patients were examined after resection of LGG in the supplementary motor area (SMA), which has induced a transient postsurgical syndrome. In comparison to the preoperative state, fMRI showed activations within the SMA and premotor cortex contralateral to the lesion. These data support the idea that postsurgical recovery relies partly on the homologuous areas of the contralateral hemisphere (figure 3).[117]

Brain plasticity applied to glioma surgery

Preoperative, intraoperative, and postoperative brain plasticity makes it possible for neurosurgeons to

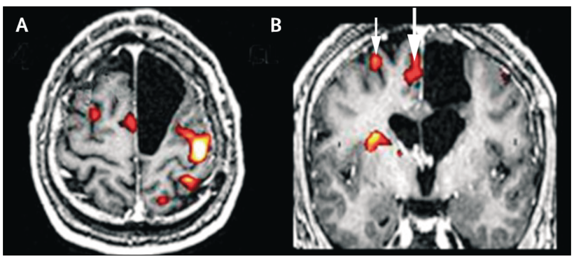

***Figure 3:* Postoperative fMRI scans showing the activations within the SMA and premotor cortex contraleteral to the lesion**

Postoperative coronal (A) and axial (B) fMRI during a motor task of the right hand after a total resection of an LGG involving the left SMA, which has generated a transient SMA syndrome followed by complete recovery. In addition to a classical activation of the left central area, this fMRI shows a recruitment of the contralesional SMA (small arrow) and premotor cortex (big arrow), likely implicated in the postsurgical functional compensation. Reproduced with permission from Lipincott Williams and Wilkins.[117]

increase the resection in eloquent areas without inducing sequelae.[4]

LGG involving the supplementary motor area

The SMA (a frontomesial motor area located in front of the paracentral lobule, and involved in the planning of movement)[118] is a common localisation for LGG.[119] Resection of LGG involving this structure induces a well-known deficit commonly called SMA syndrome.[120] This syndrome is characterised by complete akinesia and potential mutism (if the lesion involves the dominant SMA). Observations in patients under local anaesthetic show that these deficits occur about 30 min after resection.[121] After 10 days, these symptoms disappear spontaneously and suddenly, although rehabilitation is often needed for 1–3 months to allow complete recovery.

Preoperative fMRI has shown that SMA syndrome is not associated with the volume of the frontal resection, but rather with the removal of a specific structure called the "SMA proper". Consequently, presurgical fMRI enables the prediction of whether SMA syndrome will occur postoperatively, and thus the patient and family can be informed of this before surgery.[122] Recent studies have shown the existence of a somatotopy within the SMA proper by correlating the preoperative fMRI, the pattern of clinical deficit after surgery, and the extent of resection quantified on the postoperative MRI. This somatotopy ran in the anterior to posterior direction from the representation of language (at least in the dominant hemisphere) to that of the face, arm, then leg.[123] This accurate mapping enables prediction before surgery, not only of the severity of the postoperative transient deficit, but also its pattern, and, therefore, plays an important part in planning the rehabilitation procedure.

Insular LGG

The insula is also a common location for LGG.[119] The recent development of functional mapping methods have allowed investigation of this poorly understood multimodal region. The insula probably contributes to many functions, most notably language.[124]

While the tumour was present, most preoperative fMRI showed an activation of the anterior dominant insula during language tasks, as is the case in healthy controls.[124] This was confirmed by intraoperative direct electrical stimulation. Stimulation of the insula induced clear language disorders, especially articulatory disturbances.[100,125,126] These observations agree with the results gathered in patients with stroke, suggesting that the insula plays a major part in the complex planning of speech.[127] On the basis of these results, it seems that LGGs located in the left dominant frontotemporoinsular region are unlikely to be totally removed. However, recent data have shown that LGG circumscribed to the left dominant insula could be completely resected without postoperative aphasia. In this case, functional compensations are likely to involve the frontal and temporal operculae and the left putamen—as supported by use of both fMRI and direct electrical stimulation (figure 1).[41] Resection of LGG involving the right non-dominant insulo-opercular structures has smaller functional effects. Transient Foix-Chavany-Marie syndrome is nevertheless observed after some resections—ie, a bilateral palsy of the face, tongue, pharynx, and larynx leading to an inability to speak and swallow.[128]

LGG involving Broca's area

Removal of LGG within the pars opercularis and triangularis of the left inferior frontal gyrus (Broca's area) was also possible without generating aphasia. As shown by direct electrical stimulation, this absence of deficit was likely due to a perilesional reorganisation of the language areas, particularly within the ventral premotor cortex (which plays a major part in articulation),[99] the pars orbitaris of the inferior frontal gyrus, and the insula (figure 2).[4]

LGG involving the primary sensorimotor area of the face

The primary sensorimotor area of the face could also be removed without permanent central facial palsy, but only within the non-dominant hemisphere.[129] In this case, the deep functional boundaries of the resection corresponded to the pyramidal pathways of the arm running under the representation of the face.[97]

Striatal LGG

Compensation was equally possible when the glioma was located in the right striatum. A total resection was possible without permanent palsy and movement disorders.[130] However, direct electrical stimulation of the dominant striatum tended to induce language disorders, namely perseveration during stimulation of the head of the caudate nucleus and anarthria during stimulation of the lentiform nucleus.[131] Consequently, it seems judicious to preserve the dominant striatum, even if invaded by a glioma, until we have a better understanding of the actual implication of this structure in language and other cognitive function.

Other brain locations

Although the infiltration of the corpus callosum may sometimes result in an organic brain syndrome, the resection of LGG involving this structure is possible. This resection did not have any functional effect and the patient's quality of life was totally preserved, whatever the location of the LGG within the corpus callosum.[132] LGGs in other eloquent regions were also removed without sequelae, including the frontal eye fields,[133] the left angular gyrus (despite its role in calculation),[134] the left dominant posterotemporal regions near Wernicke's area,[135] and the regions involved in writing,[136] reading, or bilinguism.[137]

Surgical canalisation of brain plasticity

Recent observations have suggested that an initially partial resection could be followed by total resection of the tumour a few months or years later, owing to the long term functional reshaping induced by the initial surgery.[4] As already discussed, surgery induces compensatory mechanisms that recruit latent networks. This functional reorganisation can provide a basis for a second surgery, which could extend the initial resection without eliciting sequelae.[138]

For instance, in some patients, incomplete resections within the precentral gyrus were performed in an initial operation, due to the identification of major functional deficits induced by direct electrical stimulation. A few years later, the tumour started to grow back and surgery was done using direct electrical stimulation. Stimulation showed a clear reshaping of the motor map within the precentral gyrus. Eloquent areas corresponded to new motor sites, unmasked as a result of the first surgery. This reorganisation allowed a total removal of the glioma without deficit.[138] This long-term plasticity induced by surgical resection, and maybe also by continued glioma growth, was also used to extend tumour removal in other eloquent regions where a total resection was not initially possible, such as primary somatosensory and language areas.[138]

The results above indicate that plasticity and its variability among patients is a critical issue for neurosurgeons. These observations should be integrated into surgical indications and in dynamic surgical planning—the extent of the resection and the number of surgical acts necessary to do a resection should be adapted to the individual potential of functional compensation (ie, to its limits).

Surgical results

The advances discussed have obvious implications and have allowed the improvement of functional and oncological results of brain glioma surgery in the past decade.

Functional results

Integration of multimodal information (individual functional mapping, connectivity, and plasticity) in the surgical process (decision and planning) has allowed successful surgical procedures in areas often considered "inoperable".[139] Although transient immediate postoperative functional worsening are common (due to attempting a maximal tumour removal), most patients recover within 3 months. After this period, 95% of patients are normal when tested with a standard neurological examination.[88,91,92,96,105,139] In some patients, functional improvement is seen in comparison with the preoperative state.[139] In addition, 80% of patients with preoperative chronic epilepsy have notably fewer seizures.[125] In summary, 95% of patients operated on returned to a normal socioprofessional life. These results can be compared to other groups of patients operated on for LGG, for whom direct electrical stimulation was not used. In this case functional sequelae developed in 13–27·5%.[140,141]

Neuro-oncological results

Because mapping techniques allow individual identification of corticosubcortical eloquent structures, it is tempting to suggest that glioma surgery should be done according to functional boundaries. The idea is to proceed with the resection until direct electrical stimulation indicates that an eloquent structure has been reached. When this protocol is applied, there is a significant improvement in the quality of the glioma resection (systematically assessed by repeated postsurgical MRIs), together with a decrease in the occurrence of permanent deficits.[96,139] These results are all the more impressive because functional surgery of LGG is more likely to be done within critical areas.[139]

Surgery in LGG is still a matter of debate. There are numerous reviews and editorials outlining the difficulties in managing these lesions and evidence-based interventions are lacking.[9,142,143] However, several recent articles strongly support the positive effect of a "maximalist" surgical strategy by showing that survival rate correlated with the quality of resection[144–146] when objectively evaluated on postoperative MRI.[139,147–149] In particular, a recent prospective study has reported a mortality rate of 20·6% in partial resections, compared with 8% in subtotal resections and 0% in complete resections (median follow-up 47 months, p=0·02).[139]

Conclusions and perspectives

The surgical resection of brain gliomas may benefit from a better understanding of the dynamic biological behaviour of the tumour, the dynamic organisation of the brain, and the dynamic interaction between the tumour and the reactional plasticity of the nervous system as a result of both tumour invasion and surgery. Much information relevant to these issues has been gathered in the past decade—mainly due to technical development in the field of functional mapping. These advances have been echoed by recent progress in the field of fundamental neurosciences, including the study of functional brain organisation, anatomofunctional connectivity, and plastic potential at the individual level. This progress allows an extension of surgical indications (especially for eloquent areas) and better quality glioma resection allowing greater impact on the natural history of the tumour, minimisation of postoperative sequelae, and preservation of the quality of life of the patients.[150]

Obviously, multidisciplinary multicentre studies remain necessary to further understand the dynamic interactions between cerebral function, the tumour progression, and the potential treatments. The ultimate goal of these studies should always be to optimise the therapeutic strategy for brain gliomas.

Search strategy and selection criteria

References for this review were identified by searches of MEDLINE with the terms "gliomas", "tumour surgery", "brain mapping", "cerebral plasticity", "functional connectivity", "neurofunctional imaging", "metabolic imaging", and "intraoperative electrical stimulations". Some references were also selected from relevant articles and chapters of recent books on neuro-oncology. Abstracts and reports from meetings were not included. Only papers published in English or with an English abstract were reviewed. I searched papers published from 1991 to May 2005.

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References

1 Tzourio-Mazoyer N, Josse G, Crivello F, Mazoyer B. Interindividual variability in the hemispheric organization for speech. *NeuroImage* 2004; **21:** 422–35.
2 Ungerleider LG, Doyon J, Karni A. Imaging brain plasticity during motor skill learning. *Neurobiol Learn Mem* 2002; **78:** 553–64.
3 Rijntjes M, Weiller C. Recovery of motor and language abilities after stroke: the contribution of functional imaging. *Prog Neurobiol* 2002; **66:** 109–22.
4 Duffau H, Capelle L, Denvil D, et al. Functional recovery after surgical resection of low-grade gliomas in eloquent brain: hypothesis of brain compensation. *J Neurol Neurosurg Psychiatry* 2003; **74:** 901–07.
5 Kleihues P, Cavenee W, eds. Pathology and genetics of tumours of the nervous system. USA: WHO Publications Centre, 2000.
6 Mandonnet E, Delattre JY, Tanguy ML, et al. Continuous growth of mean tumour diameter in a subset of grade II gliomas. *Ann Neurol* 2003; **53:** 524–28.
7 Giese A, Bjerkvig R, Berens ME, Westphal M. Cost of migration: invasion of malignant gliomas and implications for treatment. *J Clin Oncol* 2003; **21:** 1624–36.
8 Walker DG, Kaye AH. Low grade glial neoplasms. *J Clin Neurosci* 2003; **10:** 1–13.
9 Wessels PH, Weber WEJ, Raven G, Ramaekers FC, Hopman AH, Twijnstra A. Supratentorial grade II astrocytoma: biological features and clinical course. *Lancet Neurol* 2003; **2:** 395–403.
10 Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol* 2002; **20:** 2076–84.
11 Stupp R, Janzer RC, Hegi ME, Villemure JG, Mirimanoff RO. Prognostic factors for low-grade gliomas. *Semin Oncol* 2003; **30** (suppl)**:** s23–28.
12 Hemm S, Vayssiere N, Zanca M, Ravel P, Coubes P. Thallium SPECT-based stereotactic targeting for brain biopsies: a technical note. *Stereotact Funct Neurosurg* 2004; **82:** 70–76.
13 Bénard F, Romsa J, Hustinx R. Imaging gliomas with positron emission tomography and single-photon emission computed tomography. *Semin Nucl Med* 2003; **33:** 148–62.
14 Schaller B. Usefulness of positron emission tomography in diagnosis and treatment follow-up of brain tumours. *Neurobiol Dis* 2004; **15:** 437–48.
15 De Witte O, Levivier M, Violon P, et al. Prognostic value positron emission tomography with [18F]fluoro-2-deoxy-D-glucose in the low-grade glioma. *Neurosurgery* 1996; **39:** 470–76.
16 Ribom D, Eriksson A, Hartman M, et al. Positron emission tomography (11)C-methionine and survival in patients with low-grade gliomas. *Cancer* 2001; **92:** 1541–49.
17 de Edelenyi FS, Rubin C, Esteve F, et al. A new approach for analyzing proton magnetic resonance spectroscopic images of brain tumours: nosologic images. *Nat Med* 2000; **6:** 1287–89.
18 Galanaud D, Chinot O, Nicoli F, et al. Use of proton magnetic resonance spectroscopy of the brain to differentiate gliomatosis cerebri from low-grade glioma. *J Neurosurg* 2003; **98:** 269–76.
19 Herminghaus S, Dierks T, Pilatus U, et al. Determination of histopathological tumour grade in neuroepithelial brain tumours by using spectral pattern analysis of in vivo spectroscopic data. *J Neurosurg* 2003; **98:** 74–81.
20 Tedeschi G, Lundbom N, Raman R, et al. Increased choline signal coinciding with malignant degeneration of cerebral gliomas: a serial proton magnetic resonance spectroscopy imaging study. *J Neurosurg* 1997; **87:** 516–24.
21 Kuztnetsov Y, Caramanos Z, Antel S, et al. Proton magnetic resonance spectroscopic imaging can predict length of survival in patients with supratentorial gliomas. *Neurosurgery* 2003; **53:** 565–76.
22 Rees J. Advances in magnetic resonance imaging of brain tumours. *Curr Opin Neurol* 2003; **16:** 643–50.
23 Mischel PS, Cloughesy TF, Nelson SF. DNA-microarray analysis of brain cancer: molecular classification for therapy. *Nat Rev Neurosci* 2004; **5:** 782–92.
24 Jbabdi S, Mandonnet E, Duffau H, et al. Diffusion tensor imaging allows anisotropic growth simulations of low grade gliomas. *Mag Reson Med* (in press).
25 Swanson KR, Bridge C, Murray JD, Alvord EC Jr. Virtual and real brain tumours: using mathematical modeling to quantify glioma growth and invasion. *J Neurol Sci* 2003; **216:** 1–10.
26 Byrne JH. Synapses. Plastic plasticity. *Nature* 1997; **389:** 791–92.
27 Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. *Science* 1991; **251:** 944–47
28 Ivanco TL, Greenough WT. Physiological consequences of morphologically detectable synaptic plasticity: potential uses for examining recovery following damage. *Neuropharmacology* 2000; **39:** 765–76.
29 Gross CG. Neurogenesis in the adult brain: death of a dogma. *Nat Rev Neurosci* 2000; **1:** 67–73.
30 Nguyen DK, Botez MI. Diaschisis and neurobehavior. *Can J Neurol Sci* 1998; **25:** 5–12.
31 Duffau H, Sichez JP, Lehéricy S. Intraoperative unmasking of brain redundant motor sites during resection of a precentral angioma. Evidence using direct cortical stimulations. *Ann Neurol* 2000; **47:** 132–35.
32 Bavelier D, Neville HJ. Cross-modal plasticity: where and how? *Nat Rev Neurosci* 2002; **3:** 443–52.
33 Draganski B, Gasert C, Busch V, Schuierer G, Bogdahn U, May A. Changes in grey matter induced by training. *Nature* 2004; **427:** 311–12.
34 Chen R, Cohen LG, Hallet M. Nervous system reorganization following injury. *Neuroscience* 2002; **111:** 761–73.
35 Rossini PM, Calautti C, Pauri F, Baron JC. Post-stroke plastic reorganisation in the adult brain. *Lancet Neurol* 2003; **2:** 493–502.
36 Meyer PT, Sturz L, Schreckenberger M, et al. Preoperative mapping of cortical language areas in adult brain tumour patients using PET and individual non-normalised SPM analyses. *Eur J Nucl Med Mol Imaging* 2003; **30:** 951–60.
37 Vinas FC, Zamorano L, Mueller RA, et al. [15O]-water PET and intraoperative brain mapping: a comparison in the localization of eloquent cortex. *Neurol Res* 1997; **19:** 601–08.
38 Moritz C, Haughton V. Functional MR imaging: paradigms for clinical preoperative mapping. *Magn Reson Imaging Clin N Am* 2003; **11:** 529–42.
39 Vlieger EJ, Majoie CB, Leenstra S, den Heeten GJ. Functional magnetic resonance imaging for neurosurgical planning in neurooncology. *Eur Radiol* 2004; **14:** 1143–53.
40 Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW. Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 2002; **51:** 350–60.
41 Duffau H, Bauchet L, Lehericy S, Capelle L. Functional compensation of the left dominant insula for language. *Neuroreport* 2001; **12:** 2159–63.

42 Holodny AI, Schulder WC, Liu J, Wolko JA, Maldjian, Kalnin AJ. The effect of brain tumours on BOLD functional MR Imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. *Am J Neuroradiol* 2000; **21:** 1415–22.
43 Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 2003; **52:** 1335–45.
44 Aubert A, Costalat R, Duffau H, Benali H. Modeling of pathophysiological coupling between brain electrical activation, energy metabolism and hemodynamics: insights for the interpretation of intracerebral tumour imaging. *Acta Biotheoretica* 2002; **50:** 281–95.
45 Schreiber AU, Hubbe U, Ziyeh S, Hennig J. The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. *Am J Neuroradiol* 2000; **21:** 1055–63.
46 Orrison WW Jr. Magnetic source imaging in stereotactic and functional neurosurgery. *Stereotact Funct Neurosurg* 1999; **72:** 89–94.
47 Nakasato N, Yoshimoto T. Somatosensory, auditory and visual evoked magnetic fields in patients with brain diseases. *J Clin Neurophysiol* 2000; **17:** 201–11.
48 Papanicolaou AC, Simos PG, Breier JI, et al. Magnetoencephalographic mapping of the language-specific cortex. *J Neurosurg* 1999; **90:** 85–93.
49 de Jongh A, de Munck JC, Baayen JC, Jonkman EJ, Heethaar RM, van Dijk BW. The localization of spontaneous brain activity: first results in patients with cerebral tumours. *Clin Neurophysiol* 2001; **112:** 378–85.
50 de Jongh A, Baayen JC, de Munck JC, Heethaar RM, Vandertop WP, Stam CJ. The influence of brain tumour treatment on pathological delta activity in MEG. *Neuroimage* 2003; **20:** 2291–301.
51 Krings T, Foltys H, Reinges MH, et al. Navigated transcranial magnetic stimulation for presurgical planning: correlation with functional MRI. *Minim Invasive Neurosurg* 2001; **44:** 234–39.
52 Kober H, Nimsky C, Moller M, Hastreiter P, Fahlbusch R, Ganslandt O. Correlation of sensorimotor activation with functional magnetic resonance imaging and magnetoencephalography in presurgical functional imaging: a spatial analysis. *Neuroimage* 2001; **14:** 1214–28.
53 Hund M, Rezai AR, Kronberg E, et al. Magnetoencephalographic mapping: basis of a new functional risk profile in the selection of patients with cortical brain lesions. *Neurosurgery* 1997; **40:** 936–43.
54 Szymanski MD, Perry DW, Gage NM, et al. Magnetic source imaging of late evoked field responses to vowels: toward an assessment of hemispheric dominance for language. *J Neurosurg* 2001; **94:** 445–53.
55 Kamada K, Takeuchi F, Kuriki S, Oshiro O, Houkin K, Abe H. Functional neurosurgical simulation with brain surface magnetic resonance images and magnetoencephalography. *Neurosurgery* 1993; **33:** 269–72.
56 Clark CA, Barrick TR, Murphy MM, Bell BA. White matter fiber tracking in patients with space-occupying lesions of the brain: a new technique for neurosurgical planning? *Neuroimage* 2003; **20:** 1601–08.
57 Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci* 2003; **4:** 469–80.
58 Sinha S, Bastin ME, Whittle IR, Wardlaw JM. Diffusion tensor MR Imaging of high-grade cerebral gliomas. *Am J Neuroradiol* 2002; **23:** 520–27.
59 Price SJ, Burnet NG, Donovan T, et al. Diffusion tensor imaging of brain tumours at 3 T: a potential tool for assessing white matter tract invasion? *Clin Radiol* 2003; **58:** 455–62.
60 Beppu T, Inoue T, Shibata Y, et al. Measurement of fractional anisotropy using diffusion tensor MRI in supratentorial astrocytic tumours. *J Neurooncol* 2003; **63:** 109–16.
61 Witwer BP, Moftakhar R, Hasan KM, et al. Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. *J Neurosurg* 2002; **97:** 568–75.
62 Krings T, Reinges MH, Thiex R, Gilsbach JM, Thron A. Functional and diffusion-weighted magnetic resonance images of space-occupying lesions affecting the motor system: imaging the motor cortex and pyramidal tracts. *J Neurosurg* 2001; **95:** 816–24.
63 Lin CP, Tseng WY, Cheng HC, Chen JH. Validation of diffusion tensor magnetic resonance axonal fiber imaging with registered manganese-enhanced optic tracts. *Neuroimage* 2001; **14:** 1035–47.
64 Sobottka SB, Bredow J, Beuthien-Baumann B, Reiss G, Schackert G, Steinmeier R. Comparison of functional brain PET images and intraoperative brain-mapping data using image-guided surgery. *Comput Aided Surg* 2002; **7:** 317–25.
65 Gumprecht H, Ebel GK, Auer DP, Lumenta CB. Neuronavigation and functional MRI for surgery in patients with lesion in eloquent brain areas. *Minim Invasive Neurosurg* 2002; **45:** 151–53.
66 Firsching R, Bondar I, Heinze HJ, et al. Practicability of magnetoencephalography-guided neuronavigation. *Neurosurg Rev* 2002; **25:** 73–78.
67 Coenen VA, Krings T, Mayfrank L, et al. Three-dimensional visualization of the pyramidal tract in a neuronavigation system during brain tumour surgery: first experiences and technical note. *Neurosurgery* 2001; **49:** 86–92.
68 Stadlbauer A, Moser E, Gruber S, Nimsky C, Fahlbusch R, Ganslandt O. Integration of biochemical images of a tumour into frameless stereotaxy achieved using a magnetic resonance imaging/magnetic resonance spectroscopy hybrid data set. *J Neurosurg* 2004; **101:** 287–94.
69 Sabbah P, Foehrenbach H, Dutertre G, et al. Multimodal anatomic, functional and metabolic brain imaging for tumour resection. *Clin Imaging* 2002; **26:** 6–12.
70 Nimsky C, Ganslandt O, Fahlbusch R. Functional neuronavigation and intraoperative MRI. *Adv Tech Stand Neurosurg* 2004; **29:** 229–63.
71 Gumprecht HK, Widenka DC, Lumenta CB. BrainLab VectorVision neuronavigation system: technology and clinical experience in 131 cases. *Neurosurgery* 1999; **44:** 97–105.
72 Reinges MH, Nguyen HH, Krings T, Hutter BO, Rohde V, Gilsbach JM. Course of brain shift during microsurgical resection of supratentorial cerebral lesions: limits of conventional neuronavigation. *Acta Neurochir (Wien)* 2004; **146:** 369–77.
73 Keles GE, Lamborn KR, Berger MS. Coregistration accuracy and detection of brain shift using intraoperative sononavigation during resection of hemispheric tumours. *Neurosurgery* 2003; **53:** 556–64.
74 Platenik LA, Miga MI, Roberts DW, et al. In vivo quantification of retraction deformation modeling for updated image-guidance during neurosurgery. *IEEE Trans Biomed Eng* 2002; **49:** 823–35.
75 Keles GE. Intracranial neuronavigation with intraoperative magnetic resonance imaging. *Curr Opin Neurol* 2004; **17:** 497–500.
76 Bradley WG. Achieving gross total resection of brain tumours: intraoperative MR imaging can make a big difference. *Am J Neuroradiol* 2002; **23:** 348–49.
77 Liu H, Hall WA, Truwit CL. The roles of functional MRI in MR-guided neurosurgery in a combined 1·5 Tesla MR-operating room. *Acta Neurochir Suppl* 2003; **85:** 127–35.
78 Nimsky C, Ganslandt O, Hastreiter P, et al. Intraoperative diffusion-tensor MR imaging: shifting of white matter tracts during neurosurgical procedures. Initial experience. *Radiology* 2005; **234:** 218–25.
79 Keles GE, Berger MS. Advances in neurosurgical technique in the current management of brain tumours. *Semin Oncol* 2004; **31:** 659–65.
80 Neuloh G, Pechstein U, Cedzich C, Schramm J. Motor evoked potential monitoring with supratentorial surgery. *Neurosurgery* 2004; **54:** 1061–70.
81 Romstöck J, Fahlbusch R, Ganslandt O, Nimsky C, Strauss C. Localisation of the sensorimotor cortex during surgery for brain tumours: feasibility and waveform patterns of somatosensory evoked potentials. *J Neurol Neurosurg Psychiatry* 2002; **72:** 221–29.
82 Cedzich C, Taniguchi M, Schäfer S, Schramm J. Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region: technical application. *Neurosurgery* 1996; **38:** 962–71.
83 Wiedemayer H, Sandalcioglu IE, Armbruster W, Regel J, Schafer H, Stolke D. False negative findings in intraoperative SEP monitoring: analysis of 658 consecutive neurosurgical cases and review of published reports. *J Neurol Neurosurg Psychiatry* 2004; **75:** 280–86.
84 Ikeda A, Miyamoto S, Shibasaki H. Cortical motor mapping in epilepsy patients: information from subdural electrodes in presurgical evaluation. *Epilepsia* 2002; **43** (suppl)**:** S56–60.

85 Lesser RP, Arroyo S, Crone N, Gordon B. Motor and sensory mapping of the frontal and occipital lobes. *Epilepsia* 1998; **39** (suppl)**:** S69–80.

86 Chitoku S, Otsubo H, Harada Y, et al. Extraoperative cortical stimulation of motor function in children. *Pediatr Neurol* 2001; **24:** 344–50.

87 Onal C, Otsubo H, Araki T, et al. Complications of invasive subdural grid monitoring in children with epilepsy. *J Neurosurg* 2003; **98:** 1017–26.

88 Berger MS, Rostomily RC. Low-grade gliomas: functional mapping resection strategies, extent of resection, and outcome. *J Neurooncol* 1997; **34:** 85–101.

89 Duffau H, Capelle L, Sichez JP, et al. Intraoperative direct electrical stimulations of the central nervous system: the Salpêtrière experience with 60 patients. *Acta Neurochir (Wien)* 1999; **141:** 1157–67.

90 Nikas DC, Danks RA, Black PM. Tumor surgery under local anesthesia. in Loftus CM, Batjer HH, eds. Techniques in Neurosurgery. Philadelphia: Lippincott Williams & Wilkins, 2001: 70–84.

91 Taylor MD, Bernstein M. Awake craniotomy with brain mapping as a routine surgical approach to treating patients with supratentorial intraaxial tumours: a prospective trial of 200 cases. *J Neurosurg* 1999; **90:** 35–41.

92 Whittle IR, Borthwick S, Haq N. Brain dysfunction following 'awake' craniotomy, brain mapping and resection of glioma. *Br J Neurosurg* 2003; **17:** 130–37.

93 Duffau H, Capelle L, Sichez N, et al. Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 2002; **125:** 199–214.

94 Ojemann GA, Ojemann JG, Lettich E, Berger MS. Cortical language localization in left, dominant hemisphere: an electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 1989; **71:** 316–26.

95 Duffau H. Intraoperative direct subcortical stimulation for identification of the internal capsule, combined with an image-guided stereotactic system during surgery for basal ganglia lesions. *Surg Neurol* 2000; **53:** 250–54.

96 Duffau H, Capelle L, Denvil D, et al. Usefulness of intraoperative electrical sub-cortical mapping in surgery of low-grade gliomas located within eloquent regions: functional results in a consecutive series of 103 patients. *J Neurosurg* 2003; **98:** 764–78.

97 Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS. Intraoperative subcortical stimulation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. *J Neurosurg* 2004; **100:** 369–75.

98 Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR. Functional cortex and subcortical white matter located within gliomas. *Neurosurgery* 1996; **38:** 678–84.

99 Duffau H, Capelle L, Denvil D, et al. The role of dominant premotor cortex in language: a study using intraoperative functional mapping in awake patients. *Neuroimage* 2003; **20:** 1903–14.

100 Duffau H, Capelle L, Lopes M, Faillot T, Sichez JP, Fohanno D. The insular lobe: physiopathological and surgical considerations. *Neurosurgery* 2000; **47:** 801–10.

101 Duffau H, Velut S, Mitchell MC, Gatignol P, Capelle L. Intra-operative mapping of the subcortical visual pathways using direct electrical stimulations. *Acta Neurochir (Wien)* 2004; **146:** 265–69.

102 Duffau H, Gatignol P, Denvil D, Lopes M, Capelle L. The articulatory loop: study of the subcortical connectivity by electrostimulation. *Neuroreport* 2003; **14:** 2005–08.

103 Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain* 2005; **128:** 797–810.

104 DeAngelis LM. Brain tumours. *N Engl J Med* 2001; **344:** 114–23.

105 Fandino J, Kollias SS, Wieser HG, Valavanis A, Yonekawa Y. Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumours involving the primary motor cortex. *J Neurosurg* 1999; **91:** 238–50.

106 Carpentier AC, Constable RT, Schlosser MJ, et al. Patterns of functional magnetic resonance imaging activation in association with structural lesions in the rolandic region: a classification system. *J Neurosurg* 2001; **94:** 946–54.

107 Schiffbauer H, Ferrari P, Rowley HA, Berger MS, Roberts TP. Functional activity within brain tumours: a magnetic source imaging study. *Neurosurgery* 2001; **49:** 1313–20.

108 Wunderlich G, Knorr U, Herzog H, Kiwit JC, Freund HJ, Seitz RJ. Precentral glioma location determines the displacement of cortical hand representation. *Neurosurgery* 1998; **42:** 18–27.

109 Thiel A, Herholz K, Koyuncu A, et al. Plasticity of language networks in patients with brain tumours: a positron emission tomography activation study. *Ann Neurol* 2001; **50:** 620–29.

110 Holodny AI, Schulder M, Ybasco A, Liu WC. Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. *J Comput Assist Tomogr* 2002; **26:** 941–43.

111 Taniguchi M, Kato A, Ninomiya H, et al. Cerebral motor control in patients with gliomas around the central sulcus studied with spatially filtered magnetoencephalography. *J Neurol Neurosurg Psychiatry* 2004; **75:** 466–71.

112 Heiss WD, Thiel A, Kessler J, Herholz K. Disturbance and recovery of language function: correlates in PET activation studies. *Neuroimage* 2003; **20** (suppl)**:** S42–49.

113 Branco DM, Coelho TM, Branco BM, et al. Functional variability of the human cortical motor map: electrical stimulation findings in perirolandic epilepsy surgery. *J Clin Neurophysiol* 2003; **20:** 17–25.

114 Duffau H. Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping. *J Neurol Neurosurg Psychiatry* 2001; **70:** 506–13.

115 Duffau H, Capelle L. Functional recuperation after resection of gliomas infiltrating primary somatosensory fields: study of intraoperative electric stimulation. *Neurochirurgie* 2001; **47:** 534–41.

116 Duffau H. Recovery from complete hemiplegia following resection of a retrocentral metastasis: the prognostic value of intraoperative cortical stimulation. *J Neurosurg* 2001; **95:** 1050–52.

117 Krainik A, Duffau H, Capelle L, et al. Role of the healthy hemisphere in recovery after resection of the supplementary motor area. *Neurology* 2004; **62:** 1323–32.

118 Picard N, Strick PL. Imaging the premotor areas. *Curr Opin Neurobiol* 2001; **11:** 663–72.

119 Duffau H, Capelle L. Preferential brain locations of low-grade gliomas. *Cancer* 2004; **100:** 2622–26.

120 Laplane D, Talairach J, Meininger V, Bancaud J, Orgogozo JM. Clinical consequences of corticectomies involving the supplementary motor area in man. *J Neurol Sci* 1977; **34:** 301–14.

121 Duffau H, Lopes M, Denvil D, Capelle L. Delayed onset of the supplementary motor area syndrome after surgical resection of the mesial frontal lobe: a time course study using intraoperative mapping in an awake patient. *Stereotact Funct Neurosurg* 2001; **76:** 74–82.

122 Krainik A, Lehéricy S, Duffau H, et al. Postoperative speech disorder after medial frontal surgery: role of the supplementary motor area. *Neurology* 2003; **60:** 587–94.

123 Fontaine D, Capelle L, Duffau H. Somatotopy of the supplementary motor area: evidence from correlation of the extent of surgical resection with the clinical patterns of deficit. *Neurosurgery* 2002; **50:** 297–303.

124 Ackermann H, Riecker A. The contribution of the insula to motor aspects of speech production: a review and a hypothesis. *Brain Lang* 2004; **89:** 320–28.

125 Duffau H, Capelle L, LopesM, BitarA, SichezJP, Van Effenterre R. Medically intractable epilepsy from insular low-grade gliomas: improvement after an extended lesionectomy. *Acta Neurochir (Wien)* 2002; **144:** 563–73.

126 Duffau H, Fontaine D. Successful resection of a left insular cavernous angioma using neuronavigation and intraoperative language mapping. *Acta Neurochir (Wien)* 2005; **147:** 205–08.

127 Dronkers NF. A new brain region for coordinating speech articulation. *Nature* 1996; **384:** 159–61.

128 Duffau H, Karachi C, Gatignol P, Capelle L. Transient Foix-Chavany-Marie syndrome following surgerical resection of a right insulo-opercular low-grade glioma: case report. *Neurosurgery* 2003; **53:** 426–31.

129 Le Roux PD, Berger MS, Haglund MM, Pilcher WH, Ojemann GA. Resection of intrinsic tumours from nondominant face motor cortex using stimulation mapping: report of two cases. *Surg Neurol* 1991; **36:** 44–48.

130 Duffau H, Denvil D, Capelle L. Absence of movement disorders after surgical resection of glioma invading the right striatum. *J Neurosurg* 2002; **97:** 363–69.

131 Gil Robles S, Gatignol P, Capelle L, Mitchell MC, Duffau H. The role of dominant striatum in language: a study using intraoperative electrical stimulations. *J Neurol Neurosurg Psychiatry* 2005; **76:** 940–46

132 Duffau H, Khalil I, Gatignol P, Denvil D, Capelle L. Surgical removal of corpus callosum infiltrated by low-grade glioma: functional outcome and oncological considerations. *J Neurosurg* 2004; **100:** 431–37.

133 Milea D, Lobel E, Lehéricy S, et al. Intraoperative frontal eye field stimulation elicits ocular deviation and saccade suppression. *Neuroreport* 2002; **13:** 1359–64.

134 Duffau H, Denvil D, Lopes M, et al. Intraoperative mapping of the cortical areas involved in multiplication and subtraction: an electrostimulation study in a patient with a left parietal glioma. *J Neurol Neurosurg Psychiatry* 2002; **73:** 733–38.

135 Gatignol P, Capelle L, Le Bihan R, Duffau H. Double dissociation between picture naming and comprehension: an electrostimulation study. *Neuroreport* 2004; **15:** 191–95.

136 Roux FE, Boetto S, Sacko O, Chollet F, Tremoulet M. Writing, calculating, and finger recognition in the region of the angular gyrus: a cortical stimulation study of Gerstmann syndrome. *J Neurosurg* 2003; **99:** 716–27.

137 Roux FE, Lubrano V, Lauwers-Cances V, Tremoulet M, Mascott CR, Demonet JF. Intra-operative mapping of cortical areas involved in reading in mono- and bilingual patients. *Brain* 2004; **127:** 1796–810.

138 Duffau H, Denvil D, Capelle L. Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy. *J Neurol Neurosurg Psychiatry* 2002; **72:** 511–16.

139 Duffau H, Lopes M, Arthuis F, et al. Contribution of intraoperative electrical stimulations in surgery of low-grade gliomas: a comparative study between two series without (1985–1996) and with (1996–2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry* 2005; **76:** 845–51.

140 Brell M, Ibanez J, Caral L, et al. Factors influencing surgical complications of intra-axial brain tumours. *Acta Neurochir (Wien)* 2000; **142:** 739–50.

141 Sawaya R, Hammoud M, Schoppa D, et al. Neurological outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumours. *Neurosurgery* 1998; **42:** 1044–56.

142 Keles GE, Lamborn KR, Berger MS. Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. *J Neurosurg* 2001; **95:** 735–45.

143 Whittle IR. The dilemma of low-grade glioma. *J Neurol Neurosurg Psychiatry* 2004; **75:** 31–36.

144 Lo SS, Cho KH, Hall WA, et al. Does the extent of surgery have an impact on the survival of patients who receive postoperative radiation therapy for supratentorial low-grade gliomas? *Int J Cancer* 2001; **96:** 71–78.

145 Nakamura M, Konishi N, Tsunoda S, et al. Analysis of prognostic and survival factors related to treatment of low-grade astrocytomas in adults. *Oncology* 2000; **58:** 108–16.

146 Scerrati M, Roselli R, Iacoangeli M, Pompucci A, Rossi GF. Prognostic factors in low grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery. *J Neurol Neurosurg Psychiatry* 1996; **61:** 291–96.

147 Berger MS, Deliganis AV, Dobbins JD, Keles GE. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. *Cancer* 1994; **74:** 1784–91.

148 Capelle L, Duffau H, Lopes M, et al. Supra-tentorial hemispheric WHO grade 2 gliomas in adults: a study of prognostic factors with special emphasis on the role of surgery. *J Neuro-oncol* 2002; **4** (suppl): S17, 69.

149 Claus EB, Horlacher A, Hsu L, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. *Cancer* 2005; **103:** 1227–33.

150 Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol* 2004; **3:** 159–68.