



# Dissociating motor–speech from lexico-semantic systems in the left frontal lobe: insight from a series of 17 awake intraoperative mappings in glioma patients

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## Abstract

Functional brain mapping during awake surgery procedures is the gold standard technique in the management of left frontal lobe tumors. Nevertheless, a unified picture of the language subsystems encountered during left frontal lobe mapping is still lacking. We retrospectively analyzed the 49 cortical and the 33 axonal sites of functional language mapping performed in 17 patients operated for a left frontal lobe glioma under awake conditions. Sites were tagged on the postoperative MRI, based on anatomical landmarks and intraoperative photography. All MRIs and tags were then registered in the MNI template. Speech disturbances related to motor functions (speech arrest—with or without superior limb arrest—, stuttering, and vocalization) were grouped together as “motor–speech” responses. Anomias, semantic paraphasia, perseverations, and PPTT errors were classified as “lexico-semantic” responses. MNI-registered axonal sites were used as seed for computing disconnectome maps from a tractogram atlas of ten healthy individuals, as implemented in the BCB toolkit. The cortical distribution of lexico-semantic responses appeared to be located anteriorly (pars triangularis of the inferior frontal gyrus and posterior end of the middle and superior frontal gyrus) compared to motor–speech responses (lower end of the precentral gyrus and pars opercularis). Within the white matter, motor–speech responses and lexico-semantic responses overlapped on the trajectory of the aslant and fronto-striatal tracts, but the lexico-semantic sites were located more anteriorly (mean Y coordinate on the MNI system was 21.2 mm for lexico-semantic sites and 14.3 mm for the motor–speech sites; Wilcoxon test:  $W = 60.5$ ,  $p = 0.03$ ). Moreover, disconnectome maps evidenced a clear distinction between the two subsystems: posterior fronto-striatal and frontal aslant tracts, corpus callosum and cortico-spinal tract were related to the motor–speech sites, whereas anterior frontal aslant tract, inferior-fronto-occipital fasciculus (IFOF) and anterior thalamic radiations were related to the lexico-semantic sites. Hence, we evidenced distinct anatomical substrates for the motor–speech and lexico-semantic systems. Regarding the aslant/fronto-striatal system, an anterior to posterior gradient was found, with a lexico-semantic role for the anterior part and a motor–speech involvement for the posterior part. For tumors abutting the precentral sulcus, posterior boundaries of the resection are made of motor–speech sites, meaning that the anteriorly located lexico-semantic system is no more functional, as a result of network reorganization by plasticity.

**Keywords** Awake surgery · Intraoperative brain mapping · Frontal lobe · Electrical stimulation · Lexico-semantic system · Speech

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## Abbreviations

DEBS	Direct electrical brain stimulation
SFG	Superior frontal gyrus
MFG	Middle frontal gyrus
IFG	Inferior frontal gyrus
FAT	Frontal aslant tract
FST	Fronto-striatal tract
fMRI	Functional magnetic resonance imaging
MRI	Magnetic resonance imaging
Pop	Pars opercularis
Ptr	Pars triangularis
SMA	Supplementary motor area
vPMC	Ventral pre-motor cortex
IFOF	Inferior fronto-occipital fasciculus

## Introduction

The human language ability is currently envisioned as emerging from a temporally orchestrated pattern of activities within a spatially delocalized set of cortical, striatal, thalamic and cerebellar areas. Neurobiologically, the most prominent view is the dual-stream model, which stipulates in its original form a dorsal pathway supporting sound to sensorimotor integration, and a ventral pathway mapping sound to meaning (Hickok and Poeppel 2004). This model was also shown to fit well with the known subdivision of the language system, inherited from studies in cognitive (neuro)psychology, in the two major dimensions that are phonology and semantics: both for auditory modality (Saur et al. 2008) and picture naming (Duffau et al. 2013), phonology is associated with the dorsal stream and semantics with the ventral stream (see also Halai et al. 2018) for a recent neuropsychological account of this anatomic-functional dissociation). In a convergent albeit slightly different perspective, another interpretation of the dual-stream model (Bornkessel-Schlesewsky et al. 2015) suggested that the dorsal stream is implicated in the treatment of order-sensitive sequence-based combinatorics [thus making a link with syntactic abilities (Friederici 2012)], while the ventral streams are involved in the building of order-insensitive dependency-based combinatorics [in keeping with the bilateral hub-and-spoke model of semantic memory (Lambon Ralph et al. 2017)]. In any case, the left frontal lobe can be viewed as the anterior convergence zone of the two streams, thus playing an essential role in cross-stream integration (Bornkessel-Schlesewsky et al. 2015; Sarubbo et al. 2016). As such, several cortical epicenters of the left frontal lobe have been identified as “language” areas (Price 2012), including the SMA and pre-SMA at the posterior end of the superior frontal gyrus (SFG) (Hertrich et al. 2016; Lou et al. 2017), the dorso-lateral premotor/prefrontal cortex at the posterior end of the middle frontal

gyrus (MFG) (Duffau et al. 2003; Sun et al. 2013; Glasser et al. 2016) and the Broca’s areas at the posterior end of the inferior frontal gyrus (IFG).

Thanks to the advent of diffusion MRI and tractography, the structural connectivity supporting the dual-stream model has been progressively elucidated (Saur et al. 2008; Axer et al. 2013; Dick et al. 2014; Friederici 2015). Briefly, the main white matter pathways of the dorsal stream are the arcuate fasciculus and the third branch of the superior longitudinal fasciculus, while the IFOF/extreme capsule fiber systems are the main associative pathways of the ventral stream, although the ILF and uncinata fasciculus are also involved (see for example Ripollés et al. (2017) and Papagno et al. (2014) for the role of these pathways in semantic learning and proper name retrieval, respectively).

In parallel to neuroscience advances gained from non-invasive functional MRI studies in healthy individuals and to cognitive neuropsychology advances from lesional studies in brain-damaged patients, direct electrical brain stimulation (DEBS) contributed to further refine the role of each pathway within the language network [see Duffau et al. (2002), (2005) for seminal studies and Duffau (2015) for a recent review]. However, contrarily to temporal tumors, for which the stems of the IFOF or AF can be selectively stimulated (typically generating semantic paraphasias and phonological errors, respectively), the observed pattern of language errors generated when mapping frontal tumors is not so clear-cut. Indeed, due to the intermingling of white matter fibers in the frontal lobe, stimulation will impact simultaneously callosal fibers, cortico-striatal fibers, thalamo-cortical fibers, intralobar associative fibers, and interlobar associative fibers of both the dorsal and ventral streams. Hence, several language pathways have been proposed as functional boundaries for the left language-dominant frontal lobe, such as the terminations of the dorsal (superior longitudinal and arcuate fasciculus) and ventral (inferior fronto-occipital and uncinata fasciculus) pathways in the SFG, MFG and IFG [see De Benedictis et al. (2012) for a review], the frontal aslant tract (FAT) joining the mesial frontal lobe to IFG (Vassal et al. 2014; Sierpowska et al. 2015; Fujii et al. 2015; Kinoshita et al. 2015; Ookawa et al. 2017), and the fronto-striatal tract (FST) joining the mesial frontal lobe to the caudate and putaminal nuclei (Kemerdere et al. 2016).

Consequently, we currently lack a clear and unified picture of the exact kind of errors that can be encountered when mapping (cortically and) axonally the left frontal lobe. In this paper, we review the functional sites constituting the boundaries of resection in a surgical series of 17 patients with left language-dominant frontal glioma, with the aim of getting an integrated anatomic-functional pattern of language errors observed during intraoperative mapping under DEBS.

## Methods

### Patient's cohort

We retrospectively reviewed a consecutive series of surgical cases of brain gliomas operated under awake conditions at Lariboisière Hospital between June 2011 and March 2017.

The inclusion criteria were: (1) glioma located in the left frontal lobe; (2) the presence of positive language functional sites evoked during the frontal brain mapping by DEBS; (3) availability of at least three brain MRIs: before surgery, immediate postoperatively, and late postoperatively (> 3 months); (4) availability of at least three complete language examinations by a speech therapist before surgery, immediate postoperatively, and late postoperatively (> 3 months).

Patients characteristics are given in Table 1. Seventeen patients (11 males and 6 females) were included. The mean patient age was 45.5 years (range 29–74 years). Thirteen patients were right-handed, two were left-handed, and two were ambidextrous. Seizures were the presenting symptoms in 12 patients (66%), and headache was the main presenting symptoms in 3 (17%). Two patients had a speech deficit as presenting symptom (11%) and none had a motor or sensory deficit. The histological results revealed ten low-grade gliomas (6 oligodendrogliomas,

3 astrocytomas and 1 oligo-astrocytoma), one anaplastic astrocytoma, two anaplastic oligodendrogliomas, and four glioblastomas. Table 1 summarizes the basic patient's demographic and clinical data.

### Tumor location

Based on the preoperative MRI, we classified the frontal lobe lesions as anteriorly or posteriorly located. Tumors were considered to be located posteriorly in the frontal lobe when they involved the posterior end of the superior, middle or inferior frontal gyrus, abutting the pre-central sulcus. Anterior-located tumors were defined as those in which the posterior limit of the tumor was located at least 1 cm anteriorly to the precentral sulcus.

According to our definition, 9 of 17 lesions were located posteriorly, accounting for 53% of cases (see Table 1). The remaining eight patients harbored anteriorly located tumors. Figures 1 and 2 show the spatial distribution of the preoperative tumors, for the anterior and posterior groups, respectively. Figure 3 gives the global distribution of the postoperative surgical cavities.

### Functional mapping

All patients underwent awake surgery under local anaesthesia for cortical and axonal language mapping. After removal of the bone flap and opening of the dura mater,

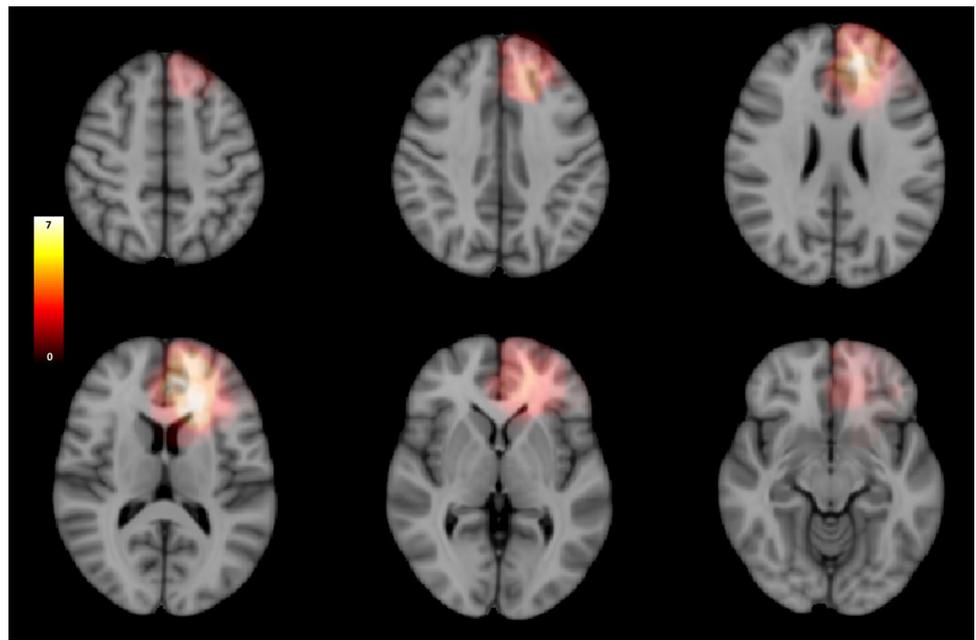
**Table 1** Summary of patient and brain lesion characteristics

Patient no.	Sex	*	Age (years)	Lesion type	WHO grade	Location group	Clinical presentation
1	M	L	52	Glioblastoma	IV	A	Aphasia and hemiparesis
2	F	R	66	Glioblastoma	IV	A	Expressive aphasia
3	F	L	46	Glioblastoma	IV	A	Headache
4	F	R	46	Oligodendroglioma	II	A	Generalized seizures
5	M	A	41	Oligo-astrocytoma	II	A	Generalized seizures
6	M	R	57	Oligodendroglioma	II	A	Generalized seizures
7	M	R	29	Oligodendroglioma	II	A	Headache
8	F	R	42	Astrocytoma	III	P	Generalized seizures
9	F	A	30	Astrocytoma	II	A	Generalized seizures
10	F	R	53	Astrocytoma	II	P	partial seizures
11	M	R	47	Oligodendroglioma	II	P	Generalized seizures
12	M	R	48	Oligodendroglioma	III	P	Generalized seizures
13	M	R	31	Glioblastoma	IV	P	Headache
14	M	R	30	Astrocytoma	II	P	Generalized seizures
15	M	R	53	Oligodendroglioma	III	P	Generalized seizures
16	M	R	29	Oligodendroglioma	II	P	Generalized seizures
17	M	R	74	Oligodendroglioma	II	P	Generalized seizures

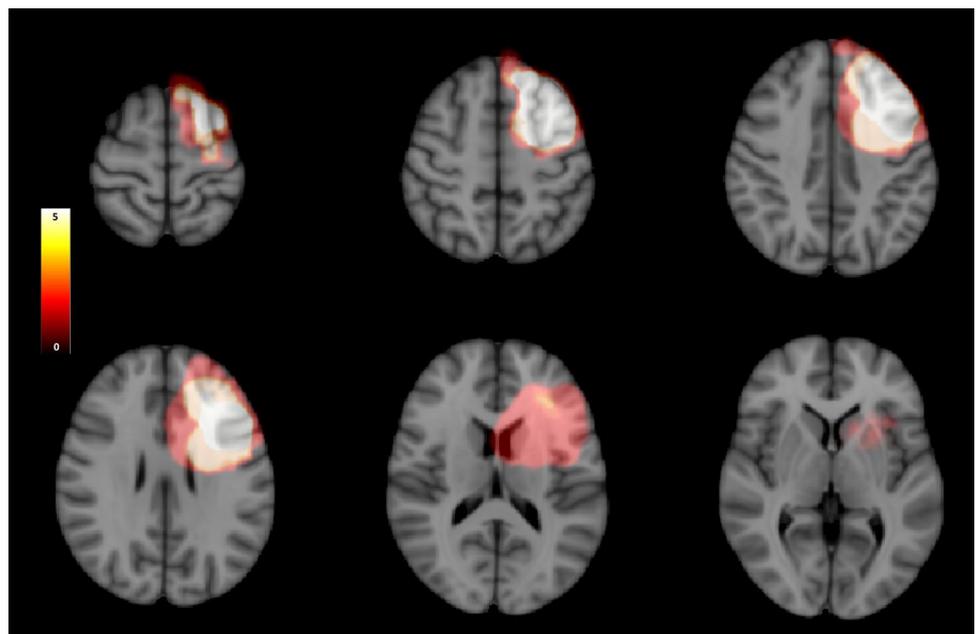
Location group: A anterior, P posterior

\*L left-handed, R right-handed, A ambidextrous

**Fig. 1** Spatial distribution of preoperative tumors for the anterior group



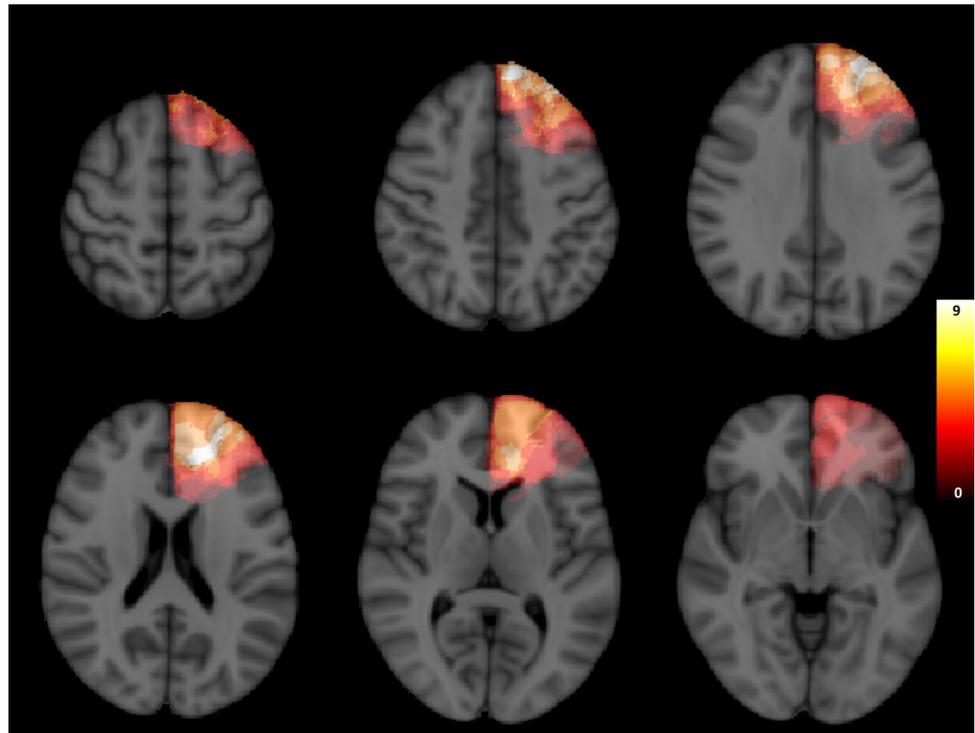
**Fig. 2** Spatial distribution of preoperative tumors for the posterior group



brain mapping was performed cortically by use of 60 Hz bipolar adjustable constant current electrical stimulation (Nimbus, Hemodia). In each case, the bone flap was made sufficiently large to expose the ventral premotor cortex, onto which intensity stimulation was progressively increased from 1 mA up to 2 mA by 0.25 mA steps until eliciting speech arrest during the counting task. Once the threshold intensity has been determined, cortical functional mapping is then started at this intensity and progressively increased by 0.5 mA steps up to 3 mA. Cognitive functions were always monitored using a double task (DO 80 picture

naming (Metz-Lutz et al. 1991) combined with continuous repetitive movement of superior limb), under the supervision of a speech therapist. Non-verbal semantic association task, i.e., pyramids palm and trees test (PPTT) (Howard et al. 1992) was also performed in 10 out of the 17 patients. In those patients, depending on the surgeon's choice for delineation of functional resection boundaries, only brain areas shown to be unresponsive to picture naming were remapped, or the whole exposed brain surface was remapped. Axonal mapping was performed at an intensity between 2 and 3 mA. Picture naming (and PPTT in 10 cases) was constantly

**Fig. 3** Spatial distribution of the postoperative cavities for the whole series



monitored throughout the resection. Stimulation was applied at regular time intervals, whenever the surgeon anticipated a likely response [based on anatomical landmarks and/or occurrence of errors, that can be spontaneous or induced by the ultrasonic surgical aspirator (Carrabba et al. 2008)]. A site was considered as eloquent if the same dysfunction was observed repeatedly in at least two out of three trials. Resection was stopped when eloquent sites were identified.

### Brain mapping responses

We considered the following responses evoked during DEBS:

- Pure speech arrest: stopping of counting (superior limb movement preserved).
- Complete motor arrest: simultaneous arrest of both speech and superior limb movement during double tasks.
- Stuttering: involuntary repetition of the first syllable of a word.
- Slow speech: involuntary slowness of elocution.
- Vocalization: involuntary speech output, like “aaaaah”.
- Anomia: impossibility to name the item in the DO 80, while the patient is still able to say “this is a...” during the naming tasks.
- Semantic paraphasias: the output belongs to the same semantic field as the target (Duffau et al. 2005).
- Verbal perseverations: the patient naming a previous picture rather than the new one.

- PPTT errors: impossibility or errors in accomplishing the semantic association in the PPTT.

Within the white matter, it was observed that anomia, verbal perseverations and semantic paraphasia could be generated during the successive stimulation trials on the same stimulation site. The final assignment of the site to one of these categories was based on the most frequent error type.

### Registration of pre- and postoperative MRI on the MNI template

Registration of native T1w images (preoperative and postoperative) to the MNI 2009c Nonlinear Asymmetric T1w template (<http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009>) was performed using ANTs (Avants et al. 2011) with the cross-correlation metric. To obtain optimal registration parameters such as the number of iterations, the smoothing and the gradient step size had to be fine-tuned.

Skull stripping is an operation that can improve registration results; the ANTs brain extraction script was used on the original data and only the skull-stripped T1w were used for the registration to the skull-stripped MNI template. Area around the tumor for the preoperative T1w image and cavity for the postoperative T1w image were used as lesion masks to stabilize the registration algorithm and improve the quality of the results.

Quality of the registrations was validated visually to ensure that the algorithm provided adequate results with pathological brains.

### Pointing cortical functional sites on the MNI template

The cortical landmarks observed in intraoperative photography were mainly based on the vasculature network at the cortical surface. Volume rendering was used to locate functional sites onto the subject native preoperative T1w in MI-Brain (Rheault et al. 2016) (<https://www.imeka.ca/mi-brain>), based on their relative position to nearby veins and arteries (see illustrative case on supplementary figure S1). The volume rendering parameters were manually set to maximize the visibility of the vasculature at the surface. Once a site was located on the 3D surface rendering, the axial/coronal/sagittal slices were used to pinpoint its exact position in the native MRI. Then, a spherical region of interest (ROI) was positioned at this location in the software. The ROIs were then moved to the MNI template using the nonlinear deformation field, resulting in ROIs aligned with the MNI template. Finally, ROIs were converted to nifti file to be visualized as overlay in MRICroGL (<http://www.cabiatl.com/mricrogl/>) along the MNI T1w image.

### Pointing white matter functional sites on the MNI template

The deep white matter functional sites observed in intraoperative photographs were located in the postoperative MNI (median time after surgery: 4 months, range 3–6 months), based on surrounding anatomical landmarks as stated in the operative report (sulcal anatomy, ventricular anatomy, deep gray nuclei anatomy, see illustrative case on supplementary figure S2). Then a spherical region of interest (ROI) of 5 mm diameter was positioned accordingly in MI-Brain. Resulting ROIs were further aligned with the MNI template and finally converted to nifti file, to be visualized as overlay in MRICroGL along the MNI T1w image.

### Color coding of the different error types

For the purpose of visualization, the different language cortical sites were tagged with a specific color: (1) sites of complete motor arrest (i.e., both speech and superior limb arrest) were colored yellow; (2) speech arrest and vocalization were marked in red; (3) sites producing anomia were colored green; (4) PPTT errors were marked in light blue.

The same color coding was used for axonal sites with:

- acceleration of both speech and superior limb also marked in yellow,

- stuttering and slow speech sites also marked in red,
- semantic paraphasias and verbal perseverations also marked in green.

All the language epicenters were also categorized more broadly into two groups. Speech arrest, complete motor arrest or acceleration of both speech and superior limb, vocalization, slow speech and stuttering were grouped together as “motor–speech” responses; while anomia, semantic paraphasias, verbal perseverations and PPTT errors were classified as “lexico-semantic” responses.

### Tractotron analysis

Tractotron of the BCBToolkit (Foulon et al. 2018) (<http://www.brainconnectivitybehavior.eu/>) was used to identify which white matter tracts were stimulated on functional sites. Tractotron is a software using FMRIB software library (FSL), as well as recently published white matter tract atlases in the MNI152 referential (Rojkova et al. 2016) to determine the pattern of disconnection induced by a lesion. For each 5 mm sphere centered on each functional site, Tractotron provides a probability of belonging to each tract of the atlas. For each site, we extracted the first three tracts with the highest probabilities. Other tracts with probability greater than 90% were also selected, up to a total of five tracts per site.

### Disconnectome maps

For each stimulation site, a disconnectome map was calculated using BCBtoolkit (Foulon et al. 2018). This approach—that was chosen because individual patients’ diffusion-weighted MRI were not available—uses a set of ten healthy controls’ (Rojkova et al. 2016) diffusion-weighted imaging datasets to track fibers passing through each 5 mm-diameter spherical ROI representing a stimulation site. For each participant, tractography was estimated as indicated in Thiebaut de Schotten et al. (2011). ROIs of stimulation sites in the MNI152 space are registered to each control native space using affine and diffeomorphic deformations (Klein et al. 2009; Avants et al. 2011) and subsequently used as seed for the tractography in Trackvis (<http://cds.ismrm.org/ismrm-2007/files/03720.pdf>). Tractographies from the stimulation site ROIs were transformed in visitation maps (Thiebaut de Schotten et al. 2011a, b), binarized and brought back to the MNI152 using the inverse of precedent deformations. Finally, we produced a probability map by averaging at each point in MNI space the normalized visitation map of the ten healthy subjects. Hence, for each stimulation site, the value in each voxel of the resulting disconnectome map takes into account the interindividual variability of tract reconstructions in healthy controls and indicates the probability (from

0 to 100%) that a voxel is connected to the stimulation site (Thiebaut de Schotten et al. 2015). Finally, disconnectome maps related to “motor–speech” responses and “lexico-semantic” responses were averaged separately and the difference between the two averaged maps was computed.

## Statistical methods

Statistical analysis made use of the non-parametric Mann–Whitney–Wilcoxon test, with the lexico-semantic or motor error types as categorical variables, and the MNI-coordinates as continuous variable. Significance was considered for  $p < 0.05$ . The tests were implemented under Rstudio (version 1.0.143).

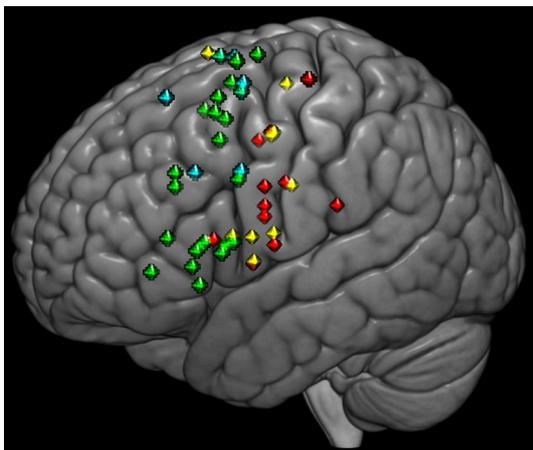
## Results

### Cortical mapping

A total of 49 cortical language sites were found. Figure 4 shows the spatial distribution of these sites on the cortical surface. Table 2 also summarizes these responses and gives MNI coordinates of the sites.

The *speech arrest sites* were located in the precentral gyrus ( $n = 8$ ), in the pars opercularis ( $n = 1$ ), or in the post-central gyrus ( $n = 1$ ). Finally, one vocalization site was also grouped with these speech arrest sites (Fig. 4 and supplementary figure S3A; total of 11 sites).

*Complete motor arrest sites* were usually evoked in the beginning of the cortical mapping. They were found in the precentral gyrus ( $n = 8$ ), [including 4 sites at the lower end of the precentral gyrus, i.e., at the level of ventral premotor cortex (vPMC)] or located in the supplementary motor area



**Fig. 4** Cortical map of motor–speech (yellow and red marks) and lexico-semantic (green and light blue marks) language sites

**Table 2** MNI coordinates of the cortical functional sites

	X	Y	Z	Language errors
1	−71	−22	28	Speech arrest
2	−65	4	24	Speech arrest
	−61	19	10	Anomia
3	−56	−1	51	CMA
	−55	36	15	Anomia
	−95	13	63	Anomia
4	−56	−3	53	CMA
	−39	6	65	Anomia
	−51	25	39	Anomia
	−51	25	39	PPTT
5	−54	2	50	Speech arrest
	−42	5	66	Anomia
	−22	8	75	Anomia
	−42	5	66	PPTT
	−22	8	75	PPTT
6	−64	3	34	Speech arrest
	−62	21	16	Speech arrest
	−44	−19	70	Vocalization
	−28	30	62	PPTT
7	−55	2	53	Speech arrest
	−60	27	12	Anomia
	−50	32	33	Anomia
8	−65	−6	35	CMA
	−32	6	68	Anomia
9	−63	−4	35	Speech arrest
	−66	1	17	CMA
	−58	11	36	Anomia
	−49	15	50	Anomia
	−37	18	58	Anomia
	−58	26	−1	Anomia
10	−40	−11	67	CMA
	−40	4	68	PPTT
11	−63	7	6	Speech arrest
	−59	28	5	Anomia
	−55	42	4	Anomia
12	−64	4	27	Speech arrest
	−61	17	14	Anomia
13	−67	1	13	Speech arrest
	−62	14	15	anomia
	−29	3	75	Anomia
14	−65	7	8	CMA
	−19	11	77	CMA
	−43	16	59	Anomia
	−26	3	75	PPTT
15	−62	15	17	CMA
	−60	25	15	Anomia
	−45	12	57	Anomia
	−59	11	39	PPTT
16	−65	9	16	CMA
17	−	−	−	−

(SMA) ( $n=1$ ) (Fig. 4 and supplementary figure S3B; total of 9 sites).

Two crucial epicenters for naming process were observed: the first corresponding to Ptr ( $n=7$ ) and Pop ( $n=3$ ) of IFG; the second epicenter located in the dorso-lateral premotor cortex at the level of the posterior end of MFG ( $n=8$ ) and SFG ( $n=3$ ). (Fig. 4 and supplementary figure S3C; total of 22 sites).

Errors in semantic association were located at the level of pre-SMA, i.e., in the posterior end of SFG ( $n=3$ ), in the posterior end of MFG ( $n=3$ ), and at the junction between MFG and the precentral gyrus ( $n=1$ ) (Fig. 4 and supplementary figure S3D; total of 7 sites). Of note, three of these sites were also referenced as anomia sites during picture naming.

Overall, the lexico-semantic responses appeared to be located anteriorly compared to motor–speech sites, and no overlapping was seen among these two epicenters.

### White matter mapping

A total of 33 sites (average 2 sites/patients, range 1–4) were identified within the white matter pathways. Figure 5a–c shows the spatial distribution of these sites, while Table 3 gives their MNI coordinates. The distribution of disturbances was as follows:

- 1) colored in yellow: 8 complete motor arrests, 1 acceleration of both speech and superior limb movement;
- 2) colored in red: 4 vocalizations, 2 stuttering, 1 slow speech;
- 3) colored in green: 11 anomia, 1 semantic paraphasia, 3 verbal perseverations;
- 4) colored in light blue: 2 PPTT errors.

Despite some degree of overlap, the lexico-semantic sites (green + light blue) are located anteriorly to the motor–speech (yellow + red) epicenters. This visual

observation was statistically confirmed: the mean Y value within the MNI system was 21.2 for the lexico-semantic sites, compared to 14.3 for the motor sites (Wilcoxon rank sum test:  $W=60.5$ ,  $p=0.03$ ).

Interestingly, in the 9 of 17 cases of posteriorly located tumors, no naming or semantic errors were evoked during axonal mapping of the posterior wall of the cavity. Instead, the posterior functional sites were related to motor–speech responses.

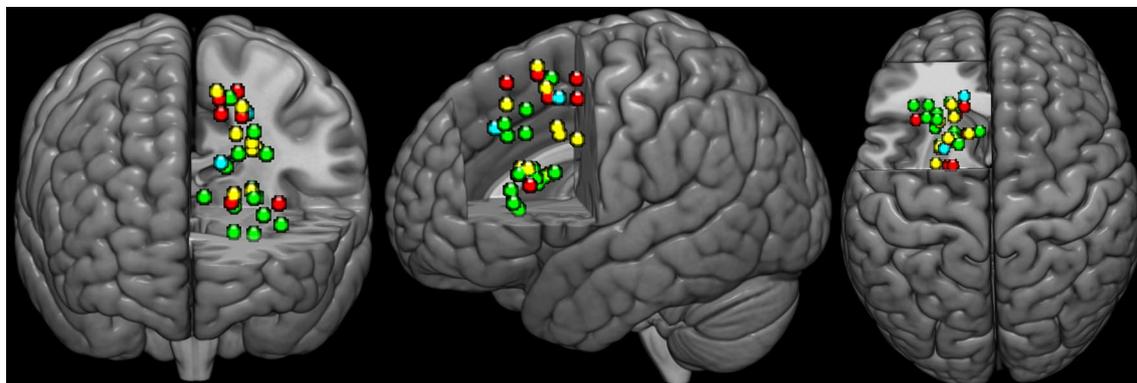
### Tractotron analysis

The selected results of the Tractotron analysis are given in Table 3, while the complete sets can be found as supplementary material. They highlight that stimulations sites affected mainly the corpus callosum and frontal commissural fibers, the frontal aslant tract, the fronto-striatal tract, the frontal superior longitudinal tract, and the anterior thalamic radiations.

### Disconnectome maps

Figure 6 shows the subtraction between the motor–speech and lexico-semantic disconnectome maps. This analysis revealed that stimulation inducing motor speech impairment was located on a circuit involving the cortico-spinal tract (CST), and posterior portions of the fronto-striatal and frontal aslant tracts. Alternatively, lexico-semantic errors were induced following a stimulation of the inferior fronto-occipital fasciculus, anterior thalamic radiation as well as the anterior portion of the fronto-striatal and frontal aslant tracts.

Finally, motor–speech and lexico-semantic systems included, respectively, middle and anterior fibers of the body of the corpus callosum.



**Fig. 5** Axonal map of motor–speech (yellow and red marks) and lexico-semantic (green and light blue marks) language sites. **a** Anterior view. **b** Lateral view. **c** Superior view

**Table 3** MNI coordinates of axonal functional sites

	X	Y	Z	Type of response	Tract 1	Tract 2	Tract 3	Tract 4	Tract 5
P1	-17	15	16	VP	ATR (1.0)	CC (0.95)	<i>FST</i> (0.86)		
P2	-5	15	20	Anomia	CC (1.0)	FC (1.0)	Cing (0.98)	Cing_ant (0.92)	
P3	-17	25	8	Anomia	CC (1.0)	ATR (1.0)	FC (1.0)		
P4	-17	12	19	VP	ATR (1.0)	CC (0.99)	<i>FC</i> (0.88)		
	-36	28	12	Anomia	SLF III (0.96)	<i>CC</i> (0.82)	<i>ATR</i> (0.66)		
P5	-25	24	7	Anomia	FST (1.0)	IFOF (0.98)	ATR (0.90)		
	-25	24	22	VP	CC (0.99)	FST (0.96)	ATR (0.96)	FC (0.94)	
	-14	27	36	SP	CC (1.0)	FC (1.0)	Cing_ant (0.99)	SLF I (0.96)	Cing (0.92)
P6	-12	32	39	PPTT	CC(1.0)	FC (1.0)	SLF I (0.97)	Cing_ant (0.94)	
	-16	23	20	Stuttering	CC (1.0)	FC (1.0)	<i>Cing</i> (0.82)		
P7	-17	10	20	CMA	ATR (1.0)	CC (0.99)	FC (0.90)		
P8	-30	22	40	Anomia	CC (1.0)	FSL (0.96)	SLF II (0.91)		
	-17	22	23	CMA	CC (1.0)	FC (1.0)	Cing (0.94)		
	-35	21	19	Slow speech	SLF III (0.98)	FAT (0.92)	CC (0.91)		
P9	-24	20	24	CMA	CC (1.0)	FAT (0.94)	FST (0.94)	ATR (0.94)	FC (0.92)
P10	-20	12	57	CMA	FAT (1.0)	CC (0.95)	FC (0.94)		
	-22	7	53	PPTT	FSL (0.92)	CC (0.91)	<i>FAT</i> (0.76)		
P11	-26	17	20	Anomia	Pons (0.98)	FST (0.96)	CC (0.94)	FAT (0.94)	ATR (0.90)
	-24	9	22	Anomia	FAT (1.0)	FST (0.94)	CC (0.92)	ATR (0.90)	
P12	-26	0	36	CMA	FAT (1.0)	CC (0.99)	CST (0.97)	FST (0.96)	Pons (0.92)
P13	-24	7	32	CMA	FAT (1.0)	CC (1.0)	FC (0.96)		
	-29	28	16	Anomia	FST (0.96)	SLF III (0.92)	CC (0.90)		
P14	-19	29	42	Anomia	FSL(0.96)	FAT (0.92)	SLF I (0.90)		
	-18	28	50	CMA	FAT (0.98)	FC (0.98)	CC (0.97)	FSL (0.96)	FST (0.9)
	-12	27	58	Vocal	FAT (1.0)	FC (0.98)	CC (0.97)		
P15	-25	21	49	Anomia	FSL(0.96)	CC (0.93)	<i>SLF I</i> (0.52)		
	-10	14	64	CMA	CC (1.0)	FC (0.98)	FAT (0.90)	ATR (0.90)	
P16	-11	14	61	Vocal	CC (1.0)	FC (1.0)	ATR (0.92)	FAT (0.90)	
	-20	11	53	Vocal	FAT (0.96)	CC (0.91)	FSL (0.90)		
	-24	8	41	Acceleration	CC (1.0)	FAT (1.0)	FC (0.98)		
P17	-20	-1	52	Vocal	CC (1.0)	CST (1.0)	SLF I (0.99)	FC (0.98)	FST (0.96)
	-15	9	60	Anomia	CC (1.0)	FAT (1.0)	FC (0.98)	ATR(0.92)	FST (0.9)
	-18	-1	60	Stuttering	CC (1.0)	CST (1.0)	FST (0.98)	SLF I (0.97)	FC (0.96)

*ATR* anterior thalamic radiations, *Cing* cingulum, *CC* corpus callosum, *CST* cortico-spinal tract, *FAT* frontal aslant tract, *FC* frontal commissural tract, *FSL* frontal superior longitudinal, *FST* fronto-striatal tract, *IFOF* inferior fronto-occipital fasciculus

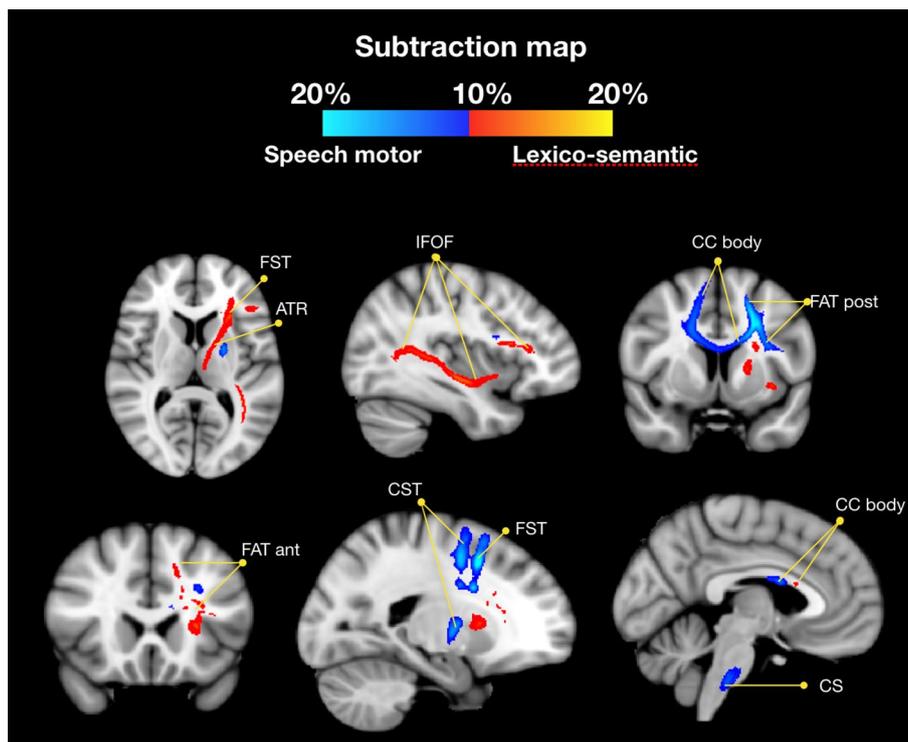
## Discussion

This study aimed to produce a map of language findings during left frontal gray and white matter intraoperative electrical stimulation. A total of 82 language disturbances evoked during functional language mapping performed in 17 patients operated on for a left frontal lobe glioma under awake conditions were categorized as part of two main categories. A motor–speech category, accounted for motor responses related to language functions, in which speech arrest, complete motor arrest, stuttering and vocalization were included. In the lexico-semantic category, anomia, semantic paraphasia, verbal perseverations, and PPTT

errors were included, as tapping different aspects of the lexico-semantic system.

The distribution of lexico-semantic responses appeared to be located anteriorly compared to motor–speech responses, at both cortical and white matter levels. Furthermore, disconnectome maps allowed the distinction between the two systems: the motor–speech subsystem correlated to the posterior part of fronto-striatal and frontal aslant tracts, whereas the lexico-semantic subsystem correlated to the anterior part of frontal aslant tract, anterior thalamic radiations, and IFOF.

**Fig. 6** Subtraction between the motor–speech and lexico-semantic disconnectome maps. The percentage corresponds to the difference between the average disconnectome map of motor–speech sites and the average disconnectome map of lexico-semantic sites. Blue color is used when motor–speech > lexico-semantic, and red color when lexico-semantic > motor–speech



### Dissociation between motor–speech and lexico-semantic sites at the cortical level

At the cortical level, speech arrests were found within the precentral gyrus, especially at the level of vPMC (foot of precentral gyrus, just above the sylvian fissure). Anomia and semantic paraphasias were located more anteriorly, at the level of pars triangularis of IFG and also in the posterior end of MFG. The present results are in line with previous reports. The largest study of language cortical mapping found most of speech arrest sites in the precentral gyrus and pars opercularis, while anomia sites were predominantly located in the pars triangularis (Sanai et al. 2008). However, no anomia sites were reported in the posterior part of the MFG in this study. Such a distribution was also confirmed in a very recent study, with an in-depth analysis of probability and variability of these two kinds of errors (Chang et al. 2017). On the contrary, another large study (Tate et al. 2014) reported anomia sites within the posterior part of MFG (confirming the preliminary data from the same group (Duffau et al. 2003), but not within the pars triangularis. Methodological differences might explain such discrepancy. First, the anomia versus speech arrest errors can be adequately identified only if the patient is asked to say “this is a” before naming the picture (Mandonnet et al. 2017). Such requirement was not systematically reported in the aforementioned studies. Furthermore, the stimulation parameters—particularly current intensities—might differ between centers. Indeed, the intensities at which the effects

are observed are usually not mentioned. In the present study, the intensity for generating speech arrest in the precentral gyrus ranged around 1–1.5 mA. At these intensities, no other sites could be identified. Indeed, anomia, semantic paraphasia and PPTT errors were generated by cortical stimulation at intensities around 2.5–3 mA. Our hypothesis is that the cortical surface involved in the lexico-semantic process of picture naming is larger than the surface involved in purely motor aspect of speech. Hence, by increasing the intensity, the stimulation impacts a sufficiently large area to inhibit the function of naming. An alternative hypothesis would be that by increasing intensity, the electrical disturbance reaches neurons located in deeper cortical layers, thus generating action potentials in the axons of associative pathways (Vincent et al. 2017). Such action potentials would disturb not only the locally stimulated patch of cortex, but also the whole network comprising cortical sites connected to the stimulated site (Mandonnet et al. 2010). Further electrophysiological studies are needed to decide between these two hypotheses.

### Dissociating the anatomical substrates of the motor–speech and lexico-semantic systems

In 2008, a tractography study described for the first time an associative fiber complex, interconnecting the SMA/pre-SMA of SFG to sus-sylvian precentral gyrus, and Ptr and Pop of IFG (Lawes et al. 2008). Following this seminal report, this fiber system was further described (Ford et al.

2010; Kinoshita et al. 2012; Vergani et al. 2014) and finally named the frontal aslant tract (FAT) (Thiebaut de Schotten et al. 2012). It was also shown that the nodes in SFG, MFG and IFG constituted a network, with the FAT and U-fibers linking any two pairs of these three cortical sites (Catani et al. 2012). Finally, electrophysiological studies with cortico-cortical evoked potentials provided evidence for the direct connection between SFG and IFG (Swann et al. 2012; Ookawa et al. 2017). Otherwise, an antero-posterior functional organization for both Broca's region and SMA/Pre-SMA areas was also demonstrated in several studies, based on brain activation on functional magnetic resonance imaging (fMRI). Amunts et al. demonstrated, using an fMRI verbal fluency task combined with a cytoarchitectonic probabilistic map of the left frontal lobe, that the anterior portion of Broca region is more implicated in semantic aspects of language, while the more posterior portion is involved in speech programming (Amunts et al. 2004). Such antero-posterior gradient organization of language in Broca's area and vPMC was also shown by electrophysiological recordings (Cerri et al. 2015). The same concept holds true regarding the posterior mesial SFG: the SMA proper is mainly activated for articulatory process, while the pre-SMA area is more involved in encoding word selection process (Alario et al. 2006).

In agreement with these previous results, our observations support an antero-posterior organization in language production within the left frontal lobe with:

- The motor–speech network that comprises the SMA area (at the level of the pre-SMA/SMA junction) and the vPMC, interconnected through the posterior part of the FAT. These two areas would constitute the core of the motor control network of speech, implementing the feedback control policy, as hypothesized in recent computational models of optimal motor control (Shadmehr and Krakauer 2008). Accordingly, these two areas also project to the striatum through the posterior part of the FST, in keeping with the computation of the “cost to go” in the basal ganglia. Of note, this motor–speech system could also encompass areas in the supramarginal gyrus, in which state estimation is supposed to be coded, based on sensory feedback from parietal operculum and superior temporal gyrus. Of note, the supramarginal gyrus and parietal operculum are connected to the vPMC through the third branch of the SLF, but in the present series, all resections being anterior to the precentral sulcus, we could not identify this so-called “articulatory loop” (Duffau et al. 2003a, b). Moreover, the contralateral SMA is also connected to this system through the corpus callosum homotopic and heterotopic projections (De Benedictis et al. 2016), explaining why callosal fibers appeared in the disconnectome map, and why patients

can recover from mutism following unilateral resection of left-dominant SMA (Krainik et al. 2004). Last but not least, it does not come as a surprise that the cortico-bulbar tract is also evidenced in the disconnectome map as part of the motor–speech system. Indeed, it is well known that the vPMC and SMA are in fact premotor areas, and that those areas have direct connections with both primary motor areas and with the spinal cord or bulbar region (Dum and Strick 1991; Schucht et al. 2013; Mandonnet and Duffau 2014).

- The lexico-semantic system comprises the pre-SMA area and the dorso-lateral premotor cortex in the posterior end of MFG and the pars triangularis in the IFG. These three sites are interconnected through branches of the FAT, with SFG–IFG long-range connections and SFG–MFG and MFG–IFG short-range connections. This lexico-semantic system is of course more widespread, as it also encompasses parietal and temporal sites, connected to the frontal lobe through the IFOF (as evidenced by disconnectome map), as well as the thalamus, connected to the frontal lobe through the anterior thalamic radiations (also evidenced by disconnectome map). Such anatomical substrate of the lexico-semantic system is in good agreement with the recent proposal of subdivision of labor in the semantic system, with an executive subsystem, gathering pars triangularis, posterior part of middle temporal gyrus and pre-SMA, acting over the semantic stores, located bilaterally in the antero-ventral temporal areas (Lambon Ralph et al. 2017). Of note, the role of the dorsal stream (and in particular, the arcuate fasciculus) in the lexico-semantic system is still a matter of debate.

### Plasticity of the lexico-semantic system

The anatomo-functional reorganization of language functions in glioma patients thanks to brain plasticity has been extensively described in the literature (Duffau 2005, 2014; Kong et al. 2016; Ghinda and Duffau 2017), the preservation of long-range associative pathways being the main condition of a successful reshaping of language networks (Herbet et al. 2016). In particular, regarding frontal language areas, several authors have reported on the resectability of Broca's area (Benzagmout et al. 2007; Wu et al. 2008; Lubrano et al. 2010), or the SMA/pre-SMA area (Peraud et al. 2002; Nelson et al. 2002; Russell and Kelly 2007; Voss et al. 2013), with no or minimal long-term deficit in picture naming. However, there are only very few reports investigating the underlying reorganization leading to recovery after the usual transient impairment following the resection of such areas. Some studies supported the recruitment of homotopic contralateral areas [see (Rosenberg et al. 2008; Kośła et al. 2015; Gębska-Kośła et al. 2017) for Broca's area resections and (Krainik et al. 2004; Acioly et al. 2015; Chivukula et al.

2018) for SMA resections], some others highlighted the role of perilesional rearrangement (Kristo et al. 2015), and one study highlighted the role of both perilesional and contralateral areas changes (Briganti et al. 2012).

To our knowledge, the question of the plasticity of the transverse connections in SFG–MFG, MFG–IFG, and SFG–IFG has never been investigated. Interestingly, in patients with posterior-most tumors, the lexico-semantic system could not be identified as the posterior boundary of the resection within the white matter, and only speech or complete motor arrest could be generated posteriorly by stimulation. We interpret this observation as a preoperative compensation of the anterior part of the FAT/FST by plasticity. Such remodeling might be favored by the triangulation between the lexico-semantic epicenters of SFG, MFG, and IFG, which are also linked through the ventral (and perhaps also dorsal) stream to the other temporal and parietal nodes of the lexico-semantic system. Last but not least, eight of the nine posterior cases were lower-grade glioma (WHO grade II and III). These tumors are characterized by a long initial period of slow growth rate that could have facilitated the implementation of efficient plasticity mechanisms.

## Limitations

This study suffers from a relatively low number of patient-cases. Moreover, the fact that tumors with different grades might lead to different levels of plasticity and network reorganization makes it difficult to generalize the present results to healthy individuals. Finally, the step consisting of locating the stimulation sites on the post-op MRI is user dependent, and we expect some uncontrolled variability, due to the fact that the grid of anatomical landmarks is rather coarse. Nonetheless, this is currently the best way to deal with the issue of reporting stimulation points on the post-op MRI, at least for teams, who, like ours, do not have the opportunity to use an intraoperative MRI. Moreover, the registration to the MNI template might also induce some uncertainty, due to the brain structure displacement caused by the surgical cavity, but in a reproducible user-independent manner.

Last but not least, the pathways of the dorsal stream (SLF III, arcuate fasciculus) were not evidenced in the present study. On one hand, this is coherent with the fact that we did not report about the white matter phonological sites, which constitute the hallmark of the arcuate fasciculus stimulation, or speech arrest, which constitutes the hallmark of the SLF III stimulation. On the other hand, this could be also due to the choice of the underlying white matter pathway atlas. Indeed, in this atlas (Rojkova et al. 2016), arcuate fasciculus and SLF III terminations are located mainly within the lower end of the precentral gyrus, with little extension to the pars opercularis, that is, within areas spared by the resections in the present series. If the underlying atlas would

have included terminations of these pathways within the pars triangularis and posterior end of MFG, as suggested by some authors (Fernández-Miranda et al. 2014; Wang et al. 2015), we might have found an implication of these pathways in the lexico-semantic and/or motor–speech functional sites.

## Conclusion

In this study, we reported that lexico-semantic errors were found anteriorly to motor–speech disturbances, both at the cortical and axonal levels. We interpret these findings as an antero-posterior functional gradient within the frontal lobe language subsystems, with an anterior part involved in lexico-semantic processing, and a posterior part involved in motor–speech aspects of language. In a near future, this distinction could be further explored by the new methodology of axono-cortical evoked-potentials (Yamao et al. 2014; Mandonnet et al. 2016; Boyer et al. 2018).

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## Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest to declare.

**Ethical approval** The study was approved by the local ethics committee of Pôle Neurosciences of Lariboisière Hospital. This study complied with the ethical standards.

**Informed consent** All patients gave signed consent for the retrospective use of clinical and radiological data.

## References

- Acioly MA, Cunha AM, Parise M et al (2015) Recruitment of contralateral supplementary motor area in functional recovery following medial frontal lobe surgery: an fMRI case study. *J Neurol Surg A Cent Eur Neurosurg* 76:508–512. <https://doi.org/10.1055/s-0035-1558408>
- Alario F-X, Chainay H, Lehericy S, Cohen L (2006) The role of the supplementary motor area (SMA) in word production. *Brain Res* 1076:129–143. <https://doi.org/10.1016/j.brainres.2005.11.104>
- Amunts K, Weiss PH, Mohlberg H et al (2004) Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space—the roles of Brodmann areas 44 and 45. *Neuroimage* 22:42–56. <https://doi.org/10.1016/j.neuroimage.2003.12.031>
- Avants BB, Tustison NJ, Song G et al (2011) A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage* 54:2033–2044. <https://doi.org/10.1016/j.neuroimage.2010.09.025>

- Axer H, Klingner CM, Prescher A (2013) Fiber anatomy of dorsal and ventral language streams. *Brain Lang* 127:192–204. <https://doi.org/10.1016/j.bandl.2012.04.015>
- Benzagmout M, Gatignol P, Duffau H (2007) Resection of World Health Organization grade II gliomas involving Broca's area: methodological and functional considerations. *Neurosurgery* 61:741–752. <https://doi.org/10.1227/01.NEU.0000298902.69473.77> (discussion 752–753)
- Bornkessel-Schlesewsky I, Schlesewsky M, Small SL, Rauschecker JP (2015) Neurobiological roots of language in primate audition: common computational properties. *Trends Cogn Sci (Regul Ed)* 19:142–150. <https://doi.org/10.1016/j.tics.2014.12.008>
- Boyer A, Duffau H, Vincent M et al (2018) Electrophysiological activity evoked by direct electrical stimulation of the human brain: interest of the P0 component. *Conf Proc IEEE Eng Med Biol Soc* 2018:2210–2213. <https://doi.org/10.1109/EMBC.2018.8512733>
- Briganti C, Sestieri C, Mattei PA et al (2012) Reorganization of functional connectivity of the language network in patients with brain gliomas. *AJNR Am J Neuroradiol* 33:1983–1990. <https://doi.org/10.3174/ajnr.A3064>
- Carrabba G, Mandonnet E, Fava E et al (2008) Transient inhibition of motor function induced by the Cavitron ultrasonic surgical aspirator during brain mapping. *Neurosurgery* 63:E178–E179. <https://doi.org/10.1227/01.NEU.0000335087.85470.18> (discussion E179).
- Catani M, Dell'acqua F, Vergani F et al (2012) Short frontal lobe connections of the human brain. *Cortex* 48:273–291. <https://doi.org/10.1016/j.cortex.2011.12.001>
- Cerri G, Cabinio M, Blasi V et al (2015) The mirror neuron system and the strange case of Broca's area. *Hum Brain Mapp* 36:1010–1027. <https://doi.org/10.1002/hbm.22682>
- Chang EF, Breshears JD, Raygor KP et al (2017) Stereotactic probability and variability of speech arrest and anomia sites during stimulation mapping of the language dominant hemisphere. *J Neurosurg* 126:114–121. <https://doi.org/10.3171/2015.10.JNS151087>
- Chivukula S, Pikul BK, Black KL et al (2018) Contralateral functional reorganization of the speech supplementary motor area following neurosurgical tumor resection. *Brain Lang* 183:41–46. <https://doi.org/10.1016/j.bandl.2018.05.006>
- De Benedictis A, Sarubbo S, Duffau H (2012) Subcortical surgical anatomy of the lateral frontal region: human white matter dissection and correlations with functional insights provided by intraoperative direct brain stimulation: laboratory investigation. *J Neurosurg* 117:1053–1069. <https://doi.org/10.3171/2012.7.JNS12628>
- De Benedictis A, Petit L, Descoteaux M et al (2016) New insights in the homotopic and heterotopic connectivity of the frontal portion of the human corpus callosum revealed by microdissection and diffusion tractography. *Hum Brain Mapp* 37:4718–4735. <https://doi.org/10.1002/hbm.23339>
- Dick AS, Bernal B, Tremblay P (2014) The language connectome: new pathways, new concepts. *Neuroscientist* 20:453–467. <https://doi.org/10.1177/1073858413513502>
- Duffau H (2005) Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol* 4:476–486. [https://doi.org/10.1016/S1474-4422\(05\)70140-X](https://doi.org/10.1016/S1474-4422(05)70140-X)
- Duffau H (2014) The huge plastic potential of adult brain and the role of connectomics: new insights provided by serial mappings in glioma surgery. *Cortex* 58:325–337. <https://doi.org/10.1016/j.cortex.2013.08.005>
- Duffau H (2015) Stimulation mapping of white matter tracts to study brain functional connectivity. *Nat Rev Neurol* 11:255–265. <https://doi.org/10.1038/nrneurol.2015.51>
- Duffau H, Capelle L, Sichez N et al (2002) Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 125:199–214
- Duffau H, Gatignol P, Denvil D et al (2003a) The articulatory loop: study of the subcortical connectivity by electrostimulation. *Neuroreport* 14:2005–2008. <https://doi.org/10.1097/01.wnr.0000094103.16607.9f>
- Duffau H, Capelle L, Denvil D et al (2003b) 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, Mandonnet E et al (2005) New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain* 128:797–810. <https://doi.org/10.1093/brain/awh423>
- Duffau H, Moritz-Gasser S, Mandonnet E (2013) A re-examination of neural basis of language processing: Proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. *Brain Lang*. <https://doi.org/10.1016/j.bandl.2013.05.011>
- Dum RP, Strick PL (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 11:667–689
- Fernández-Miranda JC, Wang Y, Pathak S et al (2014) Asymmetry, connectivity, and segmentation of the arcuate fascicle in the human brain. *Brain Struct Funct*. <https://doi.org/10.1007/s00429-014-0751-7>
- Ford A, McGregor KM, Case K et al (2010) Structural connectivity of Broca's area and medial frontal cortex. *Neuroimage* 52:1230–1237. <https://doi.org/10.1016/j.neuroimage.2010.05.018>
- Foulon C, Cerliani L, Kinkingnéhun S et al (2018) Advanced lesion symptom mapping analyses and implementation as BCbtoolkit. *Gigascience*. <https://doi.org/10.1093/gigascience/giy004>
- Friederici AD (2012) Language development and the ontogeny of the dorsal pathway. *Front Evol Neurosci* 4:3. <https://doi.org/10.3389/fnevo.2012.00003>
- Friederici AD (2015) White-matter pathways for speech and language processing. *Handb Clin Neurol* 129:177–186. <https://doi.org/10.1016/B978-0-444-62630-1.00010-X>
- Fujii M, Maesawa S, Motomura K et al (2015) Intraoperative subcortical mapping of a language-associated deep frontal tract connecting the superior frontal gyrus to Broca's area in the dominant hemisphere of patients with glioma. *J Neurosurg* 122:1390–1396. <https://doi.org/10.3171/2014.10.JNS14945>
- Geńska-Kośła K, Bryszewski B, Jaskólski DJ et al (2017) Reorganization of language centers in patients with brain tumors located in eloquent speech areas—a pre- and postoperative preliminary fMRI study. *Neurol Neurochir Pol* 51:403–410. <https://doi.org/10.1016/j.pjnns.2017.07.010>
- Ghinda CD, Duffau H (2017) Network plasticity and intraoperative mapping for personalized multimodal management of diffuse low-grade gliomas. *Front Surg*. <https://doi.org/10.3389/fsurg.2017.00003>
- Glasser MF, Coalson TS, Robinson EC et al (2016) A multi-modal parcellation of human cerebral cortex. *Nature* 536:171–178. <https://doi.org/10.1038/nature18933>
- Halai AD, Woollams AM, Lambon Ralph MA (2018) Triangulation of language-cognitive impairments, naming errors and their neural bases post-stroke. *Neuroimage Clin* 17:465–473. <https://doi.org/10.1016/j.nicl.2017.10.037>
- Herbet G, Maheu M, Costi E et al (2016) Mapping neuroplastic potential in brain-damaged patients. *Brain* 139:829–844. <https://doi.org/10.1093/brain/awv394>
- Hertrich I, Dietrich S, Ackermann H (2016) The role of the supplementary motor area for speech and language processing. *Neurosci Biobehav Rev* 68:602–610. <https://doi.org/10.1016/j.neubi.2016.06.030>
- Hickok G, Poeppel D (2004) Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition* 92:67–99. <https://doi.org/10.1016/j.cognition.2003.10.011>

- Howard D, Patterson KE, Company TVT (1992) The pyramids and palm trees test: a test of semantic access from words and pictures. Thames Valley Test Company, Bury St Edmunds
- Kemerdere R, de Champfleury NM, Deverdun J et al (2016) Role of the left frontal aslant tract in stuttering: a brain stimulation and tractographic study. *J Neurol* 263:157–167. <https://doi.org/10.1007/s00415-015-7949-3>
- Kinoshita M, Shinohara H, Hori O et al (2012) Association fibers connecting the Broca center and the lateral superior frontal gyrus: a microsurgical and tractographic anatomy. *J Neurosurg* 116:323–330. <https://doi.org/10.3171/2011.10.JNS11434>
- Kinoshita M, de Champfleury NM, Deverdun J et al (2015) Role of fronto-striatal tract and frontal aslant tract in movement and speech: an axonal mapping study. *Brain Struct Funct* 220:3399–3412. <https://doi.org/10.1007/s00429-014-0863-0>
- Klein A, Andersson J, Ardekani BA et al (2009) Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage* 46:786–802. <https://doi.org/10.1016/j.neuroimage.2008.12.037>
- Kong NW, Gibb WR, Tate MC (2016) Neuroplasticity: insights from patients harboring gliomas. *Neural Plast* 2016:2365063. <https://doi.org/10.1155/2016/2365063>
- Kośła K, Bryszewski B, Jaskólski D et al (2015) Reorganization of language areas in patient with a frontal lobe low grade glioma—fMRI case study. *Pol J Radiol* 80:290–295. <https://doi.org/10.12659/PJR.893897>
- Krainik A, Duffau H, Capelle L et al (2004) Role of the healthy hemisphere in recovery after resection of the supplementary motor area. *Neurology* 62:1323–1332
- Kristo G, Raemaekers M, Rutten G-J et al (2015) Inter-hemispheric language functional reorganization in low-grade glioma patients after tumour surgery. *Cortex* 64:235–248. <https://doi.org/10.1016/j.cortex.2014.11.002>
- Lambon Ralph MA, Jefferies E, Patterson K, Rogers TT (2017) The neural and computational bases of semantic cognition. *Nat Rev Neurosci* 18:42–55. <https://doi.org/10.1038/nrn.2016.150>
- Lawes INC, Barrick TR, Murugam V et al (2008) Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. *Neuroimage* 39:62–79. <https://doi.org/10.1016/j.neuroimage.2007.06.041>
- Lou W, Peck KK, Brennan N et al (2017) Left-lateralization of resting state functional connectivity between the presupplementary motor area and primary language areas. *Neuroreport* 28:545–550. <https://doi.org/10.1097/WNR.0000000000000783>
- Lubrano V, Draper L, Roux F-E (2010) What makes surgical tumor resection feasible in Broca's area? Insights into intraoperative brain mapping. *Neurosurgery* 66:868–875. <https://doi.org/10.1227/01.NEU.0000368442.92290.04> (discussion 875)
- Mandonnet E, Duffau H (2014) Understanding entangled cerebral networks: a prerequisite for restoring brain function with brain-computer interfaces. *Front Syst Neurosci* 8:82. <https://doi.org/10.3389/fnsys.2014.00082>
- Mandonnet E, Winkler PA, Duffau H (2010) Direct electrical stimulation as an input gate into brain functional networks: principles, advantages and limitations. *Acta Neurochir (Wien)* 152:185–193. <https://doi.org/10.1007/s00701-009-0469-0>
- Mandonnet E, Dadoun Y, Poisson I et al (2016) Axono-cortical evoked potentials: a proof-of-concept study. *Neurochirurgie* 62:67–71. <https://doi.org/10.1016/j.neuchi.2015.09.003>
- Mandonnet E, Sarubbo S, Duffau H (2017) Proposal of an optimized strategy for intraoperative testing of speech and language during awake mapping. *Neurosurg Rev* 40:29–35. <https://doi.org/10.1007/s10143-016-0723-x>
- Metz-Lutz M, Kremin H, Deloche G et al (1991) Standardisation d'un test de dénomination orale: contrôle des effets de l'âge, du sexe et du niveau de scolarité chez les sujets adultes normaux. *Neuropsychol Rev* 1:73–95
- Nelson L, Lapsiwala S, Haughton VM et al (2002) Preoperative mapping of the supplementary motor area in patients harboring tumors in the medial frontal lobe. *J Neurosurg* 97:1108–1114. <https://doi.org/10.3171/jns.2002.97.5.1108>
- Ookawa S, Enatsu R, Kanno A et al (2017) Frontal fibers connecting the superior frontal gyrus to broca area: a corticocortical evoked potential study. *World Neurosurg* 107:239–248. <https://doi.org/10.1016/j.wneu.2017.07.166>
- Papagno C, Casarotti A, Comi A et al (2014) Long-term proper name anomia after removal of the uncinate fasciculus. *Brain Struct Funct*. <https://doi.org/10.1007/s00429-014-0920-8>
- Peraud A, Meschede M, Eisner W et al (2002) Surgical resection of grade II astrocytomas in the superior frontal gyrus. *Neurosurgery* 50:966–975; (discussion 975–977)
- Price CJ (2012) A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage* 62:816–847. <https://doi.org/10.1016/j.neuroimage.2012.04.062>
- Rheault F, Houde J, Goyette N et al (2016) MI-Brain, a software to handle tractograms and perform interactive virtual dissection. Lisbon, Portugal
- Ripollés P, Biel D, Peñalosa C et al (2017) Strength of temporal white matter pathways predicts semantic learning. *J Neurosci* 37:11101–11113. <https://doi.org/10.1523/JNEUROSCI.1720-17.2017>
- Rojkova K, Volle E, Urbanski M et al (2016) Atlasing the frontal lobe connections and their variability due to age and education: a spherical deconvolution tractography study. *Brain Struct Funct* 221:1751–1766. <https://doi.org/10.1007/s00429-015-1001-3>
- Rosenberg K, Liebling R, Avidan G et al (2008) Language related reorganization in adult brain with slow growing glioma: fMRI prospective case-study. *Neurocase* 14:465–473. <https://doi.org/10.1080/13554790802459486>
- Russell SM, Kelly PJ (2007) Incidence and clinical evolution of post-operative deficits after volumetric stereotactic resection of glial neoplasms involving the supplementary motor area. *Neurosurgery* 61:358–367. <https://doi.org/10.1227/01.neu.0000279229.58449.d1> (discussion 367–368).
- Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection. *N Engl J Med* 358:18–27. <https://doi.org/10.1056/NEJMoa067819>
- Sarubbo S, De Benedictis A, Merler S et al (2016) Structural and functional integration between dorsal and ventral language streams as revealed by blunt dissection and direct electrical stimulation. *Hum Brain Mapp* 37:3858–3872. <https://doi.org/10.1002/hbm.23281>
- Saur D, Kreher BW, Schnell S et al (2008) Ventral and dorsal pathways for language. *Proc Natl Acad Sci USA* 105:18035–18040. <https://doi.org/10.1073/pnas.0805234105>
- Schucht P, Moritz-Gasser S, Herbet G et al (2013) Subcortical electrostimulation to identify network subserving motor control. *Hum Brain Mapp* 34:3023–3030. <https://doi.org/10.1002/hbm.22122>
- Shadmehr R, Krakauer JW (2008) A computational neuroanatomy for motor control. *Exp Brain Res* 185:359–381. <https://doi.org/10.1007/s00221-008-1280-5>
- Sierpowska J, Gabarrós A, Fernandez-Coello A et al (2015) Morphological derivation overflow as a result of disruption of the left frontal aslant white matter tract. *Brain Lang* 142:54–64. <https://doi.org/10.1016/j.bandl.2015.01.005>
- Sun H, Zheng D, Wang X et al (2013) Functional segregation in the left premotor cortex in language processing: evidence from fMRI. *J Integr Neurosci* 12:221–233. <https://doi.org/10.1142/S0219635213500131>
- Swann NC, Cai W, Conner CR et al (2012) Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: electrophysiological responses and functional and

- structural connectivity. *Neuroimage* 59:2860–2870. <https://doi.org/10.1016/j.neuroimage.2011.09.049>
- Tate MC, Herbet G, Moritz-Gasser S et al (2014) Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited. *Brain*. <https://doi.org/10.1093/brain/awu168>
- Thiebaut de Schotten M, Ffytche DH, Bizzi A et al (2011a) Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage* 54:49–59. <https://doi.org/10.1016/j.neuroimage.2010.07.055>
- Thiebaut de Schotten M, Dell'Acqua F, Forkel SJ et al (2011b) A lateralized brain network for visuospatial attention. *Nat Neurosci* 14:1245–1246. <https://doi.org/10.1038/nn.2905>
- Thiebaut de Schotten M, Dell'Acqua F, Valabregue R, Catani M (2012) Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex* 48:82–96. <https://doi.org/10.1016/j.cortex.2011.10.001>
- Thiebaut de Schotten M, Dell'Acqua F, Ratiu P et al (2015) From Phineas Gage and Monsieur Leborgne to H.M.: revisiting disconnection syndromes. *Cereb Cortex* 25:4812–4827. <https://doi.org/10.1093/cercor/bhv173>
- Vassal F, Boutet C, Lemaire J-J, Nuti C (2014) New insights into the functional significance of the frontal aslant tract: an anatomofunctional study using intraoperative electrical stimulations combined with diffusion tensor imaging-based fiber tracking. *Br J Neurosurg* 28:685–687. <https://doi.org/10.3109/02688697.2014.889810>
- Vergani F, Lacerda L, Martino J et al (2014) White matter connections of the supplementary motor area in humans. *J Neurol Neurosurg Psychiatr*. <https://doi.org/10.1136/jnnp-2013-307492>
- Vincent M, Guiraud D, Duffau H et al (2017) Electrophysiological brain mapping: Basics of recording evoked potentials induced by electrical stimulation and its physiological spreading in the human brain. *Clin Neurophysiol* 128:1886–1890. <https://doi.org/10.1016/j.clinph.2017.07.402>
- Voss J, Meier TB, Freidel R et al (2013) The role of secondary motor and language cortices in morbidity and mortality: a retrospective functional MRI study of surgical planning for patients with intracranial tumors. *Neurosurg Focus* 34:E7. <https://doi.org/10.3171/2013.2.FOCUS12410>
- Wang X, Pathak S, Stefanescu L et al (2015) Subcomponents and connectivity of the superior longitudinal fasciculus in the human brain. *Brain Struct Funct* doi: <https://doi.org/10.1007/s00429-015-1028-5>
- Wu C, Pu S, Lin Y et al (2008) Fractionated resection on low grade gliomas involving Broca's area and insights to brain plasticity. *Chin Med J* 121:2026–2030
- Yamao Y, Matsumoto R, Kunieda T et al (2014) Intraoperative dorsal language network mapping by using single-pulse electrical stimulation. *Hum Brain Mapp* 35:4345–4361. <https://doi.org/10.1002/hbm.22479>

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