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Surgical approaches using brain connectivity to maximize patient outcomes in glioma surgery

Abstract

Purpose: The integration of brain connectomics into neurosurgical practice represents a paradigm shift in glioma management, transitioning from lesion-centered strategies toward a network-based framework emphasizing preservation of structural and functional connectivity. Advances in diffusion and functional imaging, tractography, and computational modeling enable visualization and preservation of key white matter pathways and functional hubs, supporting safer, more effective resections. This review synthesizes current evidence on connectomics in glioma surgery, emphasizing region-specific surgical approaches and their relationships to cognitive and motor networks.

Methods: We performed a structured narrative review of the literature on connectomics in glioma surgery, focusing on clinically relevant applications. Key domains included awake brain mapping, region-specific approaches, advancements in tractography—including edema- and free water–corrected techniques—intraoperative mapping strategies, postoperative recovery, and emerging artificial intelligence (AI)–driven tools. Representative studies were synthesized to highlight translational and surgical implications.

Results: Connectomics has been associated with improved extent of resection and reduced postoperative deficits in clinical series. These benefits are driven by improved delineation of eloquent white matter tracts, including the corticospinal tract, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus. Advanced tractography enhances visualization of peritumoral networks and reduces false-negative pathway identification. Intraoperative modalities, particularly awake mapping and direct electrical stimulation, remain essential for functional validation and boundary definition. Preservation of higher-order cognitive networks improves postoperative cognition and quality of life, while AI augments tract reconstruction and prediction of functional outcomes.

Conclusion: Connectomics provides a clinically actionable framework for network-informed glioma surgery, maximizing resection while minimizing morbidity.

Keywords: brain mapping, connectomics, glioma surgery, networks, neurosurgery

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Introduction

Over the past two decades, the field of neuroscience has undergone a paradigm shift from focusing primarily on isolated brain regions to understanding the interconnectedness of neural networks —a framework known as connectomics.[1,2] This systems-level perspective has been made possible by advances in neuroimaging modalities such as diffusion-weighted magnetic resonance imaging (dMRI), functional MRI (fMRI), magnetoencephalography (MEG), and electroencephalography (EEG), combined with sophisticated computational modeling and network analysis techniques.[3,4] In the healthy brain, connectomics has provided invaluable insights into cognitive processing, neuroplasticity, and the balance between local specialization and global integration.

In neurosurgery, brain connectomics is increasingly recognized as a transformative tool for preoperative planning, intraoperative guidance, and postoperative evaluation.[5,6] Gliomas represent a challenging primary brain tumor due to their highly infiltrative nature, invading beyond white matter tracts and vessels and resulting in both local and distant network dysfunction.[7, 8]. Incorporating connectomic data into surgical navigation may improve functional outcomes by avoiding disconnection of essential hubs and white matter tracts.[5,6] Connectomic studies have revealed that gliomas can cause widespread reductions in global efficiency, disrupt hub integrity, and reorganize functional networks in ways that are not always clinically apparent.[9,10] Applications of connectomics in gliomas can also include imaging biomarkers for disease burden and treatment response, namely in the evaluation of network metrics such as global efficiency, nodal strength, and modular reorganization.[11]

Connectomic investigations can be broadly divided into structural connectomics, which examines physical white matter connections primarily using diffusion MRI, and functional connectomics, which evaluates temporal correlations of neural activity using modalities such as fMRI, MEG, or EEG. Structural connectomics provides information on anatomical disconnection risk, whereas functional connectomics reflects dynamic network organization and compensation. Both approaches are complementary; however, structural connectivity has particular relevance for surgical planning due to its direct relationship to irreversible pathway injury, greater intuitive understanding for surgeons with neuroanatomical knowledge, as well as wider availability of preoperative and intraoperative cerebral imaging tools.

Translation of connectomics into routine neurosurgical practice remains limited due to variability in acquisition protocols, analytical pipelines, and interpretative frameworks. While commercial (i.e., Quicktome) and research software exist to apply connectomic insights to patient treatment, these tools remain limited in accessibility and standardization. Functional connectomics derived from fMRI, MEG, and EEG provides complementary insights into network dynamics. Furthermore, functional pathways synergize with structural connectivity to improve direct relevance to surgical corridor selection, subcortical disconnection risk, and intraoperative decision-making. Functional connectomic approaches are discussed where they intersect with surgical planning and intraoperative mapping, but a comprehensive review of functional network analysis is beyond the scope of this overview. Previously, we reviewed the known functional connectomic networks, related white matter tracts, and potential impact on cognitive function.[12] In this review, we evaluated the current knowledge on glioma connectomics with focus on surgical strategies for the practicing surgeon (Figure 1) to reduce injury to key structural and functional landmarks with specific, clinically-relevant dissection approaches. Accordingly, this article is intended as a narrative overview highlighting key and representative studies rather than a comprehensive systematic review of the entire connectomics literature.

Figures and Figure Legends:

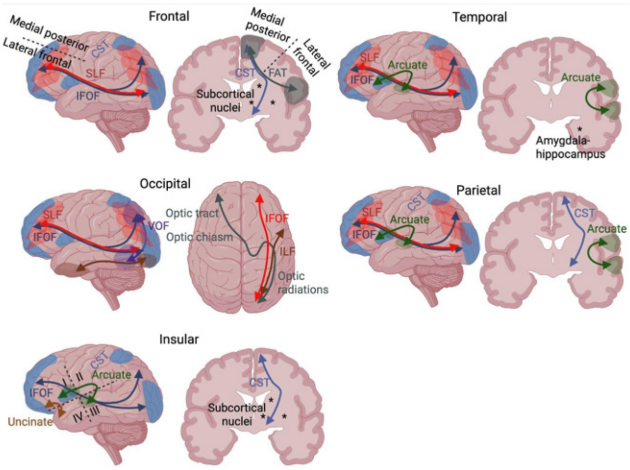

Figure 1 Summary of white matter, cortical tracts, and critical nuclei proximal to surgical approaches

Abbreviations: CST: corticospinal tract; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; SLF: superior longitudinal fasciculus; VOF: vertical occipital fasciculus

The narrative review aims to provide clinically relevant tracts relevant to neurooncological surgery. Unlike prior reviews, this work proposes a region-specific, connectome-guided surgical framework that translates network-level insights into actionable intraoperative strategies, bridging the gap between theoretical connectomics and operative decision-making. We first summarized how connectomic principles inform region-specific surgical approaches, emphasizing key white matter pathways relevant to safe resection. While important white matter tracts can be displaced by infiltrative and non-infiltrative white matter tracts, knowledge of expected pathways can aid surgeons in devising clinical approaches. We then reviewed selected clinical applications of connectomics, including network disruption, tractography refinement, intraoperative mapping, and emerging artificial intelligence (AI)–assisted tools. Finally, we discussed future methodological directions and remaining challenges for translating connectomics into routine neurosurgical practice. Given the narrative nature of this review, the approaches described represent generalized frameworks derived from anatomical and connectomic principles; individual surgical strategies must ultimately be tailored to patient-specific anatomy, tumor characteristics, and intraoperative functional mapping.

Methods

This study was conducted as a structured narrative review aimed at synthesizing clinically relevant applications of connectomics in glioma surgery, with a particular emphasis on translational and operative decision-making frameworks. Given the heterogeneity of the available literature and the evolving nature of connectomic methodologies, a narrative approach was selected to integrate findings across diverse study designs, including clinical series, technical reports, and methodological investigations.

Literature search strategy

A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, and Web of Science databases. The search encompassed studies published up to January 2026. Keywords and Medical Subject Headings (MeSH) terms included combinations of: “connectomics,” “glioma,” “brain tumor,” “tractography,” “diffusion MRI,” “functional MRI,” “awake brain mapping,” “intraoperative mapping,” “white matter,” “brain networks,” and “artificial intelligence.” Additional articles were identified through manual review of reference lists of relevant publications.

Study selection and eligibility

Studies were selected based on their relevance to the clinical application of connectomics in glioma surgery. Eligible studies included original research articles, clinical series, technical notes, and review articles that addressed connectome-informed surgical planning, awake brain mapping and intraoperative functional validation, tractography techniques, including advanced methods such as edema- or free water–corrected diffusion imaging, network disruption and postoperative functional outcomes, and emerging artificial intelligence–based approaches for connectomic analysis. Non-English publications, conference abstracts without full text, and studies lacking clear clinical or translational relevance were excluded. Given the narrative design, formal quality scoring and meta-analysis were not performed.

Data extraction and synthesis

Relevant data were extracted qualitatively, focusing on study design, patient population, imaging modality or connectomic technique, intraoperative application, and reported clinical outcomes. Rather than exhaustive aggregation, representative and high-impact studies were selected to illustrate key concepts and evolving trends. Findings were synthesized thematically to align with clinically meaningful domains, including region-specific surgical strategies, advancements in tractography, intraoperative mapping paradigms, and AI-assisted tools. Emphasis was placed on translating connectomic insights into practical surgical considerations, particularly with respect to preserving functional networks and optimizing extent of resection.

Conceptual framework development

Based on the synthesized literature, a region-specific connectome-guided surgical framework was developed. This framework integrates structural and functional connectivity principles with established neurosurgical anatomy to provide a pragmatic approach to operative planning. The framework is intended as a generalizable model and does not replace patient-specific intraoperative mapping or clinical judgment.

Connectome-guided surgical strategies

The discussed region-specific approaches in this section are described within a connectomic framework, emphasizing white matter tracts and functional networks at risk during resection. These descriptions are not intended to define fixed anatomical ‘safe corridors,’ but rather to provide guidance that must be integrated with

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intraoperative mapping and patient-specific variability. It is important to note that white matter tract anatomy demonstrates substantial inter-individual variability, particularly in the presence of glioma-induced displacement or infiltration. As such, connectomic findings must be interpreted in a patient-specific context.

Frontal lobe lesions

Frontal lobe lesions can involve areas within the superior, middle or inferior frontal gyrus extending from 1-6 cm posterior to the anterior frontal bone and extending laterally to the sylvian fissure. Lesions can involve motor pathways posteriorly and motor speech pathways on language dominant hemispheres. Critical white matter tracts include the (1) corticospinal tracts (CST) and motor pathway posteriorly; (2) pyramidal tract, supplementary motor area (SMA), premotor fibers, and frontal aslant tract (FAT) posteriorly and posteromedially; (3) the inferior fronto-occipital fascicle (IFOF) and the superior longitudinal fascicle (SLF) posterolaterally; and (4) critical subcortical nuclei inferiorly, namely inferior frontal gyrus, the head of the caudate nucleus, inferior to the inferior frontal gyrus.[13,14] Approaches often utilize the middle frontal gyrus as a commonly selected cortical entry point; however, the optimal trajectory should be individualized based on tumor location, tract displacement, and functional mapping.

Medial posterior frontal approach

Tumors located in the medial posterior frontal lobe are near motor and speech networks. Posterior margins of the approach include CST, and posterolaterally in the FAT. Laterally, the disconnection is guided by the speech networks on the dominant hemisphere, defined by SLF and inferiorly the IFOF. Medially, lesions can extend to the falx where at the inferior depth, the trajectory continues into the frontal horn of the lateral ventricle. Meanwhile, the inferolateral depth can include the head of the caudate.[15]

The IFOF, a language-associated subcortical fiber in the frontal lobe constructs a ventral pathway that passes through the deep areas of the temporal lobe and insula. It connects the occipital cortex and posterior temporo-occipitoparietal regions to the orbitofrontal, prefrontal, and dorsolateral prefrontal areas.[16] The SLF constructs a dorsal pathway in the left frontal lobe by connecting the inferior frontal gyrus and ventral premotor cortex to temporoparietal language regions. The SLF is divided into 3 distinct tracts: SLF I defines the dorsal component connecting the superomedial parietal cortex and dorsomedial frontal cortex and SMA, SLF II is the major component of the SLF connecting the inferior parietal cortex and dorsolateral prefrontal cortex, and SLF III defines the ventral component connecting the supramarginal gyrus to ventral premotor and prefrontal cortex. The FAT connects the pre-supplementary motor area (pre-SMA) and SMA in the medial frontal areas of the superior frontal gyrus, and posterior inferior frontal gyrus, which is part of Broca's area in the frontal lobe.[17,18]

Lateral frontal approach

In this approach, margins include the speech networks located posteriorly, including the SLF and FAT. The medial border is limited by deep anatomy, either the insula or, deeper to that, the basal ganglia/CST complex. The inferolateral margin is determined by the IFOF, and in depth, the basal ganglia.[15]

Temporal lobe lesions

Temporal lobe lesions are defined as lesions involving both lateral neocortical (superior, middle, and inferior temporal gyri) and mesial/basal temporal structures, including the hippocampus, amygdala, parahippocampal gyrus, and fusiform gyrus. For surgical planning purposes, lateral and mesial temporal compartments are often considered separately due to differences in functional anatomy and surgical corridors. The inferior longitudinal fasciculus (ILF) is a major occipitotemporal association tract connecting the occipital cortex to the anterior temporal lobe, coursing along the ventral temporal region lateral to the temporal horn of the lateral ventricle. Surgical entry points to temporal lesions are typically achieved via lateral temporal cortices—most commonly through the middle or inferior temporal gyri—or via the superior temporal gyrus depending on lesion location and functional mapping. Selection of the cortical entry point should be guided by lesion location, functional mapping, and tractographic relationships rather than a universally safe corridor.

Temporal approach

Key white matter tracts relevant to temporal lobe surgery include the ILF, IFOF, optic radiations, and, in posterior regions, components of the SLF. These tracts do not represent fixed surgical boundaries but serve as critical structures to be identified and preserved when feasible. Subpial dissection techniques may be employed along the cortical entry site to preserve vascular structures; however, medial resection limits are defined by deeper anatomical structures, including the temporal horn, hippocampus, and adjacent mesial temporal components, depending on tumor extent. The anterior depth of this resection, 3cm from the middle cranial fossa bone, is determined by opening to the temporal horn of the lateral ventricle, while the posterior depth can include the hippocampus, amygdala, and parahippocampal gyri.[15] Nondominant hemisphere temporal tumor resections extend 6 cm behind the temporal pole, and dominant hemisphere temporal tumor resections extend to the anterior 4–5 cm in order to avoid components of the motor pathway. The posterior border is just anterior to the vein of Labbé. Precise identification of speech areas requires surgical mapping and are variable. The depth of the approach meets the ILF at the wall of the lateral temporal ventricle.

Occipital lobe lesions

Lesions in the occipital commonly impact visual cortical pathways including the dorsal and ventral optic radiation pathways in proximity to the atrium and vertical occipital fasciculus (VOF), IFOF, and ILF. The optic radiation originates in the lateral geniculate body and projects to the visual cortex through three distinct bundles: anterior, central, and posterior. The anterior bundle, known as Meyer's loop, curves around the inferior horn of the lateral ventricle and ends at the lower lip of the calcarine fissure. The central bundle runs laterally and posteriorly before reaching the calcarine cortex, representing the macula. The posterior bundle runs straight back along the roof of the ventricle to the upper lip of the calcarine fissure, corresponding to the inferior visual quadrant.[19] The VOF is a vertical white matter tract connecting the dorsolateral and ventrolateral visual cortex involved in visual processing. Nearly any cortical entry into the occipital lobe may potentially impact eloquent visual cortex.

Occipital approach

Lesions involving occipitotemporal lesions are challenging to avoid the key optic radiation, Meyer's loop, calcarine fissure, and VOF fibers which terminate in the entire cortex and are highly associated with visual injury.[20,21] Superior margins of the approach include the SLF anterolaterally. The medial border of this approach can extend to the midline falx. At depth, the atrium of the lateral ventricle is identified with the optic radiation pathways surrounding the atrial wall. The IFOF can be avoided in some cases as it runs lateral to the ventricles.[15]

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Parietal lobe lesions

The integrity of the right dorsal IFOF and the SLF is crucial for preserving mentalizing ability, and the ventral IFOF is needed for visual semantic cognition.[22] Additionally important to preserve in parietal lobe surgery is the multilayer system with optic radiations, ILF, and IFOF primarily, as well as the SLF/arcuate fasciculus (AF), thalamocortical radiations, auditory radiations, and parieto-insular vestibular system secondarily.[22] Entry points through the interparietal sulcus and inferior parietal lobe have been generally considered safe.

Medial parietal approach

In this approach, margin of the approach include the sensorimotor networks anteriorly (e.g., CST, SLF), and IFOF inferolaterally. These anterior and posterior margins of the approach can be extended to the falx medially. The lateral disconnection is determined by the SLF and possibly a portion of the IFOF, and at depth, atrium of the lateral ventricle.[15]

Insula lesions

Insular lesions present a complex area due to the proximity of associative white matter tract fibers and eloquent subcortical connections. One classification of insular lesions, the Berger-Sanai zone classification, defined 4 quadrants with the anterior-posterior line by a plane bisecting the foramen of monroe and the superior-inferior plane defined by the Sylvian fissure.[23] This divided the peri-Sylvian language network (Zones I-III), motor-sensory cortex (Zone II), Heschl's gyrus (Zone III), and deep lenticulostriate arteries (Zone IV) and has been shown to correlate with outcomes, with zone II and IV lesions demonstrating significant morbidity with resection.[24,25]

Transinsular surgical corridors

Transinsular surgical approaches are surrounded by fibers of the IFOF, SLF, and motor fibers. The IFOF is located anteroinferiorly along the limen insulae, while the SLF and CST are located superiorly. Additionally, the anterosuperior margin contains the FAT.[15] The IFOF and uncinate fasciculus (UF) are inferior and antero-inferiorly to the insula. A transopercular corridor to the insula via the frontal lobe is defined by the SLFIII and the arcuate fascicle (AF) long segment superiorly, and the AF posterior segment postero-superiorly. Within the temporal lobe, the corridor is defined by the AF terminations in the posterior portion of the superior temporal gyrus, the IFOF, and optic radiations superiorly and posteriorly, and the ILF inferoposteriorly.[26]

In practical terms, connectome-informed surgery relies on the integration of three key components, which are detailed anatomical knowledge of white matter pathways, patient-specific tractography, and intraoperative functional validation. Failure to adequately incorporate these elements may compromise the reliability of connectomic guidance. It should also be emphasized that these approaches represent generalized frameworks derived from anatomical and connectomic principles; therefore, surgical strategies must be individualized according to patient-specific anatomy, tumor characteristics, and intraoperative functional mapping.

Clinical applications of connectomics

Disruption of connective networks in glioma

Disruptions of white matter tracts may be an a priori finding in gliomas. Yang et al. investigated 1p/19q co-deleted oligodendrogliomas and 1p/19q non-deleted gliomas affected brain connectivity in patients with left insular diffuse gliomas by using correlational and differential tractography with graph theoretical analysis.[15] Data from 32 patients with left-sided WHO grade II–III insular gliomas (13 cases with 1p/19q co-deletion and 19 cases without 1p/19q co-deletion) and compared them to 20 healthy controls. Differential tractography revealed that the patients with the 1p/19q co-deletion experienced more pronounced disruptions in deep white matter tracts than those without the co-deletion. These included anterior thalamic radiations, superior thalamic radiations, forniceal, and cingular tracts.[15] Other studies have shown the utility of differential tractography to demonstrate a priori disruption of white matter tracts in glial tumors.[21,27] One study demonstrated the disruption of distal cortical tracts impacted cognitive and functional performance before surgery, which led to shorter survival.[27] Infiltration or disruption of other critical networks have been described in glioma including: the default mode network (DMN, which is involved in introspection and memory; the salience network (SN) for controlling switching between internal and external focus and linked to mood and awareness; the central executive network (CEN) for governing active, goal-directed behavior and language pathways (e.g., AF, IFOF). Collectively, these findings suggest that gliomas should be understood not only as focal lesions but as disorders of large-scale brain networks, reinforcing the importance of connectomic analysis in preoperative planning and prognostic assessment.

Improving clinical accuracy of connectomic maps

Edema distorts diffusion tensor imaging (DTI) signals and leads to an overestimation of tumor-induced structural disconnections, making it difficult to accurately trace neural pathways that pass through or near brain tumors. Henderson et al. applied a novel algorithm called FERNET (Freewater EstimatoR using iNtErpolated iniTialization) to standardize clinical DTI scans to correct for the presence of free water in edematous regions by modeling each voxel with two compartments—one for tissue and one for edema—thereby improving the accuracy of fiber tracking through those affected areas.[28] In a study involving 10 patients with suspected high-grade gliomas, FERNET-enhanced tractography was compared to standard, uncorrected DTI. The researchers observed significant increases in fiber count, tract volume, and tract length after applying edema correction, with a corresponding decrease in fractional anisotropy, indicating increased sensitivity to previously undetectable fibers. This enhancement was particularly evident in language-related tracts like the arcuate fasciculus and inferior fronto-occipital fasciculus. Validation of these improved fiber tracts was done using three methods: overlap with functional MRI (fMRI) activation maps, correlation with intraoperative stimulation mapping (ISM) data, and comparison with post-surgical imaging when edema had subsided. In each case, the corrected tractography is more closely aligned with known functional anatomy and stimulation responses, supporting its accuracy. The authors proposed that this technique can enhance presurgical planning and may improve structural connectome mapping in glioma patients, facilitating safer and more effective tumor resections.[28]

Furthermore, Almairac et al. conducted a similar study to investigate how applying FERNET to DTI improves the accuracy and reliability of white matter tractography in glioma patients, even in the absence of significant edema.[29] They found significant improvements in anatomical plausibility, streamline count, tract volume, and length for both stimulated and peritumoral tracts by comparing FERNET-corrected tractography with standard DTI.[29] These enhancements were particularly emphasized in the peritumoral zones, which are areas adjacent to the tumor where preserving structural connectivity is

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critical for postoperative function. Although FERNET also modestly improved tractography in healthy tissue, its maximum benefit was observed in the affected hemisphere, highlighting its relevance in pathological conditions. Despite these advances, variability in diffusion acquisition protocols and tractography algorithms remains a significant limitation, highlighting the need for standardized methodologies and further validation against intraoperative findings.

Surgical planning and execution

Applications of tractography to clinical treatment of gliomas have shown promise in reducing patient morbidity. Generally direct routes through non-eloquent cortex serve as the best surgical corridor. However, results from studies using MIPS techniques have also suggested that parafascicular approaches using tubular retractors that displace rather than cut critical white matter tracts can be effective.[20,30–34] Current applications of connectomics have aimed to protect higher-order cognitive functions beyond the baseline known important fibers involved in motor activity (corticospinal tract), visual activity (optic pathways), and language function.[33] Dadario et al. described a case report of a low-grade insular glioma resection using constrained spherical deconvolution (CSD)-based tractography to identify language network, default mode network, salience network, and the central executive network, with good postoperative outcomes.[35]

Several studies have aimed to reduce the potential for supplementary motor area (SMA) syndrome. Briggs et al. studied a "connectomic" or network-based approach to reduce injury to the FAT in patients undergoing glioma resection.[36] Patients with identification and preservation of the FAT had significantly lower rates of temporary SMA syndrome and no cases of permanent SMA syndrome compared to non-guided surgery. Shah et al. also reported the importance of the FAT in reducing SMA syndrome supporting the idea that connectomic mapping was critical to identifying this tract and improving outcomes.[13] Tuncer et al.[37] evaluated tractography-based interhemispheric brain connectivity in postoperative recovery in glioma patients with SMA syndrome.[37] The authors used lesion-symptom mapping and tractography-based disconnectome analysis on MRI scans of 50 glioma patients with tumors in the SMA region. They quantified the extent of white matter disconnection caused as a result of surgery by mapping postoperative lesions onto a normative white matter atlas. They found that disconnection of the central corpus callosum was significantly associated with prolonged acute symptoms, suggesting that disruption of interhemispheric SMA-to-SMA communication delays recovery. In addition, mutism was linked to damage in a left-hemispheric network including the frontopontine tract, FAT, cingulum, and corticostriatal pathways. Long-term motor deficits were associated with disconnection of midposterior callosal fibers and lesions at the SMA–primary motor cortex border zone.[37]

Awake brain mapping remains an important strategy to improve outcomes with connectomic approaches. Albuquerque et al. reported on patients undergoing surgery for diffuse low-grade gliomas (DLGGs) showing functional responses of cortical and subcortical brain regions using direct electrical stimulation (DES) in both the left (LH) and right (RH) cerebral hemispheres (REF-1).[33] The study included 51 awake surgical procedures (26 LH and 25 RH) undergoing multimodal mapping paradigms. Intraoperative findings were correlated with postoperative MRI images and approximated subcortical mapping using MRIcroGL software and demonstrated the importance of awake brain mapping in both hemispheres. Although language deficits were more frequent in the LH, the RH also demonstrated significant contributions to language and cognition. The study also underscored the variability in individual brain organization and supported a patient-specific approach to brain mapping. Furthermore, knowledge of likely intraoperative findings by anatomical region enhanced surgical planning and patient counseling but could not replace real-time mapping by experienced clinical teams.[33]

Albuquerque et al. investigated the performance and effectiveness of various intraoperative neurocognitive tests used during awake surgeries for 51 patients with diffuse low-grade gliomas.[33] A variety of tests—such as DO80 (naming), PPTT (semantic association), Stroop, RME (Reading the Mind in the Eyes), counting, and dual tasks—were selected based on lesion location and preoperative evaluations. The study found that cortical and subcortical mapping were both essential, but subcortical findings were especially critical for defining tumor resection boundaries. A greater number of critical subcortical nuclei were found in the LH however the number of subcortical nuclei in the RH also correlated with postoperative functional outcomes. The researchers emphasized the need for more refined RH-specific cognitive tests and advocated for multimodal tasks that assess several cognitive domains simultaneously to optimize intraoperative time and reduce patient fatigue.[33]

Bennett et al. conducted a study to investigate the correlation between fMRI DES with Human Connectome Project (HCP) cortical parcellations in patients undergoing glioma surgery.[38] The study included 40 patients with supratentorial gliomas who underwent preoperative fMRI and awake craniotomy with DES mapping. fMRI results were aligned with HCP-defined cortical areas and compared against intraoperative DES findings. However, discrepancies between fMRI and DES—such as false positives—highlighted that not all activated regions are non-compensable, and some areas can be resected without resulting deficits. The authors concluded that fMRI could detect HCP-defined areas and can serve as a valuable adjunct to surgical planning, though DES remains essential for determining truly critical cortical regions.[38]

Several studies have reiterated the importance of intraoperative testing of higher cognitive functions. Duffau et al. evaluated the use of connectome-based resections, intraoperative DES, and higher cognitive level testing in a cohort of 19 professional and semiprofessional artists with WHO grade 2 low-grade gliomas.[39] With a mean extent of tumor resection was 91.2% and no permanent post-operative deficits, the authors argued that preserving higher cognitive network dynamics through real-time intraoperative multitasking is sufficient to maintain high-level artistic abilities, without requiring dedicated artistic tasks during surgery.[39] Furthermore, Duffau et al. has recently supported the framework for intraoperative multi-tasking of distinct patient tasks to potentially improve accuracy of detecting salient cortical networks for preservation.[40] Similarly, Martin-Fernandez et al. evaluated the need for intraoperative music performance mapping during awake brain surgery to preserve musical abilities in professional musicians with lower-grade gliomas.[41] A series of 3 cases using a "meta-networking" approach included tailored intraoperative testing to monitor a broad range of higher-order functions, including language, attention, emotion, executive control, and social cognition. Despite not performing music during surgery, all patients resumed their musical careers, indicating that mapping and preserving critical brain networks supporting higher-order functions may be sufficient to maintain musical skills.[41]

AI -assisted surgical planning

Applications for (AI) in glioma connectomics can help analyze complex brain network data with greater precision, speed, and clinical

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relevance. AI models, particularly machine learning and deep learning algorithms, can process large-scale neuroimaging datasets to detect subtle patterns of structural and functional disruption caused by gliomas, patterns that are often invisible on conventional imaging. AI-driven tractography reconstruction and network disruption modeling may directly influence extent-of-resection decisions and risk stratification during glioma surgery. These tools allow for more individualized, data-driven approaches to diagnosis, prognosis, and treatment planning, moving beyond traditional lesion-based assessment toward a network-based understanding of brain tumors.

Integrating AI into tractography may further enhance the accuracy and clinical utility of white matter mapping in glioma patients. Tractography traditionally suffers from limitations such as tracking failures in tumor-distorted tissue and operator dependence. Future iterations of AI may be able to automate and optimize tract reconstruction by learning from large datasets of healthy and diseased brains to predict probable fiber pathways, even in areas of disrupted anatomy. Deep learning approaches can improve segmentation of brain regions, identify abnormal tract configurations, and assist in filtering out false-positive streamlines. Additionally, AI-powered tractography tools might be integrated into surgical navigation systems, providing real-time, personalized maps of critical white matter pathways to guide safer resections.

Werninger et al. conducted a study to investigate how incorporating deep learning-based free water modeling improves diffusion MRI tractography and structural connectivity analysis in glioma patients.[42] The researchers applied a subject-specific deep learning method to model and eliminate the free water component from diffusion MRI data in 35 glioma patients and 28 matched healthy controls. The method was designed to work with clinical single-shell diffusion acquisitions and did not require specialized hardware or extended scan times. The model could estimate and subtract free water contamination on a voxel-by-voxel basis, correcting the diffusion signal and improving fiber orientation detection by training neural networks on synthetic data generated from individual brain scans. Tractography was performed both before and after free water correction using deterministic and probabilistic tracking methods. Structural connectomes were derived from these tractograms and analyzed for changes. The results showed that after free water modeling, the number of reconstructed fibers significantly increased, especially in patients with high-grade gliomas, while average fiber length remained unchanged, indicating that the correction revealed previously obscured pathways without artificially elongating them. Additional analysis revealed that inter-hemispheric and inter-subject similarities in structural connectivity increased post-correction in glioma patients. It suggested that part of the observed connectivity disruption in tumor patients without correction may be due to artifact rather than true anatomical damage. Metrics like clustering coefficients and graph density indicated that connectivity estimates became more consistent with those of healthy subjects after applying the correction, narrowing the apparent differences caused by tumor-related edema. Deep learning-assisted tractography-based connectivity analysis in glioma patients helped to separate true pathological changes from imaging artifacts, offering more accurate insights into white matter integrity with important implications for clinical connectomics, especially in surgical planning, where preserving functionally critical fiber tracts is essential.[42]

Wu et al. investigated how insulo-Sylvian gliomas affect nontraditional cognitive brain networks and evaluated the utility of diffusion tensor imaging (DTI)-based tractography and personalized brain network mapping using the machine learning–based Quicktome platform in preoperative planning to minimize cognitive deficits.[43] The study included the retrospective analysis of 45 patients with gliomas centered around the Sylvian fissure and prospective cognitive assessments in 7 additional patients, and surgical outcome tracking in 2 patients where Quicktome informed the surgical approach. 98% of tumors affected non-traditional brain networks, notably the salience network (SN), central executive network (CEN), and ventral attention network (VAN), with a correlation between the cognitive decline and the network involvement. Quicktome-aided surgical planning enabled preservation of critical networks and better cognitive outcomes.[43] Current AI models are predominantly developed using retrospective datasets, which may limit their generalizability across different institutions, patient populations, and imaging protocols, thereby constraining their immediate clinical applicability. Moreover, the translation of AI-based connectomic tools into routine practice is further challenged by issues related to interpretability, external validity, and seamless integration into real-time surgical workflows, underscoring the need for rigorous validation in prospective clinical studies.

Real-time intraoperative guidance

Real-time connectomic guidance is transforming glioma surgery from a primarily anatomical approach to a network-based strategy. These technologies improve outcomes and reduce neurological deficits by preserving critical neural pathways and adjusting in real time to intraoperative changes. The ongoing development and clinical integration of these tools are paving the way for more personalized, precise, and safe brain tumor surgeries. Traditional imaging methods provide static maps of these regions, but brain networks can shift during surgery, making real-time guidance essential. During surgery, this connectome-informed overlay enables dynamic decision-making, helping surgeons avoid disrupting essential networks while maximizing tumor removal. Recent work further supports this paradigm shift by demonstrating how network-based modeling can inform intraoperative decision-making and functional risk assessment in glioma surgery.[44]

A variety of emerging strategies have been described to improve intraoperative glioma resection (Table 1). Intraoperative resting-state functional MRI is an emerging technique that enables functional network mapping without the need for electrical stimulation.[45,46] This method offers a dynamic understanding of motor networks during surgery, particularly when combined with advanced imaging setups like saline-filled cavities to improve signal quality. Optical imaging techniques such as hyperspectral imaging and near-infrared fluorescence may be additional methods to identify intraoperative white matter tracts.[47,48] Additionally, neuronavigated ultrasound offers near-instant imaging updates during the procedure and may potentially update resection around critical white matter tracts.[49] The integration of multiple data sources, including DTI, functional MRI, transcranial magnetic stimulation, and intraoperative neurophysiological monitoring, can be a promising area needing further study. Integration of augmented and virtual reality tractography data directly overlaid onto the surgical field also shows promise.

Moretto et al. investigated the clinical utility of resting-state functional MRI (rs-fMRI) in mapping intrinsic brain networks in patients with gliomas, using intraoperative direct electrical stimulation (DES) as the gold standard for validation.[20] The authors presented an upgraded version of ReStNeuMap, a tool designed for automated extraction of resting-state networks (RSNs) from rs-fMRI data. The study included 28 glioma patients who underwent awake surgery with DES, providing 100 stimulation points across sensorimotor (SMN), language (LANG), visual (VIS), and speech articulation (SAN) domains. The spatial correspondence between the automatically detected RSNs and the DES points was quantified, showing high accuracy: median distances between DES points and corresponding network maps were ≤5 mm, with the closest matches in SMN, VIS, and SAN domains, while LANG showed slightly greater variability. Patient-specific independent components derived from rs-fMRI showed improved spatial alignment with DES compared to standard atlas-based templates.[20]

Table 1 Currently available and emerging strategies for real-time connectomic guidance in glioma surgery

Technique	Clinical utility	Advantages
Resting-state fMRI (rs-fMRI)	Automated mapping of resting-state networks; validated vs. direct electrical stimulation (DES) with ≤5mm accuracy; improved alignment over atlas-based maps	High accuracy; patient-specific; aligns well with gold standard DES.
Neuronavigated transcranial magnetic stimulation (nTMS)	Non-invasive mapping of language networks; comparable to direct cortical stimulation (DCS); broader tract coverage, especially ventral stream.	Reliable, broader mapping; non-invasive.
Intraoperative resting-state fMRI	Dynamic motor network mapping without electrical stimulation; improved signal with saline cavity filling.	Dynamic, real-time mapping of function.
Optical imaging (hyperspectral, NIR fluorescence)	Identifies intraoperative white matter tracts in real time.	Enhanced intraoperative identification of functional tracts.
Neuronavigated ultrasound	Near-instant intraoperative imaging updates; potential to guide resection around critical tracts	Rapid updates during resection; real-time adjustment.
Integration of multimodal data (DTI, fMRI, TMS, IONM)	Combines multiple modalities for network-based resection planning; promising for future precision	Comprehensive network insight; multimodal synergy.
Augmented/virtual reality tractography overlays	Projects tractography data directly onto the surgical field for real-time connectomic guidance.	Intuitive, surgeon-friendly visualization.
Advanced cortical direct electrical stimulation and mapping	Advanced paradigms involving higher cognitive function or multi-tasking used for improved functional mapping.	Rapidly deployable paradigms but may be limited for all tumor locations.

Ille et al. investigated whether non-invasive navigated transcranial magnetic stimulation (nTMS) can effectively map language networks in the brain as reliably as the invasive gold standard method, direct cortical stimulation (DCS).[26] Both techniques were applied to 27 patients with left-hemispheric perisylvian tumors undergoing awake craniotomy. The researchers used connectome-based analysis to assess the centrality of language-related brain regions. Results showed no statistically significant difference between the centralities derived from nTMS and DCS, suggesting that both methods identified similarly critical nodes in the language network. nTMS-based tractography mapped more language-related white matter tracts, especially in the ventral stream, compared to DCS-based mapping. Despite nTMS offering broader coverage, the consistency between the methods supported the clinical reliability of nTMS for preoperative language mapping.[26] A key challenge remains the translation of preoperative connectomic models into real-time intraoperative decision-making, as brain shift and tissue deformation can significantly alter anatomical relationships during surgery.

Future studies

Future studies on tractography generation and usage in glioma connectomics might prioritize standardized high-quality diffusion MRI protocols, such as high angular resolution diffusion imaging (HARDI) with optimized b-values and multiple directions, to ensure reliable and reproducible tract reconstruction across institutions. Integration of functional imaging modalities, including task-based fMRI and intraoperative brain mapping, can help validate the functional relevance of tractography findings, particularly in eloquent regions. Longitudinal approaches, such as differential tractography, should be routinely implemented to monitor white matter changes over time—before and after surgery, and during treatment—offering insights into neural plasticity and early signs of recurrence. Whole-brain connectometry can be used to capture global network disruptions and compensatory adaptations that occur beyond focal lesions. Larger, stratified patient cohorts can be used to investigate how tumor subtypes uniquely affect network integrity. Quantitative measures like fractional anisotropy (FA), normalized quantitative anisotropy (NQA), and tract volume should be correlated with clinical outcomes to build predictive models for recovery and prognosis. Automation through AI-based tract segmentation tools can reduce operator bias and enhance scalability, while more frequent imaging follow-ups will allow a deeper understanding of connectome dynamics. Validating imaging-based tract disruptions with intraoperative stimulation and integrating connectomics into surgical planning software will help translate these insights into safer, more precise glioma treatment strategies.

For future studies, it is recommended to develop AI models that are trained on multimodal data (e.g., diffusion MRI, fMRI, and clinical variables) to improve generalizability and robustness in diverse patient populations. Open-access, large-scale annotated datasets are needed to support the training and validation of these models. Researchers should explore explainable AI approaches to enhance clinical trust and transparency, especially in decision-support tools. Finally, integrating AI into real-time intraoperative tools and radiotherapy planning systems could pave the way for more adaptive, precision-guided glioma management. Collaborative efforts across institutions will be crucial for validating AI tools in prospective clinical trials and ensuring their safe translation into routine practice.

Improved paradigms for intraoperative connectomic testing are needed. Duffau et al. conducted a study for a significant evolution in the methodology of awake brain surgery for low-grade glioma patients.[40] The authors proposed that during surgery, instead of testing isolated functions sequentially, patients should engage in continuous multitasking under time constraints. This method better reflected real-life demands, allowing for the preservation of across-network dynamics, i.e., how different brain systems interact in complex behaviors. The authors critiqued the limitations of conventional intraoperative cognitive monitoring, which uses function-specific tasks not tailored to the dynamic and integrated nature of actual human cognition. Instead, they recommended combining tasks: semantic associations, mentalizing, and movement presented rapidly and adaptively during resection to increase cognitive load and test the coordination between different brain networks. This real-time stress testing helped detect subtle dysfunctions and better guide surgical decisions.[40]

Coletta et al. presented a novel framework that integrates direct electrical stimulation (DES) data from brain surgeries with functional and structural imaging from large normative datasets to map causal brain networks across 12 behavioral domains.[50] DES, conducted during awake surgeries in glioma patients, offers precise causal insights into brain function but is limited by focal sampling. To overcome this, the authors combined over 4,100 DES points from 612 patients with resting-state fMRI and diffusion-weighted imaging data from healthy individuals. This multimodal integration expanded brain coverage nearly 30-fold compared to DES alone. The resulting DES-derived networks demonstrated high predictive accuracy (97.8%) for unseen stimulation points and strong anatomical correspondence with subcortical white matter tracts. No major differences were found between networks derived from patients versus healthy subjects, supporting generalizability. A multivariate model was developed to identify individual deviations from normative brain function, showing potential for personalized brain mapping. Clinically, DES-derived networks overlapped with known neuromodulation targets, correlated with post-surgical behavioral outcomes, and were more accurate than DES atlases alone. They also showed promise in identifying therapeutic targets for disorders like aphasia and apraxia of speech. While limitations include sampling bias and the inability to infer causality at single-region levels, the study provided a robust tool for causally grounded, network-level brain mapping with implications for neurosurgery, psychiatry, and neurorehabilitation.[50]

Further research in connectomics for neurosurgery is needed (Figure 2). Improved sample size and standardized methods are needed to improve validation of testing paradigms and surgical approaches. This includes large-scale clinical trials on surgical outcomes, standardizing imaging and mapping protocols (especially for diffusion MRI and tractography), and intraoperative validation of findings with stimulation or postoperative validation with cognitive testing. Additionally, research should expand beyond motor and language networks to include cognitive and nontraditional networks. Future work should also focus on understanding neuroplasticity, developing AI tools for real-time model adaptation, improving usability and integration into surgical workflows/navigation systems, and evaluating cost-effectiveness and implementation barriers to increase accessibility.

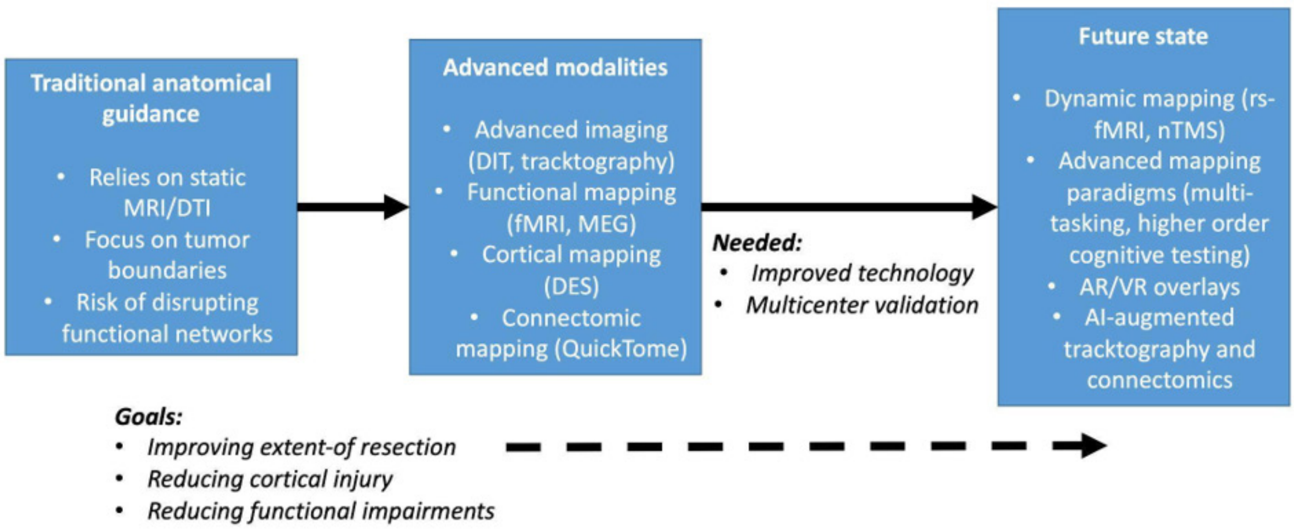

Figure 2 Schematic of current and future states in the use of preoperative and intraoperative mapping tools for improving

Abbreviations: AI: artificial intelligence; AR: augmented reality; DES: direct electrical stimulation, DTI: diffusion tensor imaging; MEG: magnetoencephalography; nTMS: navigated transcranial magnetic stimulation; rs-fMRI: resting state functional resonance imaging; VR: virtual reality

Conclusion

Connectomics is a transformative framework for neurosurgical planning and glioma management, moving beyond lesion-focused approaches to visualize and quantify network disruptions. It allows surgeons to improve odds of preserving critical pathways like language, motor, and attention networks, strengthened by intraoperative integration with awake mapping and tractography. This network-based perspective prioritizes high-value connections and functional hubs, guiding resection strategies and anticipating functional risks. Further prospective, multi-center research is needed to standardize and validate treatment strategies. As imaging and computational modeling advance, connectomics promises to become an indispensable component of modern glioma management, fostering personalized treatment strategies and aligning surgical goals with long-term patient outcomes. Ultimately, the success of connectome-guided neurosurgery will depend on its ability to integrate anatomical precision, functional validation, and patient-specific adaptation into a unified surgical strategy.

Author contributions

E.D. and M.K. conceptualized the study.; E.D., M.Z. and M.K. reviewed the literature and did the investigation.; E.D. and M.K. prepared the original first draft.; All authors edited and reviewed the manuscript.; M.K. did the supervision.; All authors have read and agreed to the published version of the manuscript.

Declarations

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