Limited Plastic Potential of the Left Ventral Premotor Cortex in Speech Articulation: Evidence From Intraoperative Awake Mapping in Glioma Patients

Kim van Geemen,¹ Guillaume Herbet,^{1,2} Sylvie Moritz-Gasser,^{2,3} and Hugues Duffau^{1,2*}

¹Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Centre, Montpellier, France

²Team “Plasticity of Central Nervous System Stem Cells and Glial Tumors,” INSERM U1051, Institute for Neurosciences of Montpellier, Montpellier University Medical Center, Montpellier, France

³Department of Neurology, Gui de Chauliac Hospital, Montpellier University Medical Center, Montpellier, France

Abstract: *Objectives:* Despite previous lesional and functional neuroimaging studies, the actual role of the left ventral premotor cortex (vPMC), i.e., the lateral part of the precentral gyrus, is still poorly known. *Experimental design:* We report a series of eight patients with a glioma involving the left vPMC, who underwent awake surgery with intraoperative cortical and subcortical language mapping. The function of the vPMC, its subcortical connections, and its reorganization potential are investigated in the light of surgical findings and language outcome after resection. *Principal observations:* Electrostimulation of both the vPMC and subcortical white matter tract underneath the vPMC, that is, the anterior segment of the lateral part of the superior longitudinal fascicle (SLF), induced speech production disturbances with anarthria in all cases. Moreover, although some degrees of redistribution of the vPMC have been found in four patients, allowing its partial resection with no permanent speech disorders, this area was nonetheless still detected more medially in the precentral gyrus in the eight patients, despite its invasion by the glioma. Moreover, a direct connection of the vPMC with the SLF was preserved in all cases. *Conclusions:* Our original data suggest that the vPMC plays a crucial role in the speech production network and that its plastic potential is limited. We propose that this limitation is due to an anatomical constraint, namely the necessity for the left vPMC to remain connected to the lateral SLF. Beyond fundamental implications, such knowledge may have clinical applications, especially in surgery for tumors involving this cortico-subcortical circuit. *Hum Brain Mapp* 35:1587–1596, 2014. © 2013 Wiley Periodicals, Inc.

Key words: ventral premotor cortex; superior longitudinal fascicle; speech articulation; awake surgery; subcortical electrostimulation; brain plasticity

*Correspondence to: Hugues Duffau, Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, 80 Avenue Augustin Fliche, 34295 Montpellier, France. E-mail: h-duffau@chu-montpellier.fr

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INTRODUCTION

The ventral premotor cortex (vPMC), i.e., the ventral component of Brodmann area 6, is a structure covering the anterior and lateral part of the precentral gyrus [Freund, 1996]. In recent years, the role of the vPMC and its subcortical connections have been studied with functional MR imaging, tractography, and magnetic transcranial stimulation. Researchers investigated the involvement of the

TABLE I. Patient characteristics

Patients	Age, gender	Handedness	Inaugural symptoms	Tumor type	Tumor location	Preoperative volume / postoperative volume / extent of resection (%)
1.	20, F	Ambidextrous	Partial seizures	LGG	Left vPMC, insula	30cc / 2cc / 93%
2.	43, M	Right handed	Partial seizures	LGG	Left vPMC	10cc / 1cc / 90%
3.	52, M	Right handed	Partial seizures	LGG	Left vPMC	15cc / 1.5cc / 90%
4.	36, F	Right handed	Partial seizures	LGG	Left vPMC, Broca's area, insula	76cc / 15cc / 81%
5.	32, M	Right handed	Partial seizures	LGG	Left vPMC	46cc / 6cc / 87%
6.	38, M	Right handed	Partial seizures	LGG	Left vPMC	14cc / 1.5cc / 89%
7.	46, F	Right handed	Partial seizures	LGG	Left vPMC, Broca's area	First surgery: 80cc / 28cc / 65%; Second surgery: 74cc / 8cc / 89%
8.	32, F	Left handed	Partial seizures	LGG	Left vPMC, Broca's area	59cc / 7cc / 88%

M, male; F, female; vPMC, ventral premotor cortex; LGG, Low-grade glioma (WHO grade II).

dominant vPMC in language production and perception, by focusing on articulation, tongue movement, counting, and sequential processing [Cunillera et al., 2009; Dick et al., 2010; Friederici, 2006; Guenther, 2006; Horwitz and Braun, 2004; Iacobini, 2008; Meister et al., 2009; Osnes et al., 2012; Sato et al., 2009; Scott et al., 2009; Szenkovits et al., 2012; Tremblay and Small, 2011]. However, the number of specific studies on the vPMC remains low, especially in comparison with the large amount of works on other language areas such as Broca and Wernicke's areas. In addition, several methodological issues make the clear understanding of the exact role of the vPMC difficult: (i) the name of vPMC may refer to different anatomical regions, e.g., lateral or more mesial part of the precentral gyrus [Cunillera et al., 2009; Sato et al., 2009; Tremblay and Small, 2011]; (ii) several studies do not distinguish the ventral PMC and dorsal PMC, while their anatomic locations are different [Friederici, 2006; Iacobini, 2008; Meister et al., 2009; Osnes et al., 2009; Szenkovits et al., 2012]; (iii) several studies discuss the function of the vPMC in combination with other areas, e.g., Broca's area or the whole inferior frontal gyrus [Dick et al., 2010; Friederici, 2006; Guenther, 2006; Horwitz and Braun, 2004; Scott et al., 2009]. Therefore, the actual participation of the vPMC in language and its plastic potential are still poorly known.

Here, we report a series of eight patients with a diffuse low grade glioma involving the left vPMC, who underwent awake surgery with intraoperative language mapping using direct cortical and subcortical electrostimulation. In the light of surgical findings and language outcome after resection, we discuss the function and the subcortical connectivity of the left vPMC, as well as its reorganization potential.

MATERIALS AND METHODS

Patients

Between April 2005 and June 2012, eight patients with a low grade glioma (World Health Organization grade II

glioma) involving the left vPMC underwent awake surgery with intraoperative language mapping. Patient characteristics are presented in Table I. There were 4 males and 4 females ranging in age from 20 to 52 (mean age of 37.4). Seizure was the initial clinical symptom in all patients. The Edinburgh inventory for handedness showed that six patients were right-handed, one patient was left-handed and one patient was ambidextrous. The neurological examination before surgery was normal in all cases.

Pre- and Postoperative Functional Assessment

Language function was assessed by a speech therapist pre- and postoperatively by evaluating the level of fluidity and informativity of spontaneous speech. In addition, the D0 80 picture naming task, which consists of 80 black and white pictures selected on variables such as frequency, age of acquisition and level of education [Metz-Lutz et al., 1991], was administered to each patient. Preoperative language examination was performed one day before surgery. Immediate postoperative assessment was achieved 3–5 days after surgery and postoperative assessment was conducted 3 months after surgery. All patients received speech rehabilitation in the postoperative period.

The Karnofsky Performance Scale (KPS) score [Karnofsky and Burchenal, 1949] was also evaluated 3 months after surgery.

Intraoperative Language Mapping

All patients underwent awake surgery under local anaesthesia to allow functional, especially language, cortical and subcortical mapping with direct electrical stimulation. This method has been extensively described in previous studies [Duffau et al., 2002, 2005, 2008].

After removal of the bone flap and opening of the dura-matter, ultrasonography was used on the cortical surface to identify the tumor location. Tumor borders were indicated with sterile letter tags. Prior to glioma resection, the

cortex was mapped in all patients. Electrostimulation was delivered to the brain using a 5-mm spaced tips bipolar stimulator and with a biphasic current intensity between 1.5 and 4 mA (60 Hz, 1 ms single pulse phase, Nimbus, Hemodia). Stimulation of each site lasted 4 s. Each cortical site was stimulated three times. However, no area was stimulated twice in succession to prevent seizures.

For language mapping, two tasks were utilized. The first one was counting, where the patients counted from 1 to 10 repeatedly, and the second one was picture naming (DO 80 task), where the patient first read a short sentence “ceci est ...” (the French translation of “This is ...”) and then named the picture presented on the screen. This allows making a distinction between a speech arrest (no sound) and naming disturbances, that is the patient’s inability to name the picture but ability to read the sentence out loud [Duffau et al., 2005; Duffau, in press; Vidorreta et al., 2011]. Both the speech therapist and patient were unaware of when stimulation was delivered to an area. If stimulation elicited a language disturbance, a sterile number tag was placed on this area. A photograph of the cortical maps was systematically taken before resection.

After the completion of cortical mapping, glioma resection was started and subcortical structures were systematically stimulated in order to identify language pathways. During the resection and stimulation of subcortical structures, the patient continued with the naming task and the speech therapist analyzed the language disturbances in real-time, i.e., articulatory disturbances, anomia, phonemic paraphasia or semantic paraphasia. To perform the best possible tumor removal and preservation of functional areas, all resections were pursued until eloquent pathways were encountered around the surgical cavity, i.e., resections were achieved according to functional boundaries. Thus, there was no margin left round the corticosubcortical eloquent areas. After tumor removal, a photograph of the cortical and subcortical maps was taken.

Resection Cavity Overlapping

Postoperative 3DT1 MRI scans acquired in the third month were normalized to a standardized common space (MNI space). Because radiologic abnormalities due to the lesion infiltration and its resection can influence the normalization process, we used cost function masking [Brett et al., 2001]. First, each operative cavity was manually drawn using MRICron software (<http://www.mccausland-center.sc.edu/mricron/mricron>). A binary mask, voluntary larger than the initial segmented volume, was created. Each individual MRI scans were then registered to the MNI space (with the mask), using normalization steps implemented in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). We further drew the resection cavity boundaries manually to create a volume of interest for each patient. Each volume was overlapped on the MNI template.

The anterior segment of the Superior Longitudinal Fascicle (SLF), the Arcuate Fascicle (AF) and the Inferior Fronto-Occipital Fascicle (IFOF) obtained from the “MR diffusion tractography atlas” [Thiebaut de Schotten et al., 2011], were superimposed on the MNI template with the resection cavity overlapping.

Anatomo-Functional Correlations

The exact location of the white matter fasciculi was determined using both the types of dysfunction during intraoperative electrostimulation mapping and anatomic correlation with postoperative MRI and tractography atlas. Indeed, the control MRI examination carried out three months after surgery allowed us to analyze accurately the anatomical location of the eloquent pathways, i.e., by definition at the periphery of the cavity, where the resection was stopped according to the functional responses eliciting by intraoperative stimulation (with no margin). It is worth noting that we have extensively used this reliable and reproducible method in many previous studies [Coello et al., 2013; Duffau et al., 2002, 2003a, 2005, 2008, 2009; Gras-Combe et al., 2012; Maldonado et al., 2011; Mandonnet et al., 2007, 2009; Schucht et al., in press].

RESULTS

Preoperative Language Assessment

Preoperatively, spontaneous speech was normal in seven patients. One patient showed slight articulatory disturbances (Table II). On the DO 80 task, seven patients scored above cut off score (73/80, which corresponds to -2SD), while one patient scored below cut off score (69/80), indicating language disorders.

Intraoperative Mapping

The surgical findings are summarized in Table III.

Mapping identified eloquent language areas in all patients, indicating crucial participation of the left hemisphere in language in the 8 cases, also for the ambidextrous and left-handed patients.

At the cortical level, stimulation of the vPMC induced an anarthria in all cases, that is, the loss of the motor ability to speak (no sound, no movement of the face). The number of cortical vPMC sites (5mm x 5mm) identified ranged from 1 to 4 (mean 2.5). A typical location of the vPMC, that is, in the more lateral part of the precentral gyrus, was observed in four patients. Interestingly, in the four other patients, the vPMC identified by intraoperative stimulation was not located in the most lateral part of the precentral gyrus, but that it was more medially located, i.e., several cm above the Sylvian fissure. However, in all cases, the vPMC was found in the precentral gyrus. Of note, a reoperation was performed in one case, five years

TABLE II. Pre- and postoperative language assessments, tested with DO 80 and analysis of spontaneous speech

Patients	Preoperative language assessment	Immediate postoperative language assessment (3-5 days)	Postoperative language assessment (3 months)	Postoperative follow-up and KPS score (>3 months)
1	DO 80 score: 75/80 (3/2/0/0) Spontaneous speech: normal	*DO 80 score: 60/80 (0/1/19/0) Spontaneous speech: phonological and articulatory disorders	DO 80 score: 79/80 Spontaneous speech: normal	Normal socioprofessional life KPS score: 100
2	DO 80 score: 77/80 (1/2/0/0) Spontaneous speech: normal	DO 80 score: 78/80 (2/0/0/0) Spontaneous speech: normal	DO 80 score: 79/80 Spontaneous speech: normal	Normal socioprofessional life KPS score: 100
3	DO 80 score: 80/80 (0/0/0/0) Spontaneous speech: normal	DO 80 score: 74/80 (1/2/1/2) Spontaneous speech: some anomias, perseverations and slight phonological disorders	DO not available Spontaneous speech: normal	Normal socioprofessional life KPS score: 100
4	DO 80 score: 80/80 (0/0/0/0) Spontaneous speech: normal	DO 80 score: 77/80 (1/2/0/0) Spontaneous speech: slight semantic access disorders and perseverations	DO 80 score: 80/80 Spontaneous speech: normal	Normal socioprofessional life KPS score: 100
5	DO 80 score: 79/80 (1/0/0/0) Spontaneous speech: slight articulatory disorders	DO 80 score: 79/80 (1/0/0/0) Spontaneous speech: some anomias and hesitations	DO 80 score: 80/80 Spontaneous speech: normal	Normal socioprofessional life KPS score: 100
6	*DO 80 score: 69/80 (9/2/0/0) Spontaneous speech: normal	*DO 80 score: 67/80 (4/1/8/0) Spontaneous speech: articulatory and phonological disorders	DO 80 score: 73/80 Spontaneous speech: normal	Normal socioprofessional life KPS score: 100
7	(1) DO 80 score: 80/80 (0/0/0/0) Spontaneous speech: semantic paraphasias (2) DO 80 score: 78/80 (0/2/0/0) Spontaneous speech: normal	(1) DO 80 score: 74/80 Spontaneous speech: articulatory disorders (2) DO score: 75/80 (0/3/2/0) Spontaneous speech: slight articulatory disorders	(1) DO 80 score: 78/80 Spontaneous speech: normal (2) DO 80 score: 78/80 Spontaneous speech: normal	(1) Normal socioprofessional life KPS score: 100 (2) Normal socioprofessional life KPS score: 100
8	DO score: 79/80 (1/0/0/0) Spontaneous speech: normal	DO score: 80/80 (0/0/0/0) Spontaneous speech: normal	DO 80 score: 78/80 Spontaneous speech: normal	Normal socioprofessional life KPS score: 100

Preoperative and immediate postoperative qualitative DO errors are specified as follows (anomia/semantic paraphasia/phonological paraphasia/hesitation).

Patient 7 received two operations: information concerning the first and second operations are identified with (1) and (2), respectively.

*DO deficit, scored below cut off score (73/80, -2SD).

after the first resection, following 18 months of chemotherapy (temozolomide). A remapping of the vPMC was noted during the second surgery, with a more medial location of the site eliciting speech disorders in comparison with the first mapping several years before. Such functional reorganization allowed the resection of the part of the tumor within the lateral part of the precentral gyrus, while it was impossible during the first operation.

Nonetheless, at least a portion of the vPMC sites detected by stimulation was still invaded by the tumor in all cases. In addition, the posterior inferior frontal gyrus was removed in five patients.

At the subcortical level, stimulation of the white matter tract underneath the vPMC induced anarthria in the eight patients. Anatomically, this bundle corresponded to the anterior segment of the lateral part of the SLF (see Fig. 1). In addition, in a sub-group of patients in whom resection

of the posterior part of the inferior frontal gyrus (invaded by the tumor) was achieved, in front of the vPMC and its subcortical pathways, other white matter fasciculi essential for language were identified. The AF was detected in five patients by eliciting phonological paraphasias, and the IFOF was identified in two patients with a tumor also involving the insula by generating semantic paraphasias.

Postoperative Language Assessment

In the immediate postoperative period, all patients except two showed transient language disorders concerning their spontaneous speech (Table II). The DO 80 task indicated a transient language disorder in two patients, as they scored below cut off score of 73/80 (- 2SD). Articulatory disturbances, phonological, and semantic paraphasias,

TABLE III. Results of intraoperative mapping

Patient	Cortical	Subcortical
1	vPMC: 2 sites elicited anarthria Both sites were inside the tumor	Two subcortical fibers were identified: Posterior and superior, the SLF III elicited anarthria Anterior part the IFOF induced semantic paraphasias
2	vPMC: 2 sites elicited anarthria One site was at the border of the tumor, while the second one was located more medially in the precentral gyrus	Two subcortical fibers were identified: Posterior and superior, the SLF III elicited anarthria More anteriorly, the AF elicited phonological paraphasias
3	vPMC: 1 site elicited anarthria The site was at the border of the tumor	Two subcortical fibers were identified: The SLF III induced anarthria
4	vPMC: 2 sites elicited anarthria Both sites were located medially in the precentral gyrus	Three subcortical fibers were identified : Posterior and superior, the SLF III elicited anarthria More anteriorly, the AF elicited phonological paraphasias The anterior part of the IFOF induced semantic paraphasias
5	vPMC: 4 sites elicited anarthria 3 sites were inside the tumor 1 site was located more medially in the precentral gyrus	Two subcortical fibers were identified: Posterior and superior, the SLF III elicited anarthria More anteriorly, the AF elicited phonological paraphasias
6	vPMC: 3 sites elicited anarthria 2 sites were inside the tumor 1 site was located at the border of the tumor	One subcortical fiber was identified: The SLF III induced anarthria
7	First surgery vPMC: 2 sites elicited anarthria. One site was inside the tumor, while the second one was located at the border of the tumor Second surgery vPMC: 2 sites elicited anarthria During the first surgery the lateral part of the precentral gyrus was removed, reorganization of vPMC occurred: due to tumor growth, sites were more medially located.	First surgery Two subcortical structures were identified: The SLF III induced anarthria More anteriorly, the AF elicited phonological paraphasias Second surgery Two subcortical structures were identified: The SLF III induced anarthria More anteriorly, the AF elicited phonological paraphasias
8	vPMC: 4 sites elicited anarthria All sites were inside the tumor	Two subcortical fibers were identified: Posterior and superior, the SLF III elicited anarthria More anteriorly, the AF elicited phonological paraphasias

vPMC, ventral premotor cortex; SLF, superior longitudinal fascicle; AF, arcuate fascicle; IFOF, inferior fronto-occipital fascicle.

anomia and perseverations were observed by the speech therapist. No language comprehension deficits were noted.

All patients benefited from postsurgical language rehabilitation.

Three months after surgery, the transient language disorders disappeared, with normal spontaneous speech in the eight patients (no articulatory, phonological, or lexical semantic disorders), and with normal DO 80 scores (between 78 and 80) in 7 patients (DO not available in one patient). The DO scores improved in four patients in comparison with the preoperative score, especially in the patient with presurgical naming deficit. All patients resumed a normal social and professional life, with no impairment in their daily activities (KPS scores of 90 or 100).

Resection Cavity Overlapping

The results of the resection cavity overlapping are presented in Figure 2. The surgical cavities of the patients are

demonstrated, as well as the subcortical structures identified during intraoperative mapping, that is, the anterior segment of the lateral part of the SLF, the AF and the IFOF.

Extent of Resection

The preoperative volume, postoperative volume, and extent of resection of the glioma have been detailed in Table I (calculation on FLAIR-weighted MRI). Of note, a total resection of the tumor infiltrating the vPMC was never achieved (extent of resection between 65% and 93%), because at least a portion of this area was still eloquent in all cases.

DISCUSSION

We investigated the function of the left vMPC, its anatomical connections and its potential for reorganization in

Figure 1.

(a) Preoperative axial FLAIR-weighted MRI (left), coronal T2-weighted MRI (middle) and sagittal enhanced T1-weighted MRI (right) revealed a low-grade glioma involving the left ventral premotor cortex (lateral part of the precentral gyrus), Broca's area (posterior part of the inferior frontal gyrus) and insula in a 36-year-old right-handed woman who experienced inaugural seizures—normal preoperative language examination (patient 4). (b) Intraoperative photographs before (left) and after (right) surgical resection. Left: the letter tags correspond to the boundaries of the tumor, identified using intrasurgical ultrasonography. The electrical cortical mapping in awake patient allowed the detection of two sites which elicited anarthria when stimulated (1, 2). These results showed that the postero-superior part of the ventral premotor cortex was still eloquent despite the tumor infiltration, supporting a limited potential of functional reorganization. Of note, more mesially, the primary motor cortex of the face was identified, with induction of involuntary face movements with no speech arrest when stimulated (4, 5). Stimulation of the retrocentral gyrus generated dysesthesia of the face (6) and stimulation of the supramarginal gyrus induced anomia (7). Right: the resection was performed

according to functional limits. Cortically, the ventral premotor cortex represented the posterior and superior boundaries (1, 2). Its antero-inferior part was removed, as well as the posterior part of the inferior frontal gyrus and a part of the insula. At the subcortical level, three pathways have been detected and preserved: posteriorly and superiorly, the SLF III elicited anarthria (48); more anteriorly, the AF elicited phonological paraphasias (46); finally, the anterior part of the IFOF induced semantic paraphasias after removal of the anterior insula (49). (c) Postoperative axial FLAIR-weighted MRI (left), coronal T2-weighted MRI (middle) and sagittal enhanced T1-weighted MRI (right) showing an incomplete resection: the postero-superior part of the tumor was not removed, because involving the ventral premotor cortex still functional; the deep part of the tumor was also left, because involving the SLF III still critical for articulation (see axial slice). The patient had transient mild spontaneous speech disturbances in the immediate postoperative period (supporting the crucial role of the ventral premotor cortex and its fibers), which completely disappeared within 3 months after surgery. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 2.

Resection cavity overlapping superimposed on the MNI template with the subcortical structures identified during intraoperative mapping, i.e., the anterior segment of the lateral part of the SLF (SLF III), AF and IFOF. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

eight [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.] patients who underwent awake surgery with intraoperative cortico-subcortical language mapping for a low-grade glioma. Our main findings show that (i) intraoperative electrical stimulation of the left vPMC elicited speech production disorders due to anarthria in all patients (ii) stimulation of the subcortical fibers connected to the vPMC also induced anarthria in the 8 cases (iii) although some degrees of relocation of the vPMC are possible, its plastic potential is limited to the lateral part of the precentral gyrus.

The Left vPMC and Its Role in the Speech Production Network Subserved by the Lateral Part of the SLF

The left vPMC seems to play a crucial role in speech production as its stimulation induced anarthria in all cases. This is in agreement with functional neuroimaging studies, which found that the vPMC subserved the control of complex movements allowing articulation, including the coordination of the tongue, lips, and pharynx [Jürgens, 2002; Peeva et al., 2009; Price, 2010; Schubotz et al., 2010; Vigneau, 2006; Wise et al., 1999; Wise, 2006]. In a previous intraoperative language mapping investigation for tumors not involving the vPMC, the implication of this region in speech articulation was already suggested [Duffau et al., 2003a].

In this study, we also demonstrated that stimulation of the subcortical fibers of the vPMC elicited speech disorders

with anarthria in all patients. Interestingly, by superimposing the resection cavity overlapping with a “MR diffusion tractography atlas” [Thiebaut de Schotten et al., 2011], it seems that this subcortical pathway terminating in the vPMC corresponds to the anterior segment of the lateral part of the SLF - also called the “SLF III” [Makris et al., 2005]. The SLF is a complex association fiber system connecting temporal, parietal and frontal regions, which can be divided into three parts: two superficial segments (anterior and posterior) and a deeper part, i.e. the Arcuate Fasciculus [Catani et al., 2005; Martino et al., in press]. The SLF III is the anterior and superficial tract, which runs from supramarginal gyrus to the lateral part of the precentral gyrus. Indeed, both anatomic dissection and tractography studies have shown that the anterior termination of the SLF III fibers corresponded to the vPMC area [De Benedictis et al., in press; Martino et al., 2013; Thiebaut et al., 2011]. Such data are in agreement with previous intrasurgical mapping studies that have identified anarthria while stimulating the fibers from the vPMC [Duffau, 2003; Maldonado et al., 2011].

Another argument supporting the role of the SLF III in speech processing is the evidence of a double dissociation by stimulating SLF III versus other white matter tracts (Fig. 1). Indeed, we were also able to identify additional subcortical structures located anteriorly to the vPMC, namely the AF and the IFOF—as demonstrated by the correlations between the resection cavity overlapping superimposed on the tractography atlas and the functional data provided by intraoperative stimulation. The AF was identified in five patients following resection of the posterior

part of the inferior frontal gyrus involved by the tumor, by inducing phonological paraphasia but no articulatory disorders [as already reported in Benzagmout et al., 2007; Maldonado et al., 2011]. As mentioned, the AF is the deep part of the SLF and connects the inferior and middle temporal gyri with the posterior portion of the inferior and middle frontal gyri [Catani et al., 2005; Martino et al., 2013]. The IFOF was also detected following resection of the left frontal operculum as well as the left insula in two patients with a left fronto-insular glioma, by generating semantic paraphasias but no articulatory disorders [as already reported in Duffau et al., 2005]. By combining DTI and dissection of postmortem brains, it was demonstrated that the IFOF consisted of two layers, a superficial layer and a deeper layer [Axe et al., in press; Martino et al., 2010; Sarubbo et al., in press]. Interestingly, the superficial layer passes through the ventral claustrum and terminates in the pars orbitalis and pars triangularis of the inferior frontal gyrus [De Benedictis et al., in press; Sarubbo et al., in press].

In other words, the detection of the anterior parts of the AF and IFOF in front of the vPMC pleads in favor of the existence of a pathway, subserved by the SLF III, connecting the inferior parietal lobule and the vPMC, and involved in motor aspects of speech processing. According to the dual stream model for language processing, based on a dorsal stream involved in the sensory motor mapping of sound to articulation and a ventral stream involved in the mapping of sound to meaning [Duffau et al., in press; Hickok and Poeppel, 2004; 2007; Saur et al., 2008], we suggest that the complex SLF III/vPMC is crucial to map the phonemic representations onto motor representations for articulation.

The Limited Plastic Potential of the Left vPMC

In the light of a better understanding of the role of the left vPMC and its connectivity, another main objective from our present study was to investigate the reorganization potential of this structure. Indeed, it has been extensively demonstrated that slow-growing low grade gliomas are able to induce mechanisms of cerebral plasticity, allowing the preservation of brain functions despite tumor invasion in “eloquent areas” [Desmurget et al., 2007; Duffau, 2005]. Such reorganization opened the door to massive surgical resection without generating permanent deficit, especially in the so-called Broca’s area [Benzagmout et al., 2007].

In the present series, because patients had a normal preoperative neurological and language examination in seven cases, with significant language deficit in only one case, one could expect functional reshaping of the left vPMC involved by the glioma. In this state of mind, we observed that the vPMC identified by intraoperative stimulation was not located in the most lateral part of the precentral gyrus in 4 cases - but that it was more medially located, likely due to the growth of the tumor in the lateral part.

Such a functional reshaping enabled the achievement of a glioma resection without eliciting permanent speech deficit, as supported by the normalization of language assessment performed 3 months after surgery, and even with an improvement of the DO80 test in four patients in comparison with the preoperative score. In addition, in the patient who was operated twice, vPMC reorganization occurred between the two surgeries, as demonstrated by comparing the results of the electrical mapping during the first operation and 5 years later. Indeed, speech areas which have been identified within the lateral part of the precentral gyrus during the first mapping shifted more medially during the second mapping, allowing an optimization of the extent of resection with no neurological consequences.

However, despite some degrees of plasticity, it is important to note that the vPMC was detected within the tumor or immediately at the border of the tumor in all cases, with a reorganization which was never outside the precentral gyrus. In other words, the plastic potential of this area seems to be very low, resulting on the fact that glioma removal was never complete in this series, conversely to many other locations (including the other left peri-sylvian regions) where total resections have regularly been achieved without permanent language deficit. Indeed, we have previously reported that it was possible to remove totally the inferior frontal gyrus in the left dominant hemisphere, that is the so-called Broca’s area, without generating any neurological worsening, due to potential of reorganization extending outside their typical location [Benzagmout et al., 2007; Duffau, 2005, 2012; Plaza et al., 2009]. We also demonstrated that Wernicke’s area could be removed with no language deficit, owing to an important plastic potential [Sarubbo et al., 2012]. However, in the present series, we should insist on the fact that it was never possible to perform a complete resection of the left vPMC, despite the slow growth of a low-grade glioma known to be able to induce a massive brain reorganization [Desmurget et al., 2007; Duffau, 2008]. In the same vein, a recent atlas of functional cerebral resectability of low-grade gliomas based on cortico-subcortical electrical mapping demonstrated the existence of a “minimal common brain” which cannot be compensated when damaged. The nonresectability was explained in a network perspective, suggesting that a lesion in a nonresectable area would disturb the whole circuit and its function. Interestingly, in this atlas, the vPMC was identified as an essential cortical area, with a very low potential of reorganization [Ius et al., 2011]. Of note, our message is not to say that vPMC has no plastic potential - but that this potential is limited.

We propose that this limitation is due to an anatomical constraint, namely the necessity for the left vPMC to remain connected to the SLF III. Indeed, plasticity in the cortical areas is only possible if subcortical connectivity is preserved [Duffau, 2012]. On the other hand, subcortical plasticity is very limited and the capacity to build a new structural connectivity, that is, the so-called “rewiring,” has not yet been demonstrated in humans following brain

injury [Duffau, 2009]. In our study, the SLF III fibers connected to the vPMC were always identified and spared. Nonetheless, because the anterior cortical termination of the SLF III is anatomically located in the lateral part of the precentral gyrus, we suggest that it explains why the vPMC was still within this specific anatomic brain region in the eight patients, with no relocation possible outside this area. In other words, because dynamic plasticity is dependent on the subcortical structures, as demonstrated by the minimal common brain atlas, vPMC reshaping may be dependent on its connectivity with the SLF III. Such theory is in agreement with a recent observation of aphasia induced by gliomas growing in the ventral precentral gyrus, in which lesion extension to the deep white matter pathways was an important mechanism for the appearance of language disorders [Bizzi et al., 2012].

Limitations of the Study

We have to acknowledge that we did not performed DTI before surgery. It is nonetheless interesting to note that the use of intraoperative electrical mapping allowed the identification of eloquent cortical and subcortical structures in all cases, with no permanent neurological worsening.

Furthermore, the method of using post-operative MRI with superimposed white matter tracts obtained from an atlas of healthy subjects may have limitations in brain tumors due to possible geometric distortion and displacement. However, we would like to insist on the fact that distortion is very rare in low-grade gliomas, conversely to high-grade gliomas. In addition, the possible displacement induced by the tumor has disappeared on post-operative MRI, because in essence the glioma was removed. This is supported by the fact that, on the resection cavity overlapping superimposed on the MNI template, the subcortical structures identified during electrical mapping (i.e at the periphery of the cavity, where the resection was stopped according to the functional responses eliciting by intraoperative stimulation), perfectly matched with the white matter tracts obtained from atlas of healthy subjects.

CONCLUSIONS

To the best of our knowledge, this is the first study specifically dedicated to the role of the left vPMC in speech, its subcortical connectivity, and its plastic potential. Our original findings indicate that the vPMC is a crucial epicentre in the speech articulation network, connected to the SLF III, with a limited reorganization potential due to anatomic constraint represented by its white matter pathways. Beyond fundamental implications, such knowledge may have clinical applications, especially in surgery for brain tumors involving this cortico-subcortical network.

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