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Mapping glioma's impact on cognition: Insights from macrostructure, microstructure, and beyond

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Abstract

Background. Cognitive impairment (CI) significantly impacts the quality of life of glioma patients. The main contributing risk factors include tumor characteristics, treatment-related factors, and their complex interplay. This review explores the role of advanced structural neuroimaging techniques in understanding CI in glioma patients.

Methods. A literature search was conducted in PubMed, PsycINFO, and ISI Web of Knowledge using specific keywords. We included studies with advanced magnetic resonance imaging techniques and objective neuropsychological exams.

Results. At diagnosis, during the pre-surgery phase, associations between glioma characteristics and cognitive outcomes have been described. Specifically, patients with isocitrate dehydrogenase (IDH)-wild-type gliomas exhibit more adverse cognitive outcomes, accompanied by disruptions in gray (GM) and white matter (WM) networks when compared to IDH-mutant. In addition, pre- and post-surgery imaging analyses highlight the importance of preserving specific WM tracts, such as the inferior longitudinal and arcuate fasciculus, in mitigating verbal memory and language processing decline. Furthermore, examining gliomas in perisylvian regions emphasizes deleterious effects on various cognitive domains. Additionally, it has been suggested that neuroplastic reorganization could serve as a compensatory mechanism against CI. Lastly, a limited number of studies suggest long-term CI linked to GM atrophy and leukoencephalopathy induced by radiotherapy ± chemotherapy in glioma survivors, highlighting the need for improving treatment approaches, particularly for patients with extended survival expectations.

Conclusion. This review underscores the need for nuanced understanding and an individual approach in the management of glioma patients. Neuroplastic insights offer clinicians valuable guidance in surgical decision-making and personalized therapeutic approaches thus improving patient outcomes in neuro-oncology.

Key Points

- Tumor location and isocitrate dehydrogenase status are relevant factors for cognition.
- Preserving strategic white matter tracts in glioma surgery protects cognition.
- Chemoradiation induces long-term diffuse brain changes and cognitive decline.

Gliomas are the most common type of malignant primary brain tumors.[1] Due to improvements in the existing multimodal treatments, patients' survival rates have significantly increased over the last few decades. Specifically, new emerging oncological schedules have proven to be efficient in extending overall survival (OS). Currently, grade 2 and grade 3 1p/19q codeleted oligodendrogliomas[2,3] exhibit a 10-year OS of 80% and 60% (according to the World Health Organization – WHO – 2007 classification), respectively, while grade 3 astrocytoma[4] shows a 5-year OS of 82%. Interestingly, a recent phase III trial in Isocitrate dehydrogenase-mutant (IDH-mt) grade 2 gliomas treated with an oral inhibitor of IDH1 and IDH2 enzymes, vorasidenib, showed promising results.[5] Furthermore, in the coming years, it is likely that new targeted therapies can lead

Importance of the Study

This review integrates advanced structural neuroimaging techniques to elucidate the complex interplay between glioma pathophysiology, treatment effects, and cognitive outcomes, providing a comprehensive understanding of brain vulnerability in glioma patients at various stages—pre-surgery, post-surgery, and throughout treatment. Despite challenges such as methodological heterogeneity, the adoption of standardized assessment and imaging protocols is crucial for future data harmonization and comparability. Overall, this review underscores the evolving landscape of neuroimaging-based research in glioma patients in improving patient care and quality of life within the neuro-oncology field.

to increased survival and long-term remissions in different histomolecular subtypes of gliomas.

The estimated prevalence of cognitive impairment (CI) in adult WHO 2007 grades 1-3 glioma patients ranges between 27% and 83%.[6] This wide range can be attributed to diverse study methodologies, including different cognitive assessments and varying definitions of CI. The cognitive domains most frequently affected include executive functioning, psychomotor speed, attention, and memory.[7] The tumor itself and glioma-directed therapies could contribute to these impairments, significantly affecting the quality of life for patients and their caregivers. Therefore, understanding and identifying the mechanisms that lead to CI in these patients is increasingly crucial. In fact, cognitive outcomes are frequently assessed as secondary endpoints in current neuro-oncological trials.

In neuro-oncology, brain morphological evaluation through neuroimaging studies has been crucial for the diagnosis and for classifying, managing, and monitoring brain tumor patients. Traditionally, these evaluations have relied on subjective and qualitative observations made by imaging experts based on their clinical expertise.[8] Over the past decade, though, the advancement in imaging post-processing has enabled automatic analysis for structural quantitative assessment of the brain, allowing a straightforward interpretation of how brain tumors alter the brain's structural architecture and connectivity. In addition, these quantitative imaging methods reduce methodological biases, enhancing reproducibility across studies and sites. This knowledge is essential for tailoring effective treatment strategies, optimizing surgical outcomes, and predicting potential cognitive deficits, ultimately leading to improved patient care and quality of life.[9,10]

The purpose of this review is thus to summarize the current literature on brain structural morphometric changes in adult patients with glioma, and their potential association with CI focused on: (1) tumor-related metrics such as molecular, histological, or tumor location; (2) surgical resection-related brain changes; and (3) alterations associated to chemoradiation therapy.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[11] (see Supplementary File 1). A comprehensive literature search was performed on September 1, 2024, using PubMed, PsycINFO, and ISI Web of Knowledge databases. The following search strategy was used: ("cognitive" OR "cognition" OR "neuropsychological" OR "neurocognitive") [All Fields] AND ("glioma")[All Fields] AND ("Magnetic Resonance Imaging" (MRI) [All Fields]). Filters were applied for articles published in English or Spanish, studies involving patients aged over 18 years, and humans only. We excluded articles in which the study sample included tumors with histological variants other than gliomas without a separate analysis. Reviews or articles with a short series of patients (≤5) were also excluded. We selected and included articles that: (1) referred to advanced structural MRI techniques: including (i) anatomical brain changes, including neuroimaging techniques such as MRI volumetry, voxel-based morphometry (or similar techniques), or surface-based methods such as FreeSurfer, and (ii) microstructural brain changes, including neuroimaging techniques such as diffusion tensor imaging (DTI) (or similar techniques), or voxel-based lesion-symptom mapping (VLSM); accompanied by (2) an objective neuropsychological examination (including Montreal Cognitive Assessment-MoCA and Mini-Mental State Examination-MMSE), ensuring an unbiased evaluation.

As summarized in Figure 1, our search initially identified a total of 607 records, of which only 25 met the inclusion criteria. Descriptions of the various advanced neuroimaging techniques used in the selected studies are provided in Supplementary Table 1. We group the selected articles based on the timing of neuroimaging analysis: pre-surgery, post-surgery, or post-radiotherapy (RT) or chemoradiation; with the aim of identifying the factors that may be involved in cognitive decline throughout the natural history of glioma patients.

Results

Pre-Surgery Neuroimaging Techniques: How Glioma Itself Affects Cognition

This section explores the multifaceted aspects of pre-surgery neuroimaging techniques and their relevance in understanding how glioma impacts on cognitive function. See Table 1 for the summary.

One aspect under investigation is the impact of glioma volume on cognition.[13–16] One of the first studies, focused on WHO grades 2-4 glioma patients, despite not being its

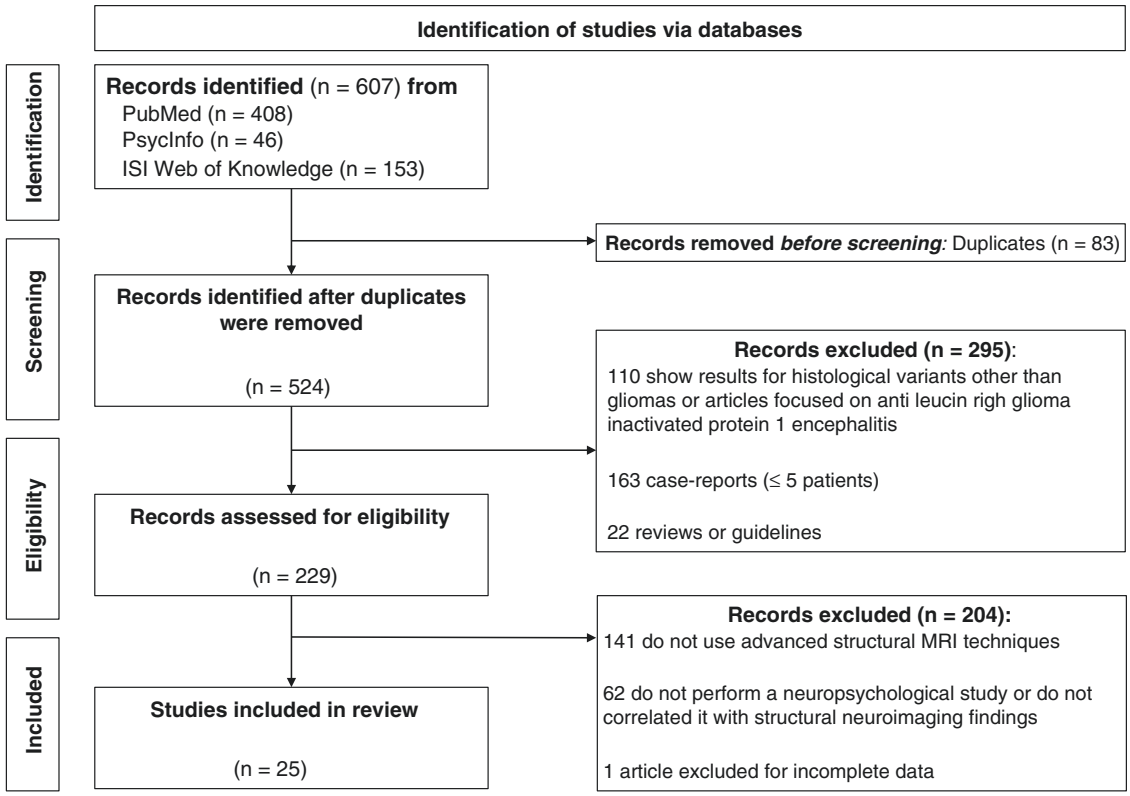

Figure 1. Flowchart Depicting the Systematic Search and Study Selection, Adapted from PRISMA Flow Diagram[12]

primary goal, observed that larger tumors were associated with poorer outcomes in visual memory. Interestingly, no such correlation was found with other evaluated cognitive domains, such as verbal memory.[13] A few years later, Romero-Garcia et al.[15] demonstrated, in patients with WHO grades 2-4 gliomas as well, that even in the long term (up to 12 months post-surgery), there was no correlation between total memory score results and pre-surgery tumor volume.[15] The observed heterogeneity in findings may be attributed, in part, to patient-related differences within the studied samples, cognitive assessment methods, and statistical approaches, considering whether to include covariates such as tumor location, for example.[13–16] Taking this into consideration, it is worth to highlight the study by Kesler et al.[16] These authors stratified their WHO grades 3-4 cohort based on the molecular signature IDH, noting that patients with wild-type (wt) gliomas appear to exhibit more cognitive deficits than IDH-mt gliomas.[27,28] In this case, they found that preoperative tumor volume had the most significant impact on cognition, categorized as CI or not, in IDH1-wt patients, as detailed in Table 1. Other factors such as education level, Karnofsky Performance Scale score, tumor lobe location, and tumor laterality showed no significant correlation with cognition in these patients. Conversely, tumor size did not predict CI in the IDH1-mt glioma group, despite their larger tumor volumes. Furthermore, IDH1-wt tumors exhibited less efficient GM networks (refer to Supplementary Table 2 for definitions) compared to the IDH1-mt group. Network efficiency, along with years of education, emerged as the most significant predictors of CI for IDH1-mt patients. In summary, the slower growth of IDH1-mt gliomas may offer an advantage for the brain to adapt to tumor presence, resulting in a more integrated neural network and less CI. Therefore, rather than tumor volume, the growth rate, and invasive characteristics of the tumor could serve as predictors of CI in glioma patients. Interestingly and to add controversy, previous studies showed that network architecture was influenced by age.[29] Thus, given that IDH1-mt patients are generally younger tan IDH1-wt patients, neglecting to include age as a covariate in the statistical analysis may lead to confusion when attributing the observed structural brain changes solely to the mutation itself. On the other hand, the network analysis in Kesler et al.,[16] had limitations, including the selection of appropriate thresholds for different networks.

Another important pre-surgical factor that plays a crucial role in surgical decision-making is the tumor's location. However, only a few studies have employed morphometric imaging analysis to precisely pinpoint regions associated with CI in glioma patients, thus identifying distinct regions at risk for CI within the same brain lobe. Almairac et al.,[17] and Banerjee et al.,[18] focused their studies on the language domain and, as expected,[30,31] found correlations with brain regions or WM fiber-pathways primarily located in, or running through, the temporal lobe.

The study by Habets and collaborators,[19] involving WHO grades 1-4 gliomas, revealed significant associations

Table 1. Pre-Surgery Studies

References	Patients	Hemisphere location	Age (years)	WHO grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assessed	Main results
De Baene et al., 2018[13]	45	Left	44.8 (21–73)[a]	2–4	Volumetry	Continuous performance test; shifting attention test; Stroop test; verbal memory test; visual memory test; symbol digit coding	Attention Executive function Memory (verbal and visual) Processing speed Psychomotor speed	Tumor volume: negative correlated with visual memory. No correlated with verbal memory and processing/psychomotor speed
Stoecklein et al., 2020[14]	34	Unknown	49 (17)[b]	2–3	Volumetry	MOCA test	Attention Memory (verbal) Language Executive function Visuospatial skills Calculation Orientation	Tumor volume: no correlated with neuro-psychological performance
Romero-Garcia et al., 2022[15]	17	11 Left (9 right-handed) 6 Right (5 right-handed)	35.1 (10.4)[b]	2–4	Volumetry and NODDI	Oxford cognitive screen-bridge tablet-based tool: DST; free verbal memory; overall verbal memory; episodic memory; orientation	Attention Memory (verbal) Orientation	Tumor volume: no correlated with memory recovery[c] Preoperative tumor overlap with the DMN is negatively correlated with memory recovery
Kesler et al., 2017[16]	69	IDH-mt: 27/37Left 10/37 Right IDH-wt: 21/32 Left 11/32 Right	IDH1-mt: 38.8 (11.2)[b] IDH1-wt: 51.3 (14.3)[b]	3–4	Volumetry and VBM	WAIS-R/III; TMT A&B; HVLT-R; BNT; Token Test; COWA	Attention Executive function Memory (verbal) Language Processing speed Visuospatial skills Praxis skills	Tumor volume: the greatest contributor to CI[d] in IDH-wt IDH1-wt vs. IDH-mt: less network efficiency in: Left: amygdala, angular gyrus, calcarine sulcus, caudate, middle frontal orbital gyrus Right: cuneus, inferior occipital gyrus, middle occipital gyrus, inferior parietal lobe Bilateral: inferior orbital gyri, lingual gyri IDH1-wt vs. IDH-mt: high nodal efficiency in left supramarginal gyrus
Almairac et al., 2015[17]	31	Left	35.7 (9.8)[b]	2	VLSM	Semantic verbal fluency task; phonological verbal fluency task	Language	Semantic fluency: WM: Left: IFOF Phonological fluency: No correlation with infiltration of IFOF, AF, UF, or ILF

Table 1. Continued

References	Patients	Hemisphere location	Age (years)	WHO grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assessed	Main results
Banerjee et al., 2015[18]	98[e]	Unknown (majority left)	46.9 (14.6)[b]	2–4	VLSM	Receptive language: BDAE-3 Commands; BDAE-3 Complex Ideational Material; BDAE-3 Reading Comprehension-Sentences and Paragraphs Expressive language: phonemic fluency; category fluency; BNT; BDAE-3 responsive naming	Language	Receptive language: GM: Left: Wernicke's area, Heschl's gyrus. WM: Left: internal capsule, external capsule, posterior thalamic radiation, ILF, and SLF Expressive language: GM: Left: Rolandic operculum, insula. WM: Left: retrolenticular limb of the internal capsule, SLF, MTG, and STG
Habets et al., 2019[19]	72	41 Left (39 right-handed) 31 Right (29 right-handed)	39.8 (12.3)[b]	1–4	VLSM	DST;TMT A&B; AVLT; Location LearningTest; Memory ComparisonTest; ROCF; categorical word fluency test; stroop color-word test; assessment of the dysexecutive syndrome (subtest: rule shifting test) Letter digit modalities test	Attention Working memory Memory (verbal and visual) Language Executive function Processing speed Visuospatial skills	[f]Attention: GM: Left: precentral and postcentral gyrus and central opercular cortex WM: Left: AF and corticospinal tract. Visual memory: GM: Left: superior parietal lobule WM: Left: AF, corticospinal tract and cingulum. Midline: corpus callosum Verbal memory and executive function: WM: Left: AF, corticospinal tract, and cingulum. Midline: corpus callosum Information processing speed: GM: Left: precentral and postcentral gyrus WM: Left: AF and corticospinal tract
Guarracino et al., 2022[20]	73	31 Left 42 Right	38.3 (11.7)[b]	2–3 (LGG)	VLSM	Left glioma: DST;TMT; objects and verbs naming word and pseudoword repetition and reading; lexical decision; naming and verb comprehension; phonological discrimination; word and pseudoword writing; oral apraxia; ideomotor apraxia; semantic fluency test; verbal fluency test;TokenTest; DSST; pyramids and palm trees test Right glioma:TMT A&B; DSST; CBT; clock drawing test; constructive apraxia; behavioral inattention test (letter cancellation, star cancellation and line bisection); little man test.	Left glioma: Attention Working memory Memory (verbal and visual) Language Executive function Processing speed Right glioma: Attention Working memory (visual) Executive function Processing speed Visuospatial skills Praxis skills	[f]Left glioma Verbal comprehension: WM: superior fronto-occipital fasciculus Executive function: GM: putamen, caudate, IFG (pars opercularis) WM: Superior fronto-occipital fasciculus, anterior and superior corona radiata, external capsule All patients (left and right gliomas) Working memory: GM: putamen, olfactory area, insula and IFG (pars opercularis) WM: anterior corona radiata, external capsule, UF All other cognitive domains: any specific brain regions

Table 1. Continued

References	Patients	Hemisphere location	Age (years)	WHO grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assessed	Main results
Incekara et al., 2018[21]	77	62 Left (all right-handed) 15 Right (all right-handed)	43 (21–74)[a]	2–4	DTI	Stroop test; TMT A&B; Words test imprinting and recall; Token Test; Aachener Aphasia; Boston Naming Test; Category and Letter Fluency	Attention Memory (verbal) Language and verbal learning Executive function Processing speed	Verbal learning and attention/executive functions: correlated with IFOF (FA) Language (repetition of speech): correlated with AF (FA) No correlations between UF and neuropsychological test results assessed.
Papagno et al., 2023[22]	48	Left (all temporal lobe and perisylvian regions and all right-handedness)	46.9 (SD, 15.4, range 22–74)	2–4	DTI	TMT A&B; Naming Test; Verbal fluency on phonemic and semantic cue.	Attention Language Executive function Processing speed	Lexical retrieval impairment from visual stimuli: correlated with damage of posterior and mid-third ILF, and the posterior segment of the AF (only ILF show a significant association when adjusting for the effects of all the fascicles together: AF, UF, IFOF, and ILF). Other regions do not show this association: IFOF, UF, ATL, Fusiform gyrus, ITG, MTG, hippocampus, Insula, STG, and occipital lobe.
Liu et al., 2020[23]	35	15 Left (all right-handed) 20 Right (all right-handed)	49.6 (14.3)[b]	1–4	DTI	DST; Similarity test; DSST; Mapping test; Visuospatial test.	Attention Working memory Memory (verbal and visual) Processing speed Visuospatial skills	Right temporal glioma Visuospatial skills: correlated with SLFTP.R (FA) Frontal glioma No associations
Zhang et al., 2018[24]	78 glioma 44 HC	Left (overlapped or within language network)	Glioma: 39.73 (12.58)[b] HC: 34.57 (13.11)[b]	2–4	VBM	BNT; Aphasia Battery for Chinese-speakers; MMSE	[g]Attention Memory (verbal) Language Visuospatial skills Calculation	LGG > HC: GM volume in the medial part of bilateral cerebellar lobule VIIa. GM volume in the medial part of bilateral cerebellar lobule VIIa: no correlated with neuropsychological performance
Hu et al., 2020[25]	17	8 Left temporal lobe (all right-handed) 9 Right temporal lobe (all right-handed)	Left glioma: 57.25 (7.52)[b] Right glioma: 51.56 (17.56)[b]	–	VBM	DST; Math Exam Test; Memory Test; DSST; Similarity Test; Mapping Test; Visuospatial Test	Attention Working memory Memory (verbal and visual) Executive function Processing speed Visuospatial skills Calculation	GM volume in the contralateral temporal lobe: positively correlated with memory test and negatively correlated with visuospatial test

Table 1. Continued

References	Patients	Hemisphere location	Age (years)	WHO grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assessed	Main results
Jütten et al., 2019[26]	Glioma: 20 (12 IDH-mt) HC: 20	13 Left 7 Right	Glioma: 44.8 (15.5)[b] HC: 45.3 (15.9)[b]	1–4	DTI	ANT; TMT A&B; Verbaler Lern- und Merkfähigkeitstest (German adaptation of RAVLT)	Attention Memory (verbal) Verbal learning Executive function Processing speed	Glioma group Verbal learning, attention and executive functions: positive correlation with FA values of the NAWM Attention: negative correlation with MD and RD values of the NAWM HC Attention: negative correlation with MD values of the NAWM

[a]Median (range);
[b]Mean (standard deviation);
[c]Total memory score was calculated as the average *z*-score of all memory screening tasks. By subtracting the preoperative *z*-score from the *z*-score of each subsequent task (within 72 hours and at 3 and 12 months after surgery), they defined the longitudinal trajectory of each assessment;
[d]CI defined as ≥2 tests with a *z*-score at or below –1.5 and/or ≥1 with a *z*-score at or below –2.0;
[e]63% of the sample had received prior surgery and 40% had received prior radiochemotherapy;
[f]Only described the significant anatomical structures with stronger association per domain;
[g]Except for language, which was assessed using specific tests, the remaining cognitive domains were evaluated through the MMSE test (Mini-Mental State Examination), a brief comprehensive cognitive screening tool. AF, arcuate fasciculus; ANT, Attention Network Test; ATL, Anterior Temporal Lobe; BDAE-3, Boston Diagnostic Aphasia Examination-Third Edition; BNT, Boston Naming Test; CBT, Corsi Block-Tapping Test; CI, cognitive impairment; COWA, Controlled Oral Word Association; DMN, Default Mode Network; DST, Digit Span Test; DSST, Digit Symbol Substitution Test; DTI, diffusion tensor imaging; FA, Fractional Anisotropy; GM, Gray Matter; HC, Healthy control; HGG, high-grade glioma; HVLT-R, Hopkins Verbal Learning Test-Revised; IDH1-mt, isocitrate dehydrogenase 1 mutant; IDH1-wt, isocitrate dehydrogenase 1 wild-type; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ITG, inferior temporal gyrus; LGG, low-grade glioma; MMSE, Mini-Mental State Examination; MD, Mean Diffusivity; MOCA, Montreal Cognitive Assessment; MTG, middle temporal gyrus; NAWM, Normal-Appearing White Matter; NODDI, Neurite Orientation Dispersion and Density Imaging; RAVLT, Rey Auditory Verbal Learning Test; RD, Radial Diffusivity; ROCF, Rey-Osterrieth Complex Figure Test; SD, standard deviation; SLF, superior longitudinal fasciculus; SLFTP.R, right superior longitudinal fasciculus temporal part; STG, superior temporal gyrus; TMT, Trail Making Test; UF, uncinate fasciculus; VBM, Voxel-based morphometry; VLSM, Voxel-based lesion-symptom mapping; WAIS-R/III, Wechsler Adult Intelligence Scale-Revised/Third edition; and WM, white matter.

between cognitive performance across many different domains including attention, visual and verbal memory, executive functioning, and processing speed, and left gray matter (GM) regions such as frontal and parietal cortex (principally precentral and postcentral gyri), as well as left-sided white matter (WM) tracts like the arcuate fasciculus (AF) and corticospinal tract. WM tracts located in the central part of the brain – including the cingulum and the corpus callosum – were associated with visual and verbal memory impairments.

On the other hand, Guarracino and colleagues research[20] focused on WHO grade 2 gliomas also revealed that gliomas located in subcortical frontal and parietal regions, inferior frontal gyrus and insular cortex correlated with deficits in working memory and executive functioning. They also demonstrated that larger WM tracts – such as the left superior corona radiata and the left superior fronto-occipital fasciculus – were associated with executive functioning and verbal comprehension scores, while the uncinate fasciculus (UF) was correlated with working memory skills. The association of prefrontal and frontal brain regions with attention, working memory, or executive functioning is well documented in the general population.[32,33]

A noteworthy remark from the studies mentioned above was that patients with left hemisphere diffuse glioma were at the highest risk of neurocognitive deficits. Furthermore, the correlation of the left AF with attention or executive functions, despite its primary association with language,[34] sparked interest. The authors themselves attribute these observations to the reliance of the neuropsychological battery employed relies on verbal comprehension and response, potentially biasing the identification of left-hemisphere regions with CI or the left AF involvement in non-language cognitive domains.

Additionally, while the study from Habets et al.,[19] and Guarracino et al.,[20] had primary tumor locations in similar brain regions, they found different results (see Table 1) probably because the first study combined findings from both low-grade (LGG) and high-grade glioma (HGG), while the second study exclusively focused on LGG. Tumor behavior and growth rate exhibit variations depending on the WHO grade. Previous studies had observed that HGG was more likely to cause cognitive deficits than LGG due to faster tumor growth and a lower functional compensation from unaffected brain regions.[35,36] Additionally, challenges in defining the exact boundaries of LGG due to the absence of contrast enhancement in MRI should be considered.[36,37]

Expanding on the influence of tumor location on CI, additional studies, through DTI analysis (see supplementary table 1), have investigated the impact of glioma on microstructural WM damage, particularly in WM tracts involved in language. These tracts include the inferior longitudinal fasciculus (ILF), which connects the occipital visual cortex with anterior portions of the temporal lobe; the inferior fronto-occipital fasciculus (IFOF), which connects the frontal lobe with occipital and parietal cortices; the above mentioned UF, which connects the prefrontal cortex and anterior portions of temporal lobe; and AF, which roughly connects Broca's and Wernicke's areas.[38] The focus on these tracts likely reflects the critical need to preserve language function during surgery, especially when tumors are located near eloquent areas. The extensive use of intraoperative imaging techniques, such as functional MRI (fMRI) and DTI-based tractography, has been shown to play a key role in mapping language-related networks to minimize surgical damage. Additionally, identifying which WM tracts are compromised by glioma and how this affects language function can crucially inform surgical planning. Also, understanding how language networks reorganize post-surgery sheds light on mechanisms of neural plasticity, offering valuable insights regarding patient recovery.

In cases where the glioma infiltrated the AF and ILF, deficits in speech repetition and lexical retrieval for visual stimulus (picture naming of objects), were observed, respectively.[21,22] Interestingly, in a subgroup of patients with infiltrated ILF but without deficits in lexical retrieval ($n = 9$), the posterior part of the AF remained intact, suggesting that the AF could serve as an alternative pathway when the ILF is damaged.[22] Further, changes in the microarchitecture of both the IFOF[21] and temporal part of the right superior longitudinal fasciculus (SLF, $n = 11$)[23] due to tumor infiltration have been correlated with cognitive deficits. The IFOF is correlated with both verbal learning and attention/executive functioning, while the SLF with visuospatial deficits.[21,23] As previously elucidated, both IFOF and SLF represent extensive bundles of association WM fibers, intricately involved in multiple cognitive functions.[17,39,40]

Finally, and quite notably, some studies have investigated morphological changes that extend beyond the tumor margins, providing insights into potential mechanisms for preserving cognitive function. Previous studies in general population demonstrated a certain degree of compensatory functional neuroplasticity after brain damage.[41–43] First study in glioma patients with left-hemispheric gliomas (WHO grades 2-4) involving language network brain areas, showed greater GM volume in the medial part of bilateral cerebellar regions compared to healthy control group. However, this increased volume in the cerebellum did not correlate with cognitive functioning, which was only assessed via the MMSE.[24] Conversely, few years later, Hu et al.,[25] evidenced a compensatory GM increase in the contralateral temporal lobe of unilateral temporal lobe gliomas. Notably, the contralateral GM increase was positively correlated with memory but negatively correlated with the visuospatial abilities. Thus, this contralateral GM volume increase in temporal regions appears to compensate only for deficits in certain cognitive domains, and it might not fully counterbalance the brain structural damage caused by glioma. While other studies do not directly correlate brain structure and cognitive outcomes, they also demonstrate that glioma induce volumetric changes in GM both in the affected hemisphere and contralaterally, as a functional compensatory mechanism.[43–45] Lastly, and in light with these findings, Jütten et al.,[26] showed a generalized disruption of normal-appearing WM (NAWM) in glioma patients. The more the disruption of NAWM the worse the cognitive outcome. Interestingly, they also observed that patients with IDH-mt glioma exhibited a more preserved NAWM integrity compared to IDH-wt tumor patients. This is in line with the aforementioned discussion regarding the slower tumor growth and additional plasticity of the surrounding nervous tissue in IDH-mt gliomas, which would be advantageous in preserving cognition in these patients.

Given the significant impact of damage or infiltration of certain GM regions and WM tracts on cognitive functions, along with the interindividual variability in compensatory neuroplastic mechanisms that may be induced by the tumor itself, the integration of advanced neuroimaging techniques should be considered in the perioperative planning process.

Post-Surgery Neuroimaging Techniques: Unraveling the Impact of Surgical Interventions on Glioma-Related Cognitive Changes

Investigating the postoperative impact of glioma surgery on cognitive function is pivotal for understanding the complex interplay between surgical interventions and cognitive outcomes. Table 2 summarizes the findings of the studies evaluated in this section.

There was consensus in describing that the volume of the resected glioma cavity did not exhibit a correlation with cognitive scores after surgery, including verbal and visual memory (LGG), or executive functioning (WHO grades 2-4 gliomas).[15,47,48] Conversely, Romero-Garcia et al.,[15] demonstrated a negative correlation between the volume of the post-surgery cavity overlapping with the default mode network (DMN) (refer to Supplementary Table 2 for definition) and memory scores at a long-term follow-up (3 and 12 months after surgery). The DMN has been showed as functional essential network for the preservation of cognition.[53]

Furthermore, the extent of ILF resection was associated with verbal memory decline only in a subgroup of patients in whom there was no pre-surgery tumor infiltration, suggesting that patients with preoperative affected tracts might undergone a brain network reorganization as a compensatory mechanism to mitigate language deficit.[22,49] In line with these findings, Ng et al.,[52] observed an association between the degree of lexical retrieval recovery and damage to the left ILF and posterior corpus callosum – using the support vector regression-based lesion-symptom mapping analysis (see supplementary Table 1) at 3 months post-surgery in LGG ($n = 400$) patients. This study also pointed out that damage to areas surrounding the glioma, such as parts of the left temporal gyrus, in addition to the left UF, were associated with limited recovery in language tasks. Hence, the extent of recovery in semantic fluency appeared to be influenced by resection of peri-tumoral areas within the left posterior precuneus, suggesting that, in terms of cognition, the specific brain regions affected by surgery are more critical than the size of the surgical cavity.

Surgical planning in glioma is crucial for improving the quality of life of these patients. The goal is maximum tumor resection while maintaining functional and cognitive integrity to improve patient survival.[54,55] By employing intraoperative brain mapping techniques, awake surgery allows for the monitoring of motor, sensory, and/or language functions, thereby demonstrating a safe and well-tolerated approach.[56] Language remains the most extensively cognitive domain tested during awake brain surgery, and its mapping continues to be refined.[57] However, other cognitive domains may also be affected post-surgery. For instance, studies converge on assessing executive functions, particularly when there is a risk of damaging the fronto-temporo-parietal cortical GM regions linked by the perisylvian WM.[46–48,50,51] Therefore, there is a clear need to develop new or revised tests and neurosurgical protocols,[58–60] in order to achieve more extensive cognitive monitoring to increase the quality of life after awake craniotomy.

As illustrated in Table 2, there is variability in the association of certain cognitive domains with glioma laterality and the specific structures affected. This variability may be attributed to the fact that each study encompasses distinct WHO glioma grades, consequently different growth rate and compensatory neuroplasticity mechanism and varied analysis times. Some evidence indicates that cognitive function may experience a slight decline shortly after surgery; however, this typically improves and resolves completely within three to six months following surgery.[61,62] In addition, the fact that similar cognitive deficits arise from tumors in different locations,[47,49,50] aligns with the understanding that cognition depends on distributed networks rather than isolated areas, allowing impairments to emerge from tumors in various regions. These findings point to the need for multicenter studies to establish firm conclusions and protocol the study of cognitive functions through intraoperative tasks to prevent postoperative CI.

See Figures 2 and 3 for illustrations of the GM regions and WM tracts, respectively, which have been damaged by the glioma or resective cavity and have been significantly associated with CI by different studies.

Long-Term Glioma Survivors and Cognition: Neuroimaging Changes Due to Adjuvant Treatments

Following surgery, the standard of care for gliomas involves RT and/or chemotherapy (CT), with temozolomide (TMZ) and PCV (Procarbazine, Lomustine, and Vincristine) being the most frequently used schedules with demonstrated improvement in patient outcomes.[2–4]

The main concern of RT is its potential cognitive toxicity especially in those patients with prolonged survivals. Preclinical models have shown that RT decreases neural proliferation and differentiation in the hippocampus, and causes vascular disturbances and microglia activation.[64,65] While the relevance of the topic is evident, only a limited number of studies have assessed cognitive outcomes in long-term glioma survivors after RT (±CT). Most studies corroborate that RT has detrimental effects on cognition. Findings in LGG treated with RT and followed up for 12 years revealed worse cognitive outcomes compared to those who did not undergo RT.[66–68]

In recent years, interest in the potential impact of CT on cognition has increased. Consequently, the term "chemobrain" has been coined to refer to the alterations in cognitive functioning reflecting the central nervous system's toxic effect of systemic CT.[69] In preclinical models, TMZ, a DNA cross-linking agent, has been implicated in the impairment of hippocampal neurogenesis,[70] while vincristine, by disrupting microtubule dynamics and axonal transport, induced lesions in the subfields of hippocampus thus impairing working memory.[71] To date, several studies and phase II and III trials have been conducted to analyze the

Table 2. Post-Surgery Studies

Reference	Patients	Hemisphere location	Age (years)	WHO grade	Neuroimaging technique	Neuropsychological assessment	Cognitive domains assessed	Surgery-imaging interval	Main results
Herbet et al., 2013[46]	10	Right (all frontal lobe)	32.1 (9.35)[a]	2	Volumetry	DST; TMT A&B; Stroop test (Stroop interference); Digit symbol	Attention Working memory Executive function Processing speed	3 mo	Neuropsychological data (DST forward and Stroop test) were negatively correlated with the resected volume in the right IFG (pars opercularis)
Romero-Garcia et al., 2022[15]	17	11 Left (9 right-handed) 6 Right (5 right-handed)	35.1 (10.4)[a]	2–4	Volumetry and NODDI	Oxford Cognitive Screen-bridge tablet-based tool: DST; Free, overall and episodic verbal memory; Orientation	Attention Memory (verbal) Orientation	72 h, 3 mo, and 12 mo[b]	Memory recovery[c]: No correlated with resection cavity volume Positive correlation with neurite density within the DMN and FPN Postoperative cavity overlap with the DMN (number of voxels) is negatively correlated with memory recovery
Cochereau et al., 2020[47]	270	134 Left (120 right-handed and 4 ambi-dextrous) 136 Right (119 right-handed and 6 ambi-dextrous)	38.7 (10.6)[a]	LGG	Volumetry, VLSM (including TLSM)	Stroop test; TMT A&B; Verbal Fluency Test	Attention Language Executive function Processing speed	6.5 mo (3–78 mo)[d]	Executive functioning: No correlated with resection cavity volume It is hardly predicted by the resection/lesion location WM (TLSM): Left: anterior limb of the internal capsule, WM lateral to the frontal horn of the lateral ventricle (including the fiber course of SLF_II, SLF_III, FAT, and FST)
Hartung et al., 2021[48]	22	Right (all parietal lobe)	39 (21–67)[d]	2–3	Volumetry, VLSM	TMT A&B; Stroop Color-Word test	Attention Working memory Executive function Processing speed	3–18 mo[e]	Attention, working memory and executive functioning (TMT B/A ratio): No correlated with resection cavity volume Correlated with damage to the posterior part of the right AF
Papagno et al., 2023[22]	48	Left (all temporal lobe and perisylvian regions and all right-handed)	46.9 (SD, 15.4, range 22–74)	2–4	DTI	TMT A&B; Naming Test; Verbal fluency on phonemic and semantic cue	Attention Language Executive function Processing speed	In the 2 weeks and 3 mo after surgery	Lexical retrieval impairment from visual stimuli: associated with percentage of ILF resected unlike IFOF, UF, or AF.

Table 2. Continued

Reference	Patients	Hemisphere location	Age (years)	WHO grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assessed	Surgery-imaging interval	Main results
Puglisi et al., 2019[49]	8	Right (all frontal lobe)	32 (8.9)[a]	2–3	DTI and VLSM	Stroop test	Attention Executive function Processing speed	1 mo	Cognitive control ability (attention, processing speed, executive functioning, cognitive flexibility and response inhibition): correlated with the integrity of IFG.R and the inferior fronto-striatal tracts.
Almairac et al., 2015[17]	31	Left	35.7 (9.8)[a]	2	VLSM	Semantic verbal fluency task; Phonological verbal fluency task	Language	3 mo	No voxels correlated with semantic or phonological fluency scores
Hendriks et al., 2017[50]	59	32 Left 27 Right (57 right-handed)	39 (18–67)[d]	1–3	VLSM	TMT A&B; DST; Stroop Color-Word test; RAVLT; location learning test; Memory comparison test; ROCF; Categoric word fluency test; Letter word fluency test; assessment of the dysexecutive syndrome (subtest: rule shifting test); letter digit modalities test	Attention Working memory Memory Language Executive function Processing speed Visuospatial skills	4 mo	[f]Attention: any specific brain regions. Executive functioning: GM: Right: frontal orbital cortex, IFG, STG (anterior division), MTG (posterior division) WM: Right: inferior fronto-occipital fasciculus Processing speed: GM: right: insula, frontal orbital cortex WM: left: cingulum. Midline: corpus callosum Visuospatial construction: GM: Right: insula, frontal orbital cortex, IFG, MTG (anterior division) WM: right: inferior fronto-occipital fasciculus
Niki et al., 2020[51]	54	33 Left (all right-handed) 21 Right (20 right-handed)	Left glioma: 41.5 (9.8)[a] Right glioma: 36.7 (11.2)[a]	2–4	VLSM	DST; Stroop Color-Word test; Letter digit substitution test; concept shifting task; Visual-verbal learning test (similar to HVLT); word fluency test	Attention Working memory Memory Language Executive function Processing speed	6 mo[g]	Left glioma Attention and working memory: GM: STG, MTG, PTG to supramarginal gyrus Memory, learning and executive functions: GM: medial temporal areas around hippocampus and posterior parietal lobe (including supramarginal gyrus) Right glioma Attention/executive functioning: associated with anterior parts of the medial frontal cortex (including frontal pole and superior frontal gyrus)

Table 2. Continued

Reference	Patients	Hemisphere location	Age (years)	WHO grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assessed	Surgery-imaging interval	Main results
Ng et al., 2024[52]	400	234 Left 166 Right	39.36 (1.38)[a]	2	SVR-LSM	Stroop test; TMT A&B; DST; Pyramid and Palm Trees Test; Buschke Selective Reminding Test; Rey/Taylor Test; Picture naming (only patients with left-sided gliomas); semantic fluency; phonological fluency; Bell Test (only patients with right-sided gliomas)	Attention Memory (verbal and visual) Language Executive function Processing speed Visuospatial skills	3 mo	Attention and processing speed: GM: Right: superior parietal lobe Verbal episodic memory: GM: Left: hippocampus, prahippocampus Lack of recovery in verbal episodic memory is associated with damage to the temporal portion of the left cingulum Language: GM: Left: mid-to-posterior part of MTG, ITG, and fusiform gyri extending to parahippocampal gyrus Lack of recovery in language is associated with damage to the left ILF and AF, posterior corpus callosum and anterior commissure Executive function: GM: Left: dorsomedial prefrontal cortex, MFG, superior frontal sulcus, posterior precuneus Lack of recovery in executive function is associated with damage to the left FAT, frontopontine tracts, corticostriatal tract, left posterior cingulum, and anterior and mid-anterior corpus callosum Semantic fluency scores are associated with the number of supra-tumor[h] resected voxels in the left hemisphere Visuospatial skills: GM: Right: dorsomedial prefrontal cortex extending to SFG. Lack of recovery in visuospatial skills is associated with damage in the right medial tracts (cingulum and SLF)

[a]Mean (standard deviation);
[b]71% of the cohort had received radiotherapy and/or chemotherapy (70.6%);
[c]Total memory score was calculated as the average *z*-score of all memory screening tasks. By subtracting the preoperative *z*-score from the *z*-score of each subsequent task (within 72 hours and at 3 and 12 months after surgery), they defined the longitudinal trajectory of each assessment;
[d]Median (range);
[e]36% of the cohort had received radiotherapy and 1 patient of these patients had also received chemotherapy;
[f]Only described the significant anatomical structures with stronger association per domain;
[g]60% of the cohort had received radiotherapy (59.3% or patients received 60 Gy) and/or chemotherapy.
[h]Supra-tumor resection mask: voxels within the resection mask but outside the tumor infiltration mask. AF, arcuate fasciculus; DMN, Default Mode Network; DST, Digit Span Test; DTI, diffusion tensor imaging; FAT, frontal aslant tract; FPN, fronto-parietal network; FST, fronto-striatal tract; GM, Gray Matter; h, hours; HVLT, Hopkins Verbal Learning Test; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ITG, inferior temporal gyrus; LGG, low-grade glioma; mo, months; MFG, middle frontal gyrus; MTG, Middle Temporal Gyrus; NODDI, Neurite Orientation Dispersion and Density Imaging; PTG, Posterior Temporal Gyrus; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure Test; SD, standard deviation; SFG, superior frontal gyrus; SLF, superior longitudinal fasciculus; STG, superior temporal gyrus; SVR-LSM, support vector regression-based lesion-symptom mapping; TLSM, Tractwise-lesion symptom mapping; TMT, Trail Making Test; UF, Uncinate Fasciculus; VLSM, Voxel-based lesion-symptom mapping; and WM, white matter.

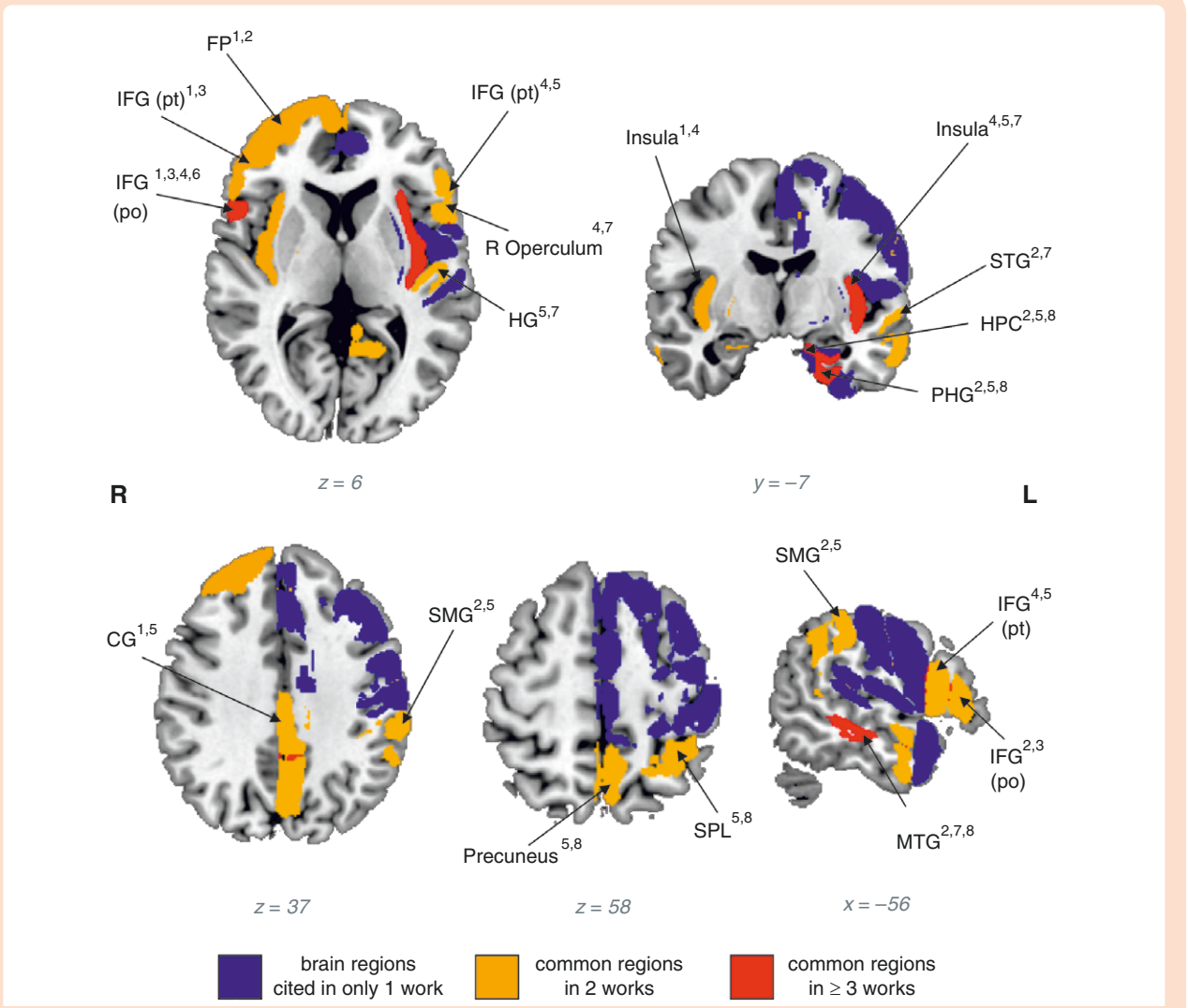

Figure 2. Gray Matter (GM) Brain Regions Affected by Tumor-Resective Cavity and Associated Cognitive Deficits. This figure illustrates the main brain GM regions affected by the tumor-resective cavity, which are associated with cognitive deficits. Following conventional radiological MRI lateralization, left hemisphere of the brain is displayed on the right side of the image while the right hemisphere is on the left side of the image. Regions identified represent areas that have been reported by (i) one study, (ii) two studies, or (iii) three or more studies in the current review: (1) Hendriks et al.[50]; (2) Niki et al.[51]; (3) Puglisi et al.[49]; (4) Guarracino et al.[20]; (5) Habets et al.[19]; (6) Herbet et al.[46]; (7) Banerjee et al.[18]; and (8) Ng et al.[52] Abbreviations: CG, Cingulate Gyrus; FP, Frontal Pole; HG, Heschl's Gyrus; HPC, Hippocampus; IFG (po), Inferior Frontal Gyrus Pars Opercularis; IFG (pt), Inferior Frontal Gyrus Pars Triangularis; L, left; MTG, Middle Temporal Gyrus; PHG, Parahippocampal Gyrus; R, Right; R Operculum, Rolandic Operculum; SMG, Supramarginal Gyrus; SPL, Superior Parietal Lobe; and STG, Superior Temporal Gyrus. The regions depicted are extracted from the Harvard-Oxford Cortical and Subcortical Atlas in the FMRIB Software Library,[63] which provides probabilistic maps set to 40% of brain regions to capture anatomical variability across individuals

impact of these CT agents on cognition in gliomas. However, definitive conclusions have not been reached, largely due to methodological disparities and insufficient neuropsychological assessments.[72–81] Ongoing trials like RTOG 0424 (NCT00114140),[74] POLCA (NCT02444000), and the NOA-18 ImproveCodel (NCT05331521) may provide more insights.

Table 3 summarizes the reviewed studies regarding neuroimaging changes resulting from RT (±CT) in cognitively impaired glioma patients.

Broadly, advanced neuroimaging techniques have revealed that RT (±CT) is associated with loss of NAWM and normal-appearing GM (NAGM), with a strong correlation observed between regions exposed to the highest RT dose.[86–89] Despite the limited literature on this topic, these changes appear significantly linked to CI.[82–84] Notably, these alterations persist over an extended period (more than 5 years after RT), with noticeable deficits specifically in executive functioning and visual memory.[82] Such findings carry substantial implications for the overall quality of life experienced by long-term survivors.

More specifically, Wang et al.,[85] analyzed MRI data approximately 5 years (with a range of 0.6-21.6 years) since the last treatment (all but one patient having received RT-CT). The results of this study suggested that RT-CT induced

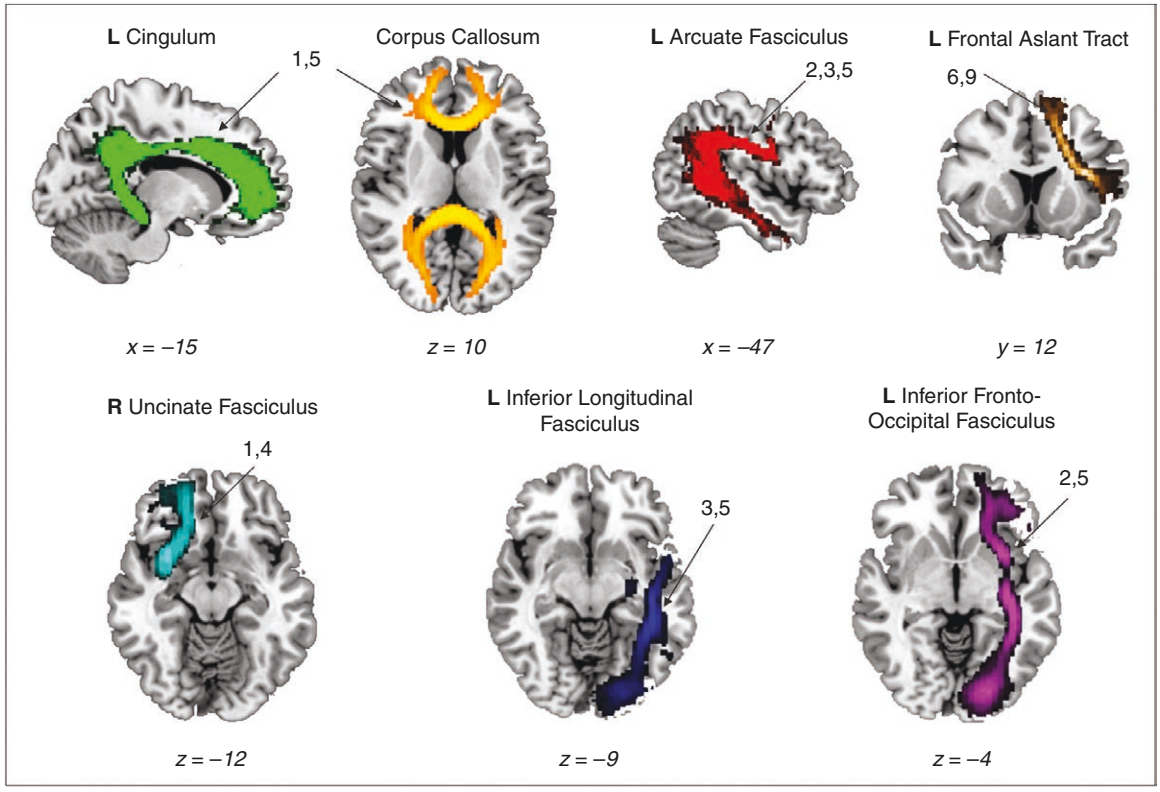

Figure 3. Main White Matter (WM) Tracts Affected by Tumor-Resective Cavity and Correlated with Cognitive Impairment (CI). This figure highlights the main WM tracts affected by the tumor-resective cavity that have been associated with CI according to various studies included in the present review. The conventional radiological MRI lateralization is used, with the left hemisphere of the brain displayed on the right side of the image and the right hemisphere on the left side: (1) Hendriks et al.[50]; (2) Incekara et al.[21]; (3) Papagno et al.[22]; (4) Guarracino et al.[20]; (5) Habets et al.[19]; (6) Ng et al.[52]; (7) Banerjee et al.[18]; (8) Almairac et al.[17]; and (9) Cochereau et al.[47] Abbreviations: L, left; R, right. The WM tracts depicted were extracted from the MegaTrack Atlas (www.megatrackatlas.org) provided by NatBrainLab. For more information, please refer to NatBrainLab (https://www.natbrainlab.com/)

changes in cortical thickness, with a gradual decrease since last treatment. Additionally, the differences observed in the degree of correlation of cortical thickness between certain brain regions among the CI and non-CI patients (see Table 3 for more detail) lead to the conclusion that the presence of cortical reorganization following tumor resection might prevent long-term glioma survivors from experiencing CI. However, this cross-sectional study had a small sample size and lacked a comparative of the clinical variables that might impact CI outcomes, such as the tumor location.

Evaluating the brain damage caused by adjuvant oncological therapies will enable better identification of patients at higher risk of CI.[90] This, in turn, allows for personalize treatments and the implementation of targeted neurorehabilitation programs, especially for long-term survivors.

Discussion

Impact of Molecular Characteristics on Cognition

Our review reveals that only a limited number of studies have examined the relationship between brain changes and molecular characteristics, with particularly few focusing on the WHO 2016 classification, where molecular data become an imperative parameter for diagnostic criteria. Nonetheless, a consensus seems to emerge regarding how IDH-wt gliomas yield more adverse cognitive outcomes compared to their IDH-mt counterparts.[27,91,92] IDH-wt gliomas exhibit lower brain network efficiency and heightened disruptions in both GM and WM integrity. The more aggressive growth and increased aggressiveness observed in IDH-wt patients result in a shorter timeframe for the brain network to adapt through compensatory mechanisms. This fact, as hypothesized by previous studies, negatively influences cognition and prognostics of survival.[60,93,94] However, the lack of studies within our review that differentiate cohorts based on histology and molecular markers limits the ability to draw definitive conclusions. In fact, several of these studies even combine LGG and HGG despite the previously described possibility that they display distinct behaviors regarding microstructural tissue patterns. Future research should focus on integrating molecular markers as key factors influencing tumor behavior, and cognitive outcomes. Such studies could provide valuable insights into how molecular characteristics predict brain changes related to CI, offering a more nuanced understanding of the cognitive impact of different glioma subtypes.

Table 3. Post-Radiotherapy (and/or Chemotherapy) Studies

Reference	Patients	Hemisphere location	Age (years)	WHO Grade	Neuro-imaging technique	Neuropsychological assessment	Cognitive domains assesssed	RT-imaging interval	Radiation dose	CT + (%)	Main results
Cayuela et al., 2019[82]	48	20 Left 28 Right	39 (20–71)[a]	2–3	Volumetry	TMT A&B; HVLT-R; ROCF; COWA	Attention Memory (verbal and visual) Language Executive function Processing speed Visuopatial skills	2–5 y, 6–10 y and >10 y	48–60 Gy	79	Greater volume loss in global GM in patients who have undergone more than 5 years of treatment is associated with poorer performance on the TMT (attention, executive function and processing speed) and the ROCF Delayed Copy (visual memory)
Kocher et al., 2021[83]	121	65 Left 56 Right (all patients except 1 were right-handed)	52 (12)[b]	3–4	Volumetry	TMT A&B; DST; CBT; word list immediate and delayed recall; Verbal Fluency Test; Number trans-coding items (language processing)	Attention Working memory (verbal and visual) Memory (verbal) Language Executive function Processing speed	30 mo (1–214 mo)[a]	60 Gy (40.1–62.0)[a]	87	T2/FLAIR hyperintensities volume and total recurrent tumor volume are negatively correlated with NPS test scores T2/FLAIR hyperintensities affecting the left-hemispheric temporal lobe impact on verbal episodic memory and other language functions deficits
Voon et al., 2023[84]	30	Unknown	48.9 (16–76)[a]	1–4	Volumetry	TICS; T-MoCA; Tele-MACE	Attention Memory (verbal) Language Executive function Visuospatial skills Calculation Orientation	6 mo to 1 y	54, 59.4, or 60 Gy	No	Volume reduction in left temporal lobe, corpus callosum, cerebellum and amygdala are correlated with worse cognitive results The brain atrophy is RT dose dependent
Wang et al, 2022[85]	24	12 Left (all right-handed) 12 Right (all right-handed)	44.5 (26–69)[a]	2–4	FreeSurfer	TMT A&B; DST; Golden Stroop Test; CPT-II; HVLT-R; BVMT-R; ROCF; Boston Naming Test; Verbal Fluency Test; coding	Attention Working memory (verbal and visual) Memory (verbal and visual) Language Executive function Processing speed Visuospatial skills	5.7 y (0.6–21.6)[a]	Unknown	95.8	Time since surgery was negatively correlated with thickness of left and right insula and left primary visual cortex Time since RT-CT was negatively correlated with thickness of left insula Cognitively non-impaired patients > cognitively impaired patients[c]: thicker GM in STG.L, ITG.L and left fusiform gyrus. Positive correlation between STG.R and MTG.R Cognitively impaired > non-impaired patients: positive correlation between the thickness of left entorhinal cortex and the left temporal pole; the left precuneus and the SFG.L; the right parahippocampus and the right pars triangularis of IFG Cognitively non-impaired patients tended to have higher network stability

[a]Median (range);
[b]Mean (standard deviation);
[c]Cognitively impaired defined as at least 2 test scores ≤ –2 Z. BNT, Boston Naming Test; BVMT-R, Brief Visuospatial Memory Test-Revised; CBT, Corsi Block-Tapping Test; CI, cognitive impairment; COWA, Controlled Oral Word Association; CPT-II, Coners' Continuous Performance Test-II; CT, chemotherapy; DST, Digit Span Test; GM, Gray Matter; Gy, gray; HVLT-R, Hopkins Verbal Learning Test-Revised; mo, months; IFG, inferior frontal gyrus; ITG.L, left inferior temporal gyrus; MRI, magnetic resonance imaging; MTG.R, right middle temporal gyrus; NPS, neuropsychological; ROCF, Rey-Osterrieth Complex Figure Test; RT, radiotherapy; SFG.L, left superior frontal gyrus; STG.L, left superior temporal gyrus; STG.R, right superior temporal gyrus; T-MoCA, Telephone Montreal Cognitive Assessment; Tele-MACE, Telephone Mini Addenbrooke's Cognitive Examination; TICS, Telephone Interview Cognitive Status; TMT, trail making test; y, years; and WM, white matter.

Influence of Tumor Location on Cognition

The influence of glioma location on CI is clearly depicted through findings of how both the gliomas themselves and their resective cavities have a significant deleterious effect on cognition, specially when located in the perisylvian region (GM and WM tracts), which affects various cognitive domains. For instance, a consistent finding is the identification of the AF as an alternative compensatory pathway for language processing when the ILF is damaged (by tumor infiltration or resective cavity).[22] Moreover, the integrity of the AF has been associated with performance in non-language cognitive domains, such as attention, working memory, and executive function,[34,48,95,96] suggesting that language and other cognitive functions may share some common neural networks.[60]

Beyond the AF, the brain exhibits other compensatory neuroplastic mechanisms in response to the tumor presence in order to preserve cognition. Concretely, changes are observed in both NAGM and NAWM. The concept of brain network reorganization as a compensatory mechanism is highly compelling and has also been explored in other cerebral damage processes, such as stroke. Although scarce, these studies appear to substantiate that both right and left-hemisphere brain lesions induce changes in GM networks and WM tracts, both ipsilateral and contralateral to the tumor-damaged regions, to support functional recovery of specific behaviors. This indicates that neuroplasticity is not confined solely to contralesional areas and is influenced by factors such as lesion location and lateralization.[44,97,98] Nonetheless, studies with larger cohorts are needed to establish robust conclusions and investigate interindividual variability in neuroplastic responses further.

Role of Brain Networks in Cognitive Decline

It is worth noting the interesting identification of a positive association between neurite density within the DMN and Fronto-Parietal Network functional brain networks (refer to Supplementary Table 2 for definitions) and memory performance in glioma patients.[15] Brain tumor locations associated with CI often encompass GM and WM structures that overlap with these well-described functional networks. These include regions known as *hubs* or high-degree nodes, which are crucial for communication and information processing, as well as for ensuring an efficient cognitive functioning.[99,100]

Our review also highlights that CI tends to be more prominent in gliomas infiltrating regions within the left hemisphere, affecting language, verbal memory and executive functioning. It is important to consider, though, that most neurocognitive tests require verbal comprehension and language production, which may introduce a bias, systematically identifying CI as predominantly associated with affected regions on the left hemisphere. However, left-lateralized gliomas seem to exhibit reduced functional connectivity in the aforementioned *hub* regions compared to right-hemisphere gliomas, regardless of tumor grade and treatment,[53] although further studies are needed to confirm this notion.

These findings underscore the importance of proper presurgery and intraoperative brain mapping to understand how the brain behaves under each specific function and cognitive requirement. Such mapping can help minimize long-term neurological deficits by guiding surgical interventions in a more precise way.

Impact of Adjuvant Therapies on Cognition

Few studies are focused on CI in long-term survivors following treatment with RT (±CT). Most existing studies are cross-sectional, making it difficult to gain insights into neurocognitive alterations over time or to attribute these changes specifically to RT (±CT). However, studies with extended follow-up period (over 10 years after treatment completion) suggest that RT (±CT) treatment induces long-term cognitive toxicity, paired with brain atrophy and WM disruption.[82] These findings highlight the importance of enhancing and advancing treatment approaches for brain tumor patients with an expected prolonged survival.

In recent years, emerging irradiation techniques with potentially lower cognitive toxicity – such as Proton Beam Radiation Therapy (PBRT) or hippocampal sparing (HS) – are being explored in glioma patients. PBRT offers improved normal-tissue sparing compared to photon-based therapy for brain malignancies by delivering maximum dose at the required depth, thus reducing irradiation of surrounding tissue.[101] Currently, two ongoing trials are investigating the efficacy of PBRT in a subset of adult gliomas with grades 2-3 IDH mutations (NCT03180502, NCT05190172). On the other hand, HS emerges as a new potential tool for patients who require whole-brain RT to reduce cognitive toxicity. While HS in brain metastases may be associated with fewer cognitive symptoms,[102,103] its applicability in glioma patients remains understudied. We should therefore await future studies that could demonstrate the applicability of these new RT techniques in glioma patients, specifically, to better understand how to protect cognition without impairing OS.

Limitations and Future Research Directions

Several critical limitations were identified across the reviewed literature. For instance, many reports fail to segregate results based on histological types or molecular characteristics, despite the known influence of these tumor features on cognition.[104,105] Another constraint for inter-study comparisons is the high heterogeneity in the neuropsychological batteries used across studies. It is important to acknowledge that several studies included in this review used cognitive screening tests, such as the MMSE or MoCA. Such tools are generally considered only moderately sensitive and may lack the precision needed to detect subtle cognitive changes. Additionally, they are susceptible to learning and practice effects, with further limit their reliability. These shortcomings are especially relevant in the context of brain tumors, where neurocognitive issues can be subtle or confined to specific cognitive domains.[6,106,107] As such, these limitations should be carefully considered when interpreting

findings from studies that rely exclusively on these screening measures. Disparities in MRI data, image processing methodologies, and data collection time points among the included studies might also partially explain the different findings observed. To address these challenges, the International Cognition and Cancer Task Force (ICCTF) addressed recommendations in 2011 to standardize neuropsychological tests employed in oncology patients.[108] This was followed by an analogous guide for neuroimaging studies in 2018, albeit focused on non-central nervous system cancer patients.[109] Moreover, it is important to highlight the considerable variability present in the cohorts of post-surgery and long-term follow-up studies. Some studies included patients with prior oncological treatments or recurrent tumors at the time of neuroimaging and/or neuropsychological assessments. This variability, along with differences in treatment protocols between studies, complicates the ability to draw definitive conclusions about the specific impact of surgery, RT, and/or CT on the structural brain changes reported. Therefore, more homogeneous studies are needed, with careful consideration of cohort variables that could act as potential confounding factors. Further, a key limitation inherent to this review is the exclusion of functional imaging studies, which offer valuable insights into the neural correlates of various cognitive processes. While these studies are important, the extensive number of available publications in this field, as well as their heterogeneity would have required a different and more complex analysis that was beyond the scope of this review. Additionally, many functional imaging protocols, especially those outside of motor- and language-related fMRI paradigms, lack standardization for clinical use at the individual level, limiting their applicability in routine clinical settings. Indeed, the need for further development of standardized protocols to quantify brain function in clinical brain mapping remains an unresolved challenge.

Despite this, we focused here on structural imaging methods, which provide highly reproducible and clinically applicable information about anatomical changes in patients with gliomas. These techniques are particularly valuable in neuro-oncology due to their capacity to detect precise morphological alterations and facilitate longitudinal tracking of tumor growth or treatment effects. Additionally, structural imaging is more time-efficient in clinical settings, requiring shorter acquisition durations compared to functional methods, which often demand extended scanning protocols to achieve reliable data. As standardized functional techniques continue to evolve, we believe that future research should aim to integrate both structural and functional imaging approaches, including also other neuroimaging techniques such as magnetoencephalography or combined MRI-EEG scans. Considering that learning-induced plasticity is a complex, dynamic, whole-brain process, multi-modal neuroimaging methods can be a powerful tool for understanding how the brain adapts in the presence of a tumor. However, to fully capture the impact of glioma on cognitive function, it is essential to integrate sensitive neuropsychological assessment with neuroimaging techniques.[110] In particular, the adoption of a standardized set of neuropsychological tests and robust criteria for defining CI, such as those proposed by the ICCTF[108] and other recent recommendations for the glioma population,[6] is essential for objectively identifying relevant impairments. These definitions, complemented by well-designed studies that link cognitive outcomes to quality of life and functional scales, will be critically important for advancing the field. The future of glioma treatment lies in combining innovative technologies with personalized approaches, targeting specific biomarkers and focusing on minimizing toxicity to the nervous system. This multidisciplinary and collaborative approach, based on rigorous clinical trials incorporating both cognitive measures and protocol-driven advanced neuroimaging techniques to monitor treatment effects, will be key to developing new therapies that maximize oncological efficacy while preserving cognitive function and the well-being of neuro-oncological patients.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

cognitive impairment | glioma | neuroimaging | structural magnetic resonance imaging

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Conflict of interest statement

Marta Simó has participated in lectures from Pfizer and Takeda. Jordi Bruna has participated in advisory boards or lectures from Pfizer, Takeda, Boehringer-Ingelheim, and Novocure.

Authorship statement

Nuria Cayuela, Cristina Izquierdo, Lucía Vaquero, Estela Càmara, Jordi Bruna, and Marta Simó conceived the review. All authors took part in discussion, analysis, editing, and final approval of the manuscript.

Data availability

This is a review article based on data extracted from publicly accessible databases, including PubMed, PsycINFO, and ISI Web

of Knowledge. All references to the studies included in this review are provided within the manuscript.

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References

1. Bale TA, Rosenblum MK. The 2021 WHO classification of tumors of the central nervous system: an update on pediatric low-grade gliomas and glioneuronal tumors. *Brain Pathol.* 2022;32(4):e13060.
2. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013;31(3):344–350.
3. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol.* 2013;31(3):337–343.
4. van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol.* 2021;22(6):813–823.
5. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al; INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med.* 2023;389(7):589–601.
6. De Roeck L, Gillebert CR, van Aert RCM, et al. Cognitive outcomes after multimodal treatment in adult glioma patients: a meta-analysis. *Neuro Oncol.* 2023;25(8):1395–1414.
7. van Kessel E, Emons MAC, Wajer IH, et al. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. *Neurooncol Pract.* 2019;6(6):463–472.
8. Chukwueke UN, Wen PY. Use of the response assessment in neuro-oncology (RANO) criteria in clinical trials and clinical practice. *CNS Oncol.* 2019;8(1):CNS28.
9. Lamichhane B, Luckett PH, Dierker D, et al. Structural gray matter alterations in glioblastoma and high-grade glioma-A potential biomarker of survival. *Neurooncol Adv.* 2023;5(1):vdad034.
10. Oshima S, Hagiwara A, Raymond C, et al. Change in volumetric tumor growth rate after cytotoxic therapy is predictive of overall survival in recurrent glioblastoma. *Neurooncol Adv.* 2023;5(1):vdad084.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006–1012.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Declaracion PRISMA 2020: una guia actualizada para la publicacion de revisiones sistematicas. *Rev Panam Salud Publica.* 2022;46:e112.
13. De Baene W, Rutten GM, Sitskoorn MM. Cognitive functioning in glioma patients is related to functional connectivity measures of the non-tumoural hemisphere. *Eur J Neurosci.* 2019;50(12):3921–3933.
14. Stoecklein VM, Stoecklein S, Galie F, et al. Resting-state fMRI detects alterations in whole brain connectivity related to tumor biology in glioma patients. *Neuro Oncol.* 2020;22(9):1388–1398.
15. Romero-Garcia R, Suckling J, Owen M, et al. Memory recovery in relation to default mode network impairment and neurite density during brain tumor treatment. *J Neurosurg.* 2022;136(2):358–368.
16. Kesler SR, Noll K, Cahill DP, Rao G, Wefel JS. The effect of IDH1 mutation on the structural connectome in malignant astrocytoma. *J Neurooncol.* 2017;131(3):565–574.
17. Almairac F, Herbet G, Moritz-Gasser S, de Champfleur NM, Duffau H. The left inferior fronto-occipital fasciculus subserves language semantics: a multilevel lesion study. *Brain Struct Funct.* 2015;220(4):1983–1995.
18. Banerjee P, Leu K, Harris RJ, et al. Association between lesion location and language function in adult glioma using voxel-based lesion-symptom mapping. *Neuroimage Clin.* 2015;9:617–624.
19. Habets EJJ, Hendriks EJ, Taphoorn MJB, et al. Association between tumor location and neurocognitive functioning using tumor localization maps. *J Neurooncol.* 2019;144(3):573–582.
20. Guarracino I, Pauletto G, Ius T, et al. Presurgical cognitive status in patients with low-grade glioma and epilepsy: testing the effects of seizures, antiseizure medications, and tumor localization. *Brain Behav.* 2022;12(5):e2560.
21. Incekara F, Satoer D, Visch-Brink E, Vincent A, Smits M. Changes in language white matter tract microarchitecture associated with cognitive deficits in patients with presumed low-grade glioma. *J Neurosurg.* 2018;130(5):1538–1546.
22. Papagno C, Pascuzzo R, Ferrante C, et al. Deficits in naming pictures of objects are associated with glioma infiltration of the inferior longitudinal fasciculus: a study with diffusion MRI tractography, volumetric MRI, and neuropsychology. *Hum Brain Mapp.* 2023;44(10):4011–4027.
23. Liu D, Liu Y, Hu X, et al. Alterations of white matter integrity associated with cognitive deficits in patients with glioma. *Brain Behav.* 2020;10(7):e01639.
24. Zhang N, Xia M, Qiu T, et al. Reorganization of cerebro-cerebellar circuit in patients with left hemispheric gliomas involving language network: a combined structural and resting-state functional MRI study. *Hum Brain Mapp.* 2018;39(12):4802–4819.
25. Hu G, Hu X, Yang K, et al. Restructuring of contralateral gray matter volume associated with cognition in patients with unilateral temporal lobe glioma before and after surgery. *Hum Brain Mapp.* 2020;41(7):1786–1796.
26. Jutten K, Mainz V, Gauggel S, et al. Diffusion tensor imaging reveals microstructural heterogeneity of normal-appearing white matter and related cognitive dysfunction in glioma patients. *Front Oncol.* 2019;9:536.
27. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. *Neuro Oncol.* 2016;18(12):1656–1663.
28. Price SJ, Allinson K, Liu H, et al. Less invasive phenotype found in isocitrate dehydrogenase-mutated glioblastomas than in isocitrate dehydrogenase wild-type glioblastomas: a diffusion-tensor imaging study. *Radiology.* 2017;283(1):215–221.
29. Martin S, Williams KA, Saur D, Hartwigsen G. Age-related reorganization of functional network architecture in semantic cognition. *Cereb Cortex.* 2023;33(8):4886–4903.
30. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex.* 2008;44(8):1105–1132.

31. Catani M, Jones DK, ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol.* 2005;57(1):8–16.
32. Posner MI, Sheese BE, Odludas Y, Tang Y. Analyzing and shaping human attentional networks. *Neural Netw.* 2006;19(9):1422–1429.
33. Skandalakis GP, Barrios-Martinez J, Kazim SF, et al. The anatomy of the four streams of the prefrontal cortex. Preliminary evidence from a population based high definition tractography study. *Front Neuroanat.* 2023;17:1214629.
34. Vavassori L, Venturini M, Zigiotto L, et al. The arcuate fasciculus: combining structure and function into surgical considerations. *Brain Behav.* 2023;13(8):e3107.
35. Faulkner JW, Wilshire CE. Mapping eloquent cortex: a voxel-based lesion-symptom mapping study of core speech production capacities in brain tumour patients. *Brain Lang.* 2020;200:104710.
36. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Psychooncology.* 2017;26(5):617–624.
37. Osborn AG, Louis DN, Poussaint TY, Linscott LL, Salzman KLT. 2021 world health organization classification of tumors of the central nervous system: what neuroradiologists need to know. *AJNR Am J Neuroradiol.* 2022;43(7):928–937.
38. Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci.* 2007;8(5):393–402.
39. Kamali A, Flanders AE, Brody J, Hunter JV, Hasan KM. Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. *Brain Struct Funct.* 2014;219(1):269–281.
40. Wu YY, Chen KT, Chu YC, et al. Neuropsychological impairment in primary malignant brain tumor patients with awake craniotomy: a hospital-based registration study. *J Neurooncol.* 2023;164(2):483–491.
41. Gauthier LV, Taub E, Perkins C, et al. Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke. *Stroke.* 2008;39(5):1520–1525.
42. Voytek B, Davis M, Yago E, et al. Dynamic neuroplasticity after human prefrontal cortex damage. *Neuron.* 2010;68(3):401–408.
43. Almairac F, Duffau H, Herbet G. Contralesional macrostructural plasticity of the insular cortex in patients with glioma: a VBM study. *Neurology.* 2018;91(20):e1902–e1908.
44. Manso-Ortega L, De Frutos-Sagastuy L, Gisbert-Munoz S, et al. Grey matter reshaping of language-related regions depends on tumor lateralization. *Cancers (Basel).* 2023;15(15):3852.
45. Yuan T, Zuo Z, Ying J, et al. Structural and functional alterations in the contralesional medial temporal lobe in glioma patients. *Front Neurosci.* 2020;14:10.
46. Herbet G, Lafargue G, Bonnetblanc F, Moritz-Gasser S, Duffau H. Is the right frontal cortex really crucial in the mentalizing network? A longitudinal study in patients with a slow-growing lesion. *Cortex.* 2013;49(10):2711–2727.
47. Cochereau J, Lemaitre AL, Wager M, et al. Network-behavior mapping of lasting executive impairments after low-grade glioma surgery. *Brain Struct Funct.* 2020;225(8):2415–2429.
48. Hartung SL, Mandonnet E, de Witt Hamer P, et al. Impaired set-shifting from dorsal stream disconnection: insights from a European series of right parietal lower-grade glioma resection. *Cancers (Basel).* 2021;13(13):3337.
49. Puglisi G, Howells H, Sciortino T, et al. Frontal pathways in cognitive control: direct evidence from intraoperative stimulation and diffusion tractography. *Brain.* 2019;142(8):2451–2465.
50. Hendriks EJ, Habets EJJ, Taphoorn MJB, et al. Linking late cognitive outcome with glioma surgery location using resection cavity maps. *Hum Brain Mapp.* 2018;39(5):2064–2074.
51. Niki C, Kumada T, Maruyama T, et al. Primary cognitive factors impaired after glioma surgery and associated brain regions. *Behav Neurol.* 2020;2020:7941689.
52. Ng S, Moritz-Gasser S, Lemaitre AL, Duffau H, Herbet G. Multivariate mapping of low-resilient neurocognitive systems within and around low-grade gliomas. *Brain.* 2024;147(8):2718–2731.
53. Saviola F, Zigiotto L, Novello L, et al. The role of the default mode network in longitudinal functional brain reorganization of brain gliomas. *Brain Struct Funct.* 2022;227(9):2923–2937.
54. Brown TJ, Bota DA, van Den Bent MJ, et al. Management of low-grade glioma: a systematic review and meta-analysis. *Neurooncol Pract.* 2019;6(4):249–258.
55. Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. *JAMA Oncol.* 2016;2(11):1460–1469.
56. Bonifazi S, Passamonti C, Vecchioni S, et al. Cognitive and linguistic outcomes after awake craniotomy in patients with high-grade gliomas. *Clin Neurol Neurosurg.* 2020;198:106089.
57. de Zwart B, Ruis C. An update on tests used for intraoperative monitoring of cognition during awake craniotomy. *Acta Neurochir (Wien).* 2024;166(1):204.
58. Erez Y, Assem M, Coelho P, et al. Intraoperative mapping of executive function using electrocorticography for patients with low-grade gliomas. *Acta Neurochir (Wien).* 2021;163(5):1299–1309.
59. Rossi M, Nibali MC, Torregrossa F, Bello L, Grasso G. Innovation in neurosurgery: the concept of cognitive mapping. *World Neurosurg.* 2019;131:364–370.
60. Gasa-Roque A, Rofes A, Simo M, et al. Understanding language and cognition after brain surgery - tumour grade, fine-grained assessment tools and, most of all, individualized approach. *J Neuropsychol.* 2023;18:158–182.
61. Ng JCH, See AAQ, Ang TY, et al. 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.* 2019;141(1):167–182.
62. Barzilai O, Ben Moshe S, Sitt R, et al. Improvement in cognitive function after surgery for low-grade glioma. *J Neurosurg.* 2018;130(2):426–434.
63. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. *Neuroimage.* 2012;62(2):782–790.
64. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. *Nat Med.* 2002;8(9):955–962.
65. Rahmathulla G, Marko NF, Weil RJ. Cerebral radiation necrosis: a review of the pathobiology, diagnosis and management considerations. *J Clin Neurosci.* 2013;20(4):485–502.
66. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8(9):810–818.
67. Correa DD, DeAngelis LM, Shi W, et al. Cognitive functions in low-grade gliomas: disease and treatment effects. *J Neurooncol.* 2007;81(2):175–184.
68. Armstrong CL, Hunter JV, Ledakis GE, et al. Late cognitive and radiographic changes related to radiotherapy: initial prospective findings. *Neurology.* 2002;59(1):40–48.
69. Lucassen PJ. Chemotherapy modulates specific aspects of cognition parallel to neurogenesis (commentary on Nokia *et al.*). *Eur J Neurosci.* 2012;36(11):3519–3520.
70. Dietrich J, Prust M, Kaiser J. Chemotherapy, cognitive impairment and hippocampal toxicity. *Neuroscience.* 2015;309:224–232.
71. Melendez DM, Nordquist RE, Vanderschuren L, van der Staay FJ. Spatial memory deficits after vincristine-induced lesions to the dorsal hippocampus. *PLoS One.* 2020;15(4):e0231941.
72. Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1521–1532.
73. Park DY, Tom MC, Chen Y, et al. Cognitive function after concurrent temozolomide-based chemoradiation therapy in low-grade gliomas. *J Neurooncol.* 2022;158(3):341–348.

74. Fisher BJ, Pugh SL, Macdonald DR, et al. Phase 2 study of a temozolomide-based chemoradiation therapy regimen for high-risk, low-grade gliomas: long-term results of radiation therapy oncology group 0424. *Int J Radiat Oncol Biol Phys.* 2020;107(4):720–725.
75. Buckner JC, Chakravarti A, Curran WJ, Jr. Radiation plus chemotherapy in low-grade glioma. *N Engl J Med.* 2016;375(5):490–491.
76. Cairncross JG, Wang M, Jenkins RB, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. *J Clin Oncol.* 2014;32(8):783–790.
77. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol.* 2014;32(6):535–541.
78. Wang M, Cairncross G, Shaw E, et al; Radiation Therapy Oncology Group (RTOG). Cognition and quality of life after chemotherapy plus radiotherapy (RT) vs. RT for pure and mixed anaplastic oligodendrogliomas: radiation therapy oncology group trial 9402. *Int J Radiat Oncol Biol Phys.* 2010;77(3):662–669.
79. Chinot OL, de La Motte Rouge T, Moore N, et al. AVAglio: phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. *Adv Ther.* 2011;28(4):334–340.
80. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med.* 2014;370(8):699–708.
81. Wefel JS, Armstrong TS, Pugh SL, et al. Neurocognitive, symptom, and health-related quality of life outcomes of a randomized trial of bevacizumab for newly diagnosed glioblastoma (NRG/RTOG 0825). *Neuro Oncol.* 2021;23(7):1125–1138.
82. Cayuela N, Jaramillo-Jimenez E, Camara E, et al. Cognitive and brain structural changes in long-term oligodendroglial tumor survivors. *Neuro Oncol.* 2019;21(11):1470–1479.
83. Kocher M, Jockwitz C, Lohmann P, et al. Lesion-function analysis from multimodal imaging and normative brain atlases for prediction of cognitive deficits in glioma patients. *Cancers (Basel).* 2021;13(10):2373.
84. Voon NS, Manan HA, Yahya N. Remote assessment of cognition and quality o life following radiotherapy for glioma: deep-learning-based predictive models and MRI correlates. *J Neurooncol.* 2023;162(2):407–415.
85. Wang C, Cho NS, Dyk KV, et al. Characterization of cognitive function in survivors of diffuse gliomas using morphometric correlation networks. *Tomography.* 2022;8(3):1437–1452.
86. de Groot JD, van Dijken BRJ, van der Weide HL, Enting RH, van der Hoorn A. Voxel based morphometry-detected white matter volume loss after multi-modality treatment in high grade glioma patients. *PLoS One.* 2023;18(5):e0275077.
87. Karunamuni R, Bartsch H, White NS, et al. Dose-dependent cortical thinning after partial brain irradiation in high-grade glioma. *Int J Radiat Oncol Biol Phys.* 2016;94(2):297–304.
88. Nagtegaal SHJ, David S, Philippens MEP, et al. Dose-dependent volume loss in subcortical deep grey matter structures after cranial radiotherapy. *Clin Transl Radiat Oncol.* 2021;26:35–41.
89. Nagtegaal SHJ, David S, van Grinsven EE, et al. Morphological changes after cranial fractionated photon radiotherapy: localized loss of white matter and grey matter volume with increasing dose. *Clin Transl Radiat Oncol.* 2021;31:14–20.
90. Alemany M, Velasco R, Simo M, Bruna J. Late effects of cancer treatment: consequences for long-term brain cancer survivors. *Neurooncol. Pract..* 2021;8(1):18–30.
91. Taylor JW, Weyer-Jamora C, Hervey-Jumper S. Molecularly determining cognition in glioma: new insights as the plot thickens. *Neuro Oncol.* 2022;24(10):1671–1672.
92. Parsons MW, Sabsevitz DS. Cognitive issues in patients with IDH mutant gliomas: from neuroscience to clinical neuropsychology. *J Neurooncol.* 2023;162(3):525–533.
93. Acevedo-Vergara K, Perez-Florez M, Ramirez A, et al. Cognitive deficits in adult patients with high-grade glioma: a systematic review. *Clin Neurol Neurosurg.* 2022;219:107296.
94. Derks J, Kulik S, Wesseling P, et al. Understanding cognitive functioning in glioma patients: the relevance of IDH-mutation status and functional connectivity. *Brain Behav.* 2019;9(4):e01204.
95. Saito S, Baddeley A. Irrelevant sound disrupts speech production: exploring the relationship between short-term memory and experimentally induced slips of the tongue. *Q J Exp Psychol A.* 2004;57(7):1309–1340.
96. Mitolo M, Zoli M, Testa C, et al. Neuroplasticity mechanisms in frontal brain gliomas: a preliminary study. *Front Neurol.* 2022;13:867048.
97. Chen Y, Jiang Y, Kong X, et al. Common and unique structural plasticity after left and right hemisphere stroke. *J Cereb Blood Flow Metab.* 2021;41(12):3350–3364.
98. Kourtidou E, Kasselimis D, Angelopoulou G, et al. The role of the right hemisphere white matter tracts in chronic aphasic patients after damage of the language tracts in the left hemisphere. *Front Hum Neurosci.* 2021;15:635750.
99. Power JD, Schlaggar BL, Lessov-Schlaggar CN, Petersen SE. Evidence for hubs in human functional brain networks. *Neuron.* 2013;79(4):798–813.
100. Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci.* 2009;29(6):1860–1873.
101. Kahalley LS, Ris MD, Grosshans DR, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. *J Clin Oncol.* 2016;34(10):1043–1049.
102. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* 2014;32(34):3810–3816.
103. Brown PD, Gondi V, Pugh S, et al; for NRG Oncology. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. *J Clin Oncol.* 2020;38(10):1019–1029.
104. Gehring K, Aaronson NK, Gundy CM, Taphoorn MJ, Sitskoorn MM. Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. *J Int Neuropsychol Soc.* 2011;17(2):256–266.
105. Yamawaki R, Nankaku M, Umaba C, et al. Assessment of neurocognitive function in association with WHO grades in gliomas. *Clin Neurol Neurosurg.* 2021;208:106824.
106. Robinson GA, Biggs V, Walker DG. Cognitive screening in brain tumors: short but sensitive enough? *Front Oncol.* 2015;5:60.
107. Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol.* 2003;21(19):3557–3558.
108. Wefel JS, Vardy J, Ahles T, Schagen SB. International cognition and cancer task force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol.* 2011;12(7):703–708.
109. Deprez S, Kesler SR, Saykin AJ, et al. International cognition and cancer task force recommendations for neuroimaging methods in the study of cognitive impairment in non-CNS cancer patients. *J Natl Cancer Inst.* 2018;110(3):223–231.
110. Simo M, Rodriguez-Fornells A, Navarro V, et al. Mitigating radiation-induced cognitive toxicity in brain metastases: more questions than answers. *Neurooncol Adv.* 2024;6(1):vdae137.