



HAL
open science

Verbal fluency predicts work resumption after awake surgery in low-grade glioma patients

Marion Barberis, Isabelle Poisson, Cécile Prévost-Tarabon, Sophie Letrange, Sébastien Froelich, Bertrand Thirion, Emmanuel Mandonnet

► **To cite this version:**

Marion Barberis, Isabelle Poisson, Cécile Prévost-Tarabon, Sophie Letrange, Sébastien Froelich, et al.. Verbal fluency predicts work resumption after awake surgery in low-grade glioma patients. *Acta Neurochirurgica*, 2024, 166 (1), pp.88. 10.1007/s00701-024-05971-w . hal-04712003

HAL Id: hal-04712003

<https://hal.science/hal-04712003v1>

Submitted on 21 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Verbal fluency predicts work resumption after awake surgery in low-grade glioma patients

Marion Barberis^{1,4} · Isabelle Poisson¹ · Cécile Prévost-Tarabon¹ · Sophie Letrange¹ · Sébastien Froelich^{1,2} · Bertrand Thirion³ · Emmanuel Mandonnet^{1,2,4}

Received: 3 October 2023 / Accepted: 25 January 2024

© The Author(s), under exclusive licence to Springer-Verlag GmbH Austria, part of Springer Nature 2024

Abstract

Background Resuming professional activity after awake surgery for diffuse low-grade glioma (DLGG) is an important goal, which is not reached in every patient. Cognitive deficits can occur and persist after surgery. In this study, we analyzed the impact of mild cognitive impairments on the work resumption.

Methods Fifty-four surgeries (including five redo surgeries) performed between 2012 and 2020 for grade 2 (45) and 3 (nine) DLGG in 49 professionally active patients (mean age 40 [range 23–58.]) were included. We retrospectively extracted the results of semantic and phonemic verbal fluency tests from preoperative and 4-month postoperative cognitive assessments. Patients were interviewed about their working life after surgery, between April and June 2021.

Results Patients (85%) returned to work, most within 3 to 6 months. Patients (76%) reported subjective complaints (primarily fatigue). Self-reported symptoms and individual and clinical variables had no impact on the work resumption. Late-postoperative average Z-scores in verbal fluency tasks were significantly lower than preoperative for the entire cohort (Wilcoxon test, $p < 0.001$ for semantic and $p = 0.008$ for phonemic fluency). The decrease in Z-scores was significantly greater (Mann Whitney U-test, semantic, $p = 0.018$; phonemic, $p = 0.004$) in the group of patients who did not return to work than in the group of patients who did.

Conclusion The proportion of patients returning to work was comparable to similar studies. A decrease in verbal fluency tasks could predict the inability to return to work.

Keywords Diffuse low-grade glioma · Mild cognitive deficits · Verbal fluency task · Ability to return to work · Awake surgery

Introduction

Diffuse low-grade gliomas (DLGG) are slowly growing (4 mm per year) brain tumors, frequently located near to motor or language functional areas. In more than 90% of cases, they are revealed by an epileptic seizure in a young

(30–50 years of age) “healthy” adult [21, 26]. Despite these patients enjoy a normal social, family, and professional life at the time of the diagnosis, early oncological treatment is recommended in order to reduce the spontaneous risk of malignant transformation, an event that hampers both overall and functional survival. The reference treatment for DLGG is surgery in first line [37], as it has been demonstrated to increase overall survival [12]. The functional risk that comes with surgery is optimally controlled when resection is performed with cortical and subcortical mapping in an awake patient whose cognitive functions can be continuously monitored [6]. Hence, the objective of the resection is twofold: to preserve quality of life by identifying functional brain areas and to increase survival by performing (supra-) maximal resection. Still, despite surgery and adjuvant treatment, median survival is about 13 years for resected grade 2 astrocytoma and more than 20 years for resected grade

✉ Marion Barberis
marion.barberis@aphp.fr

¹ Neurosurgery Unit, Hôpital Lariboisière, AP-HP, 75010, Paris, France

² Université de Paris Cité, 75010 Paris, France

³ INRIA, CEA, Université Paris Saclay, 91120 Palaiseau, France

⁴ UMR 7225, Frontlab, Paris Brain Institute, CNRS, INSERM U1127, 75013 Paris, France

2 oligodendroglioma [11] For grade 3 glioma, survival is thought to be lower [8] (about 8 years for astrocytoma and 10 years for oligodendroglioma), although other authors reported similar survivals between grade 2 and grade 3 [3], a discrepancy supposed to reflect the numerous bias affecting retrospective series (differences of inclusion criteria and type of management, including biopsy vs resection and adjuvant treatments).

A full cognitive assessment is usually carried out before the surgery, a few days after, and 3 to 6 months later. Mild cognitive deficits are sometimes detected preoperatively, even though the patient leads a perfectly normal socio-professional life. Preoperative deficits might be caused by white matter infiltration, compression exerted by glioma or oedema, and might be increased by antiepileptic treatments and fatigue [14]. Language [30, 32], executive functions, working memory, and attentional capacities [4] may be affected. A significant decline is usually observed in the immediate postoperative period: global executive functions and semantic verbal fluency [35] are the most impacted. After surgery, patients commonly undergo cognitive rehabilitation, with the intention of optimizing brain reorganization and accelerating recovery. There is a lack of studies evaluating rigorously the benefit of rehabilitation in terms of cognitive outcome. Nonetheless, current guidelines recommend multidisciplinary cognitive rehabilitation for patients with brain tumors, including DLGG [38]. At late postoperative cognitive assessment, cognitive performances are therefore comparable to preoperative, but some patients still present a slight decrease in psychomotor speed and/or mild executive deficits [13]. The most sensitive tasks for detecting these disorders include timed picture naming test [1, 31] and verbal fluency tests [1, 25, 31]. These tests are twofold: semantic fluency, during which patients are asked to list orally as many animals as possible in 2 min, and phonemic fluency, during which patients are asked to list orally as many words as possible starting with letter P in 2 min. This quick and simple task, used by more than 90% of European centers performing awake surgery, has been reported to be the minimal common core of the perioperative cognitive evaluation in surgical glioma patients [17, 21, 28]. Moreover, it is a highly sensitive test, as it taps not only into language but also into executive functions [5, 9, 15].

Since DLGG affect young adults, professional life can be impacted — sometimes even before surgery. More than 30% of patients mention changes in the year before the diagnosis of the glioma: adjustment of workload, part-time work, more frequent sick leave [34]. After surgery, returning to work is the rule in a vast majority of cases. In the large cohort study by Rydén et al. [29], 63% of patients were working again 2 years after surgery. In other smaller series, 70–90% returned to work within four to 7 months [19, 23, 24, 33]. Medical factors can delay the return to work, including, but

not limited to, antiepileptic treatment, epileptic seizures, chemotherapy, radiotherapy [33], comorbidities, and having a biopsy rather than surgery [29]. Age could be a predictive factor as well, as patients under 40 seem to resume their professional life more easily and more quickly than older ones [29, 33]. Cognitive functioning also plays a role: patients who do not work again often have language, attention, or executive functions deficits [19, 22]. On the contrary, the improvement in cognitive performance after the surgery is positively correlated with professional life resumption [23]. However, to the best of our knowledge, there is no study correlating work resumption with a cognitive impact of the resection that would be detected from longitudinal follow-up of a test as quick and simple as verbal fluency.

The objective of this study was thus to investigate the impact of mild changes in cognitive functions, such as a slight decline in verbal fluency tests, on the ability to return to work after surgery.

Materials and methods

Population

We retrospectively collected clinical data of patients who underwent surgery between January 2012 and December 2020, and were still being followed at Lariboisière Hospital for a histologically confirmed IDH-mutated grade 2, or 3 glioma. Patients were included only if they were professionally active before surgery and all underwent preoperative and late postoperative cognitive assessment at Lariboisière Hospital. As the cognitive testing strongly relied on language functions, we excluded patients who spoke very little French. Among 56 patients meeting inclusion criteria, seven did not wish to participate in the study. We thus included 49 patients, among whom five underwent two surgeries several years apart. The data concerning these five patients were treated as if they were two distinct patients in the analysis of the results. Indeed, for each surgery, they had to stop and then resume their work, and underwent cognitive assessment according to the same protocol. For the sake of convenience and readability, we will therefore write in the rest of this study that our cohort comprises 54 patients, whose characteristics are summarized in Table 1.

For four patients, some scores from the cognitive assessments were lacking. One patient could not perform the verbal fluency task postoperatively because of severe language impairments, two patients living far from Paris did not come back for the cognitive assessment 4 months after surgery, and due to lack of time, several tests (including semantic fluency) had not been performed preoperatively for one patient. These patients had all resumed their professional activity, so we decided to include them in our study for all the data

Table 1 Population's characteristics

Parameter	RTW group		Non-RTW group	
	No. of patients	%	No. of patients	%
	<i>N</i> =46	85	<i>N</i> =8	15
Age at surgery (years)				
Median	40		39	
Range	23–56		30–58	
Gender				
Female	18	39	3	38
Male	28	61	5	62
Education level				
1 (< DNB)	4	9	1	12.5
2 (> DNB/< Bac)	12	26	1	12.5
3 (> Bac)	30	65	6	75
Legal professional status				
Permanent contract	25	54	2	25
Civil servant	10	22	3	37.5
Self employed	9	20	0	0
Undeclared workers	1	2	3	37.5
Temporary employed	1	2	0	0
International Standard Classification of Occupations				
1 Legislators, senior official and managers	12	26	1	12.5
2 Professionals	11	24	3	37.5
3 Technicians and associate professionals	8	17.5	1	12.5
4 Clerks	1	2	0	0
5 Service/shop/ market sales workers	8	17.5	0	0
6 Skilled agricultural and fishery workers	1	2	0	0
7 Craft and related trades workers		0	1	12.5
8 Plant and machine operators and assemblers	4	9	1	12.5
9 Elementary occupations	1	2	1	12.5
Glioma Grade				
II	39	85	6	75
III	7	15	2	25
Tumor side				
Left	30	65	3	37.5
Right	16	35	5	62.5
Tumor location				
Frontal	28	61	4	50
Temporal	5	11	2	25
Fronto-insular	5	11	0	0
Temporo-insular	5	11	1	12.5
Insular	1	2	1	12.5
Parietal	1	2	0	0
Fronto-temporo-insular	1	2	0	0
Tumor volume (cm³)				
Median	29.8		38.2	
Range	1.7–128		13.5–150	
Extent of resection (%)				
Median	98		98	
Range	69–100		64–100	
Post-operative treatments				
Anti-epileptic drugs	39	85	7	87.5
Cognitive rehabilitation	38	83	6	75
Chemotherapy	14	32	5	62
Radiotherapy	6	12	0	0

RTW return to work, DNB Diplôme National du Brevet, equivalent of General Certificate of Secondary Education, Bac baccalaureate, equivalent of high school diploma

relating to the questionnaire but to exclude them for all the statistical tests of association between verbal fluency tests and ability to return to work. Complete data are detailed in Online resource 1.

This study was conducted with our institutions' ethical standards for a retrospective study. Patients were informed about the use of their pseudonymized data for the purpose of clinical research, and their oral consent was obtained and registered in writing by the clinicians.

Data collection

In order to collect detailed and personalized information, we elaborated a questionnaire with two parts: return to work after surgery, and cognitive changes in every day's life. Oral responses of the patients were collected one by one between April 15, 2021, and June 7, 2021, by telephone interview or during the follow-up consultation in the Neurosurgery Department at Lariboisière Hospital. The patients were all interviewed by the same speech therapist.

Patients were first asked about profession, occupational status, type of employment contract, delay before return to work after surgery, workload (number of hours per week) right after work resumption, adjustments on working conditions, and current workload. They were also questioned about change of company, change of job, and cessation of professional activity (even long after surgery).

They secondly were asked about treatments: duration of speech rehabilitation and antiepileptic drugs. Finally, they were asked about six cognitive or mood changes since the surgery: fatigue, language disorder, memory disorder, noise intolerance, irritability, and sadness/anxiety. They could mention one, several, all, or none of these symptoms.

Patient's occupations were classified into groups defined by the ISCO-08 International Standard Classification of Occupations [39].

Cognitive evaluations

At Lariboisière hospital, all patients undergoing awake surgery for a DLGG have the same cognitive assessment protocol as previously described [2, 18, 20]. A speech therapist performs the cognitive assessment of the patient the day before, a few days after, and 4 months after the operation. The speech therapy team consists of four speech therapists who use the same assessment protocol preoperatively, immediately postoperatively, and late postoperatively, administering the tests in the same order, with exactly the same instructions. Among the numerous tasks of the battery are two verbal fluency tests: semantic fluency (animal names for 2 min) and phonemic fluency (words beginning with letter P for 2 min) [10]. In this study, we were interested in preoperative and late postoperative scores only.

Scores of semantic and phonemic fluency tasks have been extracted from cognitive assessments digital reports and have been checked in the archived handwritten tests. Z-scores for the 50 patients for whom preoperative and postoperative data were available have been calculated with GREFEX standards [10] according to socio-cultural level and age of patients at time of assessment. At the individual level, we calculated the difference between the preoperative and postoperative Z-score and categorized a cognitive change if a difference of 2 standard deviation (SD) in one task or at least 1.5 SD in both tasks was observed according to the International Cognitive and Cancer Task Force (ICCTF) recommendations [36]. Scores, Z-scores, and the difference in performance between preoperative and postoperative were analyzed and compared at group-level (whole group/return-to-work (RTW) group/non-RTW group).

To precisely quantify the change in verbal fluency tests, we calculated two new indicators for each score and Z-score: the ratio score between the postoperative and the preoperative score, and the Z-score difference between the postoperative and preoperative Z-score. For example, in the verbal fluency task, one patient gave preoperatively 33 different animals ($Z\text{-score} = -0.4$) and postoperatively 29 different animals ($Z\text{-score} = -0.9$). The score ratio was calculated as $(29/33) = 88\%$. The Z-score difference was calculated as $(-0.9 - (-0.4)) = -0.5$.

Neurosurgical and adjuvant treatment

All patients were operated on by the same neurosurgeon, under awake condition, with cortico-subcortical mapping. Preoperative and postoperative tumor volume was calculated on 3D-flair sequences by manual segmentation with the Carestream software (Onex, Toronto, Ontario, Canada). Postoperatively, 19 patients received chemotherapy treatment, in the year following the surgery for nine of them. Six patients received radiotherapy: in addition to chemotherapy for four of them and radiotherapy only for the other two.

Statistics

Analyses were performed with Jamovi version 1.6.23. The association between clinical and/or individual variables with professional activity was assessed with the chi-square test or Fischer's exact test. We studied the influence of performance in verbal fluency tests on professional activity with the Student's *T* test for independent samples when the variables followed a normal distribution and the Mann–Whitney *U* test otherwise. We compared preoperative and postoperative fluency test scores with the Student's *T* test for paired samples or the

Wilcoxon test when the variables did not follow a normal distribution. The association between different self-reported cognitive impairments was analyzed; the association between self-reported cognitive impairments and verbal fluency scores was also studied. P -values < 0.05 were considered to be statistically significant.

Were derived receiver-operating characteristic (ROC) curves for each score to quantify how well taking it would predict whether individuals would resume or not. It is thus a non-parametric measure of association between a given score and the outcome, but with a prediction-oriented interpretation. Indeed, the area under the ROC curve (AUC) precisely measures whether an individual having a lower score has a greater chance to resume; the chance level is thus 0.5. Significance levels for the AUC were obtained by performing 10,000 shuffling of the variables and recomputing the AUC on these shuffled data.

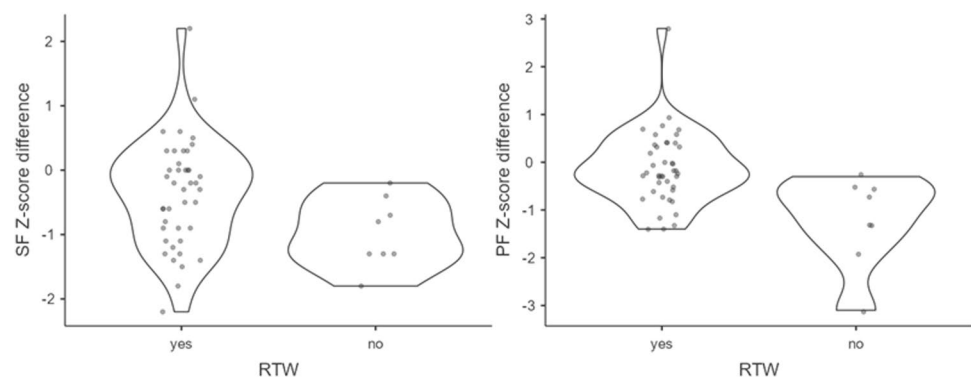
Results

Patient-level analysis of verbal fluency tasks

Figure 1 shows the violin plots of the change in Z-scores (after surgery-before surgery) for the two verbal fluency tasks. It is striking to note that in the non-RTW group, all patients had a drop in Z-scores. We also see that there is no threshold in Z-score change that would enable to predict work resumption.

Only two patients showed cognitive impairment according to ICCTF recommendation: the first one had a postoperative decrease of 2.2 SD in the semantic fluency task, and he returned to work 6 months after surgery; the second one had a decrease of 3.1 SD in the post-operative phonemic fluency task compared to preoperative, and he could not resume his job. Consequently, at individual level, no significant correlation could be found between cognitive decline in the verbal fluency tasks and return to work.

Fig. 1 Change in semantic and phonemic fluency Z-scores (after-before surgery) and return to work



Group-level analysis of verbal fluency tasks

As shown in Table 2, regarding the two verbal fluency tasks, scores and Z-scores were significantly lower post-operatively for the entire cohort. When the cohort was divided in RTW group and non-RTW group, we did not find significant differences between these two groups for preoperative and postoperative average scores and average Z-scores.

The decline in performance (score ratio and Z-score difference) was significant in both groups for semantic fluency score, semantic fluency Z-score, and phonemic fluency score (see Fig. 2). The decrease in phonemic fluency Z-score was significant only in the non-RTW group.

On the other hand, the difference in Z-score for semantic and phonemic fluency was significantly greater in the non-RTW group. In other words, the decrease in verbal fluency test affected all patients but the drop was significantly much greater in the non-RTW group.

The ROC curves corresponding to the two Z-score differences considered are displayed in the Fig. 3. We summarize them with the area under the curve (AUC).

For semantic and phonemic fluency Z-score difference, we obtained $AUC = 0.747$ ($p = 0.015$) and $AUC = 0.852$ ($p = 0.002$) respectively.

A similar analysis is provided in Online resource 2 for the score ratio rather than Z-score difference.

Factors associated with return to work

Age at surgery, gender, education level, and ISCO classification had no effect on the resumption of professional activity. The tumor side, the location, the grade of the glioma, the antiepileptic treatment, the chemotherapy, and the radiotherapy also had no effect. Likewise, following speech therapy rehabilitation had no impact on professional resumption. These results are detailed in Table 3.

Table 2 Preoperative, late post-operative verbal fluency, and work resumption

	Whole group	RTW group	Non-RTW group	<i>p. value</i>
Semantic fluency task				
Pre/post-operative average score (<i>p value</i>)	32.6/28.7 (< 0.001*)	31.98/29.12 (0.002*)	36/26.75 (0.007*)	
Pre/post-operative average Z-score (<i>p value</i>)	-0.16/-0.62 (< 0.001*)	-0.24/-0.60 (0.004*)	0.28/-0.70 (0.007*)	
Preoperative average score		31.98	36	0.867
Late post-operative average score		29.12	26.75	0.396
Score ratio (%)		91.86	71.74	0.007*
Preoperative average Z-score		-0.24	+0.28	0.918
Late post-operative average Z-score		-0.60	-0.70	0.521
Z-score difference		-0.36	-0.98	0.018*
Phonemic fluency task				
Pre/post-operative average score (<i>p value</i>)	23.8/21.7 (0.002*)	23.60/22.52 (0.022*)	25.13/17.25 (0.004*)	
Pre/post-operative average Z-score (<i>p value</i>)	0.08/-0.22 (0.008*)	0.05/-0.08 (0.075)	0.24/-0.97 (0.004*)	
Preoperative average score		23.60	25.13	0.693
Late post-operative average score		22.52	17.25	0.107
Score ratio (%)		93.91	66.05	0.004*
Preoperative average Z-score		+0.05	+0.24	0.678
Late post-operative average Z-score		-0.08	-0.97	0.053
Z-score difference		-0.13	-1.21	0.001*
Individual level				
Cognitive decline (decrease > 2SD)		1	1	
Lowered Z-scores in both tasks		15 (35.7%)	8 (100%)	0.297
Improved Z-scores in both tasks		4 (9.6%)		
One lowered/one improved Z-score		15 (35.7%)		
One stable/one lowered Z-score		6 (14.2%)		
One stable/one improved Z-score		2 (4.8%)		

SD standard deviation

* $p < 0.05$ was considered statistically significant

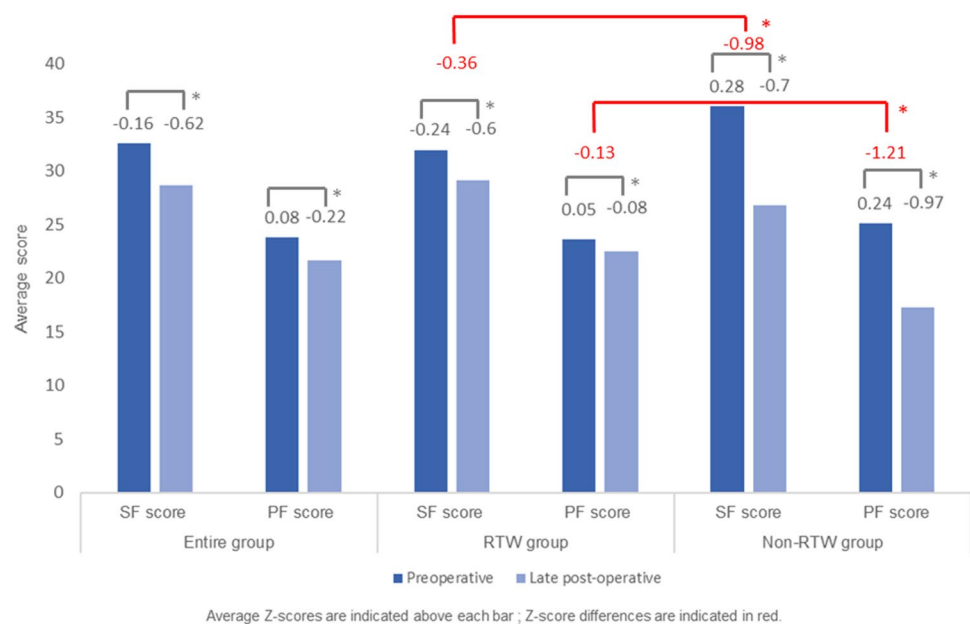
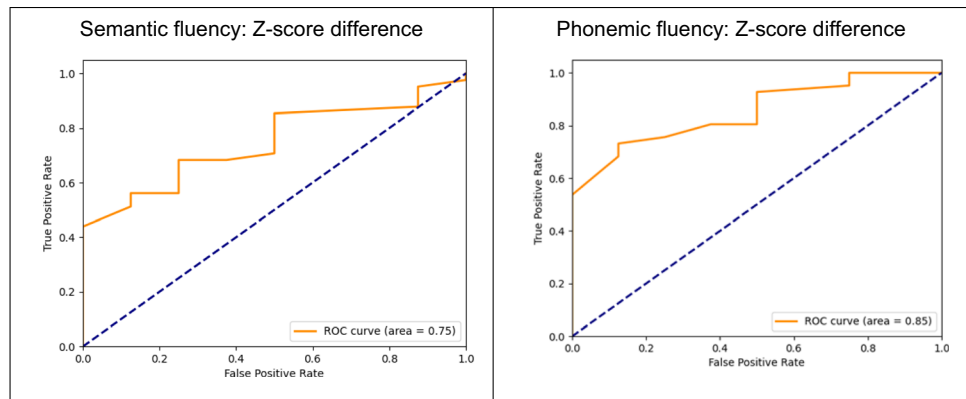
Fig. 2 Preoperative and postoperative verbal fluency performance and return to work

Fig. 3 Roc-curves for Z-score difference in verbal fluency tasks in the non-RTW group**Table 3** Correlation between demographic, clinical characteristics, and return to work

Characteristics	<i>p</i> value
Demographics	
Age at surgery	0.888
Gender	0.930
Education level	0.695
International Standard Classification of Occupations	0.222
Legal professional status	0.009*
Permanent contract-undeclared workers	0.008*
Glioma	
Grade	0.493
Side (left–right)	0.138
Location	0.319
Volume (cm ³)	0.197
Extent of resection (%)	0.740
Treatments	
Anti-epileptic drugs	0.842
Cognitive rehabilitation	0.609
Chemotherapy	0.080
Radiotherapy	0.279

* $p < 0.05$ was considered statistically significant

The ability to return to work correlated with the legal professional status before the surgery ($p = 0.009$, Fischer's exact test); working illegally rather than with a permanent contract was predictive of a higher probability of not being able to work again ($p = 0.008$, log-linear regression test). Patients who were working in the grey economy before surgery were therefore less likely to return to work: among the four patients in such situation, three did not work again, only one was able to resume a professional activity: she followed professional training as a personal assistant and was employed with a permanent contract 29 months after the surgery. Conversely, some self-employed workers resumed their activity quickly after surgery, both of them pressed by a financial constraint but facilitated by the fact of being able to adapt

Table 4 Details of work resumption

Parameters	Number of patients (%) or median [min–max]
When returning to work	
Delay before work resumption (months)	4.75 [0.3–29]
Adaptation of working conditions	20 (43.5%)
Working time 50–80%	20 (43.5%)
Working time 100%	26 (56.5%)
Duration of part-time working (months)	6 [1–50]
Current working time	
Still professionally active	40 (87%)
Full time	30 (65%)
50–80%	10 (22%)

working hours and workload: one patient returned to work 10 days after the surgery. Overall, almost half of patients with legal employment status (including self-employed patients) had their working conditions adjusted when they returned to work, at least during the first few months.

Questionnaire's answers

After surgery, 85% of patients resumed their professional activity, most within 3 to 6 months and often part-time for the first 6 months. Eight patients returned to work more than 1 year after surgery due to post-surgery chemotherapy (two); professional retraining (two); job change in the same company (two); long cognitive rehabilitation for a very cognitively demanding job (two). Details concerning work resumption are summarized in Table 4.

A few patients had ceased their activity after resuming it: one retired, one was on professional disability waiting for retirement, and a third had chosen to stop a very demanding professional activity to devote herself to her children and follow art history lessons. Three other patients were on sick leave due to a recurrence of their glioma, waiting for

a surgical decision (for more details, see Online resource 3: Work resumption, work arrangements and self-reported symptoms).

A large part of patients reported cognitive changes in every day's life after surgery (Fig. 4), whether they returned to work or not: 76% of the patients in the RTW-group and 75% in the non-RTW group reported at least one symptom.

Fatigue was by far the most frequent symptom reported by all patients. Patients who did not return to work reported significantly more symptoms than those who had resumed their professional activity (2.62 versus 1.54, $p=0.047$) and were more likely to report memory disorders ($p=0.0024$) (see Supplementary file for complete description of self-reported symptoms). Patients without any professional activity at time at the survey (including those who did not resume and those who resumed and then stopped) reported more symptoms than patients in professional activity (2.07 versus 1.57), but the difference was not significant. The total number of reported symptoms seemed to have an impact on work arrangements when resuming activity ($p=0.012$), but no symptom was identified as having a more harmful influence than the others. Finally, fatigue, irritability, sadness, anxiety, language, or memory disorders were not associated with decreased performance in fluency tests, but there was a moderate correlation (Pearson's $r = -0.386$, $p=0.005$) between noise intolerance and the Z-score difference for phonemic fluency.

Discussion

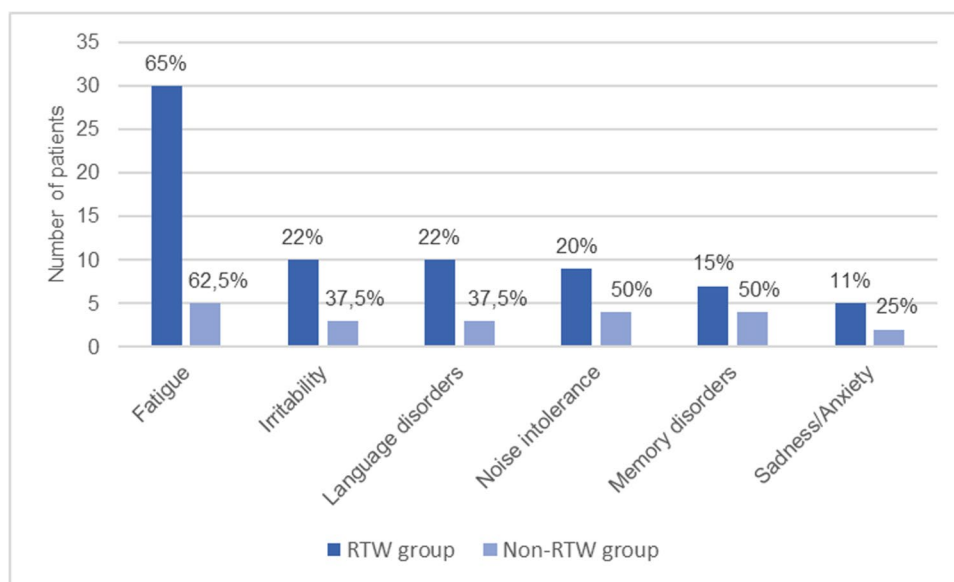
Resuming professional activity after awake surgery is an important step in the patient's journey. For medical teams, the ability of returning to work can serve as a proxy measure

of an overall successful management, encompassing surgery and neurorehabilitation. For patients, it simply means the return to a normal life. The return to work is a multifactorial outcome, as it is the result of the association of medical, individual, cognitive, professional, and even societal factors.

Among the 54 patients in our cohort, more than 80% resumed their professional activity 6 to 7 months on average after surgery. Such results are comparable to those of similar studies [19, 23, 24, 27, 33].

The decrease in the verbal fluency average scores for all patients at the late postoperative cognitive assessment was the sign that discrete cognitive deficits occurred or persisted after the surgery. These deficits were certainly mild since the scores and Z-scores globally remained within the expected norms according to socio-cultural level and age of patients, but the drop in performance was significant. The decline, which concerned phonemic and semantic fluency, was significantly more severe in the group of patients who had not returned to work. These results are in agreement with two previous studies: one showing the correlation between a decline in naming speed and the inability to return to work [22] and another one showing an interaction between postoperative cognitive improvement and return to work [23]. Moreover, authors of a recent meta-analysis study concluded that longitudinal decline were found in both verbal fluency tasks scores, semantic fluency task being the most sensitive test to detect cognitive decline in patients with DLGG [5]. Of the two measures we calculated to estimate the decrease in verbal fluency task (score ratio and Z-score difference), the Z-score difference appears to be the most relevant for detecting cognitive changes in patients' longitudinal follow-up. The score ratio is not as simple to use as the Z-score difference, and does not give additional information about the patient's cognitive function.

Fig. 4 Long term self-reported symptoms



At individual level, no correlation was found between a cognitive decline categorized according to ICCTF recommendations and the inability to return to work. However, patients who were unable to return to work all had lower Z-scores postoperatively than preoperatively with respect to semantic and phonemic verbal fluency, whereas lower Z-scores in both tasks were found in only 35% of patients who returned to work. As the verbal fluency task requires executive functions and phonemic and semantic aspects of language in equal parts, this test could therefore detect mild deficits at late post-operative assessment, provided that specific thresholds are defined. Indeed, the comparison of pre-operative and postoperative scores is essential; in our study, a moderate drop in Z-score, close to 1 standard deviation, seems to cause difficulties when returning to work.

Unlike other publications indicating that young patients were more likely resuming professional activity [34], being under 40 was not a predictive factor for returning to work in our study. Neither medical factors (glioma location, extent of resection, adjuvant treatments) nor individual factors (gender, education level, type of job) were associated with work resumption. Only the absence of legal professional status at the time of surgery was negatively associated with returning to work. Indeed, undeclared workers cannot ask adjustment of working hours and conditions, nor follow a professional retraining while benefiting from financial assistance via the French social protection system. However, we remain cautious about the effect of this variable since in our study, at time at surgery, only four patients were non-declared workers.

Physical and mental fatigue have been suggested in some studies to delay or prevent the return to work [16]. In our study, fatigue was the most common self-reported symptom. No correlation was found between receiving chemotherapy or radiotherapy and patient-reported fatigue on the questionnaire, nor between the other five self-reported symptoms. We did not find an association between fatigue and the return to professional activity after surgery, but its impact in daily life was real. The patients all explained that life “after” was necessarily different from life “before,” even if they resumed a fulfilling professional, social, and family life in a few months. Therefore, it seems essential to ask patients about their fatigability at the late postoperative cognitive assessment. There is currently no specific test to quantify it.

Limitations

Return to work is a multifactorial outcome, encompassing not only cognitive factors but also societal environment. For example, among patients able to resume their work, we cannot exclude that some of them were reemployed because of the labor law in France, which protects the employees in case of sickness: the employer is not

authorized to fire one of his employees for health issue. Moreover, on the advice of the occupational health department, a patient can be reemployed half-time, while paid full amount for 1 year (with the other half paid by the national social insurance): this arrangement certainly helped some patients to return to work. Nonetheless, the fact that almost every patient finally resumed a normal activity, and over a long period of time (average follow-up of 47 months) suggests that this arrangement did not contribute to artificially increase the rate of work resumption. On the contrary, patients working in the grey economy cannot benefit from this status, and this might have contributed to the low rate of work resumption in these patients.

In this study, we decided to focus solely on semantic and phonemic fluency tests for two reasons: they simultaneously involve language and executive functions, and they are used by almost all centers performing awake surgery for DLGG. At the individual level, we might have observed cognitive decline according to the Wefel criteria in more of our patients if we had taken into account scores of the other tests of the cognitive assessments. Nevertheless, at the group-level, the association between return-to-work difficulties and severe decline in verbal fluency tests scores encourages us to explore this task further in future studies. The current scoring of the verbal fluency tests does not take into account the strategies used by the patients (clustering, switching) or the distribution of responses during the two minutes of the task. In addition to the total number of correct responses, other measures such as the number of words every 30 s, the number and size of clusters, and the number of switches would provide a better predictive value.

The fact that fatigue was not evaluated with a validated questionnaire, but rather as a subjectively reported symptom, is another limitation of the study. Indeed, fatigue and fatigability might interfere with the cognitive performances. However, it has been demonstrated that subjective evaluation of fatigue and fatigability do not correlate with objective measures derived from decision-making in economic choices [7]. The interaction between fatigability objectively measured and cognitive performances would deserve a dedicated study: creating a test assessing impact of fatigue on cognitive functioning, and adding it to perioperative tests is the object of on-going studies in our group.

Finally, the fact that our population comprises only 50 patients suggests caution in interpreting our results. Multi-center studies and the implementation of a common cognitive assessment and follow-up protocol could make it possible to increase the size of the cohorts and analyze more precisely the impact of mild cognitive deficits on difficulties in returning to work.

Conclusion

The cognitive deficits due to gliomas being mild and specific, they are difficult to detect through the classic tests and the classical definition of a pathological score. These deficits can worsen after the surgery, and impact quality of life, including return to work. The verbal fluency task, which simultaneously involves executive functions and phonemic and semantic aspects of language, could provide a simple and efficient way to detect daily impact of the surgery despite mild cognitive changes: a drop in Z-score close to 1 SD could act as a warning that the patient is at risk of not being able to resume work. Such patients could be advised to undergo a more intensive cognitive rehabilitation and personalized support when returning to work.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00701-024-05971-w>.

Data availability All cognitive and individual data are available in Online resource 1.

Declarations

Ethical approval This study was conducted with our institutions' ethical standards for a retrospective study; all the procedures being performed were part of a routine care.

Informed consent Patients were informed about the use of their pseudonymized data for the purpose of clinical research, and their oral consent was obtained and registered in writing by the clinicians.

Conflict of interest The authors declare no competing interests.

References

- Antonsson M, Johansson C, Hartelius L, Henriksson I, Longoni F, Wengelin Å (2018) Writing fluency in patients with low-grade glioma before and after surgery: writing fluency in patients with LGG before and after surgery. *Int J Lang Commun Disord* 53(3):592–604
- Barberis M, Poisson I, Facque V, Letrange S, Prevost-Tarabon C, Houdart E, Froelich S, Levy R, Mandonnet E (2022) Group-level stability but individual variability of neurocognitive status after awake resections of right frontal IDH-mutated glioma. *Sci Rep* 12(1):6126
- Carstam L, Corell A, Smits A et al (2022) WHO grade loses its prognostic value in molecularly defined diffuse lower-grade gliomas. *Front Oncol* 11:803975
- Cochereau J, Herbet G, Duffau H (2016) Patients with incidental WHO grade II glioma frequently suffer from neuropsychological disturbances. *Acta Neurochir (Wien)* 158(2):305–312
- De Roeck L, Gillebert CR, Van Aert RCM, Vanmeenen A, Klein M, Taphoorn MJB, Gehring K, Lambrecht M, Sleurs C (2023) Cognitive outcomes after multimodal treatment in adult glioma patients: a meta-analysis. *Neuro Oncol* 25(8):1395–1414
- Duffau H (2019) Higher-order surgical questions for diffuse low-grade gliomas: supramaximal resection, neuroplasticity, and screening. *Neurosurg Clin N Am* 30(1):119–128
- Facque V, Wiehler A, Volle E, Mandonnet E, Pessiglione M (2022) Present bias in economic choice demonstrates increased cognitive fatigability of glioma patients. *Cortex* 151:281–293
- Franceschi E, Tosoni A, Bartolini S et al (2020) Histopathological grading affects survival in patients with IDH-mutant grade II and grade III diffuse gliomas. *Eur J Cancer* 137:10–17
- Gierski F, Ergis A-M (2004) Les fluences verbales : aspects théoriques et nouvelles approches. *Psy* 104(2):331–359
- Godefroy O (2012) Fonctions exécutives et pathologies neurologiques et psychiatriques : Évaluation en pratique clinique, De Boeck.
- Hervey-Jumper SL, Zhang Y, Phillips JJ et al (2023) Interactive effects of molecular, therapeutic, and patient factors on outcome of diffuse low-grade glioma. *JCO* 41(11):2029–2042
- Jakola AS, Myrmet KS, Kloster R, Torp SH, Lindal S, Unsgård G, Solheim O (2012) Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. *JAMA* 308(18):1881
- van Kessel E, Snijders TJ, Baumfalk AE, Ruis C, van Baarsen KM, Broekman ML, van Zandvoort MJE, Robe PA (2020) Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study. *J Neurooncol* 146(1):97–109
- Klein M (2012) Neurocognitive functioning in adult WHO grade II gliomas: impact of old and new treatment modalities. *Neuro Oncol* 14(Suppl 4):iv17-24
- Lemaitre A-L, Herbet G, Ng S, Moritz-Gasser S, Duffau H (2022) Cognitive preservation following awake mapping-based neurosurgery for low-grade gliomas: a longitudinal, within-patient design study. *Neuro Oncol* 24(5):781–793
- Loon E, Ernens W, Heijzenbrok-Kal M, Horemans H, Ribbers G, Bent M (2021) Long-term employment status and the association with fatigue in patients with grade II glioma. *J Rehabil Med* 53(5):jrm0198
- Loon E, Heijzenbrok-Kal M, Loon W, Bent M, Vincent A, Konig I, Ribbers G (2015) Assessment methods and prevalence of cognitive dysfunction in patients with low-grade glioma: a systematic review. *J Rehabil Med* 47(6):481–488
- Mandonnet E (2019) Transopercular resection of IDH-mutated insular glioma: a critical appraisal of an initial experience. *World Neurosurg* 132:e563–e576
- Mandonnet E, De Witt HP, Poisson I et al (2015) Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. *Neurosurgery* 76(4):382–389
- Mandonnet E, Vincent M, Valero-Cabré A, Facque V, Barberis M, Bonnetblanc F, Rheault F, Volle E, Descoteaux M, Margulies DS (2020) Network-level causal analysis of set-shifting during trail making test part B: a multimodal analysis of a glioma surgery case. *Cortex* 132:238–249
- Mandonnet E, Wager M, Almairac F et al (2017) Survey on current practice within the European Low-Grade Glioma Network: where do we stand and what is the next step? *Neuro-Oncology Practice* 4(4):241–247
- Moritz-Gasser S, Herbet G, Maldonado IL, Duffau H (2012) Lexical access speed is significantly correlated with the return to professional activities after awake surgery for low-grade gliomas. *J Neurooncol* 107(3):633–641
- Muto J, Dezamis E, Rigaux-Viode O et al (2018) Functional-based resection does not worsen quality of life in patients with a diffuse low-grade glioma involving eloquent brain regions: a prospective cohort study. *World Neurosurg* 113:e200–e212
- Ng S, Herbet G, Moritz-Gasser S, Duffau H (2020) Return to work following surgery for incidental diffuse low-grade

- glioma: a prospective series with 74 patients. *Neurosurgery* 87(4):720–729
25. Niki C, Kumada T, Maruyama T, Tamura M, Kawamata T, Mura-gaki Y (2020) Primary cognitive factors impaired after glioma surgery and associated brain regions. *Behav Neurol* 2020:1–9
 26. Pallud J, Audureau E, Blonski M et al (2014) Epileptic seizures in diffuse low-grade gliomas in adults. *Brain* 137(Pt 2):449–462
 27. Pascual JSG, Duffau H (2022) The need to consider return to work as a main outcome in patients undergoing surgery for dif-fuse low-grade glioma: a systematic review. *Acta Neurochir* 164(10):2789–2809
 28. Rofes A, Mandonnet E, Godden J et al (2017) Survey on current cognitive practices within the European Low-Grade Glioma Net-work: towards a European assessment protocol. *Acta Neurochir* 159(7):1167–1178
 29. Rydén I, Carstam L, Gulati S, Smits A, Sunnerhagen KS, Hell-ström P, Henriksson R, Bartek J, Salvesen Ø, Jakola AS (2020) Return to work following diagnosis of low-grade glioma: a nation-wide matched cohort study. *Neurology* 95(7):e856–e866
 30. Satoer D, Vincent A, Smits M, Dirven C, Visch-Brink E (2013) Spontaneous speech of patients with gliomas in eloquent areas before and early after surgery. *Acta Neurochir (Wien)* 155(4):685–692
 31. Satoer D, Visch-Brink E, Smits M, Kloet A, Looman C, Dirven C, Vincent A (2014) Long-term evaluation of cognition after glioma surgery in eloquent areas. *J Neurooncol* 116(1):153–160
 32. Satoer D, Vork J, Visch-Brink E, Smits M, Dirven C, Vincent A (2012) Cognitive functioning early after surgery of gliomas in eloquent areas: clinical article. *JNS* 117(5):831–838
 33. Senft C, Behrens M, Lortz I, Wenger K, Filipski K, Seifert V, Forster M-T (2020) The ability to return to work: a patient-centered outcome parameter following glioma surgery. *J Neurooncol* 149(3):403–411
 34. A Smits M Zetterling M Lundin B MelinFahlstrÅ¶m M, Grabowska A, Larsson E-M, Berntsson SG, 2015 Neurological impairment linked with cortico-subcortical infiltration of diffuse low-grade gliomas at initial diagnosis supports early brain plasticity *Front Neurol* <https://doi.org/10.3389/fneur.2015.00137>
 35. Talacchi A, Santini B, Savazzi S, Gerosa M (2011) Cognitive effects of tumour and surgical treatment in glioma patients. *J Neu-rooncol* 103(3):541–549
 36. Wefel JS, Vardy J, Ahles T, Schagen SB (2011) International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 12(7):703–708
 37. Weller M, van den Bent M, Tonn JC et al (2017) European Asso-ciation for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol* 18(6):e315–e329
 38. Weyer-Jamora C, Brie MS, Luks TL, Smith EM, Hervey-Jumper SL, Taylor JW (2021) Postacute cognitive rehabilitation for adult brain tumor patients. *Neurosurg* 89(6):945–953
 39. International Standard Classification of Occupations (2012) Struc-ture, group definitions and correspondence tables. ILO Publica-tions, International Labour Office, Geneva, p 420

Comments The authors present a study concerning diffuse low-grade glioma patients (DLGG) with respect to the extent in which mild cognitive deficits after surgery, affect their work resumption. Clinical and cognitive data of the DLGG patients who had undergone awake surgery were retrospectively collected. Finally 49 patients were included in the study. The cognitive data were derived from neuropsychological assessment of the patients phonemic respectively semantic verbal fluency, one day before operation, a few days after and four months postoperatively. Between April 2021 and June 2021, the patients were interviewed by the research team about their working life and subjective complaints after surgery. Interestingly the decline in the phonemic respectively the semantic fluency four months after operation was significantly more pronounced in the patients who did not return to work than in those who resumed working life. In contrast no association was found between fatigue and return to work. The results of the present study suggest that even a relatively mild decline in verbal fluency with this function still lying within normal limits according to normative data, could be a sensitive predictor of an inability to go back to working life.

Åsa Bergendal
Stockholm Sweden

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.