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Effects of Epilepsy and Anti-Epileptic Medication on Cognitive Functioning in Glioma Patients: A Systematic Literature Review

Master's Thesis

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Effects of Epilepsy and Anti-Epileptic Medication on Cognitive Functioning in Glioma Patients: A Systematic Literature Review

Abstract

Background: Thorough evidence on the effects of epilepsy and anti-epileptic medication on cognitive functioning in glioma patients is currently deficient. This systematic literature review evaluates the impact of epilepsy and antiepileptic drugs (AEDs) on cognitive domains by identifying consistent findings and discrepancies in the literature, and offering insights to guide future research and the clinical care.

Methods: A systematic search of PubMed's electronic database was conducted to identify all relevant articles published up to October 2024. Data extraction was carried out using a standardized form based on the Cochrane Handbook for Systematic Reviews of Interventions and given the variability in cognitive outcomes and the heterogeneity of the studies, a narrative synthesis guided by Popay et al., (2006) was employed as the primary method of analysis.

Results: A total of 27 studies published between 2003 and 2024 were included, involving 3,774 participants, of whom 2,920 were glioma patients. These studies explored various aspects of cognitive functioning, with a particular focus on the impact of epilepsy and anti-epileptic drugs (AEDs) on cognitive outcomes. Key areas of investigation included seizure frequency and type, assessment of cognitive domains, and the effects of different AEDs.

Conclusion: Cognitive impairment is a significant concern in glioma patients, with both epilepsy and anti-epileptic medication contributing to cognitive challenges. Regular neuropsychological evaluations can help diagnose specific cognitive impairments in this population and monitor their progression, and newer AEDs may aid in mitigating some of the common cognitive impairments.

Effects of Epilepsy and Anti-Epileptic Medication on Cognitive Functioning in Glioma Patients: A Systematic Literature Review

Gliomas, the most common malignant brain tumours, originate from the abnormal proliferation of glial or neural stem cells and account for a significant proportion of primary brain tumours (Ostrom et al., 2021). Through their invasive growth, these tumours disrupt neural networks and cause cognitive impairment due to their location and progression, while treatment side effects further exacerbate the dysfunction. Among their earliest and most debilitating manifestations are epileptic seizures (Guarracino et al., 2022). To manage these seizures, anti-epileptic drugs (AEDs) are routinely prescribed, targeting neuronal hyperactivity through voltage modulation or enhanced synaptic inhibition (Perucca & Tomson, 2011). However, while effective at seizure control (Kanner et al., 2018; Koekkoek et al., 2017), AEDs may also contribute to cognitive impairments (van der Meer et al., 2021), presenting a complex interaction between gliomas, epilepsy, and their treatments.

Epilepsy is highly prevalent among glioma patients, with seizures occurring in approximately 70–90% of patients with low-grade gliomas (LGGs) and in 30–60% of patients with high-grade gliomas (HGGs) (Beaumont & Whittle, 2000; Kerkhof & Vecht, 2013). Low-grade gliomas (LGGs) are defined as malignant brain tumours with slower growth and an indolent clinical course, which can eventually progress to high-grade gliomas (HGGs) defined by their rapid progression and high invasiveness. However, it is important to note that the WHO's 2016 update introduced a shift in glioma classification, incorporating molecular markers alongside histology for more precise grading. This change redefined some tumours previously classified as low-grade, now categorized as high-grade based on genetic factors. Consequently, it is inportant to consider the classification system used when interpreting such results. Additionally, while epileptic seizures are often triggered by excessive glutamate release from the tumour, which overstimulates nearby neurons and

disrupts inhibitory interneurons regulating brain activity, the mechanisms underlying glioma-associated epilepsy remain incompletely understood. Factors such as tumour pathology (Song et al., 2021), alterations in the tumour microenvironment (Radin & Tsirka, 2020), disruption of neuronal networks (Catalino et al., 2023), and tumour subtype or location (Lee et al., 2010) are thought to contribute to epileptogenesis.

The cognitive effects of epilepsy in glioma patients are profound. Frequent and severe seizures induce neuroplastic changes, excitotoxicity, and neuronal injury, all of which are associated with accelerated cognitive decline (Lv et al., 2022; van Dellen et al., 2012). Notably, memory and executive functions seem to be the cognitive domains most commonly affected domains in this population. Memory appears particularly vulnerable, possibly owing to the high likelihood of epilepsy developing in temporal lobe gliomas. In epileptic low-grade glioma, better verbal memory has been associated with increased brain network modularity (Lv et al., 2022). By contrast, executive function is positively linked to stronger theta wave synchrony yet negatively correlated with brain network clustering efficiency in these patients (van Dellen et al., 2012). Moreover, the unpredictability of seizures creates psychological distress, including anxiety and depression, which further compound cognitive challenges and reduce quality of life (Lilja & Salford, 1997; Rahman et al., 2015). This highlights the dual burden of epilepsy in glioma patients: as both a neurological and psychological condition that undermines overall cognitive health.

The situation is further complicated by AED treatment. While newer AEDs have fewer cognitive side effects compared to older ones (Maschio et al., 2009; Piotrowski & Blakeley, 2015), adverse effects remain significant and variable. Certain AEDs, such as levetiracetam, have been associated with cognitive improvements in some patients (de Groot et al., 2013), yet many glioma patients using other AEDs experience cognitive impairments affecting memory, attention, and executive function during treatment (Eddy et al., 2011;

Ortinski & Meador, 2004). However, these effects are not consistent across patients with some experiencing no additional cognitive impairment from these medications, while others suffering severe consequences (Aronica et al., 2023). Hence, it is argued that this variability could stem from individual differences in pharmacodynamics, seizure severity, tumour characteristics, or the type and dosage of AEDs used (Ruda et al., 2012). Additionally, the development of pharmaco-resistant epilepsy in glioma patients over time; and the high rate of treatment discontinuation due to side effects (Iuchi et al., 2015), further complicate our understanding of the effects that this can have on cognitive functioning.

Despite considerable research on glioma-related cognitive impairment, significant gaps remain in understanding how epilepsy and AED treatment collectively influence cognition. Due to the overlapping clinical features of gliomas, epilepsy, and AED side effects, existing studies rarely differentiate between the cognitive impairments arizing from each, a shortcoming that hinders the development of targeted therapeutic strategies (Piotrowski & Blakeley, 2015). Although disentangling these effects is inherently challenging given their multifactorial interactions, it is hypothesized that a more precise delineation of their distinct contributions may be achievable though well-structured methodological designs, thereby offering a theoretical framework for refining targeted therapeutic approaches. Additionally, the role of seizure frequency and severity in cognitive outcomes is underexplored, despite evidence linking frequent or severe seizures to accelerated cognitive decline (Lv et al., 2022). Therefore, addressing these gaps is crucial for advancing our understanding of the neuropsychological profiles of glioma patients and improving their quality of life.

Objectives

This systematic literature review aims to bridge existing gaps in glioma research by examining the combined effects of epilepsy and AED treatment on cognitive functioning. Specifically, it seeks to:

- Evaluate how epilepsy and AEDs influence cognitive domains such as memory, attention, executive function, and language in patients with gliomas.
- Identify patterns of cognitive impairment, considering seizure severity and AED types in patients with gliomas.
- Highlight consistent findings and discrepancies in the literature to inform future research and clinical care.

Rather than aiming to establish definitive cognitive models, this review will explore the interconnected influences between epilepsy, antiepileptic drug (AED) treatment, and cognitive outcomes in patients with gliomas. The primary objective will be to assess how both epilepsy and AEDs influence cognitive functioning by systematically identifying consistent findings and notable discrepancies in the literature. Through this comprehensive evaluation, we think that valuable insights will be generated to guide future research and enhance clinical care for this patient population.

Research Questions

The review employs the PICO framework (Richardson et al., 1995) to define its main research question and sub-questions:

- **P (Population):** Glioma patients.
- **I (Intervention):** Presence of epilepsy and use of anti-epileptic medications.
- **C (Comparison):** Glioma patients without epilepsy and/or not on anti-epileptic medications.
- **(Outcome):** Cognitive impact/profile.

Main Research Question

What is the impact of epilepsy and anti-epileptic medications on cognitive functioning in glioma patients?

Sub-questions

a) How does cognitive functioning differ between glioma patients with and without epilepsy?
b) What role do seizure frequency and severity play in cognitive outcomes?
c) Which cognitive domains are most affected by epilepsy and AED use in glioma patients?
d) How do cognitive outcomes in epileptic-glioma patients compare before and after starting AED treatment?
e) Are there differences in cognitive outcomes among epileptic-glioma patients using different AED types or regimens?

Methods

Eligibility Criteria

Given the aim of this systematic review to gather all relevant literature examining the effects of epilepsy and antiepileptic medications on cognitive functioning in glioma patients, the following filtering and inclusion/exclusion criteria were applied to ensure quality and rigour of all resulting studies from the search:

Filtering

Following the electronic search, the only additional filter applied was language, which limited the selection to English-language articles. This filter was applied to ensure the effective evaluation and accessibility of relevant literature, while also meeting the academic criteria for the project.

From the filtered selection of studies, the following inclusion and exclusion criteria were applied to ensure the relevance and quality of the studies included in the review:

Inclusion Criteria

The review included only original research articles that explicitly addressed the research question concerning the effects of epilepsy on cognitive functioning in glioma patients, as well as those assessing the effectiveness of antiepileptic drugs and their impact on cognitive functioning. Relevant primary research articles identified from secondary sources were also included, provided they met the established standards for relevance and quality.

Exclusion Criteria

The following types of publications were excluded from the review: (1) review articles, including systematic reviews, narrative reviews, and meta-analyses, due to their nature as secondary data sources; (2) case reports, given their limited generalizability due to small sample sizes and anecdotal evidence; and (3) studies involving paediatric populations or participants under the age of 18, as the focus of this review was on the adult population.

Source and Search Strategy

An initial search was conducted in PROSPERO, the international database of registered systematic review protocols, to identify any pre-existing systematic reviews on the topic, thereby ensuring a comprehensive review. Details of the complete search string can be found in Appendix 1. The search returned six results, none of which were directly relevant to our specific research question, as outlined below:

- *"A review of neuropsychological interventions during awake craniotomy for language outcome"*
- *"Patient Reported Outcomes following Gamma Knife Radiosurgery for Adults with Primary Brain Tumour"*
- *"Treatment outcomes in adults with LGI1 antibody encephalitis"*

- *"Systematic Review of Immediate versus Delayed Radiotherapy in Grade 2 and 3 Oligodendroglioma after Gross total or Subtotal Surgical Resection or biopsy"*
- *"A supportive group intervention among caregivers to patients diagnosed with a glioblastoma"*
- *"Systematic review of cognitive function and cortical thickness in the schizophrenia spectrum disorders"*

The unrelated nature of the existing reviews underscored a clear gap in the literature, highlighting the need for a tailored search strategy capable of retrieving all relevant literature required to conduct a comprehensive review of the topic. Consequently, we adhered to the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2020 checklist (Page et al., 2021) to design a focused search strategy that ensured transparency, replicability, and methodological rigour throughout the review process. The literature search was conducted using the PubMed database of the U.S. National Library of Medicine, covering all research articles up to October 2024. The search string was developed based on the following criteria: (1) selection of relevant keywords arranged hierarchically according to the PICO framework, (2) identification of appropriate Medical Subject Headings (MeSH) terms corresponding to these keywords, (3) establishment of necessary relationships between the MeSH terms using suitable Boolean operators, and (4) iterative testing of various combinations of MeSH terms and Boolean operators to identify the search string that generated the highest number of relevant results. The final search string is presented in Table 1 below.

Table 1

Search strategies

Date	Database	Strategy

19-09-2024	PROSPERO	(glioma OR gliomas OR "brain tumour") AND (epilepsy OR epileptic OR seizures) AND (cognition OR "cognitive functioning" OR "cognitive dysfunction" OR "cognitive deficit" OR "cognitive status" OR "neurocognitive functioning" OR "neurocognitive dysfunction" OR "neurocognitive deficits" OR "neurocognitive status") AND (treatment OR drugs OR "anti-epileptics" OR AEDs OR "anti-seizure medication")
23-10-2024	PubMed	("Glioma"[Mesh] OR glioma*[tiab] OR (tumo*r*[tiab] AND brain*[tiab])) AND ("Epilepsy"[Mesh] OR epilep*[tiab] OR seizure*[tiab]) AND ("Cognition"[Mesh] OR cognit*[tiab] OR neurocognit*[tiab] OR impairment*[tiab])

Selection process

The screening and selection process was facilitated by the web-based tool Rayyan, which helped streamlined the process by enabling the efficient exclusion of duplicates, initial screening of titles and abstracts, and subsequent full-text reviews. The first step involved the detection and removal of duplicates using the duplicate detection feature embedded within Rayyan. After this, papers underwent relevance screening based on their titles and abstracts. If the title and abstract did not provide sufficient clarity regarding the article's eligibility, the full text was reviewed to determine inclusion or exclusion. Additionally, the reference lists of reviews that were initially excluded but were thought to potentially contain relevant citations were examined, to ensure that no pertinent articles were missed. Papers identified through citation searching were then retrieved and included in the final sample only if deemed relevant.

Data Collection and Analysis process

Data Collection

To facilitate the data collection process, a standardized data extraction form was developed, drawing from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019), ensuring the comprehensive and accurate capture of relevant information from the selected studies. The data extracted were organized into the following key categories:

- **Study Identification:** Full & in-text APA style citation and country of study.
- **Study Characteristics:** Study design and sample size.
- **Participant Characteristics:** Age, gender, type of glioma, epilepsy status (presence/absence), seizure type, seizure frequency, and AEDs use, AEDs names.
- **Cognitive Assessments:** Types of cognitive tests used and domains assessed (e.g., memory, attention, executive function, etc.).
- **Outcomes:** Main findings related to cognitive function.
- **Confounding Factors:** Consideration of factors such as sample size, histological heterogeneity, concurrent treatments (e.g., surgery, radiotherapy, chemotherapy), etc.

Both the data extraction form and the complete data collection are available in Appendix 3. Data Extraction Form and Appendix 4. Data Collection, respectively.

Analysis

Given the variability in the cognitive outcomes reported and the heterogeneity of the included studies, the data analysis primarily relied on narrative methods, due to the scant availability of comparable quantitative data. The narrative synthesis followed the methodology outlined by Popay et al., (2006) and included:

- **Preliminary Synthesis:** Summary of each study's characteristics, participant's demographics, and key findings.

- **Grouping and Clustering:** Grouped studies based on patient populations (brain tumour-related epilepsy and glioma-related epilepsy) and assessment of the impact of epilepsy or anti-epileptic medications on cognitive functioning. This approach facilitated the identification of common patterns and differences.
- **Tabulation and Visualization:** Creation of tables and visual aids to illustrate trends and comparative findings.
- **Thematic Analysis:** Identified and synthesized key themes related to cognitive impacts of epilepsy and anti-epileptic medications, creating a coherent narrative of the data.

Results

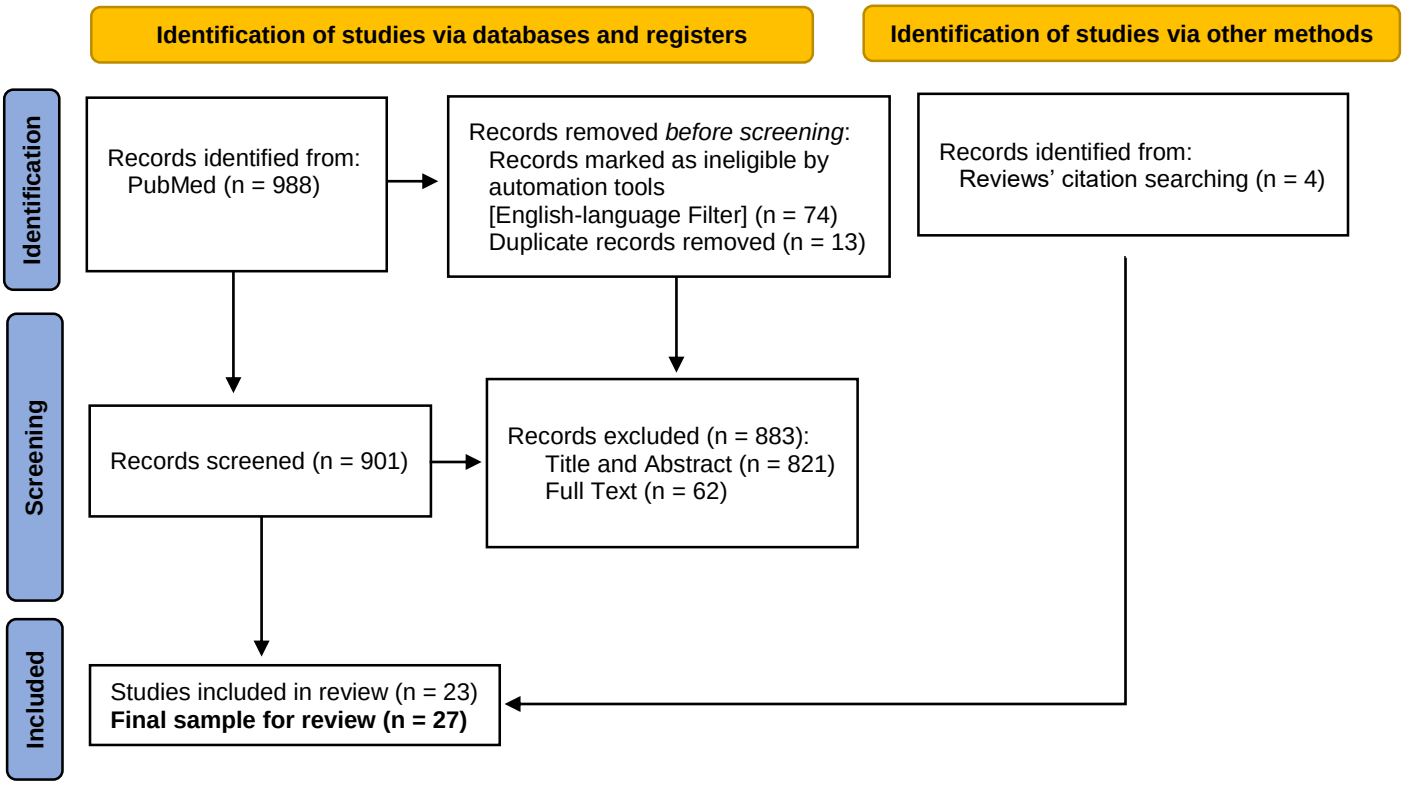
Study Selection

The electronic search yielded an initially total sample of 988 original articles for screening. Of these, 914 were retrieved under the English-language filter. This final sample of 914 articles was then imported into the online Rayyan platform for further selection and screening. During this stage, 22 duplicates were automatically flagged and reviewed, resulting in the removal of 13 confirmed duplicates. Nine articles were incorrectly flagged as duplicates and were therefore reinstated in their original form and content. Following this, the remaining 901 articles underwent a relevance screening based on their titles and abstracts, which led to a reduced sample of 80 articles. Of these, 62 were obtained in full text for further evaluation, as their titles and abstracts provided sufficient clarity regarding their eligibility for inclusion. After this final filtering process, a total of eighteen papers were ultimately selected for inclusion. In addition, thirty of the excluded reviews were identified as potentially containing relevant original studies. Of these, four papers identified through citation tracking were confirmed as relevant to the research and had not already been included in our selected sample. A comprehensive overview of these procedures can be found

in Figure 1 below, and the full list of references for all included articles can be found in Appendix 2.

Figure 1

PRISMA Flowchart



Study Characteristics

A total of 27 studies were included in this systematic review. These studies were published between 2003 and 2024 and varied in design, including observational studies (17 analytical and 3 descriptive), experimental studies (1 randomized controlled trial [RCT] and 5 quasi-experimental), and one longitudinal study. Sample sizes varied widely, ranging from 1,458 participants in an observational analytical study (e.g., Bruhn et al., 2024) to just 12 in a quasi-experimental design (e.g., Vecht et al., 2017) ($\bar{x} = 140$; $\sigma = 280$). Collectively, the studies involved 3,774 participants, 2,920 of whom were glioma patients.

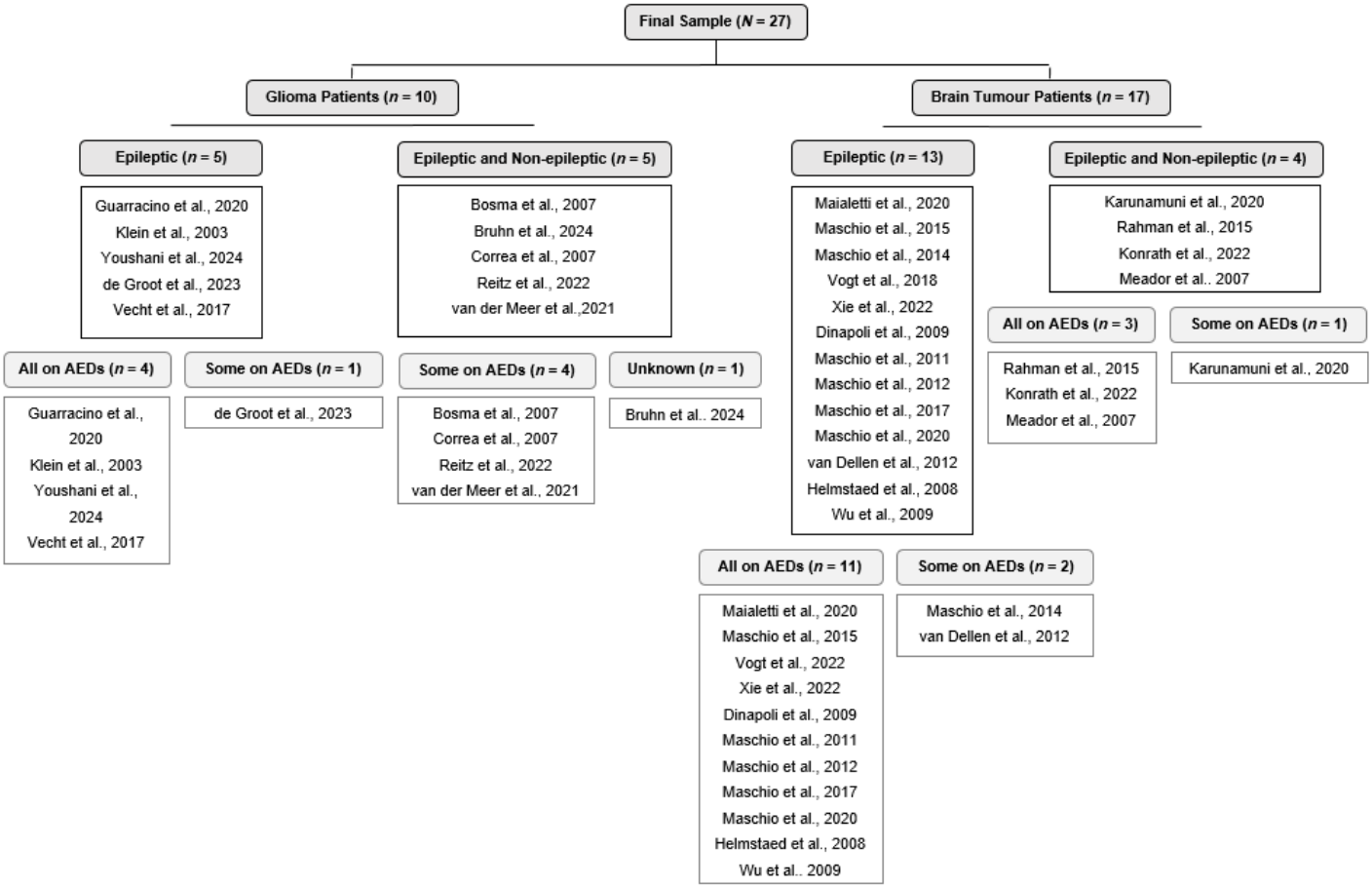
Of the 27 studies, 18 directly investigated the relationship between tumour-related epilepsy and cognitive functioning in an exclusively epileptic population, with 5 focusing specifically on gliomas. Thirteen studies researched the effectivity and side effects of various anti-epileptic drugs (AEDs), while four studies explored cognitive functioning in primary brain tumours more broadly, including both epileptic and non-epileptic tumours. And one study looked at a range of factors, including epilepsy and AED use, that could predict survival outcomes in patients with brain tumours.

In relation to specific variables assessed, 27 studies documented the presence or absence of epileptic seizures. Seizure type and frequency were recorded in 8 studies, while 16 studies examined the impact of epilepsy on various cognitive domains. Regarding the effects of anti-epileptic medications, 17 studies explored the clinical profiles of patients before and after initiating AED therapy, while another 17 focused on the broader effects of AED treatment on cognitive functioning. Among these, 14 studies specifically assessed AED effects on distinct cognitive domains.

The types of AEDs used by participants varied, with levetiracetam being to a large extend the most frequently mentioned across the studies. Additionally, 21 studies employed neuropsychological testing to assess cognitive functioning. Of these, 11 reported an overall cognition score, while specific cognitive domains were evaluated as follows: Memory in 23 studies, Executive Functioning in 15, Attention in 11, Language in 10, Visuospatial Abilities in 7, Cognitive Processing Speed in 5, Psychomotor Functioning in 5, and Abstract Reasoning in 2. A general classification of the final selection of studies based on their characteristics is presented in Figure 2, while additional details on each study are provided in Appendix 4.

Figure 2

Final selection classification based on study characteristics



Note. “Final Sample” refers to the final set of studies included in the systematic literature review. “Gliomas Patients” comprises studies that focus exclusively on glioma patients. “Brain Tumour Patients” comprises studies that investigate brain tumours including gliomas and other tumour types. "Epileptic" indicates that every participant in the study has epilepsy, as opposed to “Epileptic and Non-Epileptic" which includes both epileptic and non-epileptic brain tumour patients. Finally, “All on AEDs” denotes that every patient in the study is being treated with antiepileptic drugs (AEDs), whereas “Some on AEDs” signifies that only a portion of the study sample received AEDs.

Differences in Cognitive Functioning Between Epileptic and Non-Epileptic Glioma Patients

Several studies have compared cognitive performance between glioma patients with and without epilepsy, carefully addressing the inherent difficulty of disentangling seizure effects from those of anti-epileptic drugs (AEDs). Investigators have attempted to minimize interference either by selecting untreated or minimally treated individuals, or by statistically controlling for medication effects. For instance, Klein et al. (2003) investigated 156 glioma patients who had remained free of tumour recurrence for at least one year after histological diagnosis. These patients underwent comprehensive neuropsychological evaluations that assessed processing speed, psychomotor function, attention, verbal memory, working memory and executive functioning. When stratified by seizure frequency and AED treatment, the results revealed that glioma patients performed significantly worse across most cognitive domains compared with healthy controls. Furthermore, a higher epilepsy burden was linked with slower processing speed, reduced psychomotor function, and declines in working memory and executive function; while AED use was associated with additional deficits in attention and memory. These findings led the researchers to argue that AED use, rather than epilepsy burden per se, primarily explained the cognitive decline observed in this study.

Similarly, Guarracino et al. (2022) examined 73 low-grade glioma patients in a preoperative setting, investigating the relationship between seizure history, AED therapy and lesion localization. Although overall pre-surgical cognitive performance was within the normal range, the study revealed that language and cognitive flexibility were primarily predicted by lesion-related variables measured though MRI, whereas visuospatial planning was predominantly influenced by epilepsy-related factors derived from EEG measures and seizure reports. In addition, working memory appeared to be affected by both lesion localization and epilepsy. It is important to note however that the study controlled for AED

use in its statistical analysis, therefore it did not specifically explore how the medication might have contributed to the observed epileptic effects. Lastly, Bruhn et al. (2024) evaluated the prognostic value of initial symptoms, including epilepsy, in a cohort of 1,458 glioblastoma patients. Although this study did not report cognitive differences between gliomas with and without epilepsy, it demonstrated that tumour size was strongly linked to cognitive impairment and that deficits at diagnosis were predictive of a significantly shorter median survival. Thus, tumour size and its relation to epileptic activity should also be considered when assessing their impact on cognitive function.

In addition to glioma-specific investigations, research by Vogt et al. (2018) and Xie et al. (2022) on a broader spectrum of brain tumours consistently indicates that patients with brain tumour-related epilepsy (BTRE) perform more poorly on cognitive tasks compared with those without epilepsy. In these studies, impairments in memory, attention and executive functions were prominent, even though variability in assessment methodologies contributed to some inconsistencies in the findings. Moreover, Karunamuni et al. (2020) identified baseline neurocognitive deficits, particularly in memory and executive function, that were significantly more pronounced in individuals with a history of seizures and AED use. Rahman et al. (2015) further reported that, although cognitive deficits were present irrespective of epilepsy status, a higher seizure burden was associated with further declines in cognitive performance and a reduction in health-related quality of life. Overall, when comparing findings from studies exclusively involving glioma patients with those encompassing broader brain tumour types, both research streams indicate that epilepsy is linked to significant cognitive deficits, notably in memory and executive functioning. At the same time, the interplay between epilepsy and AED use is consistently emphasized. Notably, differences in study design, patient selection and cognitive assessment methods, together with variations in tumour characteristics and in the way seizure burden is defined, make it difficult

to directly compare studies and isolate the specific impact of epilepsy on cognition. In several cases, small sample sizes and retrospective designs further limit the generalizability of these results.

The Role of Seizure Frequency and Severity in Cognitive Outcomes Among Glioma Patients

Disentangling the effects of seizure frequency and severity from the influence of treatment also remains a significant methodological challenge. Nonetheless, several studies have suggested that the intrinsic characteristics of seizure activity are directly related to cognitive impairment. For example, as previously mentioned, Klein et al. (2003) demonstrated that increased seizure frequency was associated with greater impairments in processing speed and executive function among glioma patients. Similarly, Guarracino et al. (2022) also found that epilepsy-related factors derived from EEG measures and seizure reports influenced scores on the domain of visuospatial planning. Hence, these same investigations in the glioma population also provide reasonable evidence that both the frequency and the severity of seizure episodes can be linked with distinct cognitive impairments.

Moreover, the studies that also including other brain tumour types have additionally reported these significant associations between seizure characteristics and cognitive decline. Both Karunamuni et al. (2020) and Rahman et al. (2015) found that an increased frequency and severity of seizures was correlated with more pronounced deficits in cognitive domains, including attention and memory. In addition, research employing a different methodological approach such as Van Dellen et al. (2012) using EEG, demonstrated that reduced network integration, presumed to result from frequent seizure activity, contributed to poorer cognitive outcomes. Although glioma-specific studies predominantly highlight deficits in processing speed, executive function, language and cognitive flexibility, whereas broader brain tumour

studies emphasize impairments in attention, memory and disrupted neural network integration. Overall, evidence reinforces the notion that seizure activity has detrimental effects on cognition. Even so, direct comparisons are further complicated by differences in seizure frequency measurement, with some studies using objective counts gathered over a defined time and others using clinical tools. Moreover, variations in patient samples and treatment regimens, including differences in AED use, further complicate the generalization of these findings.

Key Cognitive Domains Affected by Epilepsy and AED Use in Glioma Patients

Across the selected studies, several cognitive domains have been identified as particularly vulnerable to the combined impact of seizures and AED treatment in glioma patients. Memory, attention, executive functioning and psychomotor speed are consistently highlighted as being at risk. For example, Bosma et al. (2006) assessed high-grade glioma patients at baseline (post-surgery, pre-radiotherapy) and at eight- and sixteen-month intervals. And although initial overall neuropsychological performance was similar across groups, those who later experienced tumour recurrence already exhibited reduced information-processing capacity prior to treatment. Over the subsequent eight months, these patients additionally demonstrated significant declines in psychomotor speed and executive functioning, a trend that coincided with an increase in the use of AEDs. Although adjusting for medication effects initially made group differences in cognitive performance non-significant, persistent psychomotor deficits remained evident at the sixteen-month follow-up.

The study of Reitz et al. (2022) investigated 27 glioma patients with tumours located in language-related regions, employing neuropsychological assessments before and after awake surgery, as well as at a nine-month follow-up. Their results revealed that 37% of patients already exhibited impairment at baseline, particularly in working memory, and that verbal fluency worsened significantly following surgery. Although slight improvements in

some domains were observed at follow-up, executive function deficits remained largely unchanged. The persistence of these deficits, even as seizure frequency decreased significantly, suggested that continued AED use could be partly counteracting the cognitive benefits of improved seizure control. Similarly, in Correa et al. (2006), cognitive outcomes in 40 low-grade glioma patients were compared between those undergoing radiotherapy (with or without chemotherapy) and untreated patients. The study indicated that patients on antiepileptic polytherapy performed significantly worse in both psychomotor and executive domains compared with those on monotherapy, regardless of treatment status or recent seizure activity, further emphasizing the potential detrimental effects of AEDs. Interestingly, when evaluating subjective cognitive functioning in 272 glioma patients using the Medical Outcomes Study-Cognitive Functioning Scale (MOS-CFS), Van der Meer et al. (2021) found that although approximately 19% were classified as cognitively impaired, no significant difference was observed between AED users and non-users after adjusting for confounders. In this case, only seizure severity emerged as being independently linked to impairment. Again, when looking at the research on broader brain tumour populations, results also report impairments in memory and executive functions, with these domains emerging as the most vulnerable across varied neuropsychological assessments (Xie et al., 2022; Dinapoli et al., 2009). However, differences in testing methods and sample characteristics limit direct comparisons between studies focusing exclusively on glioma patients and those involving a broader range of brain tumours.

Cognitive Outcomes in Glioma Patients Before and After AED Treatment

The effects of antiepileptic drug (AED) treatment on cognitive outcomes in glioma patients have mostly been studied using before-and-after study designs. In one study, Vecht et al. (2017) examined the effects of perampanel on both seizure reduction and cognitive performance in 12 drug-resistant epileptic glioma patients. The treatment regimen began with

2 mg nightly for two weeks, increasing to 4 mg daily for four weeks. Seizure response was defined as a 50% reduction or complete freedom from seizures, while cognition was measured using a computerized test battery. Notably, six of the eight seizure-free patients demonstrated cognitive improvement following the treatment. In contrast, the before-and-after study by de Groot et al. (2023), which examined patients on various AED regimens (Levetiracetam, valproic acid, and phenytoin), found that all patients on the different drug regimens performed similarly to those not receiving any AED treatment, contradicting the hypothesis that the effectiveness would vary depending on the type of treatment.

In the studies involving broader brain tumour populations, findings have been variable. Dinapoli et al. (2009), Maschio et al. (2011) and Helmstaedter et al. (2008) collectively reported that levetiracetam significantly impaired cognitive performance when compared with non-drug treatment controls. Conversely, investigations by Konrath et al. (2022) and Wu et al. (2009) did not find significant changes in overall cognitive performance, though minor improvements in memory and language domains were observed in some cases. Additional studies assessing other AEDs found that perampanel (Maschio et al., 2020) and oxcarbazepine (Maschio et al., 2012) did not induce significant cognitive changes compared with controls. Furthermore, Maschio et al. (2017) reported that while general cognitive function remained stable following zonisamide treatment, there was a specific decline in verbal fluency. A comprehensive analysis by Meador et al. (2007) further revealed that carbamazepine (CBZ) had significantly worse cognitive effects than levetiracetam (LEV), with both CBZ and LEV performing inferiorly to non-drug treatments across multiple cognitive measures. Across 34 individual cognitive variables, CBZ was worse than LEV in 44 percent of comparisons and inferior to non-drug treatment in 76 percent, whereas LEV was worse in only 12 percent of comparisons. As it is, these discrepancies may reflect

differences in patient populations, treatment protocols and clinical practice environments, and as a result, thy underscore the need for further large-scale standardized investigations.

Differences in Cognitive Outcomes Based on AED Types in Glioma Patients

Comparative studies have also evaluated the cognitive outcomes associated with different AED types in glioma patients. As an example, De Groot et al. (2023) compared older AEDs (valproic acid and phenytoin) with the newer levetiracetam in 117 high-grade glioma patients over a six-week period following surgery and prior to anti-tumour treatment. Cognitive performance was assessed across six domains: attention, executive function, verbal memory, working memory, psychomotor speed and information processing speed. While overall cognitive functioning did not differ markedly between AED users and non-users, patients receiving levetiracetam demonstrated significantly better verbal memory. A post-hoc analysis even suggested that valproic acid might yield superior performance compared with phenytoin, though the non-randomized design necessitates cautious interpretation of this result. Similarly, van der Meer et al. (2021) investigated the relationship between AED use and self-reported measures of depression, anxiety and subjective cognitive impairment in 272 glioma patients, and found no significant increase in subjective cognitive impairment among those receiving valproic acid compared with patients on levetiracetam or other AEDs. Vecht et al. (2017) also examined perampanel in 12 epileptic glioma patients and observed marked cognitive improvements in most patients who achieved seizure freedom, even though confounding factors related to adjustments in AED regimens were present.

In studies on the broader brain tumour population, research by Dinapoli et al. (2009), Maschio et al. (2011), Meador et al. (2007) and Helmstaedter et al. (2008) generally reported that levetiracetam was associated with a decline in cognitive performance. In contrast, investigations by Konrath et al. (2022) and Wu et al. (2009) observed no significant overall change in cognition, with only modest improvements in certain domains such as memory and

language. Furthermore, studies by Maschio et al. (2020) and Maschio et al. (2012) found that perampanel and oxcarbazepine, respectively, did not induce significant alterations compared with control groups. Finally, Maschio et al. (2017) noted that although general cognitive functioning remained stable following zonisamide treatment, there was a specific deterioration in verbal fluency. Collectively, these findings indicate that the cognitive impact of AEDs in a heterogeneous brain tumour population may differ from that observed in exclusively glioma cohorts, emphasizing the need for further targeted research. In summary, while glioma-specific studies indicate that newer AEDs, particularly levetiracetam and perampanel, may help preserve or even enhance cognitive functions like verbal memory, studies involving a broader range of brain tumours present more varied results. Levetiracetam, in particular, lacks consistent evidence of effectiveness, while other medications such as perampanel, oxcarbazepine, and zonisamide tend to have a more stable impact on cognition. Despite these reasonably valuable insights, the interpretation of findings is constrained once again by limitations such as non-randomized designs, small sample sizes, variability in treatment protocols and cognitive assessment methods. Making evident that future research should first address these methodological issues in order to be able to better elucidate the true cognitive impact of AEDs in the glioma population.

Table 2

Summary of Key Studies on the Effects of Epilepsy and AEDs on Cognitive Function in Glioma Patients

In-text reference	Study design	Sample/s	Epileptic status	AEDs use	Main findings
(de Groot et al., 2013)	O. Analytical	*N* = 117 epileptic-HGG	117 P, 0 A	73 AEDs, 44 No-AEDs	No significant differences in cognitive performance were found among patients on different AED regimens compared with those not receiving any AED treatment.
(van der Meer et al., 2013)	O. Analytical	*N* = 272 Gliomas	206 P, 59 A	184 AEDs, 88 No-AEDs	Approximately 19% of patients were classified as cognitively impaired. No significant differences in subjective cognitive functioning were found between AED users and non-users; only seizure severity was independently linked to impairment.
(Vecht et al., 2017)	E. Quasi-experimental	*N* = 12 Drug-resistant Epileptic Gliomas	12 P, 0 A	12 AEDs, 0 No-AEDs	Following perampanel treatment, 6 of the 8 seizure-free patients demonstrated cognitive improvement, suggesting a potential benefit on cognition when seizure control is achieved.
(Klein et al., 2003)	O. Analytical	*N* = 156 LGG	135 P, 21 A	114 AEDs, 42 No-AEDs	Higher epilepsy burden was linked to slower processing speed, reduced psychomotor function, and declines in working memory and executive function; AED use primarily explained additional cognitive decline.
(Bosma et al., 2007)	Longitudinal	*N* = 32 high-grade gliomas (HGGs)	Unknown *Estimated:* 22 P, 9 A, 2 Unknown	Unknown *Estimated:* 22 P, 9 A, 2 Unknown	Patients who later experienced tumour recurrence had reduced baseline information-processing capacity and demonstrated further declines in psychomotor speed and executive function. After adjusting for AED effects, persistent psychomotor deficits remained evident at 16 months.
(Bruhn et al., 2024)	O. Analytical	*N* = 1458 Glioblastoma	420 P, 1038 A	Unknown	Although cognitive differences between gliomas with and without epilepsy were not reported, larger tumour size was strongly linked to cognitive impairment and deficits at diagnosis predicted a significantly shorter median survival.

(Correa et al., 2007)	O. Analytical	*N* = 40 Low-grade Glioma (LGG)	12 P, 28 A	35 AEDs, 5 No-AEDs	Patients on AED polytherapy performed significantly worse in psychomotor and executive domains compared with those on monotherapy, irrespective of treatment status or recent seizure activity.
(Guarracino et al., 2022)	O. Analytical	*N* = 73 epileptic-LGG	73 P, 0 A	73 AEDs, 0 No-AEDs	Overall pre-surgical cognition was normal; however, language and cognitive flexibility were predicted by lesion localization, while visuospatial planning was predominantly influenced by epilepsy-related factors. Working memory was affected by both lesion and epilepsy factors.
(Reitz et al., 2022)	O. Analytical	*N* = 27 glioma patients	18 P, 0 A	20 AEDs, 7 No-AEDs	At baseline, 37% showed working memory impairment. Verbal fluency worsened following surgery, and despite some improvements at follow-up, executive deficits persisted suggesting that ongoing AED use might partly counteract cognitive benefits from improved seizure control.

Note. This table presents a summary of the most relevant studies form the final selection. For a comprehensive overview and additional information from these and the remaining studies, please refer to Appendix 3. Data Collection.

Discussion

Key Findings and Interpretation

This systematic review aimed to explore the multifaceted effects of epilepsy and anti-epileptic medications on the cognitive functioning of glioma patients. Drawing on evidence from 27 studies, the review shows that although patients with epilepsy are reported to experience significantly greater cognitive impairments compared to their non-epileptic counterparts (Bosma et al., 2006; Guarracino et al., 2022; Klein et al., 2003), these results are difficult to isolate for the effects of AEDs given the fact that most of these patients are treated with these medications. Furthermore, while pharmacological interventions are often effective in reducing seizure activity (Perucca & Tomson, 2011; Kanner et al., 2018; Koekkoek et al., 2017; Vecht et al., 2017), the review has also highlighted that these can often produce side effects that adversely affect cognitive functioning (Bosma et al., 2006; Correa et al., 2006; Dinapoli et al., 2009; Helmstaedter et al., 2008; Maschio et al., n.d., 2011, 2017; Meador et al., 2007; Reitz et al., 2022).

As noted, when addressing the research questions, it was difficult to study how cognitive functioning was independently affected either by the differences between glioma patients with and without epilepsy or by their use of anti-epileptic medications, given that the high prevalence of such medication use among these patients consistently acted as a potential confounding factor. Consequently, our results did not reveal a clear difference between epileptic and non-epileptic groups; however, based on studies that have attempted to account for the effects of anti-epileptic drugs (AEDs), it seems plausible that the cognitive effects observed in glioma patients can most likely be attributed to the tumour itself and the side effects of medication, rather than to the occurrence of seizures. An example of this can be seen in the studies of Klein et al. (2003) and Bruhn et al. (2024). Klein et al. (2003) reported that a higher epilepsy burden was linked to cognitive deficits across various domains, such as

processing speed, psychomotor function, working memory, and executive functioning. However, these deficits were later attributed to the use of AEDs, which were also found to account for impairments in attention and memory. This led the researchers to conclude that the cognitive decline observed in their study was primarily due to the effects of AED use rather than the presence of epilepsy itself. Similarly, Bruhn et al. (2024) demonstrated that tumour size was strongly associated with cognitive impairment, emphasizing that this is also a significant factor to consider when assessing the impact on cognitive function.

Notaby, when comparing this with similar previous literature on the cognitive profiles of non-tumour patients with and without epileptic seizures, similar findings emerge. While epilepsy is known to affect cognitive performance, with epileptic patients generally performing worse on neuropsychological tests than those with non-epileptic seizures (Dilcher et al., 2021; Guo et al., 2017), medications are also reported to adversely affect these outcomes (Dilcher et al., 2021), making it difficult to disentangle the separate effects of epilepsy and treatment.

Similarly, the role that seizure frequency and severity play in cognitive outcomes was also difficult to determine, with only the same studies cited delving into this nuance. Both Klein et al. (2003) and Guarracino et al. (2022) reported that the frequency and severity of epileptic seizures play a role in cognitive functioning. However, when discussing their predictive reliability, these studies failed to attribute a strong enough determinant effect to this factor for it to be considered highly relevant when examining changes in cognitive function. Hence, another critical insight from the review is that, although it is well documented in the literature that frequent and severe seizure episodes contribute to cumulative neuronal injury driven by excitotoxicity and disrupted neural network connectivity (Lv et al., 2022; van Dellen et al., 2012), the impact of seizure frequency and severity probably loses statistical relevance when compared with the effects of the tumour or

anti-epileptic treatment in glioma patients. Previous literature on the effects of these characteristics in non-tumoural epileptic patients also suggests that evaluating the nuanced impact of seizure frequency and the severity of epilepsy may be challenging. However, there is evidence indicating that a higher frequency and longer duration of temporal lobe epilepsy (TLE) are linked to more pronounced hippocampal atrophy and cognitive impairments, potentially due to secondary neuronal metabolic and structural degeneration (Dodrill, 1986; Jokeit & Ebner, 1999). And additionally, while the relationship between prolonged and repetitive seizures is also warranted to need further investigation, some studies in this population have been able to specifically correlated mental deterioration with repeated convulsive seizures or status epilepticus, suggesting a more direct link to cognitive decline (Dodrill, 1986, 2002; Duncan, 2002).

Continuing with the discussion, when trying to pinpoint the cognitive domains most affected by epilepsy and AED use in glioma patients, some studies have been better able to highlight these domains through the use of extensive neuropsychological assessments. For instance, Bosma et al. (2006) demonstrated that patients with tumour recurrence exhibited impairments in information-processing capacity prior to treatment and, over the subsequent eight months, showed significant declines in psychomotor speed and executive functioning, a trend that coincided with an increase in AED use. Similarly, Correa et al. (2006) found that patients on antiepileptic polytherapy performed significantly worse in both psychomotor and executive domains compared with those on monotherapy, regardless of treatment status or recent seizure activity. Notably, the findings of Van der Meer et al. (2021) also reported that seizure severity was independently linked to the subjective cognitive functioning reported by patients, providing insight into their own perceptions of their cognitive abilities.

In the case of studies exploring the cognitive outcomes before and after initiating AED treatment in patients with epileptic glioma, two key points emerge. Firstly, there is

limited but robust evidence that AEDs are both effective and indispensable for controlling seizures in the glioma population (de Groot et al., 2023; Vecht et al., 2017); and secondly, most of the research using this approach in our selected studies has been conducted in broader brain tumour populations. In these studies, the findings are mixed. For example, some reports indicate that drugs such as levetiracetam significantly impair cognitive performance (Dinapoli et al., 2009; Maschio et al., 2011; Helmstaedter et al., 2008), although other studies have even noted minor improvements in memory and language domains (Konrath et al., 2022; Wu et al., 2009). Other medications, such as perampanel and oxcarbazepine, do not appear to induce significant cognitive changes compared with controls (Maschio et al., 2020; Maschio et al., 2012). And from another perspective, comparative studies like that of Meador et al. (2007) suggest that carbamazepine (CBZ) has considerably worse cognitive effects than levetiracetam (LEV), even though patients on either medication tend to perform worse than controls across multiple cognitive measures. Ultimately, this lead to the conclusion that while AED treatment is crucial for seizure control in epileptic glioma patients, the cognitive outcomes post-treatment remain inconsistent and, in most cases, this is explored in a broader brain tumour population, underscoring the need for further research to see if results also hold form an exclusive epileptic-glioma population.

Finally, the comparative effects of different AED regimens can also be examined in light of these findings, with newer AEDs, such as levetiracetam and perampanel, appearing to offer a more favourable cognitive profile than older agents like phenytoin or carbamazepine (de Groot et al., 2023; Meador et al., 2007). However, the impact of levetiracetam remains controversial, as it has been simultaneously associated with both improved verbal memory outcomes (de Groot et al., 2023) and subtle deficits in attention and processing speed (van der Meer et al., 2021). Consequently, no definite conclusions can be drawn, apart from the possibility that these newer medications may be more advantageous for treatment.

For comparison, in patients with epilepsy not associated with tumours, studies such as Perkins et al. (2023) have found that levetiracetam, when administered in small doses over brief periods as monotherapy, has minimal impact on cognitive function. However, at higher doses, or when used as part of long-term seizure management or in combination with multiple antiseizure medications, levetiracetam is frequently linked to cognitive impairment. Moreover, some studies also suggest that it may occasionally enhance specific cognitive domains, such as executive function, in certain populations (Lin et al., 2024). And in the case of perampanel, a systematic review by Fong et al. (2022) lead to the conclusion that it was a safe and effective treatment option for patients with refractory epilepsy and had no apparent adverse effects on cognitive function. Furthermore, additional studies examining the electrophysiological effects of perampanel and its relationship with cognition reported that, although the drug induces electrophysiological slowing, this effect was not associated with any cognitive decline (Ahn et al., 2021).

Once again, it is crucial to highlight the inherent limitations of this review. Many studies employed retrospective designs or featured small sample sizes, which restrict the generalizability of the findings. Additionally, there is considerable heterogeneity in the methods used to assess both seizure frequency and cognitive outcomes. While some studies utilized objective monitoring techniques, others relied on clinical assessments or patient self-reports, contributing to variability in the data (de Groot et al., 2023; Guarracino et al., 2022). Even when researchers attempted to control for confounding factors such as tumour size, localization, and concurrent treatments (for example, radiotherapy and chemotherapy), residual confounding remained a significant concern (Bruhn et al., 2024). Furthermore, as has been consistently evident throughout this review, the dual effects of AEDs complicate efforts to disentangle the benefits of seizure suppression from their adverse cognitive impacts. Consequently, the evidence underscores the need for a more personalized approach to AED

selection, one that carefully weighs the potential cognitive risks against the imperative of seizure control (de Groot et al., 2023; Meador et al., 2007).

Clinical Implications and Future Research

The findings of this review have important implications for clinical practice and future research. First and foremost, they emphasize the need for routine neuropsychological assessment for all glioma patients, regardless of epilepsy status. Early detection of cognitive deficits can facilitate timely intervention and support, potentially mitigating further decline. Additionally, the review also underscores the importance of personalizing AED selection and monitoring for cognitive side effects. Clinicians should be carefully mindful of the potential cognitive risks when prescribing specific AEDs. While seizure control remains essential, the cognitive side effects of AEDs, particularly of older drugs, must be carefully considered when selecting the appropriate treatment. This review suggests that levetiracetam, and possibly other newer AEDs such as perampanel and valproic acid, may offer a more favourable cognitive profile, although further investigation is needed to fully understand their long-term effects on cognition in epileptic-glioma patients. Regular cognitive assessments can help detect and address emerging side effects, allowing for treatment adjustments to optimize both seizure control and cognitive function.

Future research on this topic should prioritize longitudinal studies to monitor cognitive changes over time in glioma patients with epilepsy, allowing for a deeper understanding of the long-term effects of epilepsy, AED treatment, and the cumulative chronic impacts of both; particularly suffered by patients with highly recurrent tumours. Comparative studies, to directly evaluate the cognitive effects of different AED regimens, would also benefit clinicians by guiding them towards the most cognitively sparing treatment options. Studies investigating the mechanisms underlying cognitive impairment should also be promoted in the future, as this could potentially identify novel therapeutic targets to

protect cognitive function. By addressing these research gaps, we can move towards more holistic and patient-centred treatment strategies for glioma patients, ensuring that both tumour management and cognitive well-being are prioritized.

Conclusions

In conclusion, this review has aimed to illustrate the intricate relationship between epilepsy, anti-epileptic treatment, and cognitive function in glioma patients. The evidence indicates that cognitive impairment is a multifaceted issue, influenced not only by tumour characteristics and seizure severity but also by the variable cognitive effects of AEDs. While some patients suffer significant cognitive decline, others experience minimal impact or even benefit from tailored AED regimens. This variability underscores the critical need for a personalized and integrated clinical approach that incorporates routine neuropsychological assessments, careful AED selection, and regular cognitive monitoring. With these in mind, future research should prioritize longitudinal studies, comparative AED trials, and investigations employing standardized, prospective methodologies to better delineate the individual contributions of each of these factors. By recognizing the interconnectedness of tumour management, seizure control, and cognitive health, clinicians and researchers can work together to develop more effective, targeted interventions that enhance clinical outcomes and ultimately improve the quality of life for glioma patients.

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Appendix 2. Data Extraction Form

In-text reference:	
Study design:	Experimental: Randomized Controlled Trail (RCT) or Quasi-Experimental, Observational: Descriptive or Analytical, Longitudinal
Total sample: ***Sub-samples:***	*N* = • *n* = __ Gliomas • *n* = __ Others
Country:	
Samples mean age:	__ years; *N* = • __ years; *n* = • __ years; *n* =
Samples sex:	F = __, M = __; *N* = • F = __, M = __; *n* = • F = __, M = __; *n* =
Types of gliomas:	*n* = __ Gliomas • *n* = • *n* =
Epileptic status: ***Seizure type:***	P = __, A = __; n = __ Gliomas • P = __, A = __; n = • P = __, A = __; n = _ Focal aware seizures, _ Focal unaware seizures and _ Focal to bilateral tonic-clonic seizure; *n* = __ type of glioma

	_ Focal aware seizures, _ Focal unaware seizures and _ Focal to bilateral tonic-clonic seizure; *n* = _ type glioma
Seizure frequency:	__ seizures (1month) before T0, and _ seizures at T1; *n* = __ type of glioma __ seizures (1month) before T0, and _ seizures at T1; *n* = __ type of glioma
AEDs use: ***AEDs names:***	_ AEDs, _ No-AEDs; *n* = __ Gliomas *n* = __ Epileptic-gliomas taking AEDs Base-line *n* = __ Monotherapy • *n* = _; AED name • *n* = _; AED name • *n* = _; AED name *n* = __ Polytheraphy Follow-up *n* = __ Monotherapy • *n* = _; AED name • *n* = _; AED name • *n* = _; AED name *n* = __ Polytheraphy
Cognitive tests:	
Cognitive domains:	
Main findings:	

Confounding Factors:	

Appendix 3. Data Collection

The extraction of relevant data for each research paper was carried out according to a standardized template to ensure consistency and facilitate effective analysis. While every effort was made to structure the data in a comparable format, variations in reporting may exist due to differences in the original study formats. These discrepancies were addressed by adapting the extracted data to the most comparable structure possible to allow for meaningful comparison across studies.

In-text reference:	(Bosma et al., 2007)
Study design:	Longitudinal
Total sample: ***Sub-samples:***	*N* = 32 high-grade gliomas (HGGs) • Base-line: *n* = 32 high-grade gliomas (HGGs) • Base-line and Follow-up 1 (8 months); *n* = 14 high-grade gliomas (HGGs) • Base-line, Follow-up 1 and 2 (16 months); *n* = 18 high-grade gliomas (HGGs)
Country:	Netherlands
Samples mean age:	• 60.1 ± 9.3 years; Base-line: *n* = 32 high-grade gliomas (HGGs) • 52.6 ± 10.0 years; Base-line and Follow-up 1 (8 months); *n* = 14 high-grade gliomas (HGGs) • 40.9 ± 12.6 years; Base-line, Follow-up 1 and 2 (16 months); *n* = 18 high-grade gliomas (HGGs)
Samples sex:	• F = 25%, M = 75% Base-line: *n* = 32 high-grade gliomas (HGGs)

	• F = 14%, M = 86% Base-line and Follow-up 1 (8 months); *n* = 14 high-grade gliomas (HGGs) • F = 22%, M = 78% Base-line, Follow-up 1 and 2 (16 months); *n* = 18 high-grade gliomas (HGGs)
Types of gliomas:	*n* = 32 high-grade gliomas (HGGs) • Grade III = 6%, Grade IV= 94% Base-line: *n* = 32 high-grade gliomas (HGGs) • Grade III = 29%, Grade IV= 71% Base-line and Follow-up 1 (8 months); *n* = high-grade gliomas (HGGs) • Grade III = 61%, Grade IV= 39% Base-line, Follow-up 1 and 2 (16 months); *n* = 18 high-grade gliomas (HGGs)
Epileptic status:	Unknown (presence/absence) <u>*Estimated:*</u> • P = 69%, A = 28%, Unknown = 3% Base-line: *n* = 32 high-grade gliomas (HGGs) • P = 79%, A = 21%, Unknown = 0% Base-line and Follow-up 1 (8 months); *n* = 14 high-grade gliomas (HGGs) • P = 67%, A = 33%, Unknown = 0% Base-line, Follow-up 1 and 2 (16 months); *n* = 18 high-grade gliomas (HGGs)
Seizure type:	Unknown
Seizure frequency:	Unknown

AEDs use:	• 69% AEDs, 28% No-AEDs, Unknown = 3% Base-line: *n* = 32 high-grade gliomas (HGGs) • 79% AEDs, 21% No-AEDs, Unknown = 0% Base-line and Follow-up 1 (8 months); *n* = 14 high-grade gliomas (HGGs) • 67% AEDs, 33% No-AEDs, Unknown = 0% Base-line, Follow-up 1 and 2 (16 months); *n* = 18 high-grade gliomas (HGGs)
AEDs names:	Unknown
Cognitive tests:	• The Dutch Adult Reading Test (Schmand et al., 1991) • Line Bisection Test (Schenkenberg et al., 1980) • Facial Recognition Test (Benton and Van Allen, 1968) • Judgment of Line Orientation Test (Woodard et al., 1996) • Letter-Digit Substitution Test (Lezak, 1995) • Visual Verbal Learning Test (Lezak, 1995) • Working Memory Task (Sternberg, 1975) • Stroop Color-Word Test (Lezak, 1995) • Categoric Word Fluency (Benton, 1968) • Meander (Lindeboom and Jonker, 1989) • Concept Shifting Test (Houx and Jolles, 1994)
Cognitive domains:	• Information processing • Psychomotor function • Attention

	• Verbal memory • Working memory • Executive functions
Main findings:	• *Base-line vs Follow-up 1:* decreased information processing, decreased psychomotor function, and decreased attention. • *Follow-up 1 vs Follow-up 2:* decreased information processing, decreased psychomotor function, and decreased attention. Of 32 at base-line, 15 had tumour reoccurrence at follow-up 1 (8 months). • *No Reoccurrence vs Reoccurrence:* decreased information processing, decreased psychomotor function, and decreased executive functions. (More pronounced deterioration between base-line and follow-up 1; 8 months). • HGG patients showed a marked decline in neurocognitive functioning in the course of their disease. • Patients with tumour progression performed worse on neurocognitive tests than did patients without tumour progression, but the difference may be mainly attributed to the use of antiepileptic drugs. • At baseline, the patient group that would develop tumour recurrence during follow-up already performed worse on

	information processing tasks than did the patient group without tumour recurrence. As the use of antiepileptic drugs and corticosteroids was equally distributed between these patient groups at baseline, this finding confirms that cognitive deficit is a negative prognostic factor in glioma patients. • Regarding the patients without tumour recurrence, deterioration in neurocognitive functioning was also observed between baseline and eight months. As the use of antiepileptic drugs and corticosteroids in this patient group did not vary during the eight months, antiepileptic drugs and corticosteroids did not contribute to the observed deterioration. However, these patients had no evidence of recurrent tumour growth. Therefore, radiotherapy may have played a role in cognitive deterioration.
Confounding Factors:	• Patients with tumour progression performed worse on neurocognitive tests than did patients without progression, which could be attributed to the use of antiepileptic drugs. • Decline in neurocognitive functions between baseline and follow-up 1 (8 months) could have been caused by the use of medication, such as antiepileptic drugs or dexamethasone, which were used more often at follow-up 1 compared to baseline, but could also have been

	caused by other factors such as radiotherapy and tumour progression.

In-text reference:	(Bruhn et al., 2024)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 1458 Glioblastoma • *n* = 1458 Gliomas • *n* = 0 Others
Country:	Sweden
Samples mean age:	• < 39 years; *n* = 36 • 40 - 54 years; *n* = 244 • 55 - 69 years; *n* = 625 • > 70 years; *n* = 553
Samples sex:	F = 41%, M = 59%; *N* = 1458 Glioblastomas
Types of gliomas:	*n* = 1458 Glioblastomas • *n* = 813 Grade 0 - I • *n* = 378 Grade II • *n* = 162 Grade III - IV • *n* = 42 Unknown
Epileptic status: ***Seizure type:*** ***Seizure frequency:***	P = 420, A = 1038; *n* = 1458 Glioblastomas Unknown Unknown
AEDs use:	Unknown

AEDs names:	Unknown
Cognitive tests:	Unknown
Cognitive domains:	Unknown
Main findings:	• Patients with initial cognitive dysfunction had significantly shorter survival than patients without; 265 days (245–285) vs. 409 days (365–453; P < .001). The reduced survival remained after Cox regression adjusting for known prognostic factors. • Patients with cognitive deficits were less likely to have radical surgery and to receive extensive anti-neoplastic nonsurgical treatment. • Initial cognitive impairment acts as an independent negative predictive factor for treatment decisions and adversely affects survival outcomes in glioblastoma patients. • The likelihood of having cognitive dysfunction significantly increased with increasing tumour size, from 30% at < 4 cm, to 55% at 4–6 cm, and finally 71% in tumours larger than 6 cm, P < .001 comparing all groups.
Confounding Factors:	Not specified

In-text reference:	(Correa et al., 2007)
Study design:	Observational Analytical
Total sample:	*N* = 40 Low-grade Glioma (LGG)

Sub-samples:	• *n* = 16 LGG received radiotherapy ± chemotherapy • *n* = 24 LGG no treatment
Country:	United States of America U.S.A
Samples mean age:	*Estimated: 42* years; *N* = 40 Low-grade Glioma (LGG) • 44 ± 7.8 years; *n* = 16 LGG received radiotherapy ± chemotherapy • 40 ± 10.3 years; *n* = 24 LGG no treatment
Samples sex:	F = 15, M = 25; *N* = 40 Low-grade Glioma (LGG) • F = 5, M = 11; *n* = 16 LGG received radiotherapy ± chemotherapy • F = 10, M = 14; *n* = 24 LGG no treatment
Types of gliomas:	*N* = 40 Low-grade Glioma (LGG) • *n* = 7 Low-Grade Oligodendroglioma (LGO), *n* = 4 Low-Grade Astrocytoma (LGA), *n* = 5 Low-Grade Oligoastrocytoma (LGOA), *n* = 0 Not available; *n* = 16 LGG received radiotherapy ± chemotherapy • *n* = 12 Low-Grade Oligodendroglioma (LGO), *n* = 5 Low-Grade Astrocytoma (LGA), *n* = 5 Low-Grade Oligoastrocytoma (LGOA), *n* = 2 Not available; *n* = 24 LGG no treatment
Epileptic status:	P = 12, A = 28; *N* = 40 Low-grade Glioma (LGG) • P = 5, A = 11; *n* = 16 LGG received radiotherapy ± chemotherapy • P = 7, A = 17; *n* = 24 LGG no treatment

Seizure type:	Unknown
Seizure frequency:	Unknown

AEDs use:	35 AEDs, 5 No-AEDs; *N* = 40 Low-grade Glioma (LGG)
	• *n* = 7 Monotherapy, *n* = 8 Polytheraphy; LGG received radiotherapy ± chemotherapy
	  ○ *n* = 4 Carbamazepine, *n* = 1 Phenytoin, *n* = 2 Other
	• *n* = 16 Monotherapy, *n* = 4 Polytheraphy; LGG no treatment
	  ○ *n* = 5 Carbamazepine, *n* = 6 Phenytoin, *n* = 5 Other

AEDs names:	Carbamazepine, phenytoin and others

Cognitive tests:	• Attention
	  ○ DF = Digit Span Forward
	  ○ DB = Digit Span Backward (WAIS-III)
	• Executive Functions
	  ○ BTA = Brief Test of Attention
	  ○ TMTA = Trail Making Test A
	  ○ TMTB = Trail Making Test B
	  ○ SCWTI = Stroop Color-Word Test—Interference
	  ○ ACT9 & 16 = Auditory Consonant Trigrams, 9 and 18 s trials
	  ○ VF = Verbal Fluency
	• Verbal Memory

	○ HVLTL = Hopkins Verbal Learning Test—Learning ○ HVLTD = Hopkins Verbal Learning Test—Delayed ○ HVLTDI = Hopkins Verbal Learning Test—Discrimination Index • Non-verbal Memory ○ BVMTL = Brief Visual Spatial Memory Test—Learning ○ BVMTD = Brief Visual Spatial Memory Test—Delayed ○ BVMTDI = Brief Visual Spatial Memory Test—Discrimination Index • Psychomotor function ○ GPTD = Grooved Pegboard Test—Dominant ○ GPTND = Grooved Pegboard Test—Non-Dominant • Language ○ BNT = Boston Naming Test ○ AF = Animal Fluency • Visual-Construction ○ LO = Line Orientation Test
Cognitive domains:	• Attention • Executive Functions • Verbal Memory

	• Non-verbal Memory • Psychomotor function • Language • Visual-Construction
Main findings:	• Treated LGG patients had lower scores than untreated patients on several cognitive domains; patients who completed treatment at intervals greater than 3 years and had long disease duration had significantly lower scores on the Non-Verbal Memory domain. • RT ± chemotherapy, disease duration, and antiepileptic treatment contributed to mild cognitive difficulties in LGG patients. • Patients who were experiencing seizures within at least 1 month prior to the evaluation (n = 28) did not differ significantly on any of the cognitive domain scores. The LGG patients who were treated with RT ± chemotherapy obtained lower scores than untreated patients on several cognitive domains including Attention, Executive, Psychomotor, Verbal and Non- Verbal Memory, and Language. Although cognitive test scores were not impaired in the majority of domains, the scores were below expected levels for this patient group given their education level and estimated high average intellectual abilities. Among the tests that comprised the Executive domain, measures requiring timed visual-motor and

	sequencing abilities and auditory working memory were the most sensitive; on the Verbal Memory domain, information retrieval was most affected, as evidenced by more preserved recognition than delayed recall performance. In contrast, MMSE scores were within normal limits regardless of treatment status, confirming the reported low sensitivity of the MMSE for detecting cognitive dysfunction in brain tumour patients. • Patients who received RT ± chemotherapy had significantly lower scores than untreated patients on the Psychomotor ($t(37) = -2.24$, $P = 0.03$) and Non-Verbal Memory ($t(38) = -2.45$, $P = 0.02$) domains. Treated patients also had lower scores than untreated patients on the Attention, Executive, Verbal Memory, and Language domains but the comparisons did not reach significance. There were significant correlations between the scores on the Non Verbal Memory and the Executive ($r = 0.35$, $P < 0.03$), Psychomotor ($r = 0.32$, $P < 0.05$), and Verbal Memory ($P = 0.40$, $P < 0.01$) domains. Longer time since diagnosis was significantly associated with lower Psychomotor domain score (Spearman rank correlation, $r = -0.45$, $P = 0.004$) and marginally associated with lower Non-Verbal Memory domain score (Spearman rank correlation, $r = -0.29$, $P = 0.07$).
Confounding Factors:	Not specified

In-text reference:	(Karunamuni et al., 2020)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 37 Primary Brain Tumour Previous to Radiotherapy (Pre-RT) • *n* = 22 Gliomas • *n* = 15 Others
Country:	United States of America U.S.A
Samples mean age:	*Median:* 50 years; *N* = 37 Primary Brain Tumour
Samples sex:	F = 17, M = 21; *N* = 37 Primary Brain Tumour

Types of gliomas:	*N* = 37 Primary Brain Tumour
	• *n* = 22 Gliomas
	  ○ *n* = 12 Glioblastoma
	  ○ *n* = 4 Anaplastic astrocytomas
	  ○ *n* = 2 Astrocytoma grade 2
	  ○ *n* = 2 Oligodendroglioma grade 2
	  ○ *n* = 1 Ependymoma grade 2
	  ○ *n* = 1 Pilocytic astrocytoma grade 1
	• *n* = 15 Others
	  ○ *n* = 9 Meningioma
	  ○ *n* = 2 Craniopharyngioma
	  ○ *n* = 2 Pituitary Adenoma 2
	  ○ *n* = 1 Low grade chondrosarcoma
	  ○ *n* = 1 Schwannoma

Epileptic status:	P = 20, A = 17; *N* = 37 Primary Brain Tumour

Seizure type:	Unknown
Seizure frequency:	Unknown
AEDs use:	21 AEDs, 16 No-AEDs; *N* = 37 Primary Brain Tumour
AEDs names:	Unknown

Cognitive tests:	• Memory
	  ○ BVMT Total recall
	  ○ BVMT Delayed recall
	  ○ HVLT-R Total recall
	  ○ HVLT-R Delayed recall
	• Executive functioning
	  ○ DKEFS VF Letter fluency
	  ○ WCST Perseverative error
	  ○ DKEFS VF Switching accuracy
	• Language
	  ○ BNT Total score responses
	  ○ DKEFS VF Category fluency
	• Attention
	  ○ WMS III Digit span
	  ○ DKEFS TMT Visual scanning
	• Processing speed
	  ○ DKEFS TMT Letter sequencing
	  ○ DKEFS TMT Number sequencing

Cognitive domains:	• Memory • Executive functioning

	• Language • Attention • Processing speed
Main findings:	• Statistically significant baseline neurocognitive impairments were identified on 4 memory (all $p \leq 0.03$) and 2 out of 3 ($p=0.01$, $p=0.027$) executive functioning tests. • Per-patient baseline GDS was significantly associated with tumour volume ($p=0.048$), tumour type ($p=0.043$), seizure history ($p=0.007$), and use of anti-epileptics ($p=0.009$). • The percentage of patients with the same impairment status at 3-, 6-, and 12-months as at baseline were 88%, 85%, and 85% respectively. • Memory and executive functioning impairment were the most common cognitive deficits prior to RT. Patients with larger tumours, more aggressive histology, and use of anti-epileptics had higher baseline GDS values.
Confounding Factors:	Not specified

In-text reference:	(Guarracino et al., 2022)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 73 epileptic-LGG • *n* = 73 Gliomas

	• *n* = 0 Others
Country:	Italy
Samples mean age:	38.3 years ± 11.7 years; *N* = 73 epileptic-LGG
Samples sex:	F = 24, M = 49; *N* = 73 epileptic-LGG
Types of gliomas:	*n* = 73 epileptic-LGG • *n* = 23 Oligodendroglioma • *n* = 50 Diffuse astrocytoma
Epileptic status:	P = 73, A = 0; n = 73 epileptic-LGG • P = 23, A = 0; n = 23 Oligodendroglioma • P = 50, A = 0; n = 50 Diffuse astrocytoma
Seizure type:	6 motor, 9 nonmotor sensory, 12 nonmotor cognitive, 3 nonmotor autonomic, 43 motor t-c; *n* = 73 epileptic-LGG
Seizure frequency:	47 monthly, 22 weekly, 4 daily; *n* = 73 epileptic-LGG
AEDs use:	*73* AEDs, 0 No-AEDs; *n* = 73 epileptic-LGG • *n* = 54; Levetracetam • *n* = 4; Carbamazepine • *n* = 4; Oxcarbazepine • *n* = 3; Valpronic acid • *n* = 7; Combination • *n* = 1; Zonisamide
AEDs names:	Levetracetam, carbamazepine, oxcarbazepine, valpronic acid,

	combination and zonisamide.
Cognitive tests:	• Raven matrices • Short-term memory • Working memory • Constructional praxis • Clock drawing test • Star cancellation • Trail Making Test A • Trail Making Test B • Trail Making Test B-A • Digit symbol substitution test • Oral praxis • Ideomotor apraxia • Token test • Object naming • Verb naming • Verbal fluency • Reading words • Reading pseudowords • Repetition words • Repetition pseudowords • Phonological discrimination • Auditory lexical decision • Visual lexical decision

Cognitive domains:	• Memory • Executive Function • Attention • Visuospatial Skills • Motor Function • Language • Processing Speed • Cognitive Flexibility
Main findings:	• Patients' pre-surgery cognitive status was within the normal range, with borderline performance for some tasks. • The Token test score was predicted by a model ($p = .0078$) containing the DT2T1 MRI, corrected for seizure features. Object naming performance was predicted by a model ($p = .0113$) containing the localization, the DT2T1 MRI, corrected for sex, EEG, and onset. Verbal fluency score was predicted by a model ($p = .0056$) containing the localization and the DT2T1 MRI, corrected for AEDs and EEG. Working memory score was predicted by a model ($p = .0117$) containing Engel class, the DT2T1 MRI, corrected for sex. Clock drawing score was predicted by a model ($p < .0001$) containing the Engel class, AEDs, and EEG. TMT A score was predicted by a model ($p = .0022$) containing localization, corrected for

	EEG. TMT B-A score was predicted by a model (p = .0373) containing localization. • Voxel Lesion Symptom Mapping analyses carried out on patients' lesion volumes confirmed that patients' level of performance correlated with lesion-related variables. • This preliminary study indicates that the pre-surgical level of performance for language tasks and for cognitive flexibility and shifting is mainly predicted by lesion-related variables, working memory by both lesion and epilepsy-related variables. Epilepsy clinical and instrumental characteristics predicted performance for visuospatial planning.
Confounding Factors:	Not specified

In-text reference:	(Klein et al., 2003)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 156 LGG • *n* = 156 Gliomas • *n* = 0 Others
Country:	Netherlands
Samples mean age:	• 35.8 years ± 10.1 Epilepsy-free (level 1) • 37.7 years ± 11.5 Epilepsy, seizure-free in the year before testing without AED (level 2)

	• 43.4 years ± 11.7 Epilepsy; seizure-free in the previous year with AED monotherapy (level 3) • 43.5 years ± 12.2 Epilepsy, seizure-free in the previous year with AED polytherapy (level 4) • 45.7 years ± 13.2 Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 5) • 41.0 years ± 8.5 Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 6)
Samples sex:	• M = 43 %; Epilepsy-free (level 1) • M = 62 %; Epilepsy, seizure-free in the year before testing without AED (level 2) • M = 68 %; Epilepsy; seizure-free in the previous year with AED monotherapy (level 3) • M = 70 %; Epilepsy, seizure-free in the previous year with AED polytherapy (level 4) • M = 58 %; Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 5) • M = 67 %Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 6)
Types of gliomas:	• Astrocytoma = 81%, Oligodendroglioma = 14%, Oligoastrocytoma = 5%; Epilepsy-free (level 1) • Astrocytoma = 71%, Oligodendroglioma = 24%, Oligoastrocytoma = 5%; Epilepsy, seizure-free in the year before testing without AED (level 2)

	• Astrocytoma = 56%, Oligodendroglioma = 35%, Oligoastrocytoma = 9%; Epilepsy; seizure-free in the previous year with AED monotherapy (level 3) • Astrocytoma = 70%, Oligodendroglioma = 26%, Oligoastrocytoma = 4%; Epilepsy, seizure-free in the previous year with AED polytherapy (level 4) • Astrocytoma = 67%, Oligodendroglioma = 33%, Oligoastrocytoma = 0%; Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 5) • Astrocytoma = 79%, Oligodendroglioma = 12%, Oligoastrocytoma = 9%; Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 6)
Epileptic status: ***Seizure type:*** ***Seizure frequency:***	P = 135, A = 21; n = 156 LGG Unknown Unknown
AEDs use:	114 AEDs, 42 No-AEDs; *n* = 156 Gliomas • Carbamazepine = 50%, Valpronic acid = 24%, Phenytoin = 20%; Epilepsy; seizure-free in the previous year with AED monotherapy (level 3) • Carbamazepine&Valpronic acid = 26%, Carbamazepine&Phenytoin = 13%, Carbamazepine&Phenobarbital = 9%, Phenytoin&Phenobarbital = 9%, >2 AEDs = 9%, Other

	AEDs = 34%; Epilepsy, seizure-free in the previous year with AED polytherapy (level 4) • Carbamazepine = 29%, Valpronic acid = 13%, Phenytoin = 21%, Phenobarbital = 4%, Carbamazepine&Valpronic acid = 8%, Valpronic acid&Phenytoin = 4%, >2 AEDs = 4%, Other AEDs = 17%; Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 5) • Carbamazepine = 18%, Valpronic acid = 6%, Phenytoin = 24%, Carbamazepine&Valpronic acid = 12%, Carbamazepine&Phenytoin = 3%, Valpronic acid&Phenytoin = 3%, Valpronic acid&Phenobarbital = 3%, >2 AEDs = 18%, Other AEDs = 13%; Epilepsy, 6 seizures in the previous year and on AED monotherapy or polytherapy (level 6)
AEDs names:	Carbamazepine, valpronic acid, phenytoin, phenobarbital and others.
Cognitive tests:	• Line Bisection Test • Facial Recognition Test • Judgment of Line Orientation Test • Letter-Digit Substitution Test • Visual Verbal Learning Test • Working Memory Task

	• Stroop Color-Word Test • Categoric Word Fluency Task • Concept Shifting Test
Cognitive domains:	• Information processing speed • Psychomotor function • Attentional functioning • Verbal memory • Working memory • Executive functioning
Main findings:	• Compared with healthy controls, glioma patients had significant reductions in information processing speed, psychomotor function, attentional functioning, verbal and working memory, executive functioning, and HRQOL. The increase in epilepsy burden that was associated with significant reductions in all cognitive domains except for attentional and memory functioning could primarily be attributed to the use of AEDs, whereas the decline in HRQOL could be ascribed to the lack of complete seizure control.
Confounding Factors:	Not specified

In-text reference:	(Maialetti et al., 2020)
Study design:	Observational Analytical
Total sample:	*N* = 33 Brain Tumour Related Epilepsy (BTRE)

Sub-samples:	• *n* = 25 Epileptic-gliomas • *n* = 8 Others
Country:	Italy
Samples mean age:	Males mean age 46.2 years; Females mean age, 52.7; *n* = 33 Brain Tumour Related Epilepsy (BTRE)
Samples sex:	F = 15, M = 18; *N* = 33 Brain Tumour Related Epilepsy (BTRE)
Types of gliomas:	*n* = 25 Epileptic-gliomas • *n* = 10 high-grade gliomas • *n* = 12 low-grade gliomas • *n* = 3 glioblastomas
Epileptic status:	P = 25, A = 0; n = 25 Epileptic-gliomas • P = 10, A = 0; n = 10 high-grade gliomas • P = 12, A = 0; n = 12 low-grade gliomas • P = 3, A = 0; n = 3 glioblastomas
Seizure type:	12 Focal aware seizures, 9 Focal unaware seizures and 4 Focal to bilateral tonic-clonic seizure; *n* = 25 Epileptic-gliomas 4 Focal aware seizures, 5 Focal unaware seizures and 1 Focal to bilateral tonic-clonic seizure; *n* = 10 high-grade gliomas 7 Focal aware seizures, 4 Focal unaware seizures and 1 Focal to bilateral tonic-clonic seizure; *n* = 12 low-grade gliomas 1 Focal aware seizure, 0 Focal unaware seizures and 2 Focal to bilateral tonic-clonic seizure; *n* = 3 glioblastomas

Seizure frequency:	52 seizures (1month) before T0, and 27 seizures at T1; *n* = 25 Epileptic-gliomas 24 seizures (1month) before T0, and 7 seizures at T1; *n* = 10 high-grade gliomas 25 seizures (1month) before T0, and 17 seizures at T1; *n* = 12 low-grade gliomas 3 seizures (1month) before T0, and 3 seizures at T1; *n* = 3 glioblastomas
AEDs use:	25 AEDs, 0 No-AEDs; *n* = 25 Epileptic-gliomas Base-line *n* = 14 Monotherapy • *n* = 6; Levetracetam • *n* = 3; Lamotrigine • *n* = 5; Topiramate *n* = 11 Polytheraphy Follow-up *n* = 13 Monotherapy • *n* = 6; Levetracetam • *n* = 2; Lamotrigine • *n* = 5; Topiramate *n* = 12 Polytheraphy
AEDs names:	Levetiracetam, valproic acid, oxcarbazepine, lamotrigine, topiramate, phenobarbital, lacosamide, and perampanel.

Cognitive tests:	• MMSE (Mini-Mental State Examination) • RAVEN CPM (Raven's Progressive Matrices) • Visual Search • TMT-A (Trail Making Test A) • TMT-B (Trail Making Test B) • TMT B-A (Difference between TMT-B and TMT-A) • Short Story • RAVLT Immediate Recall (Rey Auditory Verbal Learning Test Immediate Recall) • RAVLT Delayed Recall (15') • ROCF Copy (Rey-Osterrieth Complex Figure Test - Copy) • ROCF Immediate Recall (Rey-Osterrieth Complex Figure Test - Immediate Recall) • ROCF Delayed Recall (20') • TOL (Tower of London) • CDT (Clock Drawing Test) • Phonemic Fluency • Categorical Fluency
Cognitive domains:	Not defined
Main findings:	• Concerning neuropsychological performances, they observed at final follow-up a significant improvement in memory and learning domains (RAVLT immediate recall P = .01; RAVLT delayed recall P = .003) only in patients

	treated with neurocognitive training (NT); this improvement was such effective to allow them achieve the same performance of patients without neurocognitive training, which mean scores in memory tests were in normal ranges. • Regarding epileptological aspects, despite all patients already being treated for epilepsy with one or more AEDs, they observed a significant improvement in seizure control at final follow-up (P = .02), due to the therapy modification they made in 11 patients.
Confounding Factors:	• Small sample size and short follow-up. • The enrolled patients in the study were already being treated for epilepsy, with 19 experiencing good seizure control from baseline. They had diverse neuropsychological profiles and received various types of combined treatments, including epileptological care, supportive groups, social assistance, and neurocognitive training. Enrolling a larger, more homogeneous group with similar neurological and neuropsychological profiles, and a longer follow-up, would be ideal. However, the unique and individualized needs of each patient—typical in rare diseases—make it challenging to create a statistically homogeneous sample, complicating the balance between participant needs and sample size requirements for the study.

In-text reference:	(Maschio et al., 2015)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 16 Brain Tumour Related Epilepsy (BTRE) • *n* = 11 Epileptic-gliomas • *n* = 5 Others
Country:	Italy
Samples mean age:	47.2 years ± 11.4; *n* = 11 Epileptic-gliomas
Samples sex:	M = 5, F = 6; *n* = 11 Epileptic-gliomas
Types of gliomas:	*n* = 11 Epileptic-gliomas • *n* = 4 Epileptic-high-grade gliomas • *n* = 5 Epileptic-low-grade gliomas • *n* = 2 Epileptic-glioblastomas
Epileptic status: ***Seizure type:***	P = 11, A = 0; n = 11 Epileptic-gliomas • P = 4, A = 0; n = 4 Epileptic-high-grade gliomas • P = 5, A = 0; n = 5 Epileptic-low-grade gliomas • P = 2, A = 0; n = 2 Epileptic-glioblastomas 4 Simple partials, 3 Complex partial, 2 Simple partial seizures secondarily generalized, 2 Complex partial seizures secondarily generalized*; n* = 11 Epileptic-gliomas • 2 Simple partials, 1 Complex partial, 1 Complex partial seizures secondarily generalized*; n* = 4 Epileptic-high-grade gliomas

	• 2 Simple partials, 2 Complex partial, 1 Simple partial seizure secondarily generalized*;* *n* = 5 Epileptic-low-grade gliomas • 1 Simple partial seizure secondarily generalized, 1 Complex partial seizures secondarily generalized*;* *n* = 2 Epileptic-glioblastomas
Seizure frequency:	Unknown
AEDs use:	11 AEDs, 0 No-AEDs; *n* = 11 Epileptic-gliomas • *n* = 1; Carbamazepine • *n* = 4; Levetiracetam • *n* = 1; Phenobarbital • *n* = 3; Topiramate • *n* = 2; Polytherapy
AEDs names:	Carbamazepine, levetiracetam, phenobarbital and topiramate.

Cognitive tests:	• Global Neurocognitive Performances
	  ○ Mini Mental State Examination
	• Attention and Executive Functions
	  ○ Trail Making Test
	  ○ Frontal Assessment Battery
	• Abstract Reasoning
	  ○ Raven Progressive Matrices
	• Visuospatial Abilities
	  ○ Rey-Osterrieth Complex Figure, Copy (ROCF-copy)

	○ Clock Drawing Test • Long-Term Visuospatial Memory ○ Rey-Osterrieth Complex Figure, Recall (ROCF-recall) • Short-Term Auditory-Verbal Memory ○ Span Forward and Backward ○ Recall of Disyllabic Words ○ 15 Rey-Osterrieth Word List, Immediate Recall • Long-Term Auditory-Verbal Memory and Episodic Memory ○ 15 Rey-Osterrieth Word List, Delayed Recall ○ Story Recall • Language ○ Phonemic Fluency Test ○ Semantic Fluency Test • Training NeuroPsicologico (TNP) software ○ Memory ○ Attention ○ Visuo-spatial functions ○ Language ○ Reasoning
Cognitive domains:	• Global Neurocognitive Performances • Attention and Executive Functions • Abstract Reasoning

	• Visuospatial Abilities • Long-Term Visuospatial Memory • Short-Term Auditory-Verbal Memory • Long-Term Auditory-Verbal Memory and Episodic Memory • Language
Main findings:	• Statistical analysis with Student T test for paired data showed that short-term verbal memory, episodic memory, fluency and long term visuospatial memory improved immediately after the T1 and remained stable at T2. At final follow-up all patients showed an improvement in at least one domain that had been lower than normal at baseline. • Span forward, ROCF-recall, story recall and phonetic fluency test significantly improved T0 to T1 ($p = 0.017$; $p = 0.036$; $p = 0.036$; $p = 0.043$) • Span forward, ROCF-recall, story recall, and phonetic fluency significantly improved T0 T2 ($p = 0.038$; $p = 0.020$ $p = 0.017$; $p = 0.023$) • At T0 the greatest deficits were in short and long-term verbal memory: short-term (9/16 patients), long-term (7/16 patients).

	• At final follow-up (after 6 months of RehabTr) all patients showed an improvement in at least one domain that had been lower than normal at baseline.
Confounding Factors:	Not specified

In-text reference:	(Maschio et al., 2014)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 100 Brain Tumour Related Epilepsy (BTRE) • *n* = 68 Epileptic-gliomas • *n* = 32 Others
Country:	Italy
Samples mean age:	50.2 years ± 14.7; *N* = 100 Brain Tumour Related Epilepsy (BTRE)
Samples sex:	F = 47, M = 53; *N* = 100 Brain Tumour Related Epilepsy (BTRE)
Types of gliomas:	*n* = 68 Epileptic-gliomas • *n* = 51 Epileptic-high-grade gliomas • *n* = 17 Epileptic-low-grade gliomas
Epileptic status: ***Seizure type:*** ***Seizure frequency:***	P = 68, A = 0; n = 68 Epileptic-gliomas • P = 51, A = 0; n = 51 Epileptic-high-grade gliomas • P = 17, A = 0; n = 17 Epileptic-low-grade gliomas Unknown Unknown
AEDs use:	78 AEDs, 22 No-AEDs; n = 100 Brain Tumour Related Epilepsy

	(BTRE) • *n* = 5; Carbamazepine • *n* = 1; Phenitoine • *n* = 5; Valproic acid • *n* = 1; Lamotrigine • *n* = 13; Oxcarbazepine • *n* = 4; Levetiracetam • *n* = 36; Phenobarbital • *n* = 5; Topiramate • *n* = 8; Polytherapy
AEDs names:	Carbamazepine, phenitoine, valproic acid, lamotrigine, oxcarbazepine, levetiracetam, phenobarbital, topiramate and Polytherapy.
Cognitive tests:	• Mini Mental State Examination (MMSE)
Cognitive domains:	• Global cognitive performance
Main findings:	• Neurological performances and global neurocognitive status were not influenced by factors related to neoplastic disease or to epilepsy. • Side effects, cognitive deficits, and QoL concerns, as well as patients' perception of these, were significantly related to polytherapy, especially in patients who had been taking AEDs for a period longer that 6 months. • We found that the weight of epilepsy in BTRE patients was related to AED therapy.

Confounding Factors:	Not specified

In-text reference:	(Rahman et al., 2015)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 81 Primary Brain Tumours • *n* = Not specified; Gliomas • *n* = Not specified; Others
Country:	Australia
Samples mean age:	52.35 ± 18 years; *n* = 26 L1: no-epi-no-AEDs 48.97 ± 14 years; *n* = 32 L2: epi-noSz on the last 6 months-AEDs 50 ± 18 years; *n* = 23 L3: epi-Sz on the last 6 months-AEDs
Samples sex:	M = 58%, F = 42%; *n* = 26 L1: no-epi-no-AEDs M = 59%, F = 41%; *n* = 32 L2: epi-noSz on the last 6 months-AEDs M = 56.5%, F = 43.5%; *n* = 23 L3: epi-Sz on the last 6 months-AEDs
Types of gliomas:	Gliomas = 69.2%, Others = 30.8%; *n* = 26 L1: no-epi-no-AEDs • Astrocytomas = 11.5%, Oligoastrocytomas = 0%, Oligodendrogliomas = 11.5% and Glioblastomas = 46.2% Gliomas = 71.9%, Others = 28.1%; *n* = 32 L2: epi-noSz on the last 6 months-AEDs

	• Astrocytomas = 6.3%, Oligoastrocytomas = 12.5%, Oligodendrogliomas = 25% and Glioblastomas = 28.1% Gliomas = 78.2%, Others = 21.8%; *n* = 23 L3: epi-Sz on the last 6 months-AEDs • Astrocytomas = 13%, Oligoastrocytomas = 0%, Oligodendrogliomas = 39.1% and Glioblastomas = 26.1%
Epileptic status:	P = 23 on the last 6 months-AEDs, A = 32 on the last 6 months-AEDs; n = 55 Epileptic-Primary Brain Tumours
Seizure type:	Unknown
Seizure frequency:	Unknown
AEDs use:	55 AEDs, 0 No-AEDs; n = 55 Epileptic-Primary Brain Tumours Monotheraphy = 19 and Politheraphy = 13; n = 32 L2: epi-noSz on the last 6 months-AEDs • Levetiracetam = 11, Valproate = 1, Carbamazepine = 4, Phenytoin = 1 and Lamotrigine = 2; n = 19 Monotheraphy Monotheraphy = 13 and Politheraphy = 10; n = 23 L3: epi-Sz on the last 6 months-AEDs • Levetiracetam = 10, Valproate = 2, Lamotrigine = 1; n = 13 Monotheraphy
AEDs names:	Levetiracetam, valproate, carbamazepine, phenytoin and lamotrigine.
Cognitive tests:	• The Montreal Cognitive Assessment (MoCA) • Frontal Assessment Battery (FAB)

Cognitive domains:	• Global cognitive performance
Main findings:	• 68% of patients were diagnosed with primary brain tumour-related epilepsy • 50.61% patients were found to have cognitive impairment. • Six percent of patients had a MoCA score of <15/30. • Patients with cognitive impairment were found to have statistically significantly low scores in both FACT-Br 'brain' and 'functional' domains ($p \leq 0.01$; $p \leq 0.05$). • There were no statistically significant differences in mean MoCA and FAB scores among the L1, L2, and L3 groups.
Confounding Factors:	Not specified

In-text reference:	(Reitz et al., 2022)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 27 glioma patients • *n* = 27 Gliomas ○ *n* = 16 (cognition T1, T2, T3) glioma patients • *n* = 0 Others
Country:	Germany
Samples mean age:	36.1 ± 11.8 years; *N* = 27 glioma patients
Samples sex:	F = 10, M = 17; *N* = 27 glioma patients
Types of gliomas:	*n* = 27 Gliomas

	• *n* = 15 Astrocytoma • *n* = 8 Oligodendroglioma • *n* = 4 Glioblastoma
Epileptic status:	T1; n = 18/27 epileptic-glioma patients T2; n = 2/22 epileptic-glioma patients T3; n = 0/20 epileptic-glioma patients
Seizure type:	Unknown
Seizure frequency:	Unknown
AEDs use:	T1; 0 AEDs = 7, 1 AEDs = 18, ≥ 2 AEDs = 2; *n* = 27 glioma patients T2; 0 AEDs = 3, 1 AEDs = 14, ≥ 2 AEDs = 6; *n* = 22 glioma patients T3; 0 AEDs = 4, 1 AEDs = 13, ≥ 2 AEDs = 3; *n* = 20 glioma patients
AEDs names:	Unknown
Cognitive tests:	• TAP Alertness • TAP Geteilte Aufmerksamkeit II • Wortschatztest (WST) • Regensburger Wortflüssigkeitstest (RWT) • Wechsler Memory Scale – Revised (WMS-R) • Verbaler Lern- und Gedächtnistest (VLMT) • Benton Test

	• Rey–Osterrieth Complex Figure Test (ROCFT) • Leistungsprüfsystem (LPS) • Tower of London (ToL)
Cognitive domains:	• Attention • Verbal Fluency • Verbal Memory • Figural Memory • Working Memory • Executive Functioning • Visuospatial Functioning
Main findings:	• While preoperatively impairment in at least one neurocognitive domain was found in 37.0% of patients, postoperatively, in the short term, 36.4% of patients presented a significant deterioration in word fluency (p=0.009) and 34.8% of patients in executive functions (p=0.049). Over the long-term, scores improved to preoperative baseline levels. • Regarding seizures, these were present in 18 (66.7%) patients prior to surgery. • Postoperatively, 22 (81.5%) patients were treated with antiepileptic drugs with all patients presenting seizure-freedom.
Confounding Factors:	• Follow-up neurocognitive data sets were not available for all patients

	• Heterogeneity of patient cohorts

In-text reference:	(van Dellen et al., 2012)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 71 Participants • *n* = 25 Glioma patients • *n* = 10 Epileptic patients • *n* = 36 Healthy controls
Country:	Netherlands
Samples mean age:	44.1 years ± 9.7; *n* = 13 LGG 50.3 years ± 11.5; *n* = 12 HGG 30.1 years ± 6.8; *n* = 10 NGL 43.9 years ± 11.9; *n* = 36 Control
Samples sex:	M = 16, F = 9; *n* = 25 Gliomas M = 6, F = 7; *n* = 13 LGG M = 10, F = 2; *n* = 12 HGG M = 4, F = 6; *n* = 10 NGL M = 18, F = 18; *n* = 36 Control
Types of gliomas:	*n* = 25 Gliomas 13 Grade II; *n* = 13 LGG 4 Grade III, 8 Grade IV; *n* = 12 HGG
Epileptic status:	P = 25, A = 0; n = 25 Epileptic-gliomas • P = 13, A = 0; n = 13 LGG • P = 12, A = 0; n = 12 HGG

Seizure type:	2 Simple partials, 10 Generalized*; n* = 12 Epileptic-high grade gliomas 4 Simple partials, 9 Generalized*; n* = 13 Epileptic-low-grade gliomas 1 Simple partial, 2 Complex partial, 7 Generalized*; n* = 10 Epileptic-non-gliomas
Seizure frequency:	8.2 (6SD 9.9) month Low-grade Gliomas, 17.4 (6SD 43.6) month High-grade Gliomas, 28.9 (6SD 31.1) month Non-gliomas.
AEDs use:	23 AEDs, 2 No-AEDs; *n* = 25 Gliomas • None = 2, Monotherapy = 5, Polyhteraphy = 6; *n* = 13 LGG • None = 0, Monotherapy = 9, Polyhteraphy = 3; *n* = 12 HGG
AEDs names:	Unknown
Cognitive tests:	• Stroop color-word test (attention, executive functioning, mental flexibility, mental processing speed) • Categoric verbal fluency (executive functioning) • Visual verbal learning test (storage and retrieval of verbal memory)
Cognitive domains:	• Attention • Executive functioning • Verbal memory

Main findings:	• No significant differences in cognitive performance were found between LGG and HGG patients. • Decreased synchronizability and decreased global integration in the theta band seem to make LGG and NGL patients more prone to the occurrence of seizures and cognitive decline. • We found correlations between several theta band network parameters and both cognitive performance and seizure frequency in LGG patients, and it may therefore be that these clinical parameters are also correlated. We calculated the correlation between seizure frequency and cognitive performance in LGG patients and found a non-significant negative trend (Kendall's tau = 20.419; p = 0.081).
Confounding Factors:	Not specified

In-text reference:	(Vogt et al., 2018)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 166 epilepsy-associated tumours (LEATs) • *n* = 43 Gliomas • *n* = 123 Others
Country:	Germany
Samples mean age:	33.5 years ± 8.3; *n* = 24 Grade-I Pilocytic Astrocytomas (PA) 35.0 years ± 9.1; *n* = 10 Grade-II Diffuse Astrocytomas (DA)

	28.1 years ± 6.1; *n* = 9 Grade-II Pleomorphic Xanthoastrocytomas (PXA)
Samples sex:	M = 24, F = 19; *n* = 43 Gliomas • M = 13, F = 11; *n* = 24 Grade-I Pilocytic Astrocytomas (PA) • M = 6, F = 4; *n* = 10 Grade-II Diffuse Astrocytomas (DA) • M = 5, F = 4; *n* = 9 Grade-II Pleomorphic Xanthoastrocytomas (PXA) M = 64, F = 59; *n* = 123 Others
Types of gliomas:	*n* = 43 Gliomas • *n* = 24 Grade-I Pilocytic Astrocytomas (PA) • *n* = 10 Grade-II Diffuse Astrocytomas (DA) • *n* = 9 Grade-II Pleomorphic Xanthoastrocytomas (PXA)
Epileptic status:	P = 43, A = 0; n = 43 Gliomas • P = 24, A = 0; *n* = 24 Grade-I Pilocytic Astrocytomas (PA) • P = 10, A = 0; *n* = 10 Grade-II Diffuse Astrocytomas (DA) • P = 9, A = 0; *n* = 9 Grade-II Pleomorphic Xanthoastrocytomas (PXA)
Seizure type:	Unknown
Seizure frequency:	Pre-surgical monthly seizure frequency • 10.4 (15.2) month n = 95 Ganglioglioma WHO grade I

	• 3.7 (4.7) month n = 24 Pilocytic astrocytoma WHO grade I • 13.0 (13.3) month n = 9 Pleomorphic xanthoastrocytoma WHO grade II • 16.2 (10.3) month n = 10 Diffuse astrocytomas WHO grade II
AEDs use: ***AEDs names:***	43 AEDs, 0 No-AEDs; *n* = 43 Gliomas Unknown
Cognitive tests:	• VLMT-Verbaler Lern und Merkfähigkeitstest (Helms-taedter et al., 2001) • LPS Leistungsprüfsystem (Horn, 1983) • Mehrfachwahl Wortschatz Intelligenztest (Lehrl,1977) • DCS-R Diagnos-tikum für Zerebralschädigung revised (Helmstaedteret al., 1991) • Ufmerksamkeitsbelastungs-test (Brickenkamp, 2002)
Cognitive domains:	• Verbal fluency • Comprehension • Executive functions • Working memory • Interference • Verbal memory • Nonverbal memory

Main findings:	• Preoperative memory was impaired in 67.1% of all patients, executive functions in 44.7%, and language in 45.5%. • Patients with PA displayed the poorest cognitive performance. • Individual significant memory decline that was observed in 27.1% of all patients was predicted by left-sided surgery, a mesial pathology, and extended hippocampal resection. • Executive functions depended on antiepileptic drug (AED) load and remained stable (72.0%) or even improved (21.6%) after surgery. • Language functions were unchanged in 89.5% of patients. • Different tumour types appear to be associated with different cognitive and seizure outcomes with astrocytoma as the least benefitted group.
Confounding Factors:	Not specified

In-text reference:	(Youshani et al., 2024)
Study design:	Observational Descriptive
Total sample: ***Sub-samples:***	*N* = 257 LGG-operations (206 patients) • *n* = 257 Gliomas • *n* = 0 Others

Country:	United Kingdom
Samples mean age:	38.8 ± 12.2 years; *N* = 257 LGG-operations
Samples sex:	M = 151, F = 106; *N* = 257 LGG-operations
Types of gliomas:	*n* = 257 LGG • *n* = 135 Astrocytomas • *n* = 122 Oligodendrogliomas
Epileptic status:	P = 257, A = 0; n = 257 LGG • P = 135, A = 0; *n* = 135 Astrocytomas • P = 122, A = 0; *n* = 122 Oligodendrogliomas
Seizure type:	*n* = 71 Generalized tonic-clonic seizures, *n* = 35 Focal unaware seizures, and *n* = 79 Focal aware seizures; *N* = 257 LGG-operations (206 patients)
Seizure frequency:	Unknown
AEDs use:	All used AEDs *N* = 257 Epileptic-LGG-operations (206 patients) *n* = 215 Monotherapy, *n* = 42 Polytheraphy; *N* = 257 LGG-operations (206 patients) • *n* = 63; Valproate • *n* = 93; Levetracetam • *n* = 22; Lamotrigine • *n* = 4; Phenytoin • *n* = 7; Others
AEDs names:	Valproate, levetracetam, lamotrigine and phenytoin.
Cognitive tests:	Unknown

Cognitive domains:	Unknown
Main findings:	• Overall, our postoperative seizure rate was 45/257 (17.5%) at <15 days, 52/257 (20.2%) at 15 days to 3 months and 76/257 (31.1%) at 3–12 months. After 12 months, 97/257 (37.8%) cases continued to have seizures with the remaining patients maintaining seizure freedom or under control with medications. • Further histological subtype analysis showed a lower, but not significant postoperative seizure rate with grade 2 oligodendroglioma, 45.1% (preoperative: 73.8%), versus grade 2 astrocytoma patients 48.9% (preoperative: 73.3%). • Seizure was the main presenting symptom at diagnosis (62.6%). The frontal region was the most common LGG location (56.0%), followed by temporal (30.4%) and less frequently parietal or occipital (9.3% and 1.6%, respectively). Postoperative seizure frequency per location was highest in the temporal lobe (temporal, 50%; frontal, 45.1%; parietal, 33.3%; occipital, 25%; and other, 14.3%). • Postoperatively, 114 patients suffered from seizures, and approximately 45.2% of patients developed seizures at 3–12 months postsurgery, with the odds higher in patients on preoperative ASMs.

	• The extent of resection (EOR) was inversely related to seizure failure, with gross-total resection showing a statistically significant reduction in seizures in comparison to all other surgical resections. • No evidence to suggest a reduced postoperative seizure outcome when prescribing preoperative ASMs. • Gliomas of the temporal region had a higher incidence of seizure, independent of ASM use. • Patients on preexisting ASMs have a higher chance of postoperative seizures.
Confounding Factors:	• The majority of the patients in the prophylaxis group underwent an awake craniotomy, which in itself could have a greater predisposition to intraoperative seizures due to the cortical stimulation. Despite this, the findings showed no significant difference in awake versus not with respect to seizure outcome in the postoperative period. • Inclusion of patients treated from 2006 with older generation ASMs, while surgery from 2016 onward used newer generation ASMs, thus limiting comparisons regarding ASM efficacy.

In-text reference:	(de Groot et al., 2013)
Study design:	Observational Analytical

Total sample: ***Sub-samples:***	*N* = 117 epileptic-HGG • *n* = 117 Gliomas • *n* = 0 Others
Country:	Netherlands
Samples mean age:	52 ± 13 years; *N* = 117 epileptic-HGG • 55 ± 11 years; *n* = 44 epileptic-HGG no AEDs • 51 ± 14 years; *n* = 73 epileptic-HGG AEDs
Samples sex:	M = 87, F = 30; *N* = 117 epileptic-HGG • M = 37, F = 7; *n* = 44 epileptic-HGG no AEDs • M = 50, F = 13; *n* = 37 epileptic-HGG AEDs
Types of gliomas:	WHO grade III = 48 (Astrocytoma = 34, Oligodendroglioma = 11, Oligoastrocytoma = 3), WHO grade IV = 69; *N* = 117 epileptic-HGG • WHO grade III = 23 (Astrocytoma = 19, Oligodendroglioma = 4, Oligoastrocytoma = 0), WHO grade IV = 21; *n* = 44 epileptic-HGG no AEDs • WHO grade III = 25 (Astrocytoma = 15, Oligodendroglioma = 7, Oligoastrocytoma = 3), WHO grade IV = 48; *n* = 37 epileptic-HGG AEDs
Epileptic status: ***Seizure type:*** ***Seizure frequency:***	P = 117, A = 0; n = 117 epileptic-HGG Unknown Unknown
AEDs use:	73 AEDs, 44 No-AEDs; *n* = 117 epileptic-HGG

	None = 44, Levetiracetam = 35, Valpronic acid = 22, Phenytoin = 16; *N* = 117 epileptic-HGG *n* = 73 Monotherapy, *n* = 0 Polytheraphy; *N* = 73 AEDs-epileptic-HGG • None = n/a, Levetiracetam = n/a, Valpronic acid = n/a, Phenytoin = n/a; *n* = 44 epileptic-HGG no AEDs • None = n/a, Levetiracetam = 35, Valpronic acid = 22, Phenytoin = 16; *n* = 37 epileptic-HGG AEDs
AEDs names:	Levetiracetam, valpronic acid and phenytoin.
Cognitive tests:	• Letter digit substitution • Concept shifting • Stroop color and word • Visual verbal learing • Memory comparison • Categoric word fluency
Cognitive domains:	• Information processing speed, psychomotor functioning • Executive functioning, psychomotor functioning • Attention • Verbal memory • Working memory • Executive functioning
Main findings:	• Patients on older and newer AEDs performed equally well as patients not on an AED.

	• Patients on levetiracetam performed even better on verbal memory tests than patients not on an AED. • Although patients with left-sided tumours as a group performed more poorly in the domain of verbal memory, these results with respect to levetiracetam remained significant when controlling for tumour location and lateralization. • Post-hoc analyses revealed that within the group using older AEDs, patients on valproic acid performed better than patients on phenytoin. • Neither levetiracetam nor valproic acid was associated with additional cognitive deficits in HGG.
Confounding Factors:	• Results of the beneficial effects of valproic acid on verbal memory were obtained from post-hoc analyses and must therefore be interpreted with caution. • Since the patients were not randomized into treatment groups, there could be bias regarding the choice of medical anti-epileptic treatment. • Different cohorts were used in the study, which may have introduced some form of bias. However, the study protocols across the three cohorts were identical, and there were no significant differences in clinical characteristics, with the exception of performance status, for which corrections were made in the analyses.

	• Seizure burden, dosage range, and AED serum levels were not registered. Although different dosages may influence cognitive performance within a patient group using a particular AED, the group-level analyses are likely to minimize the effect of dosage on cognition.

In-text reference:	(Dinapoli al., 2009)
Study design:	Experimental Quasi-experimental
Total sample: ***Sub-samples:***	*N* = 18 brain tumour-related epilepsy (BTRE) • *n* = 15 Gliomas • *n* = 3 Others
Country:	Italy
Samples mean age:	50.6 years; *N* = 18 brain tumour-related epilepsy (BTRE)
Samples sex:	F = 8 females, M = 10; *N* = 18 brain tumour-related epilepsy (BTRE)
Types of gliomas:	*n* = 15 Gliomas • *n* = 3 Low-grade oligodendroglioma • *n* = 3 Anaplastic oligodendroglioma • *n* = 3 Low-grade astrocytoma • *n* = 3 Anaplastic astrocytoma • *n* = 3 Glioblastoma multiforme
Epileptic status:	Before levetiracetam: All presented seizures; *n* = 15 Gliomas During levetiracetam; *n* = 15 Gliomas • P = 2, A = 13; n = 15 Gliomas

	○ P = 1, A = 2; n = 3 Low-grade astrocytomas ○ P = 1, A = 2; n = 3 Anaplastic astrocytomas
Seizure type:	2 Complex partial + Secondarily generalized tonic-clonic, 1 Simple partial + Secondarily generalized tonic-clonic; *n* = 3 Low-grade oligodendroglioma 1 Simple partial, 1 Complex partial + Secondarily generalized tonic-clonic, 1 Simple partial + Secondarily generalized tonic-clonic; *n* = 3 Anaplastic oligodendroglioma 1 Complex partial, 2 Complex partial + Secondarily generalized tonic-clonic; *n* = 3 Low-grade astrocytoma 2 Simple partial, 1 Complex partial + Secondarily generalized tonic-clonic; *n* = 3 Anaplastic astrocytoma 1 Simple partial, 1 Complex partial + Secondarily generalized tonic-clonic, 1 Simple partial + Secondarily generalized tonic-clonic; *n* = 3 Glioblastoma multiforme
Seizure frequency:	*n* = 167 seizures before Levetiracetam, and *n* = 36 seizures during Levetiracetam; *n* = 15 Gliomas • *n* = 6 seizures before Levetiracetam, and *n* = 0 seizures during Levetiracetam; *n* = 3 Low-grade oligodendroglioma • *n* = 6 seizures before Levetiracetam, and *n* = 0 seizures during Levetiracetam; *n* = 3 Anaplastic oligodendroglioma • *n* = 64 seizures before Levetiracetam, and *n* = 24 seizures during Levetiracetam; *n* = 3 Low-grade astrocytoma

	• *n* = 84 seizures before Levetiracetam, and *n* = 12 seizures during Levetiracetam; *n* = 3 Anaplastic astrocytoma • *n* = 7 seizures before Levetiracetam, and *n* = 0 seizures during Levetiracetam*; n* = 3 Glioblastoma multiforme
AEDs use:	Before Levetiracetam 10 taking AEDs and 5 not; *n* = 15 Epileptic-gliomas • *n* = 1; Valpronic Acid 1000 • *n* = 2; Topiramate 150 • *n* = 4; Phenobarbital 50 – 100 • *n* = 3; Oxcarbacepine 1200 - 1800 During Levetiracetam *n* = 15 Epileptic-gliomas taking AEDs • *n* = 6; Levetiracetam 3000 • *n* = 3; Levetriacetam 2000 • *n* = 2; Levetriacetam 1500 • *n* = 3; Levetriacetam 1000 • *n* = 1; Levetriacetam 750
AEDs names:	Levetiracetam, valproic acid, topiramate, phenobarbital, and oxcarbazepine.
Cognitive tests:	• Mini Mental State Examination (MMSE)
Cognitive domains:	• Global cognitive profile
Main findings:	• After 6 months, 16 patients were seizure free (88.9%), 2 (11.1%) had reduction in seizure frequency [50%. Compared to baseline, we observed a worsening of performance (KPS p = 0.011; BI = 0.008) and global

	lower cognitive performance (MMSE p = 0.011); distress related to seizure frequency (p = 0.003) and medication effects (p = 0.046) were significantly lower. • At 6 months' follow-up, we found 88.9% of patients' seizure free.
Confounding Factors:	• Very small sample, heterogeneous histological diagnoses and administration of open-label treatment. • No independent control group. • Evaluation of several endpoints may have increased the possibility of false positive findings in our analysis.

In-text reference:	(Konrath et al., 2022)
Study design:	Experimental Quasi-Experimental
Total sample: ***Sub-samples:***	*N* = 43 Supratentorial brain tumour • *n* = 24 Gliomas (Malignant) • *n* = 19 Others
Country:	Austria
Samples mean age:	60.6 years; *N* = 43 Supratentorial brain tumour
Samples sex:	F = 25, M = 18; *N* = 43 Supratentorial brain tumour
Types of gliomas:	Unknown
Epileptic status: ***Seizure type:*** ***Seizure frequency:***	Unknown Unknown Unknown
AEDs use:	No AEDs at Base-line

AEDs names:	All *N* = 43 Supratentorial brain tumour took Levetiracetam Levetiracetam
Cognitive tests:	NeuroCogFX • Simple Reaction (Attention) • Go/No-Go (Attention) • Invers Go/No-Go (Attention) • Digit span (Working memory) • Two back (Working memory) • Verbal memory (Memory) • Figural memory (Memory) • Phonemic fluency (Language)
Cognitive domains:	• Attention • Working memory • Memory • Language
Main findings:	• There was a significant improvement of NeuroCogFX total-score at Follow-Up (p = 0.004) compared to Baseline. • LEV had no negative short-term effect on the cognitive domains studied, as the change observed between Baseline (without LEV) and Pre-op (with LEV) time-points was not significant in any subtest score. Furthermore, none of the Bonferroni-adjusted 95%

	confidence intervals of corresponding subtests included the meaningful deterioration margin. • The postoperative outcome of all subtests showed a trend toward improvement compared to Baseline. • The domain Working Memory, which consists of the subtests Digit Span and Two Back, showed a statistically significant improvement whose magnitude was clinically relevant in our opinion. This effect was presumably resulting from the surgical debulking and the reduction of tumour load, showing thus that working memory is probably very sensitive to changes in tumour volume. • Significant p-values were obtained for subtest scores Digit Span ($p = 0.005$), Two Back ($p= 0.001$), Figural Memory ($p = 0.030$), and domain scores Working Memory ($p < 0.001$).
Confounding Factors:	• No control group as our neuro-oncological centre routinely applied perioperative AEDs according to internal standard operating procedures. • Sample included brain tumours of different histology.

In-text reference:	(Maschio et al., 2011)
Study design:	Experimental Quasi-Experimental
Total sample: ***Sub-samples:***	*N* = 29 brain tumour-related epilepsy (BTRE) • *n* = 25 Gliomas

	• *n* = 4 Others
Country:	Italy

Samples mean age:	55 years; *N* = 29 brain tumour-related epilepsy (BTRE)
	• 54.4 years; *n* = 25 Gliomas
	  ○ 39 years; *n* = 1 Low-grade oligodendroglioma
	  ○ 40.3 years; *n* = 6 Anaplastic oligodendroglioma
	  ○ 53.4 years; *n* = 5 Low-grade astrocytoma
	  ○ 61.5 years; *n* = 4 Anaplastic astrocytoma
	  ○ 62.8 years; *n* = 9 Multiform glioblastoma

Samples sex:	F = 13, M = 16; *N* = 29 brain tumour-related epilepsy (BTRE)
	• F = 11, M = 14; *n* = 25 Gliomas
	  ○ F = 0, M = 1; *n* = 1 Low-grade oligodendroglioma
	  ○ F = 4, M = 2; *n* = 6 Anaplastic oligodendroglioma
	  ○ F = 2, M = 3; *n* = 5 Low-grade astrocytoma
	  ○ F = 1, M = 3; *n* = 4 Anaplastic astrocytoma
	  ○ F = 4, M = 5; *n* = 9 Multiform glioblastoma

Types of gliomas:	*n* = 25 Gliomas • *n* = 25 Gliomas • *n* = 1 Low-grade oligodendroglioma • *n* = 6 Anaplastic oligodendroglioma • *n* = 5 Low-grade astrocytoma • *n* = 4 Anaplastic astrocytoma • *n* = 9 Multiform glioblastoma

Epileptic status:	P = 25, A = 0; n = 25 Gliomas
Seizure type:	• 1 Complex partial + Secondarily generalized tonic-clonic; n = 1 Low-grade oligodendroglioma • 2 Simple partial, 2 Complex partial + Secondarily generalized tonic-clonic, 2 Simple partial + Secondarily generalized tonic-clonic; n = 6 Anaplastic oligodendroglioma • 1 Simple partial, 1 Complex partial, 3 Complex partial + Secondarily generalized tonic-clonic; n = 5 Low-grade astrocytoma • 3 Simple partial, 1 Complex partial + Secondarily generalized tonic-clonic; n = 4 Anaplastic astrocytoma • 1 Simple partial, 1 Complex partial, 5 Complex partial + Secondarily generalized tonic-clonic, 2 Simple partial + Secondarily generalized tonic-clonic; n = 9 Glioblastoma multiforme
Seizure frequency:	*n* = 233 seizures before Levetiracetam, and *n* = 51 seizures during Levetiracetam; *n* = 25 Gliomas • *n* = 2 seizures before Levetiracetam, and *n* = 0 seizures during Levetiracetam; *n* = 1 Low-grade oligodendroglioma • *n* = 98 seizures before Levetiracetam, and *n* = 35 seizures during Levetiracetam; *n* = 6 Anaplastic oligodendroglioma

	• *n* = 78 seizures before Levetiracetam, and *n* = 8 seizures during Levetiracetam; *n* = 5 Low-grade astrocytoma • *n* = 98 seizures before Levetiracetam, and *n* = 35 seizures during Levetiracetam; *n* = 4 Anaplastic astrocytoma • *n* = 28 seizures before Levetiracetam, and *n* = 7 seizures during Levetiracetam*; n* = 9 Glioblastoma multiforme
AEDs use:	Before Levetiracetam 18 taking AEDs and 7 not; *n* = 25 Epileptic-gliomas • *n* = 1; Valpronic Acid 1000 • *n* = 2; Topiramate 150 • *n* = 6; Phenobarbital 100 • *n* = 4; Oxcarbacepine 900 – 1800 Previous AEDs to be withdrawn were gradually tapered over a period of 3 weeks, starting at week 1 of LEV treatment. During Levetiracetam *n* = 25 Epileptic-gliomas taking AEDs • *n* = 7; Levetiracetam 3000 • *n* = 6; Levetriacetam 2000 • *n* = 1; Levetriacetam 2500 • *n* = 3; Levetriacetam 1500 • *n* = 5; Levetriacetam 1000 • *n* = 1; Levetriacetam 750
AEDs names:	Levetiracetam, valproic acid, topiramate, phenobarbital, and oxcarbazepine.
Cognitive tests:	• Mini Mental State Examination (MMSE)

Cognitive domains:	• Global cognitive profile
Main findings:	• Patients who reached the final follow-up of 12 months (n = 15), 1 patient had C50% reduction of seizure frequency (SF), and 14/15 were seizure free. • The difference in presence/ absence of seizures between baseline and final follow-up was significant (p \ 0.001). Responder rate was 100%. • Global neurocognitive performance: significant worsening of MMSE scores (p = 0.007) (mean scores remained in normal ranges).
Confounding Factors:	• Small sample size and not histologically homogeneous.

In-text reference:	(Maschio et al., 2012)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 25 brain tumour-related epilepsy (BTRE) Meningiomas, primary grade I gliomas, low grade gliomas, anaplastic gliomas and multiform glioblastoma.
Country:	Italy
Samples mean age:	49.7 years; *N* = 25 brain tumour-related epilepsy (BTRE)
Samples sex:	F = 11, M = 14; *N* = 25 brain tumour-related epilepsy (BTRE)
Types of gliomas:	Unknown
Epileptic status: ***Seizure type:*** ***Seizure frequency:***	P = 25, A = 0; n = 25 brain tumour-related epilepsy (BTRE) Unknown Unknown

AEDs use: ***AEDs names:***	25 AEDs, 0 No-AEDs; *n* = 25 brain tumour-related epilepsy (BTRE) Oxcarbazepine and previous unknown AEDs.
Cognitive tests:	• Mini Mental State Examination (MMSE)
Cognitive domains:	• Global cognitive profile
Main findings:	• The statistical analysis among patients who completed the 12 months of follow-up (n = 10), showed a significant reduction in mean weekly seizures number between the baseline (2.62 ± 6.35) and the final follow up (0.13 ± 0.37; P-value = 0.005). Five patients (50%) were seizure-free at follow-up. • In the ITT population (n = 25), at baseline, all patients had seizures in the previous month with a mean weekly SF of 2.37 (±4.78), and at last follow-up, available patients had a reduction in mean weekly SF of 0.55 ± 1.45 (P-value \ 0.001). Responder rate in the ITT population was 88% (three patients dropped out for seizures). Ten patients (40%) were seizure-free at follow-up. Significant difference in presence/absence of seizures between the baseline and the final follow-up calculated by the McNemar test (P value = 0.002) • No significant differences in global neurocognitive performances (MMSE). • Concerning efficacy of OXC on seizure control, we had a responder rate of 88% in the ITT population and of 100%

	in patients who completed 12 months of follow-up, and a significant reduction in weekly SF in both subgroups. • We observed a worsening of personal autonomy probably due to disease progression (10/25 patients had tumour progression) and other neuropsychological test results remained unmodified.
Confounding Factors:	• Short to medium follow-up (7.1 months) due to the five deaths resulting from the progression of the oncological disease, high number of drop-out (ten patients) and the heterogeneous histology. • The main limitation of this present study is the short to medium follow-up (7.1 months) due to the five deaths resulting from the progression of the oncological disease, the high number of drop-out (ten patients) and the heterogeneous histology.

In-text reference:	(Maschio et al., 2017)
Study design:	Experimental Quasi-experimental
Total sample: ***Sub-samples:***	*N* = 13 patients brain tumour-related epilepsy (BTRE) • *n* = 9 Gliomas • *n* = 4 Others
Country:	Italy
Samples mean age:	49.6 years; *N* = 13 patients brain tumour-related epilepsy (BTRE)

	• 12.1 years; *n* = 9 Gliomas • 13 years; *n* = 2 Oligoastrocytoma • 10.4 years; *n* = 6 Glioblastoma • 18 years; *n* = 1 Oligodendrogliomas
Samples sex:	F = 5, M = 8; *N* = 13 brain tumour-related epilepsy (BTRE) • F = 2, M = 9; *n* = 9 Glioma • F = 0, M = 2; *n* = 2 Oligoastrocytoma • F = 1, M = 5; *n* = 6 Glioblastoma • F = 0, M = 1; *n* = 1 Oligodendrogliomas
Types of gliomas:	*n* = 9 Glioma • *n* = 2 Oligoastrocytoma • *n* = 6 Glioblastoma • *n* = 1 Oligodendrogliomas
Epileptic status: ***Seizure type:***	P = 9, A = 0; n = 9 Gliomas • 1 Simple partial, 1 Complex partial; n = 2 Oligoastrocytomas • 3 Simple partial, 2 Complex partial, 1 Simple partial + Secondarily generalized tonic-clonic; n = 6 Glioblastomas • 1 Simple partial; n = 1 Oligodendrogliomas
Seizure frequency:	*n* = 167 seizures before Zonisamide, and *n* = 55 seizures during Zonisamide; *n* = 9 Gliomas • *n* = 34 seizures before Zonisamide, and *n* = 30 seizures during Zonisamide; *n* = 2 Oligoastrocytomas

	• *n* = 129 seizures before Zonisamide, and *n* = 5 seizures during Zonisamide; *n* = 6 Glioblastomas • *n* = 4 seizures before Zonisamide, and *n* = 0 seizures during Zonisamide*;* *n* = 1 Oligodendrogliomas
AEDs use:	9 AEDs, 0 No-AEDs; *n* = 9 Gliomas Before zonisamide; *n* = 9 Gliomas • *n* = 5; Levetiracetam 1000 - 3000 • *n* = 2; Valproic acid 500 - 1500 • *n* = 1; Phenobarbital 100 • *n* = 1; Politheraphy During zonisamide; *n* = 9 Gliomas • *n* = 8; Zonisamide 300 • *n* = 1; No- Zonisamide (Dropout)
AEDs names:	Levetiracetam, valproic acid, phenobarbital, and zonisamide.
Cognitive tests:	• Mini-Mental State Examination (MMSE) • Trail Making Test (TMT) • Auditory Verbal Learning test (AVLT) • Verbal Fluency test (VFT)
Cognitive domains:	• Global cognitive profile • Executive functions • Auditory Memory • Verbal Memory
Main findings:	• Of 9 patients who reached the sixth month follow-up, the mean weekly seizure number before ZNS had been 3.2 ±

	5.0, and at final follow-up, the mean weekly seizure number was 0.18 ± 0.41 (P = 0.05). • Cognitive performances remained unchanged, except for a worsening in verbal processing speed. Although having a small sample size, the worsening of verbal processing speed on the studied population does not seem to be correlated to disease progression; among patients, no significant differences in verbal fluency was noticed between those with disease progression and those with stable disease.
Confounding Factors:	• Small sample and short follow-up period.

In-text reference:	(Maschio et al., 2020)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 26 brain tumour-related epilepsy (BTRE) • *n* = 23 Gliomas • *n* = 3 Others
Country:	Italy
Samples mean age:	48.5 years; *n* = 23 Gliomas • 46.7 years; *n* = 3 Low-grade oligodendroglioma • 46 years; *n* = 5 Low-grade astrocytoma • 44.3 years; *n* = 7 Anaplastic astrocytoma • 46 years; *n* = 1 Oligoastrocytoma

	• 55.6 years; *n* = 7 Glioblastoma
Samples sex:	M = 16, F = 7; *n* = 23 Gliomas • F = 3, M = 0; *n* = 3 Low-grade oligodendroglioma • F = 1, M = 4; *n* = 5 Low-grade astrocytoma • F = 1, M = 6; *n* = 7 Anaplastic astrocytoma • F = 0, M = 1; *n* = 1 Oligoastrocytoma • F = 2, M = 5; *n* = 7 Glioblastoma
Types of gliomas:	*n* = 23 Gliomas • *n* = 3 Low-grade oligodendroglioma • *n* = 5 Low-grade astrocytoma • *n* = 7 Anaplastic astrocytoma • *n* = 1 Oligoastrocytoma • *n* = 7 Glioblastoma
Epileptic status: ***Seizure type:***	P = 23, A = 0; n = 23 Gliomas • *n* = 12 Focal aware seizures, *n* = 5 Focal unaware seizures and *n* = 6 Focal to bilateral tonic-clonic seizure; *n* = 23 Gliomas • *n* = 3 Focal aware seizures, *n* = 0 Focal unaware seizures and *n* = 0 Focal to bilateral tonic-clonic seizure; *n* = 3 Low-grade oligodendroglioma • *n* = 1 Focal aware seizures, *n* = 3 Focal unaware seizures and *n* = 1 Focal to bilateral tonic-clonic seizure; *n* = 5 Low-grade astrocytoma

Seizure frequency:	• *n* = 3 Focal aware seizures, *n* = 2 Focal unaware seizures and *n* = 2 Focal to bilateral tonic-clonic seizure; *n* = 7 Anaplastic astrocytoma • *n* = 0 Focal aware seizures, *n* = 0 Focal unaware seizures and *n* = 1 Focal to bilateral tonic-clonic seizure; *n* = 1 Oligoastrocytoma • *n* = 5 Focal aware seizures, *n* = 0 Focal unaware seizures and *n* = 2 Focal to bilateral tonic-clonic seizure; *n* = 7 Glioblastoma • *n* = 255 seizures (1month) before T0, and *n* = 31 seizures at T1; *n* = 23 Gliomas • *n* = 44 seizures (1month) before T0, and *n* = 2 seizures at T1; *n* = 3 Low-grade oligodendroglioma • *n* = 91 seizures (1month) before T0, and *n* = 6 seizures at T1; *n* = 5 Low-grade astrocytoma • *n* = 44 seizures (1month) before T0, and *n* = 22 seizures at T1; *n* = 7 Anaplastic astrocytoma • *n* = 30 seizures (1month) before T0, and *n* = 17 seizures at T1; *n* = 0 Oligoastrocytoma • *n* = 46 seizures (1month) before T0, and *n* = 1 seizures at T1; *n* = 7 Glioblastoma
AEDs use:	23 AEDs, 0 No-AEDs; *n* = 23 Gliomas Before perampanel; *n* = 23 Gliomas • *n* = 7; Levetiracetam 1000 - 3000

AEDs names:	• *n* = 1; Lamotrigine 400 • *n* = 1; Oxcarbacepine 1800 • *n* = 1; Phenobarbital 100 • *n* = 13; Polytheraphy During perampanel; *n* = 23 Gliomas • *n* = 23; Perampanel 2-12 Levetiracetam, lamotrigine, oxcarbazepine, phenobarbital, polytherapy, and perampanel.
Cognitive tests:	• Mini-Mental State Examination (MMSE) (Folstein et al., 1975) • Raven CPM (Basso, Capitani, & Laiacona, 1987) • Trail Making Test (TMT) (Giovagnoli et al., 1996) • Visual Search (Spinnler & Tognoni, 1987) • Reyauditory verbal learning test (RAVLT) (Carlesimo et al., 1996) • Rey–Osterrieth complex figure (ROCF) (Carlesimo, Buccione, & Fadda, 2002) • Phonemic and semantic fluency (Novelli et al., 1986) • Tower of London (ToL) (Krikorian, Bartok, & Gay, 1994)
Cognitive domains:	• Global cognitive status • Nonverbal abstract reasoning • Selective visual attention and oculo-manual coordination • Verbal learning

	• Visuo-spatial learning • Visuo-spatial and visuo-constructive abilities • Verbal processing speed • Executive functions
Main findings:	• The mean number of seizures/month decreased from 10.8 ± 15.03 at baseline to 1.7 ± 4.34 in the 21 patients who reached the final follow-up. • Responder rate was 88.4%: Eight patients were seizure-free, 15 had ≥50% seizure reduction, and 3 remained stable. • Four patients (15.4%) reported AEs: 2 required PER dose reduction, and 2 dropped out. • Neuropsychological, mood, and QoL questionnaires were not statistically different compared to baseline. • There were no significant differences in seizure control in patients with/without IDH1 mutation and with/without MGMT methylation. • We observed a reduction in seizure frequency in the 21 patients who reached the final follow-up, from 10.8 ± 15.03 to 1.7 ± 4.34 ($p = .01$), and from 10.6 ± 14.27 to 2.3 ± 5.3 ($p = .004$) in the ITT population (26 patients) at the recommended dosage of PER treatment. • Responder rate at 6 months (21 patients) was 95.2, with 33.3% of patients who were seizure-free after 6 months.

	Seizure frequency remained stable in 1 out of 21 patients, and none had seizures worsening. • Furthermore, our results did not evidence that the efficacy of PER on seizure control could be influenced by factors related to brain tumours, such as systemic therapy, oncological progression, different histology and malignancy, surgical procedures. This results should be cautiously considered because of low power due to small sample size and short follow-up (only 6 months). • Regarding cognitive performances, we observed stability in patients' mean scores and at final follow-up compared to baseline. However, our data on tests and questionnaires cannot be generalized due to the small number of patients who repeated control tests at 6 months.
Confounding Factors:	• Small sample size • Short follow-up

In-text reference:	(van der Meer et al., 2013)
Study design:	Observational Analytical
Total sample: ***Sub-samples:***	*N* = 272 Gliomas • *n* = 272 Gliomas • *n* = 0 Others
Country:	Netherlands

Samples mean age:	54 years; *N* = 272 Gliomas
Samples sex:	F = 113, M = 159; *N* = 272 Gliomas
Types of gliomas:	*n* = 135 LGG, *n* = 137 HGG; *N* = 272 Gliomas • *n* = 52 Diffuse astrocytoma • *n* = 73 Oligodendroglioma • *n* = 6 Oligoastrocytoma • *n* = 4 Pleomorphic xanthoastrocytoma • *n* = 5 Diffuse astrocytoma • *n* = 24 Anaplastic astrocytoma • *n* = 20 Anaplastic oligodendroglioma • *n* = 88 Glioblastoma
Epileptic status:	P = 206, A = 59, Unknown = 7; *N* = 272 Gliomas
Seizure type:	• *n* = 74 Focal, *n* = 48 Focal to bilateral tonic-clonic, *n* = 84 Focal & focal to bilateral tonic-clonic, *n* = 7 Unknown and *n* = 59 No epilepsy; *N* = 272 Gliomas
Seizure frequency:	Not specified
AEDs use:	184 AEDs, 88 No-AEDs; *n* = 272 Gliomas • *n* = 85; Levetiracetam • *n* = 32; Valproic Acid • *n* = 15; Other • *n* = 52 Polytheraphy
AEDs names:	Levetiracetam, valproic Acid and other AEDs.
Cognitive tests:	Not specified
Cognitive domains:	Not specified

Main findings:	• Subjective cognitive impairment (aOR = 0.83 [95%CI 0.34–2.04], p = 0.684) did not differ significantly before or after adjustment of confounders between patients not using (16%) and using AEDs (21%).
Confounding Factors:	Not specified

In-text reference:	(Vecht et al., 2017)
Study design:	Experimental Quasi-Experimental
Total sample: ***Sub-samples:***	*N* = 12 Drug-resistant Epileptic Gliomas • *n* = 12 Gliomas • *n* = 0 Others
Country:	France
Samples mean age:	41 years; *N* = 12 Drug-resistant Epileptic Gliomas
Samples sex:	F = 3, M = 9; *N* = 12 Drug-resistant Epileptic Gliomas
Types of gliomas:	*N* = 12 Drug-resistant Epileptic Gliomas • *n* = 1 Ganglioma • *n* = 6 Low-grade astro- or oligo(astro)dendroglioma • *n* = 3 Anaplastic astro- or oligo(astro)dendroglioma • *n* = 2 Glioblastoma
Epileptic status:	P = 12, A = 0; N = 12 Drug-resistant Epileptic Gliomas After perampanel treatment P = 6, A = 6; N = 12 Drug-resistant Epileptic Gliomas

Seizure type:	7 Simple partial seizures, 4 Complex partial seizures, 1 Generalized seizures, 2 Partial status epilepticus; n = 12 Drug-resistant Epileptic Gliomas
Seizure frequency:	Unknown seizures (1month) before T0 Seizures at T1 • n = 2; Unchanged • n = 3; 50% seizure response • n = 6; Seizure-freedom • n = 1; Increase in seizure frequency
AEDs use: ***AEDs names:***	12 AEDs, 0 No-AEDs; n = 12 Drug-resistant Epileptic Gliomas Perampanel and others.

Cognitive tests:	• Computerized test on cognitive speed (CTCS)
	  ○ n = 1; Unchanged
	  ○ n = 6; Improved
	  ○ n = 1; Deteriorated
	  ○ n = 4; Not tested

Cognitive domains:	Not specified
Main findings:	• Seizure response showed unchanged Sz. frequency in 2 out of 12 (17%) patients, a 50% Sz. reduction in 3 out of 12 (25%), seizure-freedom in 6 out of 12 (50%) and increase in seizure frequency in 1 out of 12 (8%) patients. • Cognition as examined by CTCS was applied before start of PER and during follow-up in 8 out of 12 patients.

	Deterioration of cognition was seen in one patient and no change in another, while improvement was observed in six (75%) out eight patients who had shown seizure-freedom. The improvement in attention and reaction time seems best explained by a reduction of one or more concurrent AEDs in patients with seizure-freedom upon treatment with PER.
Confounding Factors:	Not specified