Limitations of functional neuroimaging for patient selection and surgical planning in glioma surgery

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The optimal surgical management of gliomas requires a balance between surgical cytoreduction and preservation of neurological function. Preoperative functional neuroimaging, such as functional MRI (fMRI) and diffusion tensor imaging (DTI), has emerged as a possible tool to inform patient selection and surgical planning. However, evidence that preoperative fMRI or DTI improves extent of resection, limits neurological morbidity, and broadens surgical indications in classically eloquent areas is lacking. In this review, the authors describe facets of functional neuroimaging techniques that may limit their impact on neurosurgical oncology and critically evaluate the evidence supporting fMRI and DTI for patient selection and operative planning in glioma surgery. The authors also propose alternative applications for functional neuroimaging in the care of glioma patients.

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EXTENT of resection remains a critical determinant of oncological outcome for patients with high- and low-grade glioma.^{4,21,48} However, realization of the true benefit of neurosurgical resection requires a balance between surgical cytoreduction and preservation of neurological function. Multiple approaches have emerged in an effort to extend the neurosurgeon's ability to achieve maximal safe resection, including fluorescence guidance,^{50,59} direct electrical stimulation (DES),^{12,14,15,45} intraoperative imaging,^{43,47,52} and preoperative functional imaging, such as functional MRI (fMRI) and diffusion tensor imaging (DTI).^{1,39,58}

Ongoing advances in technology have led to widespread interest in functional neuroimaging for the preoperative planning of glioma surgery.⁵⁵ The motivation behind this interest can be traced directly to the hypothesis that more precise mapping of neurological function will improve extent of resection, mitigate morbidity, and broaden surgical indications for lesions in classically eloquent areas. However, data to support this hypothesis remain scarce.

While fMRI and DTI are excellent didactic and research tools, their clinical utility requires further evidence. The foundations of fMRI and DTI are well established and there are many reviews detailing the potential of func-

tional neuroimaging in brain tumor surgery.^{1,7,10,11,17,39,44} Therefore, the objective of this review is to detail nuances of functional neuroimaging techniques that may limit the ability of these techniques to impact neurosurgical oncology and to critically appraise the evidence supporting fMRI and DTI in glioma surgery for patient selection and operative planning.

Review of fMRI and DTI Clinical Utility

fMRI for Patient Selection and Preoperative Planning

The contrast mechanism of fMRI is the ratio of deoxyhemoglobin to oxyhemoglobin, known as the blood oxygen level-dependent (BOLD) signal. The BOLD signal serves as a proxy for neuronal activity and has been proposed for preoperative assessment of motor and language mapping. The patient is given a series of motor and language tasks to perform and changes in BOLD signal are measured to infer areas of functional activation.⁵⁵ More recently, there has been interest in using resting-state fMRI (rs-fMRI) to perform preoperative mapping. Resting-state fMRI does not require patient participation and can be performed under general anesthesia to detect BOLD signal variation between multiple spatially and functionally distinct resting-state networks.^{28,63}

ABBREVIATIONS BOLD = blood oxygen level-dependent; CBV = cerebral blood volume; DES = direct electrical stimulation; DTI = diffusion tensor imaging; fMRI = functional MRI; rs-fMRI = resting-state fMRI.

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However, integration of fMRI into preoperative planning carries limitations. A key concern is the sensitivity and specificity of the technique, most notably for language mapping. Giussani et al.¹⁹ examined this question by synthesizing data from studies that directly compared DES and fMRI for language localization in patients with brain tumors. The authors identified 9 studies, including 5 that reported sensitivity ranging from 59% to 100% and specificity from 0% to 97%. A limitation of this synthetic study was the underlying heterogeneity of the studies, including surgical indication, magnet strength, and task protocol. Kuchcinski et al.²⁶ remedied these limitations in a cohort of 40 glioma patients with 3-T fMRI. Preoperative fMRI was compared with the results of DES during awake glioma resection site-by-site using a cortical grid. Using DES as the reference, fMRI demonstrated a sensitivity and specificity of 37.1% and 83.4%, respectively. While no statistically significant associations with false-negative fMRI signals were identified, oligodendroglioma subtype, tumor relative cerebral blood volume (CBV) > 1.5, lower cortical CBV, and distance to the tumor were associated with false-positive discrepancies. Similar studies with smaller cohorts found higher sensitivity and specificity for motor mapping (85%–88% and 81%–87%) than language mapping (40%–80% and 74%–84%).^{2,23,37} A recent meta-analysis by Metwali et al. synthesized 8 studies (6 for language, 2 for motor) that directly compared fMRI and DES for brain tumor surgery.³⁴ The mean sensitivity and specificity of fMRI for the detection of functional motor areas were 92% (range 87.5%–100%) and 76% (range 68.1%–87.1%), respectively. The mean sensitivity and specificity of fMRI for the detection of functional language areas were 80% (range 64%–100%) and 71.5% (range 50%–89%), respectively.³⁴ Another recent synthetic study by Weng et al. extended the results of prior meta-analyses by investigating the sensitivity and specificity on both a per-site basis (i.e., each DES stimulation site was considered a separate data point across all patients) and a per-patient basis.⁵⁷ The per-site pooled sensitivity and specificity were 67% (95% CI 51%–80%) and 55% (95% CI 25%–82%), while the per-patient pooled sensitivity and specificity were 44% (95% CI 14%–78%) and 80% (95% CI 54%–93%).⁵⁷

Advocates of rs-fMRI suggest that the resting-state networks elucidated by this technique represent intrinsic functional networks and thus can be relied upon to guide resection. However, evidence to support this hypothesis remains limited. Cochereau et al.⁹ investigated this premise in a cohort of 98 patients with diffuse low-grade glioma. The authors identified a significant association between resting-state BOLD signal fluctuations and functional cortical units as defined by DES. They also observed significant between-patient variability in mapping fidelity and an accuracy rate of approximately 80% in the detection of functionally relevant cortical sites. This finding is consistent with other studies that compared DES and rs-fMRI.^{18,36,42,63}

Taken together, fMRI and rs-fMRI currently appear inadequate for standalone preoperative cortical functional mapping, particularly as it pertains to language localization. A key reason that both fMRI and rs-fMRI may have limited sensitivity and specificity when compared to DES

is that DES provides a more direct assessment of neuronal function while fMRI BOLD signal is inherently a proxy measure.

A key limitation of fMRI is that it does not offer the surgeon the ability to distinguish between compensable areas that can be resected and critical areas that should be surgically preserved. This can result in the underselection of patients for surgery⁴⁹ and may increase the likelihood of partial or subtotal resection due to concern for violation of cortical areas deemed functional by fMRI. Southwell et al. reported a series of 58 glioma patients with unifocal supratentorial disease who underwent glioma resection guided by DES within 6 months of undergoing a brain biopsy of the same lesion at another institution. They achieved an average extent of resection of nearly 90% with no new postoperative neurological deficits.⁴⁹ Their findings suggest that decision-making based solely on preoperative structural or functional imaging is likely inadequate, particularly for cortical lesions. Intraoperative DES, in contrast, offers the ability to accurately identify functional brain regions.^{12,14,15,45} The distinction between fMRI and DES is even more pronounced when considering subcortical functional mapping, where DES has demonstrated clinical utility.^{16,20} Multiple studies have demonstrated a reduction in BOLD sensitivity^{29,33,51} and greater susceptibility to physiological noise^{22,56} when applying fMRI to subcortical mapping.

DTI for Patient Selection and Preoperative Planning

DTI enables visualization of white matter tracts, revealing infiltration and displacement by intracranial lesions in order to hypothetically inform surgical planning.^{1,11,55} Recently, international, multicenter efforts have emerged to systematically validate DTI tractography. Maier-Hein et al.³⁰ described the results of an international tractography challenge involving 96 distinct submissions from 20 research groups using a data set with ground-truth white matter tracts. The findings of this effort lay bare the current limitations of using DTI for surgical planning of gliomas. While the authors found that many tractograms contained at least 90% of the ground-truth tracts, these tractograms included more invalid than valid bundles (i.e., a high false-positive rate). Pujol et al. presented a similar study more directly related to glioma surgery.⁴¹ Eight teams from international institutions reconstructed the corticospinal tract in cases of glioma adjacent to the motor cortex using multiple tractography approaches with results evaluated by neurosurgeons and DTI experts. A key conclusion from this important study was the marked inter-algorithm variability, both in the hemisphere containing the tumor and in the contralateral hemisphere. Given identical data sets, tractograms vary widely based on the reconstruction algorithm.⁴¹ An additional conclusion from this study was relatively poor performance in delineating lateral projections compared to medial projections, a finding replicated by Mandelli et al.^{31,41} A more recent international effort, the 3D Validation of Tractography with Experimental MRI challenge, provided three unique data sets, a physical phantom, and two ex vivo brain specimens to 9 research groups, garnering 176 distinct submissions.⁴⁶ Schilling et al. concluded that the anatomical accuracy of tractography

has not substantively improved despite significant advances in tractography algorithms and methods.⁴⁶

A second set of studies compare preoperative DTI tract reconstructions with intraoperative subcortical stimulation. A direct validation of DTI was performed by Leclercq et al., in which the authors preoperatively reconstructed 4 white matter tracts in 10 glioma patients and evaluated these DTI tractograms against intraoperative subcortical language mapping.²⁷ While positive stimulation sites correlated with DTI tractograms (in 17 of 21 sites), negative tractograms did not rule out the presence of a white matter tract.²⁷ Ostry et al.³⁸ prospectively enrolled 25 patients with solitary supratentorial intracerebral lesions compressing or infiltrating the corticospinal tract. Pre- and intraoperative corticospinal tract tractography was compared with intraoperative subcortical language mapping by DES. They observed that intraoperative image distortion occurred in more than one-third of patients, rendering DTI unusable in those cases. The authors concluded that DES-based subcortical mapping remains superior to DTI. Prospective studies evaluating DTI-based mapping are rare. However, Wu et al.⁶⁰ conducted a prospective study of 328 cerebral gliomas, randomizing patients to either DTI and 3D MRI (n = 118) or routine neuronavigation (n = 120). In the DTI study arm they observed a significantly higher rate of gross-total resection among high-grade glioma patients and higher Karnofsky Performance Scale scores for high- and low-grade glioma patients. However, this study has important limitations. Specifically, the increased gross-total resection rate was observed only for high-grade tumors, the routine neuronavigation in the control arm did not utilize DES, and the study chiefly reported motor function outcomes. Future prospective studies should build on the work of Wu et al. by reporting more comprehensive functional outcomes and using DES-guided resection as the control arm.

Taken together, these studies indicate that DTI is fundamentally a structural imaging modality and less a tool for functional interrogation. Surgical planning driven solely by tractography would be at risk of offering unnecessarily limited resection, as the surgeon may decide to curtail his or her operative plan in an effort to spare white matter tracts. Additionally, it may drive underselection of patients for surgery, as preoperative tractography may falsely convince the surgeon, or the patient, that resection would lead to undue morbidity.

Discussion

Given the methodological limitations discussed above, we maintain that functional neuroimaging in its current form is inadequate for patient selection and surgical planning in glioma surgery. However, there are opportunities to improve and expand the utility of functional neuroimaging. First, it must be noted that the clinical studies discussed above may not be using technologies and algorithms at the bleeding edge of functional neuroimaging. As advances in functional neuroimaging continue to manifest, it remains possible that fMRI and DTI may be better poised to inform patient selection and surgical planning. Second, the integration of multiple noninvasive map-

ping techniques may extend the promise of any individual technique. Future studies combining multiple techniques are likely nascent.

We posit that there may be intrinsic value to these techniques, if applied to the correct use case. Commonly reported outcome measures following glioma surgery account for motor and language function. However, quality of life after glioma resection must be considered broadly^{24,53} and take into account higher-order neurological functions such as mentalizing/theory of mind,^{5,6} attentional processing,^{25,35} and executive function. It is in the elucidation of these higher-order functions that functional neuroimaging is most likely to advance the neurosurgical management of glioma patients. Recent work suggests that rs-fMRI⁶¹ and DTI,⁶² in conjunction with DES, may be able to map the networks and tracts involved in mentalizing tasks. Mandonnet et al. similarly used rs-fMRI and DTI pre- and postoperatively to illustrate that resection of a right temporoparietal glioma disrupted a large-scale network involved in cognitive flexibility.³² This paradigm of pre- and postoperative functional neuroimaging could be extended to develop strategies of monitoring neuroplasticity in glioma surgery, as demonstrated by several longitudinal functional neuroimaging studies.^{3,8,13,54}

We posit that longitudinal functional neuroimaging of glioma patients would have both didactic and clinical utility. Not only would we extend our understanding of network-level neuroplasticity, but we could also use this information to personalize future neurosurgical treatment of individual patients. This could allow for the evolution of iterative, multistage surgical strategies⁴⁰ that move fundamentally closer to the goal of extending neurooncological survival through more complete resection while preserving neurological function.

Conclusions

Technological progress has fundamentally advanced neuroimaging, enabling functional neuroimaging to continue to extend our understanding of the CNS. However, these tools are derived from cohort-level statistical models and are difficult to apply to individual surgical candidates. We agree that advances in algorithms produce functional neuroimaging techniques that may be useful adjuncts to intraoperative DES but remain skeptical that these modalities meaningfully impact glioma surgery. To date, evidence that preoperative DTI or fMRI improves extent of resection, minimizes morbidity, and broadens surgical indications in classically eloquent areas remains scarce. Further work should focus on carefully designed prospective comparative studies and on longitudinal functional neuroimaging studies to better understand, and possibly clinically apply, neuroplasticity in glioma patients.

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Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Administrative/technical/material support: Duffau. Study supervision: Duffau.

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