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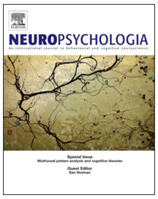

Intraoperative electrical stimulation of language switching in two bilingual patients

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ABSTRACT

Background: Language switching (LS) is an important phenomena usually observed in some bilingual communities. The ability to switch languages is a very fast, efficient and flexible process, being a fundamental aspect of bilingual efficient language communication. The aim of the present study was to characterize the specific role of non-language specific prefrontal regions in the neural network involved in LS in bilingual patients, during awake brain surgery and using electrical stimulation mapping (ESM).
Methods: In order to identify the neural regions involved in LS we used, a new specific ESM protocol in two patients undergoing awake brain surgery. Besides, functional magnetic resonance imaging (fMRI), neuropsychological testing and the assessment of daily conversational LS patterns post-surgery were used as complementary imaging and behavioral assessments.
Results: The outcome of the multimodal ESM-fMRI neuroimaging comparison in both patients pointed out to the crucial involvement of the inferior and middle frontal cortices in LS.
Conclusions: The present results add to previous findings highlighting the important role of non-language specific frontal structures in regulating LS. The new protocol developed here might allow neurosurgeons to plan ahead for surgical intervention in multilingual patients to ensure the preservation of regions involved in LS and therefore the prevention of pathological language mixing after intervention.

1. Introduction

Language switching (LS) is a very fast, efficient and flexible process that occurs when bilinguals alternate between two languages in the same conversation (Bialystok, Craik, Green, & Gollan, 2009; Penfield & Roberts, 1959). Importantly, LS supports effective communication in bilingual environments by enabling individuals to appropriately select the language spoken as a function of external cues such as linguistic knowledge of their interlocutor, face-related cues or contextual effects (Festman, 2012; Rodriguez-Fornells, Kramer, Lorenzo-Seva, Festman, & Münte, 2011; Soveri, Rodriguez-Fornells, & Laine, 2011). When this ability is impaired and the language in use becomes inappropriate to the external contexts, LS can be considered pathological (Fabbro, Skrap, & Aglioti, 2000; Paradis, 1995, 2012).

Clear anatomical evidence supporting the existence of LS has not yet been established, although several studies have pointed out to the possible involvement of the middle frontal gyrus (MFG) and the inferior frontal gyrus (IFG) (see Abutalebi & Green, 2007; Hervais-Adelman, Moser-Mercer, & Golestani, 2011; Rodríguez-Fornells, de Diego Balaguer, & Münte, 2006; Luk, Green, Abutalebi, & Grady, 2012 for a review). For example, Fabbro et al. (2000) described a bilingual case of pathological LS with a lesion encompassing the left prefrontal cortex affecting the underlying white matter of the IFG, the MFG and the superior frontal gyri [including the left anterior cingulate cortex (ACC) and the anterior callosal fibbers]. This patient, who did not show aphasic symptoms in any of his two languages, pathologically switched between them despite the instruction to speak in a particular language even at times when the patient was aware of the switches introduced. The lesions in the ACC, prefrontal cortex and the underlying white-matter lesions could have affected this patient in his ability to

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maintain the goal of the communication (e.g., which is the language in use?) or the ability to suppress the interference from the other non-used language. Similarly, it has been shown that transcranial magnetic stimulation (TMS) applied to the MFG (more precisely to the left dorsolateral prefrontal cortex—DLPFC) can induce involuntary LS (Holtzheimer, Fawaz, Wilson, & Avery, 2005). Moreover, a lesion study of a patient who suffered an ischemic stroke in the aforementioned structure (DLPFC) and presented pathological switching further supports the importance of this region in LS (Nardone et al., 2011).

In line with these findings, an enhanced activation in the posterior inferior frontal region has also been revealed in an fMRI study using an LS-related task in bilinguals (Rodriguez-Fornells, Rotte, Heinze, Nosselt, & Münte, 2002). It has been proposed that the DLPFC probably mediates cognitive control in bilinguals through the interplay between a top-down selection–suppression mechanism and a local inhibitory mechanism in charge of reducing the activation of the non-target language (Rodríguez-Fornells et al., 2006). Similar activations in cognitive control prefrontal regions such as the ACC (and supplementary motor area, SMA), left middle prefrontal cortex and in the left portions of the IFG have also been reported in other fMRI studies in language switching contexts (Abutalebi et al., 2007; Guo, Liu, Misra, & Kroll, 2011; Hernandez, Martinez, & Kohnert, 2000; Rodriguez-Fornells et al., 2005). Even in monolingual language settings, bilinguals tend to largely activate several regions in the left prefrontal and inferior frontal cortex, being these activations most probably related to the control of interference or efficient suppression of the language not in use (Green & Abutalebi, in press; Kovelman, Baker, & Petitto, 2008; Parker Jones et al., 2012; Rodríguez-Fornells et al., 2006).

Furthermore, an electrical stimulation mapping (ESM) study conducted by Kho et al. (2007) showed that a temporary disruption of the IFG may provoke an involuntary language switch. A similar effect has been recently encountered while stimulating the DLPFC in a trilingual patient (Lubrano, Prod´homme, Demonet, & Kopke, 2012). Lastly, the ESM study of Moritz-Gasser & Duffau (2009) revealed that electrical stimulation applied to the posterior part of the superior temporal sulcus or the tumoral resection at the level of the superior longitudinal fasciculus (SLF) can each elicit involuntary LS. Interestingly, the SLF connects the posterior part of the temporal sulcus with the IFG, which pinpoints the possible role of this white matter tract in LS. It is worth mentioning that the same ESM technique has been used previously to characterize overlapping as well as specific neural representations of the different languages in bilinguals (Lucas, McKhann, & Ojemann, 2004; Roux & Trémoulet, 2002; Roux et al., 2004). In summary, the present evidence supports the idea that the left middle and inferior frontal cortices play a crucial role in LS.

The aim of the present study was to investigate the specific role of the middle and inferior frontal regions in LS in two Spanish-Catalan bilingual patients using for the first time complementary ESM, fMRI and neuropsychological assessment. With that purpose in mind we developed a new LS-ESM paradigm that allows systematic evaluation of externally triggered LS (see Fig. 1a). Until now, LS-specific sites have been reported in ESM studies for involuntary LS during object naming and mostly at the moment of tumor resection (Kho et al., 2007; Lubrano et al., 2012; Moritz-Gasser & Duffau, 2009). The novelty of the present study relies on the development of a specific method that permits the control of voluntary switching using ESM in a cued-LS task before the resection. This new protocol might allow neurosurgeons to plan ahead of surgical intervention in multilingual patients to ensure the preservation not only of naming sites but also of regions involved in LS. This aspect is important for the possible prevention of pervasive and involuntary language switching after surgery, as observed in the first patient described in the present study.

2. Methods

2.1. Participants

Patient 1 was a 60-year old, right-handed male, diagnosed as having anaplasic astrocytoma located in the left hemisphere (Fig. 2a). The fronto-opercular tumoral lesion he suffered was provoking epileptic seizures followed by periods of post-ictalaphasia. In the pre-surgery fMRI study, the language lateralization of Patient 1 was considered as predominantly left. Patient 1 had Catalan as his first language (L1), however, he had received formal education in Spanish (L2), and thus, had a similar level of proficiency in both languages (Table 1).

Patient 2 was a 36-year old, right-handed male, suffering from multiple cephalalgias and had complained of occasional word finding difficulties associated with tiredness or stress for 6 months prior to the diagnosis of glioblastoma (see Fig. 3a). The tumour was localized at the temporal lobe of the left hemisphere,

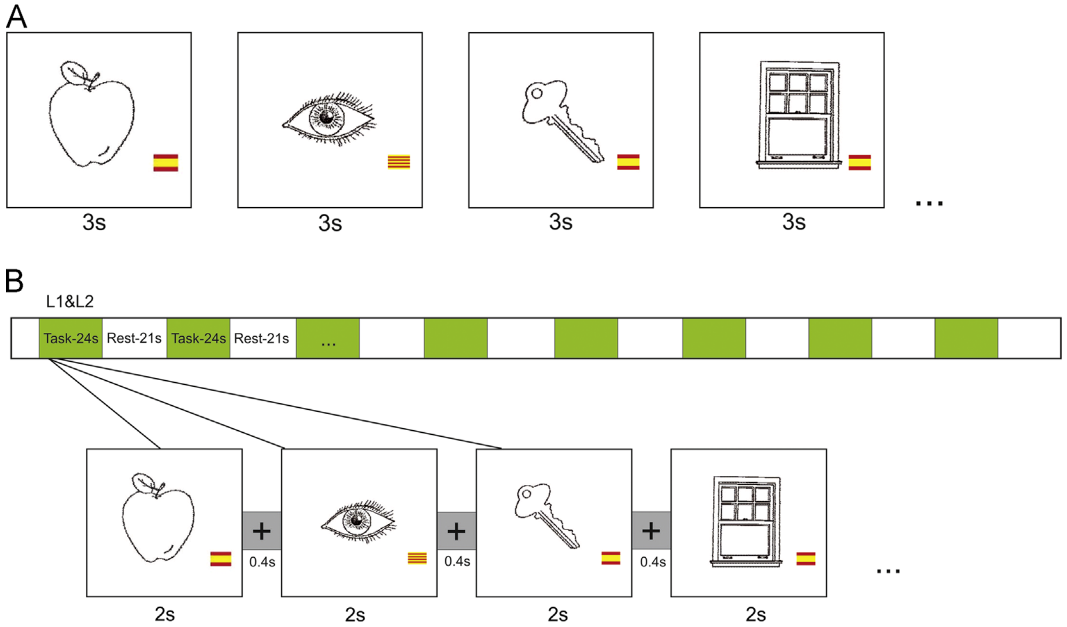

Fig. 1. (A) Example of stimuli for experimental LS naming during the ESM. Duration of single image presentation is 3 s. (B) Block-design for the fMRI procedure on LS naming. Duration of single image presentation is 2 s followed by 0.4 s of fixation point. Each trial is composed of 10 images followed by 21 s of rest. The task is made up of a total of 16 blocks (8 of active tasks and 8 of rest).

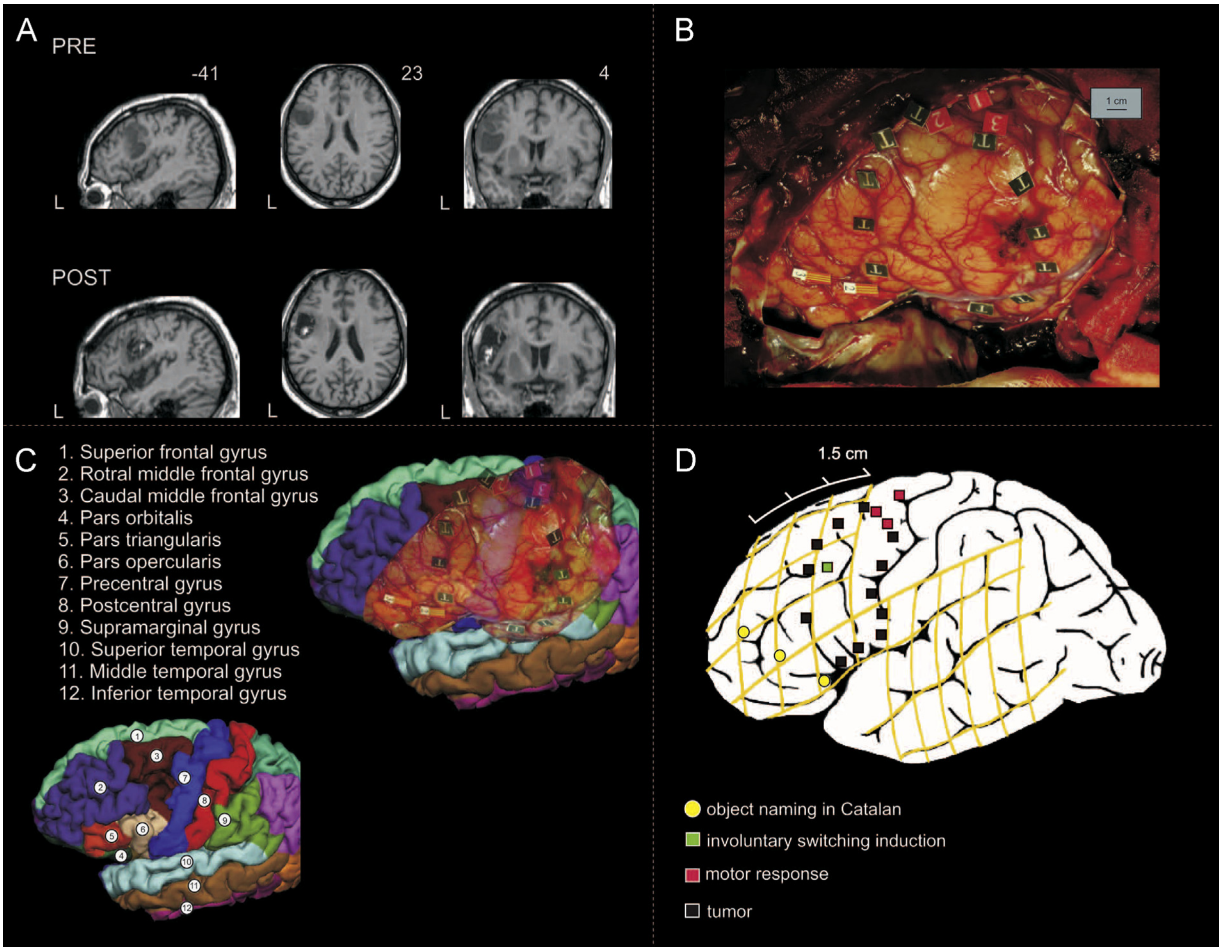

Fig. 2. (A) T1, pre- and post-surgery MRI showing an anaplasic astrocytoma and post-surgical cavity in Patient 1 (images displayed in neurological convention). (B) An intraoperative photograph of Patient 1 taken after the ESM procedure. (C) Left: Patient 1's left cortical surface, reconstructed on the basis of preoperative imaging. Right: an intraoperative photograph of Patient 1 taken after the ESM procedure and superimposed on the previously reconstructed cortical surface. (D) Points of ESM located using the arbitrary two-dimensional grid. Black labels: the contour of the tumor; Pink labels: motor response; Yellow labels: areas with evoked non-response error or delay in object naming task in Catalan; Green label: involuntary LS from Catalan to Spanish during the tumor resection. The Sylvian fissure and the motor cortex were used as landmarks for the normalization of the data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and according to the pre-surgical fMRI study, the language functions of Patient 2 were also left-lateralized. Patient 2 was bilingual, spoke both Spanish (L1) and Catalan (L2) in his everyday life with the same level of proficiency, although in his parental home he acquired Spanish as his first language (L1) (Table 1).

The neuropsychological assessment of language function carried out before surgery revealed satisfactory output for experimental object naming in both patients (Catalan for Patient 1 and Catalan and Spanish for Patient 2) and allowed them to be included in the ESM (criterion set at 65% naming accuracy, Table 2). Importantly, none of the patients manifested episodes of unintended LS during pre-surgical evaluation. Each patient signed an informed consent for the participation in this study and the protocol has been approved by the Ethical Committee of the Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona (Spain).

2.2. *Neuropsychological assessment*

Before and after surgery, patients underwent a standardized neuropsychological assessment focused on language processing. The examination included tests of Edinburgh Handedness Inventory (EDI; Oldfield, 1971), Digit Span (Wechsler, 1997), the Boston Naming Test and the verbal fluency included in the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983), the Token Test (De Renzi & Faglioni, 1978) and non-words repetition included in the Test de Barcelona (Peña-Casanova, 2005). All the tests were adapted for Spanish population. The standard examination was complemented with the examination of LS (see methods; language switching task).

Additionally, after surgery and in order to have a more ecological measure of daily conversation LS patterns, both patients were administered the Bilingual Switching Questionnaire (BSWQ; Rodriguez-Fornells et al., 2011, see Table 1). The BSWQ evaluates the tendency of a bilingual to switch between languages, the effects of contextual factors in LS and the frequency of unintended (non-aware) switching patterns. A relative was also requested to answer the questionnaire concerning the language switching pattern observed in the patient before surgery (see Table 1).

2.3. *Electric stimulation mapping (ESM)*

ESM is a technique that elicits a brief and reversible lesion of cortical function. The direct electrical stimulation applied to the small patches of cortex while the patient performs language tasks makes it possible to observe whether the stimulated area is subservient to the function examined (Duffau et al., 2003). In this study ESM was performed according to the methodology described previously by Ojemann, Ojemann, Lettich, and Berger (2008). Local anaesthesia with svedocaine 0.25% and lidocaine 2% was used for scalp and temporal muscle. Patients were under general anaesthesia until the opening of the duramater. Just before this opening, patients were awakened to enable the familiarization with the language tasks. Once the meninx opened and the patients familiarized with the situation, the ESM procedure started. The Ojemann cortical stimulator (OCS Radionics, Inc., Burlington, MA, USA) was used to stimulate the brain cortex. The inter-electrode distance of the bipolar forceps was of 5 mm. This constant current generator was set to deliver biphasic square wave pulses of 4-ms duration with a pulse frequency of 60 Hz. The duration of each stimulation train was of 3 s. The first stimulation was applied to the motor cortex. The initial intensity of the current was established at 1 mA and was progressively increasing by 0.5 mA until the desired motor responses were observed (e.g. involuntary movements of the contralateral side of the body). The final intensity of current necessary to provoke the motor responses was fixed as optimal for the language mapping. Stimulation was applied continuously, in the distance of 5 mm between the neighbouring points, until it covered the overall exposed cortical surface. The current discharge was performed once an image appeared on the computer screen located in front of the patient. Each site was stimulated at least three times while the single language naming or the switching task was performed. A site was considered to be essential for language production if two out of three stimulations caused non-response errors or delay in a single language naming trial. Similarly, for the language switching task, a site was associated to LS when the patient manifested non-response errors or delay only in these trials, that is, when the patient was cued to change the language (previous stimulation of the same sites did not

Table 1
Language history assessment (proficiency and language use of Spanish and Catalan) and Bilingual Switching Questionnaire (BSWQ).

Language history L1	Patient 1 Catalan	Patient 2 Spanish				
Age onset of Spanish (years)	7	2				
Age onset in Catalan (years)	2.5	14				
Spanish proficiency	3.5	4				
Catalan proficiency	4	4				
Language use	2.7	5.4				
BSWQ	***Patient 1***					
	pre-surgery familiar opinion			*post-surgery self-assessment*		
subscale	Score	*T*	*p*	Score	***T***	***p***
L1S	8	0.4114	*n.s.*	**14**	3.9377	**
L2S	6	−1.0445	*n.s.*	10	0.7720	*n.s.*
CS	3	−1.6507	*n.s.*	**12**	2.2589	*
US	9	0.9083	*n.s.*	10	1.3624	*n.s.*
OS	26	−0.5233	*n.s.*	**46**	2.6485	*
BSWQ	***Patient 2***					
	pre-surgery familiar opinion			*post-surgery self-assessment*		
subscale	Score	*T*	*p*	Score	***T***	***p***
L1S	**12**	2.7623	*	4	−1.9395	*
L2S	7	−0.5904	*n.s.*	5	−1.4987	n.s.
CS	8	0.5213	*n.s.*	**3**	−1.6507	*
US	4	−1.3624	*n.s.*	**3**	−1.8166	*
OS	31	0.2696	*n.s.*	**15**	−2.2678	*

Language history—L1 and L2 proficiency: averaged the global scores of self-rated skills in comprehension, reading, speaking, and writing on a 4-point scale, low scores indicate poor self-rated proficiency. Language use—overall language use across different life periods assessed on a seven point scale; low scores indicate predominance of Catalan use, and high scores indicate predominance of Spanish use. **BSWQ—**LS habits characterized behaviorally. A five-point scale (1–5) quantifies the frequency of behavior described; never (1), rarely (2), occasionally (3), frequently (4) or always (5), here presented as an addition of 3 correspondent items (min. score 3, max. 15). L1S, a tendency to switch to L1 (to Catalan for Patient 1 and to Spanish for Patient 2); L2S, a tendency to switch to L2 (to Spanish for Patient 1 and to Catalan for Patient 2); CS, contextual switching; US, unintended switching. The familiar opinion and self-assessment measures were compared to the sample of healthy bilinguals ($N=566$); $^{*}p\le 0.05$, $^{**}p\le 0.001$. [For further details see: Rodriguez-Fornells et al., 2011].

alter the language production in single language naming). The repeated use of the non-target language (at least two times in three consecutive trials) was also considered as an error. The errors in the single language naming or LS tasks were not compared to the baseline error rate for a given language, but were labelled as such using the methods described previously (Lucas, Drane, Dodrill, & Ojemann, 2008; Roux et al., 2004).

2.4. Language switching task

In order to induce LS experimentally, a specific LS task was designed to be applied during the pre-surgical neuropsychological assessment, during ESM, during fMRI and after surgery. This task was performed during the neuropsychological assessment prior to surgery and intraoperatively only with Patient 2. After surgery, the task was administered to both patients during the neuropsychological assessment and fMRI. The task comprised two conditions. During the first part (single language-naming condition), patients simply named black-and-white images separately for L1 and L2. A set of 48 images were selected from a standard database (Snodgrass & Vanderwart, 1980). To avoid the bias of between-language similarity, the words chosen in all cases were non-cognate (i.e. different phonological and orthographic forms in Catalan and Spanish, for example: "*poma*" and "*manzana*", meaning *apple*). During the pre-surgical neuropsychological assessment, Patient 2 named the different images separately for each language (beginning with L1) for screening purposes. We removed from the final task all images of objects that the patient could not name. The images correctly named during the screening were then used for the single language-naming and LS-naming conditions.

After the screening, the patient was tested with the single language naming condition (beginning with L1). In the following part of the assessment, the patient had to perform the LS-naming condition which consisted in mixing Spanish and Catalan languages. A small flag at the lower right corner of the images indicated the language which should be used, with its change being the trigger to induce LS (see Fig. 1a). The flags were assigned randomly to the images with a maximum of four consecutive trials with the same language. This LS-naming condition was comprised of two blocks: the first block had 40 images (20 with a Spanish flag and 20 with a Catalan flag) with the second block using the same images but each with the opposite flag (Fig. 1a). Images were displayed on a computer screen in front of the patient. The duration of the presentation of each image was 3 s. During surgical intervention the onset of the trial was controlled by the experimenter and synchronized with the electrical stimulation. If the name of the image was produced immediately after its appearance, the response was classified as: (i) "correct response", (ii) "delay" if the response was delayed and (iii) as "non-response error" if the response was non produced. The reaction time provided crucial information for considering whether or not the stimulated point was involved in language production or the language switching.

2.5. fMRI

The images were acquired using a 1.5 T MRI Philips Intera system at the Hospital de Bellvitge of Barcelona. Functional images were acquired in the axial plane using a single-shot T2*-weighted gradient-echo EPI sequence (slice thickness$=$3.5 mm; no gap; number of slices$=$35, repetition time (TR)$=$3000 ms; echo time (TE)$=$50 ms; flip angle$=90^{\circ}$; matrix$=64\times64$; field of view FOV$=$230 mm; voxel size$=3.59\times3.59\times3.5$ mm^3). In addition to the functional runs a high-resolution T1-weighted image (slice thickness$=$1.1 mm; number of slices$=$150; repetition time (TR)$=$25 ms; echo time (TE)$=$4.6 ms; flip angle$=30^{\circ}$; matrix$=320\times320$; field of view FOV$=$240 mm; voxel size$=0.75\times0.75\times1.1$ mm^3) was also acquired for each subject.

For the fMRI single language naming and the LS exploration a standard block-design task was developed. Three separated runs were used. For all of them, two conditions, object naming and rest, were defined. Each active block of the object-naming took 24 s (2 s for 10 different objects to name and 0.4 s for a fixation point between them) and was followed by 21 s of rest. Patients were instructed to name the objects presented exclusively in their L1 for the first run and then exclusively in their L2 for the second run (single language naming condition). Six pairs of naming and rest blocks were performed, yielding a total run time of 4 min and 30 s (Fig. 1b). During the third and final run, subjects had to perform the LS-naming condition which was extended to 8 pairs of activation-rest blocks in order to increase signal power, yielding a total run time of 6 min. For this LS-naming condition patients were instructed to name the objects in the language indicated by the flags on the lower right corner of the images (a flag change being a trigger to induce LS).

2.6. Data analysis

2.6.1. Electrical stimulation mapping (ESM)

The locations of the stimulated points were reconstructed using the intraoperative photographs. In order to report the localization of the points in two

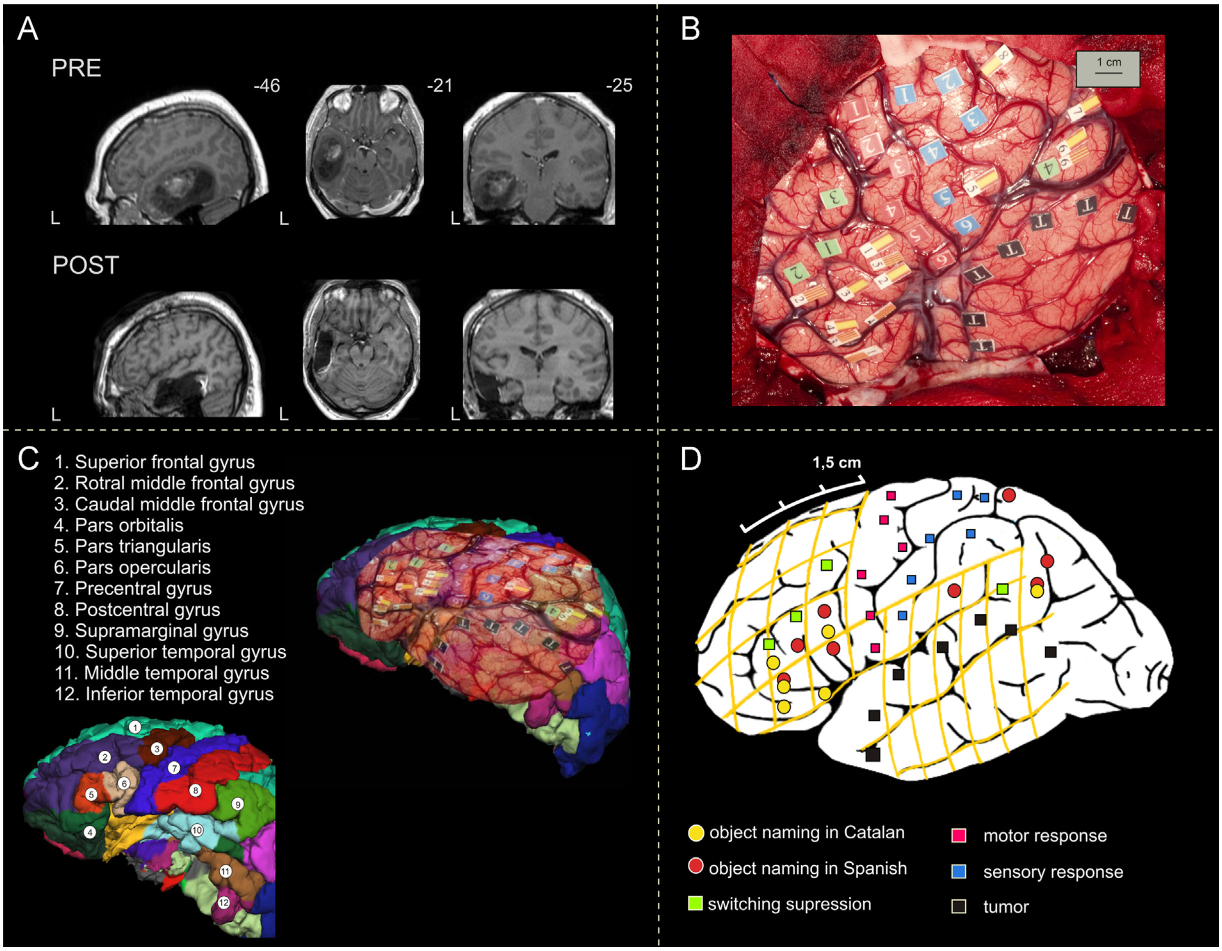

Fig. 3. (A) T1, pre- and post-surgery MRI showing a glioblastoma and post-surgical cavity in Patient 2 (images displayed in neurological convention). (B) An intraoperative photograph of Patient 2 taken after the ESM procedure. (C) Left: Patient 2's left cortical surface, reconstructed on the basis preoperative imaging. Right: An intraoperative photograph of Patient 2 taken after the ESM procedure and superimposed on the previously reconstructed cortical surface. (D) Points of ESM located using the arbitrary two-dimensional grid. Black labels: the contour of the tumor; Blue labels: sensory response; Pink labels: motor response; Yellow labels: areas with evoked non-response error or delay in single language object naming task in Catalan; Red labels: evoked non-response error or delay in single language object naming task in Spanish; Green labels: evoked non-response error or delay in LS-naming task. The Sylvian fissure and the motor cortex were used as landmarks for the normalization of the data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Neuropsychological assessment.

	Patient 1		Patient 2	
	Pre-surgery	Post-surgery	Pre-surgery	Post-surgery
Digit Span (WAIS III subscale)				
Forward	5 (Perc.41–59)	4 (Perc.11–18)	4 (Perc.2)	6 (Perc.41–59)
Backward	2 (Perc.3–5)	2 (Perc.3–5)	4 (Perc.19–28)	3 (Perc.11–18)
Verbal fluency				
Semantic	6 (Perc. < 1)	4(Perc. < 1)	16 (Perc.3–5)	19 (Perc.11–18)
Phonetic	4 (Perc.1)	1(Perc. < 1)	10(Perc.3–5)	13 (Perc.19–28)
Non-words repetition	6/8	6/8	8/8	8/8
Catalan object naming (ESM screening)	49/60	48/60	56/60	50/60
Spanish object naming (ESM screening)	–	–	46/60	52/60
Boston naming test	45/60 (Perc.41–50)	38/60 (39–42)	51/60 (Perc.29–40)	34/60 (Perc. < 1)
Token test	18,5/36 (Perc. < 1)	19/36 (Perc. < 1)	32/36 (Perc. < 1)	34.5/36 (Perc.19–28)
Edinburgh inventory	10 (right)	–	10 (right)	–

Normative data: (Peña-Casanova, 2004), Perc., percentil.

dimensions, an arbitrary grid (similar to the one used by Ojemann et al. (2008), was placed on the individual photographs of each of the two patients (Figs. 2 and 3d). To support the two-dimensional data from the intraoperative photographs, the exploration was extended by reconstructing the surface of the patients' brains in 3D. To do so, the structural MRI data (T1) was further processed using the Freesurfer image analysis suite which is documented and freely available for download online

Table 3
Brain regions activated during the single language-naming condition in L1 and L2 (L1 and L2 taken together and contrasted with their respective rest, $p < 0.01$, cluster size $n = 20$). Coordinates are in the MNI system.

Activations						
Area	BA	Cluster size (mm^3)	*t* value	Peak coordinates		
				x	*y*	*z*
R Cuneus	7	7760	7.02	26	−84	32
L Inferior/middle frontal gyrus/precentral gyrus	6	9824	6.53	−50	14	0
L Middle occipital gyrus	40	22344	6.17	−30	−94	12
R Middle/superior frontal gyrus	10	3072	5.76	36	60	12
L Middle frontal gyrus	10	2776	4.64	−38	50	10
R Middle/inferior frontal gyrus	6	3792	4.43	50	0	42
R Precuneus	7	2816	4.36	30	−50	50
R Fusiform gyrus	19	3288	4.30	30	−78	−20
L Middle occipital gyrus	18	1992	4.24	−44	−78	−16
R Middle frontal gyrus	6	1456	3.76	2	0	68
L Middle temporal gyrus	37	1112	3.74	−46	−62	−2
L Supramarginal gyrus	40	1032	3.74	−64	−26	24
R Middle occipital gyrus	37	1720	3.52	44	−60	−12
L Caudate	–	456	3.49	−16	−8	16
R Middle frontal gyrus	6	432	3.37	36	0	48
R Superior temporal/inferior frontal gyrus	38	904	3.26	52	16	−8
R Cingulate gyrus	–	344	3.25	18	6	30
L Middle frontal gyrus	11	496	3.17	−18	36	−16
L Middle frontal gyrus	6	384	3.09	−2	14	50
R Inferior frontal gyrus	9	344	3.04	60	10	26
R Putamen	–	248	2.92	22	16	6
L Postcentral gyrus	2	160	2.78	−52	−28	44
R Angular gyrus	7	200	2.65	16	−64	50

BA, Brodmann area; R, right; L, left.

Table 4
Brain regions activated during the LS task performance (LS-naming vs. L1&L2 single language-naming) $p < 0.01$, cluster size $n = 20$). Coordinates are in the MNI system.

Activations						
Area	BA	Cluster size (mm^3)	*t* value	Peak coordinates		
				x	*y*	*z*
L Parahipoccampal Gyrus	19	768	4.29	−31	−42	−4
R Middle frontal gyrus/cingulate gyrus	31	1464	3.70	10	−14	50
L Cuneus	18	488	3.65	−14	−74	16
R Inferior frontal gyrus/precentral gyrus	44	856	3.65	48	0	16
L Precentral gyrus/ L Inferior frontal gyrus	6/44	216	3.50	−60	4	16
L Uncus/ amygdala/ parahippocampal gyrus (temporal pole)	28	568	3.43	−24	4	−24
R Inferior frontal gyrus	13	1096	3.42	40	16	10
R Precentral gyrus	6	488	3.34	4	−32	66
R Precentral gyrus	4	280	3.04	36	−26	62
R Inferior frontal gyrus	47	168	3.03	30	8	−20
L Precuneus	–	160	2.93	−6	−64	16
L Middle frontal gyrus	–	200	2.76	−40	44	−12

BA, Brodmann area; R, right; L, left.

(http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999). Following this, both types of imaging were compared in order to optimize the reliability of the arbitrary grid and the interpretation of its outcome.

2.6.2. *fMRI*

Statistical comparison between single language naming and LS naming tasks were carried out for Patient 2 (the interpretation of the fMRI outcome was not possible for Patient 1, who was unable to complete the tasks properly). The analysis of fMRI was performed using SPM8 (The Wellcome Institute of Neurology, London, UK). The pre-processing included realignment, segmentation, normalization and smoothing with an 8 mm Gaussian kernel. Unified Segmentation (Ashburner & Friston, 2005) with medium regularisation and cost function masking (CFM) was applied (Andersen, Rapcsak, & Beeson, 2010; Brett, Leff, Rorden, & Ashburner, 2001; Ripolles et al., 2012). The cost function masks were defined for each patient by applying a binary mask of the lesioned tissue using the MRIcron software package (Rorden & Brett, 2000) (http://www.cabiatl.com/mricro/mricron/index.html). For the first level analysis, a general lineal model was created using task and rest conditions for each of the three runs. The translational and rotational motion parameters extracted from the realignment phase were also included in the model. Finally, after model estimation, statistical parametrical maps were created for the single language-naming in L1 and L2 activation conditions versus rest conditions (L1&L2 single language naming vs. rest) and for the LS-naming task versus L1 and L2 conditions (LS-naming vs. L1&L2 single language naming). These contrasts are reported at an uncorrected level of $p < 0.01$ and 20 voxels of cluster extent (Tables 3 and 4, Fig. 4).

2.6.3. *Bilingual switching questionnaire (BSWQ)*

The statistical comparison between the individual scores of the BSWQ was performed using a modified *t*-test allowing a comparison between an individual's test score against norms derived from small samples (Crawford & Howell, 1998). The method was developed to be used in clinical practice or for neuropsychologists

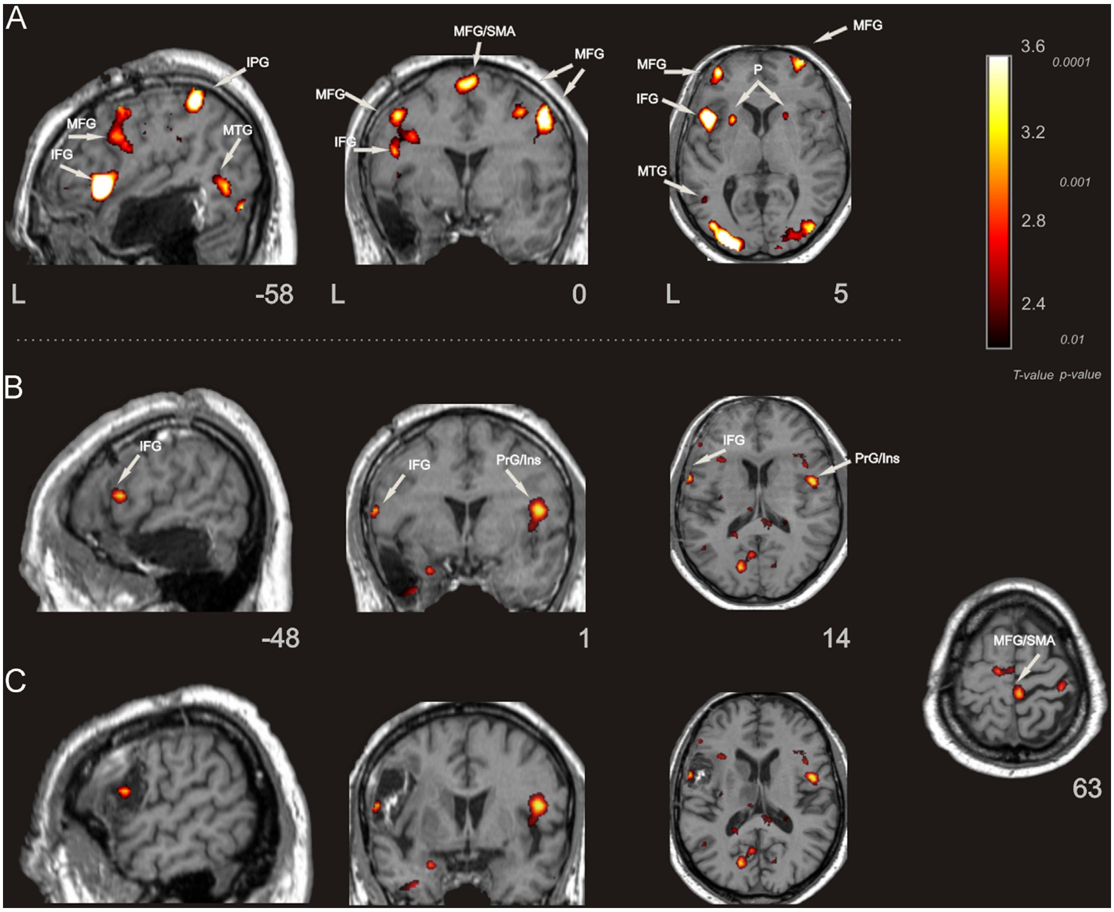

Fig. 4. (A) Activation for the single language object naming in both languages (single language-naming condition, L1 & L2 versus rest) in Patient 2 represented on sagittal, coronal and axial views. (B) Activation in the IFG/PrG, PrG/Insula and MFG/SMA during the LS (LS-naming vs. L1 & L2) of Patient 2 superimposed on the post-surgical T1 MRI for the same Patient. (C) Activation during LS (LS-naming vs. L1 & L2) for Patient 2, superimposed on the T1 anatomical image of Patient 1 (showing also the resection carried out in this patient). Notice the overlap between the cortical region resected in Patient 1 and the region activated during the LS task in Patient 2 (images displayed in neurological convention). All structural and functional images shown are normalized with coordinates in the MNI system. (L, left; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; IPG, inferior parietal gyrus, MTG, middle temporal gyrus, SMA, supplementary motor area; PrG, precentral gyrus, Ins, insula).

conducting single case research. In the present study the pre-surgical familiar opinion and patient self-assessment on the Bilingual Switching Questionnaire were compared against the normative data of 566 healthy bilinguals (see Rodriguez-Fornells et al., 2011).

3. Results

3.1. Electrical stimulation mapping (ESM)

For Patient 1 electrical stimulation during the object naming in Catalan (L1) induced alterations for points situated in the IFG (pars orbitalis and triangularis). While naming objects during the resection of the tumor at the level of the caudal MFG, Patient 1 involuntarily switched from Catalan (L1) to Spanish (L2) (see Fig. 2d). The same effect recurred in three consecutive trials and within the same structure.

Patient 2 was the first to benefit from the specific LS protocol designed for the present study. Importantly, the lesion localization and size in Patient 2 allowed the surgeons to extent the cerebral exposure to the temporal lobe and to further explore speech-related sites within this structure (notice, that in Patient1 the cerebral exposure involved mainly the frontal lobe which clearly restricted the area of stimulation). In this patient the areas stimulated, which provoked alterations during both L1 and L2 single language naming tasks, overlapped in the IFG (pars opercularis and triangularis) and in the supramarginal gyrus (SMG). For the single language naming in L1 (Spanish) the electrical stimulation also disturbed the correct naming when delivered to the superior and inferior parietal cortices. In addition, single language naming in L2 (Catalan) was altered while stimulating the points situated in the IFG (pars orbitalis) (see Fig. 3d). Surprisingly, the electrical stimulation of specific points situated in the IFG (pars triangularis), SMG and caudal MFG altered the performance only in the trials during which the patient was obliged to switch between L1 and L2 (LS naming task).The electrical stimulation applied to these areas did not alter the single language naming, but provoked an important delay for the production of the items in which the patient was forced to change between L1 and L2. The same effect recurred in at least two out of three consecutive trials of electrical stimulation delivered to the aforementioned cortical areas. It is worth mentioning that the area of caudal MFG, the stimulation of which disturbed LS abilities in Patient 2, is the same as the one associated to the spontaneous language switch in Patient 1 (see Figs. 2 and 3d). Interestingly, not only the LS related points but all the language sites in Patient 2 were redistributed from the affected temporal lobe to the frontal and parietal lobes. This effect may be explained by the substantial expansion of language sites described previously by Lucas et al. (2008) in a study of aphasic and normal speech patients, who underwent awake surgery for epilepsy. According to the results of the mentioned study, in cortical lesions located near eloquent speech areas, the functional organization of speech may redistribute in a similar manner, as the one observed in Patient 2. We observed no spatial relation between the shared L1 and L2 language production sites and the language switching sites in Patient 2.

Stimulation of the pre-central and post-central gyri was used to identify the sensory and motor cortex (see Figs. 2 and 3d).

3.2. Post-surgical neuropsychological assessment

The neuropsychological assessment performed after surgery revealed important difficulties in language production and in LS in Patient 1 (Tables 1b, 2 and 5). In the single language naming, Patient 1 was constantly producing involuntary switches. Besides, a large number of intrusions from the non-target language were observed during the LS naming task (Table 5). In the BSWQ (Rodriguez-Fornells et al., 2011), Patient 1 admitted being aware of his post-surgical difficulties (see the high scores obtained in the BSWQ LS factors, the pre-surgical familiar opinion and the mean scores of neurologically healthy individuals for comparison, Table 1 and Fig. 5).

Patient 2 presented moderate anomic aphasia after surgery (see Table 2), whereas his performance on the LS task was optimal (Table 5). In the single language naming task, Patient 2 used the target language in all cases except for two items and in the LS naming task the accurate language was used to name all of the objects. Interestingly, the surgical intervention for Patient 2 did not affect the areas mapped by ESM as associated to the LS processing. Importantly, no changes in daily LS patterns were observed in this patient (see Table 1).

3.3. Functional magnetic resonance (fMRI)

The L1 and L2 single language-naming versus rest contrast for Patient 2 revealed important bilateral clusters at the level of the superior, middle and inferior frontal gyri. Significant activations were found at the right putamen, right fusiform gyrus, right angular gyrus, anterior cingulate gyrus, SMA, left caudate and left postcentral gyrus (see Table 3 and Fig. 4a). In order to explore the LS-specific activation pattern, the contrast between active LS-naming blocks vs. L1&L2 single language-naming blocks was used. Results revealed activation in the precentral gyrus and IFG (bilaterally), in the left MFG and left parahippocampal gyrus, right cingulate gyrus and right superior frontal gyrus (see Table 4 and Fig. 4b). Importantly, the location of the tumoral resection in Patient 1 (which might have caused the LS problems observed after surgery) overlapped with one of the main activation clusters observed for LS in Patient 2 (left IFG/precentral gyrus, Fig. 4c). This observation, supported with the convergent ESM results (see Figs. 2 and 3d) and post-surgical LS task performance (see Table 5) highlights the role of IFG and caudal MFG in LS.

3.4. Anatomical images

The extent and localization of the patients' lesions (anaplasic astrocytoma for Patient 1 and glioblastoma for Patient 2) and their corresponding post-surgical cavities can be observed in Figs. 2a and 3a. The post-surgical anatomical images (3 months after surgery for Patient 1 and 1 month after for Patient 2) confirmed the absence of the vasogenic edema. In this way, it has been assured that the post-surgical language impairment is associated only to the damage of structures resected during the surgery.

4. Discussion

The main objective of the present study was to investigate, candidate LS-processing areas using ESM, and to distinguish them

Table 5
Post-surgical assessment of LS abilities.

Single language-naming task	*Patient 1*	*Patient 2*
Total of stimuli	96	
Total of missings (non-response error)/total of stimuli	25/96	12/96
Total correctly named/total of stimuli	56/96	84/96
Total involuntary language switches/total of stimuli	15/96	2/96
LS-naming task	*Patient* 1	*Patient* 2
Total of stimuli from the original task	80	
Total of stimuli (excluding non-response error-type missings from screening and from LS task)	48	67
Total correctly named/total of stimuli	34/48	67/67
Total errors in LS/total of stimuli	14/48	0/67

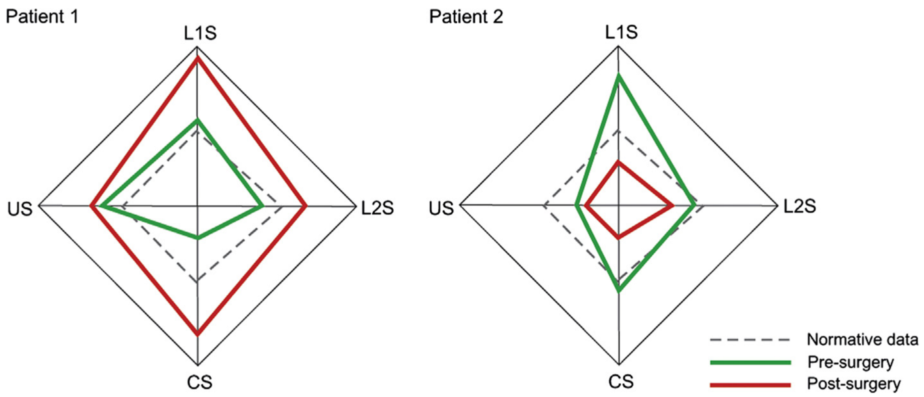

Fig. 5. Representation of the pre-surgical (green line) and post-surgical BSWQ scores (red line) for each patient separately and compared to the normative data (mean values in the $n=566$ sample of Spanish–Catalan bilinguals—gray dashed line). Larger values represent greater switching in the four factors that define the BSWQ. The values are comprised between 3 (center of rhombus) and 15 points (extreme corners). Post-surgically, a clear LS impairment can be observed in Patient 1. In contrast, Patient 2 reported after surgery overall satisfactory self-assessment of his LS skills. L1S=a tendency to switch to L1 (to Catalan for Patient 1 and to Spanish for Patient 2); L2S=a tendency to switch to L2 (to Spanish for Patient 1 and to Catalan for Patient 2); CS=contextual switching; US=unintended switching. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

from the structures associated with regular language production. In the first patient we used a single language naming task and observed that a tumoral resection at the level of the caudal MFG induced involuntary LS in three consecutive trials. Unfortunately, Patient 1 benefited only from the standard language mapping protocol, and thus, more sophisticated facets of bilingual language processing have not been explored. Nevertheless, the pathological switching that the patient presented after surgery confirmed that the MFG is an important region in the neural network subserving LS. These observations led us to later develop a multimodal ESM-fMRI imaging protocol in order to systematically explore LS intraoperatively. Therefore, to the standard single language naming task we added a new cued LS task, in which we aimed to provoke controlled LS episodes and to observe whether electrical stimulation is able to influence the performance of the task. The new LS protocol combined multimodal information of the same LS-task obtained through ESM, fMRI and neuropsychological assessment. Self-assessment of daily conversational language switching patterns was also carried out using a specific self-report measure (BSWQ). Crucially, ESM in the second patient (the first to benefit from the full LS protocol) confirmed that stimulation of specific points of the caudal MFG, the IFG (pars triangularis) and the SMG impaired LS without disrupting language production. Importantly, electrical stimulation of the left caudal MFG disturbed LS processing in both patients (see Figs. 2 and 3d). Moreover, the post-surgical neuropsychological assessment revealed correct use of both languages and adequate language switching in Patient 2. Taking into account that all the language production and LS-related sites were located outside the boundaries of the tumor and were preserved during the surgery, these results further confirmed the role of the aforementioned areas in the LS mechanism. The ESM outcome of Patient also converged with the results from fMRI, revealing activation in the left IFG and MFG (see Fig. 4b). Interestingly, the IFG and its adjacent structures revealing a significant activation during the LS task for Patient 2 were localized exactly within the area resected in Patient 1 (see Fig. 4c). This coincidence between brain regions in both patients highlights the importance of carefully evaluating the implication of these regions during surgery in bilingual populations. Notice that patient 1 was evaluated post-surgically using the fMRI language tasks, but the amount of intrusions from the non-target language evidenced in the neuropsychological testing prevented us to analyze this information. This result points to a possible limitation of using the fMRI LS-task post-surgically in other bilingual patients undergoing similar resections. We believe that the complementary imaging and LS-oriented exploration presented here may improve the language mapping strategies used with bilingual populations.

Several authors support the idea that LS is strongly related to the constant inhibition of the non-target language and therefore should be related to the executive control network and most probably subserved by prefrontal structures (Abutalebi & Green, 2007; Adrover-Roig et al., 2011; Guo et al., 2011;Hernandez et al., 2000; Rodríguez-Fornells et al., 2006, Hervais-Adelman et al., 2011). In convergence with this idea, our results also clearly show the important role of these structures mediating cognitive control during language switching, and more in particular in suppressing and inhibiting the production of the nontarget language word. However, an intriguing result from the present study is that the stimulation of the same region in the caudal part of the MFG produced different effects in both patients. While Patient 1 presented involuntary switching during ESM along the posterior middle frontal gyrus, Patient 2 experienced suppression and delayed switching during ESM along the same region. We believe that these different patterns might reflect the dynamics and interaction of the cognitive control and language processing architecture during language production. For example, the present results could be easily integrated considering a dual cognitive control architecture, in which a top-down regulatory system (e.g., the supervisory attentional system) indirectly biases the amount of activation or inhibition of the target (language in use) and non-target language schemas and a low-level system that selects automatically the most activated language schema (selection of routine actions) (e.g., Norman and Shallice, 1986; Shallice, 2004; Cooper & Shallice, 2006; see also its implementation to bilingualism in Green, 1986, 1998). It is important to bear in mind that substantial evidence exists on the partial activation of non-target language lexical candidates during language production, with the corresponding increase in the demands of cognitive control and monitoring in bilinguals. The top-down system might be in charge of regulating the amount of activation of a particular language schema (and suppression–inhibition of the non-target ones) and therefore, might be responsible for deciding which language should be activated in a particular context (task-set reconfiguration process). A failure of this top-down modulation might explain at the same time the appearance of unintended language switches as well as the lack of capacity of the system to properly regulate the activation and suppression of the target and non-target language schemes.

For example, in Patient 1, the language context during surgery evaluation was exclusively monolingual and we observed an involuntary language switch after stimulation of the MFG. Considering that this region in the prefrontal cortex has been associated to response selection, switching between tasks, maintenance of a stable representation of the current task, prevention of interference and the inhibition of irrelevant items held in working memory (Baddeley, Emslie, Kolodny, & Duncan, 1998; Cohen, Botvinick, & Carter, 2000; Curtis & D'Esposito, 2003; D'Esposito et al., 1995; Dreher, Koechlin, Ali, & Grafman, 2002; Frith, 2000; Miller & Cohen, 2001; Rogers et al., 1998), we believe that the electrical stimulation of this region disrupted the suppression on the non-target language in this patient, eliciting involuntary language switches. Thus stimulation on this region created a situation in which the language production system lacked a top-down regulatory mechanism, and therefore the most activated language candidate in the target or non-target language was simply chosen through bottom-up schema selection mechanisms (e.g., contention scheduling mechanism, Norman & Shallice, 1986; Cooper & Shallice, 2006). An alternative explanation could be that the stimulation of this region changed the imbalance of activation-inhibition of the language schemas, disrupting the inhibition on the non-target language and increasing the amount of suppression in the native language (Catalan). This latter explanation might be interpreted as triggering a task-set reconfiguration process in the MFG needed for LS. The first explanation is more plausible considering that the patient after surgery presented pervasive language switching problems, and therefore, suggesting that the removal of this region disrupted the top-down regulatory mechanism in charge of controlling the imbalance of activation/inhibition of language schemas.

Instead, Patient 2 experienced suppression or delayed language switching during ESM in the same region. It is important to bear in mind that the conditions of the intraoperative evaluation in this patient were very different, as we were implementing the language switching protocol and the patient was switching between both languages constantly. This setting is similar to the one presented in a recent fMRI study from Guo et al. (2011) in which these authors compared blocked naming conditions (where the participant used only one language) to language switching conditions in which participants switched between language schemas constantly. Interestingly, these authors showed that during constant language switching an increase of activation was observed in the ACC (SMA), most probably due to the increased demands in cognitive control. In contrast, larger activation was observed in the lateral prefrontal cortex in the blocked condition, most probably reflecting an increase of long-lasting global inhibition in the non-target language. The suppression and delayed language switching in our patient could be explained considering that the stimulation on the MFG produced a disruption of the task-set reconfiguration process, which requires first, releasing inhibition of the nonactivate language schema and second, suppressing (inhibiting) the activation of the language currently in use. Indeed, a very important process in task-switching is the suppression or inhibition of the task-set that has been previously active and therefore overcoming the "task-inertia" of the previous schema (Allport, Styles, & Hsieh, 1994). In this case, and considering the increase in cognitive control demands in the LS protocol presented to the second patient, we believe that the effect of stimulation on the MFG blocked the capacity of the patient to use this top-down regulatory mechanism in a proper and rapid way, disrupting or slowing down most probably the release of inhibition of the activated language. This interpretation is in line with a recent study on the effects of prefrontal lesions on task-switching (Shallice, Stuss, Picton, Alexander, & Gillingham, 2008; see also Rogers et al., 1998). Patients with lesions in the superior medial prefrontal cortex showed a significant delay in their switching ability (switch cost). This finding was interpreted considering the role of this region in regulating top-down activation of task-relevant cortical processes needed in a particular context and in agreement with studies showing activation in these regions in task-switching paradigms (Brass & von Cramon, 2002; Dove, Pollmann, Schubert, Wiggins, & Von Cramon, 2000). Thus the stimulation of the MFG in a constant language switching setting created inertia in the system to use the pre-activated scheme and therefore disrupting fast LS. In sum, the differences observed in both patients after MFG stimulation might be due to the different activation-suppression imbalance of the target and non-target language schemes in both protocols, a monolingual context in the first patient and a fast language switching context in the second patient.

Regarding the fMRI, our results agree with those from Quaresima, Ferrari, van der Sluijs, Menssen, and Colier (2002) and Hernandez et al. (2000); all of which revealed LS-related activations in the IFG. Hernandez also found a significant activation in the DLPFC and postulated that the representation of two languages in bilinguals may not be mediated by the neural systems typically associated to language. The IFG involvement in LS was also shown in studies using positron emission tomography imaging (PET) and ESM. Price, Green, and Studnitz (1999) performed a PET study which was one of the first to reveal the LS-related activation of the left IFG and bilateral SMA (see the results of ESM for Patient 2, Fig. 3d).It has also been shown that the ESM stimulation can induce an involuntary language switch while applied to the left IFG (Kho et al., 2007), to the posterior part of the temporal sulcus, the SLF (Moritz-Gasser & Duffau, 2009) and the DLPFC (Lubrano et al., 2012). Similarly, our ESM results show the importance of the IFG (in Patient 2) and the MFG regions (for both patients) in the neural network subserving LS. To our knowledge, the MFG involvement in LS processing has been also reported in a couple of previous fMRI studies. Wang, Xue, Chen, Xue, and Dong (2007) showed MFG activation during an English-Chinese LS task and Rodriguez-Fornells et al. (2005) found that the activation of the left MFG was crucial to control language interference. Additionally, in various neuroimaging studies it has been suggested that the dorsolateral and inferior frontal lobes participate in the network involved in inhibitory control (see Aron, Robbins, & Poldrack, 2004; Buchsbaum, Greer, Chang, & Berman, 2005; Chikazoe, 2010 for a review).

To conclude, the present case-study reports new intraoperative data from two bilingual patients who performed specific LS-oriented tasks during ESM, fMRI and neuropsychological assessment. The results highlight the crucial role of the middle and inferior frontal cortices in LS processing. Although case-studies limit the strength of possible conclusions, the precision of the ESM and the convergence of findings from different methods give further weight to the outcome of the present study.

Finally, Patients 1 and 2 varied between each other in terms of age, lesion type, the extent of cortical exposure and a protocol realized during their follow-up, all of which may be considered as the limitations of this study. However, it is important to mention that both were bilinguals undergoing an intervention using ESM and presented alterations of cognitive control over the use of both of their daily-life languages. Future studies should take into account the anatomical and functional connectivity of the LS-related network and the possibility of language reorganization due to cerebral plasticity in slow-growing lesions (Desmurget, Bonnetblanc, & Duffau, 2007). Furthermore, the possible occurrence of substantial expansion of language sites (Lucas et al., 2008), shall also be considered.

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