INVOLVEMENT OF THE MIDDLE FRONTAL GYRUS IN LANGUAGE SWITCHING AS REVEALED BY ELECTRICAL STIMULATION MAPPING AND FUNCTIONAL MAGNETIC RESONANCE IMAGING IN BILINGUAL BRAIN TUMOR PATIENTS

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LS- Language switching

ESM- electrical stimulation mapping

IFG – inferior frontal gyrus

MFG- middle frontal gyrus

SFG- superior frontal gyrus

Abstract

Neural basis of language switching and the cognitive models of bilingualism remain controversial. We explored the functional neuroanatomy of language switching implementing a new multimodal protocol assessing neuropsychological, functional magnetic resonance and intraoperative electrical stimulation mapping results.

A prospective series of nine Spanish-Catalan bilingual candidates for awake brain surgery underwent a specific language switching paradigm implemented both before and after surgery, throughout the electrical stimulation procedure and during functional magnetic resonance both pre- and postoperatively. All patients were harboring left-hemispheric intrinsic brain lesions and were presenting functional language-related activations within the affected hemisphere.

Language functional maps were reconstructed on the basis of the intraoperative electrical stimulation results and compared to the functional magnetic resonance findings. Single language-naming sites (Spanish and Catalan), as well as language switching naming sites were detected by electrical stimulation mapping in eight patients (in one patient only Spanish related sites were detected). Single naming points outnumbered the switching points and did not overlap with each other. Within the frontal lobe, the single language naming sites were found significantly more frequently within the inferior frontal gyrus as compared to the middle frontal gyrus (X^2 (1) = 20.3, $p < .001$). Contrarily, switching naming sites were distributed across the middle frontal gyrus significantly more often than within the inferior frontal gyrus (X^2 (1) = 4.1, $p = .043$). Notably, there was not always an overlap between functional magnetic resonance and electrical stimulation mapping findings. After surgery, patients did not report involuntary language switching and their neuropsychological scores did not differ significantly from the pre-surgical examinations. Our results suggest a functional division of the frontal cortex between naming and language switching functions, supporting that non-language specific cognitive control prefrontal regions (middle frontal gyrus) are essential to maintain an effective communication together with the classical language-related sites (inferior frontal gyrus).

1. Introduction

It is an intriguing topic how bilinguals are able to switch, seemingly effortlessly, between the languages they speak (Rodriguez-Fornells *et al*., 2002; Crinion *et al*., 2006). Language switching (LS) allows effective communication in bilingual communities by enabling individuals to appropriately select the target language as a function of external cues such as linguistic knowledge of their interlocutor, face-related cues or contextual effects (Gollan and Ferreira, 2009; Rodriguez-Fornells *et al.,* 2011; Soveri *et al.,* 2011; Bialystok *et al.,* 2012). When bilingual language control is impaired, LS can be considered pathological (Fabbro *et al.,* 2000). Pathological switching is defined as the phenomena of passing from one utterance/sentence to another without appropriately adapting the language in use to the given situation (Fabbro *et al.,* 2000). As every cognitive function, LS may be impaired if the intrinsic brain organization is impacted by a brain lesion (i.e. brain tumor).

Intraoperative electrical stimulation mapping (ESM) has been the gold standard technique for identifying essential sensory and motor cortex as well as cortical language areas in patients undergoing tumor resection (Penfield and Roberts, 1959; Ojemann, 1983; Duffau, 2008). Although single-language naming tasks are the most extended tool to map language function during awake brain surgery (Corina *et al.,* 2010; Lubrano *et al*., 2012; Havas *et al.,* 2015), there is an increasing need to adapt intraoperative neuropsychological tasks to map specific brain functions such as LS in order to preserve an optimal quality of life according to the patient's specific life characteristics (Fernandez-Coello *et al.,* 2013). However, the literature concerning the intraoperative monitoring of LS in multilingual brain tumor patients is rather scarce.

Even if the intraoperative evidences on LS are yet to be explored, evidence from other studies using functional magnetic resonance imaging (fMRI) (Hernandez *et al.,* 2000; 2001; 2009; Rodriguez-Fornells *et al.,* 2002; Chee *et al.,* 2003; Abutalebi *et al.,* 2008), electroencephalography (EEG) (Moreno *et al.,* 2002; Proverbio *et al.,* 2004; Khateb *et al.,* 2007; Kuipers and Thierry, 2010) and transcranial magnetic stimulation (TMS) (Holtzheimer *et al.,* 2005; Nardone *et al.,* 2011) support the idea that LS, similarly as task switching, is sustained (at least partially) by a more general executive control system (Fabbro, 2001; Hernandez *et al.,* 2001; Hervais-Adelman *et al.,* 2011; Rodríguez-Fornells *et al.,* 2006; Guo *et al.,* 2011). However, there is still no agreement concerning the brain regions selectively recruited during LS. On the one hand, Fabbro (2001) stated that voluntary language switching is based on a more general control mechanism independently of language processing suggesting that pathological LS results from pragmatic disorders of communication (not benefiting from contextual/social cues that support effective communication). Following this perspective, LS would be sustained by non-domain specific cognitive control systems. In contrast, other studies directly comparing task switching to LS suggest some differences in control mechanisms across linguistic and non-linguistic domains (Crinion *et al.,* 2006; Prior and Gollan, 2011; Weissberger *et al.,* 2012; Calabria *et al.,* 2016), proposing the implication of language domain specific areas in LS compared to cognitive switching occurring when speaking only one language.

Despite the abundance of literature showing distinct interpretations, more recent studies argue in favor of the coexistence of both mechanisms. Recently, Abutalebi and Green (2008) suggested a neurocognitive model specifying the neural networks involved in LS proposing the existence of a left cortico-subcortical network. The authors report the activation of the dorsolateral prefrontal cortex -DLPFC- (related to executive functions), anterior cingulate cortex -ACC- (related to the error detection and attention), inferior parietal lobule (related to maintenance of representations and working memory), and basal ganglia -caudate nucleus- (interpreted as language planning and lexical selection), regions subserving cognitive control and language production. Similarly, (Khateb *et al.,* 2007) proposed that language selection in bilinguals was possible by means of a left cortico-cortical fronto-parietal circuit involving precentral frontal gyrus, anterior supramarginal gyrus (SMG), and angular gyrus, brain areas involved in both general cognitive processes and in language processing. Following these integrative explanations, Duffau (2008) and Moritz-Gasser and Duffau (2009), and based on their intraoperative electrical stimulation mapping (ESM) studies on patients undergoing awake brain surgery for tumor resection, proposed a new model based on an hodological perspective. From their standpoint, distributed cortico-cortical and cortico-subcortical parallel networks could sustain LS. Specifically, they highlight the existence of extensive language sub-networks involving the supplementary motor area -SMA-/ACC, left prefrontal cortex, basal ganglia and caudate nucleus as their nodes and the superior longitudinal fasciculus -SLF-, a white matter pathway connecting posterior temporal areas with Broca’s area, enabling the connection between these epicenters (Moritz-Gasser and Duffau., 2009). In another ESM study from the same group (Kho *et al.,* 2007), involuntary language switching was elicited following electrocortical stimulation of the left inferior frontal gyrus (pars opercularis). Similar results were reported in a case of a 31-year-old multilingual, eliciting involuntary language switching while stimulating the left dorsolateral prefrontal cortex –DLPFC-, providing further evidence of the role of this brain region in LS (Lubrano *et al.,* 2012). More recently, we reported a multimodal functional fMRI and ESM case study indicating the crucial involvement of the middle and inferior frontal regions in LS and the usefulness of performing ESM to prevent the possible post-surgical appearance of pathological language switching (Sierpowska *et al.,* 2013). In this previous study, we presented two bilingual patients undergoing awake brain surgery using ESM. In the first patient, who could only benefit from single-language naming intraoperatively, resection at the level of the left lateral MFG elicited involuntary Catalan (first language - L1) to Spanish (second language - L2) switching. This critical LS-related area had to be removed given the grade and localization of the tumor, resulting in post-surgical pathological switching. This undesired consequence of the removal suggested the involvement of the MFG on LS processing. The second patient of the study, whose critical LS-related areas could be mapped and preserved during the surgery, showed an altered performance on the LS-naming task when the stimulation was applied to the left caudal MFG, again confirming the role of this structure in the LS. We interpreted these findings considering the proposed role of the MFG in mediating cognitive control in bilingual speakers through the interplay between a top-down selection-suppression mechanism and a local inhibitory mechanism in charge of changing the degree of selection-suppression between different lexicons (Rodríguez-Fornells *et al.,* 2006). In addition to the left MFG, the anterior and mesial prefrontal cortex together with the supplementary motor area (SMA) and the anterior cingulate cortex (ACC) could be involved in inhibition mechanisms and interference control of the non-target language, respectively, in this way supporting the involvement of the executive control network in language switching mechanisms (Hervais-Adelman et al., 2011). It is important to notice that the MFG is richly interconnected with other cortical and subcortical structures by the means of both short and large white matter pathways. U-shaped fibers running superficially to the left frontal aslant tract (FAT) connect the MFG to the IFG and superior frontal gyrus (SFG). Portions of MFG also connect to caudate nucleus and putamen through a system of radial projection fibers

(Catani et al., 2012). Furthermore, these connections are intermingled with long associative bundles such as the arcuate fasciculus (AF) running towards the parietal and temporal areas (Catani, Jones & ffytche, 2005). The precentral gyrus is also connected to the ventral part of the MFG by the inferior chain of the frontal longitudinal system, whereas the superior chain of the same system connects the precentral gyrus to the dorsal part of the MFG (Catani et al., 2012). Finally, the deeper layer of the inferior fronto-occipital fasciculus (IFOF) connects the middle part of MFG with the occipital lobe (De Benedictis et al., 2012).

In order to explore the brain areas related to LS and place our results in the frame of reference of the executive control network, we implemented a LS-ESM paradigm assessment in a series of 9 Spanish-Catalan bilingual patients undergoing awake brain tumor surgery that allowed a systematic evaluation of externally triggered LS synchronously with ESM. Based on previous proposals, (Kho *et al.,* 2007; Lubrano *et al.,* 2012; Sierpowska *et al.,* 2013) we expected to (i) find new evidences supporting the role of the MFG and IFG in LS when applying electrical stimulation to these cortical regions during the ESM procedure (LS -naming task) and (ii) report significant activation clusters (fMRI) on brain regions related to the ECN when performing the LS-naming task inside the scanner, as previously reported (Hernandez *et al.,* 2000; 2009; Chee *et al.,* 2003; Rodriguez-Fornells *et al.,* 2005; Crinion *et al.,* 2006; Abutalebi and Green, 2008). Moreover, we aimed to compare the patterns of activation resulting from the fMRI analysis, especially the contrasts related to the LS, to the intraoperative functional map obtained from the ESM procedure performed during awake surgery. It is important to notice that we were not able to investigate the possible role the medial and basal ganglia structure or the white-matter tracks underlying MFG and IFG by the means of ESM. Further studies using subcortical ESM in white-matter might be important in order to understand their possible involvement in the LS. Finally, we conducted a comparative analysis of the cognitive performance before and after surgery, specifically on the domains of LS and response inhibition.

2. Methods

2.1. Case reports

A prospective series of 9 patients undergoing LS multimodal protocol during awake brain surgery is reported. Clinical and lesion characteristics for all patients are presented in table 1 and figure 1. Seven out of nine patients are early bilinguals (i.e. both languages acquired before the age of 7), except for patients 8 and 9 who are late bilinguals. Patients' language lateralization was determined on the basis of the preoperative fMRI study using standardized language-related tasks (naming and verb generation). Two senior neuroradiologists (SC and/or AC) assessed the results of these standard tasks and emitted clinical reports, on which we based our inclusion. In the case of the early bilinguals (patients 1 to 7), a bilateral language lateralization was observed in 4 cases (patients 1, 5, 6 and 7), in line with recent results showing that early proficient bilinguals with brain tumors have a weaker left hemisphere laterality than monolinguals (Połczyńska *et al.,* 2017). Nevertheless, for patients 2, 3 and 4 (early bilinguals) and patients 8 and 9 (late bilinguals) a left lateralized language pattern was observed.

Table 1: Patients' and lesion characteristics.

Patient's characteristics						*Lesion details*		
Case	*Gender*	*Age*	*Years of Edu.*	*L1*	*Localization*	*Type*	*Grade*	*Surgical approach*
1	M	38	18	SPA	Left F-T-Insular	Oligodendroglioma	II	Left F-T
2	F	38	12	CAT	Left F	Anaplastic astrocytoma	III	Left F-T
3	M	35	10	CAT	Left F	Oligodendroglioma	II	Left F-T-P
4	F	30	12	SPA	Left F	Arteriovenus malformation	-	Left F-T
5	M	54	10	CAT	Left F	Anaplastic oligoastrocytoma	III	Left F
6	F	44	14	SPA	Left F	Cavernous angioma	-	Left F
7	F	35	10	SPA	Left F	Diffuse astrocytoma	II	Left F-T
8	M	33	16	CAT	Left F	Anaplastic oligodendroglioma	III	Left F
9	M	36	18	SPA	Left T	Glioblastoma	IV	Left F-T-P

SPA, Spanish; CAT, Catalan; F, frontal; T, temporal; P, parietal

The neuropsychological assessment of language function carried out before surgery revealed satisfactory output for experimental object naming in all patients and thus allowed them to be included in the ESM (criterion set at 65% object naming accuracy in L1, see Supplementary material Table A). Importantly, none of the patients manifested episodes of unintended LS during the pre-surgical neuropsychological assessment. All patients signed an informed consent for participation in this study and the protocol was approved by the Ethical Committee of the Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona (Spain).

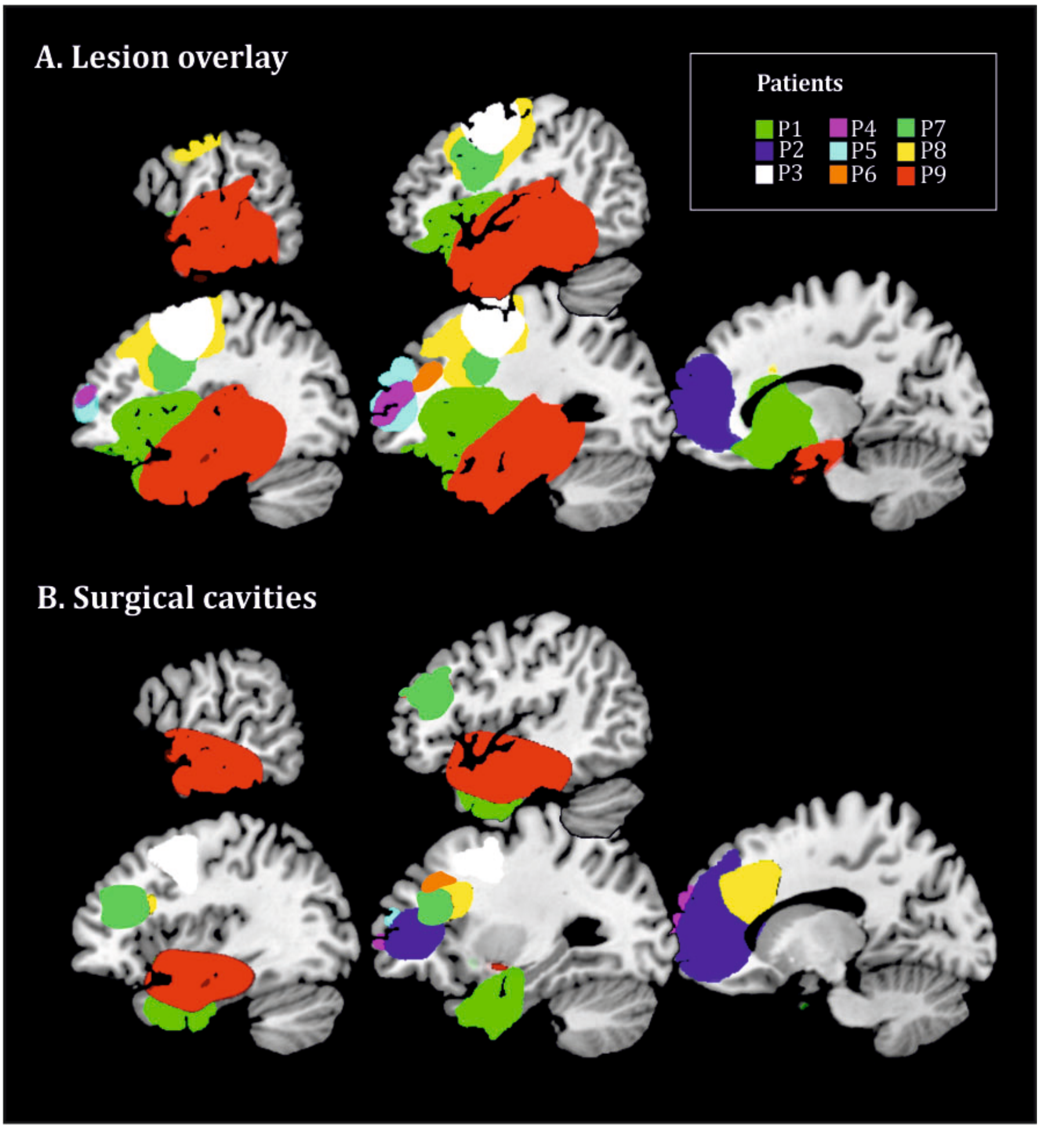

Figure 1: Patients' lesions distribution (A) and surgical cavities (B) normalized to MNI (images displayed in neurological convention). Please notice that after surgery, the neurophysiological mechanisms taking place during the recovery (e.g. disappearance of edema and mass effect, see Abd-El-Barr, Saleh, Huang, & Golby, 2013) significantly reduced the extension of lesioned area.

2.2. Neuropsychological assessment

Both before and after surgery, patients underwent a standardized neuropsychological examination in the Neuropsychology Unit of the Hospital Universitari de Bellvitge (see

Table 2). The protocol was specifically designed to assess handedness (Edinburg Handedness Inventory; Oldfield, 1971), object naming (Boston Naming Test included in the Boston Diagnostic Aphasia Examination (BDAE; Goodglass and Kaplan, 1983), comprehension (Token Test, De Renzi and Faglioni, 1978), non-words repetition included in the Test de Barcelona (Peña-Casanova, 2005), response inhibition (Stroop test (Stroop, 1935), semantic and phonological verbal fluency tests (Goodglass & Kaplan, 1972), and attention and working memory (Digit Span forward and inversed (Wechsler, 1997).

All the tasks were carried out in patients' L1, except for the object naming task and Stroop task which were performed in both L1 and L2. The Hayling test was performed in Spanish only, due to the lack of its Catalan version. Regarding language proficiency, both objective and self-reported measures were collected (see Supplementary material, Table A for individual patients' results). As objective measures, an object naming task was used to assess patient's proficiency in both Spanish and Catalan. The test consisted of naming a series of 60 black-and-white images of everyday objects. Additionally, a bilingual questionnaire of language self-assessment proficiency was administered (as in Rodriguez-Fornells et al., 2005; 2012; see description in the following section *2.2.1*). Finally, in addition to the standard neuropsychological examination, specific measures on language switching were documented (see section *2.3.*).

2.2.1. Bilingual Switching Questionnaire (BSWQ)

Language switching patterns in patients' daily life were explored using the *Bilingual Switching Questionnaire (BSWQ)* (Rodriguez-Fornells *et al.,* 2011) both before and after surgery. The BSWQ is a self-assessed questionnaire that evaluates the tendency of bilinguals to switch between languages during daily life conversation. Four constructs were defined: (i) L1 switching tendencies (the tendency to switch to L1); (ii) L2 switching tendencies (L2-switch); (iii) contextual switch, which indexes the frequency of switches usually triggered by a situation, topic, or environment; and (iv) unintended switch, which measures the lack of intention and awareness of the language switches (see Supplementary material Table B). As a part of BSWQ, a self-assessed questionnaire evaluating patients' language history and proficiency on Spanish and Catalan was administered before surgery (see Supplementary material Table A). In order to have a rating on patients' language proficiency, a series of questions were answered addressing both L1 and L2 separately for comprehension, reading, speaking and writing skills (likert scores ranging from 1 - poorly to 4 - perfectly).

2.3. Language switching task

In order to induce LS experimentally, the same specific LS protocol was implemented both before and after surgery, throughout ESM procedure and during fMRI both pre- and postoperatively (see Fig. 2 for the task design). The fMRI task was based on the same set of items that the pre-, intra- and post-surgical assessment task and the same for the pre- and post-surgical scanning sessions. The time lapse between pre-operative and intra-operative assessments depended on lesion grade (approximately one month for tumoral lesions and approximately 6 months for vascular lesions). The LS task included two conditions: a single-language naming condition and a LS-naming condition. During the first condition (single-language naming), patients had to name black-and-white images for both their L1 and L2 separately. A set of 46 images were selected from the Snodgrass and Vanderwart (1980) database. With the purpose of avoiding the bias of between-language similarity, the words included were non-cognate (the phonological forms of words are dissimilar between two languages, e.g. *manzana* [Spanish] and *poma* [Catalan] meaning *apple*).

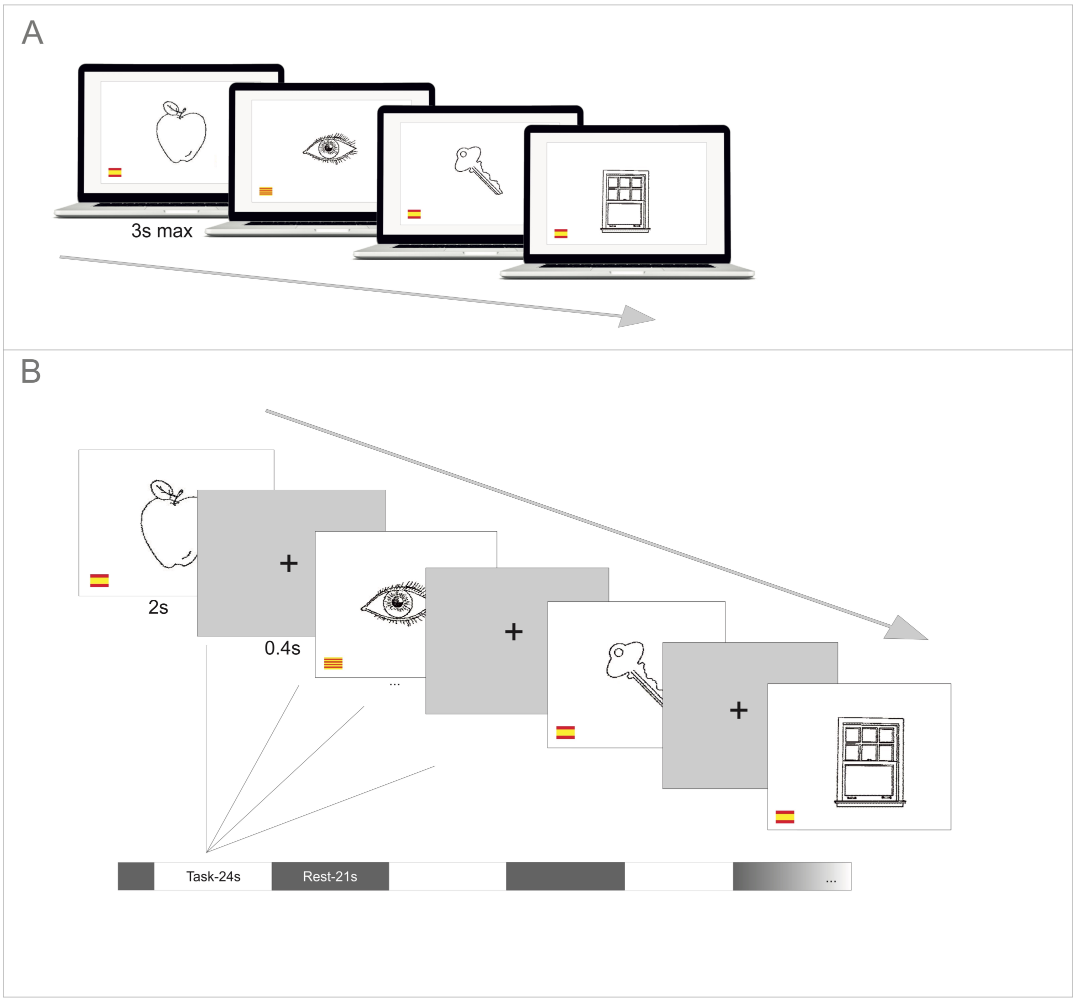

Figure 2: Intraoperative setting of the language switching task (A) and fMRI design for the language switching paradigm (B). Both task were constructed based on the same set of items and their implementation was adapted to the situation (A-consultation room and intraoperative setting, B- fMRI scanner).

After a screening phase, each patient underwent the LS-naming condition, which consisted in switching from Spanish to Catalan and vice versa. Here, the switch was cued by a small flag at the lower left corner of the screen indicating the target language (Fig. 2A), randomly assigned to the images. The randomization was computed using a homemade MATLAB script and the number of images in the LS naming condition depended on the number of images named correctly in the single naming condition. The minimum of 20 images named correctly in both languages (Catalan & Spanish) was set as a requirement for task construction. The maximum number of items for task construction was set at 36. The number of switches was applied in a proportion of number of items correctly named in both languages (starting in 5 for 20 items and ending at 11 for 36 items). The order of appearance of cues (Spanish or Catalan flag) was randomized with the minimum of 2 and maximum of 4 consecutive images from the same language. Before and after surgery, two blocks of the task were carried out for training and follow-up (respectively). For the intraoperative procedure, 4 blocks were computed based on the preoperative performance on naming task. During the surgery, the LS naming task was performed in loop until the electrical stimulation mapping was concluded covering the whole area of cranial exposure. Importantly, both single naming and LS naming task were set according to the patients' preoperative maximal score in single naming task.

In the consulting room, the task was displayed on a computer screen placed in front of the patient, whereas in the operating room setting, the computer was placed at the eye level of the patient ensuring a clear view of the stimuli. The presentation of each image had a duration of 3 s maximally. The onset of each trial was controlled by the experimenter and synchronized with the electrical stimulation. The correction norms were as follows: if the name of the image was correctly produced immediately after its appearance, the response was classified as "correct response"; if the response was correct but delayed as "delay"; if the response was not produced as "non-response error" and finally, if the item was named in a language opposite to the cue, as "switching error".

2.4. Electrical stimulation mapping (ESM)

Intraoperative electrical stimulation mapping (ESM) is the gold standard technique for identifying essential sensory and motor cortex as well as cortical language areas in patients undergoing tumor resection (Ojemann, 1983; Penfield and Roberts, 1959; Sierpowska *et al.,* 2017). ESM induces a focal and transitory virtual lesion onto discrete regions around the tumor (in our study, at the cortical level) inhibiting a neural subcircuit for a few seconds in order to obtain an individual functional mapping of the brain to test if a structure involved by a lesion is functionally relevant (Duffau, 2015).

In this study, ESM was performed according to the methodology described previously by Ojemann *et al.* (2008) during asleep-awake-asleep surgery and exactly the same as in the previous works of our team (Sierpowska *et al.,* 2013, Havas *et al.,* 2015, Fernandez-Coello *et al.,* 2016).

2.5. fMRI data acquisition

Participants were scanned in a 1.5 T MRI Philips Intera system at the Hospital Universitari de Bellvitge of Barcelona. Functional images were acquired in the axial plane using a single-shot T2-weighted gradient-echo EPI sequence with a 3000 ms repetition time (TR), 50 ms echo time (TE) and 90º flip angle (FA). Each volume consisted of 3.5 mm thick slices with no inter-slice gap; voxel size = 3.59 x 3.59 x 3.5 mm^3; FOV = 230 mm; size of acquisition matrix 64 x 64. In addition to the functional images, a high-resolution T1-weighted image (slice thickness = 1.1mm; number of slices = 150; TR = 25 ms; TE = 4.6 ms; flip angle = 30º; matrix = 320 x 320; FOV = 240 mm; voxel size = 0.75 x 0.75 x 1.1 mm^3) was also acquired for each patient.

2.6. Data analysis

2.6.1. Pre and post-surgical neuropsychological assessment

Patients underwent neuropsychological assessment at the neurological ward of the Hospital Universitari of Bellvitge before surgery (usually between 1 week and 1 month pre-op) and 4 to 6 months after intervention. The tests from a standard neuropsychological assessment carried out with the patients were further compared with the normative data, taking into account the sociodemographic characteristics of the Spanish population (Table 2). In addition, paired t-tests were used to test for the differences between preoperative and postoperative scores on the neuropsychological protocol, the language proficiency in naming task (differences between L1 and L2) and the BSWQ.

The experimental LS task was screened for the intraoperative procedures and all the tasks carried out in the operating room were set at each patient's 100% level of accuracy.

2.6.2. Electrical stimulation mapping (ESM)

In this study the anatomo-functional organization for language naming and switching were both defined on the basis of the distribution of functionally relevant sites. These discrete cortical regions (of approximately 5 mm of diameter, Thiebaut de Schotten et al., 2005) are specific points in which the electrical stimulation is expected to interfere with the function tested behaviorally. The locations of the naming and LS sites were detected during the ESM procedure were reconstructed using the intraoperative photographs of the exposed brain cortex. To enable and facilitate the localization of the eloquent points in two dimensions, these spots were transferred to an arbitrary grid (developed by Havas et al., 2015). Within this grid, we differentiated two regions of interest: inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) (see Fig. 3A, yellow sites for IFG and gray sites for MFG). The functional sites for both: single language naming and LS were then transferred for each patient individually and treated as a binary variable: (1) - site subjacent to language for this particular patient versus (0) - site on which the electrical stimulation did not disturb patient's performance. Once all the 9 templates of patients were filled, the data was transposed to a common template depicting the proportion of all the patients in whom the electrical stimulation evoked a desirable response versus no effect (Fig. 3B and 3C).

In order to observe whether the difference between sensitivity for stimulation at the level of IFG and MFG is statistically significant, Chi-Square test was implemented for the comparison between: (1) frequencies of: single language naming errors in the IFG and MFG (L1+L2) and (2) LS errors in the IFG and MFG (Table 4).

Table 2: Neuropsychological assessment results.

Case	Attention and Working memory				Response inhibition				Verbal fluency				Comprehension		Repetition		Naming	
	Digit span (Forwards)		**Digit span (Backwards)**		**Stroop**				**Semantic fluency**		**Phonetic fluency**		**Token test/36**		**Non-word repetition/8**		**Boston Naming test/60**	
	PRE	POST	PRE	POST	Raw score/30		RT (ms)		PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
					PRE	POST	PRE	POST										
1	5 (7)	7 (12)	5 (10)	5 (10)	-	-	-	-	11 (2)	16 (5)	7 (2)	16 (10)	36 (17)	35 (17)	8	8	46 (5)	46 (5)
2	6 (10)	7 (13)	4 (8)	5 (11)	-	-	-	-	17 (6)	18 (7)	17 (10)	9 (5)	33 (4)	35 (9)	8	7	57 (14)	52 (9)
3	6 (10)	6 (10)	5 (11)	3 (7)	30	30	839	852	13 (3)	13 (3)	6 (2)	6 (2)	35 (9)	33.5 (5)	8	8	54 (9)	57 (14)
4	6 (10)	7 (13)	4 (8)	5 (11)	16	29	713	621	23 (10)	28 (12)	13 (8)	16 (16)	36 (16)	36 (18)	8	8	56 (12)	57 (14)
5	5 (9)	6 (11)	4 (10)	3 (9)	26	28	592	595	9 (2)	9 (2)	13 (9)	17 (10)	28.5 (5)	30.5 (5)	8	7	50 (10)	49 (10)
6	5 (8)	6 (10)	3 (7)	3 (7)	30	29	690	635	18 (7)	19 (7)	8 (4)	11 (6)	34 (7)	35 (9)	8	8	42 (4)	50 (8)
7	6 (10)	5 (8)	4 (8)	3 (7)	26	30	774	684	28 (8)	24 (10)	13 (8)	14 (9)	35 (10)	34 (7)	8	8	56 (12)	53 (10)
8	7 (13)	-	6 (13)	-	28	-	1199	-	34 (16)	15 (5)	26 (15)	17 (10)	36 (17)	-	8	-	53 (15)	-
9	4 (4)	6 (10)	4 (8)	3 (7)	-	-	-	-	16 (5)	19 (7)	10 (5)	13 (8)	32 (2)	34.5 (8)	8	8	51 (9)	34 (2)
Mean (SD)	5.56 (.88)	6.25 (.17)	4.33 (.87)	3.75 (1.03)	26 (5.21)	29.20 (.84)	801.17 (211.81)	677.40 (102.83)	18.33 (7.71)	16.33 (5.70)	12.67 (6.16)	12.67 (4.09)	34.62 (1.50)	34.91 (.66)	8.00 (.00)	7.75 (.46)	51.67 (5.02)	49.75 (7.40)
***T* score**	-2.497		1.000		-1.439		1.977		.703		.000		-.954		1.528		.678	
Asymp. Sig.	.041		.351		.224		.119		.502		1.000		.384		.170		.520	

Pre and postoperative results on neuropsychological testing are presented in raw scores and its corresponding scaled scores: ≤ 6 considered as pathological (Normative data: Peña-Casanova, 2004). Paired *T*- test was used to test differences before and after surgery. CR: Correct responses; RT: reaction time

2.6.3. *fMRI data analysis*

The fMRI pre-processing and statistical analysis was performed with SPM8 (The Wellcome Trust Centre for Neuroimaging, London, UK). Image pre-processing included realignment, segmentation, normalization and smoothing with an 8 mm Gaussian kernel. Unified segmentation (Ashburner and Friston, 2005) with medium regularization and cost function masking (CFM) was applied (Andersen *et al.,* 2010; Brett *et al.,* 2001; Ripollés *et al.,* 2012). The cost function masks were obtained for each patient by applying a binary mask of the lesion. This lesion outline was delineated using the MRIcron software package (http://www.mccauslandcenter.sc.edu/crnl/mricron/) in the axial plane and further smoothed for sharp edges (see Fig. 1, for the visualization of lesions' variability). A General Linear Model contrastive analysis was performed for each patient. Motion parameters extracted from the realignment were included as regressors of no interest. Statistical parametric maps were obtained for each patient regarding single language naming activation conditions versus rest conditions for both L1 and L2 (L1 vs. rest and L2 vs. rest), were defined. Importantly, to exclude a purely language-related activity LS-naming task was contrasted with L1 single language naming. These contrasts are reported at an uncorrected level of $p < 0.01$.

3. Results

3.1. Intraoperative electrical stimulation mapping (ESM)

Single-language naming sites for both L1 and L2, as well as LS sites were detected by ESM in all 9 patients of the series (except for patient 4 for which only L1 sites were detected). Within the frontal lobe, single-language naming sites were predominantly found within the IFG (32 sites versus 2 sites within the MFG), more specifically at the level of the pars opercularis and triangularis, in all patients of the series (see Fig. 3B, Table 3). These results are in line with the findings described by Ojemann *et al.* (1989). Functional single language naming points outnumbered the LS-related points and did not overlap with each other.

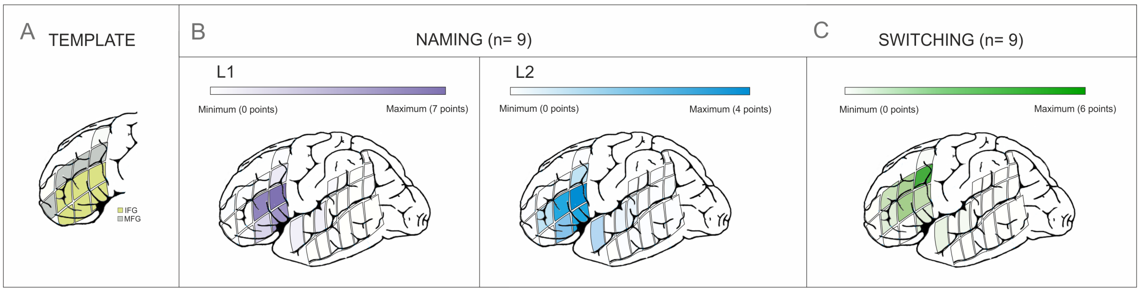

Figure 3: ESM mapping results transposed to a common template.

On the contrary, LS related points were mainly distributed across the left MFG (10 points within MFG versus 6 points within IFG), mostly on its posterior region (which corresponds to the posterior part of BA 9 and the posterior and inferior part of BA 8 - anterior premotor cortex), in distinction to language naming sites which were placed predominantly within the left IFG (32 points within IFG versus 2 points within MFG) (Fig. 3C). In 6 patients, a more extensive craniotomy was performed exposing the superior temporal lobe (patients 1, 2, 3, 4, 7 and 9) and the inferior parietal lobe (patient 1, 3 and 9) allowing the identification of LS points at the left STG in patients 1 and 2 and at the SMG in patients 1 and 9.

Chi square tests revealed that the frequencies of errors within the critical single language naming-related points within IFG versus MFG were significantly higher for IFG (X^2 (1) = 20.3, $p < .001$), whereas the opposite relationship was found for the LS-related errors, indicating stronger relationship of LS with the MFG than with the IFG (X^2 (1) = 4.1, $p = .043$). Interestingly, if the same analyses were performed only in 7 early bilinguals patients, the latter effects remained for both naming-related sites (X2 (1) = 12.1, $p = .001$) and LS-related sites (X2 (1) = 4.3, $p = .038$). A complete outline of our findings during the ESM procedure is presented in Tables 3 and 4).

Table 3. Comparison between patients in whom the fMRI activations related to language switching (upper part) and single language naming task (lower part) were found (1=yes versus 0=no) with the number of patients in whom the ESM points were mapped as functional using the same task (1=yes versus 0=no). (Only the findings related to the frontal lobe are reported).

LANGUAGE SWITCHING				
Case	*fMRI*		*Mapping*	
	L IFG	L MFG	L IFG	L MFG
1	1	0	1	0
2	1	1	0	1
3	1	0	0	1
4	0	1	0	0
5	0	1	0	1
6	1	1	0	1
7	1	1	1	1
8	1	1	1	1
9	-	-	0	1
Total cases	**6/8**	**6/8**	**3/9**	**7/9**
Frequency (/100)	**75,00**	**75,00**	**33,3**	**77,7**

SINGLE-LANGUAGE NAMING				
Case	*fMRI*		*Mapping*	
	L IFG	L MFG	L IFG	L MFG
1	1	1	1	0
2	1	1	1	0
3	1	1	1	0
4	1	1	1	0
5	0	0	1	0
6	1	1	1	0
7	1	1	1	1
8	1	1	1	0
9	-	-	1	0
Total cases	**7/8**	**7/8**	**9/9**	**1/9**
Frequency (/100)	**87,5**	**87,5**	**100,00**	**11,11**

fMRI, functional magnetic resonance, L, left, IFG, inferior frontal gyrus, MFG, middle frontal gyrus.

Table 4. Number of occurrences where the electrical stimulation did not disturb correct single language naming task (L1+L2) (A) and language switching task (B) within IFG or MFG versus the number of occurrences where the electrical stimulation resulted in errors in these areas. Frequencies of correct responses versus errors were compared using Chi-square tests and the results are reported below the table.

A. SINGLE-LANGUAGE NAMING	BRAIN AREA	
Response	IFG	MFG
Correct naming	76	70
Errors in naming task (L1+L2)	32	2
$X^2 (1) = 20.3$, $p < .001$		
B. LANGUAGE SWITCHING		
Correct switching	48	26
Errors in switching task	6	10
$X^2 (1) = 4.1$, $p = .043$		

IFG, inferior frontal gyrus; MFG, middle frontal gyrus.

3.2. fMRI

The neural networks underlying the language tasks were assessed by a whole brain analysis (at an uncorrected level of $p < 0.01$ and 20 voxels of cluster extent). For patient 9, no pre-surgical LS imaging data was available.

3.2.1. Single language naming specific activations

For the single-language naming condition (L1 & L2 single-language naming vs. rest), pre-surgical fMRI revealed important clusters at the level of the supplementary motor area (SMA) and left inferior frontal gyrus (IFG) in 7 out of 8 patients of the series, supporting the findings reported during the ESM procedure for the IFG. The left superior temporal gyrus (STG) and left inferior parietal lobe (supramarginal gyrus - SMG-) were activated in 5 out of 8 cases. These findings could not be fully confirmed by the ESM since the cortical exposure reached the SMG/STG level in 6 patients only.

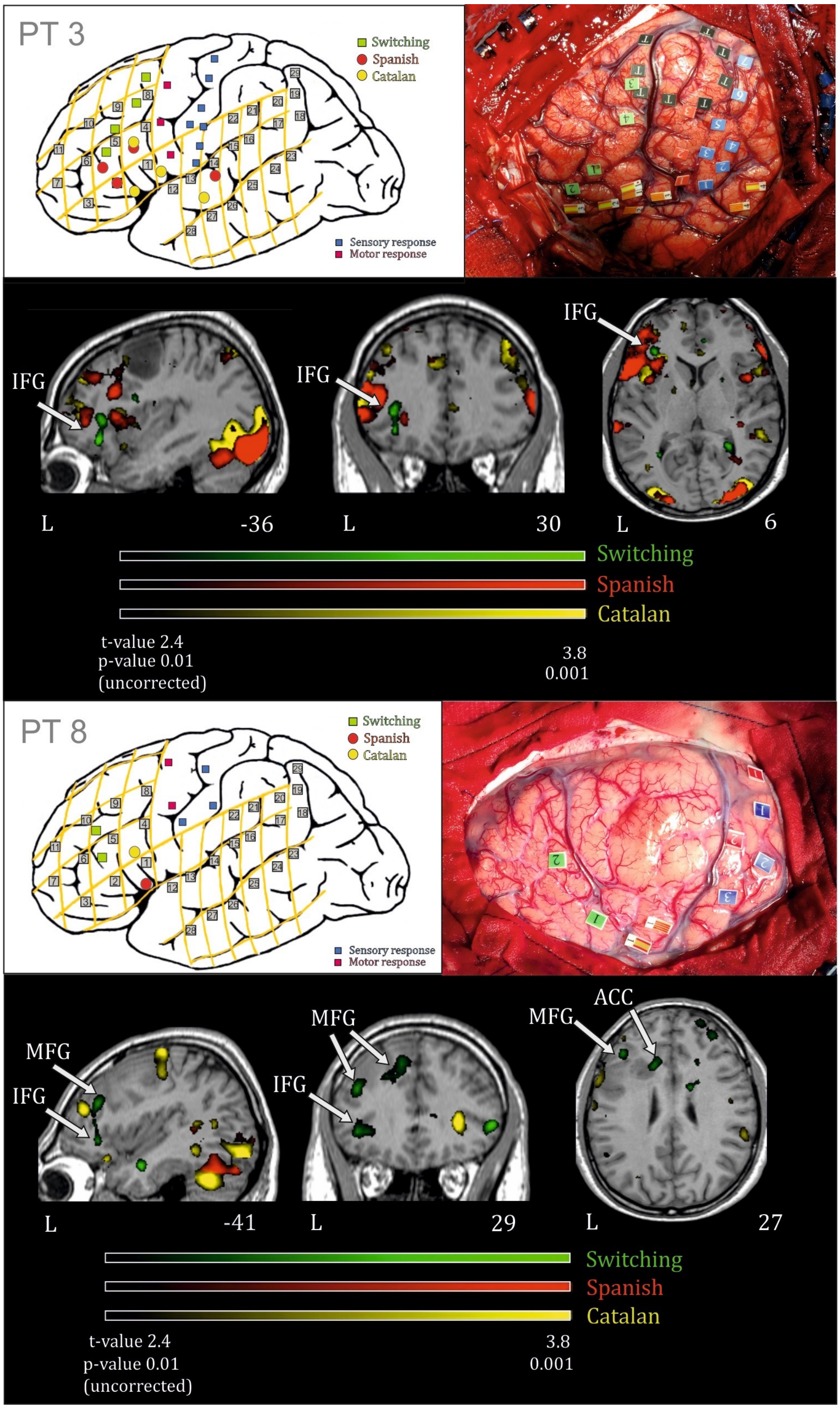

Figure 4: Example of partially convergent (Patient 3) and convergent (Patient 8) results from the comparison between ESM and fMRI. For patient 3, commonalities were found at the level of the IFG between fMRI and ESM but no convergence was observed at the level of the MFG (no MFG activations were found in the fMRI). On the contrary, for patient 8 a complete convergence of results between ESM and fMRI was found, for both IFG and MFG. (Please notice that the small size of clusters related to LS task is due to the contrast implied in the analysis - LS vs single language naming in L1).

3.2.2. LS-related specific activations

During the LS-naming condition (LS-naming vs. L1 single-language naming), significant clusters of activation were found at the level of the left IFG (mainly pars triangularis) and left MFG (especially it's posterior region) in 6 patients for both regions. Additionally, the activations within the left superior frontal gyrus (SFG) were found to be relevant for LS in 5 out of 8 cases and in the ACC in 4 out of 8 patients. Noteworthy, not always an overlap was observed between fMRI and ESM results (see Fig. 4A and 4B), a point that will be discussed in the following sections.

3.3. Neuropsychological assessment

Neuropsychological assessment performed after surgery revealed no significant differences when compared to the pre-surgical evaluation, except for the Digit span test (forwards, usually related to short term memory or attention) showing a significant improvement in patients' performance (Table 2). Verbal fluency deficits were observed in the pre-surgical evaluation for patients 1, 3 and 5. For patients 1 and 5, a significant improvement on this test was observed after surgery, whereas for patient 3, the post-surgical deficits persisted (Table 2). For patient 9, a significant decline on the Boston Naming Test, assessing object naming, was observed after surgery. Regarding language proficiency, neither object naming tasks, nor *Bilingual Switching Questionnaire (BSWQ; Rodriguez-Fornells et al., 2012)* showed significant differences between L1 and L2. These results indicated a homogenous level of oral proficiency in both Catalan and Spanish (see Supplementary Material Table A). Results on all the four constructs reported in the BSWQ after surgery and the overall score for the whole group did not differ significantly from the pre-surgical scores (see Supplementary material Table B). Additionally, patients did not report involuntary LS on their daily life conversations.

4. Discussion

In the present study, we explored the functional neuroanatomy of LS in a series of 9 Spanish-Catalan bilingual patients undergoing awake brain surgery. A multimodal ESM-fMRI protocol for LS assessment was implemented in all patients to test whether a specific brain region could be associated to LS differentially to single-language naming conditions (L1 and L2). Both our ESM and fMRI results clearly showed different functional distributions when comparing single-language naming to the LS (Tables 3 and 4). Neuropsychological performance and LS patterns during daily life conversations were assessed both pre- and post-operatively (see Table 2 and Supplementary material).

During the single-language naming condition, pre-surgical fMRI revealed important activated clusters at the level of i) the left IFG in all patients (also found during ESM), a brain region recruited when lexical and semantic representations compete for selection, (Amunts *et al.,* 2004, Badre and Wagner, 2004) and when top-down control processes guide lexical/semantic retrieval. (Buckner *et al.,*, 1996, Gabrieli *et al.,* 1998, Wagner *et al.,* 2001), ii) the left STG (also convergent with ESM results, exposed during the surgery only in 6 patients), known to be associated with lexical-semantic processing (i.e., the ability to associate a word with a picture) (Ojemann *et al.,* 1989; Baldo *et al.,* 2013), iii) the SMA (exposed in 2 patients), a brain region previously related with word selection process and word encoding (Alario *et al.,* 2006) and iv) the left IPL (SMG, 5 patients), linked to word retrieval processes, and phonological processing (see Démonet *et al.,* 1994).

In our previous study we were supporting the idea that LS is strongly related to the constant inhibition of the non-target language and hence may be subserved by several prefrontal structures, in particular a network including the MFG, IFG and ACC, as it has also been suggested by other authors (Fabbro, 2001; Hernandez *et al.,* 2001; Hervais-Adelman *et al.,* 2011; Guo *et al.,* 2011; Rodríguez-Fornells *et al.,* 2006;). In line with this assumption, our results clearly illustrate the essential role of these structures in cognitive control during LS particularly and probably associated to the need to suppress or inhibit the non-target lexicon. Results from the ESM procedure clearly highlight the implication of the posterior part of the left MFG (posterior portion of the BA 8 and 9) in LS, reporting errors in LS when inducing a transitory lesion during the experimental task performance in 7 out of 9 patients (see Table 3). These results confirm previous single-case observations (Lubrano et al., 2012; Sierpowska et al., 2013) and are also consistent with the activations obtained during the fMRI experiment in our patients and when contrasting active LS-naming blocks vs. L1 single-language naming blocks, observed in 6 out of 8 patients of the series (Table 3).

This systematic effect for left posterior MFG across different functional brain mapping modalities (ESM and fMRI) provides clear evidences that this area might be a key mediator for cognitive control in bilinguals, supporting the notion that LS is a very demanding task that shares features with other types of cognitive control conditions (Hernandez et al., 2001; Rodríguez-Fornells et al., 2006; Abutalebi and Green, 2008; Wang et al., 2009; Guo et al., 2011). Importantly, the middle frontal areas are traditionally associated with other cognitive control processes, also those not necessarily related to the language function per se (in this case, language switching). The aforementioned processes would involve: response selection, task-switching and task-set reconfiguration, prevention of interference and the inhibition of irrelevant items held in working memory (Baddeley et al., 1998; Brass & von Cramon, 2002; Cohen, Botvinick & Carter, 2000; Curtis & D'Esposito, 2003; Dove, Pollman, Schubert, Wiggins, & von Cramon, 2000; D'Esposito et al., 1995; Dreher, Koechlin, Ali & Grafman, 2002; Frith, 2000; Miller & Cohen, 2001; Rogers et al., 1998; Hirose et al., 2012; Jurado & Rosellini, 2007; Chikazoe, 2010. In this sense, Buchsbaum, Greer, Chang, & Berman (2005) reported large clusters of activations within the MFG related to a conjoined results from Wisconsin Card Sorting Task (WCST) and task switching. Konishi et al. (2010) observed that shifting to novel situations (simulated experimentally by a modified version of WCST) was impaired in patients harboring lesion involving dorsolateral and medial prefrontal cortex, whereas Shallice, Stuss, Picton, Alexander & Gillingham (2007) and Rogers et al., (1998) reported similar disturbance in task-switching for patients with lesions in the superior medial portions of the prefrontal cortex. These authors interpreted that this region might be clearly involved in regulating top-down activation of task-relevant cortical processes needed in a particular context. More recently, we reported (Sierpowska *et al,* 2013) similar results in 2 patients undergoing brain tumor resection, observing delayed and involuntary LS when electrical stimulation was applied to the left MFG. In another study, stimulation of the left DLPFC of 31-year-old multilingual, elicited involuntary language switching, providing further evidence of the role of this structure n LS (Lubrano *et al.,* 2012). Previous Language switching fMRI studies in bilinguals also support the notion that the MFG has a prominent role in LS. Wang and colleagues (2007) described activation in the MFG during an English-Chinese LS fMRI task. Similarly, Rodriguez-Fornells *et al.* (2005) found that the activation of the left MFG was crucial to control language interference, both suggesting that the regulation of the lexical representations of the two languages in bilinguals may not be exclusively mediated by neural systems typically associated with language processing.

Notice that we did not show perfect overlap between fMRI and ESM results in the present study (as shown in Fig. 4A and 4B), highlighting the importance of applying both methods allowing us to obtain an individual language network profile for each patient (Giussani *et al.,* 2010). It is important to keep in mind that when reporting fMRI activations of a certain region during a task performance, it is difficult to demonstrate the crucial relevance of this region for the processes we are trying to study. In fact, in a study evaluating the utility of preoperative fMRI in the prediction of whether a given cortical area would be deemed essential for language processing by ESM, a sensitivity of 66% for expressive linguistic tasks during fMRI was reported (Roux *et al.,* 2003). Therefore, language fMRI mapping carried alone seems not completely advisable to make critical surgical decisions requiring the application of invasive methods of brain mapping such as ESM (Roux *et al.,* 2003; Kho *et al.,* 2007; Moritz-Gasser and Duffau, 2009). Importantly, even if our ESM results showed clear predominance of the MFG over IFG involvement in switching, we sustain that MFG is not an exclusive area in charge of this process. Rather, it may be a key area ("hub") in a more extended network of regions (i.a. IFG; Green & Abutalebi, 2008; 2013). Indeed, in our study, the electrical stimulation applied at the level of the IFG level elicited LS errors/delays in 3 out of 9 patients (see also Kho et al., 2007). Regarding fMRI outcome, the left IFG was activated in 6 out of 8 patients during the LS task (Table 3), (see also Price *et al.*, 1999, Hernandez *et al.,* 2000; Quaresima *et al.*, 2002). This result may be interpreted in the light of the previously reported role of the left IFG in lexical retrieval and interference control, undoubtedly needed for the correct performance on the LS tasks (Green & Abutalebi, 2013). Importantly, both IFG and MFG are anatomically connected by a short u-shaped frontal lobe connection running superficially to the frontal aslant tract (FAT, Catani et al., 2012). The specific role of this connection may be important for further studies on LS-related networks, as explored by the means of ESM at white matter level. In the same line, it has been suggested that the dorsolateral and inferior frontal lobes play an important role in the network involved in inhibitory control (Aron *et al.,* 2004; Buchsbaum *et al.,* 2005). Bilinguals' executive control abilities are likely very demanding by the constant need to suppress irrelevant language information. Because both of the bilingual's languages are simultaneously activated during language production, non-target language lexical candidates must be ignored. This top-down regulatory system might be in charge of regulating the level of activation of the target language schema (and suppression–inhibition of the non-target one) and therefore, might be responsible for determining which language should be activated in a particular context (task-set reconfiguration process; Rodriguez-Fornells et al., 2006). When inducing a transient lesion of this brain structures, a failure of this top-down modulation might explain the appearance of unintended language switches as well as the system's inability to properly regulate the activation and suppression of the target and non-target language lexicons (for a more detailed discussion see Sierpowska *et al.,* 2013).

As a limitation of the present study, it is important to mention that craniotomy size in our patients was tailored to tumor location reducing the chances of finding functional switching points away from the exposure area, which was mainly focused on the frontal lobe (exposed in all patients of the series), although temporo-parietal areas were accessible for ESM in 6 out of 9 patients. Besides, sample size and the characteristics of our sample limit the strength of possible conclusions, but we believe that the systematic observation of LS sides in the MFG and IFG speak in favor of a functional division in the prefrontal cortex between naming and LS functions. Ideally, in future studies, patients with lesions located on more posterior temporo-parietal areas should be included in order to explore other regions involved in LS.

To conclude, our findings support the notion non-domain specific cognitive control prefrontal regions (posterior MFG) together with language frontal-related sites (IFG) mediate LS processing in bilinguals. These results support an integrative view for LS, including both general cognitive control mechanisms and the participation of linguistic regions, supporting previous case-study observations (Kho *et al.,* 2007; Lubrano *et al.,* 2012; Sierpowska *et al.,* 2013) and group studies (Hernandez *et al.,* 2000; Quaresima *et al.*, 2002). Furthermore, our results provide new evidence for the usefulness and convenience of applying a specific LS protocol intraoperatively and in order to map brain structures relevant for LS processing differentially from those related to single-language naming.

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Supplementary material

Table A: Language proficiency on L1 and L2 assessments.

L1 & L2 proficiency				
Patient	*Object naming*		*Bilingualism questionnaire*	
	Cognate and non-cognate words (60)		Overall self-rated proficiency	
	L1	L2	L1	L2
1	47	46	4	4
2	54	58	4	4
3	51	52	4	3.75
4	59	48	4	3
5	54	49	2.25	4
6	43	56	3.75	3
7	-	56	4	2.5
8	50	51	4	3.5
9	53	47	4	4
Mean	51.38	51.44	3.78	3.53
SD	4.87	4.36	0.58	0.57
t- score	0.2		0.82	
Asympt.sig.	.85		.43	

L1 and L2 proficiency was self-assessed by the patients using a likert scale bilingualism questionnaire in several domains including comprehension, reading, speaking and writing with scores ranging from 1 (poorly) to 4 (perfectly), here represented as a mean score of the four measures. Importantly, language proficiency was objectively measured with the object naming tasks, (60 items).

Table B: Language history assessment and Bilingual Switching Questionnaire (BSWQ).

Patient	*A. Language history*				*B. BSWQ*									
					L1S		**L2S**		**CS**		**US**		**Overall score**	
	L1	AoA	L2	AoA	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	SPA	3	CAT	7	9	10	9	10	8	8	10	7	36	35
2	CAT	2	SPA	6	10	7	10	7	8	7	6	8	34	29
3	CAT	3	SPA	7	10	11	7	6	9	9	8	12	34	38
4	SPA	3	CAT	4	12	8	9	8	15	8	9	10	45	34
5	CAT	2	SPA	4	7	7	8	3	5	4	5	7	25	21
6	SPA	3	CAT	6	12	12	9	10	10	9	11	12	52	53
7	SPA	1	CAT	3	10	13	6	9	10	11	9	11	35	44
8	CAT	2	SPA	15	11	11	5	6	6	6	8	8	30	31
9	SPA	2	CAT	14	12	4	7	5	8	3	4	3	31	15
T score					1.000		.652		1.760		-1.315		.963	
Asymp. Sig.					.347		.532		.116		.225		.364	

A. Language history assessment showing the age of acquisition for both L1 and L2. B. 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; L2S, a tendency to switch to L2; CS, contextual switching; US, unintended switching. Paired t- test was used to test differences before and after surgery, AoA: Age of acquisition