



Review article

Cerebral Connectivity and High-grade Gliomas: Evolving Concepts of Eloquent Brain in Surgery for Glioma

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Abstract: Technological advances in imaging the human brain help us map and understand the intricacies of cerebral connectivity. Current techniques and specific imaging sequences, however, do come with limitations. Image resolution, variability of techniques and interpretation of images across institutions are just a few concerns. In the setting of high-grade gliomas, understanding how these pathways are affected during tumor growth, surgical resection, and in the brain plasticity presents an even greater challenge. Clinical symptoms, tumor growth, and intraoperative electrical stimulation are important peri-operative considerations to assist in determining neuronal re-wiring and establish a basis of anatomic and functional correlation. The application of functional mapping coupled with the understanding of the natural history of gliomas and implications of neural plasticity, is critical in achieving the goals of maximal tumor resection while minimizing post operative deficits and improving quality of life.

Keywords: cerebral connectivity; diffusion tensor imaging; fiber tracking; gliomas; intraoperative monitoring

Abbreviations:

AF	Arcuate Fasciculus
BA	Brodmann Area
BBB	Blood-Brain Barrier
BOLD	Blood-Oxygen Level Dependent
CNS	Central Nervous System
CST	Corticospinal Tract
CT	Computerized Tomography
DES	Direct Electrical Stimulation
DTI	Diffusion Tensor Imaging
EOR	Extent of Resection
FA	Fractional Anisotropy
FLAIR	Fluid-Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
FT	Fiber Tracking
GBM	Glioblastoma Multiforme
HGG	High Grade Gliomas
ICM	Intraoperative Cortical Mapping
IE	Intraoperative Electrostimulation
IFOF	Inferior Frontooccipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
ISM	Intraoperative Subcortical Mapping
KPS	Karnofsky Performance Score
LGG	Low Grade Gliomas
MRI	Magnetic Resonance Imaging
Nn	Neuronavigation
OS	Overall Survival
PMC	Primary Motor Cortex
PmF	Premotor Fasciculus
ROI	Regions of Interest
SGZ	Subgranular Zones
SMA	Supplementary Motor Area
SubCF	Subcallosal Medialis Fasciculus
SVZ	Subventricular Zones
QoL	Quality of Life
UF	Uncinate Fasciculus
US	Ultrasonography

1. Introduction

Models of brain function and connectivity have evolved greatly with advances in magnetic resonance imaging (MRI) and functional mapping during brain tumor and epilepsy surgery. These models allow a more comprehensive understanding of brain connectivity and more completely allow for variability secondary to anatomic and functional individuality [1–5]. As complex and heterogeneous the human brain can be, the behavior of high-grade gliomas presents an exponentially greater obstacle when guiding treatments as these tumors may distort normal anatomy and encourage neural plasticity in adjacent brain [6,7].

Glioma remains the most common primary malignant tumor of the CNS [8]. One of glioma's most characteristic features is the infiltrative nature of its growth. Given the nature of the glioma's infiltration into cortical structures and destruction of myelinated pathways within the brain, it is imperative to understand the connections between traditional cortical areas of the brain and the subcortical white matter pathways which allow the eloquent connectivity and function of the human brain. As a result, efforts have been made to elucidate individualized relationships between anatomy and functionality to preserve as much function as possible during surgery and other standardized treatments [1,7].

Conventional dogma describes cortical structures relating to a specific functionality [9]. This model, which has evolved over the past two centuries, inherently generalizes the human brain and gives little room for the developing idea of anatomo-functional variability [1]. Through non-invasive functional imaging and intraoperative cortical and subcortical mapping (ISM), the understanding of regions of cortical functions as well as sub-cortical networks, of interconnected fiber tracts has been greatly improved [1,2,9,10].

When approaching clinical decision making for patients with glioma, an appreciation for neuroplasticity and the cortical functional zones and their interconnectivity must be considered in pre-operative planning, intra-operative decision-making, and post-operative prognostications on functional recovery [11–15]. This is paramount in patient selection for surgery of gliomas where the goal of surgery is the maximal tumor resection while minimizing postoperative deficits [16,17]. Rarely, gliomas are deemed inoperable solely due to their anatomic location and surgical biopsy followed by radiation, chemotherapy, immune therapy, or electrical field treatment is the preferred strategy [18,19]. Principal in surgical planning for glioma is the reduction of post-operative surgically-induced deficits, whether temporary or permanent [2,5,14].

2. Mapping the Brain: Cerebral Connectivity through Non-Invasive Imaging Modalities

Mapping the human brain with non-invasive imaging modalities to gain an acceptable appreciation of true functionality is a challenging endeavor. A brief review of the available imaging

techniques, reliabilities and pit-falls as they pertain to normal neural structures and relative networks is critical to understand their utility in surgical planning and guidance.

MRI is a non-invasive imaging modality that relies on proton equilibration and emitted radiofrequencies that produce images of anatomical structures in great detail [20,21]. T2 and fluid-attenuated-inversion-recovery (FLAIR) help determine tissue water content and ultrastructure by evaluating relaxation times. Increased water content is reflective of increased relaxation times and is represented by hyperintensities, whereas signal dropout represents calcification and hemosiderin on these sequences [7].

Functional MRI is a useful tool that works by mapping tiny blood-oxygen level dependent (BOLD) differences to identify cortical neuronal activity. An increase in neuronal activity, stimulated by a directed task, results in increased oxygen demand and due to increased blood flow that exceeds metabolic tissue demand, a net decrease in the concentration of de-oxyhemoglobin occurs in the local tissues, which gives the appearance of a homogenous MRI signal in the activated tissues [21]. Auditory, motor, visual, and language maps may be created with various tasks and hemispheric dominance may be inferred. The BOLD effect is, however is an indirect measure of neuronal activity and the effect of many confounding variables on its signal is not fully understood [21].

Diffusion Tensor Imaging (DTI) sequences have been exploited for their ability to utilize principles of anisotropic water diffusion in the CNS to define white matter tracts. A sound interpretation of DTI sequences relies on the understanding of various influences of structural components in the CNS and on the directional dependence of water diffusion. Microstructural compartments such as the extracellular space, intracellular space, neurons, glial cells, and axons act as barriers and contribute to the anisotropic behavior of water diffusion in the CNS. By evaluating the signal intensity attenuation, directional inferences and microstructural characteristics may be derived. Barriers such as elongated, organized axonal membranes and myelin sheaths inhibit the diffusion of water molecules perpendicular to white matter tracts. Water molecules more readily diffuse along the lengths of the tracts within the grey matter. White matter pathways therefore can be calculated by tracking specific algorithms comparing the direction and speed of water diffusion on a voxel-to-voxel basis [22]. Fiber crossings are not adequately represented with DTI because of its inability to display more than one axon direction per imaging voxel [5]. Thus, the assumption is made that the primary eigenvector represents the dominant orientation of the axons. Moreover, creating regions of interest (ROI) while tracking fibers requires a sound anatomical knowledge of white matter pathways, which fundamentally leads to variability [2]. The suggestion of using fMRI data as ROI for DTI tracking has been made [5].

2.1. Visual Pathways

The optic radiations are described in three bundles: anterior, central and posterior. They pass from the lateral geniculate nucleus, through the temporal stem, cover the superior and lateral wall of

the lateral ventricle, and terminate in the calcarine sulcus. Meyer's loop describes the anterior bundle as it loops the roof of the temporal horn behind the anterior commissure. The central bundle does not form a loop and the posterior bundle is said to run directly posterior to the lateral wall of the ventricle [23]. Various fibers including the inferior frontooccipital fasciculus (IFOF) and uncinate fasciculus (UF) are in proximity of the visual fibers, which can confound visual pathway DTI especially if varying degrees of anatomical knowledge inconsistently sets ROIs [2,23].

2.2. *Language Pathways*

Auditory processing of speech activates the superior temporal gyri including Heschl's gyri. On the dominant side, it has been observed that rapid processing of auditory inputs influence infero-frontal and temporo-parietal activation, and may be involved in covert articulation and higher-order language [24]. The superior temporal gyrus (Wernicke's area), supramarginal gyrus, and inferior frontal gyrus/pars opercularis (Broca's area) are connected via the arcuate fasciculus (AF) [2,24]. This acoustic-phonological-motor system is known as the "dorsal" pathway of language [24–26].

Cortical phonological processes are demonstrated through activities in temporal, premotor and subfrontal regions [24]. Subcortical phonological processing can be largely represented by the AF. Posterior temporal regions, angular gyri, and superior and inferior frontal gyri represent cortical semantic areas which are often not in their representations on individual patients. The IFOF, inferior longitudinal fasciculus (ILF) and UF are representative of subcortical lexical-semantic language processes: the "ventral" pathway [25,26]. In a study by Huth and colleagues [27], semantically selective areas have been found to be nearly symmetrical bihemispherically. It has been noted that the initiation and planning of speech involves the subcallosal medialis fasciculus (SubCF) and cortical fibers from the medial and lateral premotor areas (PmF) [2].

Functional MRIs have demonstrated a high degree of functional cortical variability with regards to speech and language. Cortically driven motor functions are more reliably and easily obtained compared to language function [3,28] (Figure 1). A priori knowledge of language fascicles must be well understood while creating ROIs purported to represent subcortical language pathways [2].

2.3. *Motor Pathways*

Somatotopy of the primary motor cortex has been demonstrated and understood through the institutionally known, "homunculus," through the works of Penfield and Boldrey [29] This Rolandic cortex has been tested and reproduced in individuals to various degrees and the somatotopic organization of the subcortical pyramidal pathway, the corticospinal tract (CST), has been demonstrated through fMRI, DTI and ISM [29,30].

Studies have demonstrated individual variability with intraoperative cortical mapping (ICM) when compared with fMRIs done in patients who were asked to execute motor tasks [3]. Activated

areas in non-primary sensorimotor areas varied depending on individual. Hand, feet and face areas revealed activation in the primary motor cortex (PMC), but also in cingulate gyrus, supplementary motor area (SMA), frontal, precentral sulcus, precentral and post central gyri. At times there were bilateral activations from unilateral tasks. Increasing the analysis threshold may decrease non-primary activation, but also decreases Rolandic activation, suggesting that much more of the brain is involved in motor tasks than the classical paradigms [3].

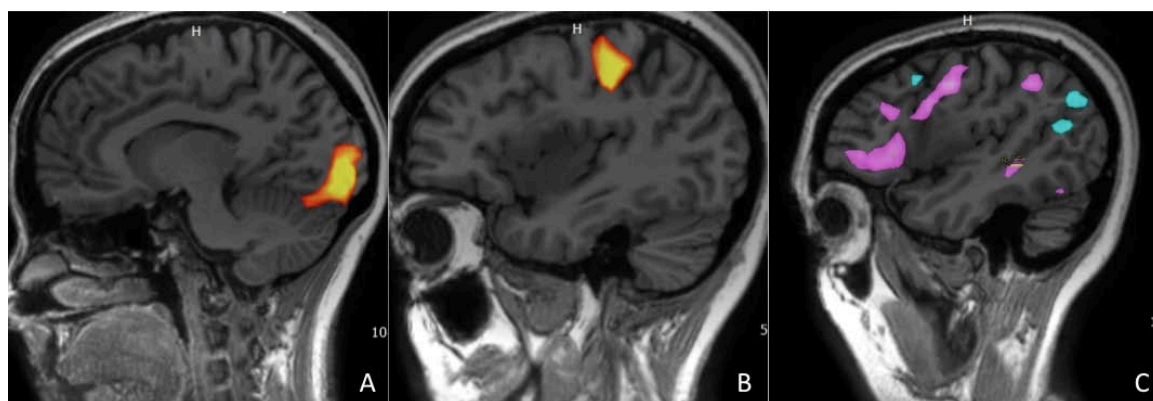


Figure 1. Value of the fMRI. Cortically driven visual (a) and motor functions (b) are more reliably and easily obtained on fMRIs. Functional cortical variability may be high especially when speech and language are tested (c) fMRI, functional magnetic resonance imaging.

2.4. *Insular/Peri-Insular Associations*

The insular lobe is located under the Sylvian fissure, extending from the anterior perforated substance to the supramarginal gyrus. It is covered superiorly by the orbito-frontal operculum and inferiorly by the temporal operculum. It lies lateral to the claustrum, external capsule, striatum, internal capsule and thalamus. It has three anterior gyri and two posterior long gyri separated by the central insular sulcus [31,32]. Lenticulostriate arteries from M1 represent the anterior limit of the insula and M2 perforators supply it. The insula plays a role in autonomic, olfactory, emotional, and cognitive function, but its discrete roles are less defined than those of most cortical areas. The peri-insular region, given its location in the brain, is adjacent to many important pathways including the posterior limb of the internal capsule, AF, IFOF, and UF [32].

3. **Cortical and Subcortical Connectivity Altered and Damaged by High-Grade Gliomas**

3.1. *Natural History/Clinical Presentation of GBM*

Glioblastoma multiforme (GBM) is the most common of the primary malignant neoplasms of

the central nervous system. GBM represents 46.1% of all primary malignant brain tumors and approximately 12,000 cases are diagnosed each year within the United States. Incidence increases with age with rates highest in 75–84 years. Survival is dismal, with 5.1% or fewer patients alive 5 years post diagnosis [8]. The standard treatment includes a multimodal approach with microsurgical resection, followed by concomitant chemotherapy and radiation therapy, which allows for a survival time of 12–15 months. QoL is primarily influenced by tumor location, progression, and treatment morbidity [33–37]. Recent advancements in genetic analysis has elucidated glioma subtypes, allowing for inferences on prognosis to be made [16,17,33,38]. Unfortunately, this has not yet translated to improved clinical outcomes or more personalized care for GBM molecular subgroups.

3.2. *Cerebral Connectivity, or the Lack of, with GBM*

MRIs play a major role in the identification, characterization and surveillance of GBMs [7]. Precise identification of the anatomic location of the neoplasm is critical in surgical planning and assessing the efficacy of therapy and tumor recurrence in the postoperative setting. Anatomical MRI including standard sequences and MR angiography and venography can be useful in assessing risk of surgical resection preoperatively. Functional imaging including fMRI and DTI, when correlated with the history and clinical exam is crucial in the preoperative risk assessment in avoidance of critical cortical and subcortical pathways. A thorough discussion of the potential areas impacted by surgical intervention is crucial in patient consent when attempting to achieve a maximal safe surgical resection [16,17]. An alternative to gross total resection of the enhancing tumor has been proposed, A “supratotal” resection of the tumor and any surrounding tissue up to any crucial cortical or subcortical pathways may offer further survival advantage [1,11,39,40].

It has been noted that many gliomas have contact on either T1WGd or T2W images with the ependymal surfaces. It has been postulated, in the cancer stem cell hypothesis, that radial stem cell migration from the subventricular zones (SVZ) and subgranular zones (SGZ) could account for gliomagenesis and tumor recurrence [31,41–45]. Therefore, when evaluating tumors for near total to supra total resections, careful evaluation of the tumor’s relationship with the ventricle and critical pathways traversing the periventricular region is imperative.

Classically, GBM is represented as the gadolinium enhancement from the accumulation of paramagnetic compounds in the interstitium of the glioma from increased blood-brain barrier (BBB) permeability, neovascularization, and necrosis [7]. Hyperintensities on T2 and FLAIR sequences are representative of increased water content and represent edema, and likely, infiltrative tumor, in these areas [6]. When using MRI for tumor surveillance, reducing variability improves the interpretation between studies. Therefore, it is prudent to: 1) avoid 1.5 to 3.0 tesla comparisons, 2) avoid use of different machines on same patients 3) avoid different consoles and software [4]. Contrast enhancement is an unreliable differentiator for LGG and high grade gliomas (HGG), though the development of tumor enhancement is used as a suggestion of anaplastic transformation or tumor

progression. Due to the irregular shape and anisotropic growth patterns along white matter tracts, of both LGG and HGG, tumor volume can be difficult to quantify and reproduce [7,46].

Inherently, the unavoidable issues of significant intra-observer variability and inter-institutional heterogeneity exist with MRI imaging. It is useful in the serial follow-up of patients with glioma to have consistent review by radiologists, surgeons, or oncologists over time. It may be especially important for an experienced observer to examine sequential studies since, conventional MRI does not provide satisfactory anatomical detail regarding the involvement of infiltrative tumor cells and does not display the location and integrity of fiber bundles [22].

Functional MRI is helpful in GBM evaluation as distorted anatomy from tumor involvement or mass effect can lead to uncertainty about function and be better outlined using neuronal activity and cerebral blood flow. One caveat, however, is that an area directly or indirectly affected by a pathologic lesion, may respond unreliably to standardized fMRI thresholds. For example, a patient who has a hand motor deficit, may require a lower fMRI threshold to be represented on imaging. A high threshold may erroneously suggest there is no cortical hand motor function [3]. Furthermore, the modified vascular bed surrounding GBMs could alter the BOLD effect and lead to unreliable results [47]. Moreover, infiltrated tissues can still hold function as demonstrated by direct cortical mapping [3,48]. Therefore, interpretation of these studies must be done with caution and be closely correlated with the clinical findings.

DTI has been used for 3-D visualization of specific white matter tracts within the region of tumors [46]. This assists the surgeon in determining the influence of infiltrating gliomas on surrounding white matter. DTI can help by demonstrating bundles of fibers that are displaced, interrupted or widened due to edema or tumor infiltrate [22,49]. When used in pre-operative planning, areas of special interest like speech, vision, and motor pathways can be mapped to correlate presenting symptoms and to help with predictive peri-operative functions.

Stadlbauer and colleagues [22] retrospectively determined predictive variations of fractional anisotropy (FA) thresholds using comparative histopathologic findings of tumor cell infiltration. These findings were also correlated with peri-operative clinical symptoms. Using a 1.5T MRI, it was found that with higher thresholds, there was an increased in distance of peri-tumoral fibers and a decrease in the number of fiber bundles. One may conclude from the data presented that decreasing FA thresholds may demonstrate non-functional fiber bundles within highly infiltrated brain parenchyma and increasing FA thresholds may under-represent functional fibers in the peri-tumoral region. That notwithstanding, it is difficult to conclude whether the interrupted fibers represented on DTI sequencing, are due to tumor edema, infiltration by tumor, or outright fiber destruction by the tumors themselves or inflammatory cells. It has been suggested that malignant infiltration in the extra-cellular space decreases water restriction allowing inferences of tumor cell infiltration from FT imaging [50]. The functionality of these disrupted fibers still remains hypothetical. Studies that used higher thresholds did report post-operative neurologic worsening though tumor resection did respect the reconstructed fiber tracts, suggesting functional fiber tracts were not adequately represented [51].

3.3. Glioma Migration and Cerebral Connectivity—Laboratory Insights

One of the most vexing problems in treatment and surgical therapy of glioma is the problem of glioma cell infiltration into normal brain parenchyma. Although brain metastases and most benign brain tumors develop within brain parenchyma as compact spheres of tumor cells with sharp borders between normal tissues and the brain tumor, that is not the case with gliomas. During development, normal glia develop from glia precursors in the subependymal zone and migrate to their position with the brain substrate [31,41–45]. If one ascribes to the stem cell model of cancer, it is not difficult to imagine the glioma stem cells which drive gliomagenesis recapitulating the phylogeny of their youth and enacting the same migratory mechanisms of glial cell precursors in moving within the brain parenchyma.

Migration of glioma cells into the normal brain parenchyma is a complex process, involving tumor cell-ECM (extracellular matrix) interactions [52–54], cell-cell interactions [55], and signaling pathways regulating the active motion of the cell [56]. Most *in vitro* studies focus on interactions between migrating glioma cells and ECM, involving adhesion, degradation and remodeling [57]. Less is known about the role of cell-cell interactions and which factors influence or direct the migration of glioma cells within the brain.

It has long been noted that glioma cells migrate preferentially in association with myelinated tracks [58] in the brain. Our laboratory has demonstrated that glioma cells form extended pseudopodia to explore the surrounding microenvironment, interact with myelinated axons and migrate preferentially along these tracks in glioma cell invasion of brain parenchyma in culture and animal models (N Tapinos, unpublished data). In these co-culture models, dorsal root ganglia neurons were cultured with oligodendrocytes to allow the formation of myelinated axons. When human glioblastoma stem cells are added to the model, video microscopy has shown the ability of glioma cells to destroy myelinated fiber bundles in these models (N Tapinos, unpublished data), as well as attaching to the myelin and using the myelinated bundles in their locomotion. Obviously the disruption of myelinated white matter connections during the glioma cell invasion is one method by which glioma cells can disrupt cerebral connectivity in gliomagenesis and progression. The infiltration and subsequent edema of invaded tissues may further disrupt neuronal function, leading to deficits.

3.4. Glioma Migration and Cerebral Connectivity—Clinical Considerations

The morbidity of gliomas is largely due to tumor cell migration and invasion into normal brain structures. During migration, glioma cells transiently arrest from the cell cycle and thus become largely refractory to the chemotherapy and radiotherapy [59]. Once these migratory cells have traveled from the primary tumor mass, they may re-enter cell cycle and form recurrent tumors [60].

During migration, these glioma cells traverse (and may disrupt) the white matter bundles connecting different regions of the brain parenchyma.

Their diffuse infiltration into the brain parenchyma distant from the solid tumor mass dooms surgical, radiation, and locally released chemotherapy treatments [61,62] to failure. In clinical neuro-oncology, by the time a tumor is diagnosed, glioma cells have migrated over large distances, often well beyond the tumor limits as seen on MRI. As a result, even following gross total surgical resections, gliomas usually recur within several months [63].

Since gliomas are primarily a disease of the white matter responsible for the brain's connectivity, planning for the surgical resection of glioma requires understanding how the white matter tracts are connected as well as how glioma cells hijack these pathways in order to escape the solid tumor mass. The logical next step in surgery for glioma, resection of the solid tumor as well as all tissue surrounding the tumor up to the point of important cortical and connecting subcortical pathways has been proposed as a potential technique to improve overall survival [1,39]. Knowledge of the connectivity of white matter tracts extending beyond the planned resection cavity may also be important in planning post surgical therapies involving diffusion of molecules along white matter pathways or exploiting these pathways for delivering therapeutic molecules through convection enhanced delivery [19].

4. Neurosurgical Considerations & Decision Making

It has been well described that the extent of resection (EOR) in high-grade gliomas holds as a significant independent value to prolong survival [16,17,35,64]. Not only the EOR, but other factors including age, Karnofsky performance score (KPS), and the use of adjuvant chemotherapy and radiation therapy have been studied to develop individualized treatment goals to patients. Treatments after tumor surgery include radiation, chemotherapy, and may be supplemented with immune therapy, or tumor treating fields [16–19]. Historically, gliomas within the conventionally described eloquent areas are either deemed inoperable or the extent of resection may be restricted due to the concern of worsening neurological deficit. As gliomas naturally migrate along white matter tracts, these challenges are not uncommon occurrences and resection to achieve increased survival while maintaining or improving quality of life is key [1,16,64–66]. New or worsening post-operative deficits should be kept to a minimum as the negative impact of postoperative neurological deficit on survival has been demonstrated [67].

4.1. Image Guided Resection vs Functional Guided Resection

With the constant advances in diagnostic imaging, the use of fMRIs and DTI sequencing are playing an increasingly critical role in tumor characterization and surgical planning. Despite imaging advances, the complete picture of the extent of tumor and function of the infiltrated neural

parenchyma remains elusive. Studies have investigated, with particular interest to high-grade gliomas, intra-operative adjuncts to assist with tumor resection with the use of 5-aminolevulinic acid (5-ALA) fluorescence [68–70]. 5-ALA is a non-toxic biochemical precursor to hemoglobin that ultimately causes an increase in fluorescent porphyrins in high-grade gliomas. Stummer et al. [70] showed clinical benefit when using 5-ALA, by demonstrating increased tumor resection and improved progression-free survival. The limitation to this technique, however, is noted with this technique's inability to functionally map the operative region. As a result, intraoperative functional mapping, by means of intraoperative electrostimulation (IE) remains an indispensable tool in the surgeon's armamentarium when attempting to achieve the maximal safe resection.

Although valuable information is gained from anatomical MRI when evaluating high-grade gliomas, we have reviewed the limitations of FLAIR and T2 sequences in demonstrating the diffuse infiltrative nature of the tumor. As a result of these limitations, DTI has proved useful in defining white matter tracts in and around gliomas. However, the interpretation of these imaging sequences and the development of fiber tracking may be highly variable due to inter-operator variability and imaging technician skill level across institutions. Bello and colleagues [49] demonstrated effective surgical resection could be achieved when using intraoperative neuronavigation with DTI fiber tracking. Duration of surgery was decreased, extent of resection was maximized, and risk of seizures (electrical and clinical) and patient fatigue were decreased. Of note, however, surgery for all patients in this study was with the aid of ICM and intraoperative subcortical mapping (ISM). Correlation between DTI fiber tracts and ISM was investigated and results were described [49]. Peritumoral edema and tumor infiltration describe regions of increased diffusivity and therefore decreased FA. Using intraoperative 1.5T MRI with DTI-based FT, Nimsky et al. [5] demonstrated the effect of brain shift on white matter tracts status post tumor resection. In an illustrative case, after resection of a WHO grade III glioma, previously suspected disruptions of the anterior corpus callosum, regained normal configuration. No predictive measures were described for intra-operative brain shift [5].

Intraoperative ultrasonography (US) and neuronavigation (Nn) with these supportive imaging sequences have also been useful techniques for real-time image guidance and anatomic orientation. These imaging studies however, cannot account for microscopic cellular invasion of tumor cells existing beyond the "borders" of the solid tumor. Moreover, significant inter-individual anatomic and functional variability exists, further suggesting anatomic mapping is insufficient [39]. Thus, a high-grade glioma distal from areas of known eloquence, where a generous resection margin is without significant consequence, which is simply removed with image guidance, does not maximize the full potential of resection extent if a supratotal resection is the goal. Consequently, this may negatively impact a patient in terms of OS when the difference of QoL would have been non-existent or negligible. In patients presenting with gliomas in conventionally eloquent areas, a declaration of inoperability based on imaging alone without attempts at ICM/ISM is not advisable. Additionally, a limited extent of resection due to presumed crucial cortical and subcortical structures, which may be

erroneously grossly over-estimated by imaging studies may have negative consequences on patient OS.

4.2. *Functional Guided: Awake Craniotomies for GBM Resection*

Awake craniotomies and IE mapping are superior methods of functionally plotting eloquent areas compared to the previously discussed imaging modalities [49,64,71]. IE has been proven to be safe, inexpensive, with high reliability and re-producible in mapping cortical and subcortical structures in real-time [72,73]. One obvious disadvantage lies in the necessity for open operative intervention to gather functional information. IE requires a skilled dedicated neurology, psychology, and intraoperative monitoring team and adds time to the surgical procedure. In addition, young children, patients with receptive language deficits and those with anxiety are not optimal candidates for awake IE techniques.

Glioma resection with the assistance of IE for functional guidance has been shown to decrease the number of “inoperable” tumors and improve patient outcomes [1,39,66]. Published studies do elucidate increase in the extent of resection, improvement of epileptic seizure control, and improvement of neuropsychological testing status post IE assisted glioma resection [30,49,74]. All of which, consequently has a positive effect on OS and QOL. Permanent neurological deficits prove to be fewer in glioma resections with awake IE assistance [75–77]. In a study by Vassal and colleagues [2], EOR was approximately 93% with all new language deficit post operatively resolved after 30 days.

4.3. *Connectivity Preservation Surgery: Dominant hemisphere & Language Pathways*

Language areas demonstrated by non-invasive studies have been unreliable at best, especially with the high variability in cortical mapping using fMRI in the presence of GBM [2,22,24]. Lateralization of language of dominance can be helpful and with the adjunct of DTI for subcortical mapping, pre-operative evaluation, disruption and displacement of ventral and dorsal language pathways, pre-operative MR imaging still holds important value for the surgeon and patient [2,5].

ICM and ISM have shown strong promise in evaluating real-time functionality in addition to pre-operative and intra-operative imaging [2,5,22,30,49]. With the FA thresholds, described by Stadlbauer and colleagues [22], Vassal et al. [2] studied 10 consecutive patients with gliomas in adjacent to language areas. Six patients had mild aphasia at presentation. Using direct electrical stimulation (DES) to specific areas of tracked fibers, a strong correlation between DTI and clinical results was demonstrated. AF induced phonemic paraphasias, IFOF induced semantic paraphasias, PmF induced dysarthria, and SubCF induced delayed speech planning, suggesting the utility of analysis of DTI when planning resections adjacent to these critical fiber bundles.

4.4. Connectivity Preservation Surgery: Motor Areas

In a study of eighteen patients with gliomas in proximity to motor structures, the use of awake craniotomies and ISM resulted in no post operative permanent deficits [29]. Another study by Bello et al. [30], DTI with fiber tracking in patients with Rolandic gliomas revealed CST at the posterior boarder of the tumor, most infiltrated and some displaced. ISM was completed and correlated well with the DTI fiber tracking sequences, with exception to one case where ISM documented 3 motor sites inside a subcortical area of the tumor that was not represented on DTI imaging. Eighty-nine percent of patients at 1-month follow up had a normal motor exam. A decrease in electrical and clinical seizure and patient fatigue was noted. It is important to note that if no language mapping is required, both cortical and subcortical motor mapping may be performed with the patient asleep with good results for both EOR and neurological functional preservation (Figure 2).

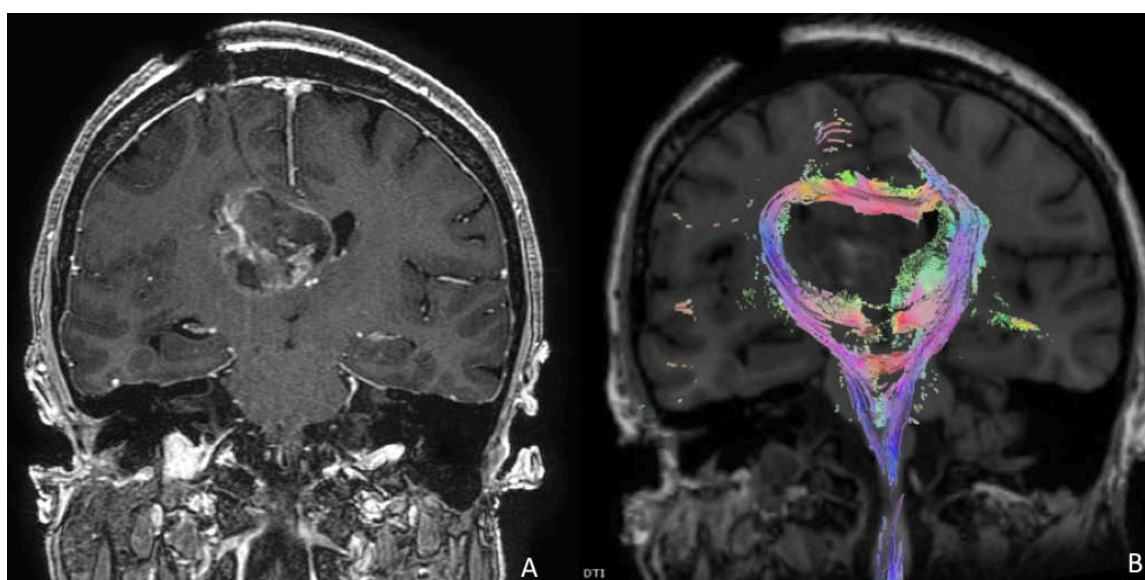


Figure 2. GBM affect on motor tracts. If no language mapping is required, both cortical and subcortical motor mapping may be performed with the patient asleep with good results for both EOR and neurological functional preservation Representation of a right frontal GBM shown on gadolinium enhanced MRI (a) with DTI-FT sequencing showing significant displacement and interruption of descending motor fibers (b). DTI-FT, DTI with fiber tracking; EOR, extent of resection; GBM, glioblastoma multiforme; MRI, magnetic resonance imaging.

4.5. Connectivity Preservation Surgery: Insular/Peri-insular

ICM and ISM has also played a vital role in safe resection of insular and peri-insular gliomas. Insular gliomas represent up to 10% of high-grade gliomas [32]. With the noted insular and peri-insular structures with a wide range of function, neuropsychological evaluation is particularly

important preoperatively in addition to non-invasive functional imaging. With ICM and ISM, a significant decrease in permanent morbidity after insular gliomas resection has been shown [77].

4.6. *Forever Learning, Forever Healing: Neuroplasticity*

In previously inoperable areas, such as motor areas, peri-insular regions, Wenicke's, Area and Broca's Areas (BA 4, 13, 23, 22, 44, 45), understanding of anatomic and functional variability and neuroplasticity in the adult brain, has made room for operative considerations [13,77]. Although plastic potential is high at the cortical level, subcortical plasticity is low, urging for the surgical preservation of axonal connections when possible [11]. According to the principles of neural connectomics, cortical plasticity may rely on the large temporal interconnections within specific spatially oriented subcortical axons [11,78]. Without the appreciation of neuroplasticity in the adult brain, extent of resection in gliomas in regions of anatomic and functional eloquence may also fall shy of full desired potential. An important principal of neuroplasticity is that, as a tumor progresses and impairs normal function, plasticity may allow for that function to move distant to the tumor and later allow for surgical resection of an area infiltrated with tumor which, at an earlier time point, contained vital functional neural tissue.

5. Conclusion

High-grade gliomas present a challenging obstacle when assessing adjacent neuronal pathways. Non-invasive imaging studies are helpful in revealing how these pathways are affected, however present with noted limitations. The demonstrated individual variability of cerebral connectivity in the cortical and subcortical structures of the human brain is complicated by the diffuse infiltrative nature of the gliomas. Cerebral connectivity is disrupted by preferential tumor migration along myelinated fiber tracts. Guiding treatment proves to be complex as gliomas not only distort normal anatomy, but also encourage neural plasticity. The surgeon's ultimate goal is to maximize surgical resection while preserving function. This not only helps minimize post operative morbidity and improves quality of life, but improves overall life expectancy as those with postoperative deficits have decreases in both the length and the quality of their lives. Understanding the role of cerebral connectivity in the preservation of neurological function, how myelinated white matter tracts are exploited by infiltrative gliomas, as well how we can use the cerebral connectome to consider more aggressive surgical resections beyond the apparent tumor border and to deliver therapeutics to the infiltrating tumor cells will be some of the challenges of the next decades in glioma surgery.

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