New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations

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Summary
Despite a better understanding of the organization of the cortical network underlying the semantic system, very few data are currently available regarding its anatomo-functional connectivity. Here, we report on a series of 17 patients operated on under local anaesthesia for a cerebral low-grade glioma located within the dominant hemisphere. Prior to and during resection, intraoperative electrical stimulation was used to map sensorimotor and language structures so that permanent neurological deficits could be avoided. In a number of cases, cortical and subcortical stimulation caused semantic paraphasias. Using postoperative MRI, we correlated these functional findings with the anatomical locations of the sites where semantic errors were elicited by stimulation, especially at the subcortical level, with the aim of studying the connectivity underlying the semantic system. In temporal gliomas, cortical sites involved in semantic processing were found around the posterior part of the superior temporal sulcus, with subcortical pathways reproducibly located under the depth of this sulcus. In insular gliomas, although stimulation elicited no semantic disturbances at the cortical level, such semantic paraphasias were generated at the level of the anterior floor of the external capsule. In frontal tumours, cortical regions implicated in semantics were detected in the lateral orbitofrontal region and dorsolateral prefrontal cortex, with subcortical fibres located under the inferior frontal sulcus. All these eloquent structures were systematically preserved, thereby avoiding permanent postoperative deficits. Our results provide arguments in favour of the existence of a main ventral subcortical pathway underlying the semantic system, within the dominant hemisphere, joining the two essential cortical epicentres of this network: the posterior and superior temporal areas, and the orbitofrontal and dorsolateral prefrontal regions. Such a ventral stream might anatomically partly correspond to the inferior fronto-occipital fasciculus.

Keywords: semantic; connectivity; language; electrical stimulation; glioma surgery

Abbreviations: BA = Brodmann area; BDAE = Boston Diagnostic Aphasia Examination; DTI = diffusion tensor imaging; DLPPC = dorsolateral prefrontal cortex; IFC = inferior frontal cortex


Introduction
Recent progress in neurofunctional imaging methods has allowed an improved knowledge of the cortical organization of the semantic system. Indeed, two regions within the left hemisphere have been regularly reported as playing a major role: the left posterior temporal regions and the left inferior frontal cortex (IFC) (Mesulam, 1990; Papathanassiou et al., 2000; Davis and Johnsrude, 2003; Friederici et al., 2003; Heim et al., 2003a).

Regarding the left temporal lobe, in which semantic content has been described as highly organized and spatially segregated (Bookheimer, 2002), the regions around the posterior part of the superior temporal sulcus (superior and...
middle temporal gyri) were reproducibly found to be activated during comprehension tasks (Wise et al., 1991, 2001; Démonet et al., 1992; Tulving et al., 1994; Stromswold et al., 1996; Müller et al., 1997; Bookheimer et al., 1998; Schlosser et al., 1998; Mummery et al., 1999; Crinion et al., 2003; Davis and Johnsrude, 2003; Devlin et al., 2003; Hamberger et al., 2003; Tyler et al., 2003), whatever the modalities of presentation of information (oral, visual or somesthetic), supporting the supramodal feature of this region in semantic processing (Michael et al., 2001; Booth et al., 2002; Decety et al., 2002; Saygin et al., 2003). Moreover, visual tasks such as reading or naming might recruit additional basal inferior temporal areas that are involved in lexical retrieval (Lüders et al., 1991; Nobre et al., 1994; Damasio et al., 1996; Schäffler et al., 1996; Price, 2000; Jobard et al., 2003).

Concerning the semantic role of the IFC (Mazoyer et al., 1993; Thompson-Schill et al., 1997, 1998; Wagner et al., 1997, 2001; Chee et al., 1998; Bookheimer, 2002; Homae et al., 2002), it would seem that its inferior and anterior parts, i.e. the pars orbitalis [Brodmann area (BA) 47] (Gabrieli et al., 1998; Poldrack et al., 1999; Bookheimer, 2002; Noppeney and Price, 2002), pars triangularis (BA 45) (Desmond et al., 1995; Gabrieli et al., 1996; Friederici et al., 2000b) and even the dorsolateral prefrontal cortex (DLPFC) (BA 46/9) (Kapur et al., 1994; Demb et al., 1995; Warburton et al., 1996; Szatowska et al., 2000; Noesselt et al., 2003) might be more specifically implicated in the executive aspects of semantic processing, while its more posterior areas (notably the pars opercularis, BA 44) could be preferentially involved in syntactic (Dapretto and Bookheimer, 1999; Kang et al., 1999; Embick et al., 2000; Friederici et al., 2000a; Moro et al., 2001; Heim et al., 2002, 2003b) and phonological processes (Démonet et al., 1992; Zatorre et al., 1992; Paulesu et al., 1993; Fiez, 1997; Fiez and Peterson, 1998; Poldrack et al., 1999).

Despite the better understanding of this cortical network organization, very few data are currently available about the anatomo-functional connectivity underlying the semantic system (Scott et al., 2000; Brugge et al., 2003), in contrast to the phonological system, for which a ‘phonological loop’ was both modelled (Baddeley, 1992, 2003) and described anatomically and functionally in vivo (Duffau et al., 2003a).

Here, we report on a series of 17 patients operated on under local anaesthesia for a cerebral low-grade glioma located within the dominant hemisphere, with intraoperative sensorimotor and language mapping in order to avoid post-operative definitive deficit, using cortical and subcortical electrical stimulation, which all induced transient semantic paraphasia. On the basis of the data of postoperative MRI, we correlated these functional findings with the anatomical locations of the sites where semantic errors were elicited by stimulation, especially at the subcortical level, with the aim of studying the connectivity underlying the semantic system.

Materials and methods

Subjects
Among a series of 150 patients operated on awake for a low-grade glioma located within the dominant hemisphere in our institution between 1996 and 2003, 17 patients who presented transitory semantic errors generated by the intraoperative electrical mapping were reviewed retrospectively. These patients are not the same as those described in our previous report of subcortical language pathway stimulation (Duffau et al., 2002).

Preoperatively, all patients had had a neurological examination. Language was tested by a speech therapist using the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1972). Hemispheric dominance was assessed using a standardized questionnaire (Edinburgh inventory) (Oldfield, 1971) and functional MRI using a protocol previously reported (Léhericy et al., 2000).

The topography of the tumour was analysed accurately on a preoperative MRI (T1-weighted and spoiled-gradient images obtained before and after gadolinium enhancement in the three orthogonal planes, and T2-weighted axial images).

Intraoperative mapping
All patients underwent surgery under local anaesthesia so that functional cortical and subcortical mapping could be carried out using direct brain stimulation. This method, including the electrical parameters and the intraoperative clinical tasks, has been described previously (Duffau et al., 2002, 2003b). A bipolar electrode with 5 mm spaced tips delivering a biphasic current with parameters non-deleterious for the CNS (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, MA) was applied to the brain of awake patients.

In a first stage, cortical mapping was performed, after tumour and sulci/gyi identification using ultrasonography, and before resection, in order to avoid any eloquent area damage. Sensorimotor mapping was performed first, with the goal of obtaining a positive response (e.g. the induction of movement and/or paraesthesia in the contralateral hemibody when the primary sensorimotor areas were stimulated in a patient at rest), since the bone flap allowed good exposure of the central region in all patients. Under local anaesthesia, the current intensity adapted to each patient was determined by progressively increasing the amplitude from 1 to 1 mA, from a baseline of 2 mA, until a sensorimotor response was elicited, with 8 mA as the upper limit, with the goal of avoiding the generation of seizures. Once this threshold was defined for sensorimotor mapping, the same intensity was used for both cortical and subcortical language mapping. Then, the patient was asked to perform an automatic task such as counting (regularly from 1 to 10 over and over), in order to confirm that the selected current amplitude allowed performance of reliable language mapping, by inducing a typical speech arrest/anarthria during stimulation of the region of Broca/ventral premotor cortex. Indeed, the essential cortical language sites are known to be inhibited by electrical stimulation (Berger, 1996; Ojemann et al., 1989; Duffau et al., 2002, 2003b). At this time, we systematically used the task most often reported during intraoperative language mapping (Ojemann et al., 1989; Berger, 1996), i.e. picture naming, preceded by a short sentence to read (the French translation of ‘this is a...’), in order to check that there were no seizures generating complete speech arrest when the patient was not able to name, i.e. that he was still capable of pronouncing ‘this is a...’. For the naming task,
we used the DO 80, which consists of 80 black and white pictures selected according to variables such as frequency, familiarity, age of acquisition and level of education (Metz-Lutz et al., 1991).

The patient was never informed when the brain was stimulated. The duration of each stimulation was 4 s. At least one picture presentation without stimulation separated each stimulation, and no site was stimulated twice in a row in order to avoid seizures. Each cortical site (size: 5 mm × 5 mm, due to the spatial resolution of the probe) of the entire cortex exposed by the bone flap was tested three times. Indeed, since the seminal publication of Ojemann et al. (1989), nowadays it is admitted that three tasks are sufficient to be sure whether or not a cortical site is essential for language, e.g. generating speech disturbances during two or three stimulations out of three, with normalization of language as soon as the stimulation is stopped. It is worth noting that this limitation of trials is required by the timing of the surgical procedure; recall that the patient was awake—thus also explaining the need to limit the number of language tasks.

The type of language disturbances was detailed by a speech therapist who was always present in the operating room during the functional mapping. Each eloquent area was marked using a sterile number tag on the brain surface, and its location correlated to the anatomical landmarks (sulci/gyri/tumour boundaries) previously identified by ultrasonography. A photograph of the cortical map was systematically made before resection.

During a second surgical stage, the glioma 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 (including both white matter pathways and deep grey nuclei), which were also identified by language inhibition during stimulation at the cortical level (Skirboll et al., 1996; Duffau et al., 2002, 2003b). In order to perform the best possible tumour removal while sparing functional areas, all resections were pursued until eloquent pathways were encountered around the surgical cavity, then followed according to functional boundaries. Thus, there was no margin left around the cortico-subcortical eloquent areas.

Postoperative functional outcome was assessed both during the immediate postoperative stage and 3 months after the surgery. It was performed by the same neurosurgeons and speech therapist who carried out the preoperative functional evaluation, using the same tasks, including the BDAE.

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, and secondly to analyse accurately the anatomical location of the language pathways, i.e. at the periphery of the cavity, where the resection was stopped according to the functional responses eliciting by intraoperative stimulation, a methodology that we used previously (Duffau et al., 2002).

Analysis of the intraoperative naming disturbances

Naming disorders, which can reflect a weakness of lexical access or loss of the semantic system, may include linguistic deviations called paraphasias.

Phonemic paraphasias

These affect the articulatory realization from one to several phonemes, by excess or failure of articulatory precision or related to motor difficulties, e.g. simplification of substitution of a phoneme.

Semantic paraphasias

These are connected to the meaning of the word target. The word target and the false production in oral meaning belong to the same semantic field. Hence, there are three correlations: the same category of meaning (e.g. orange/lemon), the opposite (e.g. low/high) and usual proximity (e.g. cigarette/lighter). For example, for the word ‘apple’, it can be a hyperonym production such as ‘fruit’ (generic term), a co-hyponym such as ‘peach’ (same category ‘fruit’ but with visual error), hyponym or categorizations such as ‘pippin’, contextual relationships such as ‘tart’, more specific attributes such as ‘pips’ or functional access such as ‘can be eaten’.

In the present study, we analysed the patients who experienced transient and reproducible semantic paraphasias during intraoperative electrical stimulation.

Although there was usually only one senior speech therapist in the operating room, each error induced by stimulations was also classified intraoperatively by a student in speech therapy and by the neurosurgeon. Moreover, each site, in particular if eliciting language disturbances when stimulated, was systematically tested at least three times, with the presentation of three different objects to name. Thus, the classification of the different types of paraphasic errors became unambiguous, particularly concerning semantic paraphasias, since the word produced by the patient was always perfectly understandable as a ‘real’ word (which is not true for phonetic and/or phonemic paraphasias), but was systematically wrong—while connected to the meaning of the word target, which differed for each new task in order to confirm the exact nature of the disorder. In addition, each error was recorded, then analysed postoperatively by at least two speech therapists: the one present during the surgery and one colleague.

Results

The clinical, radiological and surgical characteristics of the 17 patients are summarized in Table I.

Subjects

The series consisted of 11 males and six females, ranging in age from 17 to 52 years (mean 33 years). Fourteen patients were right-handed and three left-handed, as assessed by neuropsychological examination. The presenting symptoms were seizures in the 17 cases (four generalized, 13 partial with transient speech disturbances). The preoperative clinical testing was normal in all patients, in particular without any semantic disturbances on the BDAE.

The preoperative MRI showed in all cases a T1-weighted hypointense and T2-weighted hyperintense cortico-subcortical lesion, without enhancement after gadolinium injection.
**Table 1. Clinical, radiological and surgical characteristics of the 17 patients operated on for a low-grade glioma near the inferior fronto-occipital fasciculus (dominant hemisphere)**

<table>
<thead>
<tr>
<th>Glioma location</th>
<th>No. of patients</th>
<th>Sex and age (years)</th>
<th>Preoperative examination</th>
<th>Intraoperative electrical mapping semantic paraphasias</th>
<th>Postoperative examination</th>
<th>Postoperative anatomical MRI</th>
</tr>
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<tbody>
<tr>
<td>Frontal lobe</td>
<td>9</td>
<td>5 M/4 F; 37 (25–52)</td>
<td>No deficit</td>
<td>Cortical language mapping: semantic sites around the anterior part of the IFS in five patients Subcortical language mapping: semantic pathways under the IFS in all cases</td>
<td>Transient semantic disturbances then recovery within 3 months in all cases</td>
<td>Infero-lateral boundary: IFS Deep boundary: frontal part of the inferior fronto-occipital fasciculus</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Deep boundary: median part of the inferior fronto-occipital fasciculus</td>
</tr>
<tr>
<td>Insular lobe</td>
<td>2</td>
<td>2 M; 32 and 33</td>
<td>No deficit</td>
<td>Cortical language mapping: no insular cortical semantic sites detected Subcortical language mapping: semantic pathways within the anterior floor of the external capsule</td>
<td>Transient semantic disturbances then recovery within 3 months in all cases</td>
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<tr>
<td>Temporal lobe</td>
<td>6</td>
<td>4 M/2 F; 26 (17–43)</td>
<td>No deficit</td>
<td>Cortical language mapping: semantic sites around the posterior part of the STS in four patients Subcortical language mapping: semantic pathways under STS in all cases</td>
<td>Transient semantic disturbances then recovery within 3 months in all cases</td>
<td>Superior boundary: STS Infero-mesial boundary: supero-lateral temporal horn of the ventricle Deep boundary: temporal part of the inferior fronto-occipital fasciculus</td>
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</table>

M = male; F = female; IFS = inferior frontal sulcus; STS = superior temporal sulcus.
Three different groups of tumour locations were found. (i) In six patients, the lesion was located in the dominant temporal lobe (five left and one right lesion), immediately inferior and/or anterior to the posterior part of the superior temporal gyrus: one within the mid-part of the middle temporal gyrus, one within the posterior part of the middle temporal gyrus and four involving the mid- and posterior parts of the middle and inferior temporal gyri, and the fusiform gyrus (three left, one right) (Fig. 1A). (ii) In two patients, the glioma invaded the entire left insular lobe (Fig. 2A). (iii) In the nine other patients, the lesion was located immediately above and/or medially to the dominant IFC: four lesions within the fronto-mesial structures (superior frontal gyrus, three left and one right glioma), four lesions within the middle frontal gyrus (three left, one right), and one tumour involving both left superior and middle gyri (Fig. 3A).

Operative findings

Temporal gliomas

At the cortical level. In four patients with left tumour, semantic paraphasias were reproducibly elicited by cortical stimulations. These ‘semantic’ sites were located in the four cases around the posterior part of the left superior temporal gyrus, i.e. in the superior temporal gyrus immediately above the superior temporal sulcus in one case, in the middle temporal gyrus immediately below the superior temporal gyrus in one case, and in both gyri in two patients. In these four patients, these language areas constituted the postero-superior functional boundary of the glioma resection (Fig. 1B). In the two other patients, one with a left mid-temporal glioma within the middle temporal gyrus and one with a right glioma, cortical stimulations within the posterior part of the middle temporal gyri (posterior limit of the tumour removal) elicited hesitations/slowness of naming, but without any semantic paraphasia. However, following the opening of the superior temporal gyrus in both patients, during the resection, other stimulations of this buried cortex, at the postero-superior part of the tumour, then elicited semantic paraphasias.

At the subcortical level. In the second surgical stage, stimulations of the white subcortical pathways were systematically performed all along the tumour resection, as previously reported (Duffau et al., 2002, 2003b). Interestingly, they induced semantic disturbances in the six patients, in all cases during stimulations of the white bundle located under the superior temporal sulcus, above the temporal horn of the ventricle (opened in four patients). From anterior to posterior, this pathway was identified from the occipito-temporal junction posteriorly (posterior and deep functional boundary of the resection), up to the junction between the anterior temporal third and the mid-temporal third anteriorly, just below the anterior part of the insular cortex, which generated articulatory but not semantic disorders when stimulated (Fig. 1C), as we already observed (Duffau et al., 2000). At this level, it was not possible to continue to follow this pathway, which seemed to run under the anterior insula (antero-superior limit of the resection in the depth).

Insular gliomas

At the cortical level. There was no language disturbance elicited by the stimulations of the left insular cortex in the two patients, due to the glioma invasion, while language sites were detected within frontal (speech arrest) and temporal opercula (anomia) not invaded by the tumour, as previously described (Duffau et al., 2001).

At the subcortical level. Following resection of the anterior part of the insula, stimulations of the deep white fibres, i.e. corresponding to the anterior part of the external capsule (as confirmed by postoperative MRI, see below), reproducibly induced semantic paraphasias in both patients (Fig. 2B).

Frontal gliomas

At the cortical level. While frontal cortical language sites were identified by stimulation in the nine patients before resection, systematically generating production disorders such as aphasia and/or speech arrest and/or anomia, as we already reported (Duffau et al., 2003c), only five patients presented semantic paraphasia during cortical electrical mapping (four left gliomas, one right). In these five patients, the ‘semantic sites’ were located within the orbito-frontal cortex (i.e. the anterior and inferior part of the inferior frontal gyrus, in front of the sites which generated articulation disturbances when stimulated) or within the DLPFC [i.e. the middle frontal gyrus, in front of the dorsal premotor cortex which elicited anomia during stimulation, as previously described (Duffau et al., 2003c)] (Fig. 3B). It is worth noting that all four patients without any semantic site detected by cortical stimulation harboured a posterior frontal lesion, immediately in front of the precentral gyrus, i.e. within the dorsal premotor cortex (two in the posterior part of the superior frontal gyrus and two in the posterior part of the middle frontal gyrus; three left gliomas, one right).

At the subcortical level. As in the two first groups of patients (with temporal and insular lesions), subcortical stimulation reproducibly elicited semantic paraphasia in the nine patients with frontal gliomas. Concerning patients with resection involving the middle frontal gyrus, these semantic disorders were generated by stimulation of the white fibres under the inferior frontal sulci, above the anterior part of the superior insulo-opercular sulcus, in front of the pathways involved in language production that we previously detailed (Duffau et al., 2002). Concerning patients with resection involving only the superior frontal gyrus, the semantic paraphasias were induced by stimulation of the deep white matter, at the level of the antero-lateral edge of the cavity, laterally and above the anterior part of the head of the caudate nucleus (frontal horn opened in four patients), in front of the fibres coming from...
Fig. 1 (A) Preoperative axial and coronal T1-weighted enhanced MRI, showing a low-grade glioma involving the mid- and posterior part of the left temporal lobe: the middle and inferior gyri, and the fusiform gyri. Note, especially on the coronal slice, that despite sparing of the temporo-mesial structures and of the superior temporal cortex, the tumour begins to invade the subcortical white matter between the supero-lateral edge of the temporal horn of the ventricle (below) (curved arrow) and the depth of the superior temporal sulcus (above) (straight arrow). (B) Intraoperative photograph before tumour resection. The eloquent cortical sites identified using electrical stimulations were marked by numbers as follows: 1, primary motor area of the face; 10, ventral premotor cortex inducing anarthria during stimulations; 20, 21, 22, sites within the posterior part of the superior temporal gyrus (20, 21) or the middle temporal gyrus (22) eliciting semantic paraphasia when stimulated; 23, non-reproducible hesitation. The letters correspond to the limits of the tumour identified using intraoperative ultrasonography. Small arrow = superior temporal sulcus; large arrow = posterior part of the sylvian fissure; A = anterior; P = posterior. (C) Intraoperative photograph after tumour resection, showing that the posterior and deep boundaries of the cavity were represented by language cortical sites and subcortical pathways, as follows: 20, 21, 22, cortical semantic sites, which constituted the posterior limit of the resection (the area under 23 was removed because the hesitation was not reproduced during re-stimulations, and because of an invasion of this site by the glioma); 33, 32, 30, 31 (from posterior to anterior), subcortical pathway eliciting reproducible semantic paraphasia when stimulated, running in a postero-anterior direction, located between the depth of the superior temporal sulcus (above) and the temporal horn of the ventricle which was opened (below). Interestingly, this bundle continued anteriorly, by passing under the anterior insular cortex, which was surgically identified then stimulated; it elicited articulation disorders, but no semantic disturbances (29). Examples of semantic paraphasia during electrical mapping: ‘brush’ instead of ‘comb’; ‘zebra’ instead of ‘giraffe’; ‘pan’ instead of ‘ladle’; and ‘sideboard’ instead of ‘dresser’. The patient presented transient postoperative language semantic disturbances, which recovered within 2 months, following speech rehabilitation. (D) Postoperative coronal T1-weighted enhanced MRI (two slices: one posterior, one anterior), showing the resection of the left middle and inferior temporal gyri, and the fusiform gyrus. The boundaries of the cavity were: the superior temporal sulcus (superiorly, with preservation of the superior temporal gyrus) (straight arrow); and the latero-superior part of the horn of the ventricle (inferiorly, with preservation of the amygdalo-hippocampal structures) (curved arrow). Between these two limits, a postero-anterior white bundle runs, which constituted the deep functional boundary of the resection, since it elicited semantic paraphasia when stimulated. This is the reason why a tumoral residue was left at this level (T1 hyposignal, visible on both posterior and anterior slices). (E) Postoperative axial T1-weighted enhanced MRI, showing the deep residual glioma (antero-posterior rim of hyposignal in the depth of the cavity) (arrows), and the similarity of its location within the white matter in comparison with a tractography of the anterior part of the temporo-occipital portion of the inferior fronto-occipital fasciculus; from Catani et al. (2002).
the posterior part of the middle frontal gyrus (i.e. the dorsal premotor cortex), eliciting anomia during stimulation (Duffau et al., 2003c) (Fig. 3C).

In the 17 patients, cortico-subcortical eloquent structures identified by stimulations were systematically preserved, constituting the functional boundaries of the surgical resection.

Independent of the tumour location, the semantic paraphasias elicited most frequently were (i) use of a generic term (‘bird’ for ‘eagle’ or ‘woodpecker’; ‘animal’ for ‘lion’ or ‘tiger’; ‘flower’ for ‘rose’); and (ii) use of a co-hyponym (‘brush’ instead of ‘comb’; ‘horse’ for ‘donkey’; ‘zebra’ instead of ‘giraffe’; ‘pan’ instead of ‘ladle’; ‘sideboard’ instead of ‘dresser’; or ‘Little Red Riding Hood’ for ‘Father Christmas’).

**Postoperative course**

Postoperatively, the 17 patients presented transient semantic paraphasias which resolved within 7 days to 3 months, whatever the temporal, insular or frontal location of the tumour.

All patients had speech rehabilitation, which allowed a complete functional recovery systematically evaluated using the same BDAE as preoperatively, and showing a normalization of the scores. All patients returned to a normal socio-professional life.

**Histological examination**

Histological examination revealed a low-grade glioma in all cases.

**Radiological results**

In temporal lesions, the cavity came into contact superiorly with the superior temporal sulcus in six patients, up to the depth of this sulcus; and deeply, with the latero-superior part of the temporal horn of the ventricle which was opened (the middle, inferior temporal and fusiform gyri were removed, with preservation of the amygdalo-hippocampal structures since they were not invaded by the tumour). Between these two boundaries runs a postero-anterior white matter fibre bundle that constituted the deep functional boundary.
Fig. 3 (A) Preoperative axial and coronal T1-weighted enhanced MRI, showing a low-grade glioma involving the left fronto-mesial structures. Note that the tumour invades the subcortical white matter up to the antero-superior part of the head of the caudate nucleus (straight arrow). (B) Intraoperative photograph before tumour resection. The eloquent cortical sites identified using electrical stimulations were marked by numbers as follows: 1, 3, primary motor area of the hand; 12, dorsal premotor cortex inducing anomia during stimulations; 10, 11, ventral premotor cortex inducing anarthria during stimulations; 13, speech arrest site, within the pars opercularis; 14, site within the pars orbitaris of the inferior frontal gyrus, eliciting semantic paraphasia when stimulated. The letters correspond to the limits of the tumour identified using intraoperative ultrasonography. Small arrows = precentral gyrus; large arrow = sylvian fissure; curved arrow = inferior frontal sulcus; A = anterior; P = posterior. (C) Intraoperative photograph after tumour resection, showing that the posterior, inferior and deep boundaries of the cavity were represented by language cortical sites and subcortical pathways, as follows: 14, cortical semantic site, which constituted the inferior limit of the resection; 48, subcortical pathway eliciting reproducible semantic paraphasia when stimulated, running under the inferior frontal sulcus with was opened anteriorly (since the anterior part of the middle frontal gyrus was removed in addition to the superior frontal gyrus), and under the inferior frontal gyrus. These fibres run laterally and anteriorly to the head of the caudate nucleus, marked by the tag 46 under the retractor, since the lateral horn of the ventricle was opened (curved arrow). Note that more posteriorly and superiorly to this head of the caudate, subcortical stimulations elicited anomia (tag 47), at the level of pathways corresponding to the cortical site found within the dorsal premotor area (tag 12), thus constituting the postero-lateral boundary of the resection. The patient presented transient postoperative language semantic disturbances with slowness of speech, which recovered within 3 months, following speech rehabilitation. (D) Postoperative axial and coronal T1-weighted enhanced MRI, showing the resection of the left superior frontal gyrus, and the anterior part of the middle frontal gyrus, with opening of the inferior frontal sulcus (axial slice). The subcortical bundle which runs under the depth of this inferior frontal sulcus, in a postero-anterior and infero-superior direction, corresponds to the white fibres which converge in front of and laterally to the head of the caudate nucleus (between the antero-lateral striatum and the anterior part of the superior insulo-opercular sulcus) (curve arrows): this pathway induced semantic paraphasia when stimulated, and thus represented the deep functional boundary of the resection. (E) Postoperative sagittal T1-weighted enhanced MRI, with projection of the surgical cavity (blue line) on a similar MRI view, which visualizes the entire fronto-occipital fasciculus in green using diffusion tensor magnetic resonance tractography (from Catani et al., 2002): such a superimposition shows the similarity of the location of the deep inferior eloquent sites which elicited semantic paraphasias during stimulations (i.e. functional boundaries of the resection) with the tractography of the anterior part of the inferior fronto-occipital fasciculus.
of the resection, since they corresponded to the subcortical pathways eliciting semantic paraphasia when stimulated: this is the reason why a tumoral residue was left on the entire surface of the deep wall of the cavity in two patients, as shown by the immediate postoperative MRI (abnormal antero-posterior rim of the T1 hyposignal in the depth) (Fig. 1D). Interestingly, this subcortical bundle corresponds to the temporal part of the inferior fronto-occipital fasciculus, with radiations coming from the middle, inferior temporal and fusiform gyri within posterior temporal and occipital cortex, then running medially in the temporal lobe and continuing antero-superiorly to the frontal lobe via the anterior floor of the external capsule under the insular lobe (Crosby et al., 1962; Nieuwenhuys et al., 1988; Gloor, 1997; Catani et al., 2002), as shown by a comparison between the residual tumour on postoperative MRI and a similar MRI slice with delineation of the posterior part of this fronto-occipital fasciculus using diffusion tensor imaging (DTI) tractography (from Catani et al., 2002) (Fig. 1E).

In insular lesions, the (anterior) deep boundary of the cavity was the anterior part of the external capsule, since it also elicited semantic paraphasias during electrical stimulation. Postoperative MRI showed the preservation of the white pathways running at the junction of the temporal and frontal lobes, i.e. at the level where the fibres of the inferior fronto-occipital fasciculus compact and pass through the anterior floor of the external capsule (no claustrum was still visible at depth) (Fig. 2C).

In frontal gliomas, the infero-lateral limits of the cavity were by the infero-lateral and dorso-lateral frontal cortex and their corresponding white fibres, which converged in front of and laterally to the head of the caudate nucleus, in order to run posteriorly under the anterior insula. This point of convergence constituted the deep inferior and lateral boudary of the resection, since white fibres at this level induced semantic aphasia when stimulated (Fig. 3D): they correspond to the frontal part of the inferior fronto-occipital fasciculus, as shown by the projection of the surgical cavity on a similar MRI view with visualization of the entire fronto-occipital fasciculus using DTI (from Catani et al., 2002) (Fig. 3E).

Discussion
The results of the present study appears to provide new insights into the anatomo-functional connectivity of the semantic network.

Cortical organization of the semantic system
Numerous lesion, stimulation and neuroimaging works have allowed a better understanding of the cortical organization of the semantic system that is based on two essential ‘epicentres’: the dominant posterior temporal areas and the IFC/DLPFC.

Posterior temporal areas
As mentioned in the Introduction, implication of left posterior temporal areas in semantic processing is supported by neuro-functional imaging (Wise et al., 1991; Bookheimer et al., 1998; Tyler et al., 2003), lesion studies in aphasic patients (Hart and Gordon, 1990; Mummery et al., 1999; Saygin et al., 2003), as well as reports of cortical stimulation (Lüders et al., 1991; Boatman et al., 2000; Ilmberger et al., 2001; Hamberger et al., 2003; Gatignol et al., 2004).

Interestingly, in our study, electrical stimulation identified cortical sites involved in semantic processing in four patients with a temporal glioma. In all four cases, sites were located around the posterior part of the left superior temporal sulcus, i.e. in the superior temporal gyrus immediately above it (one case), or in the middle temporal gyrus immediately below it (one case), or both (two cases). Thus, our intraoperative results support data recently provided by functional neuroimaging.

The lack of detection of a cortical ‘semantic area’ in two cases could be explained first by the fact that, due to the location of the lesions within the mid-part of the temporal lobe in the two patients (one left, one right), the cortical exposure has not been sufficient posteriorly to map the semantic cortical sites. Secondly, since the ‘epicentre’ for comprehension seems to be represented by the superior temporal sulcus, according to neurofunctional imaging studies, we can consider that a major part of this cortex is not accessible to a cortical electrical stimulation before resection, due to the fact that this semantic cortex is buried within the sulcus, and not located at the surface of the brain. This hypothesis was verified in the two patients in which the lesion came in contact with the superior temporal sulcus. In these cases, the sulcus was opened in order to perform the tumour resection, and stimulation of the buried cortex then elicited semantic paraphasias.

IFC
Numerous lesion (Alexander et al., 1989; Otsuki et al., 1998), stimulation (Schäfler et al., 1993, 1996; Devlin et al., 2003) and neuroimaging (Poldrack et al., 1999; Bookheimer, 2002) studies have supported the notion that there are separate subsystems within the IFG responsible for different aspects of language: phonological, syntactic and semantic processing. As detailed in the Introduction, it would seem that phonological (Poldrack et al., 1999) and syntactic (Embick et al., 2000) regions (particularly recruited in cases of syntactic complexity) (Stromswold et al., 1994; Just et al., 1996; Caplan et al., 1998) are centred around the posterior superior IFG at the border of BA 44 and BA 6, both mutually interactive (Keller et al., 2001). Conversely, semantic areas cluster around the antero-inferior IFG (BA 47) (Noppeney and Price, 2002), the pars triangularis (BA 45) (Friederici et al., 2000b) and the DLPFC (BA 46) (mid-part of the middle frontal gyrus) (Noesselt et al., 2003). BA 45/46/47 appear important for executive aspects of semantic processing that
involve semantic working memory, directing semantic search or drawing comparisons between semantic concepts in working memory (Bookheimer, 2002). This region seems to be both modality and content independent.

In our experience, we identified cortical sites involved in semantic processing in five patients using electrical stimulations. Interestingly, in the five cases, these ‘semantic sites’ were located within the infero-lateral frontal cortex (i.e. the anterior and inferior part of the inferior frontal gyrus, in front of the sites which generated production disorders when stimulated) or within the dorso-lateral prefrontal cortex (i.e. the middle frontal gyrus, in front of the dorsal premotor cortex which elicited anomia when stimulated). Thus, our intra-operative results support the data recently provided by functional neuroimaging.

However, the lack of induction of semantic disorders during frontal mapping in the other four patients could be explained by the fact that all harboured a posterior frontal lesion, immediately in front of the precentral gyrus and thus within the dorsal premotor cortex (three left, one right). Consequently, it is likely that the cortical exposure has not been sufficient antero-laterally (i.e. at the level of the IFC and/or the lateral prefrontal cortex) to map the semantic cortical areas. Therefore, we elicited only anomia or dysarthria during stimulations of the premotor cortex, as previously reported (Duffau et al., 2003c). Moreover, similar to the temporal epicentre, it is possible that at least a part of the cortex implicated in the semantic processing was buried within the sulci, and thus not accessible to the stimulation before resection (Rutten et al., 1999).

Subcortical anatomofunctional connectivity of the semantic system
Despite recent improvement of our understanding of the intra-cortical organization of semantic processing, little is currently known concerning the anatomofunctional connectivity of this system. This can be explained by the fact that functional neuroimaging methods (PET, fMRI and MEG) up until recently have been unable to study the white matter bundles. Due to the recent development of DTI, it now becomes possible to track non-invasively in vivo the subcortical fibres (Conturo et al., 1999; Jones et al., 1999; Basser et al., 2000). An excellent illustration is given by the work of Catani et al. (2002), who defined in healthy volunteers the main white pathways of the brain. However, studies using DTI are currently limited only to the identification of the anatomy of the bundles, i.e. they allow the direct study of the anatomical connectivity but they do not allow the direct study of the functional connectivity. Conversely, the recent use of computational algorithms applied to quantities on types of functional imaging data that vary in spatial, temporal and other features have permitted the study of functional connectivity (Horwitz et al., 1998; Newman et al., 2002). Nevertheless, these methods are not able simultaneously to provide information regarding anatomical connectivity.

Consequently, despite the first experience with fusion of these complementary methods, Horwitz (2003) mentions in a recent review concerning brain connectivity, that ‘until it is understood what each definition means in terms of an underlying neural substrate, comparisons of functional and/or effective connectivity across studies may appear inconsistent and should be performed with great caution’.

The use of intraoperative cortical and subcortical electrical stimulation currently gives a unique opportunity to study directly both the anatomical and functional connectivity at the same time, as previously described (Duffau et al., 2002, 2003a,b). Indeed, in spite of the invasive feature of this method, direct brain stimulation offers the advantage of identifying with accuracy and reliability the cortico-subcortical structures essential for language (and not only those involved in this function), by eliciting language disturbances when these areas are stimulated (Ojemann et al., 1989; Berger, 1996; Duffau et al., 2002, 2003a). Thus, it is possible to perform an on-line evaluation of the functional consequences of each focal stimulation on awake patients (i.e. to analyse precisely the type of language disturbances transiently induced), and to correlate each eloquent site to its exact anatomical location on the postoperative MRI—since the edges of the surgical cavity are the functional pathways, due to the fact that the resection was systematically stopped according to functional boundaries. This anatomofunctional study can help to determine different eloquent subregions within a wider area. Although all our patients had structural lesions, language disorders only occurred when stimulating at specific electrode positions. In addition, motor responses to stimulation had a distribution (hand/finger superior, face/mouth inferior) appropriate for primary motor cortex, systematically found at least in patients operated on for a frontal lesion—since the bone flap did not expose the whole central region in cases of temporal tumours. Consequently, these findings strongly suggest that our observations accurately reflect the functional anatomy of the regions tested, particularly at the subcortical level, where brain plasticity phenomena induced by tumour growth seem less than at the cortical level (Duffau et al., 2003d). Note, nevertheless, that subcortical mapping is time consuming, and thus there is a limitation on the number of (language) tasks which can be performed by the awake patient during the surgical procedure.

Interestingly, using this method, we were able to identify subcortical sites eliciting semantic disorders when stimulated, both within the temporal lobe and near the IFC.

Temporal lobe
In the six cases of intraoperative mapping of the dominant temporal lobe, semantic disturbances were systematically induced during stimulations of the white matter located under the superior temporal sulcus. Due to the fact that the removed lesions involved the mid- and posterior parts of the temporal lobe, it was possible to detect several subcortical
sites eliciting semantic errors, from the occipito-temporal junction posteriorly to the junction between the anterior temporal third and the mid-temporal third anteriorly (approximately below the anterior part of the insula). Thus, we could hypothesize that we have identified several sites of the same bundle, running in a longitudinal direction under the superior temporal sulcus, with an inferior limit just above the temporal horn of the ventricle (since this ventricle was opened without inducing any language disorders in four patients), and a superior limit under the superior temporal gyrus.

Such a white bundle implicated in the semantic network would seem in accordance with the literature about the locations of the cortical sites involved in semantic processing (discussed above), i.e. concordant with a possible convergence of fibres coming from the posterior temporal regions (basal infero-temporal area, posterior part of the middle and superior gyri) and from the mid-part of the superior temporal gyrus, in particular concerning its cortex buried within the temporal superior sulcus.

**IFC**

While no patient in this series had a lesion directly involving the IFC, all patients harboured a frontal tumour coming into contact with the 'semantic pathways', since in the nine patients, subcortical stimulations generated semantic paraphasias. In the patient with a glioma invading the middle frontal gyrus, the semantic disorders were elicited by the stimulations of the white fibres under the inferior frontal sulcus, above the anterior part of the superior insulo-opercular sulcus, in front of the pathways involved in speech production. In the patients with a fronto-mesial glioma, the semantic disturbances were systematically generated by the stimulation of the white matter at the level of the antero-infero-lateral edge of the cavity, laterally and in front of the anterior part of the head of the caudate nucleus (frontal horn opened in found patients), and thus in front of the fibres coming from the posterior part of the middle frontal gyrus (the dorsal premotor cortex, inducing anomia when stimulated).

The locations of these subcortical 'semantic sites' are in accordance with the current literature regarding the cortical organization of the semantic system, since all these sites were situated around the IFC, at the level of the superior (medial) and anterior deep boundaries of the DLPFC and pars orbitaris, i.e. converging laterally and in front of the head of the caudate nucleus, and running to the anterior portion of the external capsule, under the anterior part of the insular lobe.

Indeed, in the two patients operated on for an insular low-grade glioma, while there was no language site detected at the surface of this lobe using electrical mapping, despite the contribution of this structure to motor aspects of speech (Duffau et al., 2000; Ackermann and Riecker, 2004), probably due to cortical functional reshaping induced by the glioma (Duffau et al., 2001), semantic paraphasias were reproducibly elicited during stimulation of the anterior floor of the external capsule, at the end of the resection.

In summary, our results provide arguments in favour of the existence of a main pathway underlying the semantic system, within the left or right dominant hemisphere, and joining the two essential epicentres of this network: the posterior and superior temporal areas and the IFC/DLPFC. Interestingly, anatomical studies (Crosby et al., 1962; Nieuwenhuius et al., 1988; Gloor, 1997) and more recent DTI studies (Catani et al., 2002) identified a bundle which connects infero-lateral and dorso-lateral frontal cortices with the posterior temporal cortex and the occipital lobe: the inferior fronto-occipital fasciculus. This fasciculus runs posteriorly from mainly prefrontal cortical areas immediately superior to the uncinate in the frontal lobe. At the junction of the frontal and temporal lobes, the fasciculus narrows in section as it passes through the anterior floor of the external capsule. As the uncinate hooks away anteromedially, the inferior fronto-occipital fasciculus continues posteriorly before running medially in the temporal lobe above and internal to the lateral ventricle, and radiating to the occipital lobe. These radiations terminate in the middle and inferior temporal gyri and in the lingual and fusiform gyri.

Due to the concordance between the anatomy of this fasciculus and the semantic pathway defined using intraoperative subcortical stimulation in our study, we suggest that the inferior fronto-occipital fasciculus might constitute the anatomic support for what could be called the 'semantic loop'. Indeed, this bundle allows the connection between two essential epicentres of the semantic network, i.e. the IFC/DLPFC and the temporal posterior regions within the dominant hemisphere, known to work together in comprehension (Mesulam, 1990; Papathanassiou et al., 2000; Davis and Johnsrude, 2003; Friederici et al., 2003; Heim et al., 2003a), with likely interactive top-down and bottom-up modulation (Tomita et al., 1999; Noesselt et al., 2003).

However, it is important to note that in addition to the inferior fronto-occipital fasciculus, primate anatomical studies have indicated at least one other tract in the temporal lobe, connecting mid-temporal and frontal regions (Petrides and Pandya, 1988). Consequently, it is possible that this bundle may also participate in subserving semantic processing. Further studies combining intraoperative subcortical stimulations and perioperative DTI are thus mandatory, in order to take a multiple pathway view underlying semantic networks.

**Conclusions**

On the basis of our findings, we can hypothesize the existence of a dual route in language connectivity: (i) a ventral semantic stream, connecting the IFC/DLPFC and the posterior temporal regions, via the inferior fronto-occipital fasciculus (± other fronto-temporal tracts); and (ii) a dorsal phonological stream, connecting the IFC/premotor cortex (Duffau et al., 2003c) and the supramarginalis gyrus/postero-superior temporal cortex, via cortico-cortical connections (Duffau et al., 2003a) and the arcuate fasciculus (Duffau et al., 2002).
Interestingly, this model is in accordance with the diagram recently proposed by Gold and Buckner (2002), showing common prefrontal regions co-activated with dissociable posterior regions during controlled semantic (posterior middle temporal gyrus) and phonological (supramarginal gyrus) tasks.

Such an organization of the anatomo-functional connectivity might support the hypothesis put forward by Tzourio-Mazoyer (2003), which consists of applying the hierarchical perception/action sensorimotor model of Fuster (1998) to the organization of language, on the basis of the classification of the cortical architecture suggested by Mesulam (1985) at three levels: processing and production of language sounds via the primary auditory and motor areas; a phonological network including the superior temporal areas and the IFC/ventral premotor cortex (unimodal associative areas); and a semantic network constituted by the posterior part of the superior temporal sulcus and pars triangularis and orbitaris of IFC (multimodal associative areas).

Finally, a better knowledge of the anatomo-functional organization of these distributed subnetworks of language may have important implications concerning the planning of brain surgery of lesions involving these structures.

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References


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References

Connectivity of the semantic system


