PAPER

Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy

H Duffau, D Denvil, L Capelle

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See end of article for authors' affiliations

Correspondence to: Dr H Duffau, Service de Neurochirurgie, Hôpital de la Salpêtrière, 47 Bd de l'hôpital, 75651 Paris, Cedex 13, France; hugues.duffau@psl.ap-hop-paris.fr

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Objectives: To describe cortical reorganisation and the effects of glioma infiltration on local brain function in three patients who underwent two operations 12–24 months apart.

Methods: Three patients who had no neurological deficit underwent two operations for low grade glioma, located in functionally important brain regions. During each operation, local brain function was characterised by electrical mapping and awake craniotomy.

Results: Language or sensorimotor areas had been invaded by the tumour at the time of the first operation, leading to incomplete glioma removal in all cases. Because of a tumour recurrence, the patients were reoperated on between 12 and 24 months later. Functional reorganisation of the language, sensory, and motor maps was detected by electrical stimulation of the brain, and this allowed total glioma removal without neurological sequelae.

Conclusions: These findings show that surgical resection of a glioma can lead to functional reorganisation in the peritumorous and infiltrated brain. It may be that this reorganisation is directly or indirectly caused by the surgical procedure. If this hypothesis is confirmed by other studies, the use of such brain plasticity potential could be used when planning surgical options in some patients with low grade glioma. Such a strategy could extend the limits of tumour resection in gliomas involving eloquent brain areas without causing permanent morbidity.

Lack of neurological deficit with either congenital or slow growing lesions such as low grade gliomas is often found. The hypothesis of compensatory recruitment of local or distant functional networks has been suggested by many authors.[1–10] This functional reorganisation should allow total removal of these lesions without inducing any neurological sequelae. However, it has been reported that functional tissue can be still detected within infiltrative tumours,[11 12] often resulting in an incomplete resection of the lesion.

We describe three cases of functional redistribution, demonstrated using intraoperative corticosubcortical stimulation mapping, which occurred between two consecutive operations performed in patients harbouring low grade gliomas. Tumour resection was incomplete during the first procedure due to infiltration of functionally important areas. Tumour recurrence and a total removal, performed 1 to 2 years later, showed that functional reorganisation had occurred.

MATERIALS AND METHODS

Three right handed patients (28, 35, and 45 years old) underwent surgery in our institution for a brain lesion discovered after seizures. Neurological examination performed by a neurologist (DD) was normal in all patients. All lesions had radiological features of low grade glioma on MRI. One tumour had a left temporal location, the second was right retrocentral, and the third left precentral.

All surgical procedures were conducted using intraoperative functional mapping with direct corticosubcortical stimulations in awake patients. The method for brain stimulations used a 5 mm bipolar stimulator probe (Ojemann Cortical Stimulator, Radionics), as previously described.[13] Stimulation parameters were set at 60 Hz, biphasic square wave pulses (1 ms/phase), with a progressive increase of the current amplitude (from 2 mA) until a motor and/or sensory response was obtained, or a language disturbance was induced. Intraoperative speech assessment included counting (used to assess articulation) and language was assessed by picture naming.[14 15] Resection was then performed sparing the functional areas detected by corticosubcortical stimulations. The interface between lesion and functional areas were precisely defined. In addition, the tumour boundaries were identified during the procedure using serial ultrasonographies.

Immediate and delayed postoperative MRI were performed to evaluate the extent of tumour removal.

RESULTS

In the first patient, with a left temporal low grade glioma (fig 1 A), intraoperative mapping during the first procedure identified three inferofrontal areas inducing speech arrest when stimulated, and two mid-temporal language sites eliciting anomia during each stimulation (intensity of 5 mA, fig 1 B). These two naming areas constituted the posterior boundary of the resection, but were nevertheless invaded by the posterior part of the glioma, and consequently not removed (fig 1 C). The postoperative MRI confirmed the subtotal resection, with less than 10 ml residual glioma at the posterior extent of the cavity. The patient initially had a complete aphasia for 5 days, which then recovered spontaneously. A severe anomia persisted for 1 month. All these symptoms disappeared within 2 months (table 1). The histological diagnosis disclosed a World health Organisation (WHO) II oligodendroglioma. No radiotherapy was performed. Despite no clinical deterioration, tumour regrowth was noted 18 months later on MRI. A second operation was performed, firstly to check the histopathology (whether there had been anaplastic transformation), and secondly to attempt a complete resection. Surprisingly, although the same frontal speech arrest areas were identified during stimulations (same intensity of 5 mA), the two naming language sites detected during the first procedure were not

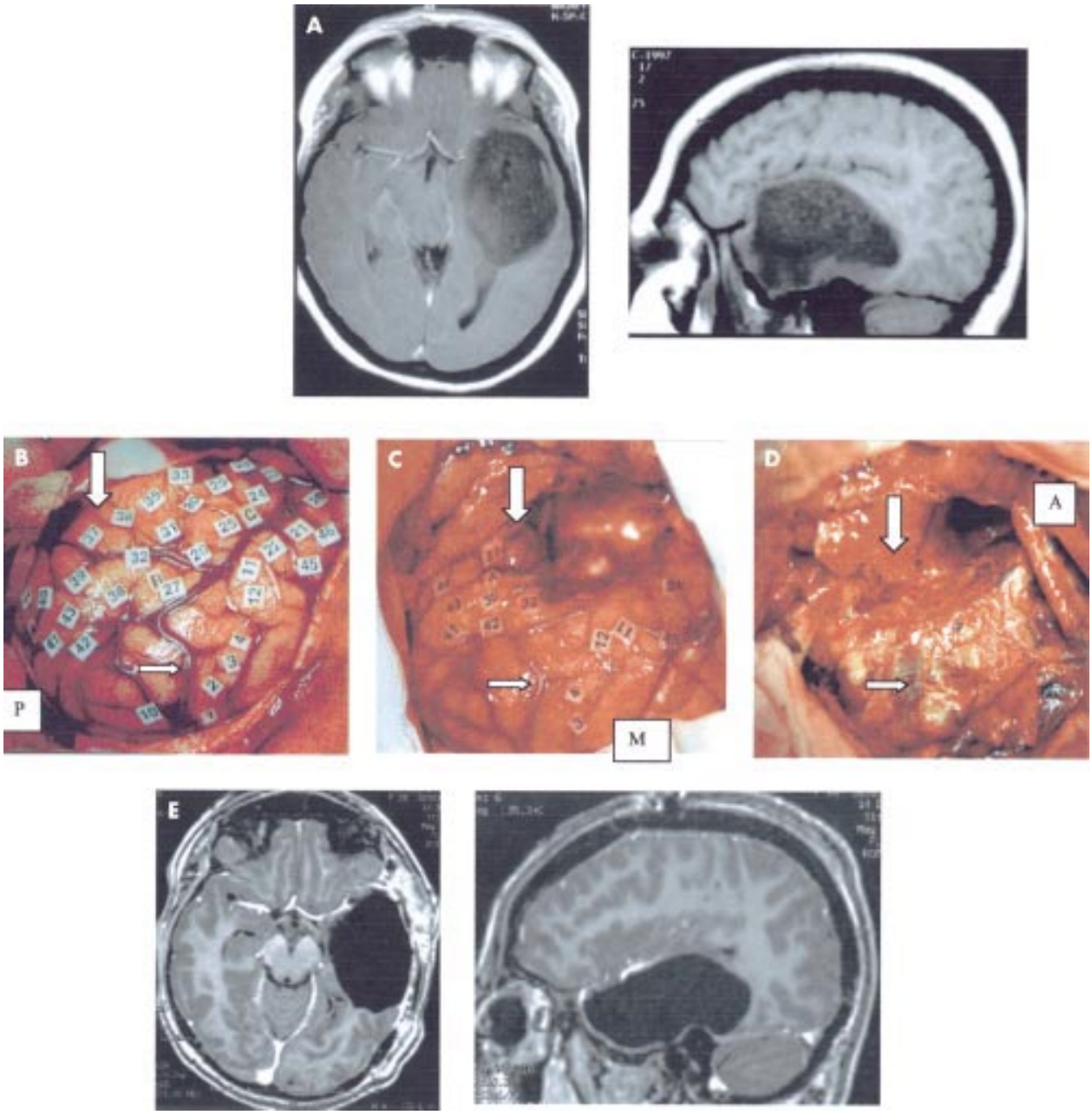

Figure 1 (A) Preoperative T1 weighted axial and sagittal MRI showing a left (dominant hemisphere) temporal low grade glioma in a patient without any neurological deficit. (B) Intraoperative photograph before resection. The functional mapping under local anaesthesia allowed detection of the following sites: 1, 2, 3, and 4, motor areas; 10, somatosensory area; 11, 12, and 21, language areas, with speech arrest during stimulations; 37 and 38, language areas with anomia induced by stimulations. Tumour boundaries (A, B, C) were identified with ultrasonography. Small arrow, central sulcus; large arrow, functional boundaries; P, posterior. (C) Intraoperative view after the first resection. The same motor and language sites were found using the same electrical parameters. For technical reasons, tag 27 was used instead of the tag 37, and tag 32 was used instead of the tag 27, but indicates the same language naming area, as confirmed by repeated stimulations. Because of glioma infiltration of the two midtemporal naming sites 32 and 27, the tumour removal was stopped posteriorly and an incomplete resection was performed. Small arrow, central sulcus; large arrow, functional boundary of resection; M, midline. (D) Intraoperative view after the second resection 18 months later, decided because of tumour recurrence. No language site was detected in the temporal lobe with electrical brain stimulations. A total glioma removal was then performed. At the end of the temporal resection, functional mapping was again realised: stimulations on the left insular cortex induced speech arrest. Small arrow, central sulcus; large arrow, functional boundary of the first resection; A, anterior. (E) Postoperative axial and sagittal MRI, after the second operation, showing a total glioma resection. The patient was not clinically worse.

found at the posterior edge of the operative cavity, and no other critical language area was identified in the exposed temporal region, even when the intensity of stimulation was increased (until 10 mA) (fig 1 D). These changes in distribution of language function allowed a total glioma removal—that is, with a resection of the left temporal lobe extended 2 cm more posteriorly than during the first operation, without producing any functional language deficit. At the end of the tumour removal, the left insular cortex was exposed and elicited anomia during stimulations (at 5 mA of intensity). The patient had no postoperative language deficit. Postoperative MRI confirmed complete resection (fig 1 E).

In the second patient, harbouring a right retrocentral glioma (fig 2 A), brain stimulations during the first operation

Table 1 Clinical outcome of the three patients

Patients	Glioma location	Preoperative neurological examination	Neurological examination after the first surgery	Outcome	Neurological examination after the second surgery	Outcome
Female 28 years old	Left temporal	Normal	Complete aphasia during 5 days	Recovery of speech within 1 week Anomia during 2 months then recovery	No aphasia MMSE=30/30 No other deficit	Return to normal life Follow up 2 y
Male 35 years old	Right retrocentral	Normal	Severe sensory loss (face, left upper limb)	Recovery within 3 months Persistence of slight paraesthesia	Transient increase of the subjective paraesthesia only	Return to normal life Follow up 1 y
Female 45 years old	Left precentral	Normal	Right upper limb paresis 3/5	Recovery within 1 month	No motor worsening (5/5) No other somatosensory or cognitive deficit (MMSE=30/30)	Return to normal life Follow up 2.5 y

MMSE, minimental state examination.

identified motor and sensory sites at a 5 mA current intensity. Two lateral suprasylvian primary somatosensory retrocentral areas (one of the face, one of the hand) were preserved, but were invaded by the tumour (fig 2 B). The patient nevertheless postoperatively had severe sensory loss of the face and the left upper limb, and was unable to reach and grasp during the first month postoperatively (table 1). By 3 months, clinical examination showed no objective deficit, except slight paraesthesis. Despite an incomplete tumour removal, as confirmed on the postoperative MRI, no additional treatment was given, as the tumour was a WHO II oligodendroglioma. As in the first patient, glioma regrowth demonstrated on repeat MRI 1 year later led to a second operation. Brain stimulations performed under the same conditions allowed identification of the primary motor and somatosensory sites using the same current parameters (intensity of 5 mA). Interestingly, the two lateral suprasylvian retrocentral face and hand somatosensory areas were not found, even with an increased intensity of stimulation (until 10 mA). More medially, hand sensory sites were still identifiable. The resection of the entire residual tumour was then performed, with anterior corticosubcortical boundaries represented by motor structures, and lateral limit constituted by the hand sensory areas (fig 2 C). Tumour removal was complete on postoperative MRI (fig 2 D). The patient had no clinical worsening after the second procedure. However, the patient noted a slight increase in the paraesthesis during the initial postoperative month.

In the third patient, with a left precentral low grade glioma, intraoperative mapping showed that the posterior part of the tumour involved the primary motor area of the hand (detected using a current intensity of 4 mA). The resection was then incomplete, as confirmed on the control MRI (fig 3 A). The patient had a postoperative right upper limb paresis (3/5), which completely recovered within 1 month (table 1). Histology disclosed an oligodendroglioma (WHO II), and no adjuvant treatment was made. Because of an increase of the volume of the residual glioma on repeated MRI, despite a normal clinical examination, a second operation was performed 24 months later. The goal was again to clarify tumour histology. Taking account of the location of the lesion in an eloquent region, debulking surgery using intraoperative brain mapping seemed preferable to a biopsy. Interestingly, intraoperative mapping showed that the primary motor areas of the hand were more posteriorly located than during the first procedure (with the same intensity of 4 mA). No motor site was found in the tumour, despite an increase of the current intensity up to 8 mA). The residual glioma was then removed while the patient continued to perform motor tasks with the right upper limb. Part of the precentral gyrus (its anterior half in front of the primary motor hand sites) was also resected (fig 3 B). The glioma was totally removed on the postoperative MRI (fig 3 C). The patient had no postoperative deficit.

All three patients returned to a normal socioprofessional life after the first and the second operations.

DISCUSSION

Although the concept of cerebral plasticity was suggested in 1929 by Bethe and Fischer,[16] this phenomenon did not generate much interest at that time. Development of non-invasive functional mapping methods in humans,[1 4 8–10 17 18] combined with advances in the field of animal experimental and laboratory investigations[7 19–21] have revived the study of compensatory mechanisms. The traditional teaching used to be that brain damage is irreversible, however this classic view has been cast aside because of accumulating evidence that the brain is endowed with remarkable plasticity. Redistribution of functional areas using essentially functional neuroimaging techniques has been reported in cases of stroke,[1 9 17 22] congenital malformations,[5 18] brain injury,[23] growing tumours,[3 8 10] and in modification of sensory input,[24] phantom limb,[25] or after digital surgery.[26] However, most of these works were purely descriptive, performed with the aim of a better understanding of the plasticity mechanisms. Some institutions have begun to try to use this plasticity, by inducing functional redistribution by training after brain lesions.[27]

In the present report, we first noticed the reshaping of motor, sensory, and language maps after a first brain operation. This reorganisation was established using the method of electrical stimulation, which constitutes an accurate (5 mm) and reliable technique of brain mapping.[3 12 14 15 28] Indeed, we previously reported that during the same surgical procedure, a repeated stimulation of exactly the same area (marked by a sterile tag) always gave the same results, whereas the stimulation 5 mm away from the first point generated a different result.[13 29 30] These findings were confirmed in the three patients of the present study. Moreover, to be sure that the same sites were stimulated during two consecutive operations, the residual tumour itself was used as a landmark—as functional areas were detected within the lesion not removed during the first procedure.

Secondly, the authors used this redistribution of essential eloquent sites to perform a more extensive resection during the second procedure, allowing a total tumour removal not attainable at the first operation. The precise mechanism of functional redistribution remains unclear. However, two hypothesis can be suggested.

Firstly, modification in the spatial enlargement and infiltrative behaviour of the tumour induced by surgery. Indeed, it is known that despite the fact that gliomas may generate peritumorous functional reorganisation allowing absence of neurological deficit,[3 8 10 28] it remains possible to find eloquent tissue in the tumour.[11 12] The present work confirms these findings, as electrical stimulations of a part of the parenchyma involved by the tumour during the first operation systematically induced transient language disturbances or sensorimotor responses. This phenomenon is likely explained by the type III spatial configuration of the low grade oligodendroglioma described by Daumas-Duport *et al*,[31]—that is, with isolated tumorous

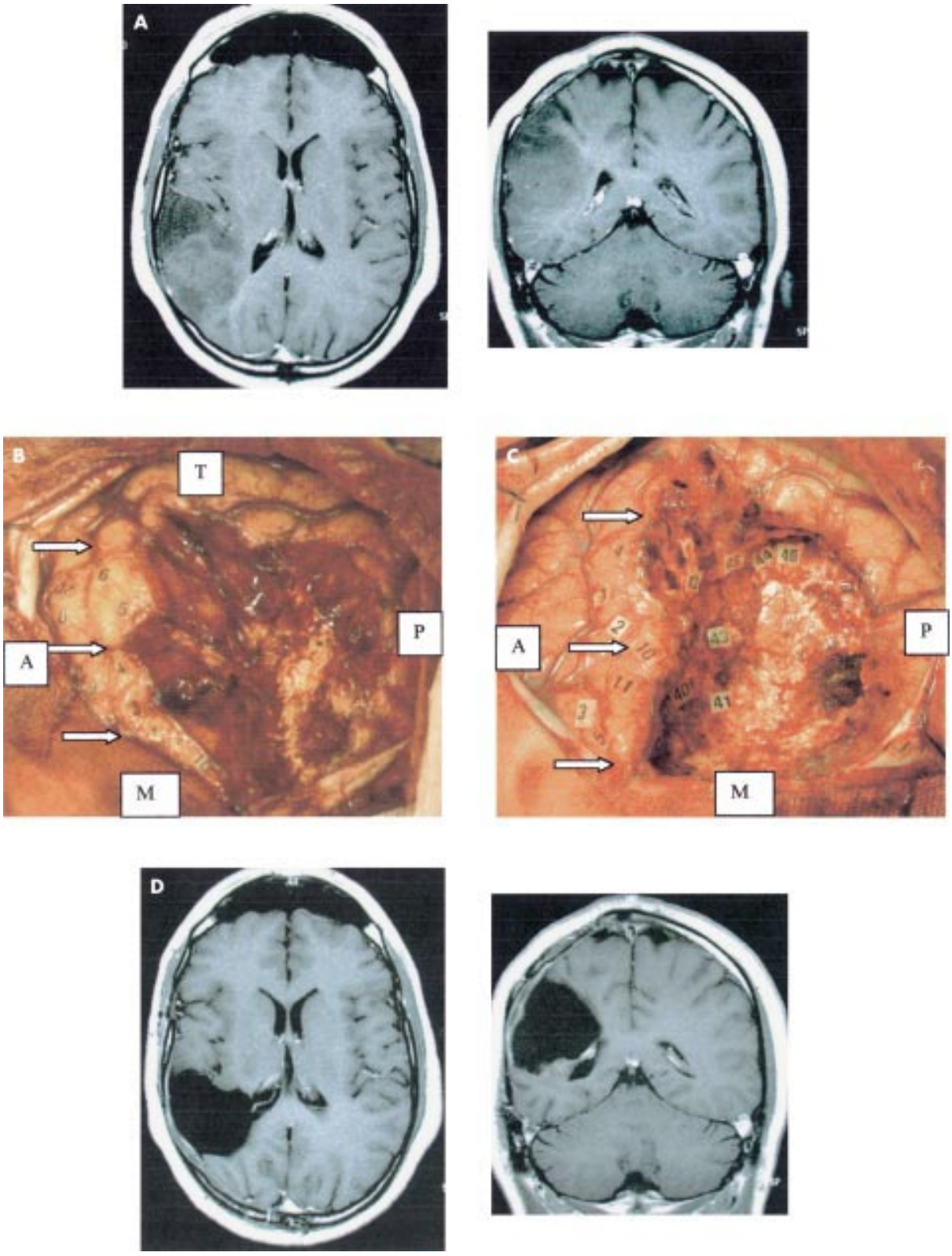

Figure 2 (A) Preoperative T1 weighted axial and coronal MRI showing a suprasylvian retrocentral low grade glioma in a patient without any neurological deficit. (B) Intraoperative photograph after the first resection. The functional mapping under local anaesthesia allowed the detection of suprasylvian primary somatosensory sites of the face (6), and of the whole left hand (5), behind the central sulcus (arrow): although these two areas were invaded by the tumour, they were preserved during resection. The other sensory sites of the fingers were 4, 3, and 1 and the forearm more medially (10). The primary motor sites were also detected: the face (7), the hand (8), and the wrist (9). A, anterior; P, posterior; M, midline; T, temporal lobe. (C) Intraoperative view after the second resection. Interestingly, the suprasylvian part of the retrocentral gyrus corresponding to the sensory sites 6 and 5 identified during the first procedure were still not detected: the resection was then conducted into the contact with the primary motor sites of the face (4), the hand (1), the wrist (2), and their subcortical pyramidal pathways (respectively tags 45, 44, and 43). The only primary sensory sites (of the hand and the fingers) detected were located in 10 and 11, behind the central sulcus (arrow). The corresponding pathways were found in 41 and 45, behind the corticospinal fibres. It should be noted that 3 and 5 show motor areas of the forearm and arm, more medially (M). A, anterior; P, posterior. (D) Postoperative axial and coronal MRI, after the second operation, showing a total glioma resection. The patient showed no clinical worsening.

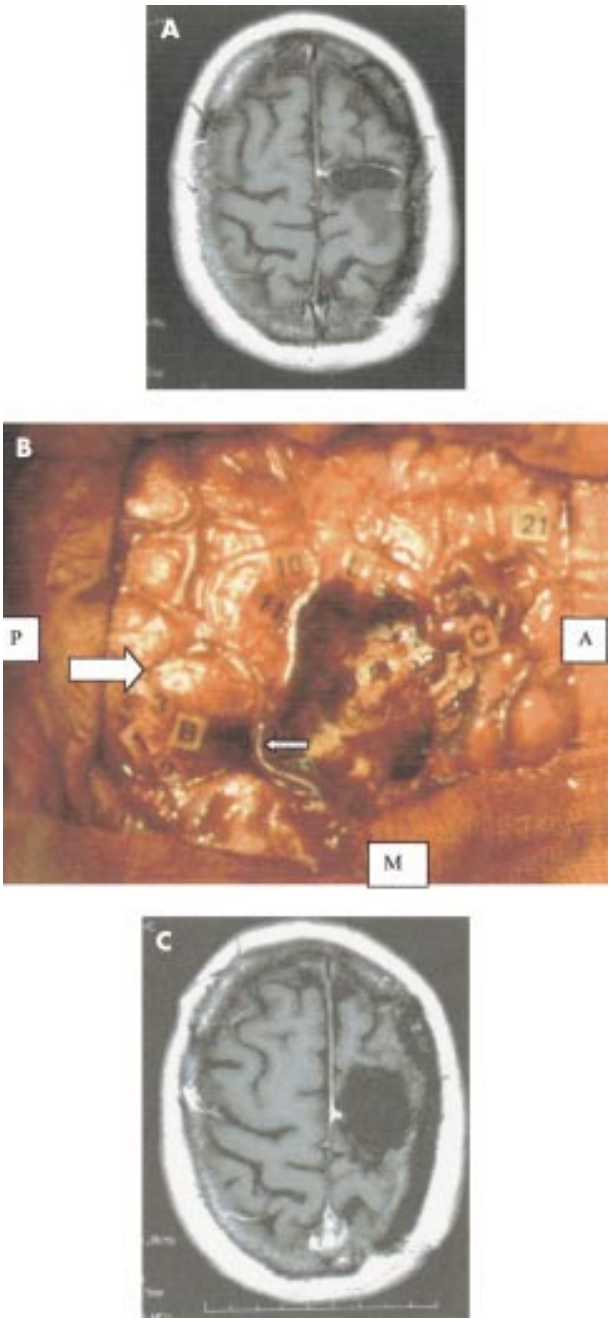

Figure 3 (A) T1 weighted axial MRI after the first resection of a left precentral low grade glioma showing a residual tumour within the primary motor area of the hand. The patient presented a transient right upper limb paresis, which completely recovered. (B) Intraoperative photograph after the second resection. The functional mapping under local anaesthesia allowed identification of the primary motor sites of the right hand and fingers (2, 1, and 3) located in the posterior half of the precentral gyrus (although they were detected in the precentral sulcus during the first procedure). The residual glioma was then resected within the anterior half of the precentral gyrus, from the precentral vein (small arrow) to the posterior part of the glioma (B), in contact with the redistributed motor areas. It should be noted that the dominant face motor sites, inducing speech arrest when stimulated (10, 11), and the naming area (21) located more anteriorly and inferiorly. A, anterior; P, posterior; M, midline; large arrow, central sulcus. (C) Postoperative axial MRI, after the second operation, showing a total glioma removal, with resection of a part of the precentral gyrus. The patient was not clinically worse.

cells able to infiltrate adjacent brain tissue without loss of essential connections or of function. It could be suggested that after the first resection, the growing pattern of the residual tumour was modified, particularly in its direction or extent, as it is well known that glioma recurrence usually takes place in the adjacent brain tissue and not in the cavity (a finding confirmed in our experience). Due to the fact that the residual tumour corresponded to the part of the lesion invading the functional areas, a tumour regrowth in this region, "selected" by the first operation (there was no recurrence at the other margins of the cavity in the three patients) could prevent the eloquent site still in the lesion to continue functioning normally. To maintain a normal function, peritumorous parallel networks were likely recruited, as previously described in slow growing lesions,[4 32] and as illustrated in our work during the second intraoperative mapping showing a high concentration of sensorimotor sites surrounding the tumour in the two patients with central lesion. Moreover, plasticity phenomena involving remote sites might have been induced to compensate language: either ispsilateral regions[33] or homotopic areas in the contralateral hemisphere as previously suggested in cases of recovery of language after lesions of eloquent regions.[6 34] Nevertheless, intraoperative electrical mapping allows performance of locoregional mapping. Consequently, an improvement of the understanding of plasticity mechanisms may necessitate the utilisation of postoperative functional neuroimaging.

Secondly, the surgery itself may directly induce the plasticity. One explanation could be that the type III spatial configuration of the glioma[31] implied that its resection (even incomplete in an essential functional area) also involved part of "non-eloquent" neural tissue (for which stimulations produce neither positive or negative signs).[6] However, although all essential functional sites (not compensable) were detected and surgically preserved using direct electrical stimulations,[3 13–15 28] it can be hypothesised that other sites not indispensable (compensable) but contributing to the function (excitatory or inhibitory networks) were not spared by the resection. This could explain the transient language, sensory, or motor deficit after the first operation, with secondary recovery due to compensatory mechanisms.

Moreover, the surgical act itself should be considered as a brain injury, and could induce GABAergic inhibition and NMDA receptor mediated excitation in the vicinity of the cavity, that might support synaptic plasticity and reorganisation by facilitating heterosynaptic long term potentiation-like mechanisms.[20] These changes in local synaptic properties may potentially lead to the unmasking of pre-existent locoregional functional sites, as already reported using intraoperative stimulations,[2 34] or to the unmasking of long distance cortico-cortical connections.[7] Indeed, we previously stated that surgical resection in eloquent areas may induce acute reshaping of functional maps, with unmasking of local[35] or regional redundancies.[2] These short term redistribution mechanisms may explain the long term functional reshaping found in this work. Indeed, experimental studies in animals previously showed the possibility of reorganisation of somatosensory[36] and motor maps[37] after peripheral or cortical lesions. Moreover, it was demonstrated that this initial rapid reshaping, sometimes transient,[38] could be durable,[39] and even reinforced by the training.[40]

The goal is now to attempt to apply this knowledge, to predict the individual ability (and the limits) of plasticity (immediate and delayed) for each patient harbouring a brain tumour invading functional areas, to plan the optimal surgical strategy. The aim is to maximise the tumour resection without inducing any definitive deficit. In other words, the number of surgical procedures, their timing, and the amount of tumour removal during each operation should be estimated at the beginning of the treatment. However, our data do not allow us to know what would have happened if the operations had

been performed differently. For example, if a total tumour resection had been performed at the time of the first operation despite the evidence of functioning tissue within the margins of the glioma, the postoperative deficits may or may not have been worse, and the same degree of recovery may or may not have been found. Alternatively, if the initial resections have not gone so close to the functional boundaries, perhaps there would have been no postoperative deficits, but then at the second operation there would have been no change in the functional boundaries (no induced plasticity), and further resection at that point would have given the patient a neurological deficit (although possibly reversible). To better understand this potential for individual brain plasticity, a possible method of differentiating the essential functional areas from those compensable, could consist of the transient modulation of each site of the network identified with functional neuroimaging, using transcranial magnetic stimulations previously reported as able to excite or inhibit neural structures,[41] and to note the corresponding clinical consequences before the first operation, after the surgical resection (during the deficit and after recovery), and before the second operation.

Authors' affiliations
H Duffau, L Capelle, Department of Neurosurgery, Hôpital de la Salpêtrière, 47 Bd de l'hôpital, 75651 Paris, Cedex 13, France
D Denvil, Department of Neurology, Hôpital de la Salpêtrière

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