BILINGUAL PATIENTS

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Abstract

Bi/multilingualism refers to the ability to use two or more languages in everyday life. Increasing interest has been paid to unveil the neural basis of bilingual language processing; however, the brain representation of language in bilinguals is still a matter of debate. Currently, there is a weak level of evidence supporting that the best probable way to avoid a selective language deficit is to perform multilingual intraoperative tests. The key point is to individualize and tailor—depending on daily needs—the neuropsychological protocol, from testing only the native language up to testing all the languages the patient speaks. Furthermore, the bilingual brain is capable of handling both languages without apparent difficulty or interference. This cognitive ability, which includes language switching, has also been studied and mapped. Results suggest a functional cortico-subcortical network that takes advantage both from language-specific areas and non-specific cognitive control regions, working together to maintain effective communication. Therefore, electrical stimulation mapping arises not only as a technique to maintain the quality of life of bilingual patients but also as a useful tool in neurocognitive research.

1. Introduction: Neural basis of Bilingualism.

The neural bases of language processing in bilinguals have been extensively investigated with the advent of neuroimaging techniques, such as the functional magnetic resonance imaging (fMRI) and the Electrical Stimulation Mapping (ESM). However, there are still many unanswered questions and live debates on (1) which cortical and subcortical areas of the language circuit show common and specific activation for the two languages; (2) to which extent overlap in the language circuit depends on the age of acquisition, proficiency, or language exposure; (3) which language control mechanism allows to manage two languages in one brain so that we can speak only in one language at a time while avoiding intrusions from the other language; (4) the brain plasticity associated to tumor growth and tumor resection in a bilingual brain.

ESM studies on bilinguals[1–4] have shown the co-existence of common brain regions for the two languages through language-specific areas. In particular, they reported disruptions during stimulations in sites where speech arrest arose for both languages and sites where speech arrest arose for one language but not for the other. Thus, language circuits are crafted with common and specific pathways. In addition, studies using ESM have revealed remarkable differences in language areas between individuals, rendering the overlapping range of sites very variable[1,2,5].

Ojemann and Whitaker[3] already noticed this variability when reporting, for the first time, different cortical-functional sites (frontal and parietal) in two bilingual patients using ESM together with naming intraoperative tests. More recently, the same team reported frequent but variable overlap in temporoparietal areas for L2 and L1. However, none of the 22 patients had complete overlapping of L1 and L2 and 8 of them had no overlap at all[1]. Similar results have also been reported in bilingual pediatric population using several tasks[6]. Serafini et al. tested bilingual patients with reading and naming tasks; they reported the existence of overlapping "multi-task" cortical areas in the frontotemporal regions and single language task sites more located in the postcentral areas. These data align with the previous results supporting the idea of a specific functional network for multilinguals with variable overlapping. Not surprisingly, European and Asian teams using ESM in multilinguals have found results that are also very similar to those summarized in 2007[2] in a review by Giussani and, more recently, in 2019, by Teo et al.[7] and Roux and Tremoulet[4]. For example, Roux and Tremoulet stimulated cortical areas of 12 right-handed bilingual patients during surgery, using counting and reading, besides naming tasks, and found strict overlapping of both languages in only 5 of them, which implies that differences in the networks subserving each language are general and not task-specific.

Similarly, neuroimaging studies have revealed common and specific activation for the two languages in a bilingual brain[8]. In a seminal work using fMRI with bilinguals, Kim et al. [9] reported overlap of activation for L1 and L2 in the left inferior frontal gyrus if both languages were acquired early, but different spots of activation if the L2 was acquired later in life. However, overlap of activation was found in the left superior temporal gyrus both for early and late bilinguals. Many other teams have reported different networks subserving the organization of multilingual brains, with variable overlapping. In fact, current evidence suggests that languages are represented mostly in overlapping networks, including areas within the left perisylvian cortex and frontal, temporal, and parietal regions as well as subcortical structures. In short, similar activation has been found for the processing of the L1 and L2 in the so-called language network[10–13]. Nonetheless, some studies have also reported language specificity in several brain regions attributed to age of acquisition (AoA) and proficiency[14,15] differences.

Whether the same or different brain areas get activated for each language seems to be modulated by age of acquisition, proficiency, usage, and exposure, among other variables. Though controversial, ESM evidence supports the idea that the languages acquired earlier in life may have a larger cortical representation[16–20]. However, others have found that the number of distinct cortical sites for L2 was much higher than for L1, suggesting that the use of L2 implies a wider functional network[21]. On the other hand, regarding similarity between languages, it is noteworthy that a recent fMRI study[22] with native speakers of four very different languages (Chinese, English, Hebrew, and Spanish) showed mostly brain activation overlap for the four languages, together with some specific activations during speech and reading. It is important to note that these four languages differ in many linguistic and orthographic dimensions (e.g., logographic vs. alphabetic Chinese vs. the three others; opaque vs. transparent orthographies: English and Hebrew vs. Spanish.), and the main result is a high overlap of activation for print and speech.

The fact that similar neural networks get activated during the processing of two different languages brings up to the table another interesting idea: how bilinguals are able to manage the two co-activated languages so that they can speak in one of them without interference from the other. Bilinguals need to focus on the target language while inhibiting the nontarget language or ignoring it. To do so, and to account for the lack of interference between languages, a language control mechanism responsible for language switching has been proposed. This control circuit would be different from the language circuit. In fact, some researchers[23,24] suggested that cortical areas outside the language circuit such as the right dorsolateral prefrontal cortex, and subcortical areas like the caudate, should be involved in language control. Specifically, the language control mechanism recruits neural regions involved in the control of action in general[25], including the dorsal anterior cingulate cortex (dACC)/pre-supplementary motor (pre-SMA) area, the left prefrontal cortex, the left caudate, and the inferior parietal lobules, bilaterally together with control input from the right prefrontal cortex, the thalamus and the putamen of the basal ganglia, and the cerebellum[24].

Finally, low-grade gliomas may induce plastic changes in the topography of brain functions[26]. In most of the cases, the slow growth of the tumors promotes neural reorganization so that patients are often neurologically normal or only slightly impaired. Eloquent functions can be redistributed in neighbor areas around the tumor, and/or recruited by a distributed network within the lesioned hemisphere and/or in the contralateral hemisphere[26], and this can change also after surgery. Some previous studies on patients with LGGs in eloquent brain areas suggested that post-surgery functional compensation occurred mainly in peritumoral and in contratumoral regions[27–31]. However, Lizarazu et al. (2020)[32], using Magnetoencephalography (MEG), found that functional connectivity in peritumoral regions was higher three months after surgery than before surgery. In contrast, alpha functional connectivity values in contra-tumoral areas did not differ between sessions. Interestingly, this enhancement of functional connectivity that emerged in the alpha frequency band was observed in all patients regardless of the LGG location. Thus, post-surgery functional reorganization in peritumoral regions may be a general mechanism of brain plasticity that plays a major role in the recovery of brain function through compensatory mechanisms. Importantly, the preservation of white matter tracts (long-distance connectivity and U-fiber white tracts) may be critical for plasticity in these regions[33]. The risk of inducing permanent deficits without functional recovery is very high in cases of white matter injury[34]. It remains to be seen whether the same compensatory mechanisms work for L1 and L2 in bilingual brains.

2. Intraoperative language monitoring in bilingual patients

Comparative data between selective impairment of one specific language in patients operated on and brain mapping and those undergoing brain surgery without are scarce. One possible explanation may be the fact that this specific language and cognitive evaluation in multilinguals, which is needed to monitor these potential sequelae, is only performed in patients undergoing mapping and awake brain surgery, with the precise purpose of reducing this kind of deficit.

Multilingual patients undergoing brain surgery without mapping are simply not tested for language in most series. Then, the specific rate of selective language impairment in this last population is widely unknown. Some limited data are available in the literature about long term impairment of a selective language in multilinguals. One of these cases of selective language impairment has been reported after stroke and left frontal brain tumor by Ibrahim[35,36] in Arabic-Hebrew bilinguals. The patient showed selective difficulty for the lexical access in one of the languages after lesioning. Others have noticed selective aphasia of one language during the Wada test[37,38] or after perisylvian surgery of MAV[39]. However, none of these data of selective language deficit in bilinguals who did not benefit from intraoperative monitoring are strong enough to compare with data from the mapped population. In any case, several considerations can be made.

To date, ESM has been established as the best way to avoid permanent deficits in brain tumor surgery[2,18,40]. Thus, there are no phase-three randomized control trials in the field comparing post-operative deficits after surgery in eloquent areas with and without ESM. Nonetheless, there is a recent meta-analysis of 10 years of published studies comparing the short and long term neurological deficits of series of patients having undergone surgery for supratentorial gliomas with and without intraoperative mapping[41]. This meta-analysis showed a rate of permanent deficits in the unmapped population of 8.3% vs. 3.4% in the mapped population, with a median resection volume of 78% in the mapped vs. 58% in the unmapped. This means that the unmapped population has almost three times more risk of developing a long-lasting neurological deficit.

The results of this meta-analysis have important implications for the intraoperative mapping in bilinguals. Considering that they have at least the same risk as monolinguals, bilinguals should be mapped. In fact, they could be tested only in one of the languages if the neural circuits underpinning the two languages overlapped. However, the empirical evidence shows that, while there is some overlap, multilinguals seem to have specific networks also not shared for all the languages. Therefore, performing multilingual intraoperative tests is probably the best way to avoid a selective language deficit, testing separately not only all the languages but also the ability to switch between them, as switching is crucial in patients using at least two languages in daily life. Not performing these tasks may result in a loss of quality of life[7], as shown for other neurological functions[40].

3. Cortical and subcortical key networks for bilinguals

The evidence from research on bilingualism studies using ESM has shown that most of the functional points are within the perisylvian classic language areas (namely the inferior frontal gyrus—pars triangularis, orbitalis, and opercularis—, superior temporal gyrus, supramarginal gyrus, angular gyrus, etc.: IFG, STG, SMG, AG). However, a significant percentage of them are still located outside of the perisylvian areas, recruiting cortical regions not traditionally regarded as subserving language functions, such as the mid-frontal gyrus (MFG).

On the other hand, it is well established nowadays that intraoperative testing of language networks implies subcortical stimulation of language-related tracts. Data on subcortical stimulation have helped to define the brain connectivity and build models of language organization[42,43]. Subcortical tracts were also reported in bilinguals. Using naming and counting tasks together with stimulation of subcortical tracts in seven high proficiency multilingual patients, Bello et al. reported specific subcortical tracts for L1 in four patients and L2 in three patients; however, authors did not specify which tracts were differentially involved[18].

Subcortical connectivity is of critical relevance to investigate the portrayal of two languages, but also to understand the ability of bilinguals to switch between languages. At the cortical level, dominant dorsolateral prefrontal cortex in the middle frontal gyrus seems to be highly specified in this shifting mechanism, as recently demonstrated by Sierpowska and Fernandez

Coello[43]. These results align with those reported by Duffau and colleagues during subcortical stimulation of the superior longitudinal fasciculus, which generated intraoperative and post-surgery involuntary language switching in bilinguals. Stimulation of this bundle generated a transitory “disconnection” of the speech areas, which need to be functional in order to avoid switching impairment [44,45]. Some other studies agree with the left dorsolateral prefrontal region as a fundamental piece in the executive control of language switching (LS). Lubrano et al. reported the participation of the left dorsolateral prefrontal region in LS in a case study in which the ESM caused involuntary LS when this region was stimulated[19]. However, other regions seem to contribute to language control. For instance, Sierpowska et al.[46] identified the posterior middle frontal gyrus as being involved in the process of controlling language because, when it was stimulated, patients showed control language difficulties in LS. In addition, Tomasino et al.[47] describe an involuntary LS after stimulation during a mapping procedure in the superior temporal region. Wang et al.[48] provided new evidence of basal ganglia involvement in LS. Using ESM during the performance of LS tasks, their results showed a participation of the head of the left caudate nucleus.

Taking into account the information about cortical and subcortical connectivity, Duffau and collaborators proposed an ESM-based model of LS that involves a large cortical-subcortical neural network. The model would include an executive system (prefrontal cortex, anterior cingulum, caudate nucleus), controlling a more dedicated language subcircuit, which involves posterotemporal areas, supramarginal and angular gyri, Broca’s area, and the superior longitudinal fasciculus[49].

To sum up, in the case of bilinguals, it is important to test both languages and language switching not only on cortical sites, but also in subcortical units and white matter tracts for cortical and subcortical connectivity.

4. Newly-designed tasks for monitoring multilingualism intraoperatively

Picture naming tasks are currently the gold standard for identifying eloquent areas during awake brain surgery[50–52]. With multilingual populations increasing worldwide, patients frequently need to be tested in more than one language. In addition, a detailed and precise language mapping procedure requires picture naming of objects and actions. Some previous studies using ESM reported a dissociation between temporal and frontal regions when stimulating objects and actions[53–56]. This dissociation between nouns and verbs has been demonstrated at the behavioral, electrophysiological, and brain activation levels[57]. Therefore, testing object and action naming in the two languages of a bilingual patient with comparable stimuli is desirable for a comprehensive mapping.

MULTIMAP[58], is an open-source battery that entails a multilingual picture naming of objects and actions for mapping eloquent areas during awake brain surgery. Pictures included in the MULTIMAP test are colored drawings of objects and actions that have been standardized in nine different languages (Spanish, Basque, Catalan, Italian, French, English, German, Modern Standard Arabic, and Mandarin Chinese), controlling for name agreement, frequency, length, and neighbors across objects and verbs in nine languages and their combinations. Thus, the database was designed for allowing direct comparisons between objects and actions within and across languages (i.e., Spanish-Basque, Spanish-Catalan, Spanish-Italian, Spanish-

French, Spanish-English, Spanish-German, Spanish-Modern Standard Arabic, and Spanish-Chinese).

MULTIMAP will improve language mapping in multilingual patients, testing objects and actions, and facilitating the identification of areas that show interference in all or only one of their languages that would not be detected by a monolingual test. Moreover, although the use of object naming tasks is widespread across surgical teams in many different geographical locations, heterogeneity in the stimuli selection criteria of pictures across different studies hinders comparison and generalization of results. The MULTIMAP battery allows for direct comparison between objects and actions as well as between pairs of languages in awake surgery.

The use of single picture naming tasks to test the different languages is mandatory but it is not fully comprehensive to capture the complexity of language. This is why, depending on the tumor, other tasks such as Counting, Reading, and Translation[59–61], to name a few, have also been used in order to preserve an optimal quality of life according to the patient's specific language requirements. Additional tasks at the sentence/discourse level are needed in the field.

Finally, to keep effective communication in bilinguals, a correct capacity for change (language switching) and control (language inhibition) of the different languages is necessary. Most of the studies to monitor language function in bilinguals used the picture naming task. This task seems to tap into single word production. In addition, picture naming has been also used to investigate LS. Participants can be instructed to name the picture in one language (e.g., Spanish) or another language (e.g., English) depending on a specific cue (i.e., the color of the picture frame or a flag, etc.). This way we can compare the responses to trials in which participants have to change the language to name the next picture (switching trials: Picture 1 in Spanish, *libro*, Picture 2 in English, *table*) with those in which the same language is used to name two consecutive pictures (repeat trials: Picture 1 in English, *book*, and Picture 2 in English: *table*). Error rates and/or reaction times are larger for switching trials as compared to repeat trials.

Interestingly, this LS task has been used intraoperatively by the group from Bellvitge, who implemented a LS-electrical stimulation mapping (ESM) paradigm assessment. Their results showed different functional distributions when comparing single-language naming to the LS. 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. Contrarily, switching naming sites were distributed across the middle frontal gyrus significantly more often than within the inferior frontal gyrus. These findings support the notion that non domain-specific cognitive control prefrontal regions (posterior MFG), together with language frontal-related sites (IFG), mediate LS processing in bilinguals[43] (see Figure 1).

5. Functional improvement in patients operated on with versus without function monitoring.

ESM studies in bilinguals have yielded heterogeneous results, ranging from a greater spatial representation for L1[2] or for L2[21] to an equivalent total cortical surface area involved in L1 and

L2 processing, with partially overlapping regions[4] or significantly different anatomical distribution[62]. This spatial separability could imply that testing only one language would put the second language abilities at risk in the postoperative period.

There is only one series of bilingual patients operated under LS monitoring using a newly developed LS-task that allowed a systematic evaluation of externally triggered LS synchronously with ESM[43]. Based on previous proposals [46], the authors evidenced that the postsurgical neuropsychological scores did not differ significantly from the presurgical ones, and patients did no report involuntary LS in their daily life conversations; however there is no evidence of improvement in comparative cohorts. On the other hand, we are not aware of any study describing a long-lasting deficit for the intraoperatively non-tested language. Nonetheless, as we mentioned in point 2, there are consistent data on global permanent deficits being twice more frequent in the unmapped patients undergoing brain surgery for supratentorial gliomas.

Numerous papers in the field of ESM in glioma surgery have reported its usefulness to minimize neurological permanent deficits and, at the same time, to improve oncological outcome[41]. It now seems well established that neuro-oncological surgery needs to get to the best balance of quality of life and survival at the same time. Identifying the "connectome" intraoperatively by means of subcortical stimulation has been consolidated as the best tool for this purpose, in a clear new surgical oncofunctional brain surgery philosophy [42,63–65], but what about not only preserving but improving?

As mentioned previously, there are no objective data in the specific field of multilingualism, unlike in the field of global neurocognition. There are no reasons to believe that bilinguals should behave differently. Actually, Duffau already reported a 10% improvement in language skills after surgery of supratentorial LGG in his early series of 103 patients in 2003[66]. This improvement in language skills is even reported for the insular lobe, probably the most challenging area for glioma surgery in awake patients. Duffau reported language improvements in 6 out of 24 patients after insular surgery [67]. These conclusions are shared by other teams, as Pallud et al., who are also reporting up to 30% of language improvement after glioma surgery with ESM[68].

Another neurocognitive aspect of language that is crucial for multilinguals is working memory. In particular, working memory capabilities are crucial for daily living, for instance, for a correct and fluid language switching. Recent data from ESM testing working memory before and after oncofunctional surgery preserving the connectome showed that, although 91% of 45 patients experienced working memory loss in the first three months, after that time, all 42 patients recovered their preoperative status and 3 of them experienced improvement [69]. Interestingly, these improvements are not only within the neurocognitive sphere; they also have an impact on the patients' daily life, according to recently-published data focusing on returning to their work status, which show that a 97% of them were able to resume their professional practice[70].

The lack of specific comparative series of a possible improvement of multilinguals that had surgery undercover of ESM implies that we cannot conclude that using this technique will improve their language skills. Nonetheless, the data for selective improvement in some patients in all the other neurocognitive aspects mentioned before, and the robust data sustaining the existence of specific functional networks for each language mentioned in the first paragraph of this chapter, partially suggest that oncofunctional surgery may also improve at least one of the languages in some selected patients. In this sense, the increase of functional connectivity observed in peritumoral regions when comparing it three months after surgery and before surgery[32] is very promising.

6. Closing remarks

The contradictory results in ESM studies testing multiple languages, ranging from a complete overlap among the different languages to spatially distinct and separate areas for each language, lead us to individualize and tailor a neuropsychological protocol testing all the languages the patient fluently speaks or test only their native language, depending on daily needs.

The results of ESM-LS studies suggest an executive control functional network that takes advantage both from language-specific areas and non-language cognitive control regions, working together to maintain effective communication. Therefore, testing LS also involves testing non-domain specific cognitive control networks, resulting in a patient-relevant medical benefit.

Finally, the gained evidence from cognitive psychology, neuroimaging studies, and ESM teaches us that the localizationist approach of trying to segregate languages topographically has not yielded conclusive results. Answers possibly lie beyond the cortex, understanding the brain as a dynamic network involving white matter tracts and subcortical structures.

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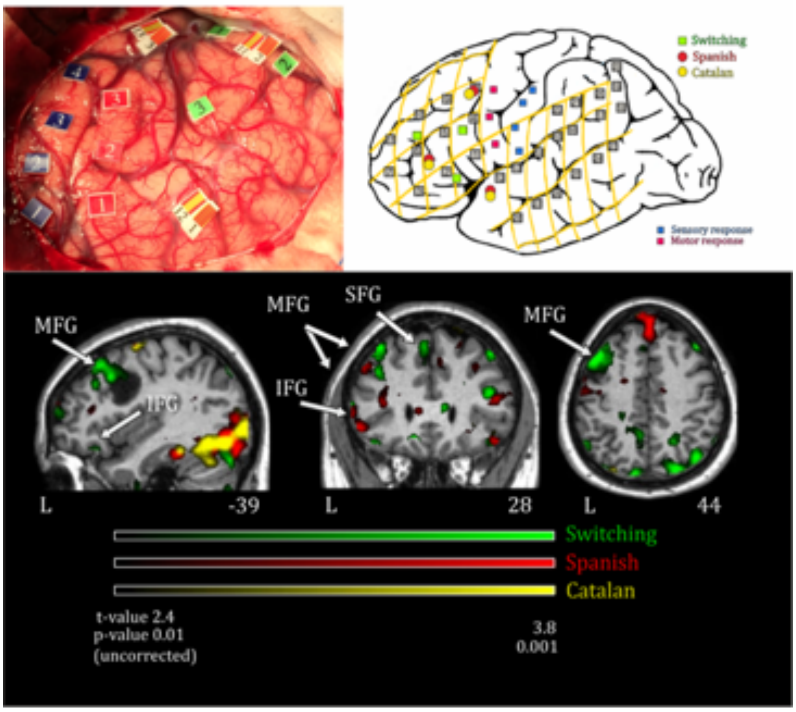

Figure 1. Language functional maps reconstructed on the basis of intraoperative ESM in comparison with neuroimaging results from fMRI in a bilingual patient. Image from the LS-patient series from Sierpowska and Fernandez-Coello[43].