

# Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study

Igor Lima Maldonado · Sylvie Moritz-Gasser ·  
Hugues Duffau

Received: 1 January 2011 / Accepted: 5 March 2011 / Published online: 16 March 2011  
© Springer-Verlag 2011

**Abstract** Recent diffusion tensor imaging (DTI) tractography studies indicate that the supramarginal gyrus (SMG) represents a relay between frontal and temporal language sites. Some authors postulate that pathways connecting SMG to the posterior temporal lobe, i.e., the posterior part of the superior longitudinal fascicle (SLF) subserve semantic aspects of language. However, DTI provides only anatomic but not functional data. Therefore, it is impossible to conclude. Interestingly, intra-operative electrical mapping of cortical and subcortical language structures during tumor surgery is recognized as a reliable technique in functional neuroanatomy research. We mapped the underlying white matter of the SMG, especially the SLF, in 11 patients who underwent awake surgery for a glioma involving the left inferior parietal lobule. Using direct electrostimulation, we investigated the exact role of the SLF in language. Our findings indicate that the white matter under the inferior parietal lobule is highly involved in the dorsal phonological system. First, the SMG, connected to the ventral premotor cortex by horizontal fibers of the SLF, subserves articulatory processing, as demonstrated by dysarthria elicited by stimulation. Second, long arcuate fibers, found deeper in the white matter, subserve phonological processing, as supported by phonemic

paraphasia induced by electrostimulation. Third, the most important result is that no semantic disturbances were elicited by stimulating the SLF, including its posterior part. Furthermore, no semantic disorders occurred postoperatively. Subcortical brain mapping by direct electrical stimulation does not provide arguments for a possible role of the left SLF in language semantic processing.

**Keywords** Awake surgery · Language mapping · Superior longitudinal fascicle · Supramarginal gyrus · Semantic processing

## Introduction

The cortical organization of language is better understood than its subcortical component. Nevertheless, since the widespread use of diffusion tensor imaging (DTI) tractography, there has been a renewed interest for the subcortical language networks. For instance, recent DTI studies suggest that in the “indirect pathway” participating in the dorsal route, the supramarginal gyrus (SMG) is a relay between the frontal and temporal language sites (Catani and Mesulam 2008; Catani et al. 2005). However, the exact role of such connections in language is poorly known. Some authors postulate that temporo-parietal fibers, belonging to the posterior segment of the superior longitudinal fasciculus (SLF), process language semantics, such as auditory comprehension (Catani and Mesulam 2008; Catani et al. 2005). Such hypothesis could explain why individuals with conduction aphasia sometimes make semantic errors, albeit much less frequently than phonological disorders. This proposal is nonetheless still debated. Indeed, several functional magnetic resonance imaging (fMRI) studies show SMG activation during phonological

I. L. Maldonado · S. Moritz-Gasser · H. Duffau (✉)  
Department of Neurosurgery, Hôpital Gui de Chauliac,  
CHU Montpellier, 80 Av Augustin Fliche,  
34295 Montpellier, France  
e-mail: h-duffau@chu-montpellier.fr

I. L. Maldonado · S. Moritz-Gasser · H. Duffau  
Team “Plasticity of Central Nervous System, Stem Cells  
and Glial Tumors”, INSERM U1051, Institut for Neurosciences  
of Montpellier, Hôpital Saint Eloi, 80 Avenue Augustin Fliche,  
34091 Montpellier Cedex 5, France

tasks, but fail to demonstrate a significant participation in the semantic processing of language (Glasser and Rilling 2008; Price 2000; Vigneau et al. 2006). However, neither fMRI nor DTI techniques are able to explore functional aspects of the white matter.

The SMG is a part of the inferior parietal lobule and corresponds roughly to the Brodmann area 40. Classically, lesions of the SMG may produce ideomotor apraxia, right–left disorientation, finger agnosia, writing and calculation disorders. Also, large temporo-parietal lesions extending from the left posterior inferior temporal cortex into the supramarginal gyrus were suggested to be associated with phonological dyslexia (Price 2000; Marin 1980). Functional MRI studies have related the activation of a region between the posterior planum temporale and the ventral portion of the SMG to the processing of syntactically complex sentences and of sentences with grammatical errors when compared to simple correct sentences (Price 2010; Raettig et al. 2009; Friederici et al. 2009). The same areas are also activated in the context of challenging perceptual or semantic elements as listening to syllables in background noise (Dos Santos Sequeira et al. 2010) or to sentences where some words were replaced by pseudo-words (Price 2010; Hicock et al. 2009). It is suggested that the SMG participates in the production and comprehension of speech in complex contexts, being implicated in subvocal articulation and short-term memory. Moreover, GSM seems to be involved in monitoring and feedback during speech production, which requires the integration of the motor output with auditory, articulatory and sensory information. It has also shown increased activation when the speech production required additional auditory monitoring, as in the context of semantic or phonologic interference and noise (Abel et al. 2009; Price 2010).

In 1974, Baddeley and Hitch proposed a framework model of working memory, which was subsequently updated in 2000 (Baddeley 2000; Baddely 1992). The phonological or articulatory loop deals with phonological information and consists of two parts: a short-term phonological store and an articulatory rehearsal component that can revitalize memorized information. The phonological store reverberates for preventing loses of material. It can maintain information by subvocal repetition and register visually presented information by subvocalization. The comparison of the distribution of the cerebral blood flow measured by positron emission tomography during tasks engaging selectively one of the two different components of the articulatory loop associated the phonological store with the left SMG, while the subvocal rehearsal system was associated with the left inferior frontal cortex (Paulesu et al. 1993). Other studies suggested that articulatory loop components might be active during both articulation and inner speech (Warburton et al. 1996; Zatorre

et al. 1996). In the work by Zatorre et al. (1996), the authors used a PET technique to analyze cerebral blood flow changes during phonetic manipulation as compared to a baseline condition. It revealed an increased cerebral blood flow in the left frontal lobe, close to the junction between Broca's area and the primary motor cortex in the precentral gyrus, and in a left parietal region near Brodmann area 40. It is also worth noting that despite strong evidence for the participation of the left SMG in phonological aspects of language, this may be bilateral. Recent evidences with transcranial magnetic cerebral stimulation demonstrated that accuracy and reaction times of phonological (not semantic, not perceptual) decisions may be selectively disrupted if stimulation is applied to the left, right, or bilateral SMG (Hartwigsen et al. 2010).

The arcuate fasciculus (AF) is a major pathway classically considered to be the core component linking Wernicke's area and Broca's area. Conduction aphasia, a language disorder characterized by repetition impairment, fluent paraphasic speech, and absence of auditory comprehension problems, is considered to result from a disconnection syndrome due to AF damage (Anderson et al. 1999; Bernal and Ardila 2009). Interestingly, recent studies showed that AF is only the deep part (the "direct pathway") of SLF, which is also constituted by the lateral "indirect pathway" already mentioned (Catani et al. 2005).

Interestingly, neurosurgeons are often confronted in brain tumors involving the temporo-parietal junction of the left dominant hemisphere. This is a challenging situation due to the proximity of language sites both at the cortical and subcortical levels. Intra-operative direct cerebral stimulation (DCS) before and throughout the resection in awake patients was extensively demonstrated to represent a precious and reliable tool to improve surgical results as well as to better understand functional neuroanatomy (Duffau et al. 2002; Thiebaut de Schotten et al. 2005).

Here, we used DCS to map the cortex as well as the underlying white matter of the left dominant inferior parietal lobule in patients who underwent surgery under local anesthesia for a tumor involving the SMG. We investigated the role of SLF in language, especially concerning its possible involvement in semantics, and we discussed our original results in the lights of the recent literature.

## Patients and methods

### Sample

This consecutive series consisted of 11 patients (4 males and 7 females) fulfilling the inclusion criteria, i.e., right-handed adult with a cortico-subcortical glioma involving

the SMG, who underwent awake surgery with intra-operative electrical language mapping. A retrospective review of the medical files from a computerized database allowed the retrieval of population characteristics, pre- and post-operative MRI, and the results of cortical/subcortical brain maps with photographic documentation. The patients had no prior history of neurologic condition or learning disability.

Neurological examination was performed by both a neurosurgeon and a speech therapist on the day before surgery. Handedness was assessed using the Edinburgh inventory. Language was evaluated using the DO-80 (Deloche and Hannequin 1997) and Boston Diagnostic Aphasia Examination (Goodglass et al. 2000).

The mean age was  $45 \pm 12.5$  years (mean  $\pm$  SD). The presenting symptoms were seizures in all cases. A pre-operative language examination revealed disturbances in five cases. The SMG was infiltrated by the tumor in all cases and the angular gyrus in nine cases.

The exact topography of the tumor was examined on a pre-operative MRI examination with enhanced T1-weighted and T2/FLAIR-weighted acquisitions in three different orthogonal planes.

The summary of patient's characteristics is shown in Table 1.

#### Intra-operative brain mapping

All patients underwent awake surgery with DCS, a method previously described by the authors (Duffau 2005; Duffau et al. 2005). A wide craniotomy exposing the sylvian fissure, the frontal operculum, the inferior parietal lobule and the superior part of the inferior temporal gyrus was performed under sedation. The tumor margins were verified in relation to the sulcal and gyral brain surface anatomy with ultrasonography. Letters tags marked the cortical boundaries of the glioma.

Prior to tumor resection, cortical sensorimotor mapping was performed in awake conditions, to avoid damage of eloquent areas. A bipolar electrode (Nimbus\*; Newmedic, Labège, France) with 5 mm tip spacing was used to apply electrostimulation with a biphasic current intensity between 1.5 and 6 mA (60 Hz pulse frequency, 1 ms single pulse phase, 4 s tissue contact) while patient performed the tasks.

Intra-operative language tasks consist of counting and picture naming tests. First, patients were asked to count from 1 to 10 over and over. The speech therapist immediately informs the surgical team of the occurrence of speech arrest, dysarthria, anarthria, speech slowness or facial movements. If the same response is obtained during at least three stimulations, a number tag is attributed to each site. With the goal of finding the optimal threshold of

current intensity, it is progressively increased from a baseline of 1.5 mA in cumulative steps of 0.5 mA until a reproducible response was obtained, i.e., the intensity eliciting a complete speech arrest when stimulating the ventral premotor cortex (Duffau et al. 2003; 2008).

For naming tasks, we used DO 80 tests (Deloche and Hannequin 1997; Metz-Lutz et al. 1991), which consists of 80 different black and white pictures selected according to patient's familiarity, age and level of education. This is the method most often reported for identifying the essential language sites, which are inhibited by DCS. The operative situation imposes the use of simple and sensitive tasks based on short answers, given the brevity of DCS. The DO 80 pictures are presented in a continuous loop on a computer screen placed in front of the patient. A new picture is shown every 4 s (simultaneously to the DCS) and is preceded by a short sentence to read (the French translation of "This is a"). The type of language disturbance (if present) is detailed to the surgical team by the speech therapist (at the bedside during the whole awake phase of the operative procedure), classified in one of the following categories, as previously reported (Duffau et al. 2005a): speech arrest, dysarthria, anarthria, anomia, phonemic paraphasia, semantic paraphasia, speech slowness, initiation troubles and perseveration (repetition of the previous item while the next item is presented to the patient).

A phonemic paraphasia was recorded in case of inadequate performance of constitutive features of phonemes, such as in any of the following situations: omission (e.g., "muroom" instead of "mushroom"), insertion (e.g., "crom" instead of "corn"), permutation (e.g., "letephone" instead of "telephone") or displacement (e.g., "streen" instead of "screen"). Semantic paraphasias were characterized by the production of a word that presented a semantic relationship with the expected response. This relationship could be categorical (e.g. "animal" instead of "kangaroo"), associative (e.g. "cat" instead of "rabbit") or attributive (e.g. "trunk" instead of "elephant"). Other possible semantic disturbances that could be observed were pure verbal paraphasia (production of a word that does not present any semantic or morphological relationship with the expected response, e.g. "mushroom" instead of "desk") and verbal morphological paraphasia (production of a word that presents a morphological but not a semantic relationship with the expected response, e.g. "duck" instead of "truck"). Articulatory troubles were characterized by the occurrence of dysarthria (alteration of muscular control during word production, such as lisping, discontinuity, strained or strangled articulation and slurred sound with difficult intelligibility) or anarthria, its extreme form with loss of the motor ability to produce speech.

Some difficulties regarding the interpretation of the kind of disorders might sometimes arise from fatigue or residual

**Table 1** Clinical, neuropathological and radiological characteristics of the 11 patients

	Sex	Age (years)	Histological type	Location	Presenting symptoms and pre-operative examination	Post-operative final clinical examination
1	M	37	Grade II oligodendroglioma	SMG, AG, T1p	Seizures, attention troubles, lexical access disorders	Normal
2	M	42	Grade II mixed astrocytoma and oligodendroglioma	SMG, AG, T1p	Normal examination, one seizure	Writing difficulties and calculation troubles
3	F	29	Grade II astrocytoma	SMG, AG	Normal examination, one seizure	Normal
4	F	52	Grade II oligodendroglioma	SMG, AG, T1p	Minimal lexical access and working memory disorders, two seizures	Normal
5	F	47	Grade II oligodendroglioma	SMGp, AG, POJ, PCLp	Epilepsy, normal examination	Attention and memory troubles but normal socioprofessional life, writing difficulties in Arabian (native language) but not in French
6	M	27	Grade II oligodendroglioma	SMG, AG	Partial seizure with speech arrest	Normal
7	F	62	Grade II oligodendroglioma	SMG, AGa	Epilepsy, mild sensitive troubles of the right lower limb	Right lateral hemianopsia, slight somatosensory troubles of the right lower limb
8	F	37	Grade II oligodendroglioma	SMG, RCG	Epilepsy, normal examination	Normal
9	M	59	Grade II glioma	SMG, AG, RCG	Epilepsy, progressive cognitive difficulties	Lexical access difficulties and articulatory problems, slight right hemiparesis
10	F	37	Grade III oligodendroglioma	SMG, AG	Partial seizure with speech arrest	Normal
11	F	61	Grade II oligodendroglioma	SMG, RCG, precentral gyrus	Partial seizures, cognitive and fluency difficulties	Normal

Follow-up =  $30 \pm 24$  months (mean  $\pm$  SD)

SMG supramarginal gyrus, AG angular gyrus, T1 superior temporal gyrus, POJ parieto-occipital junction, RCG retro-central gyrus, PCL paracentral lobule, a anterior, p posterior

anesthetic effects. In most of cases, this could be easily differentiated from a true language disturbance. More rarely, clinical responses might be ambiguous. However, since the classification of troubles during the operative procedure is based on their reproducibility and because successive stimulations are performed to the brain tissue, clarification of the clinical responses of a given parenchymal site is obtained shortly after an ambiguous response. Here are two illustrative examples during a picture recognition (DO 80) test.

1. 1st DCS: “rat” instead of “cat” → no conclusion

2nd DCS: “dog” instead of “horse”, 3rd DCS: “train” instead of “plane” etc. → semantic

2. 1st DCS: “rat” instead of “cat” → no conclusion

2nd DCS: “pottle” instead of “bottle”, 3rd DCS “ephelant” instead of “elephant”, etc. → phonological

The patient and the speech therapist are unaware of the timing of electrostimulation application. If the same response is obtained for three or more times, the location of each eloquent zone is marked with the sterile tags.

Since the seminal publication of Ojemann et al. (1989) it has been accepted that this number of trials are sufficient to ensure that a cortical site is essential for language; for example, generating speech disturbances during three stimulations, with normalization of language as soon as the stimulation is stopped. At that time, categorical classification (but not its severity) is recorded for each induced trouble at each site. The same site is never stimulated twice successively to avoid seizures. Numbered tags mark all positive stimulation sites and a photograph before resection is taken, capturing the cortical map.

After completion of cortical mapping, the glioma resection is started during which the subcortical structures, especially the white matter tracts, are systematically stimulated while the patient performed continuous picture naming to identify language pathways. The resection cavity is extended up to the connecting fascicles, with no margin, so that a maximal glioma resection is obtained, while preserving essential cortical and subcortical functional structures (Duffau 2005; Gil Robles and Duffau 2010). After completion of the resection, a second photograph was

taken with numbered tags marking subcortical positive sites.

Post-operative examinations were performed using the same tests as preoperatively.

An MRI examination was performed immediately after the surgery, at 3 months and then every 6 months. We analyzed accurately the anatomical location of eloquent sites and especially of language pathways in the periphery of the operative cavity, where the resection was by definition stopped according to the functional responses eliciting by intra-operative stimulation, as extensively reported elsewhere (de Witt Hamer et al. 2010; Duffau et al. 2002, 2003a, 2005a, 2008; Mandonnet et al. 2007).

## Results

### Intra-operative brain mapping

Cortical language areas were identified in all cases, and represented the boundaries of the tumor resection in the 11 patients. First, stimulation of the ventral premotor cortex, i.e. the rolandic operculum, induced articulatory disturbances in all cases, representing the anterior limit of the resection. Moreover, when stimulating the posterior part of the superior temporal gyrus (T1p), language disturbances were elicited in all cases, representing the lateral limit of the resection. Anomia was the most frequent disorder, induced in 6 patients. Other disorders observed were hesitation (2 patients), semantic troubles (2 patients) and perseveration (1 patient). Syntactic disturbances were induced by stimulating the middle temporal gyrus (T2p) in another case.

The subcortical mapping was also positive for language in all patients (Table 2). Articulatory problems were the most frequent findings, observed in ten cases. Dysarthria or anarthria was induced by stimulating the white matter running from the rolandic operculum to the SMG, i.e. the lateral and horizontal part of the SLF (Fig. 1).

Phonemic paraphasia was the second most common finding, observed in eight patients. This was elicited when stimulating the deep white matter under the SMG once removed, corresponding to the postero-superior portion of the arcuate fascicle (deep part of the SLF). The sites inducing pure phonological paraphasias were deeper and more posterior than those of pure articulatory problems (dysarthria, anarthria) (Figs. 1 and 2).

Interestingly, no semantic disorders were induced during stimulation of the white matter under the SMG. Since all sites have been stimulated three times, it means that articulatory and/or phonemic disturbances have been elicited in 33 ( $3 \times 11$  patients) stimulations of the SLF/AF, while the rate of semantic disturbances was 0 in 33 stimulations of the same white matter tract.

However, semantic paraphasias were observed during subcortical stimulation of the white matter under the posterior part of the superior temporal gyrus and/or under the depth of the superior temporal sulcus (Fig. 2). All cortical and subcortical language structures identified by electrostimulation were preserved.

### Post-operative patient evaluation

Transient language disorders, i.e. articulatory, phonological or naming disturbances were observed in the immediate post-operative period in 8 patients. No semantic disorders were noted. The patients had no comprehension disturbances.

Seven patients were totally asymptomatic at the end of the follow-up period ( $30 \pm 24.0$  months, mean  $\pm$  SD). Five patients still presented persistent mild symptoms that did not prevent them to carry a normal social and professional life (Table 1). Patient 2 experienced writing and calculation disorders. Patient 5, a bilingual female, presented mild attention and memory troubles as well as writing problems. Patient 7 presented a persistent right lateral hemianopsia. Finally, patient 9 experienced lexical access, articulatory disorders and slight contralateral hemiparesis that still continue to recover.

The neuropathological examination diagnosed ten WHO grade II gliomas and one WHO grade III oligodendroglioma.

## Discussion

Here, we report a series of 11 patients who underwent awake surgery for a glioma involving the left SMG, with the use of intra-operative cortical and subcortical electrostimulation mapping. Besides its oncological interest, DCS was extensively demonstrated to represent a research tool offering the unique opportunity to better understand the functional anatomy of cognition networks, especially concerning the subcortical connectivity (de Witt Hamer et al. 2010; Duffau et al. 2002, 2003a, 2005a, 2008; Mandonnet et al. 2007; Thiebaut de Schotten et al. 2005). Here, our goal was to study the functional role of the pathways running under the inferior parietal lobule, namely the different components of the SLF.

Of note, our observations were done in patients harboring gliomas, so that theoretically plasticity mechanisms may have resulted in a relocation of essential language structures (Duffau 2005a). However, despite the presence of a glioma, SLF was identifiable in all patients and its function was clearly not relocated—which is in line with previous reports showing that at the contrary of cortical plasticity, subcortical plasticity is very limited (Duffau 2009).

**Table 2** Results of white matter functional mapping

Location	White matter functional mapping	Immediate post-operative examination
1 SMG, AG, T1p	Antero-inferiorly Articulatory troubles (SLFIII) Deeper, postero-superiorly Phonological troubles (AF) Inferiorly, near the deepest portion of the STS and under STG Semantic errors (IFOF, postero-superior portion/MdLF)	Transient speech apraxia, two seizures
2 SMG, AG, T1p	Antero-inferiorly Articulatory troubles (SLF III) Deeper Phonological disorders (AF) Inferiorly, near the deepest portion of the STS Semantic and syntactic errors (IFOF, postero-superior portion/MdLF)	Transient phonemic errors, memory and calculation troubles
3 SMG, AG	Antero-inferiorly Articulatory troubles (SLFIII) Deeper, postero-superiorly Phonological troubles (AF)	Slowness
4 SMG, AG, T1p	Antero-inferiorly Articulatory troubles (SLFIII) Deeper, posteriorly Phonological troubles (AF) Inferiorly, near the deepest portion of the STS and under STG Semantic errors (IFOF, postero-superior portion/MdLF)	Transient naming disorders
5 SMGp, AG, POJ, PCLp	Antero-inferiorly Articulatory troubles (SLF III) Deeper, postero-superiorly Phonological disorders (AF)	Normal
6 SMG, AG	Antero-inferiorly Articulatory troubles (SLFIII) Inferiorly, near the deepest portion of the STS and under STG Semantic errors (IFOF, postero-superior portion/MdLF)	Transient speech apraxia and limb ataxia (right side)
7 SMG, AGa	Anterior-superiorly Thalamo-cortical somatosensory fibers of the upper limb and face: dysesthesias Deeper, posteriorly Phonological troubles (AF)	Somatosensory disorders of the right lower limb, right lateral hemianopsia
8 SMG, RCG	Anterior-superiorly Thalamo-cortical somatosensory fibers of the upper limb and face: dysesthesias Deeper, posteriorly Phonological disorders (AF)	Transient phonological disturbances and facial paresis
9 SMG, AG, RCG	Antero-inferiorly Articulatory troubles (SLFIII) Anterior-superiorly Thalamo-cortical somatosensory fibers of the upper limb and face: dysesthesias	Transient hemiparesis, limb ataxia, hemihypesthesia, and articulatory disorders
10 SMG, AG	Antero-inferiorly Articulatory troubles (SLFIII) Deeper, posteriorly Phonological troubles (AF)	Transient articulatory troubles

**Table 2** continued

	Location	White matter functional mapping	Immediate post-operative examination
11	SMG, RCG, PrCG	Antero-inferiorly Articulatory troubles (SLFIII) Anterior-superiorly Thalamo-cortical somatosensory fibers of the upper limb and face: dysesthesias	Transient attention and articulatory troubles

*SMG* supramarginal gyrus, *AG* angular gyrus, *T1* superior temporal gyrus, *T2* middle temporal gyrus, *RCG* post-central gyrus, *PrCG* precentral gyrus, *STS* superior temporal sulcus, *PCL* paracentral lobule, *POJ* parieto-occipital junction, *SLF* superior longitudinal fascicle, *AF* arcuate fascicle, *IFOF* inferior fronto-occipital fascicle, *MdLF* middle longitudinal fascicle, *a* anterior, *p* posterior

### Stimulation of the horizontal part of the lateral SLF

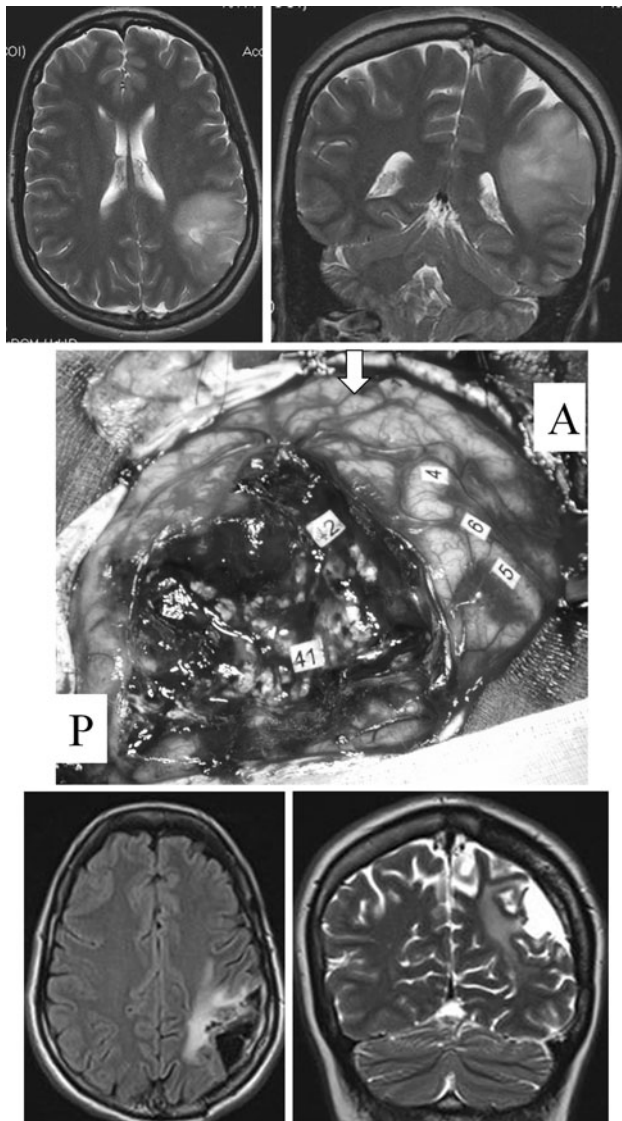
During functional mapping of the white matter in the 11 patients, articulatory disorders were the most encountered finding. Anarthria or dysarthria was induced during counting or naming by stimulating the white matter from the depth of the central sulcus (anteriorly) to the depth of the end of the sylvian fissure under the SMG (posteriorly). Thus, these language disorders were elicited by stimulation of a superficial tract running from the SMG to the rolandic operculum. This bundle could correspond to the horizontal part of the lateral portion of the SLF. Interestingly, in his model of working memory, Baddeley (2000) described an articulatory loop consisting of two parts: a short-term phonological store and an articulatory rehearsal component that can revitalize memorized information. Functional neuroimaging studies suggest that the phonological store involved the left SMG, while the subvocal rehearsal system was associated with the left inferior frontal cortex and the ventral premotor cortex (Paulesu et al. 1993).

In our study, we stimulated both frontal and parietal cortical epicenters, as well as the white matter pathway connecting them. We previously demonstrated that electrostimulation of the ventral premotor cortex (i.e. the lateral part of the precentral gyrus) elicited articulatory disturbances in a very reproducible way (Duffau et al. 2003), as confirmed in the present series. Interestingly, left SMG stimulation also induced articulatory disorders. Furthermore, electrostimulation of the white matter tract that directly connects the SMG to the ventral premotor cortex induced anarthria or dysarthria, supporting the role of this pathway in the articulatory loop—as already suggested in a preliminary case report (Duffau et al. 2003a). In 1984, Petrides and Pandya (1984) proposed a four-component subdivision of SLF from experimental observations in non-human primates. In a DTI study, it was also demonstrated that the four components could be identified and segmented in humans (Makris et al. 2005). The ventral one (SLF III) seems to originate from the SMG and terminate predominantly in the ventral premotor and prefrontal areas. We hypothesize that, in our study, articulatory disturbances were due to the stimulation of SLF III.

### Stimulation of the deep part of the SLF: arcuate fasciculus (Fig. 3)

Phonemic paraphasias were the second most encountered deficit induced during subcortical mapping. They were obtained by stimulating the white matter in the depth of the surgical cavity, namely the postero-superior portion of the arcuate fascicle (AF), after removal of at least a part of the inferior parietal lobule and its short association U-fibers. Such responses were elicited in a very reproducible way, as previously reported (Duffau et al. 2002). Here, a major result is that no semantic troubles were elicited by stimulating the SLF.

As demonstrated by dissection and DTI studies (Catani et al. 2005; Catani et al. 2008; Dejerine 1895; Ludwig and Klinger 1956), when penetrating within the white matter of the temporo-parietal region, the first long association fascicle encountered is the SLF, running under the subcortical short association U-fibers. This fascicle classically associates distant areas in the frontal, parietal and temporal lobes, dealing with high order functions, especially language in the dominant hemisphere (Anderson et al. 1999; Bernal and Ardila 2009; Catani et al. 2005). In the segmentation proposed by Makris et al. (2005), the fourth and deepest part of the SLF is the AF. This compact C-shaped structure that surrounds the insula and interconnects frontal and temporal lobes is partially exposed in its postero-superior portion by removal of the cortex and subcortical “U” fibers of the inferior parietal lobule. While it travels along perisylvian cortex, SLF/AF receives shorter fibers coming from adjacent regions, a phenomenon that seems particularly important in the inferior parietal lobule, as demonstrated by fiber dissection and DTI studies (Catani et al. 2005; Fernandez-Miranda et al. 2008). Within the temporo-parietal junction, a group of roughly vertically oriented fibers connects the posterior part of the superior and middle temporal gyri to the SMG, which also receives horizontal fibers from the anterior segment of the fascicle, as mentioned (Catani and Mesulam 2008; Catani et al. 2005). As a result, besides long arcuate fibers, frontal and temporal lobes could also be interconnected by parallel shorter fibers



◀ **Fig. 1** Upper Pre-operative axial (left) and coronal (right) T2-weighted MRI showing a WHO grade II glioma involving the left inferior parietal lobule in a right-handed patient who experienced partial seizures (patient 10). Middle Intra-operative view of the cortical and subcortical functional mapping after tumor removal according to functional boundaries. The patient's head is turned to the right. The number tags mark eloquent sites detected by direct cerebral stimulation under local anesthesia. At the cortical level: 1 anarthria (ventral motor cortex in the lateral part of the precentral gyrus); somatosensory areas in the retro-central gyrus: 4 face, 6 thumb, 5 other fingers. To be noted that a hesitation was induced during the stimulation of the posterior part of the superior temporal gyrus, not marked here. At the subcortical level: 42 dysarthria, in the antero-inferior portion of the operative cavity (articulatory loop, lateral portion of the superior longitudinal fascicle, i.e., SLF III); 41 phonemic paraphasias, deeper, in the postero-superior part of the operative cavity (arcuate fascicle, i.e. deep portion of the SLF). The anterior edge of the cavity is represented by the retrocentral sulcus, and the mesial edge by the intraparietal sulcus. A anterior, P posterior; arrow sylvian fissure. Lower Post-operative axial (left) and coronal (right) T2-weighted MRI showing a resection of the left inferior parietal lobule, with an incomplete removal of the glioma in the depth, due to an involvement of the SLF (the tumor infiltration is demonstrated by a hyper-intensity within the white matter). The patient had no post-operative semantic disorders

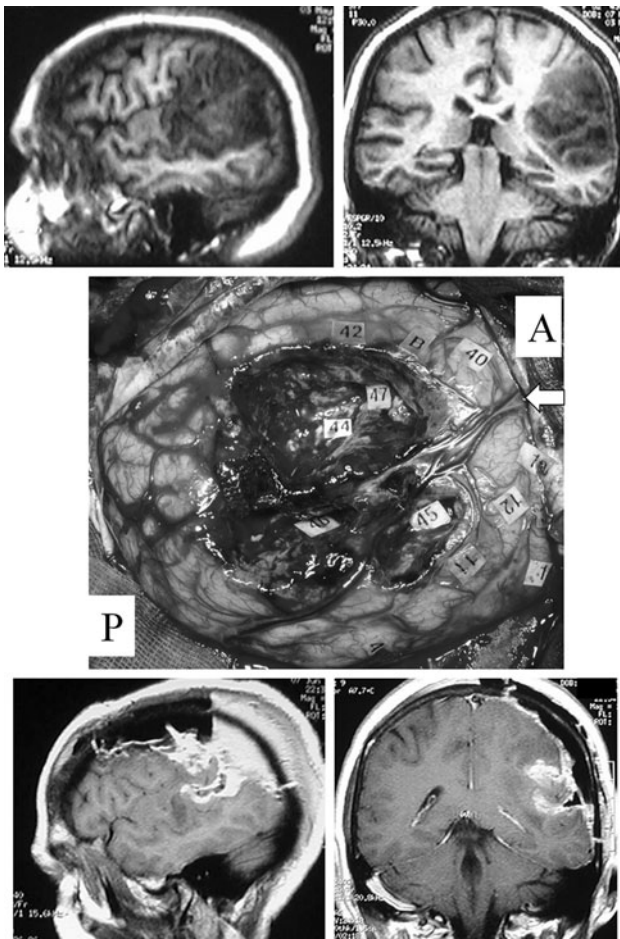
circuits that include both cortical areas and fiber bundles. Therefore, a given symptom can be generated by a damage of distant cortical sites or connecting pathways. This “hodological” point of view, emphasized by Catani and coworkers (Catani and ffytche 2005; Catani and Mesulam 2008 and 2008a; Catani et al. 2005) could explain: (1) the heterogeneity of lesions among patients with conduction aphasia; (2) the fact that repetition troubles could be induced by stimulation of the gray matter in epileptic patients (Quigg and Fountain 1999; Quigg et al. 2006); (3) the fact that phonemic paraphasia can also be induced by DCS at any point of the AF (Duffau 2008; Duffau et al. 2002, 2008).

Here, we confirm that stimulation of this pathway elicited phonemic paraphasias. Moreover, the main result is that no semantic disorders were induced during its stimulation. When Catani and Mesulam (2008, 2008a) suggested that the SLF may connect Broca's and Wernicke's area by means of shorter fibers that relay in the “Geschwind territory”, they assumed that this “expanded version” of the AF (and the SMG) might have a role in processing semantic information. Glasser and Rilling (2008) also hypothesized that the arcuate fibers might have different routes and functions, including semantic processing. For them, AF terminations in the posterior part of the superior temporal gyrus would process phonetic information and AF terminations in the middle temporal gyrus would process lexical-semantic information. Due to bilateral activation, they also implied the right AF in phonological processing. Nevertheless, here, DCS gives no consistent proof that the AF connections between the inferior parietal lobule and the

that join the so-called Geschwind's territory, which corresponds anatomically to the SMG (Catani et al. 2005).

From a functional point of view, different segments of the SLF may be related to specific aspects of language. Indeed, selective lesions or subcortical stimulations may generate different language disorders. Damage of the AF is well-known to induce a disconnection syndrome called “conduction aphasia”, which combines repetition and phonological disorders. In the classical model of Wernicke, the paraphasic speech of patients with this syndrome was interpreted as the inability for temporal language sites to monitor Broca's area speech output (Catani and Mesulam 2008). Observations are, however, heterogeneous. Conduction aphasia was reported after cortical lesions, mixed cortical and subcortical lesions or even AF lesions without repetition deficit (Anderson et al. 1999; Hickok and Poeppel 2004). Indeed, language processing involves





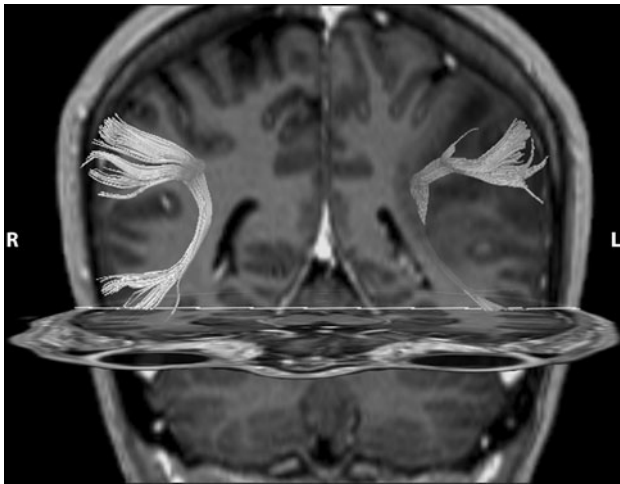
**Fig. 2** *Upper* Pre-operative sagittal (*left*) and coronal (*right*) T1-weighted MRI showing a WHO grade II glioma involving both the left inferior parietal lobule and the posterior part of the superior temporal gyrus in a right-handed patient who experienced partial seizures (patient 4). *Middle* Intra-operative view of the cortical and subcortical functional mapping after tumor removal according to functional boundaries. The patient's head is turned to the right. The number tags mark eloquent sites detected by direct cerebral stimulation under local anesthesia. At the cortical level: 10 anarthria (ventral motor cortex in the lateral part of the precentral gyrus); 1 primary motor cortex of the face; somatosensory areas in the retro-central gyrus: 12 and 11 face, 4 fingers; 40 semantic paraphasia (mid-posterior part of the superior temporal gyrus); 42 syntactic disorders (mid-posterior part of the middle temporal gyrus). At the subcortical level: 45 dysarthria, in the anterior portion of the operative cavity (articulatory loop, lateral portion of the superior longitudinal fascicle, i.e. SLF III); 46 phonemic paraphasias, deeper, in the posterior part of the operative cavity (arcuate fascicle, i.e. deep portion of the SLF); 44 and 47 semantic paraphasias, in the inferior part of the cavity, after resection of the posterior part of the superior temporal gyrus (horizontal tract corresponding to the inferior fronto-occipital fascicle and/or middle longitudinal fascicle). A anterior, P posterior; arrow sylvian fissure; B superior temporal sulcus. *Lower* Post-operative sagittal (*left*) and coronal (*right*) T1-weighted MRI showing a resection of both the left inferior parietal lobule and the posterior part of the superior temporal gyrus, with an incomplete removal of the glioma in the depth, due to an involvement of the language pathways (the tumor infiltration is demonstrated by a hypo-intensity within the white matter). The patient had no post-operative semantic disorders

posterior temporal lobe subserve semantics. Furthermore, these intra-operative results are supported by the fact that no semantic disorders were observed after the surgery—while phonological disturbances occurred in the immediate post-operative period. Indeed, SMG connections were obligatorily interrupted during tumor removal. Thus, the absence of comprehension disturbances indicate that other (parallel) pathways harbor semantic processing. We suggest that such pathways might be part of the ventral stream.

#### Ventral semantic root

It seems impossible to sum up language connections to the SLF/AF. There is growing evidence that the language connectivity is organized in two major streams (Hickok and Poeppel 2004, 2007). Saur et al. (2008) investigated this two-stream model in a hybrid study that combined functional MRI and DTI, using cortical activation nodes as seeds for fiber tractography. For these authors, a dorsal system subserving sublexical repetition of speech would be represented essentially by the SLF/AF. In contrast, language comprehension would be mediated by a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex via the extreme capsule. The middle longitudinal fascicle and the inferior longitudinal fasciculus, two long-association tracts, would contribute fibers to both the AF/SLF and the extreme capsule.

Using intra-operative cortical and subcortical electrostimulation, we confirm here that a dorsal stream, dealing with phonological integration, would be represented by SLF/AF fibers. Nonetheless, only a few semantic paraphasias were observed. At the cortical level, they were elicited by stimulation of the posterior part of the superior temporal gyrus in two patients. At the subcortical level, they were induced during stimulation of horizontal white matter tracts running under the posterior part of the superior temporal gyrus in two cases or under the depth of the superior temporal sulcus in two other cases. Anatomically, these tracts could correspond to the posterior part of the superficial and dorsal subcomponent of the inferior fronto-occipital fasciculus (Martino et al. 2010), a fascicle thought to be involved in language semantics since inducing semantic disorders when stimulated (Duffau et al. 2005a, 2008). Interestingly, these tracts could also partly correspond to the posterior part of the middle longitudinal fascicle, running under the superior temporal sulcus, and thus in agreement with the report by Saur et al. (2008). However, in our recent experience, it is puzzling to note that both stimulation and resection of the white matter of the anterior and mid-superior temporal gyrus, interrupting the fibers of the middle longitudinal fasciculus, did not induce



**Fig. 3** Pre-operative composite (coronal/axial) view of a diffusion tensor based tractography of long arcuate fibers around the insular lobe, connecting the frontal and parietal lobes. The morphological T1 sequence shows a glioma involving the left inferior parietal lobe in this right-handed patient who experienced partial seizures with speech arrest (patient 10). It is nonetheless worth noting that, in the present series, anatomo-functional correlations were not based on tractography or neuronavigation data

any language deficit (de Witt Hamer et al. 2010). Further studies combining anatomic dissections, functional MRI, DTI and DCS are still needed to better understand the anatomo-functional connectivity underlying the ventral semantic stream.

Some authors have pruned the incorporation of data from pre-operative diffusion-weighted MR imaging within an intra-operative image-guided system. However, during tumor resection, navigation becomes inaccurate because of brain shift, thus with a significant risk to induce fiber tracts injury. The use of repeated direct subcortical stimulations allows the identification of language tracts before their surgical disruption. Therefore, DTI tractography was not part of the protocol in this present study. Nonetheless, DTI may represent a powerful tool for the completion of anatomo-functional correlations using peri-operative MRIs (Fig. 3).

A limitation of the present study is the fact that functional neuroanatomy aspects are inferred from a series of pathological brains. It is known that low-grade gliomas are slow-growing tumors that may infiltrate eloquent zones with relative preservation of function (Duffau 2005a). Nevertheless, tumor invasion may be responsible for alterations of the functional organization even in distant areas of the brain, through phenomena such as cerebral diaschisis (von Monakow 1914; Price et al. 2001). It means that lesion in a given brain area may generate functional disorders related to another remote area, which is connected to the first one. Recent functional neuroimaging studies have demonstrated the occurrence of functional/

metabolic alterations even in the contralateral hemisphere. A classic example is crossed cerebellar diaschisis, which occurs following supratentorial brain lesions with motor deficit. More recently, Price and coworkers introduced the term of dynamic diaschisis to describe context-dependent effects of a brain lesion on the functional responses of a distant region, which may be evidenced by PET scan. When functional responses of a remote undamaged eloquent area depend on the damaged one, they will be abnormal. When they not depend on it, they will not. Three interesting observations derive from these studies: (1) functional responses observed during DCS result from the induction of disturbance of distributed networks responsible for functions performed by distributed groups of connected neurons rather than individual centers, and these networks may not be the same as in the normal (undamaged) brain; (2) transient language disturbances during stimulation of the white matter can be interpreted as the result of a temporary virtual disconnection between brain centers; (3) the functional responses of the area in the damaged brain may be variable depending on the task that is presented to the patient.

However, it is worth noting that despite possible mechanisms or functional reorganization due to slow-growing tumors as low-grade gliomas at the cortical level (Duffau et al. 2005a), we also previously reported that the degree of cerebral plasticity is almost nil at the level of the white matter pathways (Duffau 2009). As a consequence, it is likely that our observations about the SLF during stimulations were not disturbed by the presence of a glioma.

## Conclusions

On the basis of our findings, we can postulate that SLF/AF seems highly involved in the dorsal phonological system. To the present date, the cortical and subcortical brain mapping by direct cerebral stimulation does not provide arguments for the participation of SLF/AF in semantic processing; a hypothesis based on neuroimaging study data. Such findings may have both clinical and fundamental implications.

**Acknowledgment** We would like to thank Mr. Julien Le-Tellier for his precious assistance with the image database.

## References

- Abel S, Dressel K, Bitzer R, Kummerer D, Mader I, Weiller C, Huber W (2009) The separation of processing stages in a lexical interference fMRI-paradigm. *Neuroimage* 44:1113–1124
- Anderson JM, Gilmore R, Roper S, Crosson B, Bauer RM, Nadeau S, Beversdorf DQ, Cibula J, Rogish M 3rd, Kortencamp S, Hughes

- JD, Gonzalez Rothi LJ, Heilman KM (1999) Conduction aphasia and the arcuate fasciculus: a reexamination of the Wernicke-Geschwind model. *Brain Lang* 70:1–12
- Baddeley A (2000) The episodic buffer: a new component of working memory? *Trends Cogn Sci* 4:417–423
- Baddely A (1992) Working memory. *Science* 255:556–559
- Bernal B, Ardila A (2009) The role of the arcuate fasciculus in conduction aphasia. *Brain* 132:2309–2316
- Catani M, ffytche DH (2005) The rises and falls of disconnection syndromes. *Brain* 128:2224–2239
- Catani M, Mesulam M (2008a) The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. *Cortex* 44:953–961
- Catani M, Mesulam M (2008b) What is a disconnection syndrome? *Cortex* 44:911–913
- Catani M, Thiebaut de Schotten M (2008) A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex* 44:1105–1132
- Catani M, Jones DK, ffytche DH (2005) Perisylvian language networks of the human brain. *Ann Neurol* 57:8–16
- De Witt Hamer P, Moritz-Gasser S, Gatignol P, Duffau H (2010) Is the human left middle longitudinal fascicle essential for language? A brain electrostimulation study. *Hum Brain Mapp* [Epub ahead of print]
- Dejerine J (1895) *Anatomie des Centres Nerveux*. Tome I. Rueff et Cie, Paris
- Deloche G, Hannequin D (1997) *Test de dénomination orale de 80 images—DO 80*. Editions du Centre de Psychologie Appliquée, Paris
- Dos Santos Sequeira S, Specht K, Moosmann M, Westerhausen R, Hugdahl K (2010) The effects of background noise on dichotic listening to consonant-vowel syllables: an fMRI study. *Laterality* 15:577–596
- Duffau H (2005a) Intraoperative cortico-subcortical stimulations in surgery of low-grade gliomas. *Expert Rev Neurother* 5:473–485
- Duffau H (2005b) Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol* 4:476–486
- Duffau H (2008) The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. *Neuropsychologia* 46:927–934
- Duffau H (2009) Does post-lesional subcortical plasticity exist in the human brain. *Neurosci Res* 65:131–135
- Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, Bitar A, Fohanno H (2002) Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 125:199–214
- Duffau H, Capelle L, Denvil D, Gatignol P, Sichez N, Lopes M, Sichez JP, van Effenterre R (2003a) The role of dominant premotor cortex in language: a study using intraoperative functional mapping in awake patients. *Neuroimage* 20:1903–1914
- Duffau H, Gatignol P, Denvil D, Lopes M, Capelle L (2003b) The articulatory loop: study of the subcortical connectivity by electrostimulation. *Neuroreport* 14:2005–2008
- Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, van Effenterre R, Capelle L (2005a) Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry* 76:845–851
- Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L (2005b) New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain* 128:797–810
- Duffau H, Gatignol P, Mandonnet E, Capelle L, Taillandier L (2008) Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. *J Neurosurg* 109:461–471
- Fernandez-Miranda JC, Rhoton AL Jr, Alvarez-Linera J, Kakizawa Y, Choi C, de Oliveira EP (2008) Three-dimensional microsurgical and tractographic anatomy of the white matter of the human brain. *Neurosurgery* 62:989–1026
- Friederici AD, Makuuchi M, Bahlmann J (2009) The role of the posterior superior temporal cortex in sentence comprehension. *Neuroreport* 20:563–568
- Gil Robles S, Duffau H (2010) Surgical management of World Health Organization Grade II gliomas in eloquent areas: the necessity of preserving a margin around functional structures. *Neurosurg Focus* 28(2):E8
- Glasser MF, Rilling JK (2008) DTI tractography of the human brain's language pathways. *Cereb Cortex* 18:2471–2482
- Goodglass H, Kaplan E, Barressi B (2000) *The assessment of aphasia and related disorders*, 3rd edn. Lippincott Williams & Wilkins, Philadelphia
- Hartwigsen G, Baumgaertner A, Price CJ, Koehnke M, Ulmer S, Siebner HR (2010) Phonological decisions require both the left and right supramarginal gyri. *Proc Natl Acad Sci USA* 107:16494–16499
- Hickok G, Poeppel D (2004) Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition* 92:67–99
- Hickok G, Poeppel D (2007) The cortical organization of speech processing. *Nat Rev Neurosci* 8:393–402
- Hicock G, Osaka K, Serences JT (2009) Area Spt in the human planum temporale supports sensory-motor integration for speech processing. *J Neurophysiol* 101:2725–2732
- Ludwig E, Klingler J (1956) *Atlas humanis cerebri*. Karger, Basel
- Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, Pandya DN (2005) Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb Cortex* 15:854–869
- Mandonnet E, Nouet A, Gatignol P et al (2007) Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain* 130:623–629
- Marin OSM (1980) CAT scans of five deep dyslexic patients. Appendix 1. In: Coltheart M, Patterson KE, Marshall JC (eds) *Deep dyslexia*. Routledge & Kegan Paul, London, pp 407–411
- Martino J, Brogna C, Gil Robles S, Vergani F, Duffau H (2010) Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex* 46:691–699
- Metz-Lutz MN, Kremin H, Deloche G, Hannequin D, Ferrand I, Perrier Palisson D (1991) Standardisation d'un test de dénomination orale: contrôle de l'âge, du sexe et du niveau de scolarité chez des sujets adultes normaux. *Revue de Neuropsychologie* 1:73–95
- Ojemann GA, Ojemann JG, Lettich E, Berger MS (1989) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 71:316–326
- Paulesu E, Frith CD, Frackowiak RS (1993) The neural correlates of the verbal component of working memory. *Nature* 362:342–345
- Petrides M, Pandya DN (1984) Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J Comp Neurol* 228:105–116
- Price CJ (2000) The anatomy of language: contributions from functional neuroimaging. *J Anat* 197:335–539
- Price CJ (2010) The anatomy of language: a review of 100 fMRI studies published in 2009. *Ann NY Acad Sci* 1191:62–88

- Price CJ, Warburton EA, Moore CJ, Frackowiak RS, Friston KJ (2001) Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. *J Cogn Neurosci* 13:419–429
- Quigg M, Fountain NB (1999) Conduction aphasia elicited by stimulation of the left posterior superior temporal gyrus. *J Neurol Neurosurg Psychiatry* 66:393–396
- Quigg M, Geldmacher DS, Elias WJ (2006) Conduction aphasia as a function of the dominant posterior perisylvian cortex. Report of two cases. *J Neurosurg* 104:845–848
- Raettig T, Frisch S, Friederici AD, Kotz SA (2009) Neural correlated of morphosyntactic and verb-argument structure processing: an fMRI study. *Cortex* 46:613–620
- Saur D, Kreher BW, Schnell S, Kummerer D, Kellmeyer P, Vry MS et al (2008) Ventral and dorsal pathways for language. *Proc Natl Acad Sci USA* 105:18035–18040
- Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Levy R, Dubois B, Bartolomeo P (2005) Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science* 309:2226–2228
- Vigneau M, Beaucousin V, Herve PY, Duffau H, Crivello F, Houde O, Mazoyer B, Tzourio-Mazoyer N (2006) Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage* 30:1414–1432
- Von Monakow C (1914) Die lokalisation im Grosshirn und der Abbau der Funktion Durch Korrikale Heroe. JF Bergam, Weisbarden, pp 26–34
- Warburton E, Wise RJ, Price CJ, Weiller C, Hadar U, Ramsay S, Frackowiak RS (1996) Noun and verb retrieval by normal subjects. Studies with PET. *Brain* 119(Pt 1):159–179
- Zatorre RJ, Meyer E, Gjedde A, Evans AC (1996) PET studies of phonetic processing of speech: review, replication, and reanalysis. *Cereb Cortex* 6:21–30