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Monopolar high-frequency language mapping: can it help in the surgical management of gliomas? A comparative clinical study

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OBJECTIVE Intraoperative language mapping is traditionally performed with low-frequency bipolar stimulation (LFBS). High-frequency train-of-five stimulation delivered by a monopolar probe (HFMS) is an alternative technique for motor mapping, with a lower reported seizure incidence. The application of HFMS in language mapping is still limited. Authors of this study assessed the efficacy and safety of HFMS for language mapping during awake surgery, exploring its clinical impact compared with that of LFBS.

METHODS Fifty-nine patients underwent awake surgery with neuropsychological testing, and LFBS and HFMS were compared. Frequency, type, and site of evoked interference were recorded. Language was scored preoperatively and 1 week and 3 months after surgery. Extent of resection was calculated as well.

RESULTS High-frequency monopolar stimulation induced a language disturbance when the repetition rate was set at 3 Hz. Interference with counting ($p = 0.17$) and naming ($p = 0.228$) did not vary between HFMS and LFBS. These results held true when preoperative tumor volume, lesion site, histology, and recurrent surgery were considered.

Intraoperative responses (1603) in all patients were compared. The error rate for both modalities differed from baseline values ($p < 0.001$) but not with one another ($p = 0.06$). Low-frequency bipolar stimulation sensitivity (0.458) and precision (0.665) were slightly higher than the HFMS counterparts (0.367 and 0.582, respectively). The error rate across the 3 types of language errors (articulatory, anomia, paraphasia) did not differ between the 2 stimulation methods ($p = 0.279$).

CONCLUSIONS With proper setting adjustments, HFMS is a safe and effective technique for language mapping.

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KEY WORDS language mapping; direct electrical stimulation; glioma; awake brain surgery; diagnostic and operative techniques

The current strategy for addressing intrinsic brain lesions, such as gliomas, is aimed at maximal tumor resection while preserving the patient's functional integrity.[9,31,33,36–38] Achieving these aims can be hampered by the infiltrative nature of gliomas, which can involve essential functional structures.[16]

Intraoperative direct electrical stimulation (DES) coupled with neuropsychological testing has been increasingly recognized as an efficient strategy to improve the extent of resection (EOR) and reduce postoperative morbidity.[10,13,18] In fact, DES allows identification and localization (mapping) of eloquent structures, at both the cortical and subcortical level.[5,15,17–19,30,34,39] In addition, a tailored neuropsychological evaluation provides an appropriate cognitive picture of the patient, leading to an objective definition of their cognitive status and guiding resection during language and cognitive mapping.[27]

Language mapping is traditionally performed with

ABBREVIATIONS AD = afterdischarge; DES = direct electrical stimulation; ECoG = electrocorticography; EEG = electroencephalography; EMG = electromyography; EOR = extent of resection; HFMS = high-frequency monopolar stimulation; HGG = high-grade glioma; LFBS = low-frequency bipolar stimulation; LGG = low-grade glioma; MEP = motor evoked potential.

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DES delivered in trains of biphasic pulses at 50–60 Hz (low frequency)[6,7,25,29] through a bipolar probe. During testing, DES is applied at both the cortical and subcortical level with the patient awake, allowing identification of the essential sites involved in the various components of language function, schematically classified as articulatory, semantic, phonemic, and syntactic.[5,6,17–19,25,29,30,34] The technique is feasible and robust, and when it is toggled with tumor resection according to functional boundaries, surgeons can optimize the EOR and simultaneously maintain a high level of the patient's functional integrity.[6,10,13,17–19,34] The incidence of seizures during awake mapping is usually low.[6,13,19] However, in patients with a long history of seizures and poor seizure control,[7,26] low-frequency bipolar stimulation (LFBS) can be associated with a higher risk of seizures on stimulation, even when the modality is used at the lowest useful current intensity.[7,40,42] The likelihood of performing effective functional mapping can thus be hampered.

High-frequency (250–500 Hz) multipulse stimulation,[41] usually consisting of 5 pulses, that is, the train-of-five technique, delivered through a monopolar probe was introduced and proved to be effective in mapping motor structures. In fact, high-frequency monopolar stimulation (HFMS) was more effective and less epileptogenic than LFBS during motor mapping.[7,23,35,40,42]

To the best of our knowledge, a systematic analysis of the effect of HFMS for intraoperative language mapping has not been conducted, and thus its use has been limited.[3,23] In the current study, we explored the use of train-of-five HFMS in performing language mapping: the efficacy and safety of this stimulation paradigm were compared with those of the LFBS modality during awake neurosurgical procedures needing language mapping. The impact on neurosurgical performance, in terms of EOR and language outcome, was also investigated.

Methods

Patients

Fifty-nine consecutive patients (Table 1) affected by a presumed glioma were consecutively recruited. Inclusion criteria were as follows: 1) surgical removal of a presumed glioma in the dominant hemisphere performed with asleep-awake anesthesia; 2) lesion site including cortical and subcortical structures relevant for language; 3) standardized neuropsychological evaluation;[27] and 4) volumetric MRI studies. All patients gave written informed consent for the surgical and mapping procedures. The local ethics committee approved the study.

Neuroradiological Protocol

Magnetic resonance imaging was performed preoperatively and postoperatively on a 3-T scanner (Verio, Siemens). Image acquisition and postprocessing were performed as previously described.[6] Lesion volumes were computed on FLAIR volumetric sequences using manual segmentation with region of interest analysis using the iPlan Cranial 3.0 software suite (Brainlab). FLAIR hyperintense and gadolinium-enhanced signal abnormalities were included in the lesion load for low-grade gliomas (LGGs) and high-grade gliomas (HGGs), respectively, and then were reported in cubic centimeters. Extent of resection was measured on pre- and postoperative MRI studies

TABLE 1. Demographic and clinical features in 59 patients with glioma*

Parameter	No.	
	Group 1	Group 2
No. of patients	9	50
Sex		
Male	5	31
Female	4	19
Mean age in yrs	38.5 ± 11.3	43.1 ± 13.6
Hand dominance (rt/lt)	9/0	48/2
Median yrs of education (range)	12 (8–17)	11 (6–17)
Seizure at presentation (%)	8 (88.9)	48 (96.0)
Seizure history >6 mos (%)	8 (88.9)	21 (42.0)
No. of AEDs (%)		
1	1 (11.1)	24 (48.0)
2	7 (77.8)	22 (44.0)
3	1 (11.1)	4 (8.0)
Median KPS score at presentation (range)	100 (90–100)	100 (71–100)
Main lesion site (%)		
Frontal	8 (88.9)	26 (52.0)
Temporal	1 (11.1)	15 (30.0)
Parietal	0	5 (10)
Insular	0	3 (6.0)
Occipital	0	1 (2)
Insular involvement (%)	3 (33.3)	10 (20)
Mean lesion vol in cm^3		
LGGs (FLAIR)	39.9 ± 31.5	28.2 ± 26.4
HGGs (T1WI+Gd)	25.6 ± 18.6	28.6 ± 25.8
Histology (%)		
WHO Grade I		
Ganglioglioma		1 (2.0)
WHO Grade II	7 (77.8)	17 (34.0)
Astrocytoma	1	1
Oligodendroglioma	4	10
Oligoastrocytoma	2	6
WHO Grade III	1 (11.1)	13 (26.0)
Anaplastic astrocytoma	1	4
Oligodendroglioma		3
Oligoastrocytoma	1	5
Ependymoma		1
WHO grade IV	1 (11.1)	17 (34.0)
Glioblastoma multiforme	1	17
Others (metastases)		2 (4.0)
First surgery (%)	4 (44.4)	27 (54.0)
Median EOR in % (range)	100 (72–100)	100 (53.6–100)

AED = antiepilepsy drug; KPS = Karnofsky Performance Scale; T1WI+GD = T1-weighted imaging with gadolinium enhancement.
* Mean values are expressed with the standard deviation.

obtained within 48 hours of the end of surgery and was classified as previously reported[36] (EOR = [{preoperative volume − postoperative volume}/preoperative volume] × 100).

Neuropsychological Evaluation

A neuropsychological battery including verbal and nonverbal function assessments was performed.[27,29] Patients were evaluated at 3 time points: within 1 week before the surgical procedure (baseline T0) and 1 week (T1) and 3 months (T2) after surgery. Two board-certified neuropsychologists systematically investigated different domains of language. This evaluation was used to depict the wide spectrum of the overall language performance of the patient pre- and postoperatively. Explored domains were as follows: 1) auditory comprehension, 2) words and sentences comprehension, 3) noun and verb naming, 4) phonemic fluency, and 5) semantic fluency.

During the intraoperative session, blocks of 80 items were shown on a laptop screen. Electrical stimulation was applied just before the slide appeared, with the patient unaware of the onset of the stimulation; 2 slides without stimulation were presented after a given stimulation had been applied. Stimulation sites were selected randomly. Stimulation was repeated 3 times at the same site in case of an evoked disturbance, to acknowledge the relationship between DES and an induced response as bona fide.

Intraoperative language disturbances were classified into 3 groups: 1) articulatory (motor) disturbances (anarthria, dysarthria), 2) anomia (latency in response, perseveration, anomia), and 3) paraphasia (semantic paraphasia, phonemic paraphasia, verbal paraphasia, neologisms).

Anesthesia

Total intravenous anesthesia with propofol and remifentanil was induced, and no muscle relaxants were employed during surgery. We endeavored to prevent intraoperative seizures by closely monitoring electrocorticography (ECoG) and continuous electromyography (EMG) activity. Stimulation was stopped and cold irrigation was applied at the first ictal sign to prevent the build up of a seizure. Whenever the seizure did not stop in a few seconds and the convulsive activity spread to the entire hemibody, a propofol bolus infusion was delivered. Craniotomy and dural opening in the study group were performed with the patients under asleep anesthesia. Mapping procedures were performed after intraoperatively awakening the patient.

Surgical Protocol

Surgery was performed with the aid of intraoperative cortical and subcortical mapping of motor and language functions, associated with monitoring procedures, as previously described.[4,6,7,29] Histology was classified according to the (2002) WHO brain tumor classification.[22]

Neurophysiological Monitoring and Mapping Protocol

A multimodal electrophysiological monitoring procedure was used throughout the surgery, as previously reported.[7] Cortical and subcortical mapping was performed using an Osiris stimulator (Inomed) by adopting 2 distinct stimulation paradigms: 1) LFBS: 60-Hz biphasic pulses, total duration 1 msec, current intensity referring to each phase, interstimulus interval 16.66 msec, trains lasting 1–4 seconds; and 2) HFMS: train-of-five monophasic pulses, pulse duration 0.5 msec, interstimulus interval 2–4 msec (2 msec for language mapping, 2–4 msec for motor mapping), anodal and cathodal stimulation for cortical and subcortical mapping, respectively, train repetition rate 1–3 Hz. Stimulation was applied for language and motor mapping. Data regarding language mapping exclusively are reported. Neurophysiological recordings of brain and muscle activity were acquired using a poligraphic electroencephalography (EEG) system (Grass Technologies) and multimodal equipment (ISIS IOM system, Inomed).[7] Subcortical mapping was alternated with resection, using the same current threshold applied for cortical mapping.

Language mapping was performed first by stimulating the ventral premotor cortex in an attempt to stop counting (speech arrest, or anarthria) to identify the intensity of the working current, defined as the minimal intensity that produced anarthria without inducing any type of epileptiform activity. The working current was assessed for both types of stimulation, that is, LFBS and HFMS. During mapping, this current intensity was checked by repeatedly stimulating the ventral premotor cortex to induce anarthria, and the intensity was eventually adjusted. The same intensity was employed for the noun-naming task and further language evaluation once the working current was established. Ictal events were recorded using ECoG (afterdischarges [ADs] and electrical seizures) and EMG (convulsive seizures) as well as clinical examination.

Statistical Analysis

Features of the patients are expressed as the mean ± standard deviation or as the median and range for continuous and categorical variables, respectively.

High-frequency monopolar stimulation was employed with 2 distinct train repetition rates at the beginning of mapping, that is, 1 and 3 Hz; therefore, 2 groups of patients were identified (Group 1 and Group 2, respectively). Low-frequency bipolar stimulation was used in all patients and was compared with the HFMS modality within each group.

Two sets of analyses were applied in Group 2: patient-level and stimulation-level analyses. The percentage of language errors determined by each type of stimulation in every patient represented the patient-level analyses, whereas the stimulation-level analysis consisted of the evaluation of each stimulation trial in terms of the type of error it had produced. As previously stated, 3 types of evoked language disturbances were considered, and no stimulation data were used as a base rate. The pairwise comparison between the 2 stimulation modalities was completely available in 30 patients in Group 2. In fact, the remaining 20 patients in Group 2 displayed a high risk of intraoperative seizures triggered by LFBS, as demonstrated for motor mapping.[7] Low-frequency bipolar stimulation was ineffective for language mapping in a high proportion of these 20 patients: no language interference was found even at a high current intensity (up to 12 mA). A pairwise comparison with HFMS could not be performed, and thus a distinct set of analyses was applied.

A random-intercepts binomial model was employed at the patient-level to investigate the differences in counting and naming interference between HFMS and LFBS. The results of these analyses were checked for the following variables: lesion site, tumor volume, histology, first surgery, and log-transformed motor evoked potential (MEP) threshold. A repeated measures ANOVA with Satterthwaite correction was used to compare the current intensity of the 2 stimulation modalities.

A random-intercepts generalized linear model implemented as a series of logistic regressions[1,14] was used to perform the stimulation-level analyses, using the stimulation outcome as a binary dependent variable. Each data input was associated with 1 of the 3 following conditions: 1) no stimulus, 2) HFMS, or 3) LFBS. Responses were classified as 1) correct, 2) articulatory disturbance, 3) anomia, and 4) paraphasia, as stated above.

The performance of neuropsychological tests at the 3 time points was analyzed using a random-intercepts ANOVA with Satterthwaite correction to model the repeated-measures design of the variables.

Statistical analyses were performed with R software (http://www.R-project.org), and a p value < 0.05 was set as significant.

Results

Initial Evaluation of the Effect of HFMS

The effect of HFMS on language mapping was initially evaluated in 9 patients with nonenhancing tumors affecting the dorsal portion of the premotor cortex and with poorly defined lesion borders (Group 1; Table 1). Initial stimulation of the ventral premotor cortex with LFBS at 3–4 mA induced seizures in 2 patients and ADs and sporadic partial seizures in the following 2 patients (Fig. 1).

High-frequency monopolar stimulation was then employed in these 4 patients, starting with the stimulation parameters reported in the literature during motor mapping, that is, with a repetition rate of 1 Hz. The HFMS (10–18 mA, 1 Hz) induced an arrest in counting in all patients, without the occurrence of epileptic phenomena. Identical HFMS (10–18 mA, 1 Hz) was used at the subcortical level, where it induced both face muscle recruitment and anarthria, allowing identification of the resection margins

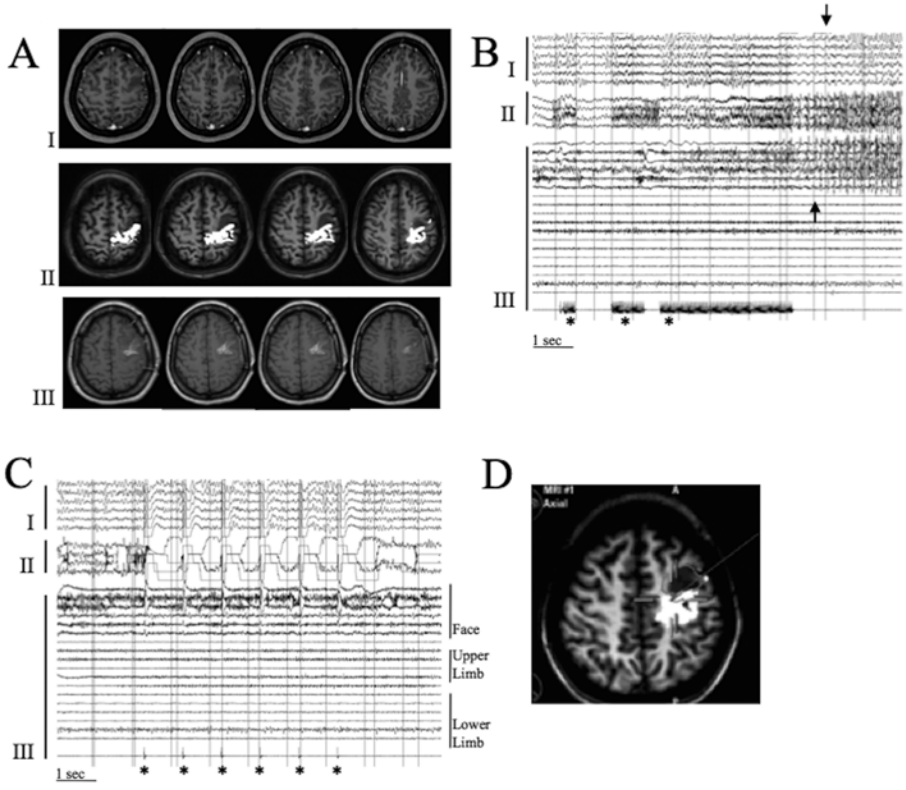

FIG. 1. Group 1. A case of LGG involving the dominant dorsal premotor cortex area. A close relationship with the corticospinal tract **(AII)** is present. The patient had a long history of partial seizures (speech arrest) poorly controlled by antiepilepsy drugs. Language mapping was started with LFBS (3 mA) of the premotor cortex, looking for anarthria and speech arrest **(B)**. The onset of ADs (*upper arrow*, B) was accompanied by the occurrence of a partial seizure *(lower arrow)* involving the face muscles, preventing reliable mapping. The mapping was resumed using HFMS **(C)** at 1 Hz, which allowed us to establish the working current and to complete the cortical mapping. The HFMS at 1 Hz was also used to perform subcortical mapping and to completely remove the lesion **(AIII)**. Intraoperative screenshot **(D)** of the subcortical site where HFMS generated anarthria. **AI:** Preoperative gadolinium-enhanced T1-weighted images. **AII:** Fiber tract reconstructions of the corticospinal tract *(white)* superimposed on T1-weighted images. **AIII:** Postoperative gadolinium-enhanced T1-weighted images. **BI:** ECoG tracings. **BII:** EEG tracings. **BIII:** EMG tracings. **CI:** ECoG tracings. **CII:** EEG tracings. **CIII:** EMG tracings for muscles belonging to the face, upper limb, and lower limb. *Asterisks* indicate a stimulus artifact.

(Fig. 1C and D). No naming tasks were performed with the HFMS. The EOR was 100% in these first 4 patients.

In the other 5 patients harboring a tumor involving the dorsal portion of the premotor cortex and the upper insula, LFBS (2.5–5 mA) induced ADs in 2 patients on stimulating the ventral premotor cortex; therefore, HFMS (8–10 mA, 1 Hz) was used. The HFMS effectively induced anarthria without seizure activity. No paraphasias or anomias were observed in these 5 patients during the naming task when HFMS with a repetition rate of 1 Hz was applied to other sites of the frontal and temporal cortex. An increase in the train repetition rate from 1 to 3 Hz and the same current intensity (8–10 mA) led to the identification of cortical sites determining paraphasias and anomias. Electromyography detected no evoked muscle potentials during these language disturbances. This adjustment of the stimulation frequency enabled the identification of essential cortical language sites over the frontal cortex as well as the surgical point of entry. When applied with a repetition rate of 3 Hz at the subcortical level, the HFMS induced phonemic and semantic paraphasias and thus identified as functional boundaries, respectively, the dorsal language tracts (that is, the arcuate and superior longitudinal fascicles) and the inferior frontooccipital fascicle, with no MEPs in these sites (Fig. 2). The EOR was 100% in 3 patients and 91.4% and 83.9% in the remaining 2. Thus, 3 Hz was effective as

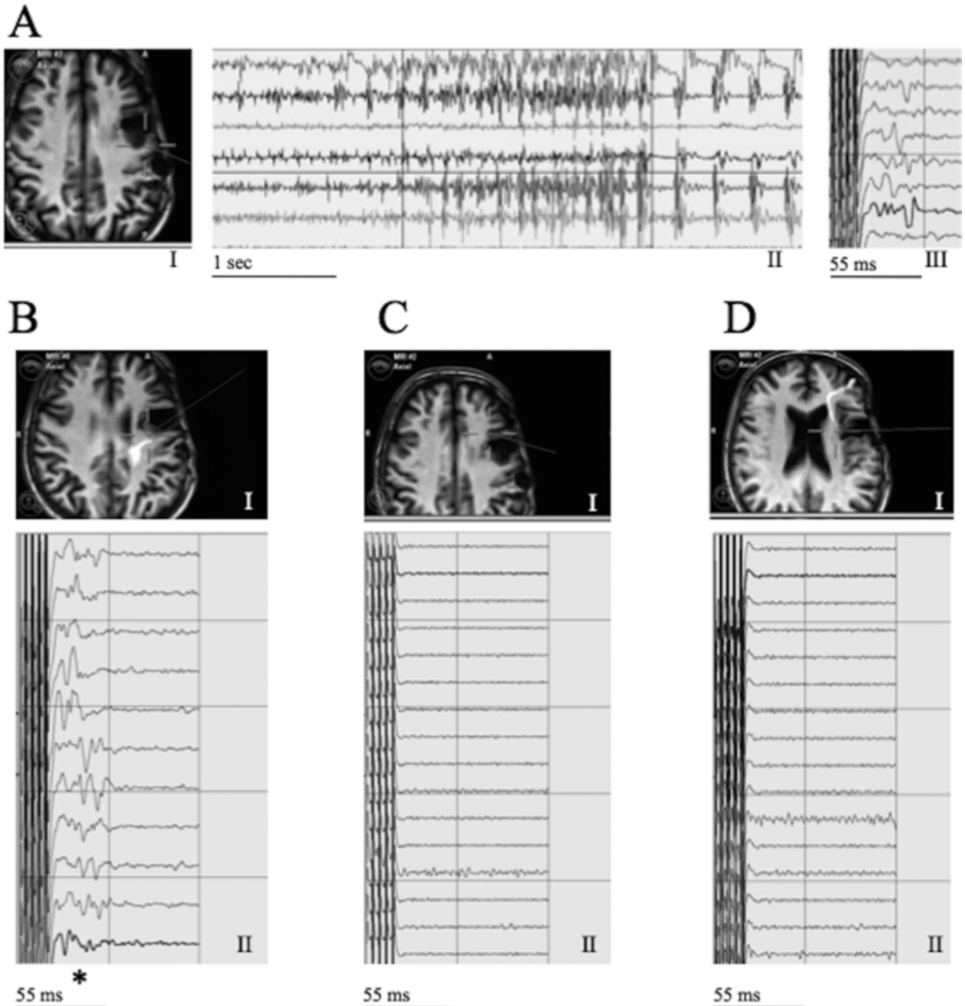

FIG. 2. Group 1. A case of LGG involving the dominant dorsal premotor cortex and the upper insula. Language mapping started with LFBS (2.5 mA) of the ventral premotor cortex (intraoperative screenshot, **AI**). The LFBS induced a partial seizure involving face and neck muscles, preventing reliable mapping **(AII)**. Mapping was performed with HFMS (1 Hz, **AIII**), which induced anarthria without ADs or seizures. The repetition rate was then increased to 3 Hz, which generated all types of the language disturbances considered herein over the frontal cortex. The same current intensity (8 mA, 3 Hz) was used to perform subcortical mapping **(B–D)** and to identify the functional boundaries. It is noteworthy that only stimulation of both the ventral premotor cortex **(AIII)** and the fibers **(BII)** generated a motor articulatory disturbance, that is, anarthria *(asterisk)*, along with MEPs in the perioral muscles. Only the mylohyoid muscle MEP is shown. **AI:** TI-weighted MR image with intraoperative acquisition of the point of interest. **AII:** Continuous EMG during LFBS with recording of the ictal activation of the perioral muscles. **AIII:** Recording from the mylohyoid muscle upon HFMS (5 mA, 1 Hz). **BI, CI, and DI:** Intraoperative screenshots of the site of induced anarthria and phonemic and semantic paraphasias, respectively. **BII, CII, and DII:** Corresponding mylohyoid muscle motor responses triggered by stimulation of the premotor component of the corticospinal tract (MEP is present with visible stimulus artifacts) and of the arcuate and inferior frontooccipital fascicles, where no MEPs are present and only the stimulus artifact is visible.

the repetition rate for language mapping, and it was then applied as such to the subsequent surgeries.

Comparative Study

A systematic evaluation of the effectiveness of HFMS at 3 Hz was performed. Pairwise data regarding the 2 distinct stimulation modalities were available in 50 consecutive patients (Group 2) affected by gliomas involving language-related structures.

Patient-Level Analysis

Counting interference did not differ statistically significantly between patients undergoing LFBS and HFMS (χ = 1.879, p = 0.17; Fig. 3 upper I–II and lower I–II). Differences between the 2 modalities were still not statistically significant after controlling for preoperative tumor volume, (χ = 1.878, p = 0.171), lesion site (χ = 1.547, p = 0.461), histology (χ = 1.621, p = 0.203), and recurrent surgery (χ = 1.459, p = 0.227).

A similar performance was observed in the noun-naming task (Fig. 3 upper III–IV and lower III–IV). In particular, LFBS and HFMS induced a naming interference in 24 (48%) and 30 patients (60%), respectively. Those percentages were not statistically different (χ = 1.453, p = 0.228). The absence of a statistically significant difference remained after controlling for preoperative tumor volume

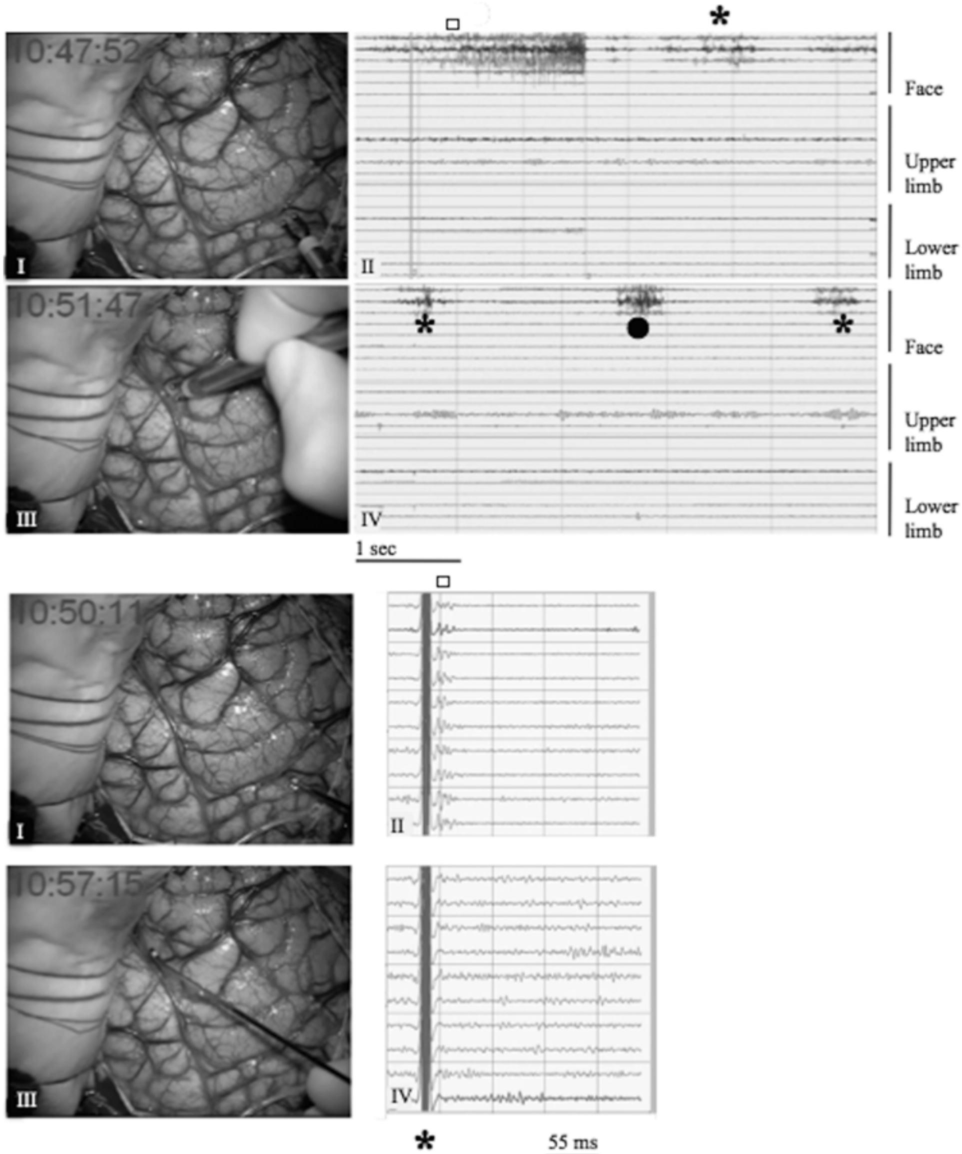

FIG. 3. Group 2. Cortical mapping with LFBS **(upper)** and HFMS **(lower)** in a case of dominant frontal LGG. Intraoperative photograph (upper I) depicting LFBS applied (4 mA) to the ventral premotor cortex, generating anarthria (upper II, *white box*) and thus interfering with normal speech *(asterisk)*. Intraoperative photograph (upper III) depicting LFBS applied (4 mA) to the pars opercularis of the inferior frontal gyrus, inducing anomia (upper IV, *black circle*). Correct responses also appear *(asterisks)*. Similarly, HFMS (lower I) applied (7 mA, 3 Hz) to the same site of the ventral premotor cortex induced anarthria and MEPs (lower II, EMG recording of the mylohyoid muscle). Moreover, HFMS (lower III) applied (7 mA, 3 Hz) to the operculum of the inferior frontal gyrus induced a language disturbance without articulatory interference (lower IV, EMG showing only the stimulus artifact *[asterisk]* and no MEPs).

(χ =1.457, p = 0.227), lesion site (χ = 0.337, p = 0.845), histology (χ = 0.281, p = 0.596), and recurrent surgery (χ = 0.067, p = 0.796).

Both LFBS and HFMS were applied in every patient; thus, it was possible to study the co-occurrence of the stimulation outcome in the same patient. The co-occurrence of task interference (Fig. 4) after LFBS and HFMS was more likely in counting (χ = 9.36, p = 0.025) than in naming (χ = 2.16, p = 0.54).

The average current intensity delivered by the HFMS (2.34 ± 0.16 mA) was significantly higher (F(1.486) = 180.107, p < 0.001) than that delivered by LFBS (1.44 ± 0.14 mA).

Motor evoked potentials were continuously monitored by stimulating the primary motor cortex with a strip electrode, as previously described.[7] The MEP threshold (range 5–35 mA) was log-transformed and used as a modulation variable for the differences in the efficacy of the 2 types of stimulation. Error rates between the stimulation modalities did not vary across patients regardless of the different MEP threshold recorded, both for counting (χ = 3.438, p = 0.064) and for naming (χ = 0.335, p = 0.563).

Intraoperative ADs and convulsive seizures were observed cumulatively in 2 (4%) and 3 (6%) patients, respectively, only on cortical LFBS.

The mean EOR was 95.3 ± 15.6%.

Stimulation-Level Analysis

During surgery, 1603 responses were collected. The effect of every stimulation was considered in the following ways: 1) the appropriateness of the patient's response (that is, correct or incorrect upon stimulation), and 2) the different outcomes determined by the 2 types of stimulation (that is, percentage of evoked errors and the type of evoked error).

Both stimulation modalities yielded a clearly different error rate as compared with baseline, when no stimulation was applied (χ = 304.119, p < 0.001; Table 2). The 2 stimulation modalities slightly differed without reaching a statistically significant threshold (z = 0.36, p = 0.06).

The LFBS and HFMS were then compared in terms of sensitivity and precision in producing a given language disturbance. Low-frequency bipolar stimulation showed a sensitivity of 0.458, which was slightly higher than the HFMS sensitivity of 0.367. Moreover, LFBS was slightly more precise (0.665) than HFMS (0.582). A specificity analysis comparing the 2 stimulation modalities was not feasible because LFBS and HFMS shared the same baseline condition, that is, the absence of stimulation (stimulus off).

Evoked language disturbances were also investigated depending on their specific nature. This analysis was aimed at establishing whether the 2 stimulation modalities determined either a different percentage of errors or a different type of error. The distribution of errors was different for both LFBS (χ = 285.405, p < 0.001) and HFMS (χ = 285.405, p < 0.001), as compared with the baseline condition of no stimulus. However, the error rate across the 3 types of language errors considered did not differ significantly between the 2 stimulation methods (χ = 3.845, p = 0.279; Table 3). The effect of LFBS and HFMS according to the site of stimulation is reported in Fig. 5.

Is There a Target Cohort of Patients for the Use of HFMS?

Data reported above showed HFMS to be 1) as effective as LFBS for language mapping when used at a repetition rate of 3 Hz and 2) less ictogenic than LFMS, although a statistical analysis could not be performed because of the limited number of recorded seizure activities.

A subset of 20 patients in Group 2 displayed distin-

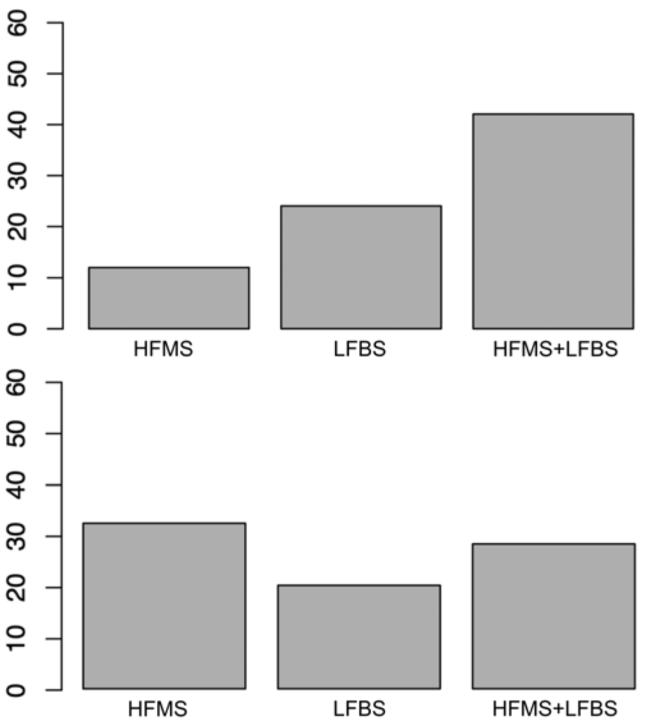

FIG. 4. Upper: Co-occurrence of stimulation-induced errors during the counting task. **Lower:** Co-occurrence of stimulation-induced errors during the naming task. The y-axis represents the percentage of patients.

TABLE 2. Percentage of responses by type of stimulation*

	Type of Stimulation		
Response	Off	LFBS	HFMS
Correct	94	54	63
Incorrect	6	46	37

Correct = no language disturbance; Incorrect = any among articulatory disturbances, anomias, or paraphasias.
* Results are expressed as percentages.

TABLE 3. Type of language disturbance by stimulation modality*

	Type of Stimulation		
Response	Off	LFBS	HFMS
Correct	93.1	54.2	63.4
Articulatory	0.5	18.5	15.5
Anomia	2.4	19.6	11.6
Paraphasia	3.3	7.7	9.7

* Results are expressed as percentages.

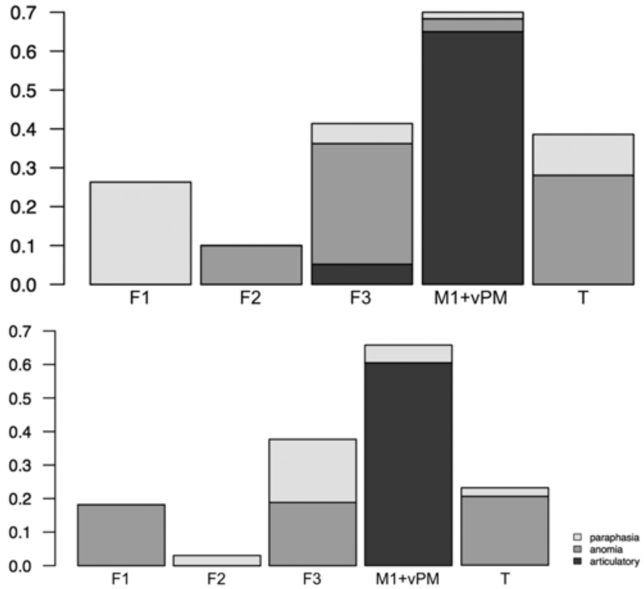

FIG. 5. Upper: Percentage of errors induced by LFBS per cortical site. **Lower:** Percentage of errors induced by HFMS per cortical site. A proper model aimed at testing whether the difference in error rates between the stimulation modalities varied across areas was not estimable because the cross-tabulation of cortical area, stimulations, and errors produces a large number of cells. Nonetheless, the effect of both LFBS and HFMS is described qualitatively. Performance after application of the 2 stimulation modalities did not differ greatly according to the different cortical sites explored, neither in terms of frequency or error type. F1, F2, F3 = superior, middle, and inferior frontal gyrus; M1 = primary motor area, that is, the precentral gyrus; vPM = ventral premotor area; T = temporal lobe.

guishing clinical features: 17 patients (85%) had a seizure history longer than 6 months before surgery and 19 patients (90%) were taking 2 or 3 antiepilepsy drugs. Thus, overall seizure control was difficult or poor in the majority of these patients. For this reason, they were also considered separately since this clinical profile was recently acknowledged as high risk in a large series of brain tumor patients undergoing mapping for motor function.[7]

When applied to the ventral premotor cortex, LFBS (median intensity 5 mA, range 2–12 mA) produced anarthria during the counting task in 11 patients (55%) and no effect in the remaining 9 (45%). This high rate of failed mapping with LFBS made a comparative analysis with HFMS unfeasible.

High-frequency monopolar stimulation (median intensity 10 mA, range 4–22 mA) created speech arrest in all patients, without inducing ADs. At the same current intensity, HFMS was then exclusively used to perform cortical mapping during the naming task, as described above. Functional cortical sites were identified in all patients, in either the frontal or the temporal lobes, without the occurrence of ADs or seizures. Similarly, HFMS was used for the subcortical mapping inducing anomia or phonemic or semantic paraphasias, allowing identification of the functional subcortical tracts and thus defining the resection margins in all patients.

As regards histological type, LFBS (range 2–5 mA) worked in only 4 of 12 patients affected by an HGG; in the remaining 8 patients, LFBS did not induce speech arrest even at a higher current intensity (6–12 mA). In the 8 patients affected by an LGG, LFBS induced speech arrest in 7 patients (2–7.5 mA) and no effect in only 1 patient (4 mA), followed by ADs.

Neuropsychological Analysis of Short- and Long-Term Outcomes

A detailed evaluation of the different language tasks is featured in Table 4. An immediate significant postoperative (T1) decrease in test performance was observed throughout all language functions explored. At the second follow-up evaluation (T2), recovery to a level comparable with preoperative levels was recorded for all tests. A slower recovery was observed in auditory comprehension and verbal fluency tests, in which the average responses at the 1-month follow-up evaluation remained significantly lower than the baseline performance, although progressive improvement since the first postoperative evaluation was noted. Nevertheless, neuropsychological performance was above the normal scores in all tests except verbal fluency with a phonetic cue at the 1-month follow-up evaluation.

Discussion

Language is a complex function schematically composed of articulatory, phonemic, semantic, and syntactic components.[2,5,11,12,20,24,27,28,34] Intraoperative testing is commonly performed with the use of DES. Low-frequency bipolar stimulation is the current gold standard technique for language mapping.[39] This method of stimulation is robust and affords a high percentage of successful mappings in most patients, at both the cortical and subcortical levels.[6,8,10,11,18,19,25,34,36] Afterdischarges can occasionally appear during stimulation, and they can evolve into electrical (that is, exclusively detected by ECoG) or clinical seizures.[7] The incidence of seizures during awake mapping is usually quite variable, ranging from 2% to 67% based on the methodology used to detect them.[7,10,12,40] In the current series the seizure incidence was 11.9% when both convulsive seizures and epileptiform activity detected by ECoG were jointly considered. In patients affected by gliomas with a long history of seizures and poor seizure control, LFBS was associated with a higher risk of seizures in response to stimulation, even when the lowest useful current intensity was used.[7] High-frequency monopolar stimulation has proved to be more effective than conventional LFBS in the mapping of motor structures.[7,23,35,40] At present, however, very few data are available on the use of HFMS for language mapping. Previous works employing transcranial magnetic stimulation and grid electrodes[3,32] have described the use of HF stimulation over the Broca's area producing speech arrest rendered results similar to those observed with LF stimulation. Our study confirmed these observations intraoperatively.

The ability of HFMS at 3 Hz to efficiently map the components of language was explored in a prospective cohort mainly affected by dominant frontal and temporal tumors. These patients, given their clinical, radiological, and neuropsychological features, were the best candidates for conventional LFBS. Therefore, a comparison

TABLE 4. Analysis of the neuropsychological outcomes*

Test Type	Normal Value	T0†	T1†	T2†	T0 vs T1 p Value	T0 vs T1 t Value	T0 vs T2 p Value	T0 vs T2 t Value	ANOVA p Value	ANOVA F Value
Auditory comprehension	**>26.5**	31.2	20.6	27.6	**<0.001**	(68, 9) = −9.7	**0.008**	(73, 4) = −2.7	**<0.001**	(2, 71) = 47.7
Object naming	**87.3%**	93.1	72.9	88.1	**<0.001**	(68, 9) = −5.2	0.126	(72, 3) = −1.6	**<0.001**	(2, 70) = 13.8
Action naming	**73.4%**	87.9	68.9	84.5	**<0.0001**	(66, 7) = −5.1	0.319	(70, 2) = −1.0	**<0.001**	(2, 69) = 13.8
Verbal fluency										
Semantic cue	**>24**	37.3	17.7	26.8	**<0.001**	(67, 1) = −9.7	**<0.001**	(70, 8) = −4.4	**<0.001**	(2, 69) = 46.8
Phonetic cue	**>16**	27.4	9.7	15.5	**<0.001**	(70, 4) = −9.7	**<0.001**	(72, 6) = −5.5	**<0.001**	(2, 71) = 47.9
Word comprehension	**>96%**	99.7	93.8	96.9	**0.027**	(67, 5) = −2.3	0.307	(74, 2) = −1.0	0.085	(2, 72) = 2.6
Sentence comprehension	**>90%**	96.8	82.3	93.7	**<0.001**	(53, 9) = −4.0	0.651	(56, 5) = −0.5	**<0.001**	(2, 58) = 9.8

T0 = preoperative evaluation; T1 = evaluation at 1 week since surgery; T2 = evaluation at 3 months since surgery.
* Bold values are statistically significant and values within parentheses represent degrees of freedom.
† Mean values.

between the 2 techniques was expected to lead to reliable findings, although patient selection biases cannot be completely ruled out. No difference in the rate, site, and stability of response was observed when the 2 techniques were compared within each patient. Current data showed that HFMS, compared with motor mapping, can robustly generate a wide spectrum of language interference at a higher repetition rate (that is, 3 Hz), which is needed to interfere with the more associative component of language, such as semantics and phonetics. The current intensity needed to generate language disturbances with HFMS is usually higher than that needed with LFBS, demonstrating a linear relationship ($r^2 = 0.515$; Fig. 6); on average, double the intensity of that required for LFBS is required to obtain comparable effectiveness with HFMS.

Mapping during the resection of tumors affecting language areas and pathways has multiple aims: 1) to identify eloquent cortical sites and a safe entry point, and 2) to find the essential subcortical structures defining the functional boundaries and EOR. Resection performed according to the functional boundaries implies reaching essential subcortical tracts, characterized by the sudden appearance of various language disturbances, each one typically associated with each tract.[6,7,18,19] Functional resection in the immediate postoperative period is associated with the occurrence of language deficits, generally starting in the 1st or 2nd postoperative days and progressively recovering within 1 or 2 weeks from surgery. In fact, the rate of permanent deficits is usually 2% in most series,[6,7,10,13,17–19,31,34,36] and most patients have a complete recovery 3 months after surgery. The thorough neuropsychological evaluation performed in our series showed that HFMS can identify the essential subcortical tracts as efficiently as LFBS, determining a high percentage of complete resection and an optimal postoperative functional outcome, as supported by data regarding the EOR and the distinct language domains tested at the 3 time points. Such an extensive neuropsychological evaluation significantly highlighted how distinct components of language behave differently following surgery, especially in the postoperative recovery. In particular, object and action naming and sentence comprehension reached a similar level of proficiency compared with baseline after 1 month postsurgery, whereas fluency and auditory processing remained impaired at a midterm follow-up evaluation, although they were slowly recovering compared with the immediate postoperative levels. These results also highlighted the relevance of a wide analysis of language performance in patients undergoing this type of surgery to detect as many treatment effects as possible. The current data showed that while LFBS remains the neurophysiological standard, HFMS can be regarded as an efficient and safe alternative in patients considered at high risk because of their clinical and radiological characteristics, in whom, for instance, a long history of seizures and poor seizure control are present. In these patients, LFBS can be associated with a higher risk of seizures in response to stimulation, even when stimulation at the lowest working intensity is used.[7,40] The epileptic threshold for LFBS may be very close to or even lower than that inducing a language response; therefore, the chance of performing effective functional mapping may be limited with a high rate of failure, as found in the current study. In patients with such a profile, LFBS mapping could not be completed and yielded false-negative results when applied to the ventral premotor cortex in up to 45% cases. High-frequency monopolar stimulation was then used as the exclusive tech-

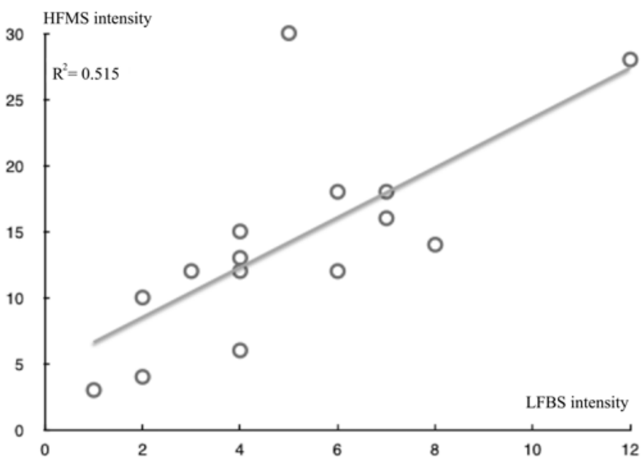

FIG. 6. Relationship between the current intensity (mA) of LFBS and HFMS.

nique of DES, enabling successful mapping of the different language components.

The lower ictogenicity of HFMS may be mainly attributable to the fact that it delivers very short trains (10.5–18.5 msec) of high-frequency (250–500 Hz) stimuli. Instead, long trains (1–4 seconds) of 60-Hz stimuli characterize LFBS. Although the current intensity is significantly higher when using HFMS, it is applied for a much shorter time than LFBS and thus delivers less electric charge to the tissue. The HFMS may also be less ictogenic because the stimulation is less concentrated over tissue with aberrant excitability.

Some limitations of this study must be acknowledged. In fact, a more detailed neurophysiological understanding of the stimulation effects on the axons of different neurons is still lacking, and thus a different type of analysis is required to better elucidate this relationship.[21] A blinded comparison between the 2 stimulation modalities should be performed to address this issue in a more robust way. However, such a study is unlikely to be easily realized with appropriate statistical power for the following reasons. First, LFBS remains the gold-standard DES technique,[12] and as such, a patient cannot be deprived of this technique. Second, large multicenter studies are required to perform such an extensive blinded trial given the epidemiology of intrinsic brain tumors. Moreover, HFMS is less available throughout distinct centers given its status as a relatively newer technique than LFBS. Spatial accuracy may also be limited with HFMS because of possible current spreading, and thus affecting a greater cortical area. Finally, more extensive experience with this type of stimulation is advocated to refine these data.

Conclusions

This work shows that language mapping performed with HFMS at a repetition rate of 3 Hz is feasible and effective, both at the cortical and subcortical levels, with a level of proficiency comparable to that for LFBS. Given its lower ictogenicity, HFMS can be successfully applied to patients with a long history of seizures and poor seizure control. In such patients, LFBS can be associated with a higher incidence of epileptic events negatively affecting the success rate of complete language mapping and eventually the EOR. High-frequency monopolar stimulation can be regarded as an additional tool for the resection of brain lesions in eloquent areas during awake anesthesia. It can thus help to achieve a complete EOR and full preservation of a patient's functional integrity. It can also represent a neurophysiological tool for investigating the neural bases of language.

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Disclosure

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: Bello, Riva. Acquisition of data: Bello, Riva, Fava, Comi, Casarotti, Alfiero, Raneri, Pessina. Analysis and interpretation of data: Bello, Riva, Fava, Gallucci, Comi. Drafting the article: Bello, Riva, Fava. Critically revising the article: Bello, Riva, Fava, Pessina. Reviewed submitted version of manuscript: Riva, Gallucci, Comi, Raneri. Approved the final version of the manuscript on behalf of all authors: Bello. Statistical analysis: Riva, Gallucci. Study supervision: Bello.

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