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Preliminary experience in Awake Surgery: Functional recovery profile

Abderrahim Bouadel[1], **Mohamed Yassaad Oudrhiri**[2], **Mohamed El Hassani**[2], **Mohamed Jiddane**[3], **Abdessamad El Ouahabi**[2]

[1]ERNONFOR Neurosciences Center, Faculty of Medicine and Pharmacy, Mohamed 5 University, Rabat, Morocco
[2]Neurosurgery Department, Neurosurgery Pedagogy and Research Unit, Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5, Rabat, Morocco
[3]Radiology Department, Neuroradiology Unit, Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5, Rabat, Morocco

ABSTRACT

Background. Until the advent of new exploration techniques: functional magnetic resonance imaging (fMRI) and surgical protocols such as exeresis in awake mode, the functional recovery potential of postoperative deficits was limited by conventional tumor surgery. The use of these methods simultaneously improves the quality of life and survival medians, mainly for removing low-grade gliomas massively infiltrating subcortical networks in eloquent regions where surgery is historically not associated with high functional recovery rates. Accordingly, the results from the awake brain surgery literature motivate us to establish a new baseline on the relationship between electrical stimulation mapping (ESM) threshold, the extent of resection (EOR), neuroplastic typology, and functional recovery after intraoperative crises or postoperative care deficits using induced neuroplasticity.

Materials and patients. This is a retrospective analytical study of 35 brain tumor cases of gliomas, operated by common craniotomy in awake conditions from September 2016 to July 2022. Before entering awake resection mode, all patients underwent brain mapping (ESM) by direct electrical stimulation (DES) according to standard conditions and Helsinki ethical guidelines. Analysis according to ESM was done for two groups (group 1 and group 2) of different intensities of DES.

Outcomes. The ESM by threshold intensity expressed in mean ± deviation standard was: 2,45 ± 0.125 mA for sensorimotor functions against 1.35 ± 0.175 mA for cognitive mapping. These stimulation currents were optimum thresholds which allowed us during control mapping to overcome all boundary conditions, mostly false negative results. The functional recovery time (FRT) following stimulation-induced seizures was varied from 2 s to 6.26 s, marking the intraoperative neuroplasticity operated mainly by synaptic remodeling during the functional reactivation. The EOR was better for group 1 with 82.35 % gross total resection (GTR) with only 8.75% of the occurrence of transient seizures against 45.7% for group 2 and only 2.86% suffered from neurological permanent deficits in group 1 against 11.42% in group 2.

Conclusions. ESM in the range of [2.35 - 2.45 mA] improved DES sensitivity without false negatives. We had a compromise of improved results between these stimulation thresholds, the duration of the craniotomy, the functional recovery time, the EOR and overall the occurrence of neurological deficits, which explain the processes involved in the success of awake surgery.

Keywords: functional brain mapping, direct electrical stimulation, functional recovery, intraoperative neuroplasticity

INTRODUCTION

In conventional glioma surgery, the occurrence of neurological deficits remains a major limitation for the use of new innovative techniques to improve both patient health and the quality of care towards maximalist resection according to functional rather than onco-anatomical limits. Thus, the use of awake surgery as an alternative has clearly upset the practice of neurosurgery and has allowed us to understand better and better the mechanisms of brain

Corresponding author:
Abderrahim Bouadel
E-mail: abdel.bouadel@gmail.com

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functioning, in particular the induced neuroplasticity towards total functional recovery.

Currently, awake resection's role in gliomas is gradually becoming more accepted and brain tumor treatment remains challenging by the development of functional magnetic resonance imaging (fMRI) and functional mapping using DES. In this study, we aim to examine the effectiveness of awake craniotomy for resection in different ranges of DES threshold intensities and to highlight the potential profile of neuroplasticity, especially in intraoperative care and the postoperative recovery of neurological damage and functional deficits.

MATERIALS AND METHODS

In this retrospective study, 35 patients were recruited from September 2016 to July 2022 and diagnosed with 25 cases of low-grade glioma (LGG), 7 high-grade glioma (HGG), and 3 patients had arterio-venous malformations (AVMs). All patients gave informed consent after having the full procedure explained to them. However, cases that did not meet the candidacy criteria for awake surgery were excluded from the study, namely patients with tumors in the brainstem, metastases or meningeal tumors. In awake craniotomy, unlike conventional excision surgery, it is essential to preserve as much functional brain tissue as possible in order to maximize the EOR for a GTR characterized by a longer progression-free survival. Thus, the equation for the tumor growth curve:

$$Di = \sqrt[3]{\frac{6\,V}{\pi}}$$

Di: Average lesion diameter.

V: Lesion volume.

Previous studies revealed that lesions progress slowly but steadily, and the evolution between two MRIs 6 weeks to 3 months apart before any treatment shows a linear radiological growth in average diameter of about 4 mm per year [1].

Functional brain mapping (FBM)

DES was done utilizing a bipolar electrode stimulation on the neuronal membrane potential (5 mm probe spacing). The FBM highlights the normal or malignant structure "positively mapped" that will be the target of the excision. A negative FBM is characterized by a transient change in local brain activity when a "negative" response is required from the patient in response to a stimulus. The biphasic electrical current had the following parameters: 1 ms rectangular pulses; 60 Hz frequency; intensities ranging from 1 to 8 mA in increments of 0.5 mA; stimulation time of 1 second (sensorimotor areas) or 4 seconds (cognitive function) (Figure 1) [2,3,4].

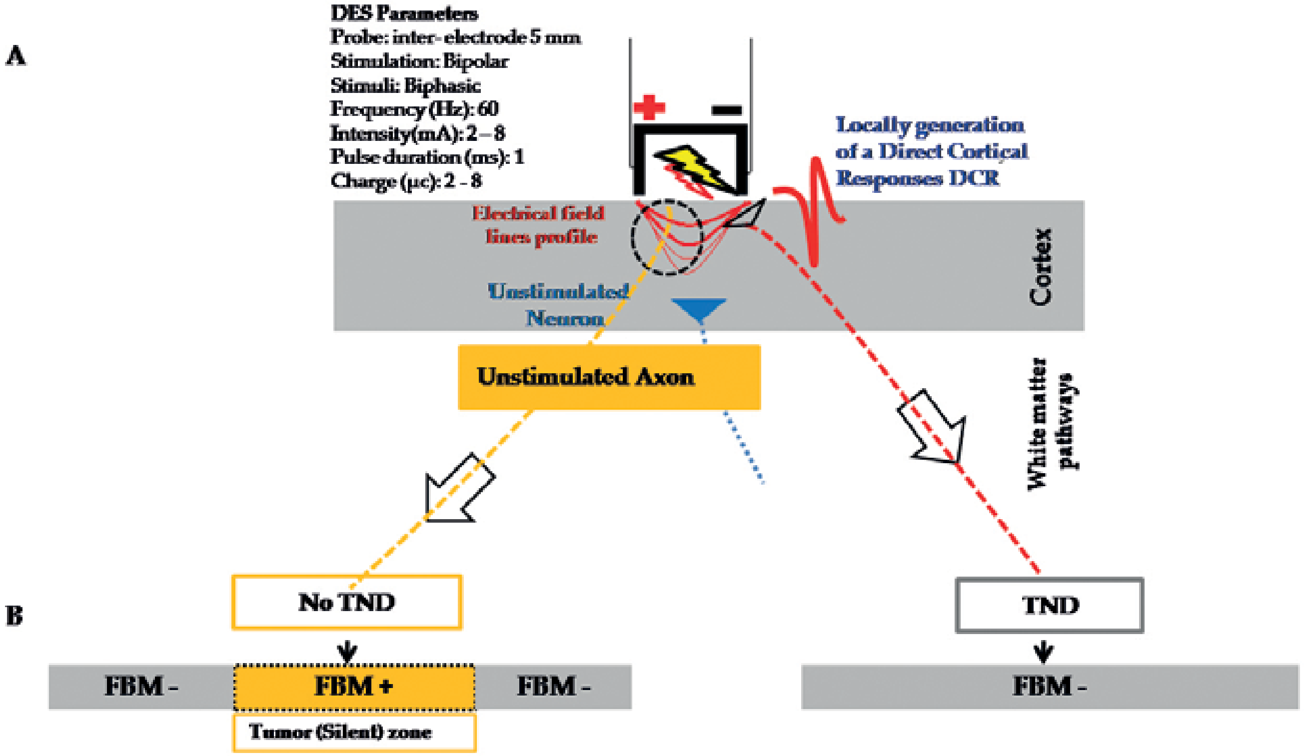

FIGURE 1. (**A**) DES parameters and cortical effects of electrical stimulation to map functional limit of the brain tumor. (**B**) Functional positive mapping no marked by the occurrence of transient neurological deficits in DES due to the non-stimulation of neurons and axons

Boundary conditions

To avoid false negative mapping for a sensitive DES, a range of stimulation threshold intensities [2-8 mA] were utilized. Current strategy for resections of low-grade and high-grade gliomas in language-eloquent regions includes awake surgery coupled with intraoperative direct electrical stimulation (DES) and intraoperative neuromonitoring (Electrocorticography). Because measuring language function requires an attentive patient, intraoperative DES is utilized. Current above the threshold induces partial or total seizures.

Statistical analysis

We performed statistical analysis using the R software version 3.6.1. Quantitative variables were expressed as a mean ± standard deviation (SD) or a median [quartiles]. Statistical significance was determined with 95% confidence intervals with a threshold of significance of 0.05. The Students Test was used for the univariate comparison of quantitative variables.

RESULTS

During our study, the data of the 35 patients was summarized in Table 1 and reveals that the average age of our overall sample was 34 ± 10.5 years, with a sex ratio (M/F) of 2.18 and a significant predominance in females of 68.6% versus 31.4% in males (P = 0.001). Twenty-seven patients (77.14%) were from rural environments; the remaining 22.86% were from urban areas, and the predominance was always in favor of women (P< 0.001). Clinically, LGG is the most common tumor among the various disorders listed in the study area, with a percentage of 71.4%, followed by HGG with a proportion of 20%, and then AVMs with a proportion of 8.6%. Three patients were tired during the surgery due to the long duration and continuous repetitive tasks established to map functions. Also, two cases had problems with the appropriate quality of awakening and had no intraoperative mortality.

TABLE 1. Demographics data

Characteristics	Effective	%
Demographics		
Gender (Male/Female)	11 / 24	31.4 / 68.6
Age (sex Ratio)	34 ± 10.5	2.18
Residence (Urbain/Rural)	8 / 27	22.86 / 77.14
Diagnosis		
LGG	25	71.4
HGG	7	20
AVMs	3	8.6

LGG: low-grade glioma; HGG; high-grade glioma; AVMs; arterio-venous malformations.

Stimulation threshold: correlation

According to statistical analysis by Student T-test, the stimulation threshold intensity (STI) in the cortical area was in the interval of confidence: [2.2-2.45] with 2.45 ± 0.125 mA (mean ± sd) in sensorimotor mapping, versus [1.2-1.47] with 1.35 ± 0.175 mA in cognitive function. However, in subcortical and deeper areas the STI of the two compartments of gray than white matter was increased, respectively, at 5.45 ± 0.1 and 7.35 ± 0.15 mA.

The STI appears to be doubling from sensorimotor to cognitive mapping (STIc). In contrast, the analysis revealed a significant positive correlation between the intraoperative seizures and the electrical stimulation mapping (ESM) with a correlation coefficient (CC) of 0.75 in sensorimotor functions (STIsm) versus 0.6 for STIc. Indeed, this correlation prompted us to consider the analysis results for two STIsm threshold intensity ranges: group 1: [2.35 - 2.45 mA] and group 2: [2.5-8 mA], for which a result disparity was noted after patient data analysis.

FRT after transient stimulation-induced seizures

In eight cases (15.4%), complete seizures occurred at the conclusion of exeresis conducted on patients in whom the functional limit of the tumor emerged in the deep eloquent zones during intraoperative treatment. In addition, transitory seizures were observed in 34.3% of individuals (Table 2). The distribution of FRT recovery times after the occurrence of transient seizures varies according to the intensity of stimulation in DES. In group 1, these times did not exceed 1.8 s with a median of 0.96 s [0.8-1.35 s], whereas in group 2, these times varied between [1.02-7.6 s] with a minimum not exceeding 1.175 s for three patients and one case whose stimulation threshold during the ESM was close to 2.5 mA. In addition, the FRT time was larger than 6.26 s in the other cases, demonstrating a rise proportionate to stimulation intensity at high levels exceeding 2.5 mA (Figure 2).

Craniotomy duration

Group 1 had a significantly shorter craniotomy duration of 240.7 ± 45.7 min (range: 156-360 min) compared to group 2’s 286.6 ± 54.8 min (range: 217-405 min) ($p = 0.01$; Figure 1). Figure 3 shows a significant improvement of almost 50% in the median craniotomy time (177.8 min) performed by ESM for group 1 versus (353 min) in intensities beyond 2.5 mA for group 2. Also, in the same context, a significant reduction in the occurrence and event time of transient deficits in intraoperative care was observed in both groups (Figure 3).

Resection dimension

As shown in Table 2, the global extent of the craniotomy was 8.7 ± 0.8 cm (range: [6.5-10 cm]) in the

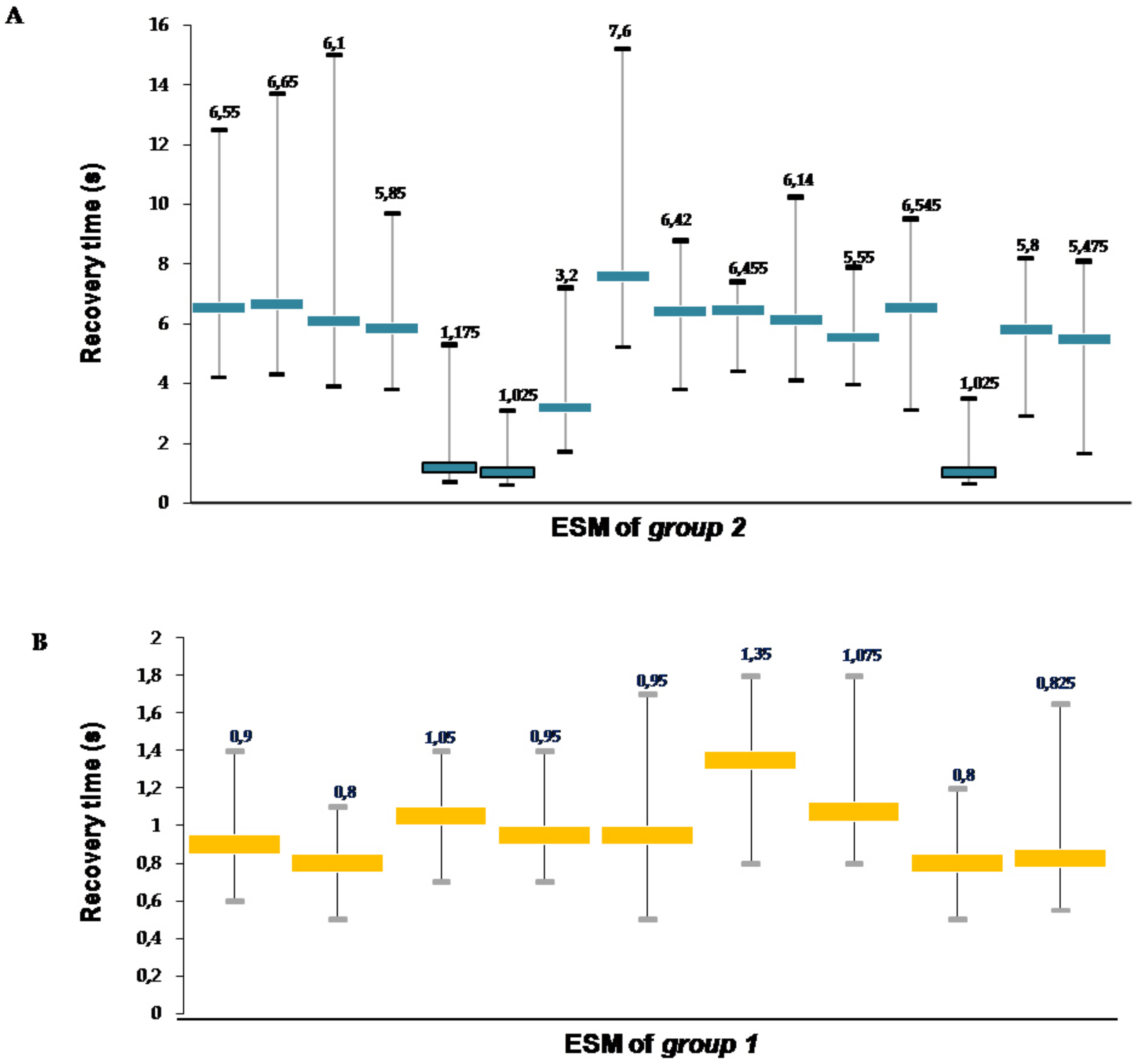

FIGURE 2. FRT distribution following transient seizures during awake craniotomy (A) FRT for group 2 with a median quartile box of 6.26 s for ESM greater than 2.5 mA and 1.6 s for thresholds around 2.5 mA. (B) Recovery time after stimulation-induced seizures for group 1 treated to a low-threshold ESM between 2.35 and 2.45 mA, with a median quartile of 0.96 s in the [0.8 - 1.35 s] range. The difference in FRT between groups was statistically significant (p = 0.01)

first group of patients (group 1) of patients with STIsm = [2.35 -2.45 mA] and 7.5 ± 1.5 cm (range: [4.5-9.8 cm]) in the second group (group 2) *(p = 0.02)*. The resulting overall area of the craniotomy was 37.3 ± 11.7 cm^2 (range: [18.2- 71.2 cm^2]) in group 1 and 35.7 ± 15.2 cm^2 (range: [11.2-78.3 cm^2]) in group 2 *(p = 0.78)*. Also, for group 1 (low STI), 95.15% of the initial mean volume of 37.1 ± 15 cm^3 were resected with a tumor residual volume of 1.8 ± 1.4 cm^3 versus 94.67% of the preoperative tumor volume of 41.3 ± 15.2 cm^3 were surgically removed, whereas the postoperative residual volume was 2.2 ± 1.2 cm^3 in group 2. So, there is no statistically significant difference according to the difference in residual tumor volumes between groups *(p = 0.85)*.

Finally, GTR was achieved in 14 patients (82.35%) of group 1 and 11 patients (68.75%) of group 2 (*p* = 0.4). Furthermore, four patients (23.5%) in group 1 and five patients (31.25%) in group 2 had unexpected residuals (estimation of the intraoperative EOR versus postoperative IRM). This difference between groups, however, was not statistically significant (p = 0.07). As a result, residual tumor tissue was discovered in the postoperative MRI of four patients (23.5%) in group 1 and six patients (37.5%) in group 2 (p = 0.03; Figure 4).

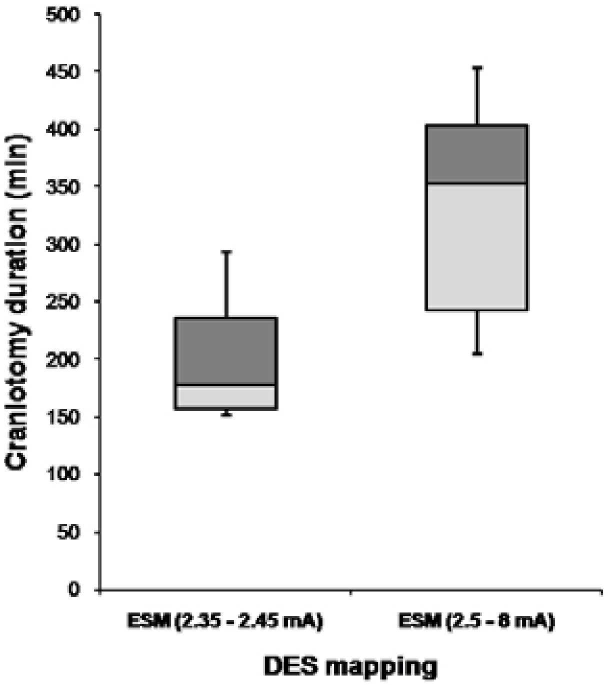

FIGURE 3. Boxplot of awake craniotomy duration for ESM 1 and 2 groups, with median and quartile boxes. There was a statistically significant difference between groups in resection duration (p = 0.01)

Neurological deficits

Unlike conventional surgery, the functional outcome for group 2 with ESM greater than 2.5 mA resulted in a minimal frequency of neurological deficits. (14.3%) of patients achieved a partial deficit and 54.3% achieved 5 transient speech deficits (fully recovered at 6 months). In addition to the 2 cases that presented neither complications nor deficits, all neurological deficits were fully recovered at 6 months, and rehabilitation was required for 8 cases. Indeed, 73% of LGG are under epileptic control, of which 8 cases are still on antiepileptics (AED) and nearly 13 cases of LGG (50%) can work and maintain their profession (Table 3).

Overall, ESM in low intensities for group 1 clearly improves the resection volume (GTR) as mentioned above and the percentage of occurrence of intraoperative transient and permanent postoperative neurological deficits. Figure 4 shows that these deficits pass successively from (45.7%) of intraoperative transients to (8.57%) and from 11.42% to 2.86% for permanent postoperative care. In summary, the GTR increased by 13.6% and the number of people without deficits increased by 5.7%.

DISCUSSION

This retrospective analysis study was designed to investigate and analyze awake surgery using ESM in threshold conditions. A better outcome was demonstrated in patients who additionally underwent low threshold intensities for DES. The observed improvement in functional recovery was independent of age and gender. With technological developments in fMRI, sensitive DES for intraoperative functional mapping and neuronavigation techniques, exeresis in awake conditions is likely considerably safer today than in the past. Therefore, ESM in the [2.35-2.4 mA] range, expressed by mean and standard deviation in a 95% confidence interval, was significantly higher for sensorimotor functions than for cognitive stimulation: 2.45 ± 0.125 mA versus 1.35 ± 0.175 mA.

Following exeresis, transient seizures result from the disconnection of the extracted portion, and their displacement outside somatotopic structures is facilitated by postlesional reshaping of somatosensory maps [5,6,7]. Multiple mechanisms are implemented to allow the brain time to reorganize in preparation for a rapid functional recovery. Consistent with the implementation time of neuroplasti-

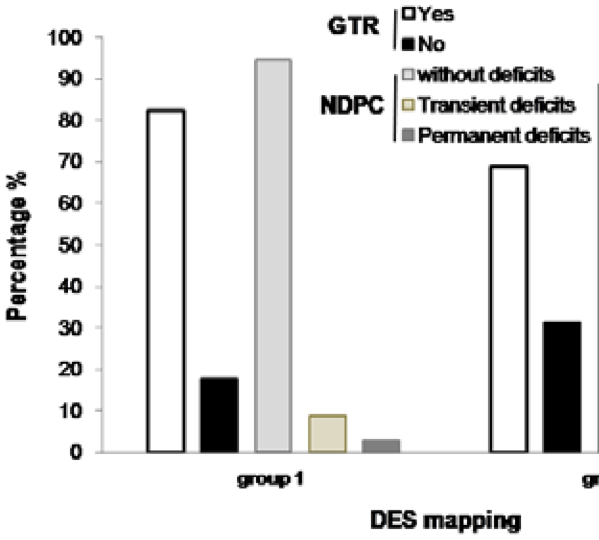

FIGURE 4. Bar chart comparing gross total resection (GTR), intraoperative seizures and permanent neurological deficit in postoperative care for group 1: ESM: [2.35-2.45 mA] and group 2: ESM: [2.5-8 mA]. GTR for group 1 was 82.35% against 68.75% in group 2 (p = 0.04). Occurrence of transient seizures was 8.75% in group 1 against 45.7% for group 2. Whereas, only 2.86% of patients in group 1 suffered from neurological permanent deficits against 11.42% in group 2. Finally, there was no statistically significant difference (p=0.4) between groups regarding the No occurrence of deficits 94.3% in group 1 versus 88.6% for group 2. GTR: Gross total resection, NDPC: Neurological deficit in postoperative care

TABLE 2. Relationship and comparative features of awake resection for group 1 and group 2

Variable	***Group 1*: ESM (2.35-2.45 mA)**		***Group 2*: ESM (2.5-8 mA)**	
	mean ± sd	**Range**	**mean ± sd**	**Range**
Craniotomy duration	230.5 ± 25.7 min	[152.3-320 min]	312.8 ± 52.4 min	[205-415 min]
FRT	0.96 ± 0.15 s	[0.8-1.35 s]	6.26 ± 1.25 s	[1.02-7.6 s]
EOR	8.7 ± 0.8 cm	[6.5-10 cm]	7.5 ± 1.5 cm	[4.5-9.8 cm]
Overall area (p=0.3)	37.3 ± 11.7 cm^2	[18.2-71.2 cm^2]	35.7 ± 15.2 cm^2	[11.2-78.3 cm^2]
mean ± sd				
Tumor mean volume	37.1 ± 15 cm^3		41.3 ± 15.2 cm^3	
EOR vs Postop imaging	1.8 ± 1.4 cm^3		2.2 ± 1.2 cm^3	
%				
GTR	95.15		94.67	
Residual tumor	4.85		5.33	

FRT: functional recovery time; EOR; extent of resection; GTR: Gross total resection.

TABLE 3. Occurrence of intraoperative clinical signs and postoperative neurological deficits recovered by reeducation and rehabilitation programs

Clinical incidences	**Effective**	**%**
Intraoperative clinical signs		
Total seizures	8	15.4
Partial seizures	12	34.3
Tiredness	3	8.6
Problems of awakening quality	2	5.7
Postoperative course		
Functional outcomes		
Partial deficit	5	14.3
Transient deficit	19 (recovered fully at 6 month)	54.3
Profession and return to work	13	50 (of LGG patients)

city modes, the FRT varies from a minimum of 1.8 s in cortical and subcortical regions to a maximum of 6.26 s in deep eloquent regions, primarily during excision (Figure 2).This induced recovery, known as "intraoperative neuroplasticity," occurs through a process of synaptic remodeling (milliseconds to minutes) of an entire functional network followed by pruning (minutes to days) of the network's branches, resulting in the new network neurofunctional system [8,9].

According to some studies, a short time of 3 s precludes observing any of the aforementioned time-dependent phenomena, such as a delayed onset of the deficit, a fast recovery by short-term dynamical plasticity, and a late recovery by long-term biological plasticity [8]. However, two main types of processes support the neurobiological mechanisms of recovery through functional reactivation or functional reorganization [10,11,12]. During surgery, the brain is allowed to recover inhibited function even following partial seizures within seconds by the momentary cessation of excision, allowing time for reorganization to occur in the ipsilesional and homologous areas of the contralesional hemispheres or reactivate to other neurofunctional pathways in the perilesional areas of their previous functions without forgetting the importance of U fibers [13,14,15].

The optimal ESM in the range of [2.35-2.45 mA] allowed us to achieve a GTR resection of 82.35% with a reduction of the intervention time by half (50%) compared to the current DES (Figure 3). Also, in connection with the intraoperative and post-lesional induced neuroplasticity in the series of group 1, there was a qualitative improvement in the course of the resection through a quantitative reduction in the occurrence of neurological deficits in per (2.86%) and postoperative care (8.45%) (Figure 4).

The rehabilitation of neurological seizures has been achieved by inducing neuroplasticity using function consolidation techniques stimulating neuromodulation mechanisms for a few weeks [16]. Indeed, the efficacy and efficiency of this technique show that induced neuroplasticity is still a promising therapeutic approach, particularly at the molecular level, such as with allosteric modulators of AMPA receptors [17,18].

These were the limitations of this study: a limited number of cases, geographical disparity in the distribution of cases, and the absence of socio-demographic studies relating to the daily routine.

CONCLUSION

The ESM threshold within the range of group 1 significantly improved DES sensitivity by promoting brain mapping without false negatives, allowing us to achieve a large extent of resection in half the time of previous excisions. This study has also revealed that the manifestation of neuroplasticity, particularly in intraoperative care, is a completely dynamic process that allows for advantageous resection in the functional borders, as opposed to the oncoanatomical limits of MRI. Thus, the neuroplasticity potential has not yet been exhausted, which opens up new perspectives for the pursuit of physiological adaptation to therapy, namely non-invasive stimulation.

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