Intraoperative mapping of the subcortical language pathways using direct stimulations
An anatomo-functional study

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Summary
Functional neuroimaging has improved pre-planning of surgery in eloquent cortical areas, but remains unable to map white matter. Thus, tumour resection in functional subcortical regions still presents a high risk of sequelae. The authors successfully used intraoperative electrical stimulations to perform subcortical language pathway mapping in order to avoid postoperative definitive deficit, and correlated these functional findings with the anatomical location of the eloquent bundles detected using postoperative MRI. At the same time, this also improved knowledge of fibre connectivity. Thirty patients harbouring a cortico-subcortical low-grade glioma in the left dominant hemisphere were operated on whilst awake using intraoperative electrical functional mapping during surgical resection. Language cortical sites and subcortical pathways were clearly identified and preserved in the 30 cases. The anatomo-functional correlations between data obtained using intraoperative subcortical mapping and postoperative MRI revealed the existence in all patients of common pathways which seem essential to language. This was shown by inducing reproducible speech disturbances during stimulations as follows: the subcallosal fasciculus (initiation disorders), the periventricular white matter (dysarthria), the arcuate fasciculus and the insular connections (anomia). Clinically, all patients except three presented a transient postoperative dysphasia, which resolved within 3 months. On control MRI, 14 resections were total and 16 subtotal due to infiltration of functional bundles described above. It is recommended that the combination of the techniques as described could prove ideal for future non-invasive reliable subcortical mapping both in healthy volunteers and in patients harbouring a (cortico)subcortical lesion in order to optimize surgical pre-planning.

Keywords: intraoperative electrical stimulations; functional brain mapping; language; white matter; brain connectivity

Abbreviations: AF = arcuate fasciculus; F1 = superior frontal gyrus; F2 = median frontal gyrus; F3 = inferior frontal gyrus; PVWM = periventricular white matter; ScF = subcallosal fasciculus

Introduction
The development of functional neuroimaging methods has allowed more effective pre-planning of the neurosurgical procedures in eloquent (i.e. functional) brain areas during the last decade (Buchner et al., 1994; Morioka et al., 1994; Fried et al., 1995; Gallen et al., 1995; Nyberg et al., 1996; Hund et al., 1997; Alberstone et al., 2000). However, although these techniques nowadays can provide accurate functional mapping of the grey matter (cortex (Sanes et al., 1995; Yetkin et al., 1996; Lehéricy et al., 2000a) and basal ganglia (Lehéricy et al., 1998)), this is not the case for the white matter. Consequently, recent progress in anatomo-functional tracking of the organization of individual subcortical pathways is slow, particularly for those concerning language function, in spite of the development of diffusion-weighted MRI. This has been tested only recently for tracking of association fibres (Makris et al., 1997; Conturo et al., 1999). Thus, a surgical resection in functional regions conducted at the subcortical level still presents a high risk of neurological sequelae, despite the preservation of eloquent cortical structures.

The authors report first the intraoperative mapping of the white matter using direct electrical stimulations, focusing on
the language pathways: in a series of 30 patients operated on for a cortico-subcortical low-grade glioma invading language areas, the use of this method allowed us to minimize the definitive morbidity while increasing the quality of resection, which is known to improve the median survival in these tumours (Berger et al., 1994). Secondly, anatomo-functional correlations between the data of intraoperative subcortical mapping and those of postoperative anatomical MRI were studied, with the aim of improving knowledge on the subcortical connectivity, then of applying these results to future surgical interventions in eloquent white matter.

**Patients and methods**

Among a series of 140 patients operated on for a brain lesion in functional areas in our institution between November 1996 and July 2000, 30 right-handed patients harbouring a cortico-subcortical low-grade glioma located in language regions (left dominant hemisphere) were studied. The hemispheric dominance was defined using neuropsychological examination and functional MRI. The topography of the tumour was analysed accurately on a pre-operative MRI [SPGR in the three planes, with CA–CP (anterior–posterior commissure) as the reference plane].

All patients underwent surgery under local anaesthesia so that functional cortical and subcortical mapping could be carried out using direct brain stimulations. This method, including the electrical parameters and the intraoperative clinical tasks, was described previously by the authors (Duffau et al., 1999). Briefly, a bipolar electrode with 5 mm spaced tips delivering a biphasic current (pulse frequency of 60 Hz, single pulse phase duration of 1 ms, amplitude from 2 to 8 mA) (Ojemann Cortical Stimulator 1, Radionics*, Inc., Burlington, Mass., USA) was applied on the brain of awake patients.

In a first stage, cortical mapping was performed, after tumour identification using ultrasonography, and before resection, in order to avoid eloquent area damage. Sensorimotor mapping was performed first, to confirm a positive response (movement and/or paraesthesia). The bone flap allowed good exposure of at least a part of the central region in all patients. Then, the patient was asked to perform counting and naming tasks, in order to map the cortical language sites known to be inhibited by stimulations (i.e. inducing speech arrest, dysarthria or anomia) (Ojemann et al., 1989; Berger and Ojemann, 1992; Duffau and Capelle, 2000).

During a second surgical stage, the tumour was removed, by alternating resection and subcortical stimulations. The functional pathways were followed progressively from the cortical eloquent sites already mapped, to the depth of the resection. The patient had to continue to count or name when the resection became close to the subcortical language structures, which were also identified by speech inhibition during stimulations as at the cortical level (Skirboll et al., 1996). To perform the best possible tumour removal with preservation of the functional areas, all the resections were pursued until eloquent pathways were encountered around the surgical cavity, then followed according to functional boundaries (Fig. 1). Postoperative clinical outcome was assessed systematically by a neuropsychologist and/or a neurologist, both during the postoperative stage and 3 months after the surgery.

A control MRI was performed in all cases, immediately and 3 months after the surgery. This imaging allowed us first to evaluate the quality of glioma removal using the classification reported by Berger et al. (1994) (total resection, no visible residue; subtotal resection: <10 cm³ of residue; partial resection, >10 cm³ of residue) and secondly to analyse the anatomical location of the language pathways (at the periphery of the cavity, where the resection was stopped).

**Results**

The clinical, radiological and surgical characteristics of the 30 patients are summarized in Table 1.

**Clinical presentation**

The series consisted of 20 males and 10 females, ranging in age from 23 to 59 years (mean 41 years). All patients were right-handed, as assessed by neuropsychological examination and functional MRI (semantic fluency, story listening and
Table 1  Clinical, radiological and surgical characteristics of the 30 patients (20 M, 10 F, mean age: 41 years) with a glioma involving subcortical language pathways

<table>
<thead>
<tr>
<th>Glioma location (dominant hemisphere)</th>
<th>No. of cases</th>
<th>Subcortical anatomo-functional boundaries identified by stimulations intraoperatively (functional) and verified on post-operative MRI (anatomical)</th>
<th>Clinical results</th>
<th>Quality of resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 Precentral</td>
<td>18</td>
<td>Posteriorly: pyramidal pathways (8 cases) or language structures (10 cases) Laterally: ScF (anomia and reduction of spontaneous speech) Postero-laterally: PVWM (dysarthria)</td>
<td>18 immediate postoperative dominant SMA syndromes, with recovery within 3 months</td>
<td>Total (8 cases)</td>
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<td></td>
<td></td>
<td></td>
<td>Mild reduction of fluency in 3 cases</td>
<td>Subtotal (10 cases)</td>
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<tr>
<td>F2 Precentral</td>
<td>3</td>
<td>Medially: ScF (anomia and reduction of spontaneous speech) Laterally: subcortical pathways from Broca’s area (speech arrest) Posteriorly: language pathways, issuing from the primary cortical motor face area and joining the PVWM (dysarthria)</td>
<td>3 severe postoperative dysphasias and right central palsies, with complete recovery within 3 months</td>
<td>Subtotal (3 cases)</td>
</tr>
<tr>
<td>F3 Precentral</td>
<td>2</td>
<td>Medially: subcortical pathways from F2 language cortical sites (speech arrest) Posteriorly: language pathways, issuing from the primary cortical motor face area (dysarthria)</td>
<td>Normal examination in the 2 cases</td>
<td>Total (2 cases)</td>
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<tr>
<td></td>
<td></td>
<td>Deeply: insular cortex (speech arrest) and insulo-opercular connections (anomia)</td>
<td></td>
<td></td>
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<tr>
<td>Retrocentral supra-sylvian</td>
<td>3</td>
<td>Anteriorly: sensorimotor pathways joining the PVWM (dysarthria) Infero-laterally: language pathways issuing from the supramarginalis gyrus and joining the postero-superior part of the arcuate fasciculus (anomia)</td>
<td>6 postoperative somatosensory deficits and anomia with complete recovery within 3 months</td>
<td>Total (1 case)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 postoperative anomas with complete recovery within 3 months</td>
<td>Subtotal (2 cases)</td>
</tr>
<tr>
<td>Anterior and mid-temporal</td>
<td>3</td>
<td>Posteriorly (superiorly and laterally): language pathways corresponding to the antero-inferior part of the arcuate fasciculus (anomia)</td>
<td></td>
<td>Total (3 cases)</td>
</tr>
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<td>Deeply: insular cortex (speech arrest)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal tempor-occipital</td>
<td>1</td>
<td>Anteriorly (superiorly and laterally): language pathways corresponding to the postero-inferior part of the arcuate fasciculus (anomia)</td>
<td>Normal examination</td>
<td>Subtotal</td>
</tr>
</tbody>
</table>

All cases presented with seizures and were normal at clinical examination. M = male; F = female; SMA = supplementary motor area; ScF = subcallosal fasciculus; PVWM = periventricular white matter; F1 = superior frontal gyrus; F2 = median frontal gyrus; F3 = inferior frontal gyrus.
covert sentence repetition tasks) (Lehéry et al., 200b). The presenting symptoms were seizures in all cases. No patient had medically intractable epilepsy. The preoperative clinical testing was normal in the 30 patients.

**Preoperative MRI**

All the tumours appeared as T₁-weighted hypointense and T₂-weighted hyperintense lesions, without enhancement after gadolinium administration.

The locations in the left hemisphere were distributed as follows: (i) 23 precentral lesions, with 18 tumours within the superior frontal gyrus (F₁) (invading the supplementary motor area), three tumours in the median frontal gyrus (F₂) and two tumours in the inferior frontal gyrus (F₃) (within the classical ‘Broca’s area’); (ii) three retrocentral supra-sylvian lesions; (iii) three gliomas invading the anterior and mid-temporal regions; and (iv) one basal lesion at the temporo-occipital junction, with an anterior expansion into the mesiotemporal region.

The 30 tumours extended from the cortical surface to the ventricle.

**Operative findings**

The surgical procedure under local anaesthesia was well tolerated by the 30 patients. In all cases, sensorimotor and language cortical sites and subcortical pathways were clearly identified. The language white matter areas detected by stimulations differed according to the tumour location.

**F₁ precentral lesions (18 patients)**

The anterior limit of resection was given by ultrasonography, when no residual tumour was still visible, because of the lack of functional boundaries (detectable by stimulations).

Medially, the resections in all cases were conducted up to the falk.

The posterior limit of resection was defined by the identification of the cortico-spinal pathways in eight cases: medially, the motor tracts of the inferior limb (stimulations eliciting leg and/or foot movements), and, more laterally, those of the superior limb (induction of arm and/or hand movements); in 10 cases, a reduction of fluency with disorders of initiation of speech were induced by stimulation of the posterior wall of the cavity, in front of the motor pathways (since detected more posteriorly at the cortical level).

The lateral limit was determined systematically when inducing anoma during stimulations of the cortical language sites (most of the time located in F₂, in four cases in the lateral part of F₁), and the subcortical fibres converging on the antero-lateral border of the frontal horn of the ventricle. It is to be noted that after stimulation, the patients frequently remain for several seconds with limited spontaneous speech.

The postero-lateral limit was determined in all patients by eliciting a dysarthria during stimulations of the pathways converging on the the periventricular white matter (PVWM) near the body of the lateral ventricle. Most of the time, fluency normalized immediately after the end of the stimulations.

The ventricle was opened in all cases.

**F₂ precentral lesions (three patients) (Fig. 1)**

The anterior limit of resection was determined by ultrasonography, when no more tumour was visible, because of the lack of functional response.

Medially, the limit at the subcortical level was represented by the medial wall of the surgical cavity, where reduction of spontaneous speech was induced by stimulation of fibres joining the antero-lateral border of the frontal horn of the ventricle. For this reason, the ventricle could never be opened.

Laterally, the limit was represented by the cortical language sites systematically identified in F₃, and the corresponding subcortical pathways directly below the cortical language areas both eliciting speech arrest during stimulations.

Posteriorly, the resection was stopped: (i) at the cortical level, and at the subcortical level corresponding to the superomedial wall of the surgical cavity, by the identification of the cortico-spinal tracts of the superior limb, joining the PVWM deeply, medially and posteriorly; (ii) at the subcortical level (infero-lateral wall of the cavity), due to the detection of language pathways by inducing dysarthria during stimulations, coming from the cortical primary motor face areas also identified by electrical mapping more laterally (also inducing dysarthria), and joining the PVWM medially, in front of the previous motor hand fibres.

**F₃ precentral lesions (two patients)**

The anterior limit was defined ‘anatomically’ using ultrasonography, due to the lack of functional response elicited by stimulations.

The lateral boundary was represented by the sylvian fissure which was opened to remove the F₃ operculum totally, since no language disturbance was elicited during cortical mapping of the whole F₃ invaded by the glioma.

The medial limit was represented by the cortical language sites identified in F₂ in both patients, and the corresponding subcortical pathways directly below the cortical language areas, both eliciting speech arrest during stimulations.

The posterior boundary of resection was defined at both cortical and subcortical levels by inducing dysarthria during electrical mapping.

In the particular case of the F₃ tumours, the depth of the cavity was represented anatomically by the insular cortex, surgically preserved because it was not involved in the tumours in these two patients.

Interestingly, the stimulation of the white matter in these two cases in the depth of the superior insulo-opercular sulcus systematically induced language disturbances: dysarthria...
posteriorly, anomia with reduction of spontaneous speech and even speech arrest more anteriorly. Consequently, the ventricle was not opened in these cases. It is to be noted that the stimulation of the insular cortex elicited speech arrest in one patient, but no speech disorder in the second.

Retrocentral supra-sylvian lesions (three patients)
The posterior and medial boundaries were defined anatomically using ultrasonography, due to the lack of functional response elicited by stimulations.

The anterior limit was represented by the primary somatosensory cortico-subcortical structures when not invaded by the glioma. However, in cases of retrocentral gyrus infiltration, the resection was pursued anteriorly until the motor pathways were encountered (Duffau and Capelle, 2000). These descending fibres were followed up until they joined the PVWM, also with induction of dysarthria during stimulation. The ventricle was opened in all cases.

The inferior limit was determined when eliciting speech arrest during stimulation of the supra-sylvian structures, i.e. the supramarginalis gyrus and the subcortical white matter immediately below.

Anterior and mid-temporal lesions (three patients)
The anterior and inferior resections were conducted up to the dura mater.

The superior boundary was represented by the opening of the sylvian fissure.

At depth, the functional limit was represented by the insular cortex, which induced speech arrest in all cases when stimulated.

Posteriorly, the boundary was given using stimulations: (i) at the external surface of the ventricle (temporal horn); the postero-temporal cortico-subcortical structures induced anomia when stimulated; (ii) at the inner surface of the ventricle; the invaded hippocampus was resected until no tumour was visible on ultrasonography.

Basal temporo-occipital lesion
The inferior (dura mater) and posterior (no residual tumour on ultrasonography) boundaries were anatomical.

The anterior and superior limits were defined functionally, by eliciting anomia during stimulations of the cortical postero-temporal eloquent sites and subcortical white matter directly below (outside the ventricle). It is to be noted that at the medial surface of the ventricle, the mesio-temporal resection was performed anteriorly until the glioma seemed anatomically totally removed.

Clinical results
All patients with precentral F1 lesions presented an immediate postoperative dominant supplementary motor area syndrome, with motor aphasia (and right hemiparesia in eight cases). Recovery occurred within 3 months in the 18 patients, with persistence of a mild reduction of spontaneous speech in three cases.

The three patients with precentral F2 lesions presented a severe postoperative dysphasia with a right central facial palsy. All symptoms disappeared within 3 months.

In the two cases with precentral F3 lesions, there was no postoperative deficit.

In retrocentral lesions, all patients had a severe somatosensory deficit which recovered with mild residual sensitive disorders. Moreover, the three patients presented a postoperative aphasia with anomia which disappeared in all of them.

In anterior and mid-temporal lesions, all patients presented a postoperative aphasia with anomia and memory disorders, which recovered within 3 months.

Fig. 2 (A) and (B) Preoperative axial (A) and coronal (B) T1-weighted MRI, showing a cortico-subcortical low-grade glioma invading the left middle frontal gyrus (F2). (C) Intraoperative view before resection (A = anterior; P = posterior; M = midline). The letter tags (A, B, C, D, E and F) show the tumour boundaries. The numbers mark the cortical functional areas—from posterior to anterior: primary somatosensory sites (10–17) in the retrocentral gyrus; primary motor site of the hand (1) and of the face (2, 22, 20, 21 and 24)—inducing anarthria during stimulations—in the precentral gyrus; language area (25) eliciting speech arrest when stimulated, in the inferior frontal gyrus (F3). (D) Intraoperative view following tumour removal. The cortical functional sites have been preserved (even if the tag '25' was not still visible in this photograph, F3 was not resected). Three language pathways were identified subcortically: medially, the subcallosal fasciculus (I), coming from the fronto-mesial structures which have been preserved, joining the antero-lateral border of the frontal horn of the ventricle (41), and inducing a transcortical motor aphasia when stimulated; posteriorly, the pyramidal pathways (II) coming from the primary face area (2, 22, 20, 21 and 24) and joining the lateral wall of the ventricle (42), behind the subcallosal fasciculus, to constitute the PVWM. The stimulations of these fibres generate a dysarthria, as during the stimulations of the corresponding cortical sites; laterally, the bundles (III) connecting the language area in F3 and the primary motor face area, and potentially also corresponding to insulo-opercular connections (40), eliciting speech arrest when stimulated. (E) Postoperative axial T1-weighted MRI showing a subtotal tumour removal. The resection stopped posteriorly at the level of the primary motor cortical area of the face partially invaded by the glioma (straight arrow), and at the level of the corresponding subcortical pathways joining the PVWM (symbolized by the red arrow). It should be noted that the postero-medial part of the cavity contains the subcallosal fasciculus (curved arrow). (F) Postoperative coronal T1-weighted MRI showing the subcortical language pathways around the cavity, preventing the opening of the ventricle: the subcallosal fasciculus (curved arrow) medially, the pyramidal fibres of the motor face area (straight arrow), and laterally the insulo-opercular connections (red arrow).
In the patient with the basal temporo-occipital glioma, there was no postoperative deficit.

**Radiological results**

In F1 precentral lesions (Fig. 2), the cavity came into contact posteriorly with the precentral gyrus in the eight patients without language structures in front of the cortico-spinal pathways, and laterally and deeply (near the ventricle) with two anatomical structures studied accurately by Naeser and colleagues (Naeser et al., 1989): the subcallosal fasciculus (ScF) (its internal surface), surrounding the anterolateral angle of the frontal horn, and, more posteriorly, the PVWM (its middle third on slices involving bodies of lateral

Fig. 3 (A) Preoperative 3D MRI (A = anterior; P = posterior), showing a left low-grade glioma involving the fronto-opercular region (Broca’s area). The functional limits of the resection are given: posteriorly, at both cortical and subcortical levels by inducing dysarthria during electrical mapping (I); medially, by the language sites identified in F2, and the corresponding subcortical pathways—eliciting speech arrest or anomia when stimulated (II); deeply, by the insulo-opercular connections. (B and C) Postoperative axial (B) and coronal (C) T1-weighted MRI showing a total tumour removal. Deeply, the resection stopped when it came into contact with the insular cortex, and subcortically when it came into contact with the insulo-opercular connections (arrows) (separated from the ventricle by the subcallosal fasciculus), which both induced speech arrest during stimulation.
ventricle). Due to tumour infiltration in these areas in 10 patients, the resections were total in eight cases and subtotal in 10 cases.

In F2 precentral lesions (Fig. 3), the medial boundaries of the cavity were represented by the same two white matter bundles: the ScF (its external surface) and, more posteriorly, the middle third of the PVWM; posteriorly, the cavity stopped at the level of the precentral gyrus and corresponding pathways; laterally, the limit was represented by the cortical language sites and corresponding pathways identified in F3. The three resections were subtotal, because of the infiltration of the white matter by the tumour under the primary cortical motor area of the face.

In F3 precentral lesions (Fig. 4), the cavity came into contact with the precentral gyrus and the corresponding pathways posteriorly, the cortical language sites and corresponding pathways identified in F2 medially, and deeply with two different structures: the insular cortex inferiorly and the ScF (its infero-external surface) above. The resections were total in the two cases.

In retrocentral lesions (Fig. 5), the cavity stopped anteriorly at the level of the retrocentral gyrus (and sometimes the central sulcus itself if there had been a resection of a part of the primary somatosensory area when invaded), of the supramarginalis gyrus (cortical language sites) and corresponding pathways laterally, and of the middle third of the PVWM (its posterior surface) deeply. The resections were total in one case, and subtotal in two patients because of the infiltration of the PVWM.

In anterior and mid-temporal lesions (Fig. 6), the cavity surrounded the brainstem medially, and came into contact posteriorly and laterally with the mid-temporal cortical language sites with corresponding pathways around the sphenoidal horn of the ventricle. The three resections were total.

In the basal temporo-occipital lesion (Fig. 7), the cavity stopped anteriorly and superiorly in contact with the cortical language sites and corresponding white fibres, joined the ventricle deeply and extended to the level of the hippocampal structures medially. Because of infiltration of the anterior white matter, the resection was subtotal.

In summary, 14 resections were considered as total, without any residual sign of abnormality on postoperative

Fig. 4 (A) Preoperative sagittal T₁-weighted MRI showing a low-grade glioma involving the left parietal lobe. (B and C) Postoperative coronal (B) and sagittal (C) T₁-weighted MRI showing a subtotal glioma removal. Deeply, the anterior boundary was represented by the posterior surface of the PVWM, and antero-infero-laterally by the corresponding subcortical pathways of the supramarginalis gyrus (curved arrows); these fibres joined the postero-superior part of the arcuate fasciculus (eliciting anoma when stimulated), as shown by the projection of the surgical cavity (blue line) on a classical anatomical schema (from Bossy, 1991) (D).
MRI, and 16 subtotal, because of infiltration of functional white matter fibres in all cases. It should be noted that a residual rim of signal change was interpreted as a residual tumour, when still visible on the delayed MRI (in the third month).

**Discussion**

Understanding of the organization of the human brain remains limited, because there is no method available currently to perform an accurate and reliable non-invasive tracking of the neuronal connections between cortical functional regions, despite the recent attempts using diffusion-weighted MRI, which is still in the evaluation stage (Jones et al., 1999; Pajevic and Pierpaoli, 1999). Indeed, although autoradiographic techniques have been used in animals (Barnes et al., 1980; Benjamin and Van Hoesen, 1982), most of the studies in humans have only examined the relationship between the location and extent of the lesions on anatomical brain imaging, and the severity of their clinical consequences (Knopman et al., 1983; Alexander et al., 1987; De Renzi et al., 1991; Naeser et al., 1989, 1998), without direct identification of the different white bundles. Thus, a better knowledge of the connectivity of pathways of fibres seems mandatory to minimize the risk of neurological sequelae in cases of brain surgery in cortico-subcortical eloquent areas.

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**Fig. 5** (A) Preoperative sagittal T₁-weighted MRI showing a low-grade glioma invading the left temporal lobe. (B and C) Postoperative axial (B) and sagittal (C) T₁-weighted MRI showing a total tumour removal. Deeply, the posterior boundary was represented laterally (small arrows) and superiorly (curve arrow) by the antero-inferior part of the arcuate fasciculus (eliciting anomia when stimulated), as shown by the projection of the surgical cavity on a classical anatomical schema (from Bossy, 1991) (D). It should be noted that the red line corresponds to the posterior part of the cavity, i.e. the subcortical resection under the arcuate fasciculus, although the anterior part of the cavity (blue line) involves the cortical and subcortical structures in front of the eloquent mid-temporal sites.

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**Fig. 6** (A) Preoperative axial T₂-weighted MRI showing a low-grade glioma invading the left basal temporo-occipital occipital region. (B–D) Postoperative axial (B and C) and sagittal (D) T₁-weighted MRI showing a total tumour removal. Deeply, the anterior boundary was represented laterally and superiorly (arrows) by the postero-inferior part of the arcuate fasciculus (eliciting anomia during intraoperative stimulations), as shown by the projection of the surgical cavity on an anatomical schema (from Bossy, 1991) (E). The red line corresponds to the anterior part of the cavity (subcortical resection under the arcuate fasciculus), although the posterior part of the cavity (blue line) involves the temporo-occipital cortico-subcortical structures behind the mid-temporal language sites.
The technique of intraoperative direct electrical stimulations was described previously as a safe, precise and reliable method of detection of functional cortical areas (Ojemann et al., 1989; Berger and Ojemann, 1992; Ebeling et al., 1992; Haglund et al., 1994; and also subcortical supra-tentorial (Skirboll et al., 1996; Duffau, 2000; Duffau et al., 2000b), infra-tentorial (Duffau and Sichez, 1998) and spinal (Duffau et al., 1998) pathways. However, there is no study to our knowledge that attempts to correlate the functional results obtained intraoperatively with the classical anatomical data, particularly for the language association fibres, with the aim of defining the location of the main essential eloquent white bundles which must be preserved during surgical resections. Indeed, such a correlation should allow a better knowledge of the precise role of the white matter pathways and their organization in language function, a better appreciation of the respective clinical consequences in cases of damage of each fibre bundle, and hence better surgical pre-planning in cases of an infiltrative tumour invading the subcortical structures in the dominant hemisphere, in order to avoid a definitive postoperative deficit.

Several subcortical language pathways were identified in this study.

The subcallosal fasciculus (ScF)

First described by Muratoff (1893) in the dog, then by Déjerine (1895) in humans, the ScF is a white matter area surrounding the lateral angle of the frontal horn containing a pathway through which fibres pass from the cingulate gyrus and supplementary motor area to the caudate nucleus. In 1961, Yakovlev and Locke reported that these cortico-striate fibres were, in fact, contained in the medial division of the ScF, and that cortico-cortical fibres of the superior fronto-occipital bundle constituted the lateral division of the ScF (Yakovlev and Locke, 1961). These data were confirmed by CT scan studies, showing that lesions of the ScF have an effect on the initiation and preparation of speech movements, with the most important limitation produced when the stroke was located in the most medial portion of the ScF (Naeser et al., 1989). Moreover, this aphasia seemed to be more severe when combined with middle-third PVWM lesions (Naeser et al., 1989).

In our study, in all cases of precentral glioma, the electrical stimulations of white matter around the lateral angle of the frontal horn induced an anomia with reduction of spontaneous speech. This effect was obtained: (i) in F1 precentral lesions, by stimulating the lateral border of the cavity (after opening the ventricle), corresponding to the medial wall of the medial ScF; (ii) in F2 precentral lesions, by stimulating the posterior medial border of the cavity (preventing the opening of the ventricle), corresponding to the lateral wall (superior part) of the ScF; (iii) in F3 precentral lesions, by stimulating the depth of the superior insulo-opercular sulcus (again preventing the opening of the ventricle), corresponding to the lateral wall (inferior part) of the ScF.

The clinical symptom during stimulations, i.e. limited spontaneous speech, but preservation of normal articulation, could be identified as a transcortical motor aphasia, and could be explained by a disruption between the supplementary motor area and the perisylvian speech zone (Freedman et al., 1984) by inhibition of the ScF. Interestingly, Van Buren already observed during surgery for basal ganglia disorders that lower range electrical stimulation in the vicinity of the head of the caudate nucleus induced a ‘disturbance in which the impulse to speak has been dulled or forgotten’ (Van Buren, 1963, 1966). This description resembles the response obtained from the supplementary motor area disruption elicited by ScF stimulation in our work.

Moreover, all patients with F1 glioma presented a postoperative dominant supplementary motor area syndrome with the same transcortical motor aphasia that was induced transitorily during intraoperative ScF stimulation. Although this prolonged syndrome was probably explained by the removal of the supplementary motor area itself, in the eight patients in whom the resection was conducted posteriorly up to contact with the motor pathways (since this supplementary motor area region was invaded by the tumour, and because these symptoms are well known to resolve within 3 months; Rostomily et al., 1991; Bleasel et al., 1996), this syndrome cannot be explained by a supplementary motor area injury in the other 10 patients. Among them, the recovery was not complete in three cases, with persistence of a mild reduction of spontaneous speech: interestingly, the glioma removal was subtotal in these three patients, because of a large tumour infiltration of the medial ScF (not resected as it constituted the functional limit of resection). We can hypothesize that the functioning of this widely invaded eloquent white matter was not completely normal and, consequently, that complete language compensation was not possible in the other patients. This observation seems to be in agreement with the findings described by Naeser and colleagues who suggest that it is the involvement of primarily subcortical white matter pathways (not basal ganglia and cortical lesions) which produces more severe limitation in spontaneous speech (Naeser et al., 1989). Finally, since in the eight patients with supplementary motor area resection, intraoperative stimulations of the ScF also induced worsening of speech disturbances, it is likely that this pathway contains some additional connection fibres, in particular between cingulum (non-resected) and the caudate, participating in the limbic aspects of spontaneous speech, and cortico-cortical tracts potentially coming from the language sites in F2 (running in the lateral part of the ScF) (Yakovlev and Locke, 1961).

This consideration would suggest that the ScF seems to be an essential structure for speech, which must be preserved during surgical resection, thus preventing total tumour removal in cases where it is infiltrated. If this could be confirmed by other studies, it would then be possible to predict preoperatively the feasibility of a complete resection,
and to optimize the pre-planning by defining the subcortical boundaries of the surgical procedure.

**The PVWM near the body of the lateral ventricle**

This white matter, located beneath the lower motor/sensory cortex area of the mouth, was widely described as the PVWM on CT slices involving bodies of lateral ventricle by Naeser and colleagues. These authors reported that a lesion in this area ‘may interrupt the pathways necessary for motor execution as well as possibly those pathways necessary for sensory feedback’ (Naeser et al., 1989).

Our intraoperative findings seem concordant with this hypothesis, since stimulations of these ‘mouth pathways’ systematically induced a dysarthria or anarthria. This effect was obtained: (i) in F1 precentral lesions, by stimulating the postero-lateral border of the cavity (after opening of the ventricle), behind the ScF, corresponding to the antero-medial wall of the PVWM (i.e. motor execution); (ii) in retrocentral lesions, by stimulating the antero-lateral border of the cavity (after opening of the ventricle), corresponding to the postero-medial wall of the PVWM (i.e. sensory feedback); (iii) in F2 precentral lesions, by stimulating the postero-lateral wall of the cavity, corresponding to the face cortico-spinal tracts, coming from the primary motor cortex also identified more laterally using stimulations, and joining the PVWM medially and inferiorly; (iv) in F3 precentral lesions, by stimulating both the posterior wall of the cavity and the depth of the superior insulo-opercular sulcus (posterior part), corresponding to the face cortico-spinal tracts with its motor cortex identified immediately above.

Although it had already been reported that the resection of the non-dominant primary motor area of the face can be performed in cases of glioma infiltration, with secondary recovery of the initial facial palsy (LeRoux et al., 1991), there was no description of removal of the dominant face primary motor area because all authors agree that this cortical structure seems essential for speech (Mori et al., 1989; Lüders et al., 1997). In this study, we showed, using intraoperative direct stimulations, that the subcortical pathways corresponding to the dominant face motor and sensory cortex areas (from their cortico-cortical junction to their deep trajectory in the PVWM) also represent an essential language structure which must be preserved during surgical procedures.

**Arcuate fasciculus (AF)**

The fibres of the AF connect the frontal gyri to the medial and infero-lateral part of the temporal lobe, via the extrema capsule around the insula (Bossy, 1991). The different parts of this AF were identified using intraoperative subcortical stimulations, by eliciting transient language inhibition: these symptoms, particularly anomia, corresponded to those described in a conduction aphasia syndrome. These effects were obtained (i) in F2 lesions, by stimulating the lateral wall and the depth of the cavity, which correspond to the white bundles joining the F3 cortical sites (‘Broca’s area’) also identified by the intraoperative mapping, to the Wernicke’s area; (ii) in F3 lesions, by stimulating the medial wall of the surgical cavity and the depth of the superior insulo-opercular sulcus, which correspond to the fibres coming from the language cortical sites located in F2 (indeed, no eloquent site was detected in F3 in the two patients, probably because of a total F3 infiltration by the glioma, thus a functional reorganization due to brain plasticity would explain the lack of deficit) (Atlas et al., 1996; Duffau et al., 2000a, 2001; Duffau, 2001); (iii) in retrocentral lesions, by stimulating the antero-inferior wall of the cavity, under the supramarginalis cortex which itself induced anomia when stimulated: it can be hypothesized that the deep white matter may in fact represent fibres of the AF (at the level of its postero-superior loop); (iv) in anterior and mid-temporal lesions, by stimulating the posterior border of the cavity, which correspond to the anterior wall of the temporal part of the AF (under the mid-temporal cortical sites also identified using stimulations); (v) in tempo-ro-occipital junction lesions, by stimulating the antero-superior border of the cavity, corresponding to the posterior wall of the temporal part of the AF (located at the outer surface of the ventricle, since it was possible to continue the resection deeply and anteriorly in the mesio-temporal structures).

These findings show that the AF can be identified intraoperatively, with accuracy and reliability, to avoid definitive postoperative conduction aphasia. These data also illustrate that this association pathway seems to connect fronto-opercular cortical areas (or F2 sites in the case of functional redistribution due to glioma infiltration of F3), the postero-superior temporal cortex and probably the supramarginalis gyrus already suspected to play an important role in conduction aphasia (Corina et al., 1999).

**Other white matter association pathways**

It is likely that other eloquent subcortical white bundles were inhibited by stimulations in our experience, particularly the association pathways of the insula. Indeed, it was reported previously that the left dominant insular lobe seems to play an important role in speech planning (Dronkers, 1996; Duffau et al., 2000b). Moreover, the insula was found to connect with frontal, parietal, temporal, cingulate, basal nuclei and limbic areas (Augustine, 1996). Thus, we can hypothesize that the stimulations in the depth of the superior insulo-opercular sulcus, particularly described in this work, may induce language disorders by functional disruption of the insulo-frontal connections.

It also seems likely that the inhibition of the inferior longitudinal fasciculus at the mid- and posterior temporal levels, of the uncinate fasciculus at the fronto-temporal junction, and of cortico-cortical connections from one gyrus
to another has been induced by subcortical stimulations, maybe sometimes in combination with the main pathways described above. For this reason, additional anatomo-functional correlation studies concerning the subcortical pathways should be performed.

In summary, subcortical stimulations seem to constitute a reliable method of identification of essential language pathways. Indeed, in three patients with large glioma infiltration of the white matter defined as essential by the intraoperative stimulations, persistence of speech disturbances >3 months after the surgery was noted. Moreover, the patients with subtotal tumour resection have had lesser and shorter immediate postoperative deficit than the group with a total resection. These observations are in agreement with the series using cortical stimulations during surgery in language areas, which showed that tumour resection should preserve a margin around the eloquent site determined by stimulations to avoid a definitive functional impairment (Haglund et al., 1994). Finally, since bipolar stimulations were demonstrated previously as able to provide an accurate mapping at the cortical level, i.e. without spreading, using intensity lower than 16 mA, as shown by optical imaging (Haglund et al., 1993), and at the subcortical level concerning the identification of the pyramidal pathways (Duffau and Sichez, 1998; Duffau et al., 1998, 2000; Duffau and Capelle, 2000), it seems likely that the present results have not been caused by spread to white matter structures deeper than areas being directly stimulated.

Consequently, the results of intraoperative cortico-subcortical stimulations are crucial to optimize the removal of any brain infiltrative lesion such as low-grade glioma, known to involve both cortical and subcortical structures: the limits of resection were defined according to functional and not anatomical boundaries, at each moment of the surgery, thus with on-line modification of the surgical plan based on electrical mapping findings. The use of this method assists in the postoperative recovery as opposed to standard techniques with cortical stimulations alone, in which the preoperative neurofunctional imaging fails to map the white matter, thus preventing pre-planning of surgery in deep regions. Indeed, the prediction of the exact location of language structures is complicated by the existence of reorganization phenomena induced by the glioma as already demonstrated at the cortical level (Duffau et al., 2001). Since no patient had preoperative deficits, this reorganization potentially could also occur at the subcortical level. This raises the question of possible reshaping of language pathways in the postoperative recovery phase, due to potential redundancies organized in parallel networks, as previously suggested in somatosensory and motor functions using intraoperative stimulations (Duffau and Capelle, 2000; Duffau et al., 2000, 2000a; Duffau, 2001) and functional MRI (Krainik et al., 2001), i.e. that the surgical resection has involved pathways and cortical sites implicated in language (explaining the immediate postoperative deficit) but not essential for language (explaining the ability for secondary recovery).

However, regarding the anatomo-functional correlations, stimulations only provide data on a limited portion of the white matter and do not indicate where those fibres may be going. Thus, although patterns of language pathways were identified in our work with reproducibility from one patient to another (in spite of a degree of interindividual variability due to the tumour), showing fibres which seem to correspond to the fairly classical subcortical bundles that have been hypothesized to be important to language in the past decades using clinico-anatomical comparisons, our findings do not necessarily only support the pathways that we describe, but might equally support alternative connections, in particular fibres running from cortex to the thalamus. Further series are needed to complete our preliminary results, and to improve knowledge of the language subcortical connectivity.

Conclusions
The findings described in this work show the following. (i) Intraoperative electrical stimulation of the white matter represents, as at the cortical level, a precise and reliable method of direct detection of subcortical eloquent fibres, allowing an optimization of glioma removal (100% of total or subtotal resections, known in both cases to improve the median survival in low-grade gliomas by minimizing their anaplastic transformation; Berger et al., 1994) and a minimization of neurological sequelae (recovery in all cases—complete in 27 cases, with mild reduction of speech in three cases—beyond the third month following surgery). (ii) Common language pathways, detected with reproducibility in all patients in the dominant hemisphere using stimulations, seem essential and hence should be surgically preserved to avoid definitive speech disturbances: the ScF (eliciting initiation disorders during stimulation), the PVWM containing motor and sensory fibres of the face (inducing anarthria when stimulated), the AF and the insulo-opercular connections (generating anaomia during stimulations). (iii) An accurate detection of these pathways in the preoperative stage could be very helpful: a validation of the diffusion-weighted MRI method by intraoperative electrical stimulations should be considered. Indeed, reliability of this non-invasive technique could allow improvement of the knowledge of the subcortical brain connectivity, in particular in healthy volunteers.

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Received June 28, 2001.
Accepted September 10, 2001