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Presurgical predictors of early cognitive outcome after brain tumor resection in glioma patients

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ABSTRACT

Gliomas are commonly characterized by neurocognitive deficits that strongly impact patients' and caregivers' quality of life. Surgical resection is the mainstay of therapy, and it can also cause cognitive impairment. An important clinical problem is whether patients who undergo surgery will show post-surgical cognitive impairment above and beyond that present before surgery. The relevant rognostic factors are largely unknown.

This study aims to quantify the cognitive impairment in glioma patients 1-week after surgery and to compare different pre-surgical information (i.e., cognitive performance, tumor volume, grading, and lesion topography) towards predicting early post-surgical cognitive outcome.

We retrospectively recruited a sample of N = 47 patients affected by high-grade and low-grade glioma undergoing brain surgery for tumor resection. Cognitive performance was assessed before and immediately after (~1 week) surgery with an extensive neurocognitive battery. Multivariate linear regression models highlighted the combination of predictors that best explained post-surgical cognitive impairment.

The impact of surgery on cognitive functioning was relatively small (i.e., 85% of test scores across the whole sample indicated no decline), and pre-operative cognitive performance was the main predictor of early post-surgical cognitive outcome above and beyond information from tumor topography and volume. In fact, structural lesion information did not significantly improve the accuracy of prediction made from cognitive data before surgery.

Our findings suggest that post-surgery neurocognitive deficits are only partially explained by preoperative brain damage. The present results suggest the possibility to make reliable, individualized, and clinically relevant predictions from relatively easy-to-obtain information.

1. Introduction

Gliomas are the most frequent primary malignant intracranial tumors in adults, and represent 81 % of all primary central nervous system tumors (Ostrom et al., 2014). Neurocognitive deficits are commonly experienced and strongly impact the quality of life of both patients and caregivers (Bergo et al., 2016). An important question in the clinical routine is whether cognitive performance will deteriorate after brain

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surgery, the mainstay of glioma therapy, above and beyond the clinical status pre-surgery.

The literature on cognitive impairment in gliomas has mainly focused on tumor malignancy (Bosma et al., 2007; Desmurget et al., 2006), volume and topography (Arbula et al., 2021; Banerjee et al., 2015). Tumor malignancy is taken into account by categorizing gliomas as low-grade (LGG; grade I and II) vs high-grade (HGG; grade III and IV) according to the WHO grading system, with the latter being more fast-growing, aggressive, and more frequently associated with cognitive deficits (Bosma et al., 2007). In contrast, LGG preserve patient's cognitive performance for years (Desmurget et al., 2006). Tumor volume is also correlated with cognitive decline (e.g., executive functions, verbal fluency and perceptual speed; Hendrix et al., 2017; van Kessel et al., 2020).

Tumor topography also plays a role in cognitive outcome, especially when the dominant hemisphere is affected (Hendrix et al., 2017; Taphoorn and Klein, 2004). An attempt to reach a more fine-grained comprehension of the link between lesion anatomy and cognitive deficits in gliomas has been made through the voxel-based lesion symptom mapping (VLSM) approach (Bates et al., 2003), a popular technique in the stroke literature. However, these studies (Banerjee et al., 2015; Shallice et al., 2010) suggest that lesion topography accurately predicts deficits in some domains (e.g., language; Banerjee et al., 2015; visuospatial; Herbet and Duffau, 2022), but not in others (e.g., visuospatial memory; Campanella et al., 2018). These findings could be explained by considering that some neuropsychological tests are not optimized for anatomical damage localization (Campanella et al., 2018). Another possible explanation is that VLSM may not be sensitive in gliomas given their slow infiltration into healthy tissue which may lead to functional reorganization (Aerts et al., 2016; Desmurget et al., 2006; Duffau, 2003; Hendriks et al., 2018), weakening the link between lesion localization and cognitive deficits. This idea fits with both LGG (Rijnen et al., 2020) and HGG (Fandino et al., 1999; Majos et al., 2017), and it is particularly true for cognitive functions that are more distributed across different brain regions. Accordingly, when a brain lesion is characterized by a sudden blood supply interruption (such as in stroke) these functions are better predicted by functional networks alterations than lesion location *per se* (Siegel et al., 2016). Moreover, the edema surrounding glioma lesion also contributes to neurological deficits (Butterbrod et al., 2019).

Taken together, these findings suggest that focusing only on tumor-related information might lead to inaccurate prediction of cognitive deficits in glioma patients (Aerts et al., 2016; Rijnen et al., 2020; Taphoorn and Klein, 2004). This explains why a key challenge in neuro-oncology is to predict cognitive disability following tumor resection (for a recent review see Sinha et al., 2019), the first mainstay of glioma treatment. Since one of the main goals of tumor resection is to maintain the highest quality of life (QoL), of which cognition is a major contributor (Klein et al., 2012; Taphoorn and Klein, 2004),

a critical issue in counselling patients and caregivers on the opportunity of brain surgery is whether surgery will cause cognitive impairment (Hendriks et al., 2018). This issue is only partly understood. Some studies (Campanella et al., 2018, 2015) have investigated the acute effects of glioma surgery, but focusing either on specific tasks (Charras et al., 2015; Herbet and Duffau, 2022; Wilson et al., 2015) or only on left-lateralized tumors (Satoer et al., 2012). Immediately after surgery, sensory, motor, and language deficits have been reported mainly in LGG patients with recovery within three months (e.g., Bello et al., 2007; Teixidor et al., 2007). Conversely, HGG patients show milder changes in cognition post-surgery (Ng et al., 2019; Santini et al., 2012; Talacchi et al., 2011). A recent *meta*-analysis (Ng et al., 2019) including both LGG and HGG patients reported a positive impact of surgery on measures of attention, language, learning and memory, but a negative impact on executive functions. In clinical practice the pre-surgical cognitive status is considered a strong prognostic indicator for survival (Johnson et al., 2012) and a reliable index of tumor progression (Butterbrod et al., 2019), and several authors have pointed out that a pre-surgical neuropsychological assessment in glioma patients shall be a goal of future research (Lemaitre et al., 2022; Ng et al., 2019).

In this study we aimed to measure whether surgery worsens cognitive functions trying to answer the question "will my dad be worse after surgery?". A second aim was to measure the value of pre-surgery cognitive measures as predictors of early (1 week) post-surgery cognitive function as compared to other prognostic factors, specifically age, education, tumor location, grading and volume.

2. Materials and methods

2.1. Participants

A sample of $N = 49$ glioma patients undergoing brain surgery for tumor resection were retrospectively recruited from the University Hospital of Padova (Italy) between March 2011 and March 2017. All patients underwent awake surgery using the sleep-awake-sleep anaesthetic procedure (Della Puppa et al., 2015) with the aid of MRI navigation and intraoperative neurophysiological monitoring. Pre-surgical mapping involved functional MRI in 12.8 % (N = 6) and tractography in 6.4 % (N = 3). Moreover, 5-ALA fluorescence guidance was adopted in 29.7 % patients (N = 14) as in (Della Puppa et al., 2013).

To be included in the study patients had to be (I) aged 18 years or older (no upper age limit), (II) free from other neurological or psychiatric disorders and (III) having been administered an extensive neurocognitive battery (see below) both before (T0) and shortly after the surgery (~1 week; T1). Moreover, we excluded patients with multiple lesions. Two patients were excluded because imaging data were not available, thus the final sample was composed of $N = 47$ patients (mean age = 51.6y, age standard deviation (SD) = 12.7y; 25F; Table 1). Patients were diagnosed both LGG (49 %) and HGG (51 %), more specifically WHO grade I was diagnosed in 12 patients (26 %), grade II in 11 (23 %), grade III in 14 (30 %) and grade IV in 10 (21 %). All patients gave their written informed consent to use their data for research when they were hospitalized, and our retrospective study was approved by the Bioethical Committee of the University Hospital of Padova.

2.2. MRI data acquisition and lesion segmentation

T1-weighted (both with and without contrast agent, i.e., gadolinium) and FLAIR images were preoperatively acquired on a 3 T Philips Ingenia scanner for 26 out of 47 patients. For the remaining patients, analogous clinical protocols have been acquired on a 1.5 T Siemens Avanto scanner (13 patients) and on a 1 T Philips Polaris scanner (8 patients).

FLAIR-hyper-intense areas were manually drawn in the patient's native space by an expert neuroradiologist using ITK-SNAP software (https://www.itksnap.org; Yushkevich et al., 2006). Then, the advanced normalization tools (ANTs; Avants et al., 2008) was used to non-linearly register individual anatomical images to the symmetric MNI atlas (1 mm^3) and each binary tumor mask was then normalized to this space. The tumor mask included both lesion boundaries and edema, which is known to impact cognition(Campanella et al., 2015; Tucha et al., 2000). Tumor volume was computed as the extent of the entire mask (in mm^3). Lesion locations scarcely represented within our sample (i.e., voxels lesioned only in few patients) were discarded from the subsequent statistical analysis by retaining only voxels lesioned in at least 10 % of the sample (5 out of 47).

2.3. Neurocognitive data

We used the Esame Neuropsicologico Breve 2 (ENB2; Mondini et al., 2011), a neuropsychological battery validated on the Italian population and employed in previous investigations on glioma patients (Della Puppa et al., 2015). This battery is composed of 16 tests, i.e., digit span, immediate and delayed prose memory, interference memory (10 and 30 secs), trail making test parts A (TMT-A) and B (TMT-B), token test (five

Table 1
Demographic and clinical information on all patients. L = Left, R = Right; Education is expressed in years. Classification and grading reported in Table 1 relates to the guidelines active when patients underwent surgery.

Patient ID	Tumor type	Surgery date (year)	Grade	Hemisphere affected	Tumor volume, ml	Gender	Age	Education
1	Glioma	2016	II	R	18.42	Male	65	11
2	Glioblastoma	2012	IV	R	98.82	Male	45	8
3	Glioma	2016	I	L	3.28	Female	54	8
4	Astrocitoma	2011	IV	L	45.95	Female	58	8
5	Glioblastoma	2013	III	L	19.24	Male	68	8
6	Glioma	2014	III	L	13.35	Female	29	18
7	Astrocitoma	2014	IV	L	38.92	Female	43	18
8	Glioma	2013	II	L	33.50	Female	49	8
9	Glioma	2014	II	R	11.67	Male	64	8
10	Astrocitoma	2015	IV	L	99.26	Male	70	13
11	Glioma	2013	I	R	11.85	Female	23	18
12	Glioblastoma	2014	III	L	371.36	Male	50	16
13	Glioma	2017	I	R	192.11	Male	37	13
14	Glioblastoma	2014	IV	R	12.19	Female	69	8
15	Glioma	2012	II	L	23.97	Female	64	8
16	Oligodendroglioma	2013	III	L	56.35	Female	65	8
17	Glioma	2012	III	L	20.39	Male	59	13
18	Glioma	2012	I	L	94.46	Female	46	13
19	Glioma	2017	III	L	34.47	Male	71	5
20	Astrocitoma	2016	IV	R	27.32	Male	50	8
21	Glioma	2011	III	R	125.20	Male	41	8
22	Glioma	2013	II	L	44.46	Male	66	5
23	Astrocitoma	2017	IV	L	89.21	Male	59	4
24	Glioblastoma	2013	III	L	8.72	Female	52	12
25	Glioma	2012	II	R	23.09	Female	52	5
26	Glioma	2012	II	R	150.87	Female	47	13
27	Glioma	2012	III	L	272.77	Male	65	8
28	Glioma	2013	I	L	37.52	Male	32	13
29	Glioma	2015	I	L	5.59	Female	34	11
30	Glioblastoma	2013	III	L	30.57	Male	72	5
31	Glioma	2014	I	L	31.57	Female	37	13
32	Glioma	2011	II	L	36.12	Male	26	13
33	Glioma	2014	I	L	8.36	Male	42	8
34	Astrocitoma	2015	III	L	30.17	Female	43	13
35	Glioblastoma	2013	IV	R	34.1	Male	49	13
36	Glioma	2013	I	L	3.99	Female	44	18
37	Glioblastoma	2012	III	L	55.98	Female	46	8
38	Astrocitoma	2016	IV	R	12.47	Female	67	11
39	Glioma	2012	II	L	31.24	Female	57	18
40	Glioma	2013	III	R	13.08	Male	51	18
41	Glioma	2014	I	L	107.50	Female	45	18
42	Glioblastoma	2014	IV	L	32.47	Female	39	18
43	Glioma	2011	I	L	26.82	Male	45	9
44	Glioblastoma	2012	III	L	25.77	Female	63	8
45	Glioma	2011	I	L	15.79	Male	63	18
46	Glioma	2015	II	L	14.36	Male	52	13
47	Glioma	2012	II	L	40.30	Male	56	13

items), phonemic fluency, abstract reasoning, a brief version of the cognitive estimation, overlapping figures, spontaneous drawing, copy drawing, clock drawing, ideational and ideomotor praxis test. Cognitive scores were first Z-scored on data from $N = 370$ age-matched healthy controls. Then, to study how cognitive functions were affected by surgery, we calculated a ΔZ score (i.e., T1 —one week post-surgery—minus T0 –pre-surgery) for each test and we investigated the post-surgical decline by means of a series of one-sample t-tests. Moreover, the proportion of ΔZ scores revealing a significant cognitive decline ($\Delta Z \leq -1$) was compared to that of ΔZ scores suggesting a stable/improved performance ($\Delta Z > -1$) after the surgical procedure (van Kessel et al., 2020) (Supplementary Fig. 1). The percentage of patients showing worsening of performance between T0 and T1 ($\Delta Z \leq -1$) was statistically compared to the percentage of patients showing stable or improved performance ($\Delta Z > -1$) by means of a series of chi-square tests. Finally, to rule out the possibility that the resulting cognitive changes were biased by practice effect, we computed the Reliable Change Index (RCI; Jacobson and Truax, 1991) for individual patients and each test. Notably, since the ENB2 battery provides test–retest reliability values only for 10 tests (digit span, immediate and delayed prose memory, interference memory at 10 and 30 secs, TMT-A, TMT-B, phonemic fluency, overlapping figures, clock drawing test) the RCI was computed only for these tests. Values of RCI < -1.96 or > 1.96 indicate significant worsening or improvement, respectively, while values in between suggest a stable performance (Jacobson and Truax, 1991; Maassen et al., 2009).

Finally, a Principal Component Analysis (PCA) was run on T0 cognitive data to reduce their dimensionality (Corbetta et al., 2015; Ramsey et al., 2017). Components were retained only if their eigenvalue was > 1 (Kaiser's criterion; Kaiser, 1960), moreover the cumulative variance explained by the set of retained components had to be ≥ 80 %. This procedure resulted in $N = 8$ retained components (Supplementary Fig. 2), whose individual scores were included in the statistical models described in paragraph 2.5. The first component (PC1) mainly loaded on visuospatial analysis and planning; PC2 loaded on verbal comprehension; PC3 and PC4 related to praxis; PC5 and PC8 loaded on working memory, attention and executive functions; and, finally PC6 and PC7 loaded on working memory and language.

2.4. Tumor features and topography

We took into consideration tumor grading and volume as features potentially related to cognition. Tumor grading was classified according

to the WHO (grade I to IV), while volume was calculated on the MNI normalized lesion masks (in cm^3), as specified above. Furthermore, we included tumor topography in the statistical analysis. To this end, we ran a PCA on lesion locations (in MNI space) across all patients to reduce data dimensionality (first row Fig. 1; see Fig. 2 for the first three PCs). Then, like for the neurocognitive data, components with associated eigenvalues > 1 and showing a cumulative variance explained > 80 % were retained for further analysis ($N = 10$; Supplementary Fig. 3). Individual scores were computed for each component and used as predictors in the regression models.

2.5. Models' comparison and prediction of early post-surgical cognitive outcome

Our main aim was to compare different sets of information available preoperatively (T0) in predicting cognitive test scores at T1. More specifically, we identified four sets of predictors (each one including several variables): demographics (age and years of education), cognition at T0 (8 variables representing the first eight PCs), tumor features (volume and grading) and tumor topography (10 PCs). Then, we tested which combination of these sets of variables best predicted cognitive scores 1-week after the surgery. To this end, we built a series of multivariate linear regression models with the full set of T1 cognitive scores as dependent variables, with the aim of predicting the cognitive profile as described by the neuropsychological battery employed. In other words, each model (M*i*) included a specific combination of sets of predictors (Table 2), spanning from the baseline model (M1) including only demographics to the full model (M4) including all predictors (Fig. 1 shows a representation of the method).

The nested models were compared by means of three independent Likelihood Ratio Tests (LRTs) testing whether the addition of a set of predictors to a simpler model significantly improved model fit. This procedure identified three models that were then compared in a higher-order LRT to find the best model to describe T1 cognitive data. Furthermore, we also compared the multivariate models by means of the corrected Akaike Information Criterion (AICc; Akaike, 1987; Hurvich and Tsai, 1989). The AICc is a widely recommended index (Burnham and Anderson, 2002) to select the model (with the lowest AICc value) with the best balance between likelihood and parsimony (i.e., number of predictors), hence accounting for the risk of overfitting. Moreover, it allows to compare non-nested models. Since this measure was designed for univariate models, we built all models independently for each dependent variable (i.e., T1 cognitive scores). Then, for each univariate model, we computed the AICc and we averaged AICcs within each model to obtain a single model-specific value.

The best model resulting from this comparison was then evaluated in terms of accuracy in the prediction of T1 cognitive scores by means of a leave-one-out design (i.e., the model was trained on N-1 observations and its predictive ability was tested on the left-out observation). All statistical analyses were performed by means of R software (R Core Team, 2019) and Matlab version R2017b (Mathworks Inc.).

3. Results

A sample of glioma patients with cognitive impairments undergoing surgery for tumor resection was retrospectively recruited at the University Hospital of Padova (Italy), with N = 47 being included in the final analysis. All patients were MRI scanned and underwent a neurocognitive assessment both before and after surgery. Lesion volume was highly variable across patients (range = 4.95–442.27 cm^3; median = 37.65 cm^3, MAD = 30.76 cm^3) and the lesions were more frequently located in the left hemisphere specifically in the frontal and temporal

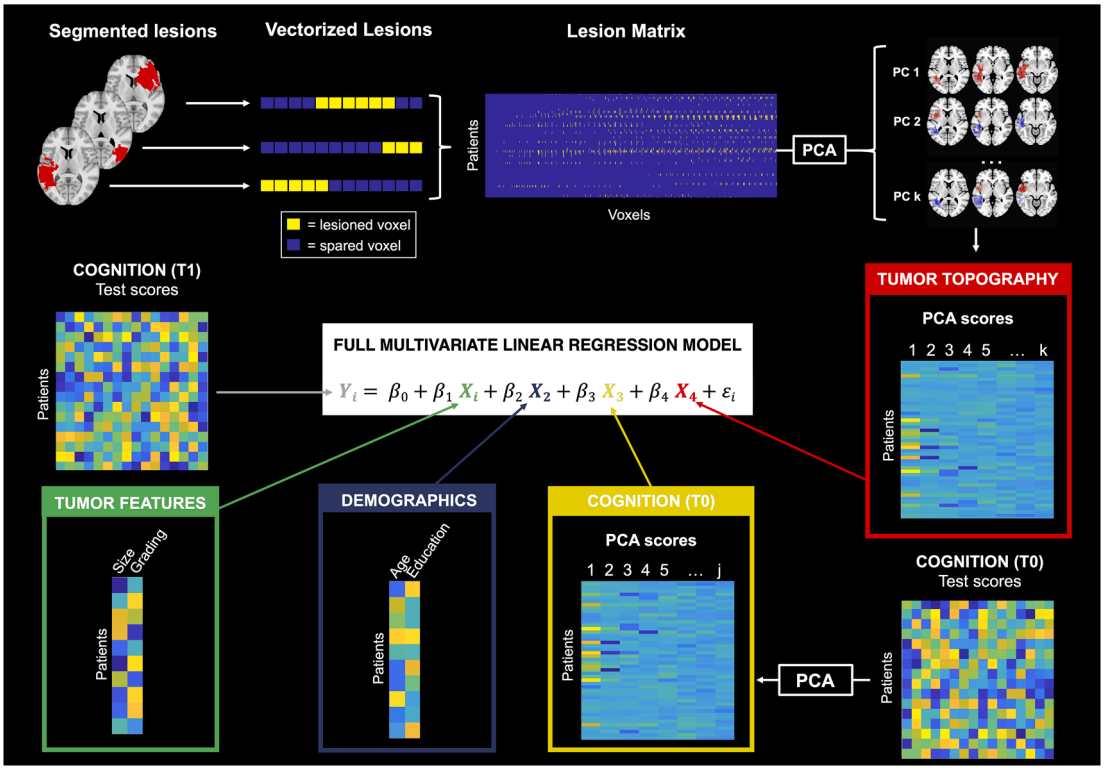

Fig. 1. Analysis flowchart. Lesion masks were first vectorized and then only voxels damaged in at least 5 out of 47 patients were retained in the final lesion matrix. After scaling data, a Principal Component Analysis (PCA) was run to reduce dimensionality of both lesion and cognitive (T0) data. The PC individual scores were then computed both for Tumor topography (in red) and Cognition in T0 (in yellow) and used as predictors of post-surgical (T1) raw cognitive scores. Patients' age and education were used as demographic predictors (in blue), while tumor size and grading were used as Tumor Features predictors (in green). All these sets of predictors were included in a series of multivariate linear regression models which underwent a model selection procedure. In the central part of the figure the model including all predictors is shown as an example.

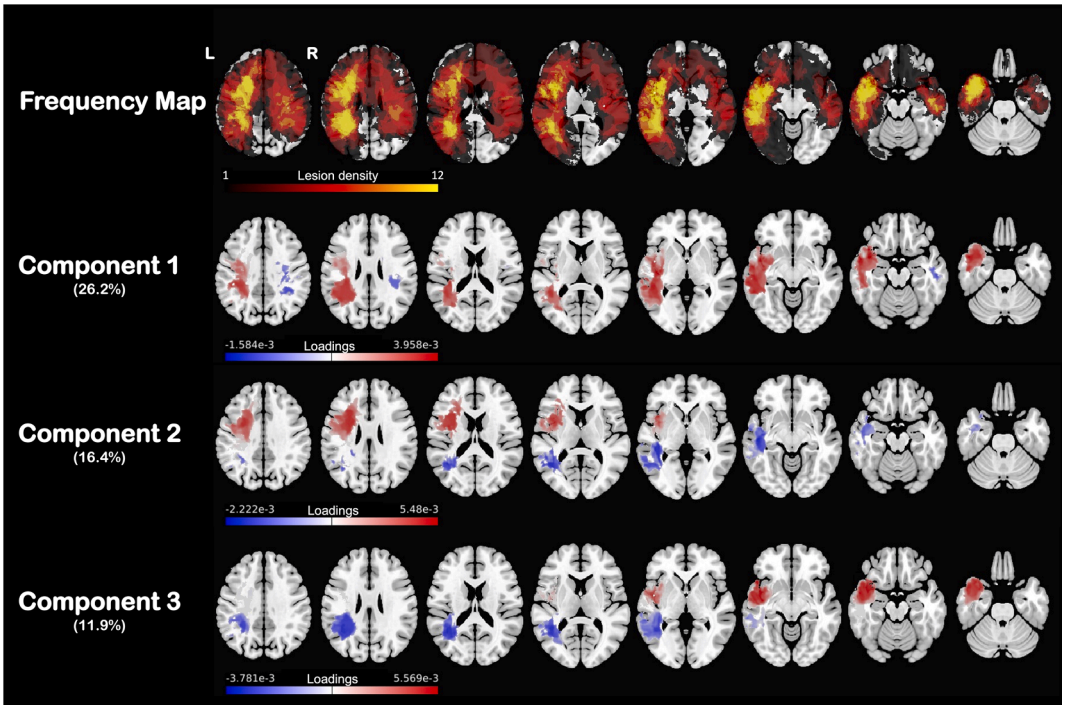

Fig. 2. Lesion anatomy and Principal Components. Line 1: overlap of lesion topography for 47 glioma patients. The color bar indicates the number of patients with lesion at each voxel. We found a high variability in lesion topography (max overlap = 12 patients). Line 2–4: for graphical purpose, only the first three PCs are reported with the relative percentage of explained variance (while in regression models the first 10 PCs were included). For each voxel, the PC loading is depicted (red = positive, blue = negative). Taken together, these 3 PCs explained roughly 55 % of the variance of lesion topography. Importantly, the PCA on lesions was run on thresholded maps, i.e., including only voxels lesioned in at least 5 patients. This explains the topographical differences between the frequency map (on all patients) and the components maps. L, left; R, right.

Table 2
Description of the models. Each model was built using different sets of predictors, each one including 2 to 10 variables. Demographics included 2 variables (age and education), Cognition (T0) included 8 variables (8 PCs of cognitive scores at T0), tumor features included 2 variables (size and grading), and tumor topography included 10 variables (10 lesions PCs).

Model	Sets of predictors included	Number of predictors
M1	Demographics	2
M2a	Demographics + Cognition (T0)	10
M2b	Demographics + Tumor topography	12
M2c	Demographics + Tumor features	4
M3a	Demographics + Cognition (T0) + Tumor features	12
M3b	Demographics + Tumor topography + Cognition (T0)	20
M3c	Demographics + Tumor features + Tumor topography	14
M4	Demographics + Cognition (T0) + Tumor features + Tumor topography	22

lobes (Fig. 2, line 1). The first three PCs explained ~ 55 % of lesions variance and captured temporo-parietal (PC1), frontal (PC2) and temporal (PC3) components of lesions. Fig. 2 (line 2 to 4) shows the topographical distribution of the first three components. The individual scores of the first 10 PCs (Supplementary Fig. 4) were used in the statistical analysis.

3.1. Small impact of surgery on cognition

The representation of the patients showing declined, stable, or improved performance (in terms of ΔZ) are shown in Fig. 3. Taking into account the cognitive scores across the whole sample (i.e., 47 patients * 16 scores = 752 scores), 85 % of scores showed a stable or improved performance (70 %: $-1 < \Delta Z \leq 0$; 15 %: $\Delta Z > 0$), with only 15 %

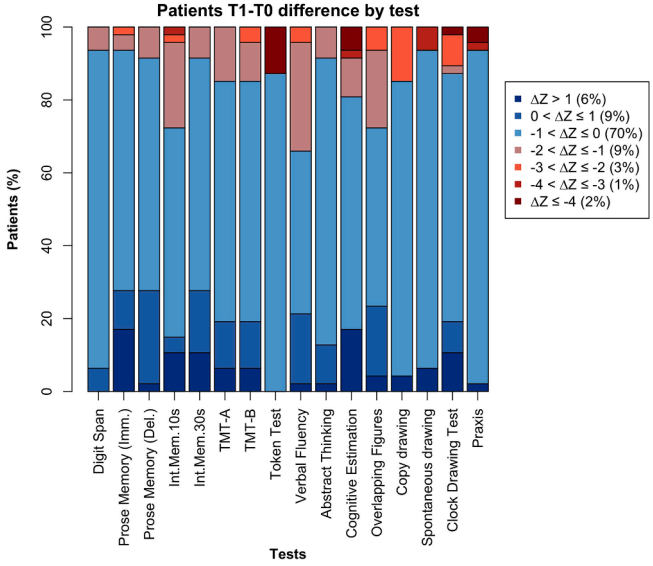

Fig. 3. Difference (ΔZ) between post- (T1) and pre-surgical (T0) cognitive scores. Each bar represents a cognitive test and colors indicate the level of T1-T0 difference. In the legend on the right, the percentage of patients showing a difference falling within each level of ΔZ is reported in brackets. Imm. = immediate; Del. Delayed; Int. Mem. = Interference memory.

showing a clinically relevant worsening, quantified as a within-patient decline of at least 1 SD ($\Delta Z \leq -1$) as in previous studies (e.g., van Kessel et al., 2020).

At the group-level, we found ΔZ scores indicating a significant decline (after Bonferroni correction) only for TMT-A ($t[46] = -3.73$, 95 %, C.I = [−0.58, −0.17], p =.004), verbal fluency ($t[46] = -4.37$, C.I =

[−0.80, −0.29], p <.001) and overlapping figures (t[46] = −3.48, C.I = [−0.72, -0.19], p =.009). Conversely, no significant differences emerged when comparing the proportion of patients with worsened (ΔZ ≤ −1) vs stable/improved (ΔZ > −1) performance over time (all chi-square ps > 0.55) in any of the neurocognitive tests. These findings were confirmed (all chi-square ps > 0.47) also when running the same chi-square analysis on the percentage of patients with RCI indicating worsened (RCI < -1.96) or stable/improved performance (RCI > -1.96), thus ruling out practice effect. The patients per each RCI category (i.e., worsened, stable, improved) are depicted in Supplementary Fig. 5. Importantly, we did not find a significant relation between the proportion of worsened vs stable/improved patients and tumor grade (HGG vs LGG) both considering ΔZ (all chi-square ps > 0.127) and RCI (all chi-square ps > 0.19).

Overall, these results suggest that most within-patient changes in cognitive performance following surgery for tumor removal were not significant (see also Supplementary figure 7), also considering practice effect.

Aside from highlighting changes in cognitive performance due to surgery, more clinically relevant information is that related to the prediction of post-surgical cognitive performance (T1) from information available at T0. To this end, we ran a model comparison to highlight which set of predictors led to the best predictive performance (see the next paragraph), thus quantifying which baseline information is most useful for this purpose.

3.2. Early post-surgical cognitive outcome is better predicted by pre-surgical cognition than by tumor features and topography

To test which set of predictors best explained cognition after surgery we built three sets of models with different combinations of predictors, which were compared by means of three LRTs (Fig. 4). The statistical assumptions for multivariate regression were met. Specifically, we tested the multivariate normality of residuals using the Mardia's test (Mardia, 1970), we controlled all models for multicollinearity by means of the Variance Inflation Factors (VIF) which should be < 10 to suggest no potentially harmful collinearity (Bowerman and O'Connell, 1990; Myers, 1990). Finally, we checked for homoscedasticity (Goldfeld-Quandt test; Goldfeld and Quandt, 1965) and for autocorrelation of residuals (Durbin-Watson test; Durbin and Watson, 1971).

The first model comparison (LRT 1) showed that the addition of cognition PCs significantly improved a demographics only model (Pillai = 5.48, F[128,104] = 1.77, p =.001). Conversely, the further addition of tumor features (Pillai = 3.56, F[80,50] = 1.54, p =.051) and tumor topography data (Pillai = 5.45, F[160,150] = 1.12, p =.24) did not significantly improve model likelihood. In LRT 2 tumor topography significantly improved a demographics-only model (Pillai = 5.98, F [160,150] = 1.39, p =.02), however the model was significantly improved after adding pre-surgical cognitive components (Pillai = 5.29, F[128,104] = 1.59, p =.007), and did not further improve with the inclusion of tumor features. LRT3 showed that adding tumor features significantly improved a model with only demographics (Pillai = 3.82, F [80,50] = 2.03, p =.004), but did not improve after adding tumor topography PCs (Pillai = 5.81, F[160,150] = 1.30, p =.051). Conversely, a full model including also T0 cognitive data was significantly more accurate (Pillai = 5.28, F[128,104] = 1.57, p =.008).

These results suggest that tumor features and topography slightly improved a simpler model based only on demographics, but the best prediction was obtained by inserting pre-surgical cognition (Fig. 4). To formally test this, a higher order LRT was run including the best models from each LRT (*M2a*, *M3b* and *M4*, respectively) to identify the final best model. This comparison confirmed that neither the addition of tumor topography (*M3b*; Pillai = 5.68, F[160,150] = 1.23, p =.097) nor the combination of tumor features and topography (*M4*; Pillai = 3.44, F [80,50] = 1.38, p =.11) significantly improved a model that included only demographics and pre-surgical cognition (*M2a*). The AICc computation showed that model *M2a* was that with the lowest value, thus indicating the best balance between model likelihood and parsimony (Supplementary Fig. 6).

Taken together, these results show that adding the pre-surgical cognitive components as predictors significantly improved simpler models. Furthermore, a model including only demographics and pre-surgical cognitive components emerged as a more parsimonious choice which allows to keep a high level of predictive ability while including less variables.

The same procedure was repeated using the percentage of worsened tests as dependent variables and the results were confirmed

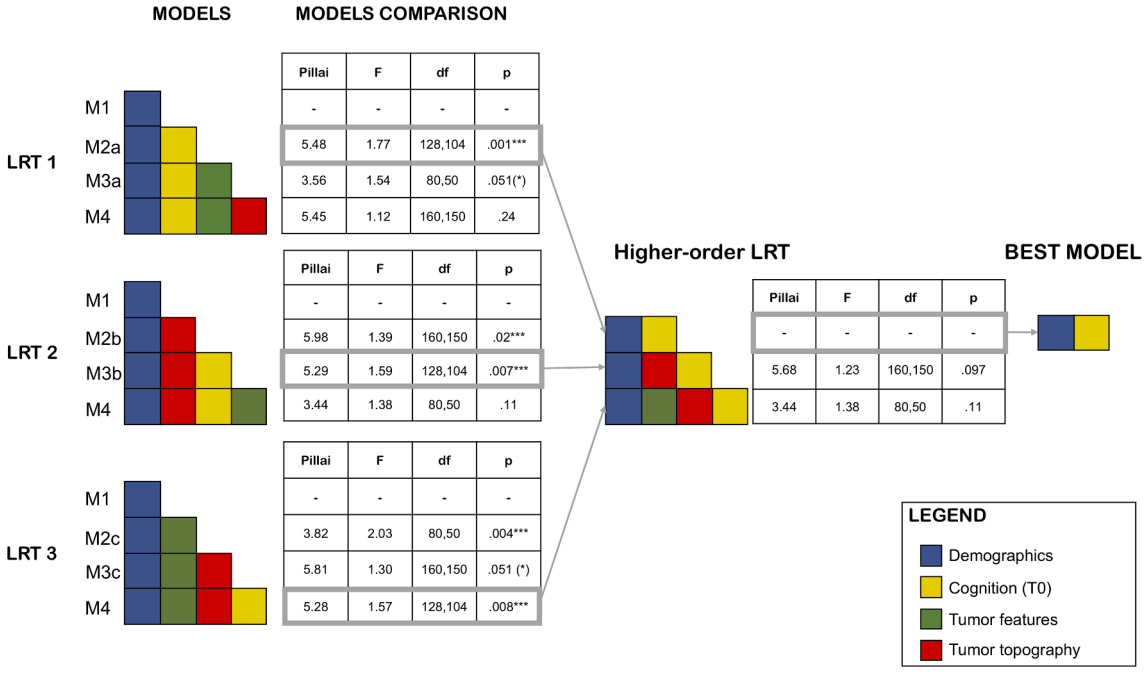

Fig. 4. Model comparison by Likelihood Ratio Tests (LRT). Each LRT included nested models, i.e., each model included the previous and added a set of predictors. ***=p <.05; (*) = p <.06.

(Supplementary Figure 8). Then, to rule out the possibility that the results were driven by specific individuals (e.g., outliers), we ran a sensitivity analysis by repeating the LRTs for *N* times, each time on data from *N*-1 patients, confirming *M2a* as the most frequently selected model across all iterations (Supplementary Figure 9). Finally, as a further control analysis, we ran a subject-specific model selection by testing the accuracy of each model in predicting T1 cognitive scores in a leave-one-out design, and by checking which model was the best in explaining each patient data (Supplementary Figure 10). The results showed that *M2a* was the most frequently selected model also at the individual level.

3.3. Glioma lesion topography and early post-surgical cognitive worsening

The previous results highlight that glioma topography did not significantly improve a model including pre-surgical cognitive data in predicting individual post-surgical cognition. This is surprising given the traditional emphasis on localization of function in neurology. However, in the models the cognitive status was summarized by PCs that sum up variability across different tasks and de-emphasize the importance of more specific lesion topography information as overall changes in cognition may be less localized than more specific deficits. We could observe that lesions associated with worsening or improved/stable cognitive performance were largely overlapped. This suggests that lesion topography is poorly informative about surgery-based cognitive worsening, and lesion *per se* do not seem to localize well cognitive functions, thus confirming previous results. This is also supported by the maps of worsening probability shown in Fig. 5.

In line with previous literature, lesion topography explains early post-surgical worsening only in few cognitive domains, e.g., verbal working memory (Interference Memory) was more likely worsened in patients with left frontal and temporo-parietal lesions (Emch et al., 2019), analogical reasoning (Abstract Thinking) worsened in patients with left frontal pole lesions (Urbanski et al., 2016), memory retrieval (Prose Memory) by tumors involving prefrontal cortex (Barredo et al., 2015), and cognitive flexibility (Overlapping Figures) was related to bilateral fronto-parietal lesions (Uddin, 2021).

3.4. Prediction of cognitive outcome 1 week after surgery

The best model resulting from the previous analyses (including demographics and T0 cognitive scores) was then used to predict the pattern of cognitive scores at T1 with a leave-one-out design. Prediction accuracy was quantified by computing Pearson's correlation between actual and predicted T1 cognitive scores (see Fig. 6; prediction error distribution is shown in Supplementary Figure 11). The multivariate

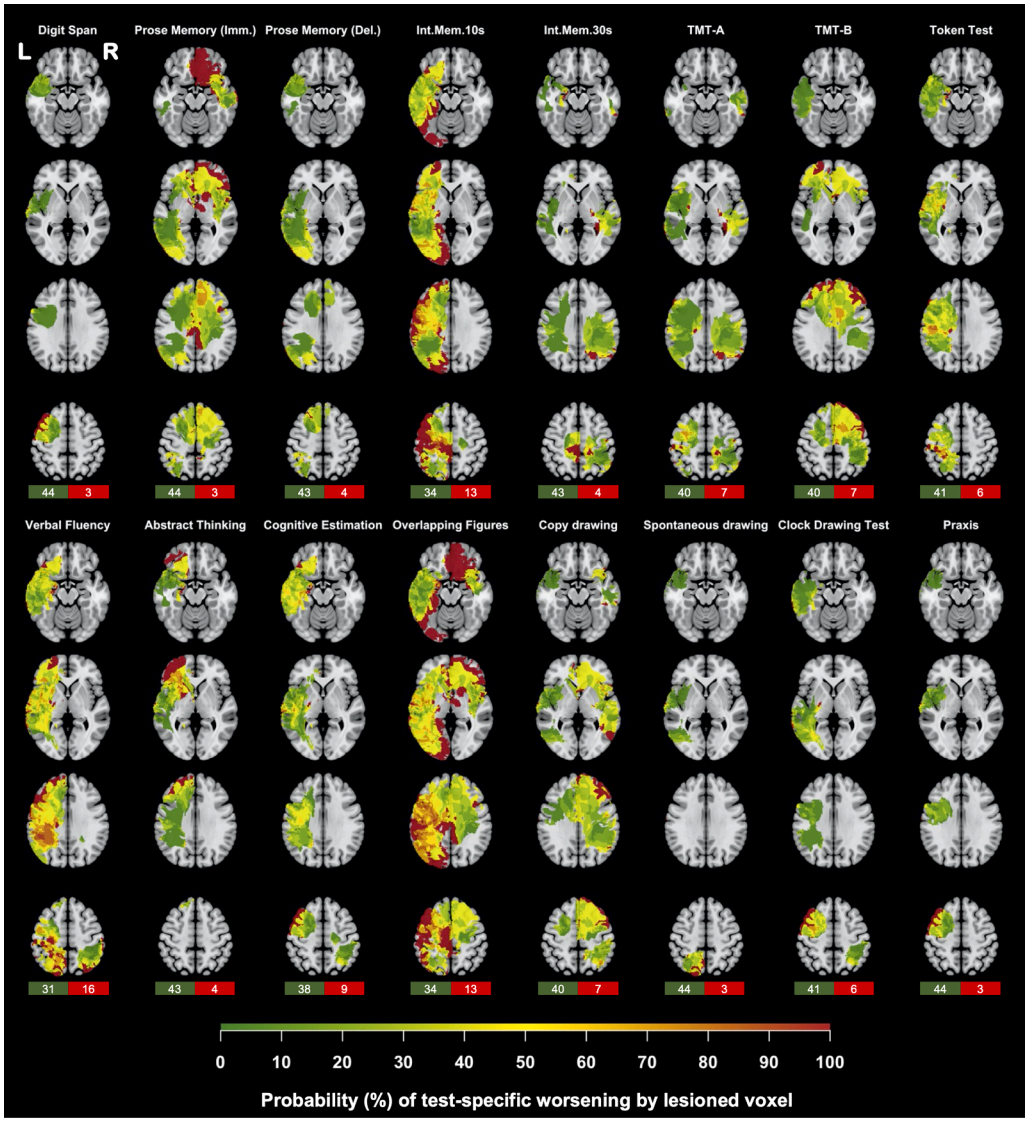

Fig. 5. Test-specific post-surgical cognitive worsening maps. For each test the ratio between the lesion frequency map of patients who showed a worsening after surgery ($\Delta Z \leq -1$) and the total frequency map was computed. The resulting maps show the voxelwise probability of post-surgical worsening in each test when that voxel was lesioned by the tumor. The colored boxes below each test-specific map report the number of patients who improved/remained stable (green) or worsened (red) after surgery. Imm. = immediate; Del. Delayed; Int. Mem. = Interference memory. Maps displayed in neurological orientation. L, left; R, right.

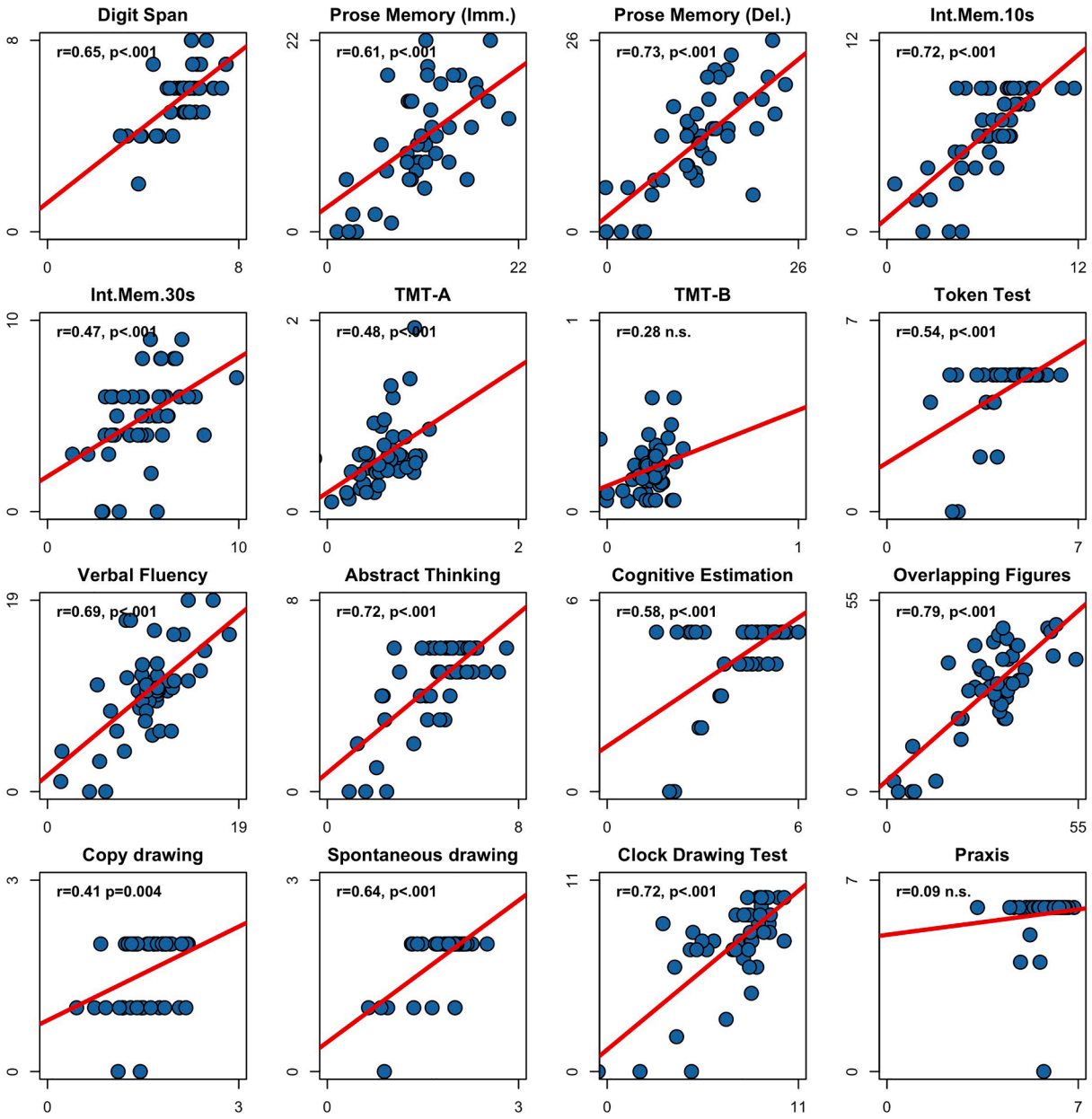

Fig. 6. Prediction of T1 cognitive scores. The figure shows the correlation between actual and predicted T1 cognitive scores using model M2a (including demographics and cognition before surgery as predictors) with a leave-one-out design. n.s. = not significant.

prediction showed an overall mean actual-predicted correlation r = 0.57 (p <.001, SD = 0.19, range 0.09-0.79), with all significant correlations but those related to TMT-B (r = 0.28) and Praxis (r = 0.09) test scores. This indicates that the model including demographics and PCs of T0 cognitive scores accurately predicted 14/16 T1 scores at the individual level.

4. Discussion

The present study aimed to quantify and predict the short-time cognitive sequelae of surgery for glioma resection, by comparing lesion topography, volume, tumor grading, and cognitive functioning prior to surgery.

As a first result, the analysis on cognitive changes between T0 and T1 using ΔZ scores revealed that only TMT-A, overlapping figures and verbal fluency showed a significant decline one week after surgery. These results are in line with the literature on cognitive deficits occurring early after surgery for gliomas which shows the main involvement of executive functions (for a review see Ng et al., 2019). On the other hand, the decline in verbal fluency could be explained by the unbalance of our sample towards left hemisphere lesions. However, when considering RCI and ΔZ levels, we did not find significant differences in any of the neurocognitive tests, with most scores across patients remaining relatively stable post-surgery (e.g., ΔZ > -1). These two findings are not in contradiction: a consistent weak worsening from pre- to post-surgery at the group level does not deny that clinically most patients remained stable within one standard deviation from normal across time points. Taken together, these results are consistent with studies showing that post-surgical cognitive deficits were not caused by surgery nor by perioperative causes in LGG (Klein et al., 2002; Schei et al., 2022) and HGG (Klein et al., 2001; Ng et al., 2019; Santini et al., 2012; Schei et al., 2022; Talacchi et al., 2011). Our results are in line with these findings and suggest that cognitive deficits occurring shortly after surgery (~1 week) mainly depend on cognitive deficits already

present pre-surgically. Conversely, some studies suggest that specific cognitive deficits can emerge immediately after surgery because of the resection of key cortical regions or white matter tracts. For instance, neurosurgical resections involving supplementary eye field (SEF) and cingulate eye field (CEF) can immediately impair visuospatial attention (Herbet and Duffau, 2022); damage to the posterior-prefrontal (PPF) and the medial orbito-frontal (mOF) regions can lead to deficits in emotional recognition (Nakajima et al., 2022); finally, the resection of inferior fronto-striatal tracts can cause inhibitory control deficits (Puglisi et al., 2019). However, as compared to the present work, these studies employed only specific cognitive tests instead of an extensive neurocognitive assessment and did not consider the variability of tests' scores in the healthy population (i.e., Z-scoring of patients' scores on controls), which can help to better quantify the possible cognitive decline after surgery.

Our findings could be explained considering the functional brain reorganization taking place during insidious tumor growth, such as in the case of gliomas (Cargnelutti et al., 2020) and relates to the so-called *lesion momentum,* an important risk factor for cognitive deficits in glioma patients (Klein, 2016; Wefel et al., 2016). This concept refers to the time the tumor growth permits to neuroplasticity processes to compensate for the functional consequences of the lesion (Gempt et al., 2017), and could explain the differential pattern of cognitive impairment in HGG and LGG patients (Bosma et al., 2007) with the latter showing milder deficits or even nearly-normal cognitive functioning for years (Desmurget et al., 2006). Recent studies have found altered functional resting-state networks topography in structurally normal regions outside the tumor or the oedema in gliomas (Silvestri et al., 2022), and impaired functional brain reorganization also in areas not directly related to the tumor or the neurosurgery act (De Baene et al., 2019; Jütten et al., 2020). In this perspective, clinical manifestation of cognitive deficits could be seen as the net result of the compensatory role of brain plasticity and functional network reorganization processes that have acted while tumor was infiltrating healthy brain tissue.

The second aim of our study was to directly compare lesion topography, tumor features and preoperative cognitive status towards predicting cognitive deficits 1-week after surgery. Our results suggest that cognitive status prior to surgery predict postsurgical cognition better than tumor features and lesion topography. This is in line with previous studies showing that cognitive deficits are only partially explained by tumor grade, size or location (Taphoorn and Klein, 2004). One possible explanation is that glioma progression impacts functional networks organization (Aerts et al., 2016; Cargnelutti et al., 2020) and structural connectivity causing both local and long-distance cognitive dysfunctions. In other words, cognitive deficits depend only partially on tumor location *per se* and presumably reflect networks disconnection (Aerts et al., 2016). For these reasons it is plausible that cognitive deficits emerging from a neurocognitive assessment are more informative than structural damage alone, as they reflect both local (i.e., damaged tissue) and long-distance (e.g., altered structural and functional network) effects of glioma proliferation.

This could also account for the differential neurocognitive effects between intrinsic tumor and other kinds of physiological events (e.g. stroke). Similarly as in gliomas, stroke can also cause functional alterations in brain regions that appear structurally normal (Carter et al., 2012, 2010; He et al., 2007), and it has been highlighted that stroke focal brain lesions have a widespread impact on both structural and functional connectome (Griffis et al., 2020, 2019; Salvalaggio et al., 2020). For these reasons, symptom-mapping can benefit from the combination of connectivity- and lesion-based approaches to explain neurocognitive deficits both in stroke (Yourganov et al., 2016) and glioma patients (De Baene et al., 2019; Nakajima et al., 2022).

Given the focal nature of structural damage caused by stroke, we could speculate that the correspondence between structural damage and neurobehavioral deficits is stronger in stroke than in glioma patients. Accordingly, our results suggest that presurgical cognitive data can better predict postoperative cognitive deficits compared to lesion topography. It is important to note though, that we are not claiming that cognition explains a higher proportion of behavioral variance than lesion or tumor features (or their combination), but rather that a model including only cognition shows a higher likelihood given postsurgical cognitive data. Importantly, our findings apply both to LGG and HGG patients, since models including grading were not comparatively selected, and since we did not find grade-related differences in our best model.

Taken together, our results have important implications for the estimation of the cognitive risk of surgical resection in terms of presurgical mapping. Indeed, we suggest that it is critical to consider the brain networks potentially affected by a lesion and not only its topographical location, and that an indirect way to do it is to quantify presurgical neurocognitive impairments. Moreover, it should be noticed that, although prediction of long-term cognitive outcome (e.g., 3–6 months) in glioma patients is an important indicator of good survival QoL, short-term prediction is also desirable since it can help caregivers and family members in knowing what to expect immediately after surgery. This also supports a recent study highlighting cognitive assessment into the clinical management of glioma patients as a crucial tool to inform patients, caregivers, and clinicians on the cognitive functioning they should expect (Rijnen et al., 2020). An early post-surgical cognitive assessment may also help in settings a prompt cognitive treatment and in understanding the effects of surgery without the confounding of post-surgical adjuvant therapy.

The present study suffers from some limitations. First, our prediction may be enhanced by information about resection volume. Unfortunately, this information was not available. Second, given the retrospective nature of the present work we could not control for practice effect in cognitive retesting by using parallel forms. Thus, we made use of test–retest data available for the ENB2 battery, that regarded 10 tests out of 16, and with retesting at 1-month. Third, we had to deal with structural images acquired with different scanners and this could affect the generalizability of our results. Moreover, the cognitive battery adopted includes brief versions of well-known cognitive tests which could have limited application for the accurate cognitive profiling of patients. Finally, further limitations of the present investigation are represented by small sample size and by the topographical representation of tumors in this sample (mainly left-lateralized). Given these limitations, further studies are required to confirm our findings on independent and larger samples.

In conclusion, since human cognition arises from a complex interplay between networks of functionally connected brain areas, it is plausible that neurocognitive deficits are only partially explained by preoperative brain damage. Importantly, these deficits may also be linked to altered long-distance connectivity in critical functional networks. Neurocognitive assessment tools are designed to capture cognitive deficits which depend on both structural and functional brain alterations. In the present work, we demonstrated that cognitive performance before surgery can reliably estimate post-surgical cognitive deficits and does not benefit from the addition of neuroimaging data. In the precision medicine framework, the present results support the systematic inclusion of neurocognitive testing in the clinical routine of glioma patients to help making clinically relevant individualized outcome predictions.

CRediT authorship contribution statement

Andrea Zangrossi: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Erica Silvestri:** Data curation, Formal analysis, Methodology. **Marta Bisio:** Data curation. **Alessandra Bertoldo:** Data curation, Formal analysis, Methodology, Supervision. **Serena De Pellegrin:** Data curation, Investigation. **Antonino Vallesi:** Data curation. **Alessandro Della Puppa:** Investigation. **Domenico D'Avella:** Investigation. **Luca Denaro:** Investigation. **Renato Scienza:** Investigation. **Sara Mondini:**

Data curation. **Carlo Semenza:** Conceptualization, Supervision, Writing – review & editing. **Maurizio Corbetta:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available upon reasonable request.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103219.

References

Aerts, H., Fias, W., Caeyenberghs, K., Marinazzo, D., 2016. Brain networks under attack: robustness properties and the impact of lesions. Brain 139, 3063–3083. https://doi.org/10.1093/brain/aww194.

Akaike, H., 1987. Factor analysis and AIC. Psychometrika 52 (3), 317–332.

Arbula, S., Della Puppa, A., De Pellegrin, S., Denaro, L., D'Avella, D., Semenza, C., Corbetta, M., Vallesi, A., 2021. Rule Perseveration during Task-Switching in Brain Tumor: A Severe Form of Task-Setting Impairment. J. Cogn. Neurosci. 1–18. https://doi.org/10.1162/jocn_a_01674.

Avants, B.B., Epstein, C.L., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med. Image Anal. 12, 26–41. https://doi.org/10.1016/j.media.2007.06.004.

Banerjee, P., Leu, K., Harris, R.J., Cloughesy, T.F., Lai, A., Nghiemphu, P.L., Pope, W.B., Bookheimer, S.Y., Ellingson, B.M., 2015. Association between lesion location and language function in adult glioma using voxel-based lesion-symptom mapping. NeuroImage Clin. 9, 617–624. https://doi.org/10.1016/j.nicl.2015.10.010.

Barredo, J., Öztekin, I., Badre, D., 2015. Ventral fronto-temporal pathway supporting cognitive control of episodic memory retrieval. Cereb. Cortex 25, 1004–1019. https://doi.org/10.1093/cercor/bht291.

Bates, E., Wilson, S.M., Saygin, A.P., Dick, F., Sereno, M.I., Knight, R.T., Dronkers, N.F., 2003. Voxel-based lesion–symptom mapping. Nat. Neurosci. 6, 448–450. https://doi.org/10.1038/nn1050.

Bello, L., Gallucci, M., Fava, M., Carrabba, G., Giussani, C., Acerbi, F., Baratta, P., Songa, V., Conte, V., Branca, V., Stocchetti, N., Papagno, C., Gaini, S.M., 2007. Intraoperative subcortical languagetract mapping guides surgical removalof gliomas involving speech areas. Neurosurgery 60, 67–82. https://doi.org/10.1227/01.NEU.0000249206.58601.DE.

Bergo, E., Lombardi, G., Pambuku, A., Della Puppa, A., Bellu, L., D'Avella, D., Zagonel, V., 2016. Cognitive rehabilitation in patients with gliomas and other brain tumors: state of the art. Biomed Res. Int. 2016, 1–11. https://doi.org/10.1155/2016/3041824.

Bosma, I., Vos, M.J., Heimans, J.J., Taphoorn, M.J.B., Aaronson, N.K., Postma, T.J., van der Ploeg, H.M., Muller, M., Vandertop, W.P., Slotman, B.J., Klein, M., 2007. The course of neurocognitive functioning in high-grade glioma patients1. Neuro. Oncol. 9, 53–62. https://doi.org/10.1215/15228517-2006-012.

Bowerman, B.L., O'Connell, R.T., 1990. Linear statistical models: an applied approach. Pacific Grove, Duxbury.

Burnham, K.P., Anderson, D.R., 2002. Information and Likelihood Theory: A Basis for Model Selection and Inference, in: Model Selection and Multimodal Inference. A Practical Information-Theoretic Approach. Speinger, pp. 49–97.

Butterbrod, E., Bruijn, J., Braaksma, M.M., Rutten, G.-J.-M., Tijssen, C.C., Hanse, M.C.J., Sitskoorn, M.M., Gehring, K., 2019. Predicting disease progression in high-grade glioma with neuropsychological parameters: the value of personalized longitudinal assessment. J. Neurooncol. 144, 511–518. https://doi.org/10.1007/s11060-019-03249-1.

Campanella, F., Fabbro, F., Ius, T., Shallice, T., Skrap, M., 2015. Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. Neurol. Oncol. 17, 1121–1131. https://doi.org/10.1093/neuonc/nov065.

Campanella, F., Del Missier, F., Shallice, T., Skrap, M., 2018. Localizing memory functions in brain tumor patients: anatomical hotspots over 260 patients. World Neurosurg. 120, e690–e709. https://doi.org/10.1016/j.wneu.2018.08.145.

Cargnelutti, E., Ius, T., Skrap, M., Tomasino, B., 2020. What do we know about pre- and postoperative plasticity in patients with glioma? A review of neuroimaging and intraoperative mapping studies. NeuroImage Clin. 28, 102435 https://doi.org/10.1016/j.nicl.2020.102435.

Carter, A.R., Astafiev, S.V., Lang, C.E., Connor, L.T., Rengachary, J., Strube, M.J., Pope, D.L.W., Shulman, G.L., Corbetta, M., 2010. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann. Neurol. 67, 365–375. https://doi.org/10.1002/ana.21905.

Carter, A.R., Shulman, G.L., Corbetta, M., 2012. Why use a connectivity-based approach to study stroke and recovery of function? Neuroimage 62, 2271–2280. https://doi.org/10.1016/j.neuroimage.2012.02.070.

Charras, P., Herbet, G., Deverdun, J., de Champfleur, N.M., Duffau, H., Bartolomeo, P., Bonnetblanc, F., 2015. Functional reorganization of the attentional networks in low-grade glioma patients: a longitudinal study. Cortex 63, 27–41. https://doi.org/10.1016/j.cortex.2014.08.010.

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C.D., Siegel, J.S., Astafiev, S.V., Rengachary, J., Zinn, K., Lang, C.E., Connor, L.T., Fucetola, R., Strube, M., Carter, A.R., Shulman, G.L., 2015. Common behavioral clusters and subcortical anatomy in stroke. Neuron 85, 927–941. https://doi.org/10.1016/j.neuron.2015.02.027.

De Baene, W., Rutten, G.M., Sitskoorn, M.M., 2019. Cognitive functioning in glioma patients is related to functional connectivity measures of the non-tumoural hemisphere. Eur. J. Neurosci. 50, 3921–3933. https://doi.org/10.1111/ejn.14535.

Della Puppa, A., De Pellegrin, S., D'Avella, E., Gioffrè, G., Rossetto, M., Gerardi, A., Lombardi, G., Manara, R., Munari, M., Saladini, M., Scienza, R., 2013. 5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature. Acta Neurochir. (Wien) 155, 965–972. https://doi.org/10.1007/s00701-013-1660-x.

Della Puppa, A., De Pellegrin, S., Lazzarini, A., Gioffrè, G., Rustemi, O., Cagnin, A., Scienza, R., Semenza, C., 2015. Subcortical mapping of calculation processing in the right parietal lobe. J. Neurosurg. 122, 1038–1041. https://doi.org/10.3171/2014.10.JNS14261.

Desmurget, M., Bonnetblanc, F., Duffau, H., 2006. Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain 130, 898–914. https://doi.org/10.1093/brain/awl300.

Duffau, H., 2003. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. J. Neurol. Neurosurg. Psychiatry 74, 901–907. https://doi.org/10.1136/jnnp.74.7.901.

Durbin, J., Watson, G.S., 1971. Testing for serial correlation in least squares regression. III. Biometrika 58, 1. https://doi.org/10.2307/2334313.

Emch, M., von Bastian, C.C., Koch, K., 2019. Neural correlates of verbal working memory: an fMRI meta-analysis. Front. Hum. Neurosci. 13 https://doi.org/10.3389/fnhum.2019.00180.

Fandino, J., Kollias, S.S., Wieser, H.G., Valavanis, A., Yonekawa, Y., 1999. Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. J. Neurosurg. 91, 238–250. https://doi.org/10.3171/jns.1999.91.2.0238.

Gempt, J., Lange, N., Bette, S., Foreman, S.C., Cammardella, J.H., Albertshauser, J., Gradtke, C., Buchmann, N., Ryang, Y.-M., Schmidt-Graf, F., Meyer, B., Ringel, F., 2017. Factors influencing neurocognitive function in patients with neuroepithelial tumors. Sci. Rep. 7, 17764. https://doi.org/10.1038/s41598-017-17833-w.

Goldfeld, S.M., Quandt, R.E., 1965. Some tests for homoscedasticity. J. Am. Stat. Assoc. 60, 539–547. https://doi.org/10.1080/01621459.1965.10480811.

Griffis, J.C., Metcalf, N.V., Corbetta, M., Shulman, G.L., 2019. Structural disconnections explain brain network dysfunction after stroke. Cell Rep. 28, 2527–2540.e9. https://doi.org/10.1016/j.celrep.2019.07.100.

Griffis, J.C., Metcalf, N.V., Corbetta, M., Shulman, G.L., 2020. Damage to the shortest structural paths between brain regions is associated with disruptions of resting-state functional connectivity after stroke. Neuroimage 210, 116589. https://doi.org/10.1016/j.neuroimage.2020.116589.

He, B.J., Snyder, A.Z., Vincent, J.L., Epstein, A., Shulman, G.L., Corbetta, M., 2007. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53, 905–918. https://doi.org/10.1016/j.neuron.2007.02.013.

Hendriks, E.J., Habets, E.J.J., Taphoorn, M.J.B., Douw, L., Zwinderman, A.H., Vandertop, W.P., Barkhof, F., Klein, M., De Witt Hamer, P.C., 2018. Linking late cognitive outcome with glioma surgery location using resection cavity maps. Hum. Brain Mapp. 39, 2064–2074. https://doi.org/10.1002/hbm.23986.

Hendrix, P., Hans, E., Griessenauer, C.J., Simgen, A., Oertel, J., Karbach, J., 2017. Neurocognitive status in patients with newly-diagnosed brain tumors in good neurological condition: the impact of tumor type, volume, and location. Clin. Neurol. Neurosurg. 156, 55–62. https://doi.org/10.1016/j.clineuro.2017.03.009.

Herbet, G., Duffau, H., 2022. Contribution of the medial eye field network to the voluntary deployment of visuospatial attention. Nat. Commun. 13, 328. https://doi.org/10.1038/s41467-022-28030-3.

Hurvich, C.M., Tsai, C.-L., 1989. Regression and time series model selection in small samples. Biometrika 76, 297–307. https://doi.org/10.1093/biomet/76.2.297.

Jacobson, N.S., Truax, P., 1991. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J. Consult. Clin. Psychol. 59, 12–19. https://doi.org/10.1037/0022-006X.59.1.12.

Johnson, D.R., Sawyer, A.M., Meyers, C.A., O'Neill, B.P., Wefel, J.S., 2012. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. Neuro. Oncol. 14, 808–816. https://doi.org/10.1093/neuonc/nos082.

Jütten, K., Mainz, V., Delev, D., Gauggel, S., Binkofski, F., Wiesmann, M., Clusmann, H., Na, C., 2020. Asymmetric <scp>tumor-related</scp> alterations of <scp>network-specific</scp> intrinsic functional connectivity in glioma patients. Hum. Brain Mapp. 41, 4549–4561. https://doi.org/10.1002/hbm.25140.

Kaiser, H.F., 1960. The application of electronic computers to factor analysis. Educ. Psychol. Meas. 20, 141–151. https://doi.org/10.1177/001316446002000116.

Klein, M., 2016. Lesion momentum as explanation for preoperative neurocognitive function in patients with malignant glioma. Neuro. Oncol. 18, 1595–1596. https://doi.org/10.1093/neuonc/now266.

Klein, M., Taphoorn, M.J., Heimans, J.J., van der Ploeg, H.M., Vandertop, W.P., Smit, E. F., Leenstra, S., Tulleken, C.A.F., Boogerd, W., Belderbos, J.S.A., Cleijne, W., Aaronson, N.K., 2001. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. J. Clin. Oncol. 19, 4037–4047. https://doi.org/10.1200/JCO.2001.19.20.4037.

Klein, M., Heimans, J., Aaronson, N., van der Ploeg, H., Grit, J., Muller, M., Postma, T., Mooij, J., Boerman, R., Beute, G., Ossenkoppele, G., van Imhoff, G., Dekker, A., Jolles, J., Slotman, B., Struikmans, H., Taphoorn, M., 2002. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. Lancet 360, 1361–1368. https://doi.org/10.1016/S0140-6736(02)11398-5.

Klein, M., Duffau, H., De Witt Hamer, P.C., 2012. Cognition and resective surgery for diffuse infiltrative glioma: an overview. J. Neurooncol. 108, 309–318. https://doi.org/10.1007/s11060-012-0811-x.

Lemaitre, A.-L., Herbet, G., Ng, S., Moritz-Gasser, S., Duffau, H., 2021. Cognitive preservation following awake mapping-based neurosurgery for low-grade gliomas: A longitudinal, within-patient design study. Neuro. Oncol. https://doi.org/10.1093/neuonc/noab275.

Maassen, G.H., Bossema, E., Brand, N., 2009. Reliable change and practice effects: Outcomes of various indices compared. J. Clin. Exp. Neuropsychol. 31, 339–352. https://doi.org/10.1080/13803390802169059.

Majos, A., Bryszewski, B., Kośla, K.N., Pfaifer, L., Jaskólski, D., Stefańczyk, L., 2017. Process of the functional reorganization of the cortical centers for movement in GBM patients: fMRI study. Clin. Neuroradiol. 27, 71–79. https://doi.org/10.1007/s00062-015-0398-7.

Mardia, K.V., 1970. Measures of multivariate skewness and kurtosis with applications. Biometrika 57, 519. https://doi.org/10.2307/2334770.

Mondini, S., Mapelli, D., Vestri, A., Arcara, G., Bisiacchi, P.S., 2011. Esame neuropsicologico breve 2: Una batteria di test per lo screening neuropsicologico.

Myers, R.H., 1990. Classical and Modern Regression with Applications. Bost, Duxbury.

Nakajima, R., Kinoshita, M., Okita, H., Nakada, M., 2022. Posterior-prefrontal and medial orbitofrontal regions play crucial roles in happiness and sadness recognition. NeuroImage Clin. 35, 103072 https://doi.org/10.1016/j.nicl.2022.103072.

Ng, J.C.H., See, A.A.Q., Ang, T.Y., Tan, L.Y.R., Ang, B.T., King, N.K.K., 2019. Effects of surgery on neurocognitive function in patients with glioma: a meta-analysis of immediate post-operative and long-term follow-up neurocognitive outcomes. J. Neurooncol. 141, 167–182. https://doi.org/10.1007/s11060-018-03023-9.

Ostrom, Q.T., Bauchet, L., Davis, F.G., Deltour, I., Fisher, J.L., Langer, C.E., Pekmezci, M., Schwartzbaum, J.A., Turner, M.C., Walsh, K.M., Wrensch, M.R., Barnholtz-Sloan, J. S., 2014. The epidemiology of glioma in adults: a "state of the science" review. Neuro. Oncol. 16, 896–913. https://doi.org/10.1093/neuonc/nou087.

Puglisi, G., Howells, H., Sciortino, T., Leonetti, A., Rossi, M., Conti Nibali, M., Gabriel Gay, L., Fornia, L., Bellacicca, A., Viganò, L., Simone, L., Catani, M., Cerri, G., Bello, L., 2019. Frontal pathways in cognitive control: direct evidence from intraoperative stimulation and diffusion tractography. Brain 142, 2451–2465. https://doi.org/10.1093/brain/awz178.

R Core Team, 2019. R: A language and environment for statistical computing.

Ramsey, L.E., Siegel, J.S., Lang, C.E., Strube, M., Shulman, G.L., Corbetta, M., 2017. Behavioural clusters and predictors of performance during recovery from stroke. Nat. Hum. Behav. 1, 38.

Rijnen, S.J.M., Kaya, G., Gehring, K., Verheul, J.B., Wallis, O.C., Sitskoorn, M.M., Rutten, G.-J., 2020. Cognitive functioning in patients with low-grade glioma: effects of hemispheric tumor location and surgical procedure. J. Neurosurg. 133 (6), 1671–1682.

Salvalaggio, A., De Filippo De Grazia, M., Zorzi, M., Thiebaut de Schotten, M., Corbetta, M., 2020. Post-stroke deficit prediction from lesion and indirect structural and functional disconnection. Brain 143, 2173–2188. https://doi.org/10.1093/brain/awaa156.

Santini, B., Talacchi, A., Squintani, G., Casagrande, F., Capasso, R., Miceli, G., 2012. Cognitive outcome after awake surgery for tumors in language areas. J. Neurooncol. 108, 319–326. https://doi.org/10.1007/s11060-012-0817-4.

Satoer, D., Vork, J., Visch-Brink, E., Smits, M., Dirven, C., Vincent, A., 2012. Cognitive functioning early after surgery of gliomas in eloquent areas. J. Neurosurg. 117, 831–838. https://doi.org/10.3171/2012.7.JNS12263.

Schei, S., Solheim, O., Salvesen, Ø., Hansen, T.I., Sagberg, L.M., 2022. Patient-reported cognitive function before and after glioma surgery. Acta Neurochir. (Wien) 164, 2009–2019. https://doi.org/10.1007/s00701-022-05261-3.

Shallice, T., Mussoni, A., D'Agostino, S., Skrap, M., 2010. Right posterior cortical functions in a tumour patient series. Cortex 46, 1178–1188. https://doi.org/10.1016/j.cortex.2010.04.005.

Siegel, J.S., Ramsey, L.E., Snyder, A.Z., Metcalf, N. V., Chacko, R. V., Weinberger, K., Baldassarre, A., Hacker, C.D., Shulman, G.L., Corbetta, M., 2016. Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. Proc. Natl. Acad. Sci. 113, E4367–E4376. https://doi.org/10.1073/pnas.1521083113.

Silvestri, E., Moretto, M., Facchini, S., Castellaro, M., Anglani, M., Monai, E., D'Avella, D., Della Puppa, A., Cecchin, D., Bertoldo, A., Corbetta, M., 2022. Widespread cortical functional disconnection in gliomas: an individual network mapping approach. Brain Commun. 4 https://doi.org/10.1093/braincomms/fcac082.

Sinha, R., Stephenson, J.M., Price, S.J., 2019. A systematic review of cognitive function in patients with glioblastoma undergoing surgery. Neuro-Oncology Pract. https://doi.org/10.1093/nop/npz018.

Talacchi, A., Santini, B., Savazzi, S., Gerosa, M., 2011. Cognitive effects of tumour and surgical treatment in glioma patients. J. Neurooncol. 103, 541–549. https://doi.org/10.1007/s11060-010-0417-0.

Taphoorn, M.J., Klein, M., 2004. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 3, 159–168. https://doi.org/10.1016/S1474-4422(04)00680-5.

Teixidor, P., Gatignol, P., Leroy, M., Masuet-Aumatell, C., Capelle, L., Duffau, H., 2007. Assessment of verbal working memory before and after surgery for low-grade glioma. J. Neurooncol. 81, 305–313. https://doi.org/10.1007/s11060-006-9233-y.

Tucha, O., Smely, C., Preier, M., Lange, K.W., 2000. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery 47, 324–334. https://doi.org/10.1097/00006123-200008000-00011.

Uddin, L.Q., 2021. Cognitive and behavioural flexibility: neural mechanisms and clinical considerations. Nat. Rev. Neurosci. 22, 167–179. https://doi.org/10.1038/s41583-021-00428-w.

Urbanski, M., Bréchemier, M.-L., Garcin, B., Bendetowicz, D., Thiebaut de Schotten, M., Foulon, C., Rosso, C., Clarençon, F., Dupont, S., Pradat-Diehl, P., Labeyrie, M.-A., Levy, R., Volle, E., 2016. Reasoning by analogy requires the left frontal pole: lesion-deficit mapping and clinical implications. Brain 139, 1783–1799. https://doi.org/10.1093/brain/aww072.

van Kessel, E., Snijders, T.J., Baumfalk, A.E., Ruis, C., van Baarsen, K.M., Broekman, M. L., van Zandvoort, M.J.E., Robe, P.A., 2020. Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study. J. Neurooncol. 146, 97–109. https://doi.org/10.1007/s11060-019-03341-6.

Wefel, J.S., Noll, K.R., Rao, G., Cahill, D.P., 2016. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. Neuro. Oncol. 18, 1656–1663. https://doi.org/10.1093/neuonc/now165.

Wilson, S.M., Lam, D., Babiak, M.C., Perry, D.W., Shih, T., Hess, C.P., Berger, M.S., Chang, E.F., 2015. Transient aphasias after left hemisphere resective surgery. J. Neurosurg. 123, 581–593. https://doi.org/10.3171/2015.4.JNS141962.

Yourganov, G., Fridriksson, J., Rorden, C., Gleichgerrcht, E., Bonilha, L., 2016. Multivariate connectome-based symptom mapping in post-stroke patients: networks supporting language and speech. J. Neurosci. 36, 6668–6679. https://doi.org/10.1523/JNEUROSCI.4396-15.2016.

Yushkevich, P.A., Piven, J., Hazlett, H.C., Smith, R.G., Ho, S., Gee, J.C., Gerig, G., 2006. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. Neuroimage 31, 1116–1128. https://doi.org/10.1016/j.neuroimage.2006.01.015.