

Variability of intraoperative electrostimulation parameters in conscious individuals: language cortex

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OBJECTIVE Electrostimulation in awake brain mapping is widely used to guide tumor removal, but methodologies can differ substantially across institutions. The authors studied electrostimulation brain mapping data to characterize the variability of the current intensity threshold across patients and the effect of its variations on the number, type, and surface area of the essential language areas detected.

METHODS Over 7 years, the authors prospectively studied 100 adult patients who were undergoing intraoperative brain mapping during resection of left hemisphere tumors. In all 100 cases, the same protocol of electrostimulation brain mapping (a controlled naming task—bipolar stimulation with biphasic square wave pulses of 1-msec duration and 60-Hz trains, maximum train duration 6 sec) and electrocorticography was used to detect essential language areas.

RESULTS The minimum positive thresholds of stimulation varied from patient to patient; the mean minimum intensity required to detect interference was 4.46 mA (range 1.5–9 mA), and in a substantial proportion of sites (13.5%) interference was detected only at intensities above 6 mA. The threshold varied within a given patient for different naming areas in 22% of cases. Stimulation of the same naming area with greater intensities led to slight changes in the type of response in 19% of cases and different types of responses in 4.5%. Naming sites detected were located in subcentimeter cortical areas (50% were less than 20 mm²), but their extent varied with the intensity of stimulation. During a brain mapping session, the same intensity of stimulation reproduced the same type of interference in 94% of the cases. There was no statistically significant difference between the mean stimulation intensities required to produce interference in the left inferior frontal lobe (Broca's area), the supramarginal gyri, and the posterior temporal region.

CONCLUSIONS Intrasubject and intersubject variations of the minimum thresholds of positive naming areas and changes in the type of response and in the size of these areas according to the intensity used may limit the interpretation of data from electrostimulation in awake brain mapping. To optimize the identification of language areas during electrostimulation brain mapping, it is important to use different intensities of stimulation at the maximum possible currents, avoiding afterdischarges. This could refine the clinical results and scientific data derived from these mapping sessions.

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KEY WORDS electrostimulation; language; brain tumor; brain mapping; awake surgery; diagnostic and operative techniques; oncology

ELECTROSTIMULATION in awake patients has been used intensively in neurosurgery to map language functions, and a large body of work has been published on the subject.^{13,24,32} Debates have primarily focused on the types of tasks considered the best predictors of language outcome, and naming has long been used for this purpose.¹⁸ Although the technique has become popular over the last 20 years, it must be acknowledged that the practice of electrostimulation for brain mapping relies mainly on empirical data. Studies that have investigated the optimal stimulation parameters for human brain mapping (intensity

of stimulation, duration of stimulation, extent of the stimulated area) are relatively rare.^{8,15,26,28,36,38} However, the parameter of intensity of stimulation alone may vary across individuals²⁶ or with age⁷ or with the presence of cerebral edema,³⁸ for instance, and questions about this most basic mapping parameter are still numerous. What is the “optimal” intensity to detect essential language sites for naming? Does this optimal intensity of stimulation vary with the task used or across the cortex (some language areas being detected at different levels of intensity)? Does the stimulation threshold differ across the exposed cortex (frontal

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versus temporal, for instance)? Could the variation of the level of intensity at a given essential site lead to a different type of response (e.g., anomia at 3 mA but speech arrest at 5 mA)? These questions are important if a standardized stimulation protocol is to be used by all practitioners to improve the accuracy of the procedure, the safety of the patient, and the comparability of the resulting scientific data among the different neurosurgical centers worldwide.

In 2008, we decided to design a prospective study that would include a substantial number of patients studied with the same protocol over many years. This protocol, based at that time on our 10 years' experience in awake brain mapping by electrostimulation,³¹ needed to be simple enough to be applicable to a large number of patients and reproducible by other neurosurgical teams. Although Penfield and Roberts^{23,24} used at least 3 different stimulators, the works of Ojemann et al.¹⁸ popularized the use of bipolar electrodes with biphasic square wave pulses, each of 1-msec duration, at 60 Hz with a maximum stimulation duration of 4 seconds. These standard parameters of stimulation were used in this study, which was intended to clarify 3 main points: 1) What is the minimum intensity required to observe naming interference in awake patients? 2) Does the type of naming interference observed differ according to the level of stimulation? 3) Can we accurately discern the real surface area of these interferences? In addition to these main points, we also wanted to test secondary issues, such as the range of intensities evoking interference according to the gyri simulated and whether the type of interference was reproducible over a given area during a brain mapping session at constant intensity.

Methods

Inclusion Criteria

This was a prospective study. From the outset, our plan was to close the study once 100 brain mappings had been included. We studied electrostimulation data from brain mappings performed for the removal of recently discovered brain lesions in conscious individuals (mean age 52 years, range 20–79 years, SD 6 years, 42 women) (Table 1). The lesions included 29 WHO Grade I and II gliomas, 46 WHO Grade III and IV gliomas, 8 arteriovenous malformations or cavernomas, 16 metastases, and 1 atypical meningioma, and the mean time between the first clinical sign and the operation was 35 days (range 14–86 days). Data from the brain mapping sessions were prospectively collected by the same team using the same protocol throughout the 7 years of the study (June 2008–April 2015). The National Consultative Ethics Committee (Comité Consultatif National d'Éthique) of INSERM (Institut National de la Santé et de la Recherche Médicale) gave its approval for the storage of patients' data and procedures to ensure preservation of their anonymity. All of the patients and in most cases also their families gave their informed consent for study of their functional areas by direct brain mapping. All patients underwent an assessment of handedness²² and standardized, preoperative language tests (administered by our speech therapist) as follows: visual naming using the DO80 test (this test was also performed postoperatively in all cases, between 2 days to 2 weeks after the operation);⁵

tests of written, auditory, and visual comprehension abilities; and oral fluency, reading, dictation, repetition, written transcription, and object handling tests.¹⁶

Exclusion Criteria

Not all consecutive patients who underwent awake surgery were included in this study. Ten dysphasic patients (with an error rate greater than 10% in the DO80 naming test) and patients with chronic epilepsy were initially excluded. Eleven additional patients were excluded subsequently because they were unable to perform the naming task accurately for various reasons: 2 patients were unable to awake correctly for brain mapping; 6 patients experienced spontaneous naming difficulties between the preoperative language test and the operation; and in 2 patients brain mapping was constrained by clinical requirements (brain swelling in 1 case and subarachnoid hemorrhage at the dura opening in the other). One patient younger than 18 years old was also excluded. Age can be a confounding factor for calculating the intensity of stimulation during brain mapping sessions.¹⁹

Anesthetic Protocol for Awake Craniotomy

Patients were all operated on using the “awake surgery” technique. Anesthetic drugs can, in theory, interfere with stimulation thresholds. Our objective during brain mapping was to avoid any anesthetic drugs. One hour before admission to the operating room, a patch containing a eutectic mixture of prilocaine (2.5 mg/g) and lidocaine (2.5 mg/g) (EMLA) was applied in the supraorbital and auriculotemporal regions. Lidocaine 1% with epinephrine 1:100,000 was infiltrated to block the supraorbital, auriculotemporal, and occipital nerves. Additionally, the Mayfield head holder (Ohio Medical) pin site and the surgical skin incision line were infiltrated. Sedation with spontaneous respiration was provided by continuous infusion of propofol (1–3 mg/kg/hr). Fentanyl (1–3 µg/kg/hr) or remifentanyl (0.01–0.25 µg/kg/hr) was used for analgesia. The depth of procedural sedation was adjusted to maintain acceptable comfort and stable vital signs in the patient. Propofol infusion was stopped during the dural opening (around 10 minutes before brain mapping). Once the cortical mapping procedure was completed, patients were put back to sleep using the same protocol for the rest of the operation.

Cortical Mapping

Basic Procedure

Our standard protocol has been described elsewhere.^{29,31} Briefly, a neuronavigational system was used in all 100 cases to guide tumor removal, and intraoperative cortical stimulation was used to localize areas of functional cortex. Anatomical structures (gyri and sulci) were identified according to the neuronavigational data and the visual identification of the shape of gyri and sulci (i.e., 3D anatomy of the circumvolutions). Before starting a direct cortical stimulation procedure, we chose a substantial number of sites on the brain surface. Each site was separated from the others by 3 mm. The number of stimulation sites varied among patients depending on the size and the location of the craniotomy.

TABLE 1. Summary of patient data

Case No.	Sex	Age (yrs)	Main Symptoms	Tumor Location	Pathology	DO80 Score*	
						Preop	Postop
1	F	60	Seizures	AG, SMG	Metastasis	75	76
2	M	64	Seizures	MTG	Astrocytoma, Gr III	78	74
3	F	35	Headaches	SFG	Astrocytoma, Gr II	78	79
4	M	67	Seizures	MTG, ITG	Astrocytoma, Gr III	76	77
5	F	66	Headaches	Insula	Glioblastoma	78	73
6	M	71	Gerstmann syndrome	SMG	Metastasis	76	74
7	F	45	Seizures	SFG, MFG	Astrocytoma, Gr III	77	78
8	M	60	Seizures	STG, MTG	Glioblastoma	77	79
9	M	57	Motor defect	Insula	Ependymoma, Gr II	70	75
10	F	31	Seizures	MFG, IFG	Cavernoma	80	80
11	M	36	Headaches	RF, SMG	Cavernoma	78	79
12	M	54	Asymptomatic	IFG	Astrocytoma, Gr II	76	73
13	M	28	Seizures	ITG	Ependymoma, Gr III	79	77
14	M	67	Seizures	MTG	Glioblastoma	78	72
15	F	25	Seizures	STG	Ganglioglioma, Gr I	79	79
16	M	50	Seizures	IFG	Glioblastoma	73	69
17	F	31	Headaches	MFG, IFG	Astrocytoma, Gr II	79	76
18	M	59	Seizures	STG	Astrocytoma, Gr III	75	71
19	M	54	Seizures	STG, MTG	Astrocytoma, Gr III	80	77
20	F	54	Speech disorders	RF, SMG	Metastasis	78	73
21	M	49	Asymptomatic	IFG	Oligodendroglioma, Gr II	80	80
22	M	50	Seizures	RF, IFG	Glioblastoma	72	65
23	F	69	Seizures	SMG	Glioblastoma	77	75
24	F	38	Seizures	MTG	Astrocytoma, Gr II	77	78
25	M	79	Seizures	SMG	Glioblastoma	77	71
26	M	41	Seizures	STG, SMG	Astrocytoma, Gr II	78	73
27	M	68	Speech disorders	AG, SMG	Glioblastoma	76	77
28	M	47	Seizures	SMG	Ganglioglioma, Gr I	79	74
29	M	70	Seizures	STG	Glioblastoma	79	73
30	M	53	Seizures	SMG	Metastasis	78	79
31	M	76	Seizures	MTG	Astrocytoma, Gr II	78	75
32	M	57	Asymptomatic	STG, MTG	Astrocytoma, Gr II	75	74
33	F	47	Seizures	IFG, RF	Oligodendroglioma, Gr III	77	80
34	M	54	Seizures	AG	Glioblastoma	78	76
35	M	74	Speech disorders	STG, SMG	Metastasis	80	80
36	M	25	Sensory defect	MFG	Cavernoma	80	80
37	F	57	Seizures	IFG	Glioblastoma	78	79
38	M	36	Seizures	SMG	Astrocytoma, Gr III	80	80
39	M	54	Seizures	MFG	Glioblastoma	80	80
40	M	44	Seizures	SFG	Astrocytoma, Gr III	79	80
41	F	69	Headaches	MTG	Glioblastoma	77	75
42	M	47	Seizures	RF, SFG	Metastasis	80	80
43	M	66	Sensory defect	RF	Glioblastoma	72	73
44	F	64	Asymptomatic	RF	Metastasis	80	80
45	F	60	Facial palsy	RF, IFG	Glioblastoma	77	76
46	M	28	Memory troubles	STG, hippocampus	Ganglioglioma, Gr I	79	80
47	M	49	Seizures	STG, MTG	Astrocytoma, Gr III	80	78
48	F	32	Seizures	MTG	Cavernoma	77	75

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TABLE 1. Summary of patient data

Case No.	Sex	Age (yrs)	Main Symptoms	Tumor Location	Pathology	DO80 Score*	
						Preop	Postop
49	M	21	Seizures	IFG	Xanthoastrocytoma, Gr I	80	80
50	F	35	Headaches	SFG	Astrocytoma, Gr III	78	79
51	F	77	Speech disorders	MFG, IFG	Glioblastoma	74	70
52	F	40	Seizures	IFG	Atypical meningioma	80	80
53	F	58	Headaches	STG, MTG	Glioblastoma	78	80
54	F	79	Seizures	MFG, IFG	Glioblastoma	77	74
55	M	40	Headaches	SFG	Metastasis	80	80
56	M	57	Seizures	MFG	Oligodendroglioma, Gr II	78	77
57	M	43	Hemorrhage	STG, hippocampus	Astrocytoma, Gr II	76	74
58	F	67	Speech disorders	SMG	Oligodendroglioma, Gr III	78	74
59	F	52	Hemiparesis	SMG	Ependymoma, Gr II	80	79
60	M	50	Speech disorders	MFG	Glioblastoma	75	76
61	M	58	Apraxia	SMG	Glioblastoma	79	73
62	F	33	Seizures	ITG	Cavernoma	80	80
63	M	36	Seizures	MFG	Oligodendroglioma, Gr II	78	80
64	F	66	Speech disorders	IFG	Glioblastoma	79	74
65	M	72	Seizures	AG	Metastasis	79	80
66	F	64	Seizures	MTG	Glioblastoma	72	71
67	F	64	Seizures	AG	Metastasis	78	75
68	F	55	Motor defect	SFG, MFG	Metastasis	78	78
69	F	67	Seizures	STG, MTG	Glioblastoma	77	76
70	M	63	Motor defect	IFG	Glioblastoma	79	77
71	M	20	Seizures	STG	Astrocytoma, Gr I	76	76
72	M	68	Seizures	IFG	Oligodendroglioma, Gr II	80	78
73	M	31	Asymptomatic	STG, MTG	Oligodendroglioma, Gr II	80	80
74	M	57	Speech disorders	STG, SMG	Astrocytoma, Gr II	78	75
75	M	73	Seizures	STG, MTG	Cavernoma	76	75
76	M	22	Seizures	STG, MTG	Astrocytoma, Gr II	79	78
77	F	52	Speech disorders	STG, SMG	Cavernoma	79	80
78	M	46	Headaches	SFG	Cavernoma	80	80
79	F	37	Seizures	MTG	Ganglioglioma, Gr I	80	80
80	M	22	Seizures	MFG	Metastasis	80	80
81	M	56	Hemiparesis	SMG	Metastasis	78	79
82	F	42	Hemiparesis	RF	Metastasis	80	80
83	F	57	Hemiparesis	SFG	Glioblastoma	77	78
84	M	67	Asymptomatic	RF, IFG	Glioblastoma	75	75
85	M	62	Speech disorders	SMG	Glioblastoma	72	65
86	F	46	Seizures	STG, MTG, insula	Astrocytoma, Gr II	78	76
87	F	68	Seizures	IFG	Astrocytoma, Gr III	76	73
88	F	37	Speech disorders	Insula	Astrocytoma, Gr III	77	80
89	F	47	Seizures	MFG, IFG	Glioblastoma	72	79
90	M	68	Speech disorders	AG, SMG	Glioblastoma	74	74
91	M	48	Seizures	IFG, MFG	Oligodendroglioma, Gr II	77	76
92	F	30	Seizures	SFG	Ganglioglioma, Gr I	79	79
93	F	68	Seizures	IFG, MFG	Glioblastoma	72	69
94	M	51	Seizures	SFG, MFG	Astrocytoma, Gr II	80	80
95	M	35	Seizures	RF	Oligodendroglioma, Gr II	80	80

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TABLE 1. Summary of patient data

Case No.	Sex	Age (yrs)	Main Symptoms	Tumor Location	Pathology	DO80 Score*	
						Preop	Postop
96	M	47	Seizures	RF, MFG	Metastasis	79	77
97	M	42	Seizures	IFG, MFG, SFG	Astrocytoma, Gr II	80	80
98	F	69	Seizures	AG	Metastasis	72	61
99	F	69	Speech disorders	MTG	Glioblastoma	73	72
100	F	77	Speech disorders	MFG, IFG	Glioblastoma	72	69

AG = angular gyrus; Gr = Grade; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; RF = rolandic fissure; SFG = superior frontal gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus.

* Visual naming test DO80.⁵

Naming Task

We used a standard naming task. Images were chosen for their high familiarity, with a mean familiarity value above 2 (Table 2) according to the image familiarity ratings of Snodgrass and Vanderwart.³³ During the procedure, images were randomly selected from this set, and stimulation was applied just before the image was displayed and during the picture presentation. We refined this brain mapping image set over more than 10 years, presenting only highly familiar stimuli to patients.³⁰

Protocol Used in This Study

Two types of thresholds were defined: the minimum positive threshold necessary to produce interference in a cortical area (the main threshold used in this study) and the “afterdischarge threshold,” a current intensity producing afterdischarges, sources of mislocalizations during brain mapping.

A checklist was established for each brain mapping session, based on 3 main parameters: the minimum positive threshold level of each positive site; its surface area; and its changes in terms of surface area and type of interference detected when the area was stimulated above its threshold level.

The cortex was directly stimulated using the bipolar electrode separated by 3 mm from the Nimbus cortical stimulator (1-mm electrodes, Newmedic) with biphasic square wave pulses of 1-msec duration and 60-Hz trains. The maximum train duration of each stimulation was 6 seconds in total (around 1 or 2 seconds before picture presentation and 4 or 5 seconds after). The “afterdischarge threshold” was determined by electrocorticography using a strip electrode. Although this point remains controversial,^{11,26} the “afterdischarge threshold” has been found to change little from site to site in a single short mapping session.¹⁷ The level of electrostimulation was always kept 1 mA below the level expected to cause electrical diffusion and afterdischarges so as to ensure that the stimulated area remained accurately localized on the area of cortex under study. If any afterdischarge (or epileptic seizure) was detected, the protocol was adapted to the “afterdischarge threshold” found.

During the mapping session, cortical stimulation was performed over the whole exposed brain surface at 5 mA, at 7 mA (excluding the positive sites already found at 5

TABLE 2. Mean and standard deviation of the familiarity rating of the images used for the naming test*

Image No.	Description	Familiarity	
		Mean	SD
1	Airplane	3.78	0.99
2	Arrow	3.38	1.23
3	Apple	3.98	1.08
4	Ball	3.20	1.21
5	Banana	3.65	1.04
6	Bed	4.72	0.77
7	Belt	4.12	1.05
8	Bicycle	3.78	1.04
9	Bird	3.63	1.16
10	Bus	4.50	0.74
11	Butterfly	2.92	1.17
12	Cake	4.02	1.06
13	Carrot	3.55	0.97
14	Chair	4.58	0.86
15	Cherry	3.38	1.18
16	Car	4.70	0.60
17	Corn	3.50	1.05
18	Couch	4.40	0.74
19	Duck	2.75	1.11
20	Frog	2.48	1.05
21	Guitar	3.58	1.09
22	Helicopter	2.55	1.12
23	Lemon	3.25	1.22
24	Mouse	2.45	1.02
25	Onion	3.32	1.31
26	Pipe	2.90	1.14
27	Table	4.35	0.88
28	Scissors	3.98	0.99
29	Tree	4.68	0.61
30	Watch	4.58	0.73

* Images were chosen for their high familiarity (mean familiarity > 2) according to the familiarity ratings of Snodgrass and Vanderwart as published in their 1980 article.³³ The mean and SD values shown were extracted from Appendix B of that paper and are based on a 5-point rating scale, with 5 indicating “very familiar” and 1, “very unfamiliar.”

mA), and finally at 10 mA (excluding the positive sites already found at 5 and 7 mA). This step defined 3 approximate stimulation levels for the positive sites.

Once this step was completed, all the positive areas found were tested again (at levels below their positive threshold stimulation levels) with the aim of refining the exact level of current necessary to detect the positive cortical area found and determining the minimum positive threshold. For instance, if a positive area was found at 7 mA, the area was tested at 6.5 mA, 6 mA, 5.5 mA, and so on for all the positive area found. If a positive area was detected at 5 mA, it was tested at 4.5 mA, 4 mA, 3.5 mA, and so on until its minimum positive threshold was found.

Although this can be debated, we thought that the direct advantage of this protocol (5, 7, and 10 mA) was to shorten the time necessary for a brain mapping. The postulate underlying this approach is that an area identified at its minimum intensity threshold would also be positive at higher thresholds. Stimulating at 7 and 10 mA directly allows all the standard increments (0.5 mA by 0.5 mA) between 5 and 7 mA, and then 10 mA, to be skipped. We also considered that patient fatigue during language mapping can be an important factor and that all modifications that could reduce the time of brain mapping would be welcome.

It is worth remembering that the number of naming interferences found was usually low (1–3 in many brain mapping sessions). Thus, this protocol was usually completed in less than 15–20 minutes.

Prospective Collection of Data

Video recordings were made of all brain mapping sessions. Intraoperative photographs of the brain were taken, showing the sites validated according to this procedure. In the hours after the operation, all data regarding brain mapping results were stored in an Excel database and each positive cortical point found was labeled with Talairach coordinates.³⁰

Criteria for Positive Interference

Only unequivocal brain mapping results were included in this study. The patient's performance in the absence of stimulation was regularly measured throughout the testing, as further assurance that changes during stimulation were not random events. Nonreproducible interferences were not included in this study. The reproducibility criterion was 3/3 (i.e., 3 interferences to validate a cortical site as "positive" for the naming task). When a site had a reproducibility of 2/3 we stimulated it at least 1 more time: reproducibility criteria of 3/4 (or 4/5) were validated but *not* 2/4 or 3/5. At least 3 trials were performed on positive sites.

No initial (i.e., preoperative) instruction was given to the patients to report unintelligibility, but the patients were systematically debriefed during the operation when they made naming errors. The language interferences found in the pre- and postcentral gyrus (considered as language interferences due to blockade of articulatory mechanisms) were not included in the final analysis, because they can be considered nonspecific.

Classification of Naming Interferences

We classified the naming interferences found in 5 categories as:

1) global behavior arrest (patient stopped talking during stimulation); 2) anomia (patient said "yes, I know... yes...I know but I can't find the word..." and, as soon as stimulation was stopped, the target word was produced); 3) phonological interference (the target word seemed to be identified but was not correctly pronounced; for instance during stimulation one patient said "c'est un rococopder" ["it's a rococopder"] when the target was "helicopter" [hélicoptère]); 4) semantic interference (the target word was not identified, and patients showed verbal paraphasia suggesting semantic errors—for instance, 1 patient said "this is a banana" when a car was presented); or 5) various other interferences, classified as "hesitation" (i.e., upon stimulation, patients did not produce the correct response at once, hesitated, and were not sure of their final response). This classification system can be debated. Although other authors have used slightly different classifications, the basis of many classifications consists of anomia, speech arrest, and semantic and phonologic errors.⁴ The main topic under study here was not directly based on the type of interference found, and we considered that this classification suited the main objectives of the study.

Evaluation of the Interference Category According to the Intensity

The identified positive areas were stimulated above their minimum positive threshold level to test whether the type of response obtained at a given intensity remained at higher intensity. To avoid excessive testing time and patient fatigue, all positive areas found under 7 mA were tested at 7 and 10 mA (e.g., when a positive area was detected at 4.5 mA, it was tested again at 7 and 10 mA to observe any changes in the type of response obtained). Others were tested at 10 mA (e.g., when an area was detected at 7.5 mA, it was tested again at 10 mA).

Evaluation of the Area of the Interference Site

When a functional site was found, it was marked by a sterile tag before moving on to the next test site. Because the distance between the tips of the bipolar electrode was 3 mm, we considered this distance (3 mm) the minimum spatial resolution of our electrosimulation technique. Once the minimum positive threshold of an area was found, we tested the cortical surface of the area detected. The cortical areas located in the immediate vicinity were tested using the same intensity to find out whether they were positive or negative. Once a surface had been defined, the 2 sides of the area (considered as a rectangle) were measured and its surface area was calculated. The minimum surface area detected by our mapping was a square of 3×3 mm (i.e., 9 mm²) but larger surfaces were also detected.

Extension of the Area of the Interference Site When the Intensity Increased

The immediate areas located close to the interference area were also tested using 7 mA and/or 10 mA when the positive threshold level was below these intensities. We tested whether the cortical surface area was extended with higher intensities (for instance, when an interference area was positive at 5.5 mA, the cortex located immediately close to it was stimulated at 7 mA and 10 mA to test whether the positive area increased with increasing current intensity).

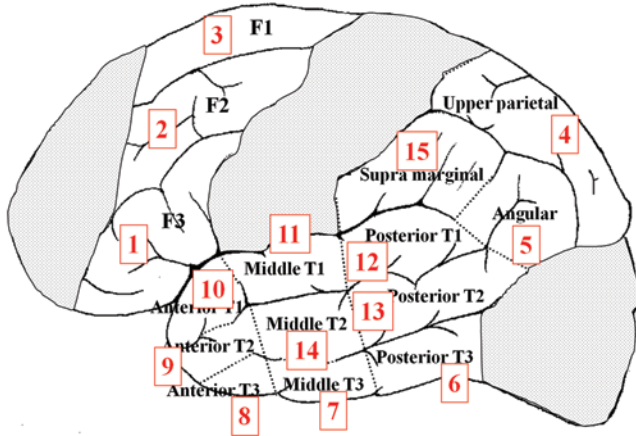


FIG. 1. Scheme of the gyral anatomy used to perform the statistical analysis. Several regions were defined, from 1 to 15. As the terms “Broca’s” or “Wernicke’s” regions were imprecise and not very informative, we decided to perform statistical analysis to define regions by using the gyral and sulcal anatomy. For instance, the supramarginal gyrus was considered as a region, as was the angular gyrus. Large gyri, such as the temporal gyri, for example, were arbitrarily divided into 3 segments by drawing an imaginary line extending the pre- and postcentral sulci. All negative cortical sites were also included in this system of cortical localization. Figure is available in color online only.

Statistical Analysis

Descriptive statistics were used to compute the total number of positive sites per patient, the intensity of stimulation evoking interference in each positive site, and the minimum intensity inducing interference in all positive sites for each patient.

The mean minimum intensity of stimulation was compared across cortical regions by first grouping the positive sites according to our scheme for dividing up gyri (see Fig. 1).

The influence of the locations of positive sites on the stimulation intensities was assessed by means of a 1-way ANOVA and post hoc pairwise comparisons through Student t-tests. A similar approach was used to study the influence of the stimulation intensity on the type of interference induced by the stimulation.

Results

Overall, the data set comprised 3790 stimulated cortical sites obtained from cortical mapping in 100 patients (average per patient 38 sites, range 8–90 sites). Afterdischarges were seen in 9 cortical mapping sessions—for 4 mA (1 case), 8 mA (5 cases), 8.5 mA (1 case), 9.5 mA (1 case), and 10 mA (1 case). The other 91 brain mappings were all conducted up to 10 mA. Intraoperative epileptic seizures were observed in 4 cases (1 generalized, 3 partial) and were rapidly controlled by irrigating the cortex with cold Ringer’s lactate. Of these 4 cases, 3 were detected with afterdischarges; the last patient had a partial seizure during stimulation of the superior frontal gyrus at 10 mA. We waited for a few minutes and repeated this brain mapping at a lower intensity. No stimulation was performed above the “afterdischarge threshold” in these 9 patients.

In 20 patients, no language interference sites were de-

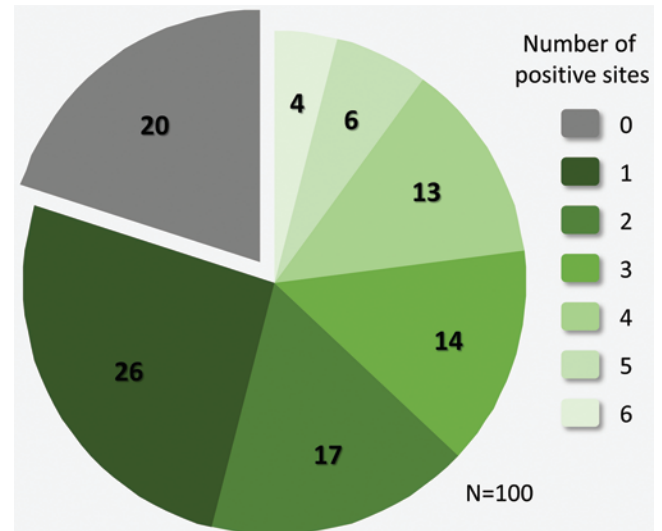


FIG. 2. Pie chart showing the number of patients for whom 0, 1, 2, 3, 4, 5, or 6 naming sites were identified. No language site was evidenced in 20 patients, despite the fact that stimulations were performed in presumed language regions of the left hemisphere. In line with most electrostimulation brain mapping studies, most patients (90 of 100) had less than 5 sites detected. Figure is available in color online only.

tected, even with the maximum intensity of stimulation of 10 mA. In the other 80 patients, at least 1 site was detected by electrostimulation (Fig. 2). Overall, 208 naming interference sites (5.5% of the total number of sites stimulated) were detected. According to our classification, we found (with the minimum positive threshold) 55 speech arrest, 61 anomia, 62 phonemic, 20 semantic, and 10 “hesitation” interferences.

In 22 mapping sessions (22% of the cases), various current intensities were needed at different cortical sites to obtain language interferences. To detect all language interferences, 2 different intensities were necessary in 12 mapping sessions, 3 different intensities in 5, and 4 different intensities in 2.

Although it is beyond the scope of this paper to discuss the aspects of the postoperative language outcomes in detail according to brain mapping results, we noticed that in 16 patients the number of images named in the DO80 visual naming test decreased by 5%–10% compared with preoperative data. In 1 patient, the number of images named postoperatively decreased by 15% compared with preoperative DO80 results. In 2 patients, the number of images named increased after the operation by more than 5%. In other patients, the number of images named during the visual naming test either improved after the operation or remained stable at around $\pm 5\%$. Because many of the patients had postoperative radiotherapy and chemotherapy, the time course of the language outcome was not systematically studied afterward.

Minimum Positive Thresholds for Naming Interference

The mean intensity required to detect the 208 naming interference sites (with their minimum positive thresholds) was 4.46 mA (range 1.5–9 mA, SD 1.44 mA) (Fig. 3 left). Overall, 28 sites (13.5%) were detected using an intensity

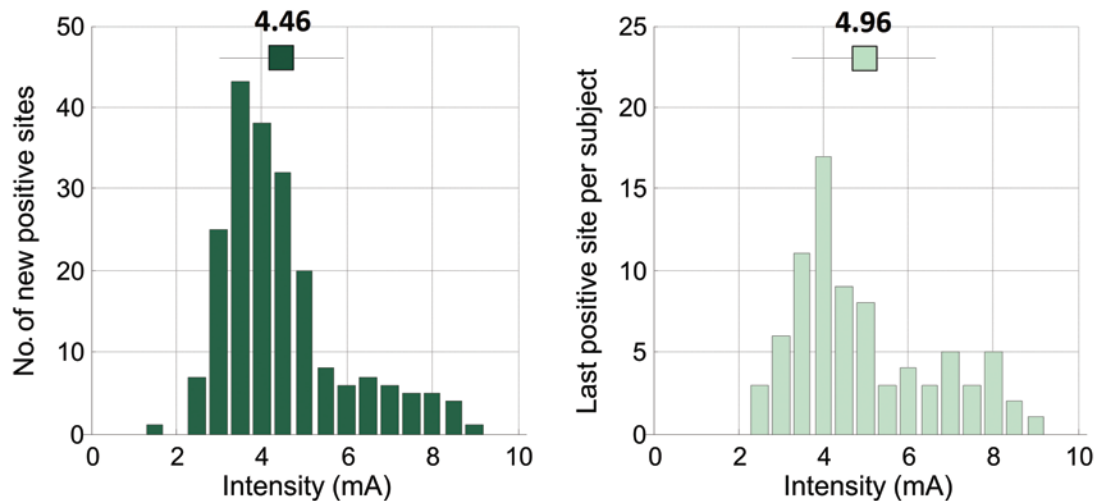


FIG. 3. Illustration of the intensities required to obtain a language interference. **Left:** Distribution of minimum intensities required to induce an interference from positive sites (208 interferences in 80 patients with positive mapping). **Right:** Distribution of maximum intensity required to trigger all the positive sites in each of the 80 patients. Note that, for instance, in nearly 25% of the patients (19 of 80), the mapping would not have been complete if an intensity higher than 6 mA had not been used. The *solid squares* and *horizontal lines* in the upper part of the graphs indicate, respectively, the means and standard deviations of the distributions. Figure is available in color online only.

of stimulation above 6 mA. When we studied the higher stimulation intensity required to obtain all interferences in a given patient, we noted a mean intensity of 4.96 mA (range 2.5–9 mA, SD 1.69 mA) (Fig. 3 right). The minimum positive activation threshold did not differ significantly between female and male patients ($p = 0.055$) or between patients less than 50 years old and those more than 50 years old ($p = 0.98$). The interferences appeared as an “on/off” effect in 191 cases (for instance, no interference at 4 mA and anomia at 4.5 mA). In 17 cases (9%), the response to stimulation increments of 0.5 mA was less clear-cut, with delays, hesitations, and wondering about the type of response.

Does the Level of Intensity Differ According to the Location of the Interference?

A 1-way analysis of variance revealed a very significant effect of the cortical location on the minimum level of intensity required to produce a naming interference (1-way ANOVA $df(3,167)$, $F = 16.58$, $p = 1.78 \times 10^{-9}$). Post hoc t -tests indicated that there was no statistically significant difference in the level of intensity for Broca’s area (inferior frontal gyrus), the posterior temporal region, and the supramarginal gyrus (Fig. 4), but the main intensity used in the middle and superior frontal gyri was significantly higher than the main intensity of stimulation used in the other 3 regions ($p < 0.0001$ for all 3 comparisons).

Reproducibility of the Type of Response

Each positive site was labeled with a type of interference (i.e., speech arrest, naming, phonological, semantic, or hesitation interferences) but repetitions of the same stimulation over the same site could modify the type of interference obtained. For instance, the first stimulation induced a naming interference at 5 mA and a second stimulation (a few minutes later), also at 5 mA, induced a

semantic interference. These variations of the type of interference over the brain mapping session with the same intensity of stimulation were observed at 13 sites (6%) out of 208. In these cases, we classified the type of interference by performing more than 3 stimulations and labeling this site with the type of interference most frequently observed.

Does the Type of Naming Interference at a Site Differ According to the Intensity of Stimulation?

Increasing the intensity of stimulation on an interference site did not modify the type of interference observed in 168 (81%) of 208 interferences. At 30 other interference sites (14.5%), the type of interference was slightly modified. This was particularly the case for phonemic interferences (13 sites) where the interferences were more pronounced, with more syllables distorted. Some “hesitation” (12 sites) and semantic (5 sites) interferences were also more clearly detected (i.e., patients took longer to answer). Finally, in 10 interferences (4.5%) (in 3 patients) the type of interference changed when the intensity of stimulation increased (always below the afterdischarge threshold). In all cases, anomia interferences found with the minimum positive threshold clearly became speech arrest interferences when the current intensity increased.

Can We Accurately Discern the Cortical Extent of These Interferences?

When detected with their minimum positive thresholds, the cortical extent of the positive sites varied from 9 to 120 mm² with a mean area of approximately 20 mm² (mean 19.74 mm², SD 10.71). Fig. 5 illustrates the cortical extent of the interference sites detected.

The area of each interference site was evaluated by using the minimum positive threshold intensity and stimulating all the cortex located in the immediate vicinity. An increase in the stimulation intensity (below the “afterdis-

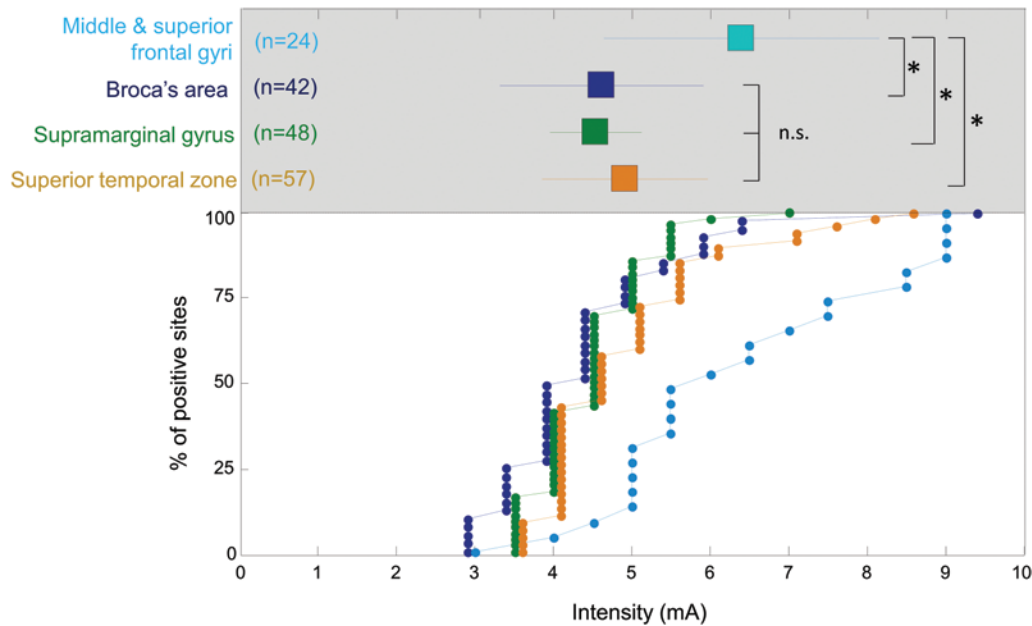


FIG. 4. Illustration of the intensity used according to some selected cortical regions. The lower part of the graph shows the distributions of intensities necessary to obtain language interference for different regions of the brain. The *solid squares* and related *horizontal lines* in the upper part of the graph indicate the mean intensity values and standard deviations for the different regions. The mean level of intensity necessary to obtain language interference was higher in the middle and frontal gyri (6.35 ± 1.78 mA) than in Broca's area (4.48 ± 1.23 mA), the posterior temporal region (4.46 ± 0.73 mA), or the supramarginal gyrus (4.81 ± 1.19 mA). The "posterior temporal region" corresponds to the posterior part of the superior and middle temporal gyri (Regions 11, 12, and 13 of our classification scheme as illustrated in Fig. 1). *Statistically significant. n.s. = nonsignificant. Statistical significance is based on Student t-tests applied to differences in mean intensity. Figure is available in color online only.

charge threshold") led to an increase in the area of the positive sites in 94 (45%) of 208 areas (i.e., stimulation of the cortex in the immediate vicinity of these areas resulted in new interference when the current increased). Overall, this phenomenon was found in 43 of the 80 positive mappings.

Does the Level of Intensity Differ According to the Type of Interference Observed?

As shown in Fig. 6, we found no significant relation between the type of interference observed and the minimum positive threshold intensity evoking that interference (1-way ANOVA, $df(4,202)$, $F = 1.54$, $p = 0.19$).

Patients With No Response at 10 mA: Localization of the Areas Stimulated

There were 20 completely negative brain mapping sessions involving various hemispheric regions—for instance, the inferior frontal gyrus (Broca's area), with 6 negative mappings for 98 stimulated sites; or the posterior temporal area, with 6 negative brain mappings for 84 stimulated sites. Other completely negative mapping sessions involved the middle and frontal gyri (130 sites tested) and upper parietal region (66 sites).

Discussion

Of the numerous publications on the topic, only a few have questioned the variability of brain mapping results according to the different electrostimulation parameters used.^{8,11,26,36,38} Other parameters being constant, only the

intensity of stimulation for language can vary among authors, from those who did not stimulate the brain above 5 mA,²⁰ 6 mA,^{3,6,9,32} or 10 mA¹⁸ to those who used intensities as high as 12 mA,³⁶ 15 mA,³⁷ or 16 mA.^{25,26} Some influential authors did not use electrocorticography² or found that a single current could often be selected for mapping, a current that just straddled the "afterdischarge threshold" in the left or right hemispheres.³ However, in rather small series, it has been shown that essential language areas could be detected at different intensities during extraoperative¹¹ or intraoperative mapping.²⁶ Furthermore, experimentation on macaques demonstrated that there was a graded increase in the area of activation when the stimulation current was increased.⁸ Finally, many debates have focused on the brain organization according to the type of response (for instance phonologic versus semantic response) found during electrostimulation brain mapping.⁴ Demonstrating that the type of response obtained may differ according to the level of stimulation could be not only clinically relevant but also of scientific value.

In this clinical trial with direct consequences for patient management, the intention was to focus on what could be considered as a main parameter for brain mapping—the intensity of stimulation. This parameter has rarely been studied intraoperatively in a prospective study involving a large cohort of patients. This study was not designed to test the effect of different frequencies (for instance 30 vs 60 Hz), as has been done in other studies,³⁸ or durations of stimulation on patients. Our results can be summarized in 5 points. First, we found that, although a large majority of essential

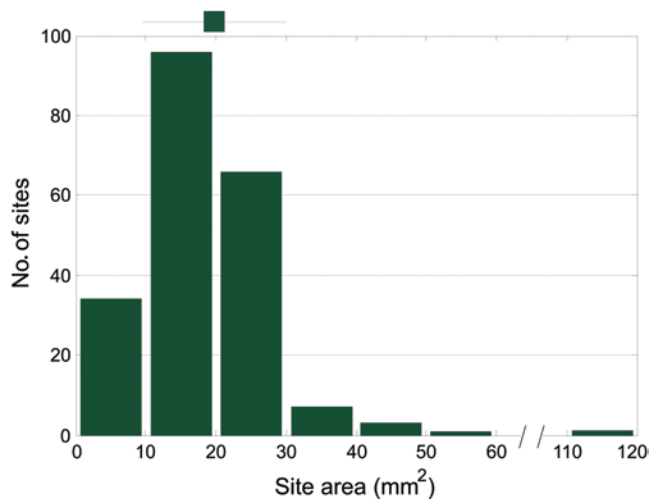


FIG. 5. Extent of the naming sites found. Naming areas were located in very small patches of cortex and were often separated by cortex unrelated to language. It was always surprising to observe that the displacement of the bipolar electrode on the cortex very close to a language area often induced no interference. Overall, 134 interference sites (60%) were localized on cortical patches having a surface area of 20 mm² or less. The *solid square* and the *horizontal lines* indicate the mean site area and its standard deviation. Figure is available in color online only.

language areas could be found by electrostimulation with a mean intensity of 4.46 mA, a significant number of language areas (13.5%) were detected with intensities above 6 mA—a threshold considered in many publications as the maximum level of stimulation.³² This mean intensity of stimulation was higher than those found by some authors² but quite similar to the findings of others.³⁶ Thus, the positive minimum thresholds of essential areas varied among patients (from 1.5 to 9 mA) but also within individual patients for different language areas (in 22% of cases). Second, stimulation of the same naming area with different intensities did not modify the type of response overall in the vast majority of cases (81%). Nevertheless, in other cases, slight changes in the type of response or different types of responses (mainly transforming anomia into speech arrest) were detected. Third, essential areas detected were located in very small, subcentimeter cortical areas (25% of the areas detected measured between 9 and 12 mm² and 50% were smaller than 20 mm²). But this extent varied with the intensity of stimulation. Fourth, slightly higher thresholds of stimulation were observed in the left middle and superior frontal gyri compared with the inferior frontal and posterior temporal gyri. Finally, it has been shown experimentally that bipolar stimulation is able to reproduce similar activation patterns with the same stimulation parameters.⁸ This experimental finding was also observed in this clinical study: stimulation, with the same parameters, of the same cortical area across the brain mapping session reproduced the same type of interference in most cases. In some cases, we detected some variations in the type of response at some sites. It has already been shown by Lesser et al.¹⁰ that responses might occur at a given location during one trial but not in the next. However, the variability of the type of positive response to electrostimulation has rarely been described in the literature. Nevertheless, over

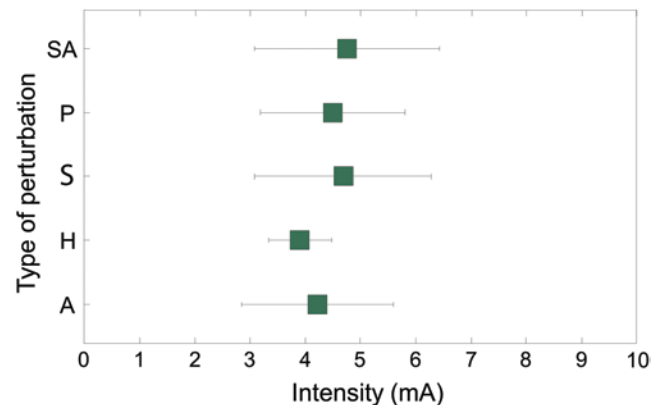


FIG. 6. Illustration of the intensity used according to the type of interference found. Although the mean intensity required to obtain a speech arrest was slightly higher than those required for other interferences, no significant relation was found between the type of interference and the current intensity. A = anomia; H = hesitation interference; P = phonemic interference; S = semantic interference; SA = speech arrest. Figure is available in color online only.

these 100 mapping sessions, this response variability was not frequent (6% of the interferences detected).

Intensity of Stimulation and Afterdischarges

Overall, essential language sites were detected in most cases through an “on/off” effect. Similar threshold effects on naming tasks were also observed with repetitive transcranial magnetic stimulation.³⁴ But graded responses were sometimes detected (9% of the cases) when varying the stimulation threshold by 0.5 or 1 mA. In these cases, language function could just be perturbed (by a subthreshold effect) rather than inhibited.²⁷ Beyond this specific finding, in 10 sites (4.5%) a marked increase in the level of stimulation intensity (for instance, when language areas detected at 4.5 mA were stimulated at 7 mA) completely changed the type of response obtained. We hypothesize that this might have been due to recruitment of a distant motor area, the existence of areas with graded responses to stimulation, or the existence of an undetected stimulation bias.

Larger currents may generate local afterdischarges, which may spread to distant areas.³⁵ Afterdischarges can be sources of mislocalization in language brain mapping. In this study, we detected afterdischarges in 9% of cases, a result in line with the findings of Blume et al., who detected afterdischarges in 8% of their stimulations.¹ Various interpretations could be put forward for this finding. The authors who argue against the systematic use of electrocorticography² would consider that this number is rather low and that 8 of our 9 brain mappings had afterdischarges detected with stimulation above 8 mA (i.e., stimulating below these intensities would avoid most afterdischarges). However, other authors found afterdischarges during electrostimulation mappings with lower intensities, such as a mean current intensity of 5.7 mA in the study by Zangaladze et al.³⁸ Furthermore, if stimulation above 7.5 mA had been avoided in the present series, 5% of the essential language sites (10 of 208) would have been missed. Finally, the main issue could be: should brain mappings be performed using intensities just under the “afterdischarge

threshold” or is it desirable to detect the minimum positive threshold of essential areas? These 2 thresholds are not always identical (the “afterdischarge threshold” is often higher than the minimum positive threshold). This study showed that, for some brain mapping sessions, varying the intensity did not change anything. Nevertheless, for a substantial number of patients, the number and extent of the areas detected and the type of response could vary. The use of different intensities of stimulation seemed essential to optimize brain mapping.

Frontal Versus Temporal Differences and Extent of the Areas

The mean stimulation threshold could be different in the frontal and temporal lobes. In their retrospective study of 39 patients, Wang et al.³⁶ found a mean mapping threshold of 4.91 mA (a finding close to that of the present study) with an estimated mean stimulus threshold for the temporal language cortex 1.45 times higher than that for the frontal cortex. A similar frontal versus temporal difference was observed by Pouratian et al.²⁶ in their 17 patients. We did not use the same definitions of “frontal” and “temporal” as these previous teams. This could explain why we detected no significant difference between Broca’s area and the posterior temporal and supramarginal gyri (although the mean positive intensity was lower in Broca’s area). Considering these results as a whole, we hypothesized that left hemispheric regions directly involved in language (such as inferior frontal, posterior temporal and supramarginal gyri) could globally have rather lower stimulation thresholds than other left hemispheric regions that are presumably less involved in language (such as the middle and superior frontal gyri or the upper parietal region).

Ojemann et al.¹⁸ stated that stimulated areas had “sharp boundaries” and “the estimated total surface area of essential sites was rather small, 2.5 cm² or less in 50% and exceeding 6 cm² in only 16% of the 117 subjects.” The results reported here are in line with these findings and refine them. Our systematic measurements on each site revealed that cortical essential language sites were very discrete and slightly smaller than measured by Ojemann et al.: 50% of the detected sites had areas of less than 20 mm². This very localized effect of bipolar stimulation is a clinical confirmation of the experimental findings of Haglund and others.^{8,15} Since detected areas can be very small, this could imply a need, in practice, to test more cortical areas by electrostimulation than previously advocated.

Negative Brain Mapping Sessions

Finally, many authors have pointed out that in a significant number of patients no essential language areas are detected in brain areas presumed to be involved in language.^{18,32} This was also the case in the present study. The reasons are probably multifactorial. In left hemispheric regions supposedly less involved in language (such as the middle or superior frontal gyri or anterior temporal regions), it was not surprising to find negative brain mapping. But variability was already frequent across the entire superior temporal gyrus in the landmark study of Ojemann et al.,¹⁸ in which only 66% of the patients had a site where stimulation interfered with naming, or in Broca’s

area, where 20% of the stimulations were negative. Were these negative brain mapping sessions “really” negative (no naming area in the exposed cortex) or were they false negatives? According to some authors, certain patients showed reorganization of their language in these language regions, and tumor removal could be performed without language damage.^{6,12} But to err on the side of caution, it is worth remembering that negative brain mapping does not guarantee the absence of eloquent sites³² and naming should not be the sole task used to test language.

Although considered as the gold standard in many neurosurgical publications, electrostimulation brain mapping is not without drawbacks. Among other factors, some sources of false negatives during naming brain mapping sessions⁴ could be stimulation during the refractory period, inappropriate parameters of stimulation, or localization of the essential language sites in the sulci. This last hypothesis has very rarely been considered,¹⁹ but every neurosurgeon knows that it is difficult to stimulate within sulci. There is a lack of data regarding the possible location of essential areas within the sulci, and we hypothesize that naming areas may also be located there but could have remained undetected. This study also showed that sub-threshold stimulations could be a potential source of false negatives. Another such source in our study could be the fact that stimulation did not exceed 10 mA. It is possible that essential language areas would have been detected above this threshold as evoked by other authors.²⁶

Conclusions

This prospective study showed that significant variations in the number of interferences, the type of interference detected, and their cortical extent were observed when the intensity of stimulation was increased. Considering these findings, we think that electrostimulation for cortical brain mapping should be performed using different intensities of stimulation. This could refine the clinical results and scientific data derived from brain mapping.

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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: Roux. Acquisition of data: Roux. Analysis and interpretation of data: Roux, Durand, Djidjeli. Drafting the article: Roux, Djidjeli. Critically revising the article: Durand, Djidjeli, Giussani. Statistical analysis: Durand. Administrative/technical/material support: Djidjeli, Moyse. Study supervision: Giussani.

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