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Language Paradigm Reliability in fMRI: Implications for Pre-surgical Mapping

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ABSTRACT

Background: Human language function is highly complex, and surgery in eloquent cortical regions carries a high probability of functional deficits following surgery. Functional magnetic resonance imaging (fMRI) has emerged as a non-invasive approach compared to direct cortical stimulation (DCS) for pre-operative language mapping. However, variability in cortical organization and tumor-related distortion challenge its reliability.

Objectives: This prospective cohort study aimed to assess the clinical reliability of fMRI language paradigms in mapping eloquent cortical regions in patients with brain tumors and to examine the association between the language activation distance (LAD)—defined as the distance from the tumor border to functionally active language areas—and its influence on surgical decision-making.

Patients and methods: Twenty-five patients with different brain tumor pathologies underwent pre-operative fMRI using standardized language paradigms. Activation maps were analyzed to identify eloquent language areas, and determine the Language Activation Distance (LAD) between tumor margins and functionally active regions. Surgical decisions and postoperative outcomes were correlated with fMRI findings.

Results: Functional magnetic resonance imaging (fMRI) successfully identified language-related cortical regions in the majority of patients. Language lateralization patterns varied across tumor locations and grades. A shorter LAD was associated with modifications in surgical planning, including extent of resection and the decision for awake craniotomy. fMRI findings demonstrated good concordance with intraoperative mapping where available.

Conclusions: fMRI-based language mapping is a reliable, non-invasive tool for guiding preoperative planning in patients with brain tumors. By providing critical information on hemispheric dominance and proximity of tumors to eloquent cortex, fMRI can guide surgical strategies, optimize tumor resection, and minimize postoperative functional deficits.

Keywords: Functional MRI (fMRI), Language mapping, Language eloquent cortex, LAD, Pre-surgical planning.

INTRODUCTION

Complex functions such as language, vision, sensation, and motor control are indispensable to quality of life. Performing surgery in brain regions associated with language function, particularly within the eloquent cortex, present a particular challenge because tumor invasion often leads to a high risk of functional impairment[1].

In order to provide safe surgery, functional magnetic resonance imaging (FMRI) can aid in mapping the anatomical as well as functional brain landmarks. However, identifying language-related regions is challenging in the absence of dependable cortical surface markers[2, 3].

Moreover, determining the impact of tumor expansion and invasion in regions bordered by normal tissue is frequently complicated by substantial individual differences and additional influence [4].

Direct cortical stimulation (DCS) during awake craniotomy is the clinical gold standard for mapping eloquent language areas. Despite its high spatial and temporal resolution, DCS is invasive, time-intensive, and dependent on awake craniotomy for validation[5, 6].

In the context of language function, fMRI is now widely applied as a preoperative brain mapping method [7]. Mapping and identifying brain regions associated with speech and language expression represent the principal clinical applications of fMRI in preoperative surgical planning. The chief purpose of surgery is the resection of tumors while preserving as much healthy cortex in areas involved in language, visual, sensory, and motor abilities as feasible [8].

Results obtained from preoperative fMRI mapping can be used to localize language-related activity and analyze the influence of hemispheric lateralization [9].

This method has the potential to precisely delineate ipsilateral functional cortical regions relative to the tumor that needs to be removed, which has important implications for guided neuro-surgery [10].

The purpose of this study was to determine the clinical value of fMRI language paradigms in localizing brain regions associated with language-related function, in brain tumor patients through assessment of the distance between the tumor border and functionally active language regions (language activation distance) and its impact on surgical decision-making.

PATIENTS AND METHODS

A total of twenty-five patients with various pathological types of brain tumors were included in this prospective cohort study, conducted between February 2024 and March 2025. All patients were referred from the Department of Neurosurgery to the Department of Radiodiagnosis, Tanta University. Comprehensive neurological examinations were performed in the Department of Neurosurgery prior to imaging.

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Inclusion criteria:

Adult patients presenting with radiological findings consistent with resectable brain tumors were included.

Eligible participants were right-handed, as determined by verbal self-report, with confirmed left-sided resectable primary brain neoplasms involving the frontal, temporal, or parietal lobe.

The study focused on right-handed patients, as more than 95% of this population has language functions localized to the left hemisphere.

Inclusion was limited to patients with tumors in the left hemisphere, aligning with the hemisphere dominant for language.

Exclusion criteria: Patients were excluded if they had irresectable brain tumors, claustrophobia, or contraindications to MRI, including MR-incompatible metallic devices, cochlear implants, or cardiac pacemakers.

Imaging study:

All cases underwent MRI on a 1.5 Tesla MRI unit (GE Sigma Explorer). Metallic objects were removed, and imaging was performed with patients in the supine, head-first position. Imaging parameters included a slice thickness of 4 mm, matrix 256 × 256, and field of view 220–240 mm.

A high-resolution 3D T1-weighted spoiled gradient-echo sequence was performed for anatomical reference using the following settings: TR 9.7 ms, TE 4.6 ms, TI 400 ms, flip angle 35°, 124 slices of 0.8 mm thickness, matrix 208 × 170, FOV 23 cm, yielding 260 contiguous sections with an acquisition time of 5.25 minutes. Contrast material was administered in selected cases.

For functional MRI: It was performed using a T2*-weighted EPI sequence (TR/TE 2540/45 ms; matrix 64 × 64; FOV 224 mm; slice 5 mm; 50 slices) to measure blood oxygen level–dependent (BOLD) contrast. The total acquisition time was approximately 5 minutes and 12 seconds.

Tasks:

All participants underwent a single 20-minute training session, before functional imaging, to familiarize them with the paradigm. The fMRI was performed using a block design with alternating task and rest periods of 30 seconds each, comprising a total of 10 task blocks.

Broca's area activation was assessed with two word-generation paradigms: antonym generation and letter-based word generation, each alternating with 30-second rest blocks, while, localization of Wernicke's area was achieved with alternating 30-second blocks of text reading and symbol reading. Patients silently read paragraphs during text blocks, while in symbol blocks they scanned for specified symbols.

FMRI data processing and analysis:

All fMRI data were processed on a GE workstation (ADW 4.7).

Tumor volume for each patient was measured using 3D T1-weighted images.T2*-weighted functional images were realigned and block-timing corrected in accordance with the paradigm, then co-registered and fused with high-resolution 3D T1-weighted anatomical images.

Statistical parametric mapping was carried out using the general linear model (GLM). Task ("active") and baseline ("rest") conditions were modeled with a boxcar function convolved with the hemodynamic response function. A t-contrast was subsequently calculated to compare activation during task versus rest conditions.

Lesion-Activation distance Measurement:

Threshold task-based fMRI activation maps were produced for clinical application. These maps were later reviewed to determine the lesion-to-activation distance (LAD) for both Broca's and Wernicke's areas. The shortest distance between the tumor margin and the activation site (either at the edge or center) was measured using PACS.

Primary language center activation was identified on the slice showing maximal activation within the anatomical region of Broca's or Wernicke's area.

Each patient was assigned a unique identification number, and all data were anonymized.

Impact of Assessment on Treatment Planning:

Neurosurgeons completed questionnaires on their treatment plans before and after reviewing functional MR imaging (fMRI) results. Pre-fMRI plans included options ranging from no surgery to biopsy, or craniotomy with/without cortical mapping. The responses were analyzed to assess how fMRI influenced changes in surgical decision-making.

Ethical approval:

Ethical approval was secured from Tanta Faculty of Medicine (Approval Code: 36264PR648/4/24), and informed written consent was obtained from all participants. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics Version 28.0. Descriptive statistics were generated, with categorical variables expressed as frequencies and percentages, and continuous variables summarized as mean ± SD or median with IQR, Group comparisons for continuous data were conducted using the Mann–Whitney U test (two groups) or the Kruskal–Wallis test (more than two groups). The significance of the change in management strategy was assessed using McNemar's test. Associations between categorical clinical variables (e.g., LAD and final surgical approach) were analyzed using Fisher's Exact Test or the X^2-Test, with the Linear-by-Linear Association (Chi-Square for Trend) applied for ordered categories. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

This prospective cohort study was performed from February 2024, to March 2025, after obtaining approval from the institutional ethics committee, and a written informed consent was secured from all participating patients. A total of 25 patients with left-hemispheric brain lesions were enrolled in the study cohort. The population was predominantly males (64%) with a mean age of 46.4 years. Male predominance was consistent with epidemiological trends in primary brain tumors. All patients were right-handed, eliminating handedness as a confounding factor in functional language lateralization, thus strengthening the interpretation of fMRI mapping results **(Table 1)**.

Table (1): Demographic Characteristics of the Study Population (n = 25)

Variable	Mean ± SD / n (%)	p-value
Age (years)	46.4 ± 12.7, Range (30–70)	– = independent t-test
Sex	Male 15 (60%), Female 10 (40%)	0.317 (NS) = X^2-test
Handedness	Right-handed 25 (100%)	–

The study encompassed various pathological types of brain tumors, with gliomas of different grades representing the most common diagnosis. Glioblastoma was the most frequent pathology, representing nearly half (52%) of all cases, followed by low-grade gliomas (28%). Tumor location clustered around classical eloquent areas parietal, temporal, and frontal lobes reinforcing the relevance of fMRI in guiding surgical strategies with predominance at the parietal lobe (40%). Tumor volume showed relatively low variance with mean 41.5 ± 4.6 cm³ allowing more reliable correlations with functional laterality. Pathology showed a statistically significant distribution (p = 0.041), while tumor site and grade differences were not significant **(Table 2).**

Table (2): Tumor Characteristics

Variable	n (%)	P -value
Tumor site		
Left parietal	10 (40%)	0.482 (NS)
Left temporal	9 (36%)	
Left frontal	6 (24%)	
Pathology		
GBM	13 (52%)	
LGG	7 (28%)	
Oligodendroglioma	2 (8%)	0.041*
Astrocytoma	2 (8%)	
DNET	1 (4%)	
Grading		
Low grade	13 (52%)	
High grade	12 (48%)	0.792
Tumor volume	Mean 41.5 ± 4.6 cm³ (range 33–49)*	(NS)

LGG=low-grade glioma; GBM=glioblastoma multiform. DNET=Dysembryoplastic Neuroepithelial Tumor.

P-values calculated using Chi-square test for categorical variables (site, pathology, grading), and independent sample t-test for tumor volume. *: significant.

Most patients demonstrated left-hemisphere dominance for language (84%), with highly significant predominance of left-hemispheric language dominance (p < 0.001). That was in line with normal population data. Interestingly, a subset (16%) exhibited bilateral activation, likely reflecting neuroplasticity and functional reorganization secondary to tumor mass effect. These findings highlight the importance of individual pre-operative mapping, as reliance on normative assumptions could underestimate atypical reorganization **(Table 3).**

Table (3): Functional MRI Language Laterality Distribution

Language Laterality	n (%)
Left hemisphere	21 (84%)
Bilateral	4 (16%)
Right hemisphere	0 (0%)

Significant activation was observed in Broca's & Wernicke's areas on fMRI were identified and LAD (Lesion-to-Activation Distance) was measured for 25 patients, LAD was a critical parameter in surgical planning. The majority of patients (72%) had LAD >1 cm, suggesting safer margins for resection. However, 28% had LAD <1 cm or intra tumoral activation, indicating a high surgical risk and the potential for language deficits. This supports LAD as a predictive biomarker for post-operative outcome **(Table 4).**

Table (4): Lesion-to-Activation Distance (LAD) in Relation to Tumor Location

LAD Category	n (%)	p-value
>2 cm	10 (40%)	
1–2 cm	8 (32%)	0.04* = X^2
<1 cm	4 (16%)	
Within tumor	3 (12%)	

*Significant

A statistically significant difference was observed in tumor volume across the different LAD groups (p = 0.005). The data indicate a trend whereby smaller tumors are more frequently located closer to eloquent cortical regions (LAD < 1 cm), whereas larger tumors are more often found at greater distances (LAD > 2 cm). This finding is clinically intuitive, as larger tumors may displace or infiltrate functional cortex, thereby altering the measured distance, or they may arise within less eloquent white matter regions, allowing greater expansion before reaching critical language areas **(Table 5).**

Table (5): Comparison of Tumor Volume by LAD Group

LAD Group	N	Median Volume (IQR) (cm^3)	p-value
< 1 cm	5	36.0 (34.0, 38.0)	0.005 = Kruskal-Wallis Test
1-2 cm	8	41.0 (40.0, 42.0)	
> 2 cm	9	44.0 (42.0, 46.0)	
Within Tumor	3	41.0 (41.0, 44.0)	

The association between LAD and the aggressiveness of the final therapeutic decision was assessed with the Chi-Square test for trend. A statistically significant trend was observed (p = 0.047). As the distance between the lesion and functional cortex increased, the management strategy progressed significantly from conservative management to maximal resection.

All patients with LAD > 2 cm underwent surgery, with the vast majority (88.9%) undergoing resection. In contrast, the cohort with LAD ≤ 2 cm had a higher proportion of biopsies (18.8%) and non-surgical management (12.5%), reflecting a more cautious approach when tumors encroach on eloquent areas. This decision-making gradient underscores the central role of functional anatomy in tailoring surgical risk-taking **(Table 6).**

Table (6): Association between Final Therapeutic Decision and LAD

LAD Category	Final Therapeutic Decision			Total (n)	P-value
	No Surgery	**Biopsy**	**Maximal Resection**		0.047 $=X^2$-Test
LAD ≤ 2 cm	2 (12.5%)	3 (18.8%)	11 (68.8%)	16	
LAD > 2 cm	0 (0.0%)	1 (11.1%)	8 (88.9%)	9	
Total	2	4	19	25	

The introduction of fMRI significantly influenced the neurosurgical therapeutic plan. The proportion of patients planned for "no surgery" decreased markedly from 36% to 8%, while surgical interventions, particularly craniotomy with intraoperative mapping, increased from 40% to 52%. Biopsy and GA craniotomy also showed moderate increases. These changes reflect the decisive role of fMRI in enabling safer, more extensive resections while minimizing risk to eloquent cortex. The rise in biopsy cases post-mapping also demonstrates its role in identifying high-risk surgical candidates. Statistical analysis using McNamara's test revealed a significant difference between pre- and post-fMRI decisions (p = 0.023), confirming that fMRI provided critical information that altered management strategies in a substantial number of patients **(Table 7).**

Table (7): Comparison of therapeutic decision before and after fMRI language mapping

Decision	Before fMRI n (%)	After fMRI n (%)
No surgery	9 (36%)	2 (8%)
Craniotomy with mapping	10 (40%)	13 (52%)
General anesthesia **craniotomy**	5 (20%)	7 (28%)
Biopsy	1 (4%)	3 (12%)
Overall change (No surgery → Surgery)	–	–
McNemar's test p-value		0.023*

*Significant

There was a significant association between age and tumor grade (p = 0.004), with older patients more likely to harbor high-grade tumors, consistent with known oncological patterns. No significant associations were found between sex, tumor characteristics, and language laterality, underscoring the complex and individualized nature of cortical reorganization in brain tumors. The trend between grading and laterality (p = 0.084) may warrant further exploration with larger samples **(Table 8)**.

Table (8): Association between clinical variables and language laterality

Comparison	Test	p-value
Sex vs Language laterality	χ^2 test	0.22
Tumor grading vs Language laterality	χ^2 test	0.084
Tumor volume vs Language laterality	ANOVA	0.37
Age vs Tumor grading	t-test	0.004*

*Significant

CASES

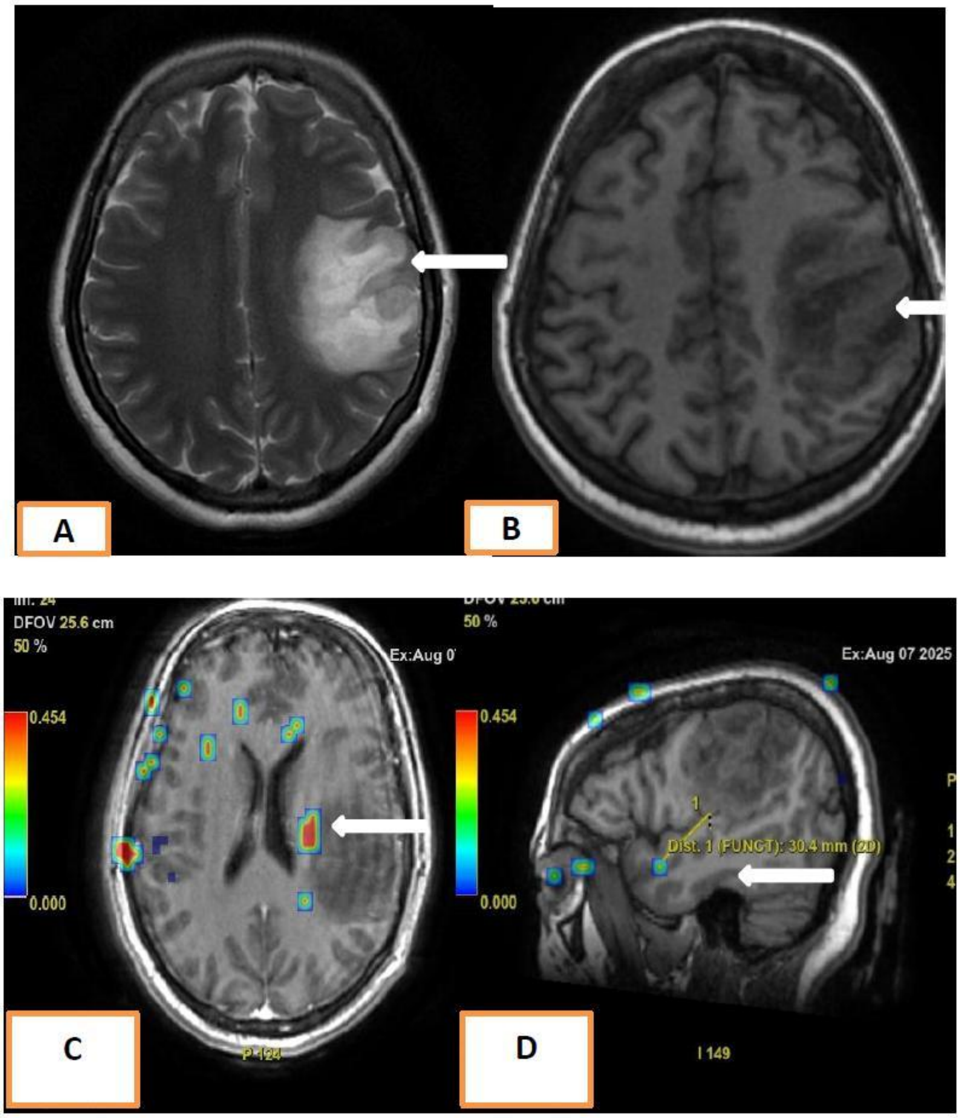

Figure (1): A 45 year's old female patient, with focal epilepsy. Axial T2WI (A) & axial 3DT1 with contrast (B) revealed left parietal cortical and subcortical lesion of diffuse astrocytoma (white arrows) showing high T2 signal with minimal enhancement at post contrast T1 image. Images from presurgical functional MRI (fMRI) for language mapping revealed activation of Wernicke's area (C) seen at superior-medial surface of the lesion, with zero distance in between, while the Broca's area (D) seen away from the lesion with LAD >2 cm from the tumor (white arrows).

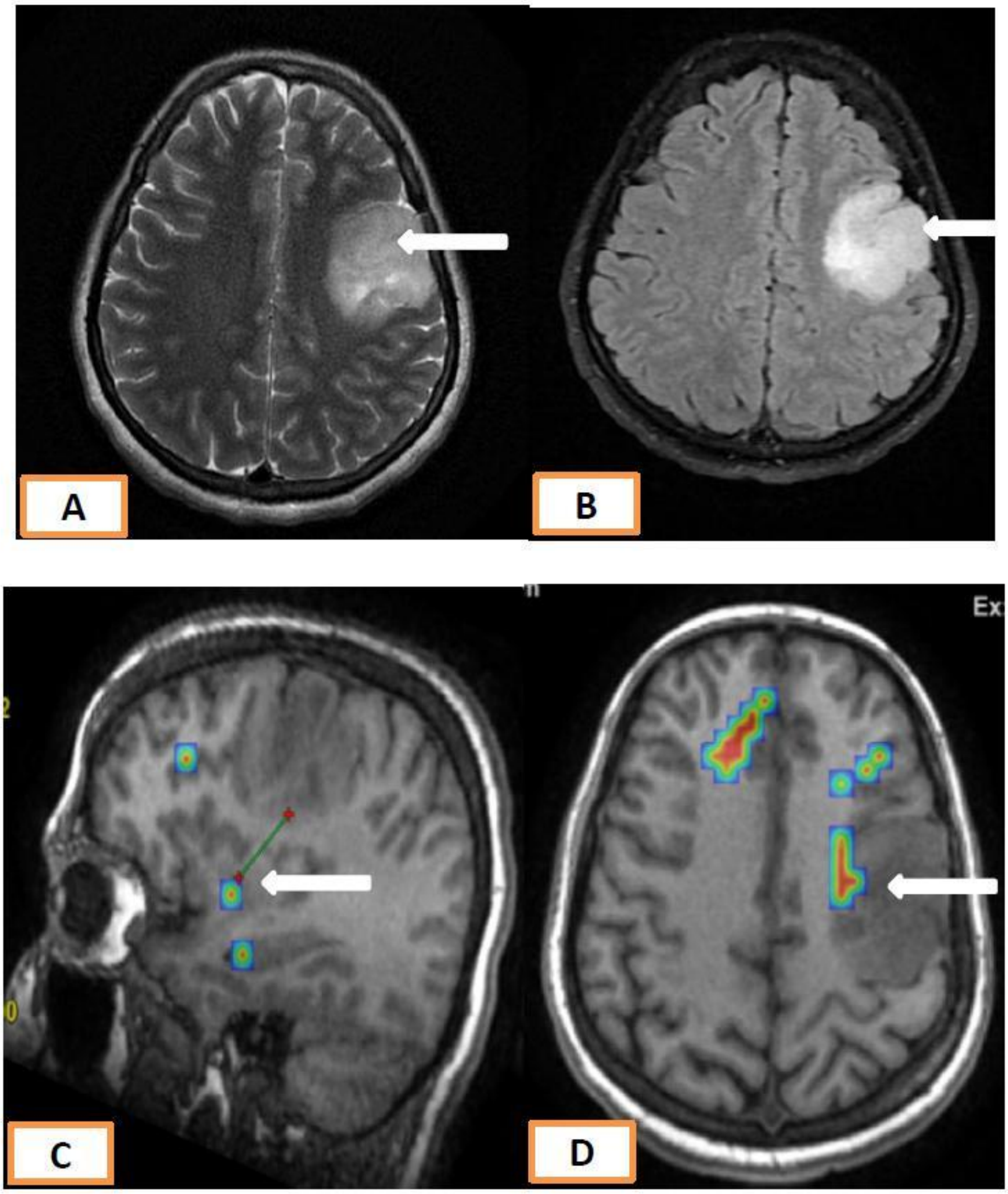

Figure (2): A 36 year's old female patient, with headache and focal convulsions .Axial T2WI (A) & Axial FLAIR (B) revealed left parietal cortical and subcortical lesion (oligodendro-glioma), showing hyper T2WI and FALIR signal. Images from presurgical functional MRI (fMRI) for language mapping were taken. Sagittal (C) and axial (D) views of the language paradigm with activation of Broca's area (C) (white arrow) seen away from the lesion with LAD >2 cm from the tumor, while the Wernicke's area (D) seen at superior surface of the lesion, with zero distance in between.

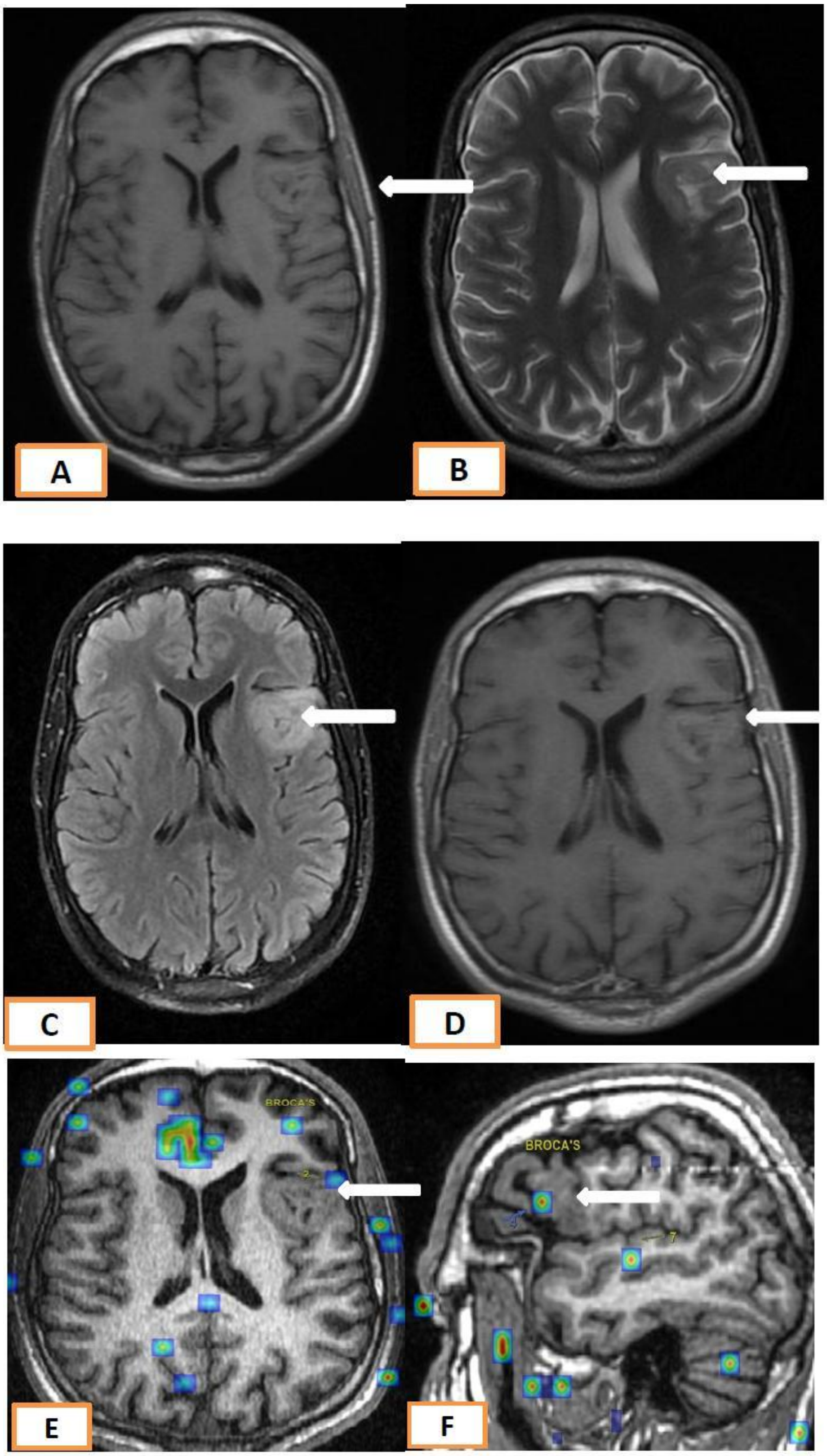

Figure (3): A 20 year's old male patient, with focal epilepsy and aphasia during the attacks .Axial T1WI (A), Axial T2WI (B), Axial FLAIR (C), and AXIAL T1WI with contrast (D) revealed left frontal low grade glioma. Images from presurgical functional MRI (fMRI) for language mapping were taken. Axial (E) and sagittal (F) views of the language paradigm with activation in the inferior frontal gyrus corresponding to the traditional Broca area showing that Broca's area (white arrow) is less than 1 cm from the tumor, which was confirmed intraoperatively.

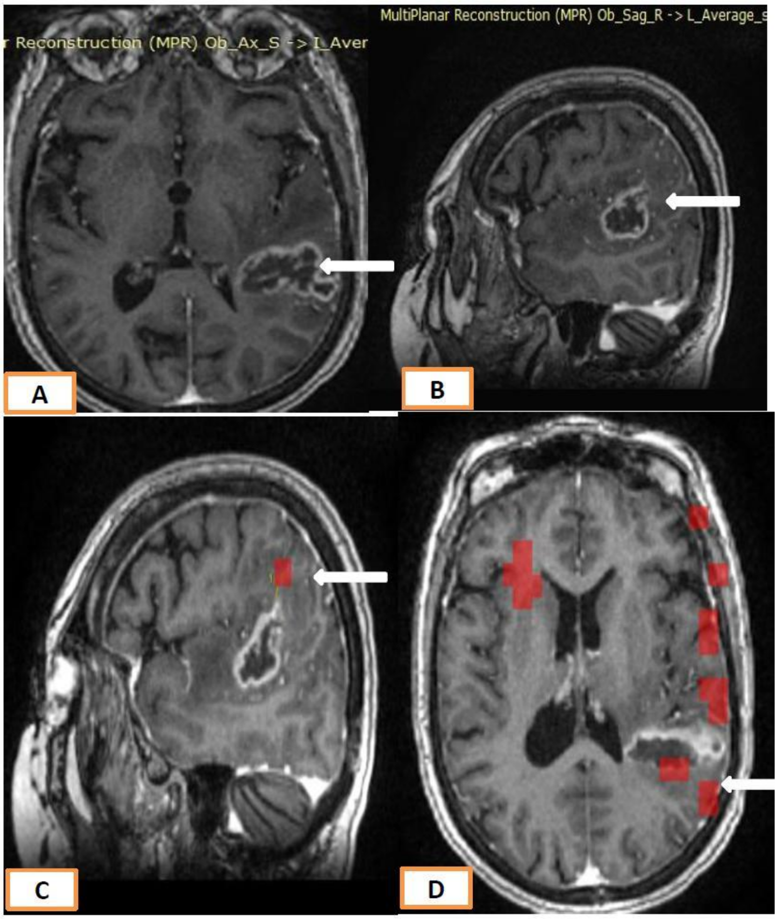

Figure (4): A 56 year's old female patient, complained from aphasia, conventional MRI axial and sagittal T1WI with contrast (A&B) revealed left parietal intra-axial SOL showing heterogeneous mainly marginal contrast enhancement with internal irregular non enhancing area, it is seen surrounded by moderate vasogenic edema, both exerts mass effect in the form of effacement of the overlying cortical sulci and compression of occipital horn of the left lateral ventricle …. GBM (white arrows). Functional MRI Language paradigm revealed that the broca's area (C) seen away from the tumor LAD > 2 cm (white arrow), while the wernike's area seen with in the tumor mass (D) (white arrow).

DISCUSSION

Although fMRI is widely used for preoperative tumor planning, evidence linking it to surgical outcomes remains limited. Although fMRI has been associated with reduced postoperative functional deficits and slightly higher Karnofsky performance scores, most studies incorporate additional mapping techniques—such as awake mapping with direct cortical stimulation (DCS), intraoperative MRI, and diffusion tensor imaging (DTI), making it difficult to isolate the independent effects of fMRI[11].

Brain tumor surgery seeks to maximize tumor resection while minimizing the risk of permanent deficits, as aggressive resection near critical functional areas can negatively affect both quality of life and overall survival. To optimize outcomes, neurosurgical techniques including preoperative functional neuroimaging, fluorescent dyes, neuronavigation intraoperative MRI, as well as intraoperative stimulation mapping, are routinely employed enabling precise localization of both tumors and critical brain regions [11].

Mapping of the eloquent cortex prior to surgery, in clinical settings, is usually invasive. Functional magnetic resonance imaging (fMRI) provides a noninvasive alternative, allowing reliable assessment of brain function using standard MRI scanners. Presurgical mapping is, indeed, the most frequently used clinical application of fMRI [12, 13].

This technique enables clinicians to map brain regions involved in cognition and language, as well as to identify hemispheric dominance for language function. Maintaining language function during surgery is essential for optimizing patient outcomes and preserving quality of life [14].

This study provides compelling evidence that preoperative fMRI language mapping is a pivotal tool that significantly alters the surgical management paradigm for patients with left-hemispheric brain tumors. Our most critical finding—that fMRI data facilitated a shift from conservative management to surgical intervention in 70% of initially inoperable patients—was objectively guided by the Lesion-to-Activation Distance (LAD). The statistically significant trend (p=0.047) whereby increasing LAD predicted a more aggressive surgical strategy affirms a core neurosurgical principle: the use of functional margins is a primary determinant of surgical risk.

This observed clinical behavior finds its rigorous scientific basis in the neuroanatomical principles elucidated by **Wood *et al.*** [15]. Their demonstration that language deficits increase exponentially once the LAD decreases below a critical threshold of 10 mm underscores the exquisite vulnerability of language networks and provides a powerful rationale for our results. This non-linear risk curve explains the surgical team's pronounced caution in cases with a short LAD and their confidence to pursue maximal resection when a sufficient functional margin was present. Thus, our surgical decision-making data empirically reflect this inherent, non-linear biological risk.

It is important to understand our findings in the context of a long-standing debate about fMRI's accuracy. Earlier, pioneering research, such as that conducted by **Roux *et al.*** [16] and **Giussani *et al.*** [17] rightly urged caution, their work concluded that fMRI could not replace the definitive gold standard of intraoperative direct cortical stimulation (DCS) for precise localization, citing concerns over its spatial inaccuracies.

Our research does not challenge this vital rule. Instead, it builds upon it by demonstrating a different, yet equally critical, clinical application for fMRI: preoperative triaging and strategic planning. We prove that fMRI's power lies in answering the critical questions before an operation begins: Should we operate? And if so, what is the safest overall surgical approach?

While DCS remains irreplaceable for defining safe resection margins during surgery, our results demonstrate that preoperative fMRI—specifically the derived LAD metric—is highly effective for deciding whether to offer surgery and which type of approach is most appropriate before the operation.

This role is supported by the work of **Petrella *et al.*** [18] who found that fMRI findings prompted a shift toward a more aggressive treatment strategy in 18 of 19 patients. The technical reliability of fMRI is further corroborated by **Wengenroth *et al.*** [19] who demonstrated that fMRI enabled localization of the motor cortex corresponding to the hand in 99% of cases (76/77), a significantly higher success rate ($p<0.002$) to the analysis of structural MRI alone, even in the presence of tumor-associated anatomical distortion.

This consensus confirms that the primary value of preoperative fMRI lies in providing a macroscopic road-map for safe maximum resection. As highlighted in the systematic review by **Abu Mhanna *et al.*** [20], fMRI is critical for achieving a balancing maximal tumor resection with the protection of brain function increasing surgical precision and maintaining quality of life for patient. Thus, we posit that fMRI and DCS are complementary: fMRI excels in preoperative risk-benefit analysis and surgical trajectory planning, while DCS is essential for final, precise execution.

While the Lesion-to-Activation Distance (LAD) emerged as a primary and statistically significant driver of the surgical strategy, it operates within a broader clinical context. Established factors like tumor grade and tumor volume are undoubtedly critical in the overall management plan, influencing decisions regarding adjuvant therapy, prognosis, and the overall goals of care.

Our finding suggests that for the specific decision of surgical approach and resectability in eloquently located tumors, the anatomical relationship to functional cortex (LAD) may be the immediate and overriding factor that determines feasibility. This refines the surgical question from a purely biological one ("What is it?") to a functional-anatomical one ("Can we safely remove it, regardless of what it is?"). A high-grade tumor may warrant the most aggressive treatment possible, but if it is located within the language cortex (LAD = 0 mm), a radical resection may not be safe or feasible. Conversely, a large, low-grade tumor may be deemed resectable if a sufficient functional margin (LAD > 2 cm) exists.

Therefore, LAD does not replace traditional metrics but rather integrates with them, providing a crucial anatomical risk assessment that directly shapes the surgical tactic. The final decision represents a synthesis of all these factors: the what (grade), the how much (volume), and the where (LAD).

LIMITATIONS

The interpretation of our findings should be interpreted in light of limitations. The sample size, while sufficient to detect large effect sizes, limits power for nuanced sub-group analyses. Finally, the absence of postoperative outcome data prevents us from correlating surgical decisions with their ultimate functional consequences, which is the true measure of efficacy.

CONCLUSION

This study highlights the pivotal role of functional MRI in guiding modern neurosurgical practice. Our findings demonstrate that language activation distance is a reliable predictor of surgical strategy and postoperative outcomes, underscoring its clinical relevance in preoperative planning. Beyond tumor location alone, the proximity of lesions to functional networks emerges as a critical determinant of postoperative language deficits. These results affirm the utility of fMRI as a noninvasive tool for risk assessment, surgical decision-making, and optimizing patient outcomes in brain tumor management.

Based on our findings, we recommend the following for future research:

Ongoing data collection in a larger cohort over an extended period is strongly recommended to validate these findings and to correlate specific LAD thresholds with long-term postoperative neurological outcomes.

Collaborative research across centers employing higher-field MRI scanner (e.g., 3T and above) are recommended to further improve the accuracy and reliability of fMRI data for surgical planning.

Future prospective studies following these recommendations are warranted to refine guidelines for achieving the optimal balance between tumor control and functional preservation.

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