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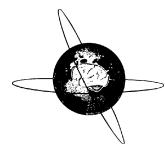
Technical report

Monopolar 250–500 Hz language mapping: Results of 41 patients

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ABSTRACT

Objectives: To determine whether high-frequency 250–500 Hz monopolar stimulation is effective for mapping cortical and subcortical language structures during brain tumor resection.
Methods: Using high-frequency monopolar stimulation, we mapped the speech areas of 41 awake patients undergoing brain tumor resection in the dominant hemisphere, subject to risk of lesions in the cortical and subcortical speech tracts. Patients were tested for object naming, semantic and other language tasks.
Results: Mapping was positive in 22 out of 41 patients. Nine patients presented clinical worsening immediately after surgery. Only one patient did not recover after the 30-day follow-up. Nineteen patients showed negative mapping for language tracts, none of whom exhibited worsening of symptoms at the final evaluation. The applied method showed 89% sensitivity and 56% specificity rates.
Conclusions: The applied method was effective in identifying cortical and subcortical speech areas during the surgical resection of brain tumors.
Significance: Determining whether monopolar high-frequency stimulation is effective for language mapping is important, since it may be very effective in infiltrating tumor areas and nearby edema region.
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1. Introduction

Cortical mapping has greatly improved the outcome of brain surgeries. (Beez et al., 2013; Benzagmout et al., 2007; Chang et al., 2015; Duffau, 2010, 2011; Hamer et al., 2012; Mandonnet et al., 2017; Mathias et al., 2016). The main goal in glioma surgeries is to try to achieve gross resection with as much safety as possible. Improvement or maintenance of the quality of life of patients is very important (Beez et al., 2013; Bello et al., 2014; Duffau, 2009, 2011; Hamer et al., 2012). Within such a context, it is crucial to locate eloquent areas and to identify their relationships with the tumor. Preservation of subcortical white fibers is crucial, due to the vast spectrum of interconnectivity between speech areas and reduced axonal plasticity (Bello et al., 2014; Chang et al., 2015; Duffau, 2010, 2015). Among these areas, we highlight the inferior frontal gyrus, arcuate fasciculus, inferior fronto-occipital fascicle (IFOF), superior and inferior longitudinal fasciculi, insular-opercular connections, and periventricular white matter, constituting a vast, important network of interconnected structures.

Electric stimulation helps to identify the anatomical and physiologic differences between individuals, in both cortical and subcortical areas (Duffau, 2010, 2011; Ojemann and Whitaker, 1978; Ritaccio et al., 2018). Electric stimulation also helps to understand the plasticity already induced by the slow growth of an LGG (low-grade glioma) or the damage caused by the rapid growth of a HGG (high-grade glioma) and the resulting changes in normal connectivity between these pathways (Benzagmout et al., 2007; Duffau, 2011, 2015; Ritaccio et al., 2018; Wu et al., 2015). Both the mapping and speech tests reveal the reshaping of eloquent centers with adjacent areas (Benzagmout et al., 2007; Chang et al., 2015; Duffau, 2009; Ojemann and Whitaker, 1978; Ritaccio et al., 2018; Tate et al., 2015).

Duffau et al. (2002) utilized the electrical stimulation method during performance of a variety of tasks, such as the naming of figures, semantics, visual fields, and facial recognition, tailored to the patient's native language. (Duffau, 2009, 2011). We also performed language tasks as described in the method section.

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Electrical mapping assemblies are individually planned to ensure reliable identification of eloquent tracts, thereby improving patient safety and the degree of tumor resection. (Bello et al., 2014; Ritaccio et al., 2018; Szelenyi et al., 2010). The most accurate method for identifying the language area during surgery is direct cortical stimulation (Bello et al., 2014; Ritaccio et al., 2018; Riva et al., 2015; Rogic et al., 2014). Therefore, the use of adequate probe type and adoption of suitable stimulation parameters, such as intensity, frequency, pulse duration and polarity (Szelenyi et al., 2010) is of paramount importance.

The Ojemann method (Ojemann, 1991; Ojemann and Whitaker, 1978), involving 50 or 60 Hz bipolar mapping, is the most traditional method for identifying language areas. The use of 250–500 Hz train stimulation for intraoperative neurophysiological monitoring was described by Pechstein and Taniguchi in 1993 (Kothbauer, 2017) and began to be utilized for intraoperative motor monitoring in the late 1990s. The motor evoked potential was first performed by transcranial electrical stimulation using a train of pulses and muscle recording. The application of this method increased in the following decades, with the development of stimulation protocols for continuous direct cortical monitoring and, later, cortical and subcortical mapping of motor fibers.

The use of high-frequency monopolar mapping of speech areas is still anecdotal. Riva et al. (2015) compared the application of 60 Hz versus 250–500 Hz in the same patient and concluded that both assemblies were effective for language tract identification, depending on local edema and infiltrative characteristics.

The impairment of speech fibers in neuro-oncological diseases may determine the degree of fiber excitability to stimulation. The possibility of using different stimulating techniques could magnify the identification of speech fibers, whose suffering led to different physiological conditions. It might improve the degree of tumor resection and patients' quality of life.

The series of 41 patients described herein was evaluated with the aim of demonstrating that the high-frequency monopolar method may be efficient in mapping and identifying the cortex and white fibers related to speech.

2. Methods

Between 2012 and 2017, we retrospectively assessed 41 patients who underwent tumor resection in the dominant hemisphere under local anesthesia, in the awake state. These patients were monitored during surgery to assess speech and communication during tumor resection. All patients previously signed informed consent forms. The project (identifier: 386/2017) was approved by the Committee on Ethics in Research of the Hospital Sírio-Libanês, São Paulo, SP, Brazil.

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The patients presenting tumors in the right hemisphere were either left-handed or ambidextrous. The patients' age varied from 15 to 66 years, and the group consisted of 14 women and 27 men.

The neurosurgical team evaluated preoperatively the clinical speech symptoms of the patients using a summed version of the intraoperative language tests, then again before patient hospital discharge, and at 2 weeks and 30 days after surgery. Intraoperative language testing was performed by a trained neurophysiologist (S. M.V.). The clinical presentation of the patients is described in Table 1.

All patients underwent postoperative magnetic resonance imaging (MRI) up to 48 h after surgery, in which the extension of tumor resection was evaluated. Gross total resection was defined as more than 95% removal of the tumor mass.

Either the Nim Eclipse Medtronic, USA or ISIS Inomed System, Germany (randomly chosen) was utilized for intraoperative monitoring of this series of patients. Cortical and subcortical stimulation was performed using a monopolar probe referenced for Fpz with a train of 3–5 pulses, a duration of 0.5 ms, and an inter-stimulus interval of 2–4 ms, with maximum intensities of 16 mA at train repetition rate of 2 Hz (Table 2). To ensure an adequate stimulus intensity, we determined the current needed to trigger muscle motor potential since we had no previous knowledge of the current needed to evoke speech arrest. In most cases, this current ranged between 7 and 10 mA (Fig. 1). It is important to highlight that the monopolar stimulation intensity was maintained unchanged during the mapping afterwards, and we did not intend to estimate the probable distance of the eloquent fiber. Each patient was tested for the most effective inter-stimulus interval, in which switching among 250, 333 and 500 Hz was performed to identify the interval that resulted in the largest muscle motor evoked potential for a given intensity. Then, we tested the ability of the same current to evoke speech arrest. The same stimulation intensity resulted in motor and speech effects in most cases. The first 10 patients received anodal stimulation for both cortical and subcortical mapping. The other 31 patients were submitted to anodal cortical and cathodal subcortical stimulation.

The patients were subjected to multimodal intraoperative neurophysiological monitoring. The patient's preparation included the placement of paired straight monopolar needle electrodes on the mentalis, deltoid, brachioradialis extensor digiti comuni, abductor pollicis brevis, anterior tibial and abductor hallucis muscles, contralateral to the cortex addressed. Three corkscrew electrodes were placed at Fpz to serve as a reference for the monopolar probe, the strip electrode, and the somatosensory evoked potential. Patients were assessed through electrocorticography to identify after-discharges and epileptogenic activity. In cases in which Fpz corkscrew electrode placement was not possible, we placed the electrode as near to Fpz as possible. The somatosensory evoked potentials were obtained from contralateral ulnar and tibial nerves, and the motor evoked potential was obtained through direct cortical stimulation. Background muscle activity was also monitored from the beginning of surgery through multiple electromyography recordings.

We used standard T1, T2 and FLAIR MRI in all cases and tractography in some cases. A neuronavigator system tailored all craniotomies, and the shift was considered by the surgeon during tumor resection. Intraoperative ultrasound was performed in 32 patients to detect the tumor prior to cortical opening, during resection and after final hemostasis. Intraoperative next-door MRI was performed in 8 patients, resulting in 4 cases of further tumor resection.

Initial cortical mapping was used to identify negative speech and motor areas, allowing the entrance of the cortical area to be assessed by the surgeon. Subcortical mapping and image evaluation with a neuronavigator and ultrasound were intercalated during tumor resection.

During mapping, the patient was shown the screen of a tablet presenting images to be named, numbers and arithmetic operations, letters to be used to formulate words, phrases to be read and interpreted, geometric shapes, colors, and a semantic test of figure association. Some patients performed nomination or counting from 1 to 10, associated with forearm flexion and extension, with the objective of apraxia assessment.

During tumor resection in areas free of mapping, the patients were encouraged to maintain a free conversation about their life and family. When lesions were proximal to the hippocampus, the patients were instructed to memorize a word and repeat it after a second image was shown to assess short-term memory.

The patients were asked to say "this is" before naming an item so that pure aphasia could be differentiated from anomia. The

Table 1
Clinical presentation, tumor location, mapping results and outcome.

	Clinical presentation	Site	Map	Immediate status	30-day follow-up
1	Seizures	LF_T	Neg	No new deficits	No deficit
2	Seizures + headaches	LF	Neg	Worse: Discrete aphasia	No deficit
3	Seizures + discrete aphasia	LF	Pos	Worse	Discrete aphasia equal to before
4	No deficit	LF	Neg	No new deficits	No deficit
5	No deficit	R FT	Pos	No new deficits	No deficit
6	Seizures + motor dysphasia	L T	Pos	Motor dysphasia = equal to before	Better than before
7	Discrete aphasia + hemiparesis	LT_P	Pos	Worse	Discrete aphasia equal to before
8	Seizures + discrete aphasia	L F	Neg	Discrete aphasia = equal to before	Discrete aphasia equal to before
9	No deficit	LF	Pos	No new deficits	No deficit
10	Seizures + discrete aphasia + hemiparesis	LT_P	Neg	Worse	Discrete aphasia equal to before
11	Headaches	LF	Neg	No new deficits	No deficit
12	Discrete anomia phonetic	LP	Pos	Discrete anomia phonetic	Discrete anomia phonetic
13	Discrete aphasia	LT_P	Pos	Discrete aphasia = equal to before	Discrete aphasia equal to before
14	Hemiparesis + discrete aphasia	LF	Pos	Worse	Better than before
15	Seizures + headaches	L T	Neg	No new deficits	No deficit
16	Hemiparesis	LF	Pos	No new deficits	No deficit
17	Discrete aphasia	LT_P	Pos	Worse	Discrete aphasia equal to before
18	No deficit	LFTI	Neg	No new deficits	No deficit
19	Discrete aphasia	L F	Neg	Discrete aphasia = equal to before	Better than before
20	Hemiparesis + discrete aphasia	LTI	Pos	Worse	Better than before
21	Seizures	LT	Pos	No new deficits	No deficit
22	Seizures	L T	Neg	No new deficits	No deficit
23	Seizures + fluency alteration	R FTI	Pos	Speech lentification	Better than before
24	No deficit	L T	Pos	Discrete nominative aphasia	No deficit
25	Seizures + headaches	LF I	Neg	No new deficits	No deficit
26	Fluency alteration + hemiparesis	L F	Pos	Worse	Better than before
27	Seizure + ambidextrous	R T	Neg	No new deficits	No deficit
28	No deficit	L T	Neg	No new deficits	No deficit
29	Seizures + headaches	L T	Neg	No new deficits	No deficit
30	Discrete anomia phonetic	L T	Neg	Discrete anomia phonetic	Discrete anomia phonetic
31	No deficit	L T	Neg	No new deficits	No deficit
32	Discrete aphasia	L T	Pos	Discrete aphasia = equal to before	Better than before
33	Hemiparesis grade IV	L T	Neg	No new deficits	No deficit
34	No deficit	L F T	Pos	No new deficits	No deficit
35	No deficit	L F	Neg	No new deficits	No deficit
36	No deficit	L F	Pos	No new deficits	No deficit
37	Hemiparestesis	L FTI	Pos	Discrete nominative aphasia	Partial improvement
38	Discrete aphasia	L T	Pos	Discrete aphasia = equal to before	Discrete aphasia equal to before
39	No deficit	L F	Pos	No new deficits	No deficit
40	Seizures	R T	Neg	No new deficits	No deficit
41	Seizures	L I	Pos	Discrete nominative aphasia	Death on the 3rd day after surgery due to aspiration during a seizure

L = left, R = right, F = frontal, T = temporal, I = insular, P = parietal, pos = positive, neg = negative.

subjects were instructed to name the object as quickly and precisely as possible.

If the patient exhibited refractive issues and needed corrective lenses, the shaft of the eyeglasses on the side of the craniotomy was removed, thus allowing the patient to see the figures during the neurolinguistic tests.

The picture naming task consisted of 250 color or black-and-white images of items such as simple objects encountered in daily life, animals, tools, geometric figures, places, people, and activities. The test was usually individualized according to each patient's profile by considering their degree of education, professional activity, life history, and personal interests.

To localize the primary language and motor cortex, electrical stimulation was applied in increments of 1 mA, starting at 5 mA; a cortical area was considered eloquent if a motor response or twitch was generated or if language errors consistently occurred in at least two separate trials. No cortical site was stimulated twice in succession. Multiple sites located close to one another were chosen on the cortex exposed by craniotomy. When language areas were identified, the resection margin was maintained 1–2 cm away from those cortical areas. Resection was stopped if speech function deteriorated but was restarted if full recovery occurred within 5 min. Positive points were defined as those that caused speech arrest, anomia, semantic, phonetic, phonemic, and nominative paraphasia, misidentification of colors, geometric shapes, and

numbers, and reverberation. Negative points were defined as those wherein no changes in the tests occurred. The functional limit of resection was established when positive points became frequent and were confirmed by image evaluation.

Awake craniotomy procedures are usually performed under an asleep–awake–asleep (AAA) technique or under sedation. We have been using a slightly modified AAA technique described by Huncke et al. (1998), referred to as the asleep–awake method (AA). To induce anesthesia, we administered 50–100 mg of propofol plus 0.1–0.2 μg/kg/min of remifentanil with or without 50 mg of rocuronium. A laryngeal mask (LM) was then inserted, and the patient was gently turned to the appropriate position, with adequate padding of any bony prominences lying against the mattress of the operating table. Then, approximately 40 ml of 0.5% ropivacaine with 1:200,000 epinephrine was used to block sensation in the scalp and forehead. The cutaneous nerves supplying the scalp that were regionally blocked included the greater occipital, lesser occipital, auriculotemporal, zygomaticotemporal, and supraorbital nerves. The head was immobilized using a head holder connected to the stereotactic frame, and the surgical field was prepped and draped. The patient's face was left exposed so that the anesthesiologist could manage the airway and the neurophysiologist could apply the neurolinguistic test. During the asleep phase, anesthesia was maintained with propofol and remifentanil (0.05–0.2 μg/kg/min). It is important to use a drug that exhibits fast metabolism

Table 2
Mapping parameters and results and intraoperative clinical alteration.

Patient	Parameter	Result	Clinical alteration
1	16 mA, To3, pulse duration 0.3 ms, ISI 4 ms	Neg	
2	16 mA, To3, pulse duration 0.3 ms, ISI 4 ms	Neg	
3	15 mA, To3, pulse duration 0.3 ms, 4 ms	Pos	Naming colors, anomia, speech arrest
4	7 mA, To4, ISI 4 ms	Neg	
5	10 mA, To4, ISI 4 ms	Pos	Naming colors and animals
6	15 mA, To3, pulse duration 0.3 ms, ISI 4 ms	Pos	Anomia
7	12.5 mA: To3, pulse duration 0.3 ms, ISI 4 ms	Pos	Naming Colors, anomia, letter reverberation
8	15 mA, To3, pulse duration 0.3 ms, ISI 4 ms	Neg	
9	10 mA, To4, ISI 2 ms	Pos	Anomia
10	10 mA, To3, ISI 2 ms	Neg	
11	10 mA, To3, ISI 3 ms	Neg	
12	8 mA, To4, ISI 3 ms	Pos	Phonetic paraphasia, anomia, counting
13	10 mA, To3, ISI 2 ms	Pos	Anomia
14	10 mA, To3, ISI 2 ms	Pos	Anomia
15	10 mA 10 mA, To3, ISI 2 ms	Neg	
16	11 mA, To3, ISI 3 ms	Pos	Phonetic paraphasia, anomia
17	8 mA, To4, ISI 3 ms	Pos	Phonetic paraphasia, anomia
18	7 mA, To4, ISI 4 ms	Neg	
19	10 mA, To3, ISI 2 ms	Neg	
20	8 mA, To4, ISI 3 ms	Pos	Phonetic paraphasia, perseveration
21	8 mA, To4, ISI 2 ms	Pos	Semantic paraphasia, anomia, memory
22	8 mA, To4, ISI 4 ms	Neg	
23	8 mA, To4, ISI 2 m	Pos	Anomia
24	10 mA, To4, ISI 3 ms	Pos	Anomia, reverberation
25	6 mA, To4, ISI 3 ms	Neg	
26	8 mA, To4, ISI 2 ms	Pos	Anomia
27	8 mA, To4, ISI 2 ms	Neg	
28	8 mA, To4, ISI 2 ms	Neg	
29	8 mA, To4, ISI 2 ms	Neg	
30	7 mA, To4, ISI 2 ms	Neg	
31	7.5 mA, To5, ISI 3 ms	Neg	
32	8 mA, To4, ISI 3 ms	Pos	Anomia, memory
33	10 mA, To3, ISI 2 ms	Neg	
34	6 mA, To4, ISI 4 ms	Pos	Phonetic paraphasia, anomia, perseveration
35	7.0 mA, To4, ISI 3 ms	Neg	
36	10 mA, To3, ISI 2 ms	Pos	Anomia
37	8 mA, To4, ISI 4 ms	Pos	Phonemic paraphasia, anomia, perseveration
38	8 mA, To4, ISI 3 ms	Pos	Phonemic paraphasia, anomia, perseveration,
39	8 mA, To4, ISI 2 ms	Pos	Semantic, phonetic, nominative paraphasia
40	8 mA, To4, ISI 3 ms	Neg	
41	8 mA, To4, ISI 3 ms	Pos	Semantic, phonetic, nominative paraphasia

ISI = interstimulus interval. To3 = train of 3 pulses, To4 = train of 4 pulses.
To5 = train of 5 pulses, pos = positive, neg = negative.

and does not affect electrophysiological monitoring. Ropivacaine (0.5%) with epinephrine was also used along the skin incision. After the craniotomy flap was elevated, anesthetic blockage of the dura mater was performed using a 1:1 mixture of 1% lidocaine and 0.25% bupivacaine. Once the dura mater was opened, the patient was gradually awakened by suspending the administration of all medications. It took approximately 20–30 min for the patient to be able to cooperate with the neurolinguistics tests. Concern regarding analgesia, hemodynamic control, nausea, vomiting, and seizures guided the anesthesiologist's actions during this phase. If the patient became uncomfortable during resection, remifentanil (0.02 µg/kg/min) was restarted. Under sedation, ventilation failure, CO_2 retention, and brain swelling were additional concerns.

The stimulus intensity was felt by the patient, but it was not uncomfortable, and he/she was unaware of the moment at which the stimulus would be applied. The stimulus intensity applied to the first patients was between 15 and 16 mA, with a train of 3 pulses (To3) and a 0.3 ms duration of the pulse. From the ninth patient onward, we maintained the maximum stimulation at 10 mA and the pulse duration at 0.5 ms, except in patient 16, who had hemiparesis and was stimulated with 11 mA. The patients with positive mapping during stimulation had presented with phonemic and semantic paraphasia, reverberation, speech arrest, anomia, and memory changes (Table 2).

Intraoperative biopsy was performed in all cases.

The patient's functional status was evaluated in the immediate postoperative period, before hospital discharge, 2 weeks and 30 days after surgery. Data were analyzed using the absolute (n) and relative (%) frequency and contingency matrices by Pearson's Chi-square or McNemar's test if necessary. Complex matrices (2×3, 3×4, etc.) were simplified to a simple matrix to obtain a better understanding of causality. We considered an α risk ≤ 0.05 for type error I and β risk ≤ 0.20 for type error II. The statistical program IBM SPSS 23.0 was used.

3. Results

Biopsies showed low-grade glioma in 21 patients (51.2%), high-grade glioma in 19 others (46.3%), and breast cancer metastasis in one patient (2.4%).

Gross total resection was achieved in 20 patients (48.7%), as shown in the immediate postoperative MRI, whereas 21 patients (51.2%) presented subtotal resection. The reason for the high rate of subtotal resection was positive mapping in 13 patients, preventing further resection, and the occurrence of intraoperative seizures in patients 10, 17 and 37.
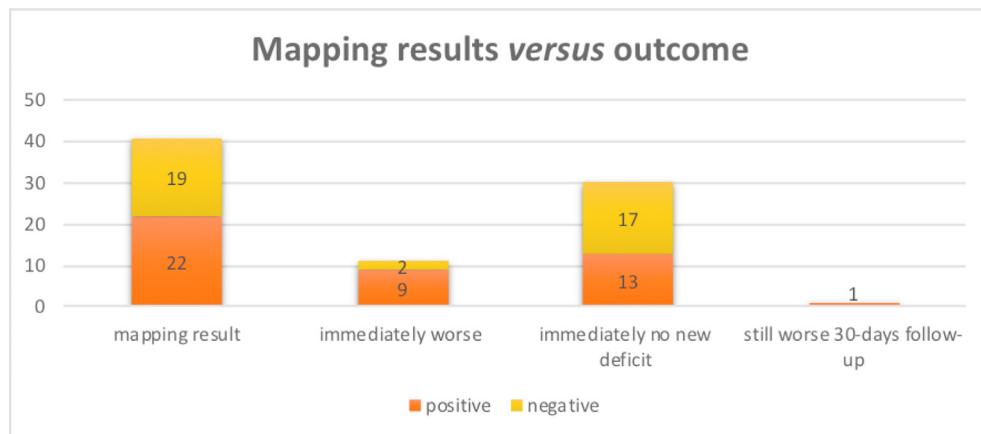
Fig. 1. There is no important relation between negative mapping and worsening, considering the negative or positive mapping results during the stimulation versus the follow-up period. The negative predictive value is important to predict the safety of a given technique.
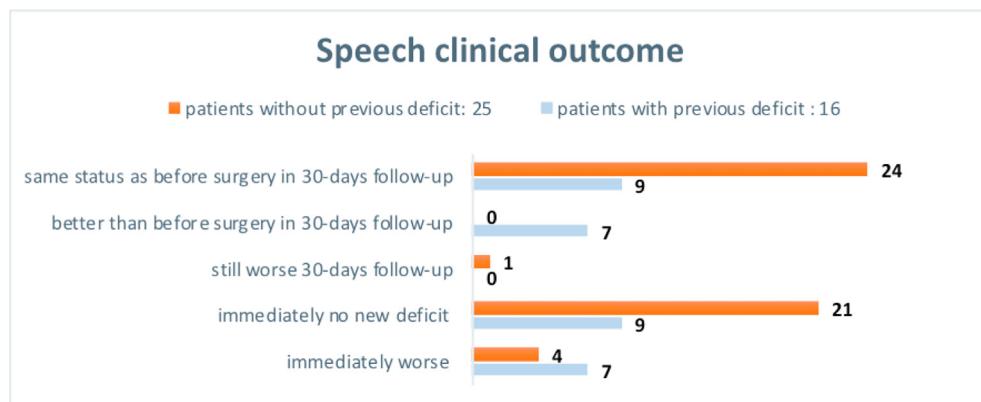

Fig. 2. Initial versus final outcome in patients with and without previous deficits. Patients' groups according to the presence or absence of previous deficits, showing better overall outcome of the patients without previous deficits. Among symptomatic patients, the results were immediately worse, but not during the 30-day follow-up.

Mapping was positive in 22 cases (53.6%) and negative in 19 (46.3%). Of the 22 positive cases, 9 (40.9%) had worsened at the immediate postoperative evaluation. In the 30-day follow-up, only 1 patient still showed worsening of speech (Fig. 1). Among the 19 patients who exhibited negative mapping, only 2 (10.5%) presented immediate worsening, which resolved during the 30-day follow-up in both cases.

We compared speech outcomes from the perspective of previous deficits (Fig. 2). Among the 16 patients with deficits in presentation, 7 showed improvement in the 30-day outcome, and none performed worse. Twenty-five patients displayed no previous speech alteration, but 4 exhibited immediate impairment, which did not resolve in 1 case during the 30-day follow-up.

Improvement of previous epilepsy was not evaluated in the present study.

We did not identify specificity of positive mapping to a given cortical or subcortical location. Instead, positive mapping was possible independent of the tumor site. The analysis of tumor location versus the results of mapping versus outcome revealed homogeneity of the data, suggesting uniform effectiveness of the employed technique (Fig. 3).

In our series, seven patients presented EEG alterations (17%), from whom three developed convulsive crises. Two of these patients had previously presented clinical seizures (Table 1) and the intraoperative event was related to mapping. After-discharges were four of the EEG alterations, being only one was related to stimulation. Tumor manipulation was the cause of EEG

alterations of the other four cases. All cases were treated by applying cold saline on the cortex and one to two intravenous injections of 10 mg of propofol. The surgery continued after the normalization of the EEG, except in patients 10, 17 and 37.

4. Discussion

The use of monopolar high-frequency methodology for studying the white fibers and speech-related cortex is not yet widespread and was first proposed by Riva et al. (2015). The proposal of a new mapping assembly elicits many questions whose answers may help ensure its feasibility. Thus, it is necessary to understand the mapping concepts of high-frequency motor fibers to justify its use in speech fiber stimulation.

For many decades, the Ojemann bipolar method has been applied for language (Ojemann, 1991, Ojemann and Whitaker, 1978) and motricity. The bipolar technique is very specific because the current diffuses between the 2 poles of the probe. The electric current that is spread is therefore homogeneous, although limited to the identification of eloquent fibers existing only within a 5 mm space (Duffau, 2015), which hinders the identification of adjacent fibers (Bello et al., 2014; Rogic et al., 2014). The margin of error for this methodology is 10 mm (Ojemann and Whitaker, 1978; Picht et al., 2013).

The application of 250–500 Hz mapping for motor fibers can be monopolar or bipolar. In monopolar mapping, the stimulus travels
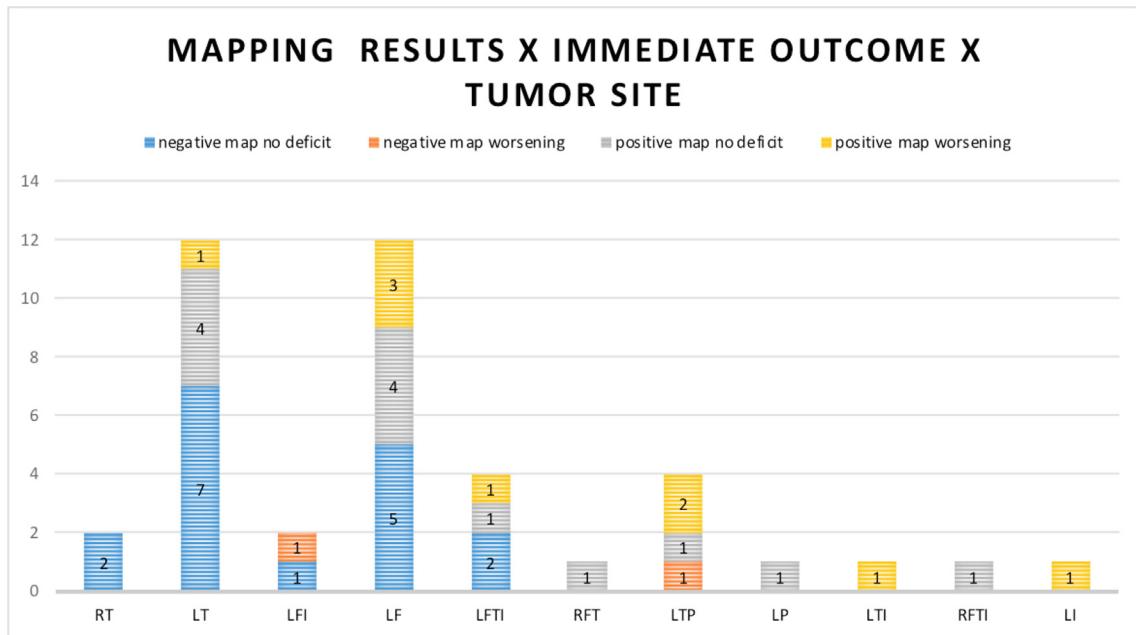
Fig. 3. Mapping results versus the outcomes for different tumor sites. The tumor site played no role on the mapping results or the clinical outcomes. The data was uniformly distributed. R = right, L = left, T = temporal, F = frontal, I = insular, P = parietal, map = mapping.

over a larger area and shows radial spreading, entering axons perpendicularly (Seidel et al., 2013). In this case, cortical stimulation is anodal, and subcortical stimulation is cathodal (Szelenyi et al., 2010, Seidel et al., 2013). Our first 10 cases were stimulated only with anodal probe, but we changed the methodology once we read the publication of Seidel et al (2013). So, from our 11th case on, we used anodal for cortical and cathodal for subcortical stimulation.

The monopolar technique can be employed to estimate the approximate distance of the adjacent white motor fiber by using the formula indicating that the closer the fiber, the lower the intensity needed to stimulate it (Kamada et al., 2009; Ohue et al., 2012; Seidel et al., 2012, 2013). The 250–500 Hz technique allows the continuous monitoring of motor pathways through the motor evoked potential (MEP), thus allowing objective analysis and prognosis (Kothbauer, 2017; Macdonald et al., 2013; Neuloh et al., 2004; Seidel et al., 2012, 2013). Surgical resection of tumors located in speech areas often requires the identification of both motor and speech pathways (Bello et al., 2014).

After-discharges must be identified since they can simulate the stimulation effect and prevent mapping (Ojemann and Whitaker, 1978; Ritaccio et al., 2018; Riva et al., 2015). There is a risk of mapping inducing intraoperative epileptogenic activity ranging from 2 to 67%, especially in patients with a previous history of convulsive crises and depending on the means used for registration. (Macdonald et al., 2013, Beez et al., 2013; Bello et al., 2014; Ritaccio et al., 2018). Riva et al., (2015) reported an incidence of epileptogenic activity of 11,9% in their series. In ours, the incidence of epileptogenic activity related to stimulation was 7,3%, pretty much within the literature range for speech mapping. From these three cases related to mapping, one was after-discharge and the other two were seizures. For 250–5600 Hz motor mapping there is a lower epileptogenic risk of approximately 1%, despite the higher stimulus intensity (Riva et al., 2015; Szelényi, 2011). Our incidence of 7,3%, higher than for motor mapping, might be related to longer stimulation, lasting 3–4 s, while motor fibers are stimulated for 2 s.

To assess the efficacy of the chosen method, we should observe its effect on adjacent tissue (Ritaccio et al., 2018). Concerning speech tests, positive effects are expressed, for example, by anoma-

lies in figure identification, speech arrest, aphasia, dysphasia, reverberation, and phonetic, phonemic or semantic paraphasia (Bello et al., 2014; Benzagmout et al., 2007; Chang et al., 2015; Duffau, 2011, 2015; Hamer et al., 2012; Mandonnet et al., 2017; Mathias et al., 2016; Ojemann and Whitaker, 1978; Picht et al., 2013; Riva et al., 2015). The effect ceases when the electrical stimulus is stopped. We present all the results of mapping in Table 2. Positive mapping resulted in the same alterations described above.

Positive mapping was related to subtotal resection in 13 patients, leading the surgeon to check anatomy on intraoperative image devices, such as ultrasound and neuronavigation system, and previous tractography to support his decision of ending the resection. This evaluation identified eloquent areas that were spared, thus defining the functional resection margins. Another 5 patients had subtotal resection despite negative mapping and based sole on anatomy correlations. The positive mapping alone was not the decision maker, but was always correlated to anatomy, which corrected any bias provoked by a false positive mapping.

The positive predictive value (PPV) for the immediate deficit was 40%. Comparing our result to the PPV of subcortical motor mapping, which varies from 4 to 76% depending on different thresholds (Seidel et al., 2013), we can assume that our assembly is quite equivalent. As Seidel et al. (2013) noted, their best PPV could have resulted from the fact that motor mapping was associated with MEP, increasing the safety margin for predicting new immediate deficits.

Negative responses do not trigger changes in the tests and are more difficult to interpret because they may be due to the inadequate application of the technique, a nontested function (Ritaccio et al., 2018), misinterpretation because of inexperience, or an absence of eloquent fibers in the vicinity (Duffau, 2011). Therefore, it is important to observe the behavior of negative mappings, and how many of these events result in new deficits. We had 19 negative mappings (46,3%), from whom 2 patients (4,8%) were immediately worse after surgery, but recovered in the 30 days follow up (Fig. 1). It suggests that the negative mapping was true absence of eloquent fiber in its vicinity. The negative predictive value (NPV) is crucial for intraoperative decision making regarding whether to continue or stop the surgery. The negative predictive

value was 89%, considering the immediate postoperative deficits, but it was 100% in the final assessment, 30 days later. A high NPV enhances the safety of the assembly. True negative mapping presumes correct technical steps and an experienced neurophysiological team.

It is also important to observe if the mapping was tumor location sensitive, which means that certain speech fibers would not react to high frequency stimulation. Fig. 3 shows the mapping results among all tumor locations. We had negative and positive mappings in frontal, temporal and insular regions. There are 5 cases of parietal location with only positive mappings. It is expected that the mapping technique results in positive and negative effects. Analysis of the outcome in this series showed that the worsening or preservation of the clinical status is uniformly distributed, suggesting that this technique has uniform effectiveness for different cortical regions.

Bello et al. (2014) have shown that when the 50–60 Hz method is compared to the 250–500 Hz method for motor mapping, the 250–500 Hz techniques results in an electromyographic recordable muscle motor response, whereas the 50–60 Hz method fails or induces convulsive crises that impede further stimulation. Patients with a previous deficit, a long history of convulsive crises that are difficult to control or infiltrating tumors with unclear margins as well as those who had received prior radiotherapy did not respond to the 50–60 Hz stimulation or did so only at the end of resection.

After their work with motor fibers, Riva et al. (2015) compared speech cortical and subcortical mapping at 50–60 Hz and 250–500 Hz in the same patient and for the first time. The application of 250–500 Hz stimulation was equally efficient and could be used in cases in which the epileptogenic activity induced by the 50–60 Hz method had prevented its utilization. These authors utilized high-frequency trains at a repetition rate of 1, 2 and 3 Hz. The best mapping results were associated with 3 Hz, due to the more associative character of the speech networking. We used a repetition rate of 2% for all cases. We performed only high frequency stimulation, resulting in effective fibers mapping proven by our good outcome. Our series corroborates their conclusions.

In our series, we achieved 81% sensitivity (considering the cases that exhibited positive mapping and development of a deficit among all patients who developed a deficit) and 56% specificity (considering the patients who exhibited negative mapping and no deficits among all patients who did not develop a deficit) for speech monopolar mapping. In the literature, the rates reported for high-frequency motor fiber mapping vary from 40 to 100% (sensitivity) and 24 to 76% (specificity), according to the threshold (Seidel et al., 2013). These values are very similar to ours, thus supporting the efficacy of monopolar stimulation for speech fibers.

The goal of mapping is to enhance tumor resection and improve safety. Combining two different methodologies either at different points during surgery, or according to different characteristics of the tissue, could increase favorable results. It is important to ensure the efficacy of high-frequency monopolar mapping for language areas so that the use of this technique can become widespread.

We should consider that the results presented in this series translate a retrospective analysis of a small number of patients. We had no comparison group with the 60 Hz technique, so we cannot make any statement about superiority of this assembly.

5. Conclusions

In this retrospective study, we identified the efficacy of 250–500 Hz monopolar stimulation for mapping the eloquent areas of speech. We did not conduct a randomized study with separation of some patients into a 60 Hz control group; therefore, we cannot

assert the superiority of the studied technique. Our small retrospective study suggests that high-frequency mapping can reliably identify eloquent cortex. Future studies should compare the positive and negative predictive values of the 50–60 Hz and 250–500 Hz stimulation techniques. It is likely that the simultaneous use of both techniques in the same patient may magnify the identification of eloquent fibers and improve the extension of tumor resection, also reducing surgery-related morbidities.

Statement

All authors have approved the final article.

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