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The Glioma-Network Interface: A Review of the Relationship Between Glioma Molecular Subtype and Intratumoral Function

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Gliomas are a major cause of morbidity. Direct cortical stimulation mapping offers the ability to identify functional areas within the broader neural network both cortically and subcortically. Since the World Health Organization (WHO) 2016 classification categorized gliomas into molecular subgroups with varied molecular signatures and clinical behavior, it is possible that gliomas may demonstrate rates of functional network integration. We therefore retrospectively reviewed a data registry of 181 patients with dominant hemisphere frontal, parietal, insular, or temporal gliomas. Our goal was to test the hypothesis that WHO glioma histopathology and molecular subtype influences functional language or motor sites identified within the tumor. Intratumoral function as determined by direct cortical and subcortical stimulation mapping was identified at the highest rate in isocitrate dehydrogenase mutant astrocytomas and oligodendrogliomas. Finally, we reviewed the emerging literature exploring the interface between functional neural networks and gliomas. These data shed light on glioma molecular and histological characteristics most commonly associated within intratumoral function.

KEY WORDS: Glioma, High-grade glioma, Low-grade glioma, Intratumoral function, Functional mapping

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The goal of glioma surgery is to balance maximum resection with preservation of functional neural networks. If accomplished, cytoreduction is able to simultaneously increase overall survival while preserving health related quality of life.[1] Cortical and subcortical functional mapping by direct cortical stimulation (DCS) is an established method used to identify safe corridors to approach intrinsic brain tumors.[2] Many gliomas, however, are established within functional neural networks therefore, beyond establishing a function free corridor of entry, DCS is critical to identify intratumoral areas in which functional networks and neoplastic cells are intermixed.[3] Human in Vivo measures of glioma-network integration are often indirect based on biomedical imaging measures however DCS permits the identification of functional areas within the broader neural network.

ABBREVIATIONS: AF, arcuate fasciculus; **CST,** corticospinal tract; **DCS,** direct cortical stimulation; **DTI,** diffusion tensor imaging; **FLAIR,** fluid-attenuated inversion recovery; **IDH,** isocitrate dehydrogenase; **MR,** magnetic resonance; **MRI,** magnetic resonance imaging; **SLF,** superior longitudinal fasciculus; **WT,** wild type; **WHO,** World Health Organization

Interactions between neurons and neoplastic glial cells are complex and multifaceted involving both electrochemical synapses and paracrine signaling.[4-6] For decades, surgeons have known that functional neural tissue can reside within the nidus of a glioma,[7] and recent evidence suggests that neuronal activity promotes glial precursor cell proliferation.[8] Additionally, the World Health Organization (WHO) 2016 classification of tumors of the central nervous system confirmed the importance of genetic mutations, such as isocitrate dehydrogenase (IDH) and 1p/19q, to diagnosis and outcome.[9] Interestingly, genetic diversity has recently been used to categorize astrocytes into diverse subpopulations, and these populations appear to differentially support synaptogenesis and are thought to correspond to unique malignant analogs.[10] However, little is known about how the interface between functional neural networks and glioma cells impacts cognition,

whether tumor histopathology influences network integrity, and how the identification of intratumoral function by DCS may differ by WHO grade and histopathology.

In this manuscript, we review the frequency of intratumoral sensorimotor and language function identified within low- and high-grade gliomas as determined by intraoperative DCS functional mapping. Furthermore, we determine how pathological characteristics of gliomas influence this glioma-network relationship. We also review the emerging literature on the cellular mechanisms of glioma-network interactions and discuss the importance of this relationship to clinical neurosurgery.

METHODS

Patient Selection and Characteristics

After obtaining approval from the the University of California, San Francisco Institutional Review Board (Study Number 19-28 271), the tumor registry was searched for adult patients who underwent awake mapping for tumor resection between 2014 and 2018. All patients consented to be included in the registry at the time of surgery. The operative, pathology, radiological, and discharge reports were retrospectively analyzed from the electronic medical record to acquire patient demographics, mapping outcomes, and tumor grade, and molecular characteristics. All gliomas were graded according to WHO 2016 diagnostic criteria.[9] Of note, Grade II astrocytomas that are found to be IDH wild type (WT) undergo additional molecular characterization and are classified as molecular GBM, thus are not included as Grade II tumors. Intratumoral function was determined by positive cortical and subcortical DCS responses for sensorimotor and language behavioral tasks within the T1 post gadolinium enhancement (WHO IV gliomas) or the fluid-attenuated inversion recovery (FLAIR) tumor boundary (WHO II-III gliomas) on preoperative magnetic resonance imaging (MRI).

Intraoperative Sensorimotor and Language Tasks

Intraoperative awake craniotomy technique including all sensorimotor and language tasks have been previously described in detail.[11-13] Briefly, patients completed a combination of picture naming, counting, sentence completion, and repetition tasks during cortical and subcortical stimulation. A positive DCS site, as established in prior published reports, was defined as a transient behavioral response elicited immediately following stimulation which returned to prestimulation baseline immediately following stimulation confirmed on at least 66% of stimulation trials.[11-13]

Imaging Analyses

Preoperative magnetic resonance (MR) images were reviewed by a board certified neuroradiologist (JEVM) and the proximity of tumor to motor and language tracts to the tumor was recorded. Cortical and subcortical DCS sites were identified as within the confines of glioma based on confirmation by both visual tissue inspection plus neuro-navigation confirmation using either the T1 post gadolinium enhancement (if applicable) or the FLAIR signal hyperintensity. High angular resolution diffusion-weighted imaging tractography was used to map the corticospinal tract (CST) as well as the arcuate fasciculus (AF) and the superior longitudinal fasciculus (SLF) to the preoperative and postcontrast T1 and T2 weighted images.[14,15] Postoperative MR images were reviewed in conjunction with the preoperative MR images to verify resection cavity proximity to the aforementioned tracts relative to the tumor margin. All diffusion tensor imaging (DTI) tractography measures were recorded qualitatively as either (1) remote from the glioma, (2) integrated with tract preserved, (3) integrated with tract invaded, or (4) tract displaced (Figure 1). Quantitative assessments based on distance from the tract to the tumor margin (in millimeter) were performed for both the nonenhancing (T2 hyperintense) and enhancing components of tumor.

Statistical Analysis

Descriptive statistics were used to define the patient cohort, tumor characteristics, treatment details, and neurological outcomes. A Pearson's χ^2 test was performed to compare the effect of glial cell on DCS identified intratumoral function. Student's t test and ANOVA was used to compare means between groups. The level of significance was a $P < .05$ for all analyses. Statistical analysis was performed using JMP Pro 14 (SAS Institute, Cary, North Carolina).

RESULTS

Intratumoral Function

We first set out to determine the rate at which sensorimotor or language function sites were identified within WHO 2016 molecularly defined perisylvian low- and high-grade gliomas. Cortical or subcortical intratumoral function was identified by DCS in 19.3% of all patients who underwent awake craniotomy with intraoperative mapping for glioma resection (Table 1). This includes function identified within 24.7% of the WHO grade II gliomas, 24.0% of the WHO grade III gliomas, and 8.3% of the WHO grade IV gliomas ($P = .02$). (Table 2). We then set out to determine whether glioma molecular characteristics as defined by WHO 2016 classification schema influenced the identification of intratumoral function. Unsurprisingly, there was more intratumoral function identified in IDH-mutated gliomas compared to IDH WT tumors (24.6% vs 10.6%, $P = .03$). When considering all WHO grades, a higher rate of intratumoral function was identified within oligodendrogliomas (14/48, 29.2%) compared to IDH mutated astrocytomas (15/70, 21.4%) and IDH WT astrocytomas (7/61, 10.3%) ($P = .03$) (Table 3). Considering only WHO II gliomas, intratumoral function was identified most frequently within IDH-mutated oligodendrogliomas (10/28, 35.7% oligodendrogliomas compared with IDH-mutated astrocytomas 9/40, 22.5%, $P = .04$). According to established protocol no cortical or subcortical DCS positive language or motor sites were removed during tumor resection.

DTI Tractography Correlates With Intratumoral DCS Sites

In addition to DCS, biomedical imaging methods such as DTI permit indirect assessment of glioma-network dynamics. DTI tractography has proven to be a clinically useful method to identify subcortical tracts of functional significance within and in close proximity to gliomas.[14] For gliomas where the motor

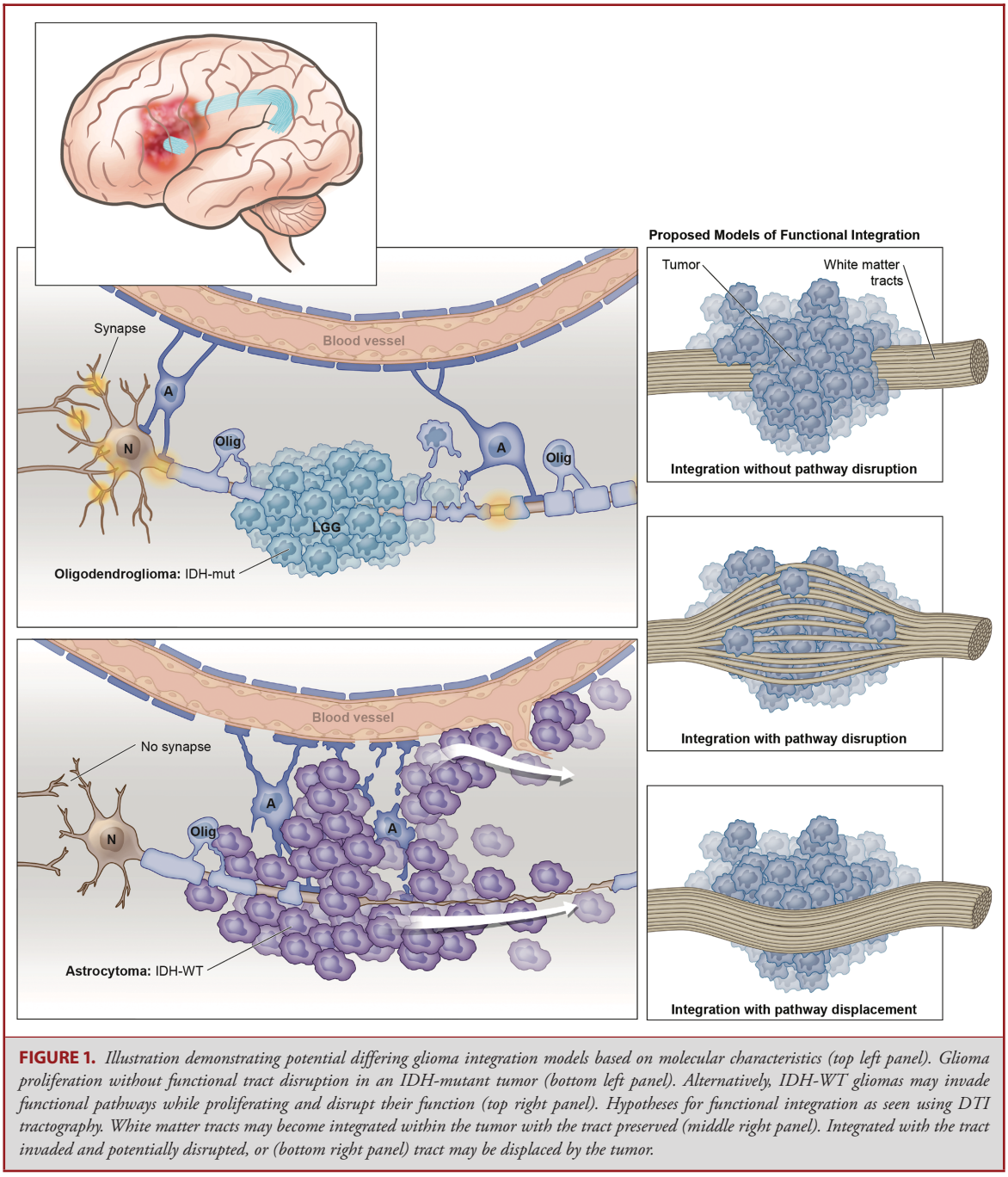

FIGURE 1. *Illustration demonstrating potential differing glioma integration models based on molecular characteristics (top left panel). Glioma proliferation without functional tract disruption in an IDH-mutant tumor (bottom left panel). Alternatively, IDH-WT gliomas may invade functional pathways while proliferating and disrupt their function (top right panel). Hypotheses for functional integration as seen using DTI tractography. White matter tracts may become integrated within the tumor with the tract preserved (middle right panel). Integrated with the tract invaded and potentially disrupted, or (bottom right panel) tract may be displaced by the tumor.*

system was mapped we reviewed proximity to the CST with intratumoral subcortical DCS sites. The proximity to the CST was closer when intraoperative motor DCS sites were identified (mean 0.5 cm when DCS motor sites identified vs 2.7 cm when motor DCS sites were not identified, $P = .13$); however, that did not reach statistical significance. We then sought to understand the relationship between histopathology and CST tract displacement or disruption. CSTs were defined as having the following patterns: (1) remote from the glioma, (2) tract preserved, (3) tract invaded, or (4) tract displaced (Figures 1 and 2). Motor system high- and low-grade gliomas identified as having CST integration with invasion were most likely to have DCS motor sites identified within the tumor (6/8, 75%), compared to gliomas with tract preserved (7/22, 31.8%), gliomas with tract

TABLE 1. Patient Demographics and Tumor Characteristics

Age (mean ± yr)	45.3 ± 13.5 yr
Gender	
Male	108 (57.7%)
Female	79 (42.2%)
Laterality	
Right	50 (26.7%)
Left	137 (73.3%)
Tumor location[a]	
Frontal	83 (44.4%)
Parietal	22 (11.8%)
Insular	39 (20.8%)
Temporal	43 (23.0%)
WHO grade	
II	77 (41.2%)
III	50 (26.7%)
IV	60 (32.1%)
Histological diagnosis	
Astrocytoma	139 (74.3%)
Oligodendroglioma	48 (25.7%)
IDH status	
WT	66 (35.3%)
Mutant	118 (63.1%)
Unknown	3 (1.6%)
New diagnosis	110 (58.8%)
Recurrent disease	77 (41.2%)
Functional language or motor identified within tumor	36/187 (19.3%) 36/187 (19.3%)

[a]Tumors in multiple lobes were classified according to the hemisphere in which the majority of the tumor was located.

TABLE 2. Relationship Between Tumor Grade and Intratumoral Function

Intratumoral function	Yes	No	*P* value
Grade			$P = .02$[b]
II	19/77 (24.7%)	58/77 (753%)	
III	12/50 (24.0%)	38/50 (76.0%)	
IV	5/60 (8.3%)	55/60 (91.7%)	

[b]$P < .05$.

displaced (2/13, 15.4%) and gliomas that were not in direct proximity with the CST tract (1/13, 7.7%) ($P < .001$) (Table 4).

As the motor system functions primarily through single tract processing, language processing relies on broader range network dynamics. Language networks responsible for phonological and articulatory processing are centered on the SLF and AF. Similarly, when considering gliomas involving the perisylvian language network, proximity of the AF or the SLF was closer when DCS language sites were identified (0.39 cm when DCS language sites were identified vs 4.0 cm when DCS language sites were no identified, $P < .001$). Low- and high-grade gliomas with tracts

TABLE 3. Pathological Grade and Mutational Correlates of Intratumoral Function

	Function within tumor	*P* value
All grades		$P = .03$[b]
Oligo	14/48 (29.2%)	
Astro		
IDH-WT	7/68 (10.3%)	
IDH-mut	15/70 (21.4%)	
Grade II only		$P = .04$[b]
Oligo	10/28 (35.7%)	
Astro[a]		
IDH-mut	9/40 (22.5%)	

[a]Grade II astrocytomas that are IDH-WT are treated as molecular GBM and thus are not included as Grade II tumors. Eight tumors fit this classification and there was no intratumoral function identified in any of these lesions.
[b]$P < .05$.

preserved were most likely to have DCS language sites identified within the tumor (12/41, 29.3%), compared to gliomas with tract invasion (1/7, 14.3%), gliomas with tracts displaced (4/37, 10.8%) and gliomas that were not in direct proximity with the AF or SLF (1/33, 3.0%) ($P = .01$).

DISCUSSION

Functional brain mapping is the gold standard for safely resecting low- and high-grade gliomas within eloquent areas.[16] Tumor integration into functional neural networks is the major limitation to achieving maximal extent of resection.[4] Previous work has shown that functional sites, as determined by DCS, within or at the border of gliomas located in the vicinity of eloquent cortex may be found in 18% of Grade II tumors, 17% of Grade III tumors and only 8% of Grade IV tumors.[17] Our findings show very similar rates of intratumoral function, confirming intratumoral function can be identified in tumors regardless of tumor grade. Moreover, using WHO 2016 glioma classification we show for the first time that the molecular and histological characteristics of a glioma, such as IDH status, influence the likelihood of finding cortical or subcortical function within the tumor itself. We hypothesize this finding may be related to the mechanisms by which glioma cells integrate along axonal projections, however integration purely related to cellular rate of growth remains possible (Figure 1).

In prior published reports radiographic evidence suggests differences between functional tract integration of astrocytoma and oligodendrogliomas. For example, apparent diffusion coefficient (ADC) values have been shown to reliably distinguish between oligodendrogliomas and astrocytomas, with higher ADC values associated with astrocytomas, potentially suggesting infiltrating tumor cells that disrupt intact neuronal structure more readily with the astrocytic histology.[18] Here, we similarly found there was a difference between IDH-WT astrocytomas and

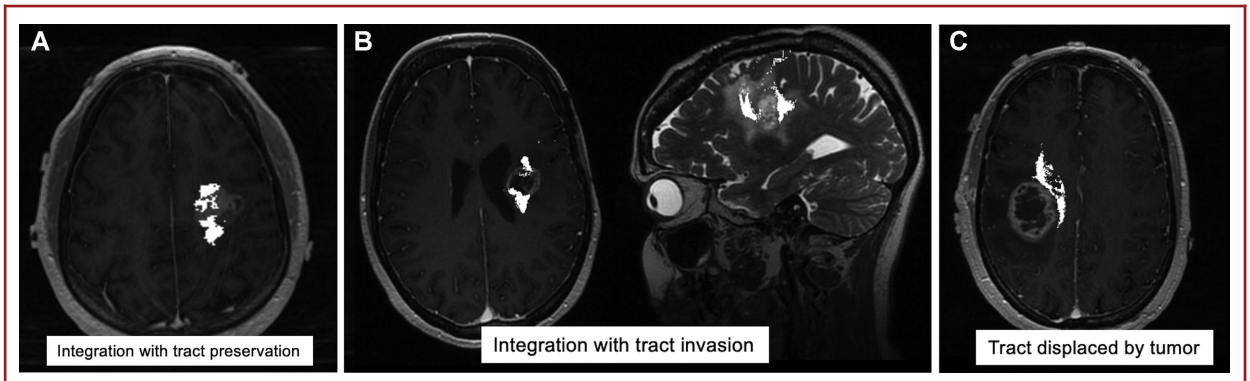

FIGURE 2. *Representative photos showing the different glioma/tract relationships.* **A**, *Axial contrast enhanced MRI showing the CST passing through the tumor with preservation of the tract.* **B**, *Axial contrast enhanced and sagittal FLAIR MRIs showing CST being splayed by the tumor invasion.* **C**, *Axial contrast enhanced MRI showing the CST being displaced and abutted by the tumor.*

TABLE 4. DTI Tractography and Intratumoral Function

Tract	Positive function within tumor	*P* value
CST	16/56 (28.6%)	$P < .001$
Tract invaded	6/8 (75%)	
Tract preserved	7/22 (31.8%)	
Tract displaced	2/13 (15.4%)	
Tract not in direct proximity with tumor	1/13 (7.7%)	
AF/SLF	18/117 (15.4%)	$P = .01$
Tract invaded	1/7 (14.3%)	
Tract preserved	12/41 (29.3%)	
Tract displaced	4/37 (10.8%)	
Tract not in direct proximity with tumor	1/22 (3.0)	

CST = corticospinal tract, AF = arcuate fasciculus, SLF = superior longitudinal fasiculus.
Note: some patients were mapped for both language and motor function.

IDH-mutant astrocytomas/oligodendrogliomas and rates of intratumoral function, suggesting that the molecular make-up, and not just WHO grade is important for determining the glioma-network relationship.

Although these results are unlikely to directly change the operative management for most patients, we hope they are hypothesis generating for neurosurgical oncologists and may be of assistance during preoperative planning and patient counseling. Investigating the relationship between the tumor and the DTI tractography on the preoperative films may help the surgeon predict the likelihood of finding intratumoral function, and can discuss with the patient the benefits and risks of proceeding with an aggressive resection if the setting of positive intratumoral function. Additionally, for patients who undergo biopsy at an outside facility before presenting for definitive resection, if histopathology or 2-HG spectroscopy indicate an IDH-mutant tumor in presumed functional cortex, the surgeon may need to be prepared to be more conservative if the intraoperative mapping confirms eloquent tissue. Future work will be needed to determine if all cortical regions and white matter tracts interact with tumors in a similar manner, as we restricted our investigation to tumors involving the motor or language systems due to the well-established protocols for mapping these functions intraoperatively. Moreover, this manuscript focuses on an anatomical connectivity measure (DTI), but this is likely to simplistic view of the functional connectivity necessary for higher order cognitive functions, and other modalities such as functional MRI may be important to consider during the patient's preoperative assessment to better determine how tumors interact with functional networks.[19]

Cellular Mechanisms Underlying the Glioma-Network Interaction Impact Glioma Invasion and May Contribute to Network Connectivity

An emerging area of scientific investigation, communication between neurons and glioma cells has been shown to influence the malignant phenotype of high-grade gliomas. Similar to healthy glia, glioma cells form an interconnected cellular network connected via gap junctions that enable signaling, often via calcium channels, to occur between neighboring cells.[5] These interconnected networks of gap junctions in gliomas are called tumor microtubes, and they extend into surrounding brain parenchyma contributing to tumor infiltration.[6] These microtubes have a structure similar to excitatory synapses, with glutamate receptors present and nearby neurons containing clusters of neurotransmitter containing vesicles.[20,21] Moreover, neuronal activity has been shown to create changes in calcium ion transient across these tumor-microtube connected networks, and this effect leads to increased invasiveness and glioma growth.[20] Interestingly, the formation of microtubes was dependent on neuronal growth associated protein 43, and oligodendrogliomas

are deficient in this mechanism,[6] suggesting there may be a biochemical and molecular difference between the ability of oligodendrogliomas and astrocytomas to interact with neuronal networks. Importantly, blocking the depolarization of glioma cells that is created by neuronal activity led to increased survival in murine glioma models.[21,22]

The well-established mitogenic effect of neuronal activity on normal neuronal and glial progenitor cells may be used by gliomas to promote proliferation.[22] The importance of this neuronal-glioma relationship is further highlighted by the negative correlation between patient survival and expression levels of the neuronal activity induced soluble factor NLGN3 and the corresponding effectiveness of therapeutic agents that downregulate NLGN3 secretion in preclinical animal models of high grade glioma.[23]

It therefore remains possible that similar mechanisms which promote glioma-neuron interactions to facilitate proliferation may also network dynamics. For example, it is well established that gliomas cause neurological impairments by their ability to alter normal white matter tract and neural network dynamics.[11] However, it remains unclear if neurological impairments result to the greatest degree from (1) altered glioma-neural signaling (ie, altered synaptic processing) or (2) destruction of the white matter tracts (ie, impaired myelin integrity and regulation).

Imaging Correlates of Glioma-Network Proximity

The ability to safety resect tumors in functional areas without causing permanent neurological impairments has been improved by advances in anatomical and functional imaging modalities that aid in tumor localization and tumor-white matter tract relationships. However, there have been multiple studies that have shown that, although there is a correlation between functional sites on preoperative functional imaging and intraoperative DCS, imaging studies alone are not sufficient to predict the exact location of function.[17,24] Intraoperative functional mapping therefore remains necessary to accurately preserve function in patients with intra-axial tumors, such as gliomas.

Prior work has shown that white matter tracts, as determined by DTI tractography, are more commonly found inside the tumor mass for low-grade gliomas compared to high-grade gliomas.[25] Unsurprisingly, we found that proximity to either motor (CST) or language (AF/SLF) pathways was associated with an increased rate of identifying intratumoral function during DCS mapping. Furthermore, when white matter tracts were integrated with the tumor, there was a higher likelihood of identifying function by DCS. Future work is needed to further define the glioma-network relationship at the point of tumor recurrence.

Limitations

One limitation of this paper is our inability to review spatial aspects of glioma-network integration. It is possible that particular cortical or subcortical intratumoral regions may preserve functional network significance longer than other regions presenting a heterogeneous pattern. Moreover, the ability to identity nonlanguage cognitive functional sites of significance using direct stimulation mapping may be variable and therefore not included in this study. Finally, we are unable to account for the rate of tumor growth and the effect growth rates may have on preserved vs invaded white matter tracts. One possibility is that the faster growing, IDH-WT tumors are more likely to disrupt function because of their rate of growth, which does not permit for the normal central nervous system plasticity mechanisms to maintain a functional balance. Future work will be needed to determine the clinical significance of intratumoral function and glioma-network integration on long-term neurological impairment rates, and postoperative recovery. A clear understanding of these processes is critical to the care of patients with gliomas within functional areas.

CONCLUSION

In this manuscript, we review the differing rates of intratumoral function identified by DCS based on glioma molecular subtype and histology. These data suggest that oligodendrogliomas, IDH-mutant astrocytomas, and IDH-WT astrocytomas differentially integrate within functional neural networks. Differing rates of intratumoral function are significant to clinical neurosurgery as both surgical planning and intraoperative treatment goals depend on identifying regions of functional significance.

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