Research Article *Volume 6, Issue 3*

JCMCRI

Journal of Clinical & Medical Case Reports, Images

Received: July 10, 2026 Published: July 17, 2026

DOI: 10.55920/3064-8025/1228

Neuroplastic Reorganization of the Cerebral Cortex in Brain Tumors and Malignancy: Mechanisms, Evidence, and Clinical Significance

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Abstract

The cerebral cortex remains capable of substantial structural and functional reorganization even while under chronic assault from an expanding malignancy. This review synthesizes current mechanistic, imaging, and clinical evidence on neuroplastic change in the brain tumor setting, with a particular focus on glioma, the most common primary malignant tumor of the central nervous system. A structured literature search across six databases identified studies spanning molecular signaling, network-level connectivity, functional neuroimaging, and neurosurgical outcomes. Slow-growing, low-grade lesions generally permit gradual recruitment of perilesional and, when needed, contralateral cortex; rapidly dividing high-grade tumors more often outstrip this compensatory capacity and produce abrupt deficits. At the molecular level, neurons form genuine electrochemical synapses onto glioma cells, and brain-derived neurotrophic factor signaling through TrkB receptors strengthens these connections in a manner that mirrors the synaptic plasticity underlying memory formation, only here it accelerates tumor growth rather than learning. Neuroimaging and direct intraoperative stimulation have made it possible to trace these changes in living patients and to guide maximal safe resection during awake craniotomy. Taken together, the evidence indicates that neuroplasticity is not a peripheral curiosity in neuro-oncology but a central determinant of how tumors present, how surgery is planned, and how patients recover.

Keywords: neuroplasticity; cerebral cortex; glioma; brain tumor; cortical reorganization; neuron-glioma synapse; awake craniotomy.

1. Introduction

A tumor growing inside the skull does something no cancer elsewhere in the body can do: it settles into a network that thinks, moves, and speaks, and that network often keeps working around it. Neuroplasticity, the capacity of the brain to reshape its structure, connectivity, and function in response to internal or external demands, has long been studied in the context of development, learning, and recovery after stroke. Over the past two decades, it has become clear that a growing intracranial tumor is itself a powerful and unusually persistent driver of this same process.

Gliomas, arising from glial or glial-progenitor lineages, account for the large majority of malignant primary brain tumors diagnosed in adults, and they frequently invade regions long regarded as "eloquent," including the language, motor, and executive networks [1]. Because these tumors, particularly their low-grade forms, often grow over years rather than weeks, the surrounding cortex has time to adapt. Patients can carry a lesion within classically indispensable territory and show little or no measurable deficit, a state that reflects active compensation rather than any tendency of the tumor to spare functional tissue.

What has reframed the field more recently is the discovery that gliomas are not inert passengers in this process. They wire themselves into existing circuits, receive genuine synaptic input from neurons, and use that input to grow [2,3]. Neuroplasticity, in other words, cuts both ways: it protects the patient, and it feeds the tumor. This review works through both sides of that relationship, moving from molecular mechanism to network-level reorganization to the imaging and surgical tools built on this knowledge, before considering what remains unresolved.

2. Materials and Methods

This review followed a narrative synthesis approach rather than a formal systematic review protocol, reflecting the breadth and methodological heterogeneity of the underlying literature, which spans molecular neuroscience, radiology, and neurosurgery.

2.1 Search Strategy

PubMed/MEDLINE, PubMed Central, Nature.com, Frontiers, MDPI, and ScienceDirect were searched for records published between 2005 and 2026. Search terms were combined using Boolean operators and included "glioma AND neuroplasticity," "cortical reorganization AND brain tumor," "neuron-glioma synapse," "awake craniotomy AND cortical mapping," and "functional MRI AND glioma plasticity." Reference lists of retrieved articles were hand-searched for additional relevant sources.

2.2 Eligibility Criteria

Peer-reviewed, English-language articles reporting mechanistic (molecular or electrophysiological), neuroimaging, or clinical mapping data on cortical plasticity in the context of primary brain tumors were included. Case reports lacking mechanistic or mapping data, conference abstracts, and non-peer-reviewed sources were excluded. The selection process is summarized in Figure 1.

3. Results

The reviewed literature converges on a picture of tumor-associated neuroplasticity operating across several nested levels, from single synapses to whole-hemisphere network reconfiguration. Table 1 summarizes the principal studies underlying this synthesis; Table 2 organizes the mechanisms themselves by level of organization.

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Citation: Gautam Mangesh Bhaskare *, Neuroplastic Reorganization of the Cerebral Cortex in Brain Tumors and Malignancy: Mechanisms, Evidence, and Clinical Significance. Jour of Clin & Med Case Rep, Imag 2026; 6(3): 1228.

Figure 1: *Literature identification and selection process used for this narrative review.*

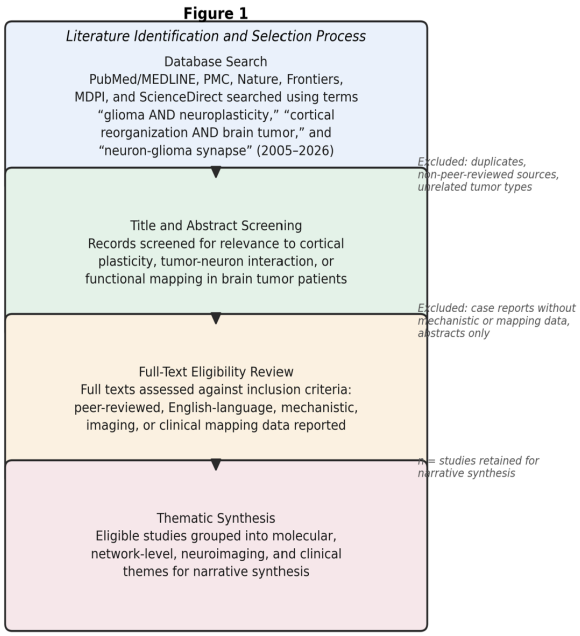


Table 1: *Representative studies informing this review, organized by design and principal finding.*

Study (Year)	Model / Design	Principal Finding
Venkatesh et al. (2019)	In vivo optogenetics and electrophysiology, patient-derived glioma xenografts	Identified bona fide AMPA-receptor-dependent neuron-glioma synapses; neuronal depolarization directly drives tumor proliferation.
Taylor et al. (2023)	Xenograft models, electrophysiological recording	BDNF-TrkB signaling strengthens neuron-glioma synapses, linking activity-dependent malignant plasticity to tumor progression.
Krishna et al. (2023)	Intraoperative electrocorticography and behavioral testing in glioblastoma patients	Glioma-infiltrated cortex loses the capacity to decode complex speech despite preserved neuronal firing; network remodeling predicts survival.
Lv et al. (2022)	Structural MRI, DTI, and graph-theory network review	Documented altered topological network organization extending into peritumoral and contralateral hemispheric regions.
Mitolo et al. (2022)	Prospective fMRI cohort, 15 patients with frontal glioma	Contralateral frontal recruitment during a phonemic fluency task correlated with white-matter tract integrity.
Cirillo et al. (2019)	Systematic review of 8 longitudinal fMRI, nTMS, and DES studies	Language networks display substantially greater reorganization than motor networks in glioma patients.
Southwell et al. (2016)	Repeat awake craniotomy with intraoperative mapping	Eloquent sites shifted location between sequential operations in the same patient, directly confirming adult cortical plasticity.
De Witt Hamer et al. (2012)	Meta-analysis of pooled surgical cohorts	Intraoperative stimulation mapping increased extent of resection and reduced neurological morbidity across glioma grades.

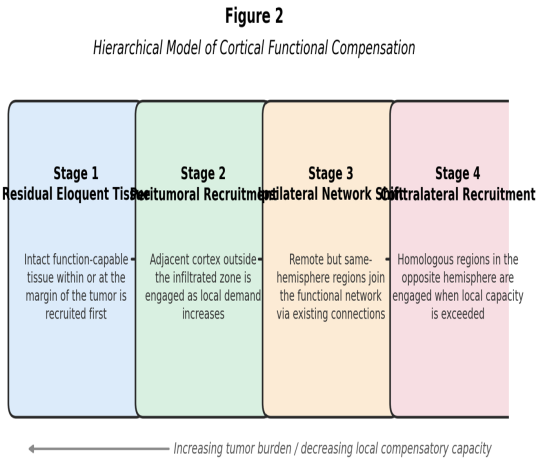
3.1 Molecular and Synaptic Reorganization

The clearest mechanistic advance in this field is the demonstration that neurons form real, functional synapses onto glioma cells. Using in vivo optogenetics, Venkatesh et al. [2] showed that neuronal activity depolarizes glioma cell membranes through AMPA-receptor-dependent synapses and that this depolarization is sufficient to drive proliferation; gap junctions between tumor cells then relay the resulting electrical signal across the mass, effectively turning the tumor into an electrically coupled network in its own right.

A second layer of this story concerns plasticity of the malignant synapse itself. Taylor et al. [3] found that brain-derived neurotrophic factor, acting through TrkB receptors, drives AMPA receptor trafficking to the glioma membrane and increases the amplitude of glutamate-evoked currents, closely paralleling the BDNF-TrkB mechanisms that strengthen synapses during memory formation in the healthy brain. Genetically or pharmacologically interrupting this pathway substantially slowed tumor progression in xenograft models, which places malignant synaptic plasticity among the drivers of disease rather than a downstream curiosity.

This synaptic remodeling has functional consequences that extend well beyond the tumor margin. Direct electrocorticographic recordings in glioblastoma patients performing language tasks show that infiltrated cortex can maintain near-normal neuronal firing while losing the ability to decode complex speech, and the specific pattern of network remodeling around the tumor has been linked to survival [1]. Peritumoral tissue also tends toward hyperexcitability, a state that likely underlies the high rate of tumor-associated epilepsy and simultaneously sustains the activity-dependent signaling that favors further tumor growth [4].

Figure 2: *Hierarchical model of cortical functional compensation, adapted from network-level findings reported by Krishna et al. (2023).*



3.2 Regional and Interhemispheric Reorganization

Above the synapse, reorganization proceeds in a roughly graded sequence (Figure 2). Compensation draws first on residual functional tissue within or bordering the tumor, then on adjacent peritumoral cortex, and, when local capacity is exceeded, on homologous regions of the opposite hemisphere. Structural and functional connectivity studies support this progression: unilateral frontal gliomas have been associated with increased activity and connectivity in the contralateral parietal cortex, which appears to function as a compensatory hub protecting executive performance from tumor-related disruption [5]. Consistent with this, Mitolo et al. [6] found that patients with left-sided frontal glioma showed increased right-hemisphere frontal activation during a phonemic fluency task, and that the degree of this

shift correlated with the integrity of specific white-matter tracts, tying network-level reorganization to underlying structural connectivity rather than treating it as a purely functional phenomenon.

3.3 Domain-Specific Differences: Motor Versus Language

Reorganization is not uniform across cognitive domains. A systematic review of eight longitudinal imaging and mapping studies found that motor networks reorganize modestly, largely through recruitment of secondary motor areas within the same hemisphere, whereas language networks show substantially greater capacity for reshaping, primarily through recruitment of perilesional cortex [7]. This asymmetry has practical significance for surgical planning, since it suggests language function may tolerate a broader resection margin than motor function under equivalent mapping conditions.

3.4 Evidence from Neuroimaging and Intraoperative Mapping

Functional MRI remains the primary tool for preoperative localization of eloquent cortex, though the reliability of task-based lateralization indices is still debated [7]. Transcranial magnetic stimulation offers a non-invasive, repeatable alternative that has been used to track reorganization longitudinally, before and after resection, particularly in slow-growing low-grade gliomas [8]. The most direct evidence, however, comes from intraoperative direct electrical stimulation. In one striking demonstration, Southwell et al. [9] mapped the same patients across sequential awake craniotomies and found that sites classified as eloquent during the first operation were sometimes silent during the second, and vice versa, providing unambiguous proof that the adult cortex continues to reorganize between surgeries.

3.5 Clinical and Surgical Outcomes

These mechanistic and imaging findings translate directly into surgical practice. A pooled meta-analysis of intraoperative stimulation mapping found improved extent of resection and reduced postoperative neurological morbidity relative to resection performed without mapping, an effect present across both low-grade and high-grade tumors [10]. Building on this, connectome-guided, individualized surgical planning now treats each patient's mapped functional anatomy, rather than a fixed anatomical atlas, as the reference standard for what can safely be removed [11].

Table 2: *Levels of neuroplastic reorganization identified in the reviewed literature.*

Level of Organization	Representative Mechanism	Key Source(s)
Molecular / synaptic	AMPA-receptor-mediated neuron-glioma synapses; BDNF-TrkB potentiation of glutamatergic currents	Venkatesh et al. (2019); Taylor et al. (2023)
Cellular / local network	Peritumoral hyperexcitability; gap-junction and tumor-microtubule coupling between glioma cells	Bhat & Kumar (2025)
Regional / perilesional	Recruitment of adjacent, non-infiltrated cortex within the same functional network	Cirillo et al. (2019); Mitolo et al. (2022)
Interhemispheric	Engagement of homologous contralateral regions when local capacity is exceeded	Lv et al. (2022); Krishna et al. (2023)
Clinical / behavioral	Preserved function despite eloquent-area infiltration; variable postoperative recovery trajectories	Duffau (2005); Duffau (2020)

4. Discussion

Two threads run through this literature, and they pull in opposite directions. The first is protective: cortical reorganization allows patients to tolerate tumors in regions that would otherwise be considered inoperable, and it is the reason surgeons can now pursue more extensive resections with mapping guidance than would have seemed safe a generation ago [12]. The second is exploitative: the very same activity-dependent machinery, AMPA receptor trafficking, BDNF-TrkB signaling, gap-junction coupling, is co-opted by the tumor to grow. A therapy that simply suppressed neural activity near a tumor would presumably slow its growth, but it would also strip away the very compensatory capacity that keeps patients functional. This tension, more than any single finding, is what makes tumor-associated neuroplasticity difficult to act on clinically.

The pace of tumor growth appears to be the variable that determines which side of this tension dominates. Low-grade gliomas, expanding over years, give the cortex time to shift load gradually through the hierarchy outlined in Figure 2; high-grade tumors compress that timeline and more often overwhelm it, producing the abrupt deficits typically seen at presentation. If this reading is correct, therapies that slow tumor kinetics, even without directly attacking the tumor's synaptic biology, might indirectly preserve function simply by buying the cortex time to adapt.

Domain-specific differences also deserve more attention than they currently receive. Why language networks reorganize more readily than motor networks is not fully explained by current models, though the more distributed and bilaterally represented architecture of language processing, relative to the comparatively focal organization of primary motor cortex, is a plausible starting point. Clarifying this distinction could refine how aggressively surgeons pursue resection near each type of eloquent tissue.

4.1 Limitations

Several limitations temper these conclusions. Much of the mechanistic work on neuron-glioma synapses derives from xenograft and rodent models, and the degree to which BDNF-TrkB dynamics generalize to the diversity of human gliomas in situ is not yet settled. Clinical mapping studies, meanwhile, are frequently limited by small sample sizes and heterogeneous outcome measures, which restricts direct comparison across studies. Finally, this review concentrated on glioma; meningiomas, metastatic lesions, and other tumor types may engage distinct or additional plasticity mechanisms not captured here [13].

4.2 Future Directions

The most promising direction may be pharmacological dissociation of malignant from adaptive plasticity, for instance through selective disruption of BDNF-TrkB signaling in tumor cells while sparing normal synaptic function elsewhere in the brain. Longitudinal, multimodal studies that combine molecular, imaging, and cognitive outcome data in the same patients would also help clarify how the mechanisms summarized in Table 2 relate to one another across time, rather than being studied largely in isolation as they are at present.

5. Conclusion

Brain tumors do not simply displace cortical tissue; they provoke a layered, active reorganization of it, from receptor trafficking at individual synapses to the redistribution of entire functional networks across hemispheres. Slow tumor growth favors more complete compensation, while rapid growth tends to outpace it, and the same molecular machinery that supports this compensation is also used by the tumor to sustain its own expansion. Neuroimaging and intraoper-

ative mapping have turned this understanding into practical surgical tools, most visibly in awake craniotomy and connectome-guided resection, and continued work at the interface of cancer neuroscience and clinical neuro-oncology is likely to further refine how function is preserved during treatment.

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