Clinical Neurology and Neurosurgery 200 (2021) 106363

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Intraoperative brain mapping of language, cognitive functions, and social cognition in awake surgery of low-grade gliomas located in the right non-dominant hemisphere

Ricardo Prat-Acín [a,*], Inma Galeano-Senabre [a], Pilar López-Ruiz [b], Angel Ayuso-Sacido [c], Raul Espert-Tortajada [b]

[a] Department of Neurosurgery Hospital Universitario I Politècnic La Fe, Valencia, Spain
[b] Department of Psicobiology, University of Valencia, Spain
[c] Investigation Foundation HM Hospitals, Madrid, Spain

ARTICLE INFO

Keywords:
Awake surgery
Brain mapping
Intraoperative brain stimulation
Low-grade glioma
Right hemisphere

ABSTRACT

Objective: The aim of our study was to evaluate the usefulness of cortical-subcortical intraoperative brain mapping (ioBM) in resective awake surgery of low-grade gliomas (LGG) of the right non-dominant hemisphere (RndH). It was estimated how ioBM may affect both the extent of resection and postoperative outcome of language, spatial cognition, social cognition, and executive functions including attention and working memory.
Patients and Methods: : Fifteen patients that underwent ioBM in resective awake surgery of LGG located on the RndH, were included. A cohort of 15 patients with the same tumour location operated under general anaesthesia without brain mapping was used as control. Specific intraoperative tasks for each location were carried out and results registered. Neuropsychological assessment was performed preoperatively and at 6 months after surgery.
Results: In the group of patients operated by using ioBM in awake surgery, an 86.66 % mean of resection was obtained compared to 60.33 % in the control group. Speech arrest and incorrect naming responses were elicited in higher proportion in frontal and insular locations. Parietal stimulation associated higher number of incorrect responses in social cognition task. Parietal and temporal stimulation were more frequently associated with incorrect performance of spatial cognition task. Parietal stimulation associated with higher frequency incorrect execution of attention and working memory tasks. After comparing clinical and neuropsychological results in both cohorts, worst outcome at 6 months was observed in the group of patients operated under general anaesthesia without brain mapping, especially in parietal and insular locations.
Conclusions: Intraoperative identification of language, cognitive functions, and social cognition of RndH by means of ioBM, can be of paramount importance in improving the extent of resection of low-grade gliomas and positively affects clinical and neuropsychological outcome at six months.

1. Introduction

Intraoperative cortical and subcortical brain mapping (ioBM) in awake surgery is increasingly used in the surgical management of diffuse low-grade gliomas (LGG), mainly in those located in so-called “eloquent areas”. This procedure is considered by a growing number of studies as an intraoperative gold standard technique for the surgical removal of LGG of the left dominant hemisphere [1,2]. Moreover, intraoperative language mapping under local anaesthesia has been probed to minimize the risk of postoperative language deficit in these patients [1,3]. However, intraoperative monitoring of higher functions attributed to the right non-dominant hemisphere (RndH), including visuospatial cognition, sociocognitive functions and executive functions have been frequently neglected in diffuse LGG surgery. Rationale used to justify the lack of intraoperative assessment of those functions on the RndH include overall poor benefit-risk analysis (considering the procedure uncomfortable and risky), and unavailability of appropriate intraoperative neuropsychological tasks to study the above mentioned RndH functions.

* Corresponding author at: Hospital Universitario I Politècnic La Fe, Departament of Neurosurgery, Avenida de Fernando Abril Martorell, 106, 46026, Valencia, Spain.
E-mail address: prat_ric@gva.es (R. Prat-Acín).

https://doi.org/10.1016/j.clineuro.2020.106363
Received 27 April 2020; Received in revised form 24 October 2020; Accepted 7 November 2020
Available online 11 November 2020

As a result, systematic monitoring of RndH has not been included in brain mapping surgery protocols and therefore, limited experience on intraoperative cortico-subcortical stimulation and its influence in outcome have been reported. Meanwhile, recent published papers [4–6] show a growing interest in ioBM of tumours of the RndH to increase safe resection and minimize postoperative deficits. Avoiding related morbidity in RndH surgery, significantly improve the quality of life of these patients and contribute to their fast reintegration to previous work [7].

In the present study, we evaluate the usefulness of cortical-subcortical ioBM during awake surgery of diffuse LGG of RndH in terms of clinical and neuropsychological outcome and its impact in the extent of diffuse LGG resection.

2. Patients and methods

2.1. Patient selection

We analysed fifteen consecutive patients with diagnosis of diffuse low-grade glioma (WHO grade II astrocytoma) located on the right non-dominant hemisphere, that underwent ioBM in asleep-awake-asleep surgery.

A cohort of 15 patients with the same tumour location and the same histological diagnosis, operated under general anaesthesia without brain mapping, was used as a control.

All patients underwent preoperative neuropsychological assessment.

All 15 patients of the observational cohort were operated by the same senior neurosurgeon in the period 2014−18. Written informed consent was obtained from each patient.

2.2. Stimulation

Intraoperative brain stimulation in the awake phase of surgery was performed with bipolar stimulation, frequency of 60 Hz, pulse duration 1 ms and intensity range from 2 to 4 mA. We used the method developed by Ojemann and Mateer [8] including that electrical stimulation was not applied to the cortical or subcortical studied area of the brain for more than 5 s, it was never consecutively applied twice at the same location, and the result of a task in one location was recorded when the same result was obtained during three non-consecutive stimulations in that location.

2.3. Intraoperative tasks

All patients underwent preoperative neuropsychological assessment. In the group of patients having ioBM, we recorded the results of the planned tasks after stimulation (cortical and subcortical) of the same lobe that harboured the tumour. A task was considered as performed incorrectly if an error or an absence of response was observed after stimulation was applied. The stimulation coordinates were registered on original MRI scans via a neuronavigation system.

Intraoperative tasks [9,10] included: number counting 1–10 to record areas of speech arrest, D-80 oral picture as naming task, the Pyramid and Palm Trees Test (PPTT) as nonverbal semantic association task, a simultaneous task of left arm movement and naming to check multitasking abilities, working memory and attention, a line bisection test to check disturbances of spatial cognition, the modified version of the "Reading the Mind in the Eyes'' (RME) test [11,12] to check mentalizing (i.e., the sociocognitive function that enables human beings to attribute mental states to others) [13], and a famous faces task to check face-naming process [9].

Spatial cognition was tested with stimulation of supramarginal gyrus in parietal lesions. Naming and semantic association were tested with stimulation of ventral premotor cortex (articulatory disorders), dorsal premotor cortex (anomia) and dorsolateral prefrontal cortex (semantic disturbances) in frontal lesions. Naming, mentalizing and semantic association were tested in temporal lesions. Naming (to check phonemic paraphasia) and mentalizing were tested in parietal lesions. Working memory and attention were tested by stimulation of angular gyrus in parietal lesions. All the tasks used to test temporal and frontal areas were used in insular lesions. Face-naming was tested by stimulation in all tumour locations.

At the subcortical level, the superior longitudinal fascicle (SLF)) was stimulated to check spatial cognition, working memory and attention (in frontal, temporal and parietal lesions). Arcuate fascicle (in temporal and frontal lesions) to register phonological disturbances, and the inferior fronto-occipital fascicle (IFOF) in frontal and temporal lesions, to register semantic paraphasia. Mentalizing was tested by stimulation of the arcuate fascicle (in temporal and frontal lesions) SLF and cingulum (in frontal lesions). In frontal and temporal lesions subcortical stimulation of IFOF was used to test nonverbal semantics processing.

2.4. Postoperative follow-up

Postoperative control 3D MRI was scheduled at 1 month after surgery to calculate percentage of resection. Neuroradiology evaluators were blinded to whether electrical stimulation was applied during surgery.

Neuropsychological assessment at 6 months after surgery was performed. A patient was considered to have deficit if a decrease of performance of each task was observed compared to preoperative evaluation.

2.5. Statistical analyses

To determine the statistical significance of our results we used chi-square and Fisher's exact test for comparing categorical variables and unpaired *t*-test for continuous variables. A level of significance of $p < 0.05$ was considered.

3. Results

Our observational cohort consisted of 8 female and 7 male patients with a mean age of 53y (SD+- 11.1,range: 29–69 years). The control cohort consisted of 9 male and 6 female patients with a mean age of 49y (SD+- 8.2, range: 38–66 years). In both the observational and the control cohorts, tumours were located in 7 cases in the frontal lobe, 2 in the temporal lobe, 2 in the parietal lobe and 4 in the insula. New onset seizures were the most frequent clinical presentation at diagnosis (Table 1).

3.1. Percentage of resection (*Fig. 1*)

In the group of patients operated by using ioBM during awake surgery, 86.66 % (SD +-7.71) of resection was obtained, and gross total resection (GTR) or near GTR (resection >90 %) was achieved in 7 out of 15 patients. On the other hand, 60.33 % (SD +-16.74) of resection, and any case of GTR or near GTR was achieved in the control group. We did not observe statistically significant difference in the percentage of resection between the different tumour location inside each cohort. However, when comparing the observational cohort with the control cohort, we observed 87 % (SD +-7.5) of resection in frontal tumours operated with ioBM in awake patients compared with 72 % (SD +-9.5) in frontal tumours operated under general anaesthesia ($p = 0.0067$), and 85 % (SD +-7) and 50 % (SD +-0) respectively in parietal tumours ($p = 0.019$). 81 % (SD +-6.2) of resection was obtained in patients with insular tumours that underwent awake ioBM compared to 40 % (SD +-8.1) of resection in patients with insular tumours in the control group ($p = 0.0002$). Obtained resection in temporal tumours was 95 % (SD +-7) in awake procedures and 67 % (SD +-10.6) ($p = 0.09$) in the control group ().

In our series we did not observe a statistically significative

Table 1
Patients demographic and clinical data in both the observational and the control cohorts.

Case	Gender	Age	Awake surgery	Location	Clinical presentation
1	male	42	awake surgery	FRONTAL	seizures
2	female	56	awake surgery	FRONTAL	headache
3	female	47	awake surgery	TEMPORAL	seizures
4	male	55	awake surgery	PARIETAL	headache
5	male	69	awake surgery	FRONTAL	seizures
6	male	67	awake surgery	FRONTAL	focal deficit
7	male	58	awake surgery	INSULAR	seizures
8	female	42	awake surgery	FRONTAL	headache
9	male	44	awake surgery	TEMPORAL	headache
10	male	46	awake surgery	PARIETAL	seizures
11	female	29	awake surgery	FRONTAL	seizures
12	female	66	awake surgery	INSULAR	seizures
13	female	57	awake surgery	FRONTAL	
14	female	61	awake surgery	INSULAR	seizures
15	female	55	awake surgery	INSULAR	headache
16	male	48	non awake surgery	FRONTAL	focal deficit
17	male	66	non awake surgery	FRONTAL	seizures
18	male	58	non awake surgery	TEMPORAL	focal deficit
19	female	41	non awake surgery	PARIETAL	seizures
20	male	44	non awake surgery	FRONTAL	headache
21	male	45	non awake surgery	FRONTAL	headache
22	female	57	non awake surgery	INSULAR	seizures
23	male	38	non awake surgery	FRONTAL	seizures
24	male	53	non awake surgery	TEMPORAL	seizures
25	female	42	non awake surgery	PARIETAL	headache
26	female	43	non awake surgery	FRONTAL	headache
27	female	44	non awake surgery	INSULAR	focal deficit
28	female	52	non awake surgery	FRONTAL	headache
29	female	62	non awake surgery	INSULAR	headache
30	male	49	non awake surgery	INSULAR	seizures

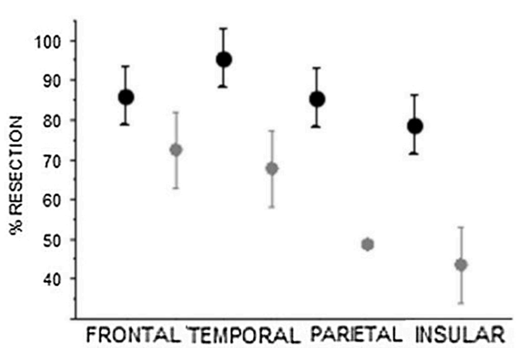

Fig. 1. Percentage of resection (mean+-SD) calculated by cerebral lobe location in patients with ioBM in awake surgery (black) and in patients under general anaesthesia (grey). We observed statistically significant difference in the percentage of resection between the observational cohort with the control cohort, in frontal, parietal and insular locations. (Unpaired *t*-test with a level of significance of $p < 0.05$).

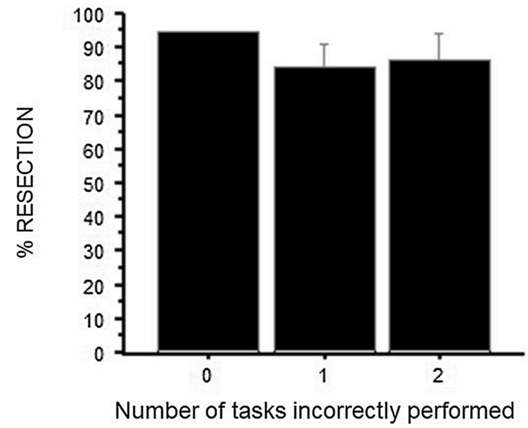

Fig. 2. Percentage of resection (mean+-SD) calculated by the number of tasks incorrectly performed after ioBM in awake surgery patients. No statistically significant difference was observed.

correlation between percentage of resection ant the number of tasks incorrectly performed after ioBM (Fig. 2).

3.2. *Tasks and locations (Figs. 3,4)*

In frontal and insular locations speech arrest response was significatively elicited in higher proportion ($p = 0.018$). Parietal location was significantly associated with higher number of incorrect responses to facial emotion recognition task ($p = 0.04$) Parietal and temporal locations were more frequently associated with intraoperative incorrect performance of bisection line task ($p = 0.018$). Parietal locations were associated with higher number of incorrect responses to working memory task ($p = 0.018$) ().

Intraoperative stimulation of temporal and parietal areas was associated with a higher proportion of incorrectly performed tasks (mean of 2) compared with frontal stimulation (mean of 0.85, $p = 0.06$).

Speech arrest was observed in 11 out of 15 patients, being the most frequently observed finding after stimulation ($p = 0.024$). On the other hand, incorrect performance of PPTT semantic task, line bisection task and working memory tasks during stimulation were only registered in 4 patients, which represent the less observed events during ioBM.

As we said, four patients did not present speech arrest after stimulation, however, in all four patients a mean of 2 incorrect responses to other tasks were observed whereas in the group of 11 patients in which speech arrest was observed, a mean of 1.09 incorrect tasks was obtained. This represents that in practically all patients showing speech arrest, this was the only finding during stimulation.

D80 naming task was recorded as incorrect mainly in frontal (2 out of 7 patients) and insular locations (3 out of 4 patients), while incorrect PPTT was observed in 2 frontal and 1 insular tumour.

3.3. *Outcome*

Neuropsychological assessment at 6 months showed that in the observational group, only one patient worsened compared to preoperative baseline, this patient suffered a decrease in the performance of naming task and semantic task. In the control group, 6 patients presented decreased performance at 6 months in at least one task: 3 cases in naming task and semantic task, 2 cases in working memory and attention, and 1 patient in mentalizing task.

Comparing both studied cohorts according to tumour location, we observed an increased rate of postoperative neuropsychological deficit at 6 months in the group of parietal tumours (2 patients) and insular tumours (3 patients), operated without awake brain mapping (Chi square $p = 0.008$)

In the observational group, postoperative neuropsychological deficit

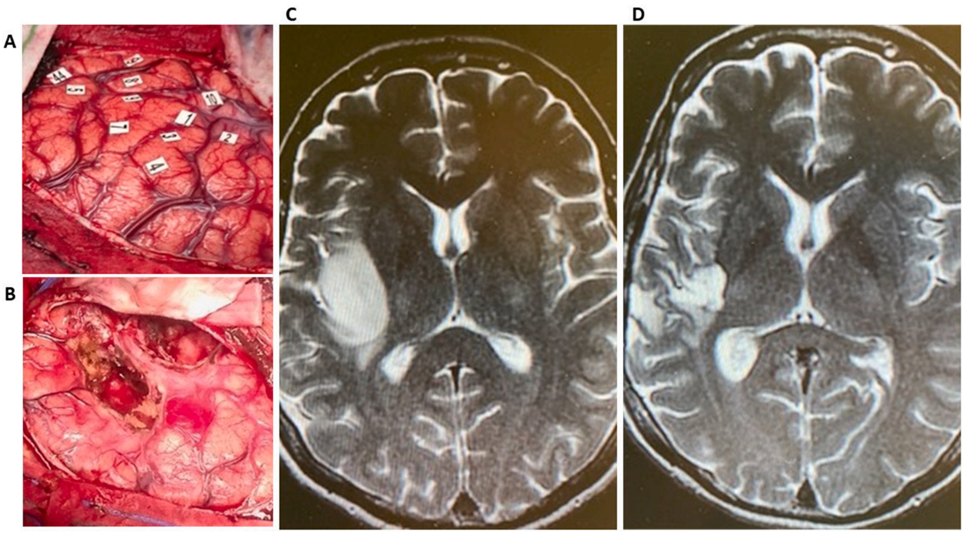

Fig. 3. **A.** Surgical field in a patient with a low-grade glioma of the right insula, after performing ioBM. Speech arrest area (label 1). Motor strip (label 3 and 4). Incorrect RME test (label 2). Incorrect famous faces task (label 10). Semantic disturbances (label 6,8 and 9) Incorrect working memory (label 5, 7 and 44). **B.** Surgical field during subcortical stimulation and resection. Inferior fronto-occipital fascicle (IFOF) was identified to register semantic paraphasia. **C.** Preoperative axial T2-weighted MRI with a right insular low-grade glioma. **D.** Postoperative axial T2-weighted MRI, showing a 10 % residual tumour at the posterior area of resection related to semantic paraphasia.

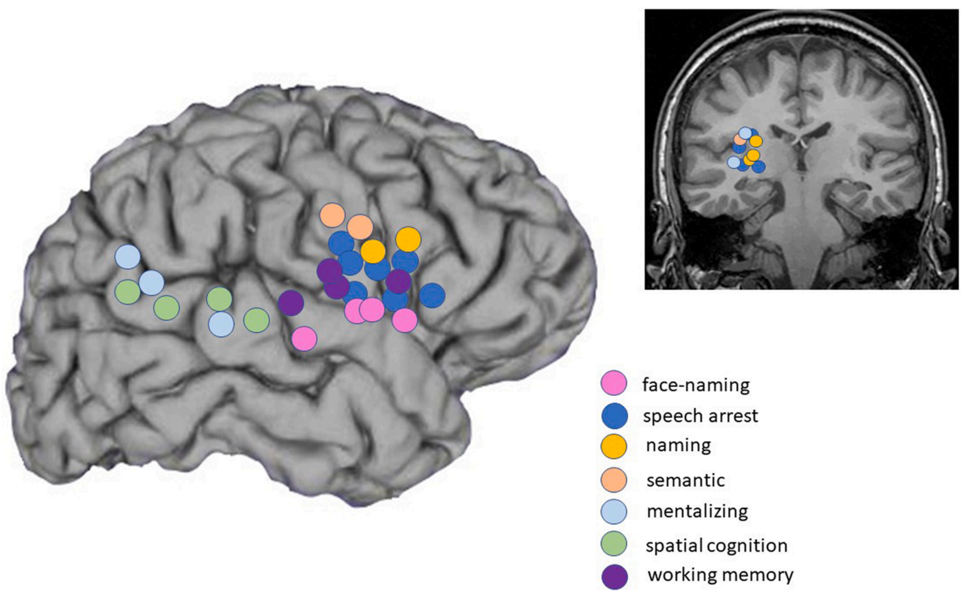

Fig. 4. Cortical and subcortical mapping data of response errors to intraoperative tasks observed after ioBM of 15 patients with right non-dominant hemisphere LGG.

at 6 months had no correlation with the results of intraoperative tasks except for semantic task. In all cases where semantic task was registered intraoperatively as correct (14 out of 15 in our series), patients were free of neuropsychological deficit at six months, which represents a positive predictive value of 85 % (p = 0.0384).

4. Discussion

Low grade gliomas can be considered pre-malignant tumours that evolve with time to more aggressive lesions such as anaplastic glioma or glioblastoma [10,14]. Therefore, an aggressive surgical approach of LGG should be always taken into consideration, provided that maximal LGG significantly increase overall survival [15,16]. However, maximal resection requires safe procedures to avoid unaffordable postoperative morbidity. Accordingly, LGG extent of resection around 90 % with minimal permanent neurological deficits, has been reported after ioBM in awake surgery, mainly in left dominant hemisphere lesions [7,17–19].

Our study suggests that intraoperative knowledge of cortico-subcortical functionality, also increases the percentage of resection of LGG in RndH as has been demonstrated in left dominant hemisphere lesions. In our series, the percentage of resection was clearly superior in the observational group than in the control group (operated without ioBM). In our experience, brain stimulation in the awake patient helps the neurosurgeon to take intraoperative decisions about when to stop resection or go further until obtain a resection with functional boundaries [4,14,20].

Location of brain tumour in a so-called non-eloquent area, has usually been a criterion to dismiss surgery with ioBM in awake patients, therefore, ioBM in RndH tumours has been rarely performed. However, it exists evidence that postoperative neuropsychological assessment of gliomas located in so-called non-eloquent areas frequently shows disabling cognitive and emotional disorders [19,21–24]. Furthermore and most importantly, not only preoperative neuropsychological assessment, but intraoperative tasks as the line bisection task [25,26], the semantic association task [5,25,27,28], the famous faces task [9] or mentalizing tasks as RME have been proved to be useful in ioBM as indicator of subjacent high cognitive and emotional functions [6].

Along these lines, our study reflects that cortical and subcortical stimulation during surgery of RndH LGG elicits a broad spectrum of functions, challenging settled assumptions that questioned the usefulness of ioBM in RndH lesions. Moreover, our findings suggest that considering RndH a non-eloquent uniform structure neglects the functional variability of this hemisphere, and that by mean of specific intraoperative tasks it is possible to accurately check specific functions, some of them unexpected, in different locations of RndH. For example, and interestingly, speech arrest during stimulation was observed in most of our patients (11 out of 15), all in frontal or insular locations. This finding has been reported elsewhere to occur after stimulation in RndH in left-handers, ambidextrous patients, and in right-handers with language disturbances during seizures [4]. However, in our experience obtaining a speech arrest response after stimulation of RndH frontal and insular locations, seems to be the rule rather than the exception. Nevertheless, we did not observe the same finding when using other intraoperative tasks of the linguistic domain such as naming and semantic tasks. I any case, it has been reported that mapping nonverbal functions is of paramount importance in RndH lesions because it may help to prevent affection of high-level functions of cognition in certain patients [4,29].

Our study suggests that could exist a pattern in the topographical distribution of functions elicited in the RndH during ioBM. For instance, and with respect to parietal tumours, stimulation of parietal lobe offered, in our experience, a wide range of findings including errors in working memory and attention, spatial cognition and mentalizing. This rich semiology of parietal lobe of RndH is consistent with other more in-depth works, that report that preservation of right angular gyrus and SLF is crucial in preservation of this high-order cognitive functions [4,19]. In our experience, right temporal lobe stimulation did not associate frequent semiology, although RndH cortico-subcortical temporal stimulation has been reported to be linked to disturbances of nonverbal semantic processing mainly through superior temporal gyrus [4,30].

Regarding outcome, most of patients in both groups presented with subtle or any neurological symptomatology at diagnosis, being new onset seizures the most frequent symptom [10]. In our study, all patients had neuropsychological assessment preoperatively based on intraoperative tasks and their performance was established as baseline to compare outcome at 6 months. Nevertheless, we did not address the issue of extensively analyse preoperative neuropsychological disturbances due to LGG. However, in the revised literature it is reported that preoperative neuropsychological evaluation shows that most patients with LGG are not asymptomatic [17] and moreover, almost two thirds of the patients had mild impairment of cognitive functioning before surgery. This findings also raise the issue of the appropriate tests and timing to establish a preoperative neuropsychological baseline. Besides, although cognitive functions have been poorly studied in the field of neuro-oncology, it is well known that brain tumour patients usually suffer postoperative cognitive disorders when some functions, including visuospatial cognition and executive functions, are not tested intraoperatively [19,21,24].

In previous studies on ioBM in awake surgery patients harbouring a brain tumour, it has been reported a decline of neurological functions immediately after surgery, with a sustained improvement between 3–6 months postoperatively [10,31]. This recovery, mostly observed in damaged language functions, has been linked to mechanisms of brain plasticity [32] that could also play an important role in the improvement of cognitive functions disturbed after surgery of RndH-located lesions [24,33]. In our study, we observed that trend in the observational group, but in the control cohort an increased rate of deficit at 6 months, particularly in parietal and insular tumours, was identified. It is noteworthy in our series that intraoperative correct performance at nonverbal semantic task has predictive value of good neuropsychological outcome. This finding could be related to wide cortico-subcortical representation of this function [14] and to disproportion of dorsolateral prefrontal cortex tumours in our series.

Although the aim of our study was to evaluate the usefulness of cortical-subcortical ioBM during awake surgery, other non-invasive techniques are available to preoperatively assess location of language and non-language functions in LGG patients, including functional MRI (fMRI), transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG). However, in our opinion, all these non-invasive options present limitations compared to ioBM. Preoperative fMRI provides a localization of eloquent functional cortex and its relationship with the tumoral lesion [34,35] but lacks the necessary sensitivity and specificity when used intraoperatively [36]. TMS is a reliable and clinically validated tool to identify functional areas belonging to the motor system, but its application in presurgical language mapping is still quite limited [37]. Finally, preoperative mapping of language and motor areas is feasible by using MEG [38], however, its use in presurgical setting is still limited and MEG systems are scarce, and indeed expensive.

4.1. Limitations of the study

One of the main limitations of our study is the small number of cases included in both groups that makes difficult to identify significant relationships from the data. Although both groups are similar in terms of tumour location, age and histological diagnosis, our research design may have included selection bias and bias due to uncontrolled variables including tumour volume, time of tumour evolution. With the purpose of obtaining meaningful results, we have included functionally different cortico-subcortical areas into larger anatomic structures, classifying our findings in four main locations (frontal, temporal, parietal and insular). This terminological simplification may lead us to imprecise conclusions regarding the effect of intraoperative stimulation on specific locations. The potential lack of accuracy of coordinates registration via a neuronavigation system may lead to substantial uncertainties in the results. Due to the characteristic displacement in brain structures originated by slow-growing lesions like LGG, and the well-known problem of intraoperative brain shift, the use of neuronavigation may carry out some inaccuracies in establishing functional locations intraoperatively. Finally, another limitation involves the definition of neuropsychological outcome. In our study, we consider a patient to have a deficit at 6 months if neuropsychological assessment worsened compared to preoperative baseline, whereas other authors advocate to define deficit more precisely (for example as a score decrease of 1,5 SD or more at 1 year after surgery) [39] in order to obtain reliable and comparable results.

Therefore, taken together our results and the mentioned limitations, the present study should be interpreted with full consideration of the exploratory nature of the analyses, and thus should be validated with confirmatory analysis within other prospective large databases.

5. Conclusions

Our study suggests that awake surgery with ioBM in RndH low grade gliomas should be considered as a useful tool to increase extent of resection especially in frontal, parietal and insular lesions. ioBM may improve outcome at 6 months in language, cognitive functions, and social cognition in awake surgery mainly in parietal and insular RndH low-grade gliomas.

Funding

No funding was received for this research.

This study was conducted in accordance with the ethical principles stated in the Helsinki Declaration and approved by the institution's ethics committee, Hospital Universitario I Politècnic La Fe Biomedic Research Ethics Committee (2014/0202)

Informed consent was obtained from all individual participants included in the study.

This article does not contain any studies with human participants performed by any of the authors.

CRediT authorship contribution statement

Ricardo Prat-Acín: Conceptualization, Methodology, Software, Supervision. **Inma Galeano-Senabre:** Data curation, Writing - original draft. **Pilar López-Ruiz:** Visualization, Data curation. **Angel Ayuso-Sacido:** Visualization, Investigation. **Raul Espert-Tortajada:** Resources, Supervision.

Declaration of Competing Interest

None of these authors has any conflict of interest to disclose.

References

[1] P.C. De Witt Hamer, S.G. Robles, A.H. Zwinderman, H. Duffau, M.S. Berger, Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis, J. Clin. Oncol. 30 (2012) 2559–2565.

[2] H. Duffau, S. Moritz-Gasser, P. Gatignol, Functional outcome after language mapping for insular World Health Organization Grade II gliomas in the dominant hemisphere: experience with 24 patients, Neurosurg. Focus 27 (2009) E7.

[3] J. Ilmberger, M. Ruge, F.W. Kreth, J. Briegel, H.J. Reulen, J.C. Tonn, Intraoperative mapping of language functions: a longitudinal neurolinguistic analysis, J. Neurosurg. 109 (2008) 583–592.

[4] T. Vilasboas, G. Herbet, H. Duffau, Challenging the myth of right nondominant hemisphere: lessons from corticosubcortical stimulation mapping in awake surgery and surgical implications, World Neurosurg. 103 (2017) 449–456.

[5] G. Herbet, S. Moritz-Gasser, H. Duffau, Direct evidence for the contributive role of the right inferior fronto-occipital fasciculus in non-verbal semantic cognition, BrainStructFunct. 222 (2017) 1597–1610.

[6] R. Nakajima, M. Kinoshita, H. Okita, T. Yahata, M. Matsui, M. Nakada, Neural networks mediating high-level mentalizing in patients with right cerebral hemispheric gliomas, FrontBehavNeurosci. 139 (2018) 215–223.

[7] Sam Ng, G. Herbet, S. Moritz-Gasser, H. Duffau, Return to work following surgery for incidental diffuse low-grade glioma: a prospective series with 74 patients, Neurosurgery (2019) doi: 10.1093/neuros/nyz513. [Epub ahead of print].

[8] G. Ojemann, C. Mateer, Human language cortex: localization of memory, syntax, and sequential motor-phoneme identification systems, Science 205 (1979) 1401–1403.

[9] E. De Witte, D. Satoer, E. Robert, H. Colle, S. Verheyen, E. Visch-Brink, P. Mariën, The Dutch linguistic intraoperative protocol: a valid linguistic approach to awake brain surgery, Brain Lang. 140 (2015) 35–48.

[10] H. Duffau, Diffuse Low-Grade Gliomas in Adults, 2nd ed., Springer, London, 2017.

[11] S. Baron-Cohen, S. Wheelwright, J. Hill, Y. Raste, Plumb I The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or highfunctioning autism, J. Child Psychol. Psychiatry 42 (2001) 241–251.

[12] G. Herbet, G. Lafargue, S. Moritz-Gasser, F. Bonnetblanc, H. Duffau, Interfering with the neural activity of mirror-related frontal areas impairs mentalistic inferences, Brain Struct. Funct. 220 (2015) 2159–2169.

[13] D. Premack, Woodruff G Does the chimpanzee have a theory of mind? Behav. Brain Sci. 1 (1978) 515–526.

[14] H. Duffau, Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible? Neurosurg. Rev. 41 (2018) 133–139.

[15] L. Capelle, D. Fontaine, E. Mandonnet, L. Taillandier, J.L. Golmard, L. Bauchet, J. Pallud, P. Peruzzi, M.H. Baron, M. Kujas, J. Guyotat, R. Guillevin, M. Frenay, S. Taillibert, P. Colin, V. Rigau, F. Vandenbos, C. Pinelli, H. Duffau, French Réseau d'Étude des Gliomes, Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article, J. Neurosurg. 118 (2013) 1157–1168.

[16] A.S. Jakola, A.J. Skjulsvik, K.S. Myrmel, K. Sjåvik, G. Unsgård, S.H. Torp, K. Aaberg, T. Berg, H.Y. Dai, K. Johnsen, R. Kloster, O. Solheim, Surgical resection versus watchful waiting in low-grade gliomas, Ann. Oncol. 28 (2017) 1942–1948.

[17] J. Boisgueheneuc, G. Herbet, H. Duffau, Patients with incidental WHO grade II glioma frequently suffer from neuropsychological disturbances, Acta Neurochir. 158 (2016) 305–312.

[18] P. Schucht, F. Ghareeb, Duffau H surgery for low-grade glioma infiltrating the central cerebral region: location as a predictive factor for neurological deficit, epileptological outcome, and quality of life, J. Neurosurg. 119 (2013) 318–323.

[19] P. Teixidor, P. Gatignol, M. Leroy, C. Masuet-Aumatell, L. Capelle, H. Duffau, Assessment of verbal working memory before and after surgery for low-grade glioma, J. Neurooncol. 81 (2007) 305–313.

[20] G. Puglisi, T. Sciortino, M. Rossi, A. Leonetti, L. Fornia, M. Conti Nibali, A. Casarotti, F. Pessina, M. Riva, G. Cerri, L. Bello, Preserving executive functions in nondominant frontal lobe glioma surgery: an intraoperative tool, J. Neurosurg. 131 (2018) 474–480.

[21] F. du Boisgueheneuc, R. Levy, E. Volle, M. Seassau, H. Duffau, S. Kinkingnehun, Y. Samson, S. Zhang, B. Dubois, Functions of the left superior frontal gyrus in humans: a lesion study, Brain 129 (2006) 3315–3328.

[22] A. Mainio, H. Hakko, A. Niemelä, J. Koivukangas, P. Räsänen, Depression and functional outcome in patients with brain tumors: a population-based 1-year follow-up study, J. Neurosurg. 103 (2005) 841–847.

[23] A. Mainio, S. Tuunanen, H. Hakko, A. Niemelä, J. Koivukangas, P. Räsänen, Decreased quality of life and depression as predictors for shorter survival among patients with low-grade gliomas: a follow-up from 1990 to 2003, Eur. Arch. Psychiatry Clin. Neurosci. 256 (2006) 516–521.

[24] H. Duffau, Awake surgery for nonlanguage mapping, Neurosurgery 66 (2010) 523–528.

[25] E. Mandonnet, P. De Witt Hamer, I. Poisson, I. Whittle, A.L. Bernat, D. Bresson, C. Madadaki, S. Bouazza, R. Ursu, A.F. Carpentier, B. George, S. Froelich, Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25cases, Neurosurgery 76 (2015) 382–389.

[26] G. Vallar, L. Bello, E. Bricolo, A. Castellano, A. Casarotti, A. Falini, M. Riva, E. Fava, C. Papagno, Cerebral correlates of visuospatial neglect: a direct cerebral stimulation study, Hum. Brain Mapp. 35 (2014) 1334–1350.

[27] G. Herbet, S. Moritz-Gasser, H. Duffau, Electrical stimulation of the dorsolateral prefrontal cortex impairs semantic cognition, Neurology 90 (2018) 1077–1084.

[28] W.H. Chang, Y.C. Pei, K.C. Wei, Y.P. Chao, M.H. Chen, H.A. Yeh, F.S. Jaw, P. Y. Chen, Intraoperative linguistic performance during awake brain surgery predicts postoperative linguistic deficits, J. Neurooncol. 139 (2018) 215–223.

[29] S. Moritz-Gasser, G. Herbet, H. Duffau, Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: a brain electrostimulation study, Neuropsychologia 51 (2013) 1814–1822.

[30] G. Herbet, S. Moritz-Gasser, H. Duffau, Direct evidence for the contributive role of the right inferior fronto-occipital fasciculus in non-verbal semantic cognition, Brain Struct. Funct. 222 (2017) 1597–1610.

[31] E. Finch, D.A. Copland, Language outcomes following neurosurgery for brain tumours: a systematic review, Neuro Rehab. 34 (2014) 499–514.

[32] G.S. Robles, P. Gatignol, S. Lehéricy, H. Duffau, Long-term brain plasticity allowing multiple-stages surgical approach for WHO grade II gliomas in eloquent areas: a combined study using longitudinal functional MRI and intraoperative electrical stimulation, J. Neurosurg. 109 (2008) 615–624.

[33] K. Motomura, L. Chalise, F. Ohka, K. Aoki, K. Tanahashi, M. Hirano, T. Nishikawa, J. Yamaguchi, H. Shimizu, T. Wakabayashi, A. Natsume, Neurocognitive and functional outcomes in patients with diffuse frontal lower-grade gliomas undergoing intraoperative awake brain mapping, J. Neurosurg. 17 (2019) 1–9.

[34] Y. Tie, L. Rigolo, I.H. Norton, R.Y. Huang, W. Wu, D. Orringer, S. Mukundan Jr, A. J. Golby, Defining language networks from resting-state fMRI for surgical planning, a feasibility study, Hum. Brain Mapp. 35 (2014) 1018–1030.

[35] A. Bizzi, Presurgical mapping of verbal language in brain tumors with functional MR imaging and MR tractography, Neuro Imaging Clin. N. Am. 19 (2009) 573–596.

[36] Td Azad, H. Duffau, Limitations of functional neuroimaging for patient selection and surgical planning in glioma surgery, Neurosurg. Focus 48 (2020) E12.

[37] T. Picht, J. Schulz, M. Hanna, S. Schmidt, O. Suess, P. Vajkoczy, Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex, Neurosurgery 70 (2012) 1248–1257.

[38] P.E. Tarapore, M.C. Tate, A.M. Findlay, S.M. Honma, D. Mizuiri, M.S. Berger, S. S. Nagarajan, Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation, J. Neurosurg. 117 (2012) 354–362.

[39] E. Mandonnet, G. Herbet, Duffau H. Letter, Introducing new tasks for intraoperative mapping in awake glioma surgery: clearing the line between patient, Care Sci. Res. Neurosurg. 86 (2020) 256–257.