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Age of language acquisition and cortical language organization in multilingual patients undergoing awake brain mapping

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OBJECTIVE Most knowledge regarding the anatomical organization of multilingualism is based on aphasiology and functional imaging studies. However, the results have still to be validated by the gold standard approach, namely electrical stimulation mapping (ESM) during awake neurosurgical procedures. In this ESM study the authors describe language representation in a highly specific group of 13 multilingual individuals, focusing on how age of acquisition may influence the cortical organization of language.

METHODS Thirteen patients who had a high degree of proficiency in multiple languages and were harboring lesions within the dominant, left hemisphere underwent ESM while being operated on under awake conditions. Demographic and language data were recorded in relation to age of language acquisition (for native languages and early- and late-acquired languages), neuropsychological pre- and postoperative language testing, the number and location of language sites, and overlapping distribution in terms of language acquisition time. Lesion growth patterns and histopathological characteristics, location, and size were also recorded. The distribution of language sites was analyzed with respect to age of acquisition and overlap.

RESULTS The functional language-related sites were distributed in the frontal (55%), temporal (29%), and parietal lobes (16%). The total number of native language sites was 47. Early-acquired languages (including native languages) were represented in 97 sites (55 overlapped) and late-acquired languages in 70 sites (45 overlapped). The overlapping distribution was 20% for early-early, 71% for early-late, and 9% for late-late. The average lesion size (maximum diameter) was 3.3 cm. There were 5 fast-growing and 7 slow-growing lesions.

CONCLUSIONS Cortical language distribution in multilingual patients is not homogeneous, and it is influenced by age of acquisition. Early-acquired languages have a greater cortical representation than languages acquired later. The prevalent native and early-acquired languages are largely represented within the perisylvian left hemisphere frontoparietotemporal areas, and the less prevalent late-acquired languages are mostly overlapped with them.

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KEY WORDS electrical stimulation mapping; multilingual brain; language mapping; diagnostic and operative techniques

In today's society, with easy access to travel and numerous opportunities for communication between people from different cultural backgrounds and languages, it has become customary to learn more than one language throughout life. The term bilingualism is used when someone speaks 2 languages with high proficiency, while multilingualism refers to people who speak 3 or more languages fluently.[13] Even in individuals who are highly bilingual, one language usually dominates over the other. Second-language learners seldom achieve the same level of profi-

ABBREVIATIONS AoA = age of acquisition; ESM = electrical stimulation mapping; fMRI = functional MRI; L1 = native language; L2 = acquired language.

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ciency in a second language as they have in their mother tongue, especially when the second language is learned relatively late in life. Some authors[5,27] argue that the cortical representation of languages is linked to age of second-language acquisition, such that additional languages acquired in adulthood (late multilinguals) are located in different brain regions to those of languages acquired in earlier stages of development (early multilinguals).

Although several studies have examined cortical language organization in multilingual patients, most of them are based on functional MRI (fMRI) performed in bilingual patients.[27,33,41,42] Neuroscientific studies with multilingual participants are rare, and most fMRI studies to date show an increased activation for acquired language (L2) processing compared with native language (L1).[3,55,58] fMRI is a guidance tool that has yet to be validated by electrical stimulation mapping (ESM) during awake surgery.[18] ESM is an excellent technique for localizing functional areas in a patient, helping not only to preserve language function but also to understand language organization in humans.

ESM studies in bilinguals have yielded heterogeneous results, ranging from a greater spatial representation for L2[7] to an equivalent total cortical surface area involved in L1 and L2 processing, with partially overlapping regions[53] or significantly different anatomical distribution[31] (for a review, see Rodriguez-Fornells et al.[16]). To our knowledge, however, only one study has so far investigated multilingualism using ESM.[4] The authors of that study involving 7 patients concluded that sites for the first acquired language were more numerous than were those for the second or subsequent languages, and that the former sites were always distinct from the latter. These results may support the hypothesis that neural traces of L2 and further acquired languages are more widely distributed in the brain and probably extend to nonclassic perisylvian regions. In this context, it is worth noting that the majority of studies based on ESM have been conducted in patients with lesions within the perisylvian cortex of the dominant hemisphere, thereby restricting stimulation to these regions. Consequently, the regions where language function is located are influenced not only by the age of language acquisition or proficiency but also by the type of lesion, in terms of tumor growth rate, lesion size, and proximity to eloquent areas. These factors can produce considerable variability among patients in the cortical organization of language. It is not surprising, therefore, that most studies conclude that patterns of language areas in multilingual patients are unpredictable, and they recommend the use of ESM for each language to prevent postoperative deficits (see the review in Giussani et al.[17]).

In the present study, we describe language organization obtained by ESM in 13 highly proficient multilingual patients harboring lesions within the dominant left hemisphere. The focus of our research is on how age of language acquisition may influence the cortical organization of language in this specific group of multilinguals.

Methods

Patient Group

Between January 1998 and December 2012 a total of 153 patients with brain lesions in eloquent areas were operated on under awake conditions.[49] Seventy-two of these patients had perisylvian lesions in the dominant language hemisphere, and 13 of them met all the following inclusion criteria for the study: 1) age between 18 and 65 years; 2) bearers of expansive brain lesions within or in the vicinity of the perisylvian language region in the left, dominant hemisphere, as assessed by preoperative language fMRI; 3) the ability to speak at least 3 different languages to a high level of proficiency (according to a modified version of the Boston Naming Test adapted for intraoperative purposes); 4) ability and willingness to cooperate during the surgical procedure while awake, and 5) a medical interview in which every patient request to preserve all the languages spoken.

The 5 men and 8 women included in this study were between 20 and 62 years of age (mean 35 years), and they were all right-handed. Nine patients spoke 3 languages, 3 patients spoke 4, and 1 patient spoke 5 languages. The languages were of the following language families: Romance (Spanish, French, Catalan, Galician), Germanic (English, German), Slavic (Russian), and isolate (Basque).

In all cases we considered the language first acquired in childhood as the native language (L1). Languages other than the native tongue that were acquired before the age of 7 years were considered early-acquired languages (early L2), while languages that were used routinely by the patient but were acquired after that age were considered late-acquired languages (late L2).

Nine patients presented with seizures preoperatively: generalized seizures in 3 cases and partial seizures in 6 cases. Language function was intact preoperatively in all of the patients except for one who had mild dysphasia. Two patients reported headache, and 1 patient had mild motor weakness of the upper limb contralateral to the lesion. Presurgical neuropsychological test scores were higher than 85% for all languages in all patients. Language lateralization assessed by fMRI was left dominant for 10 patients and bilateral for 3.

In terms of lesion histopathology we considered 2 kinds of growth rates: 1) fast-growing tumors, including high-grade glioma (anaplastic astrocytoma and glioblastoma) and metastases, and 2) slow-growing tumors, including gliosis, low-grade glioma, and cavernoma.

Preoperative Assessment

Detailed neurological examination was performed by senior neurosurgical staff the day before surgery to detect deficits in language, motor, sensory, visual, and visuospatial skills. Karnofsky Performance Status was assessed preoperatively in all cases.[24]

All patients underwent neuropsychological examinations in the period 1–4 weeks before surgery. Each language was tested using the Boston Diagnostic Aphasia Examination (BDAE), the Boston expressive subtest, and the Boston Naming Test.[19,50] We used the Edinburgh dominance test to determine handedness,[39] and the brief version of the Token Test[10] to assess verbal comprehension. Neuropsychological testing also included a subset of the revised Barcelona test: digit span memory, automatic language, phonemic (words beginning with P) and semantic (animal names) verbal fluency test, reading task, and a nonword repetition task.[40] The Vocabulary subtest from the Wechsler Adult Intelligence Scale was used to assess verbal expression and comprehension.[57] Patients also repeated an object naming task (modified version of the Boston Naming Test) on the day of the surgery for each language.

A conventional 1.5-T structural MRI study was performed in each case. This included axial (simple and contrast-enhanced), sagittal, and coronal T1-weighted images, axial and coronal T2-weighted images, and axial and coronal fluid-attenuated inversion recovery (FLAIR) images. Additionally, high-resolution T1-weighted anatomical images were obtained to assist in identifying anatomical landmarks during the analysis of fMRI data. In each case, fMRI was performed to determine whether the dominant hemisphere matched the location of the lesion. Each operation was carried out with prior consent of the patient and after assessment by an anesthetist.

Intraoperative Protocol

All patients were operated on by the same senior neurosurgeon (A.G.) at the Department of Neurosurgery of Bellvitge University Hospital. A neuronavigational system (Brainlab) was used in all cases to design the bone flap and to determine the lesion area and its boundaries when the dura was opened. The anesthetic agents used were propofol (0.5–2 mg/kg/hr) and remifentanyl (0.03–0.08 μg/kg/min); curare was not used, and halogens were avoided. A local anesthetic mixture (lidocaine 2%, mepivacain 0.25%, and bicarbonate 1 M) was injected before the skin incision was made.

A wide frontotemporoparietal craniotomy was performed in all cases, thus providing good exposure of the entire perisylvian region. ESM was performed using an Ojemann cortical stimulator (Radionics, Inc.) under awake conditions. The interelectrode distance of the bipolar forceps was 5 mm. The stimulator delivered a biphasic current with a pulse frequency of 60 Hz and a single-pulse phase duration of 1 msec. The duration of each stimulation train was 3 sec. The current amplitude was progressively increased by 0.5 mA, beginning at 1 mA, until the desired responses were observed. Thereafter, we used this minimum efficient current intensity to obtain a muscle contraction or speech arrest for the rest of the mapping process. We stimulated the different cortical areas as follows. In the first stage, we mapped the primary motor and sensory cortex. We considered a stimulated site as part of the primary motor cortex when the stimulation elicited involuntary muscle contraction or speech arrest while the patient was counting. The primary sensory cortex was determined by sensory disturbances perceived by the patient upon electric stimulation. In a second stage, we conducted ESM on the exposed cortical area, stimulating every 5 mm^2 and each site at least 3 times per language. During the ESM procedure we never stimulated the same cortical area twice in succession, so as to avoid seizures, and between each set of 2 stimulations we always performed a control trial without applying electrical current.

Images from the object naming task were presented on a laptop screen, and electrical stimulation and picture presentation were synchronized in order to evaluate the effect of the electrical impulse on speech production. Patients were acquainted with the task during the presurgical neuropsychological assessment. For each patient, pictures that were incorrectly named or were not correctly identified during the presurgical evaluation were deleted from the set of images that were shown during surgery. In this way we ensured that speech arrests or language errors were produced due to electric stimulation and not to previous word retrieval difficulties for these items. The different languages were tested sequentially, and language order was partly chosen by the patient (one language-mapping session was performed after another, beginning with the most-used language, so that in the event of procedure failure, at least the most important language would already have been studied). Finally, at the end of language mapping, and to validate our findings, the language-specific sites found were confirmed by an alternative means of mapping for each language.

Sterile waterproof paper labels were placed on the brain surface in the sites where cortical stimulation caused speech arrest, paraphasia, latency, perseveration, hesitation, or errors in speech. The labels included flags corresponding to the different languages being tested. All of the language disturbances were assessed by the same senior neuropsychologist (M.J.) during the brain mapping process. Photographs were taken during the procedure (Fig. 1A).

Postoperative Protocol

We performed clinical neurological examinations in the immediate postoperative period, at the time of the patient's discharge, and at 1, 3, 6, and 12 months after surgery. Imaging follow-up was performed as follows: CT scan in the immediate postoperative period (approximately 6 hours after the procedure); MRI during the early postoperative period (within the first 72 hours); and MRI at 3, 6, 9, and 12 months after surgery. A complete neuropsychological test was administered to each patient at the 3-month follow-up visit, and this included the same tests as were used in the preoperative assessment.

Data Analysis

The location of stimulation sites in relation to the central sulcus, sylvian fissure, and sulci separating the major gyri was determined from the intraoperative photographs. To normalize this information, an arbitrary grid (similar to the one used by Ojemann et al.[37]) was placed on the individual photographs. In the frontal cortex, the grid included 1.5-cm grid segments in each gyrus, beginning with the most anterior evoked motor response on the vertical axis. On the horizontal axis the grid was determined by the major sulci dividing the superior, middle, and inferior frontal gyri. In addition, the inferior and middle gyri were divided into halves (inferior and superior) by a line parallel to the sylvian fissure. After identification of the zones to which each point belonged, the data were transferred to a model based on the same landmarks (Fig. 1A and B). For the temporal cortex on the horizontal axis, the grid was delimited by the sylvian fissure and the major

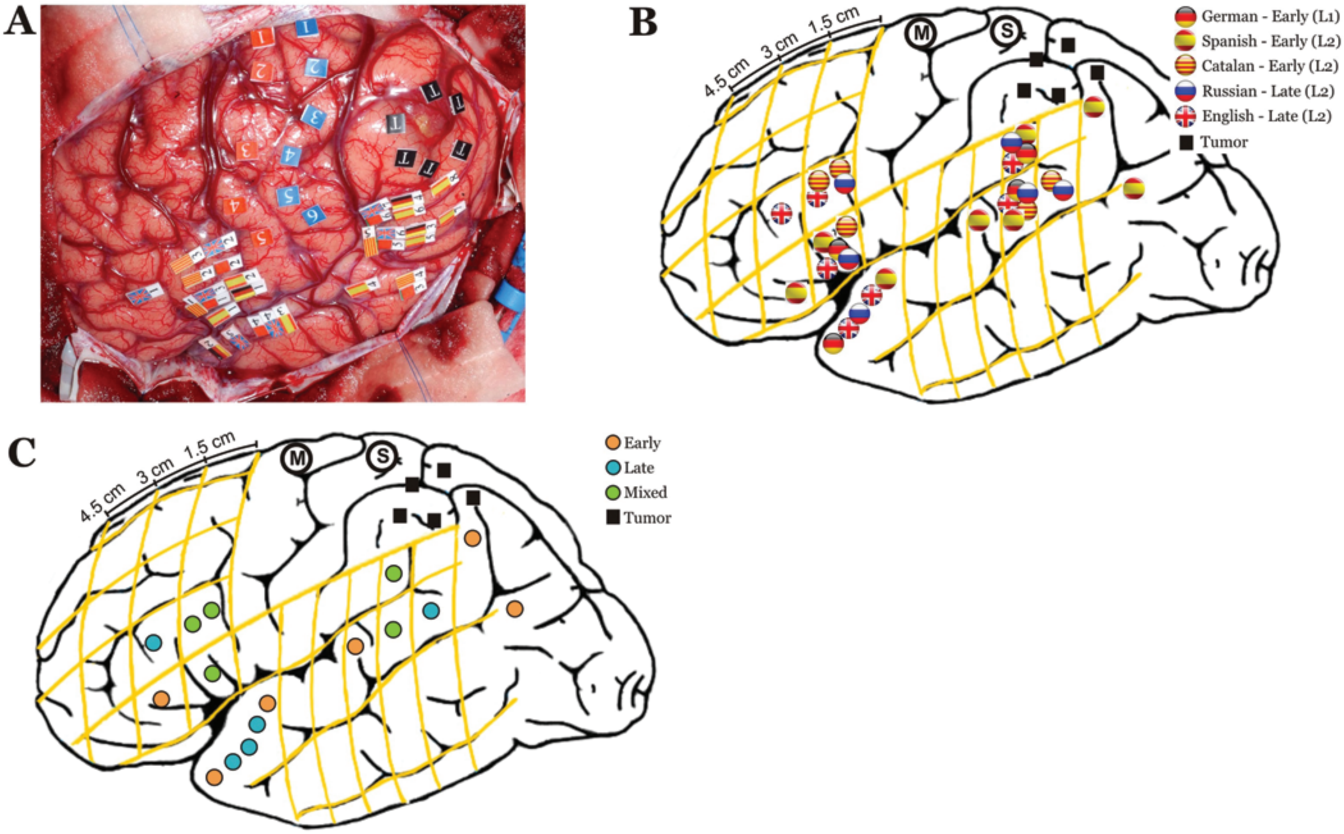

FIG. 1. Case 5. A representative example of the data recording and data processing used in this study. A photograph was taken during surgery after the completion of ESM (**A**). Sites where electric stimulation caused disturbances in the different languages were transferred onto a schematic model (**B**). For the statistical analysis we assigned each stimulated site to 1 of the following categories: early (sites where stimulation caused speech arrest only in the case of early-acquired languages), late (sites where stimulation caused speech arrest only in the case of late-acquired languages), and mixed (sites where stimulation caused speech arrest in both early and late languages) (**C**). Figure is available in color online only.

sulci dividing the superior, middle, and inferior temporal gyri. On the vertical axis the line between the foot of the central sulcus and the posterior end of the sylvian fissure was divided into fourths. Counting the area anterior to the line of the central sulcus and the area posterior to the posterior end of the sylvian fissure, both superior and middle temporal gyri were divided into 6 regions.

To evaluate the spatial distribution of the language sites in general and the language sites depending on the AoA, we divided the cortical areas into 7 anatomical regions (depicted in Fig. 2): inferior frontal gyrus, middle frontal gyrus, anterior superior temporal gyrus, posterior superior temporal gyrus, supramarginal gyrus, angular gyrus, and middle temporal gyrus. In the statistical analyses we only included the data from the first 5 regions for which we had data from all patients; descriptive data are presented from all of the regions, but the angular gyrus and middle temporal gyrus were not included in the statistical analyses because we had data for these 2 regions for only 4 and 8 patients, respectively.

We calculated the frequency of the sites where speech disturbances during language production occurred for each language and for each area delimited by the grid. After obtaining these data we calculated the proportion of language-related sites that belonged to each experimental condition: 1) early-acquired—language-related sites that responded to languages acquired before the age of 7; 2) late-acquired—language-related sites that responded to languages acquired after the age of 7; or 3) mixed—language-related sites that responded to both early- and late-acquired languages.

Results

Ten patients had 2 early-acquired languages, 2 patients had 1 early-acquired language and 1 patient had 3 early-acquired languages (all learned before the age of 7). A summary of the patients' demographic, language, and lesion characteristics is shown in Table 1.

Sites related to language production were found in the middle and inferior frontal gyri and perisylvian areas (superior and middle temporal gyri and supramarginal gyrus).

Functional cortical locations for language were identified in 12 of the 13 patients, with a total of 107 sites. Of these 107 language sites, 71 responded specifically to 1 language (66% of the total), while the remaining 36 (34% of the total) responded to more than 1 language. Of the latter group, 15 sites showed a complete overlap—that is, every language spoken by a given patient shared the same

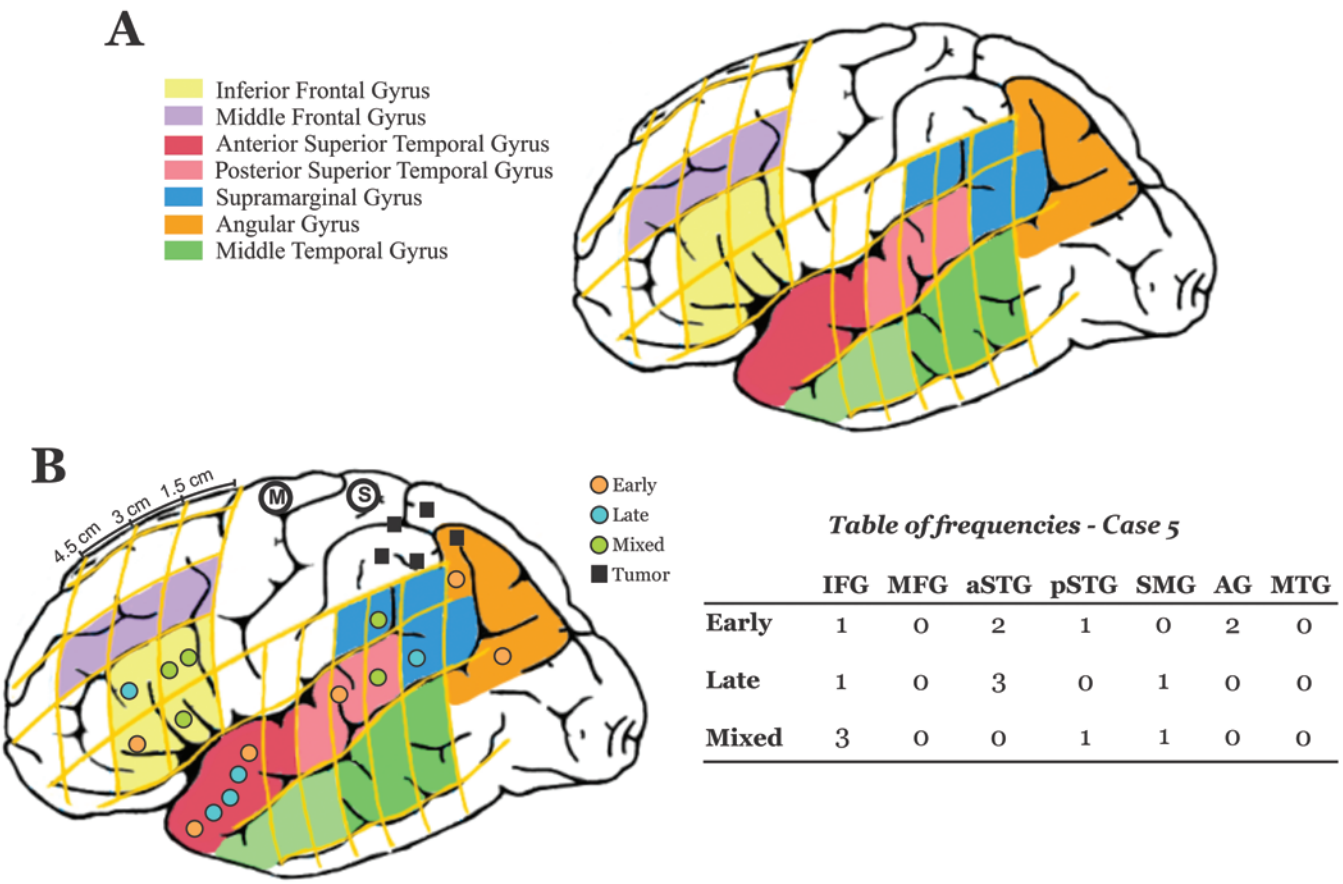

Table of frequencies - Case 5

	IFG	MFG	aSTG	pSTG	SMG	AG	MTG
Early	1	0	2	1	0	2	0
Late	1	0	3	0	1	0	0
Mixed	3	0	0	1	1	0	0

FIG. 2. Illustration of the anatomical areas that were compared in our data analysis. The image in the upper part of the figure (**A**) shows the anatomical areas superimposed over the grid. We used this model to calculate the frequency of each type of language site per area per patient, as shown in the lower part of the figure (**B**) using the example of Case 5. AG = angular gyrus; aSTG = anterior superior temporal gyrus; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; pSTG = posterior superior temporal gyrus; SMG = supramarginal gyrus. Figure is available in color online only.

location (14% of the total number of language-related sites). Interestingly, all but 1 of the patients had at least 1 site where stimulation caused speech arrest in all of the languages. In most cases (9 patients) this site was located within Broca's area (either the pars opercularis or pars triangularis), in some cases (4 patients) the location was the superior temporal gyrus, either exclusively or in addition to Broca's area, and in 2 patients the site was located in the supramarginal gyrus. In almost all instances (13 of the 15 sites), the sites that were responsive to all languages were located within the classic language areas.

We found 47 sites that responded selectively to L1. Patients had, on average, 3.92 (SD 1.93, range 2–9) stimulated sites that responded to L1. Early-acquired languages (excluding native languages) were represented in a total of 50 sites, and late-acquired languages in 70 sites. Early-acquired languages (including native languages) were represented in 97 sites. We found the following distribution of overlapping language sites (stimulated sites that responded to more than 1 language): at 7 sites (20% of the total), 2 or more early-acquired languages overlapped; at 25 sites (71% of the total), at least 1 early- and 1 late-acquired language overlapped; and at 3 sites (9% of the total), 2 or more late-acquired languages overlapped. The distribution of cortical language sites documented during intraoperative mapping is summarized in Table 2. Figure 3 provides an overview of the descriptive statistics for the distribution of language-related grid segments.

Language Distribution in the Cortex

First, we conducted a repeated-measures ANOVA with the factor "location" to study in which anatomical areas we found more sites where ESM produced language disturbances. The analysis showed a significant main effect (F[4, 44] = 9.414, $p = 0.0001$). Post hoc pairwise comparison with Bonferroni correction showed that the inferior frontal gyrus had more language sites that any other region ($p < 0.02$) except for the superior middle gyrus ($p = 0.211$). The rest of the pairwise comparisons yielded no statistically significant result (p value approximating 1).

Age of Acquisition and Language Distribution

For the purpose of studying whether the age of acquisition of a language plays a role in the cortical distribution of the language, we performed a repeated-measures ANOVA involving 2 factors: 1) location, as defined in Fig. 2; and 2) AoA, with 2 levels—early and late. We classified

TABLE 1. Patients' demographic, language, and lesion characteristics

Case No.	Sex, Age (yrs)	No. of Languages	L1	Early AoA	Late AoA	Lesion Histopathology	Lesion Growth Rate	Lesion Size (cm)*	Lesion Location
1	M, 20	3	Catalan	Catalan, Spanish	English	Gliosis	Slow	1	T
2	F, 56	3	Catalan	Catalan, Spanish	French	Metastasis	Fast	1.2	F
3	F, 25	4	Spanish	Spanish, Catalan	English, Galician	LGG	Slow	7	T
4	F, 27	4	Catalan	Catalan, Spanish	English, French	LGG	Slow	3	F
5	F, 39	5	German	German, Spanish, Catalan	Russian, English	GBM	Fast	2,5	P
6	F, 28	3	Spanish	Spanish, Catalan	English	HGG	Fast	3.5	P
7	F, 25	3	Spanish	Spanish, Basque	English	LGG	Slow	4.5	F
8	M, 32	4	Spanish	Spanish, Basque	English, French	LGG	Slow	2	F
9	M, 62	3	German	German	French, Spanish	GBM	Fast	3	F-P
10	F, 34	3	Spanish	Spanish, Catalan	English	Cavernoma	Slow	2.6	T
11	F, 39	3	German	German	Spanish, English	HGG	Fast	6.5	T-Ins
12	M, 37	3	Spanish	Spanish, Catalan	English	LGG	Slow	7	F-T-Ins
13	M, 31	3	Catalan	Catalan, Spanish	French	LGG	Slow	3.5	F

F = frontal; GBM = glioblastoma multiforme; HGG = high-grade glioma; Ins = insular; LGG = low-grade glioma; P = parietal; T = temporal.

* Maximum diameter.

as early-AoA sites those sites where electrical stimulation caused disturbance exclusively in languages acquired before the age of 7, while late-AoA sites were those where stimulation caused disturbance exclusively in language(s) acquired after the age of 7.

The results showed a difference in language representation in the perisylvian cortex based on AoA (F[1, 11] = 6.284, p = 0.029) and location (F[4, 44] = 3.800, p = 0.01); we found no interaction between the 2 factors (F[4, 44] = 1.155, p = 3.44). Post hoc pairwise comparison showed a significantly greater number of language sites in the inferior frontal gyrus compared with the middle frontal gyrus (p = 0.028); however, we found no differences between the other regions.

These results show that there are more early-specific language sites than late-specific sites throughout the cortex, irrespective of the location of the stimulated area.

Tumor Growth Rate and Effect of Lesion Proximity in Language Distribution

Next we investigated if tumor growth rate influenced the location of language sites. This was done by means of a repeated-measures ANOVA with 2 within-group factors (location and AoA) and 1 between-groups factor (growth rate, with 2 levels, slow and fast). The analysis showed neither a main effect of growth rate (F[1, 10] = 1.77, p = 0.212) nor an interaction of growth rate with either of the other 2 factors (F < 2, p > 0.2 in all cases). In almost all cases, language areas were not encountered within the tumor cortical boundaries. Only one language site was encountered within the cortical border of the tumor extension, and this occurred in Case 5.

Stimulated Sites That Respond to More Than 1 Language

We then conducted further analyses to evaluate what type of overlap was predominant. As the number of language sites where 2 or more languages overlapped was limited, we used Friedman's nonparametric test to compare the following conditions: 1) early-early (where 2 or more early languages overlapped regardless of whether one of them was L1), 2) late-late (where 2 or more late languages overlapped), and 3) early-late (where at least 1 early and 1 late language overlapped). The frequency of each type of overlap was calculated. Friedman's test confirmed there was a significant difference between the 3 types of overlaps (χ^2 = 16.33, p = 0.0001). As we found differences between conditions we then compared them with Wilcoxon's signed-rank test, which showed that both early-early and late-late overlaps differed from early-late overlaps, but early-early and late-late did not differ from one another (early-early vs late-late: Z = −0.87, p = 0.380; early-early vs early-late: Z = −2.79, p = 0.005; late-late vs early-late: Z = −3.03, p = 0.002). Thus, there was no statistically significant difference between the number of early-early overlaps and the number of late-late overlaps, but the number of early-late overlaps was significantly greater than the numbers of each of the other 2 kinds.

Complications and Follow-Up

One patient had intraoperative electrical seizures lasting a few seconds and rapidly disappearing after irrigation with cold saline, and another had immediate postoperative seizures. Both episodes were partial seizures, and in one of these cases the patient was found to have a low serum level of the antiepileptic drug that he had been taking since diagnosis of his tumor. Other complications were pulmonary atelectasis (1 patient) and upper-extremity phlebitis related to venous puncture (1 patient), both of which had resolved completely at discharge.

In the immediate postoperative period, language function worsened in 11 patients (85%) and showed no change in 2 patients (15%). Motor function worsened in 3 patients (23%) and sensory deficit was observed in 1 patient (7.7%). The language deficit was transient for 10 of the 11 patients (91%), and full recovery was achieved within 2–10 days. Postoperative neuropsychological tests showed a perma-

TABLE 2. Cortical language sites per patient*

					Types of Overlap			Location of Language Sites				
Case No.	Total No. of Language-Related Sites†	Languages	No. of Sites per Language‡	No. of Sites w/ Overlap per Language§	Early–Early	Early–Late	Late–Late	Frontal	Temporal	Parietal	Classic	Nonclassic
1	5	**Catalan**	**2**	**2**	1	2	0	3	3	3	8	1
		Spanish	**4**	**3**								
		English	3	2								
2	8	**Catalan**	**3**	**1**	0	1	0	10	0	0	6	4
		Spanish	**5**	**1**								
		French	2	1								
3	0	**Spanish**	**0**	**0**	0	0	0	0	0	0	0	0
		Catalan	**0**	**0**								
		English	0	0								
		Galician	0	0								
4	21	**Catalan**	**9**	**5**	3	2	0	21	6	2	10	19
		Spanish	**7**	**4**								
		English	6	2								
		French	7	2								
5	16	**German**	**4**	**3**	0	5	0	11	14	5	24	6
		Spanish	**8**	**4**								
		Catalan	**5**	**5**								
		Russian	6	6								
		English	7	5								
6	4	**Spanish**	**4**	**3**	1	2	0	5	3	0	5	3
		Catalan	**2**	**2**								
		English	2	2								
7	5	**Spanish**	**2**	**2**	1	2	0	0	3	6	5	4
		Basque	**5**	**3**								
		English	2	2								
8	10	**Spanish**	**5**	**2**	1	2	0	10	3	2	9	6
		Basque	**5**	**4**								
		English	4	2								
		French	1	1								
9	10	**German**	**4**	**2**	0	2	2	7	5	4	13	3
		French	6	4								
		Spanish	6	4								
10	4	**Spanish**	**3**	**1**	0	1	0	5	1	0	6	0
		Catalan	**2**	**1**								
		English	1	1								
11	11	**German**	**5**	**3**	0	3	1	9	4	5	8	10
		Spanish	7	4								
		English	6	4								
12	5	**Spanish**	**2**	**2**	0	2	0	4	3	0	3	4
		Catalan	**3**	**0**								
		English	2	2								
13	8	**Catalan**	**4**	**1**	0	1	0	7	3	0	6	4
		Spanish	**4**	**1**								
		French	2	1								

* Spatial and functional distribution of the language-related sites is summarized in the table for each patient. Boldface type indicates early-acquired languages (including the patient's native language [L1]).

† The number of stimulated sites per patient that responded to at least 1 language.

‡ The number of language-related sites that responded to a given language (since 1 site could respond to multiple languages, the sum of the sites per language can be greater than the total number of language-related sites).

§ The number of sites within each language that responded to other languages in addition to the language in question.

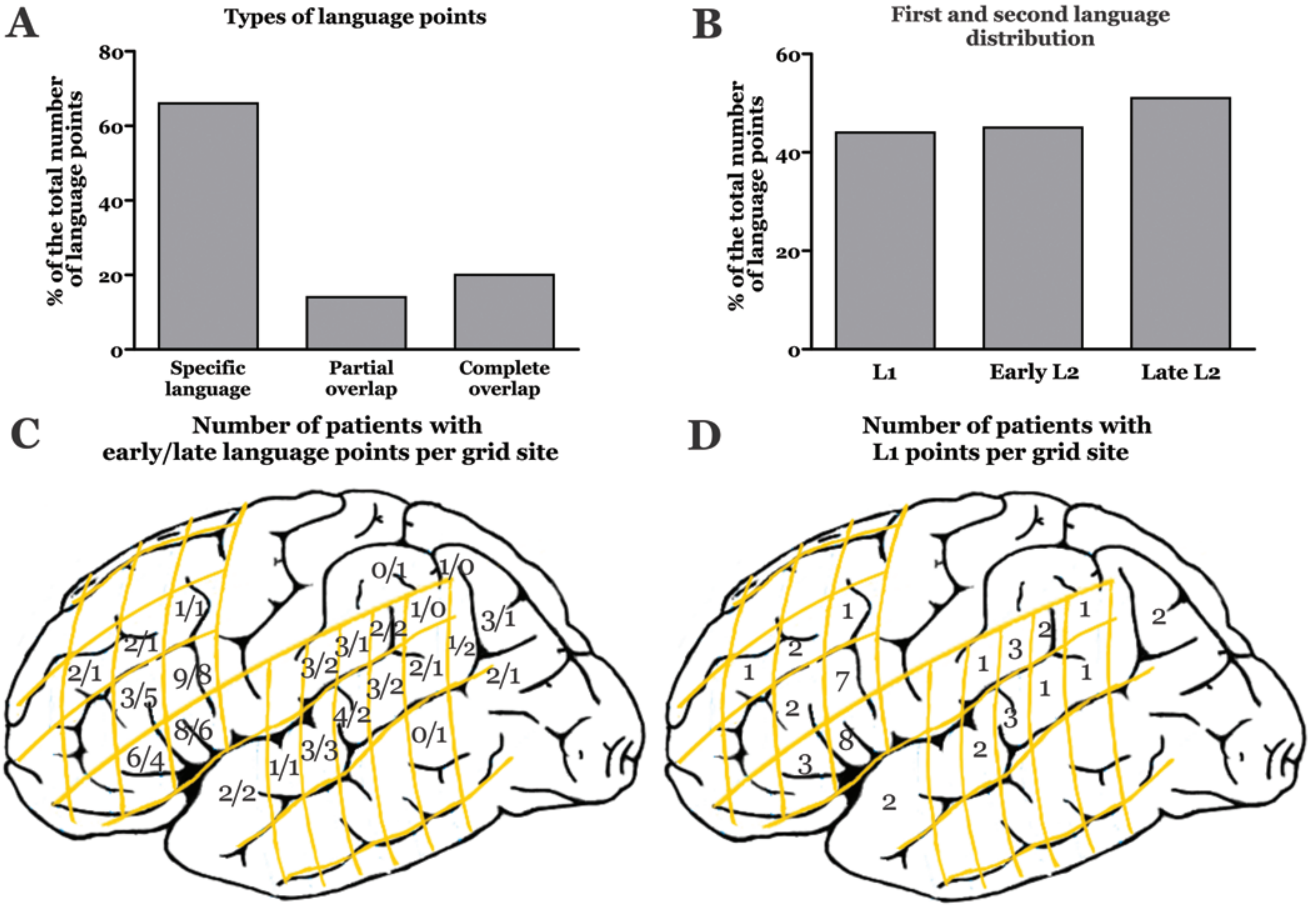

FIG. 3. Spatial distribution of the language-related sites as a function of AoA. **A:** Percentage of language-related sites that responded to only 1 specific language, to several but not all languages (partial overlap), and to all the languages the patient spoke (complete overlap). **B:** Percentage of language sites that responded to L1, early L2, and late L2. Because there can be an overlap between these categories, the values add up to more than 100. **C and D:** The numbers within each grid segment represent the number of patients who had 1 or more sites within the grid area that responded to early (L1 included) and late languages (C) and L1 (D). Figure is available in color online only.

nent impairment of language function (mild dysphasia) in 1 patient (7.7%) at the end of the follow-up period.

The extent of resection, evaluated by postoperative MRI, was complete (gross total) in 9 cases and subtotal or partial in 4 cases. Among the latter group, the extent of resection was greater than 95% (subtotal) in 2 cases and 70%–95% (partial) in the other 2 cases.

Discussion

With regard to cerebral language organization in patients who speak 2 or more languages, debate continues as to whether the different languages are located in the same or different brain areas. This question is not only of academic interest but also has profound clinical importance in terms of preserving language function during a neurosurgical procedure, such as might be carried out in the context of epilepsy or a brain tumor. Clinical and experimental studies employing ESM have yielded heterogeneous results, ranging from a complete overlap among the cortical representation of different languages, through an organization that is partially overlapped in common areas and partially separated in specific areas,[4,7,31,38,47,52,53,54,56] to spatially distinct cortical areas for each language. Given these contradictory results it is recommended that intraoperative mapping be performed for all the languages the patient speaks fluently in order to preserve functional integrity.

In this cortical stimulation study we focused on how age of language acquisition influences the cortical spatial organization of language in 13 polyglot patients, taking advantage of the unique situation in Spain, where Spanish coexists alongside other Romance and non-Romance languages such as Catalan, Galician, or Basque. In fact, many Spanish citizens consider their regional language to be their mother tongue and Spanish their second language. Consequently, our selected patients constitute an ideal example of a highly proficient multilingual group.

Several studies indicate that the age limit for acquiring complete and correct pronunciation and grammar of a given language is about 6–8 years,[14,20,23] suggesting that late learners are typically less proficient than early learners, since most forms of late language acquisition are unlikely

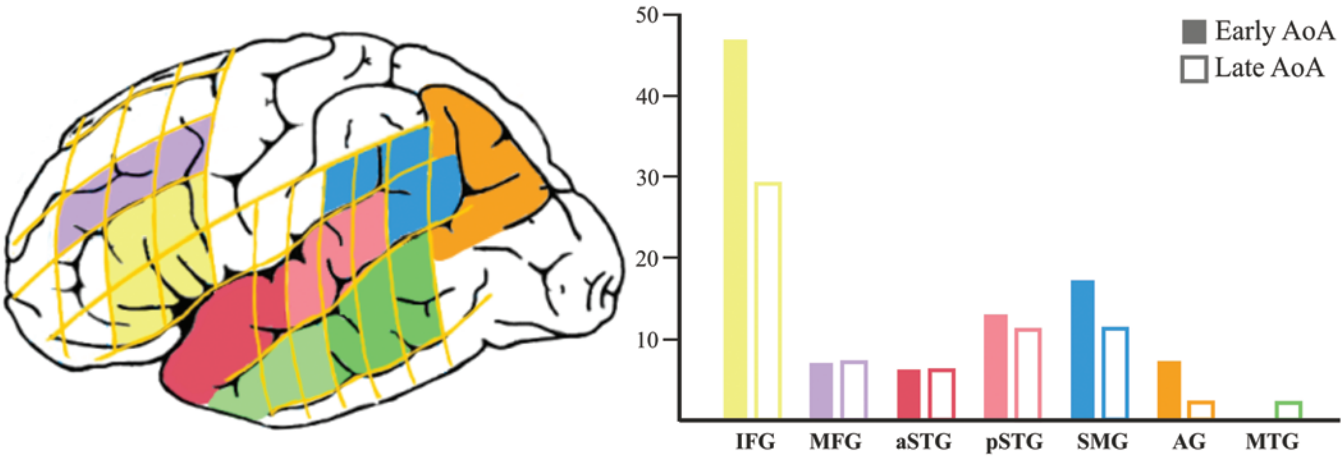

FIG. 4. Cortical distribution for language functional sites in terms of age at the time of language acquisition. Figure is available in color online only.

to lead to native-level competence. Given that the consensus in the aforementioned studies is that the critical period for language learning ends around 7 years of age, we used this age to differentiate between early-acquired and late-acquired languages in our study. It is also important to note that more recent literature[28,42] argues that it is the lack of proficiency rather than age of acquisition that determines the recruitment of nonclassic areas for word processing. As stated earlier, our patients used their second acquired languages in their everyday life, but there was no case of "inverted proficiency," as reported by Leonard,[28] because they kept their native language as the dominant language.

Our results identified a total of 47 native language sites. Early-acquired languages (excluding native languages) were represented in a total of 50 sites and late-acquired languages in 70, there being no statistically significant differences with respect to age of language acquisition. These results are in agreement with other ESM studies in bilingual patients,[31,53] showing a similar cortical representation for early- and late-acquired languages.

The only previous ESM study of multilingual patients reported greater representation for the first acquired language in comparison with the second or further acquired languages.[4] In our study, if we consider together the amount of language sites for the native language and languages that were learned before the age of 7 years (early-acquired languages), these languages have a greater representation than those languages acquired subsequently (late-acquired languages). These results contrast with the findings of other fMRI studies.[1,5,6,41,42,55,58] To explain the discrepancy, it is important to bear in mind that the higher workload or effort needed for processing L2s seems to be responsible for the enhanced activation in fMRI. However, it seems that this is not the "real" language-specific site activation, since fMRI is tied to the stimulus modality, thus confounding critical and participating language areas[18] and demonstrating a sensitivity of around 66% for language areas.[51] By contrast, ESM provokes temporary functional inhibition in a specific cortical critical site, and it is thus a more precise and reliable method. Furthermore, it is worth noting that the acquisition of the second and further languages is a dynamic process that depends not only on the age of acquisition but also on the level of proficiency.[42] Taking this into account, and given also that our patients form a highly specific group with high proficiency in all their corresponding languages, it is not surprising that the secondary acquired high proficiency languages showed a similar cortical representation to native and nonnative early-acquired languages.

Although we found no statistically significant effect for AoA in terms of cortical prevalence, we did find more language sites in Broca's area (inferior frontal gyrus), the posterior superior temporal gyrus, and the supramarginal gyrus (Fig. 4), which is consistent with other classic ESM studies.[36,37] If we take into account only the native language, we observed a trend toward greater representation in the posterior Broca's area. Early-acquired languages (including the native language) tend to be largely represented within the perisylvian left hemisphere frontoparietotemporal areas and are overlapped. These results suggest that early-acquired languages may recruit the same neuronal networks and, therefore, have similar cortical language representation, as reported in previous studies.[5,27,28] In other words, we can hypothesize that native and other languages acquired early in life, in parallel with cerebral cortex development, are initially "fixed" in classic regions.

The location of language sites in our study was distinct and separate for 71 sites (66%) and overlapped in 36 (34%). In terms of age of language acquisition, the distribution of cortical language sites documented during intraoperative mapping is summarized in Table 2. The analysis showed that age of language acquisition had a statistically significant effect on the overlapping cortical distribution: 7 sites for early-early overlap, 25 sites for early-late overlap, and 3 sites for late-late overlap, indicating that overlap was much more common among early-acquired and late-acquired languages.

In the field of psycholinguistics, proficiency and age of acquisition of a given second language have been a controversial topic of debate in relation to cortical organization in the bilingual or multilingual brain. The "crystallization hypothesis" suggests that the later a second language is learned, the more the cortical representations of the second and first languages will differ. However, the level of

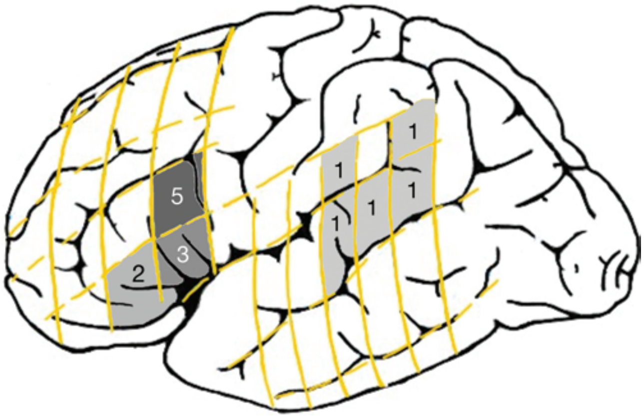

FIG. 5. Spatial representation of the all of the overlapping language sites for the 13 patients—language "epicenters," where all languages spoken by a given patient share the same location. The numbers in the figure indicate the number of patients for whom the indicated area included a language epicenter. Figure is available in color online only.

proficiency, more than the age of acquisition, seems to be the predictor of early- and late-acquired language–related sites.[11,42] In this context, our results showing a predominance of overlap between early-acquired language sites and late-acquired language sites would seem to support the latter hypothesis, bearing in mind that our group of patients can be considered an exceptional set of high-proficiency individuals.

Despite the high percentage of overlapping sites in our patients, we found more language-specific sites for each different language. This finding has also been reported in previous fMRI and ESM studies.[27,31,32,37,51,53,56] It should also be noted that overlapped sites tended to be located within the classic so-called perisylvian areas; these distinct and separate sites were located both within and outside the perisylvian region, as well as in both frontal and temporoparietal areas, in agreement with most reports.[30,44,52,53]

Notably, 15 sites showed a complete overlap; that is, every language spoken by a given patient shared the same location. Interestingly, these sites tended to be located within the inferior frontal gyrus (Broca's area) and the supramarginal gyrus (Fig. 5). Functional imaging, lesion, transcranial, and direct brain stimulation studies[3,8,9,15,21,22,25,26,34,35,45,46,48] support the direct relationship between frontal and posterior temporoparietal areas in language switching. A more recent review[34] of the previous findings proposed a new hodological model of language switching and also highlighted the fundamental role of these cortical epicenters that match with the complete-overlap regions in our study. In almost all instances (13 of the 15 sites), these sites that were responsive to all languages were located within the classic perisylvian language areas. We hypothesize that these important functional sites characterized by overlapping of all languages in a multilingual patient play an important role in language selection and, therefore, must be preserved while operating on this location.

The functional language-related sites were distributed as follows: 55% in the frontal lobe, 29% in the temporal lobe, and 16% in the parietal lobe. Of all the sites identified as essential for language in this study, 38% were outside the sites accepted by classical models. Although there were more language-related sites in the perisylvian region, our results show that there are more early-specific language sites than late-specific sites throughout the cortex irrespective of the location of the stimulated area. The unpredictability of functional eloquence has previously been reported.[12,43] Nonetheless, the trend is for early-acquired languages to be represented in classical areas, as shown in Fig. 4. Our results highlight that due to major interindividual anatomofunctional variability, relying solely on anatomical considerations is not sufficient when it comes to deciding which surgical tissue can or cannot be removed without the risk of permanent postoperative deficits.

Finally, it is important to consider whether tumor growth rate may affect the distribution of language sites in the different languages tested. This is especially crucial when treating patients with brain tumors, as areas of cortical eloquence may vary dramatically from one patient to another due to brain plasticity–related changes produced by a growing intrinsic lesion. Lubrano et al.,[29] in an ESM study, found displacement of critical structures by mass effect for circumscribed lesions, as well as reshaping that they attributed to brain plasticity in infiltrating lesions. Given the rarity of our specific patient group, our sample size is insufficient to enable us to assess all the relevant aspects of tumor properties. This is potentially a major drawback of our study, as we studied with ESM only patients who harbored lesions that may modify language organization. Although our results cannot be extrapolated to the general population, they remain valid for neurosurgeons dealing with lesions located in eloquent language areas in multilingual patients.

Only 1 language site was encountered within the cortical border of the tumor extension, and this was in Case 5, involving a highly aggressive small glioblastoma. On the other hand, we found a clear trend to displace language function in cases of slow-growing large infiltrating lesions; Cases 3, 7, and 12 are representative. The patient in Case 3 harbored a 7-cm low-grade glioma in the left, dominant hemisphere. No functional area was encountered during brain mapping in this patient, despite bilateral preoperative activation for language tasks in fMRI, thus suggesting a change in essential language areas due to brain plasticity. The patient in Case 7 had a 4.5-cm frontal low-grade glioma, and ESM showed no language sites in the frontal lobe. Finally, the patient in Case 12 had a 7-cm frontotemporo-insular low-grade glioma showing extension to the frontal operculum, and no language function was encountered in this otherwise commonly eloquent region.

Craniotomy size is considered a classical limitation in language ESM studies, as it reduces the chances of finding functional areas. However, in contrast to the only other published study to date in multilingual patients,[4] in which the authors only found eloquent language areas in the frontal lobe, we systematically performed a wide frontotemporoparietal craniotomy, which allowed us to have good exposure of the entire perisylvian region in each patient.

Conclusions

The distribution of cortical language areas in multilingual patients is not homogeneous, and it is influenced by language acquisition time, since early-acquired languages have a greater cortical representation than those that are acquired subsequently. The prevalent native and early-acquired languages are largely represented within the perisylvian left hemisphere frontoparietotemporal areas, and the less prevalent late-acquired languages are mostly overlapped with them. A large percentage of functional language cortical spots are located away from the theoretical anatomical location and not overlapped. These findings indicate that age of language acquisition, which is intrinsically linked to proficiency, plays a fundamental role in the highly variable interindividual cortical language organization in multilingual patients.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Fernández-Coello, Gabarros. Acquisition of data: Fernández-Coello, Juncadella, Gabarros. Analysis and interpretation of data: Fernández-Coello, Havas, Sierpowska, Rodriguez-Fornells. Drafting the article: Fernández-Coello. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fernández-Coello. Statistical analysis: Havas.

Supplemental Information

Previous Presentations

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