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Enhancing brain tumor surgery precision with multimodal connectome imaging: Structural and functional connectivity in language-dominant areas

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ABSTRACT

Objectives: Language is a critical aspect of human cognition and function, and its preservation is a priority for neurosurgical interventions in the left frontal operculum. However, identification of language areas can be inconsistent, even with electrical mapping. The use of multimodal structural and functional neuroimaging in conjunction with intraoperative neuromonitoring may augment cortical language area identification to guide the resection of left frontal opercular lesions.

Methods: Structural and functional connectome scans were generated using a machine learning software to reparcellate a validated schema of the Human Connectome Project Multi-Modal Parcellation (HCP-MMP) atlas based on individual structural and functional connectivity identified through anatomic, diffusion, and resting-state functional MRI (rs-fMRI). Structural connectivity imaging was analyzed to determine at-risk parcellations and seed-based analysis of regions of interest (ROIs) was performed to identify functional relationships.

Results: Two patients with left frontal lesions were analyzed, one with a WHO Grade IV gliosarcoma, and the other with an intracerebral abscess. Individual patterns of functional connectivity were identified by functional neuroimaging revealing distinct relationships between language network parcellations. Multimodal, connectome-guided resections with intraoperative neuromonitoring were performed, with both patients demonstrating intact or improved language function relative to baseline at follow-up. Follow-up imaging demonstrated functional reorganization observed between Brodmann areas 44 and 45 and other parcellations of the language network.

Conclusion: Preoperative visualization of structural and functional connectivity of language areas can be incorporated into a multimodal operative approach with intraoperative neuromonitoring to facilitate the preservation of language areas during intracranial neurosurgery. These modalities may also be used to monitor functional recovery.

1. Introduction

The principle of maximal safe resection is central to the neurosurgical management of brain tumors, as reducing tumor burden benefits patient outcomes only when essential functional brain regions are preserved [1]. Traditional neurosurgical planning, therefore, prioritizes avoiding damage to "eloquent" cortical and subcortical regions responsible for key functions, including movement, speech, language, and vision. However, recent advances in structural and functional connectivity research have redefined neurological eloquence, emphasizing the importance of interconnected networks rather than isolated anatomical zones [2,3].

This paradigm shift is particularly relevant for language regions, where the variability in functional localization and distribution poses challenges for both preoperative planning and intraoperative navigation [4]. Language processing depends on a broad, interconnected network

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encompassing both cortical and subcortical regions, extending beyond classical anatomical landmarks like Broca's and Wernicke's regions [5]. As a result, effective surgical planning requires a network-based approach that accounts for individual differences in connectivity to identify and preserve critical pathways [6–8].

With the advent of "connectome" imaging technologies, structural and functional brain connectivity can now be visualized in patient-specific maps [5,9,10]. Diffusion tensor imaging (DTI) and resting-state functional MRI (rs-fMRI) provide complementary insights into the structural integrity and functional dynamics of language networks, as well as their broader role in higher-order functions such as memory, and executive processing [11–15]. This multimodal imaging approach helps reveal essential functional regions while identifying areas affected by pathology-related damage, allowing for more precise surgical planning. Connectome imaging, when combined with neuronavigation and intraoperative neuromonitoring, enables individualized surgical strategies that balance maximal tumor resection, with the preservation of critical language functions [11].

Here, we present two cases of patients with left lateral frontal lobe lesions where structural and functional connectome imaging, integrated with intraoperative neuromonitoring, facilitated safe resections while preserving critical language function. These cases highlight the potential of connectome imaging to enhance neurosurgical workflows and improve outcomes in complex, language-dominant brain regions.

2. Methods

2.1. Personalized connectome construction

Institutional review board exemption and patient consent waivers were sought prior to data collection. Preoperative MRI sequences were obtained consisting of anatomic imaging (3-dimensionsal T1 weighted), diffusion imaging (multi-dimension diffusion weighted imaging), and resting state functional imaging (axial blood oxygen level dependent [BOLD] echo-planar imaging), using a Siemens MAGNETOM Vida 3 T MRI scanner (Siemens Medical Solutions USA Inc., Malvern, PA, USA). High-resolution anatomical imaging was acquired with magnetization-prepared rapid gradient echo (MPRAGE) with the following parameters: field of view (FoV): 256 mm, FoV phase: 100 %, slice thickness: 1.00 mm, slices per slab: 190 (adjusted for full head), TE/TR: shortest, PAT mode: GRAPPA, and acceleration factor PE: 2. Diffusion weighted imaging was obtained with the parameters: FoV: 240 mm, slice thickness 2.00 mm, TE/TR: shortest, slices: 90 (adjusted for full brain), slice gap: 0, base resolution: 120, phase resolution 100 %, PAT mode: GRAPPA, acceleration factor PE: 2, interpolation: off, diffusion mode: MDDW, directions: 30, diffusion scheme: bipolar, and diffusion weightings: 2 (b-values of 0 and 1000). BOLD sequences were acquired with the following parameters: FoV: 240 mm, slice thickness: 3.00 mm, TE: 30 msec, TR: shortest, slices 45, slice gap: 0 %, flip angle: 90°, base resolution: 80, phase resolution 100, and motion correction: off. During resting state imaging patients were instructed to rest quietly with eyes open, clear their minds, and avoid falling asleep.

Connectome scans were generated using the Quicktome Neurological Visualization Software v2.1.0 (Omniscient Neurotechnology Pty Ltd, Haymarket, NSW, Australia). This methodology has been previously described in detail [16–20]. Briefly, MRI sequences, including rs-fMRI were uploaded to the Quicktome platform for analysis in a HIPAA-compliant manner. Image preprocessing was conducted using Quicktome's proprietary cloud-based machine learning algorithm to create a patient-specific structural connectivity atlas using a Human Connectome Project Multi-Modal Parcellation (HCP-MMP)-based schema, reparcellated based on patient-specific structural connectivity.

Whole-brain tractography was generated from multi-directional DWI sequences using several preprocessing steps, including motion correction, skull stripping, gradient distortion correction, eddy current correction, fiber response function measurement using a constrained spherical deconvolution (CSD) algorithm, and deterministic tractography with random seeding to generate streamlines. Resting state images were preprocessed with motion correction to T1 and BOLD sequences using rigid body alignment, skull stripping, slice time correction, global intensity normalization, gradient distortion correction, regressing out high variance confounds, and spatial smoothing. Personalized atlases were constructed by extracting BOLD time series from 360 cortical regions and 17 subcortical structures and registering these to the T1 image. Parcellations were assigned to large-scale brain networks through coordinate-based meta-analyses, assigning HCP-MMP parcellations to coordinates of the activation likelihood estimation (ALE) in Montreal Neurological Institute (MNI) reference space.

Seed-based analysis was performed on functional connectivity imaging to identify connectivity of a region of interest (ROIs) and visualized using quantitative connectivity matrices of adjacent language network parcellations as highlighted by Rolls et al [4]. Anomaly detection was performed to identify anomalous connectivity between parcellations relative to normative matrices generated from healthy adults, and results quantitatively displayed in an anomaly matrix [20, 21].

2.2. Intraoperative neuromonitoring technique

A comprehensive multimodal neuromonitoring approach was employed for both procedures. In Case 1, we utilized somatosensory evoked potentials (SSEP), transcranial motor evoked potentials (TCMEP), electroencephalography (EEG), and dynamic subcortical stimulation. Although subdural electrode placement was not possible for direct cortical MEP, SSEP and EEG were performed according to established guidelines and facility protocols. TCMEPs were conducted following standard procedures, carefully controlling for crossover responses that would indicate excessive stimulation depth. Dynamic subcortical stimulation was implemented using high-frequency short train (HFST) multipulse stimulation, as described by Taniguchi et al [22]. To create a monopolar stimulation device, we used a custom subcortical stimulation device [23,24]. Subcortical stimulation began at 20 mA and was reduced upon positive MEP responses from targeted muscle groups. For asleep motor speech mapping, our institution follows a protocol that targets orofacial muscles (lower face, tongue, vocalis, and cricothyroid) to infer Broca's area, in addition to limb muscles [25].

In Case 2, a multimodal neuromonitoring approach was also used; however, TCMEPs were excluded as the patient was awake. SSEP, EEG, DCMEPs, HFST direct cortical stimulation for motor mapping, and low-frequency long train (LFLT) stimulation at 60 Hz with a 2-pronged bipolar probe was applied for language mapping. Dynamic subcortical stimulation involved the insulated suction technique for identifying motor fibers, alongside continuous LFLT at a static 5 mA to identify subcortical language areas.

3. Results

3.1. Patients

3.1.1. Patient 1

A 35-year-old right-handed Spanish-speaking man presented to the emergency department with acute onset headache, right arm spasticity, word-finding difficulty, and seizure. Imaging revealed a solid-cystic, enhancing lesion in the left frontal operculum (Fig. 1). Structural connectivity analysis indicated that language network regions were located near the tumor boundary (Fig. 2), with area 45 identified at the anterior margin of the tumor. Fiber tracts were observed medially around the inner enhancing capsule, extending posteriorly to the inferior parietal and temporal language areas.

Functional connectivity imaging was performed using seed-based analysis on resting-state fMRI, confirming area 45 as a significant language hub for this patient (Fig. 2). Seeding in area 44 showed limited

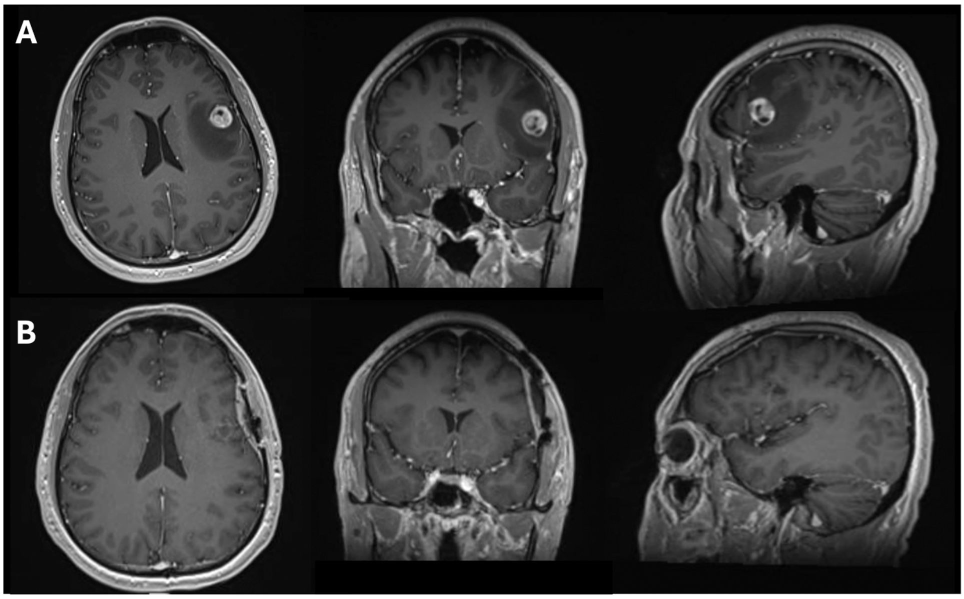

Fig. 1. T1 post-contrast MRI (A) Preoperative axial (left), coronal (middle), and sagittal (right) T1 post-contrast MRI depicting a solid-cystic enhancing left frontal WHO Grade IV gliosarcoma in the left frontal operculum. (B) 3-month postoperative axial (left), coronal (middle), and sagittal (right) T1 post-contrast MRI demonstrating supratotal resection of the left frontal operculum lesion.

connectivity to adjacent regions, including areas 6r, 43, and FOP4. In contrast, seeding in area 45 revealed broader, diffuse connectivity to regions including area 9a, area 55b, area PFm, STSdp, and TE1p, supporting left-sided language dominance and underscoring area 45's critical role in language function for this patient.

The patient underwent a left craniotomy for resection and biopsy of the lesion under general anesthesia, as awake surgery was contraindicated due to the patient's anxiety and limited exam reliability from expressive aphasia. Connectomic imaging was overlaid on standard neuronavigation and complemented by conventional neurophysiologic monitoring, including asleep motor speech monitoring as previously described [11]. Additionally, 5-ALA fluorescence guidance was employed. Using navigation guidance, a region immediately posterior to area 45 (corresponding to area 44) was identified through negative stimulation and selected as the operative approach to the tumor

At the posterior margin of the tumor, subcortical stimulation identified proximity to orofacial motor regions (cricothyroid, tongue, and face) at 12 mA, correlating with structural connectomic imaging. At the anterior and medial margins, navigation was used to identify the arcuate fasciculus and superior longitudinal fasciculus (SLF) fibers, limiting resection in these regions. Surgery continued until 5-ALA fluorescence dissipated, which occurred before encountering these tracts. Pathological analysis confirmed a WHO Grade IV IDH-wildtype gliosarcoma, and postoperative MRI demonstrated a supratotal resection (Fig. 1).

Postoperatively, the patient was discharged home with gradually improving expressive aphasia. One month after surgery, he experienced persistent mild word-finding difficulty but maintained intact receptive language, with his neurological status stable at his preoperative baseline. At four-month follow-up, language demonstrated continued improvement with no new deficits, however, MRI was significant for leptomeningeal disease.

3.1.2. *Patient 2*

A 57-year-old right-handed woman presented with word finding difficulties for 2 days and was found to have a left frontal lesion on MRI (Fig. 3). Preoperative structural connectivity analysis identified language network regions adjacent to the lesion boundaries, including Brodmann areas 44 and 45 along the anterior and superior margins (Fig. 4). Seed-based functional connectivity analysis was conducted using Brodmann areas 44 and 45 as regions of interest (ROIs). Area 44 showed functional correlation with several adjacent regions, including area 45, area 6r, and FOP4. Area 45 demonstrated more extensive connectivity with area 44, area 55b, FOP4, STSdp, and area 6r.

Preoperative neuropsychological testing revealed significant expressive aphasia with preserved receptive language (RBANS Naming: 9/10). The patient's reading ability was within normal limits, though she performed below her baseline in verbal tasks with notable paraphasic errors. Intraoperatively, awake language mapping was performed, revealing intact receptive language with expressive language impairments characterized by paraphasic errors and word-finding difficulty, consistent with her preoperative presentation. Regions of orofacial motor were identified through cortical stimulation posterior to the entry point to the lesion. No regions of complete speech arrest were identified anteriorly. Similar to the previous case, HFST subcortical stimulation identified proximity to motor regions (cricothyroid, face and hand) at 8.5 mA at the posterior margin of the lesion, correlating with structural connectomic imaging. At the anterior and medial margins, navigation was again used to identify the arcuate fasciculus and superior longitudinal fasciculus (SLF) fibers, limiting resection in these regions. However, during dissection at the superior and deep medial tumor margins, using LFLT bipolar stimulation at 5 mA paraphasic errors and speech arrest were observed, which resolved when stimulation in these regions was paused.

Pathological analysis confirmed brain tissue with acute and chronic inflammation, necrosis, and histologic features consistent with abscess. Cultures ultimately identified *Actinomyces meyeri* and *Streptococcus intermedius* as the causative organisms, and the patient was treated with intravenous followed by oral penicillin maintenance therapy.

Postoperatively, the patient initially experienced worsening expressive aphasia, which began to improve by the third postoperative day. At her three-month follow-up, she demonstrated substantial recovery in expressive language, reflected by improved scores on detailed neuropsychological testing (Boston naming test: 60/60; RBANS Naming test: 10/10; RBANS Fluency test: 23 zoo animals in 60 seconds; BDAE Repetition: 10/10; Nonsense words: 5/5; Repeating high-probability phrases: 8/8; Repeating low-probability phrases: 8/8). A repeat structural and functional connectome scan was performed, showing gross preservation of parcellations adjacent to the lesion (Fig. 5). Seed-based

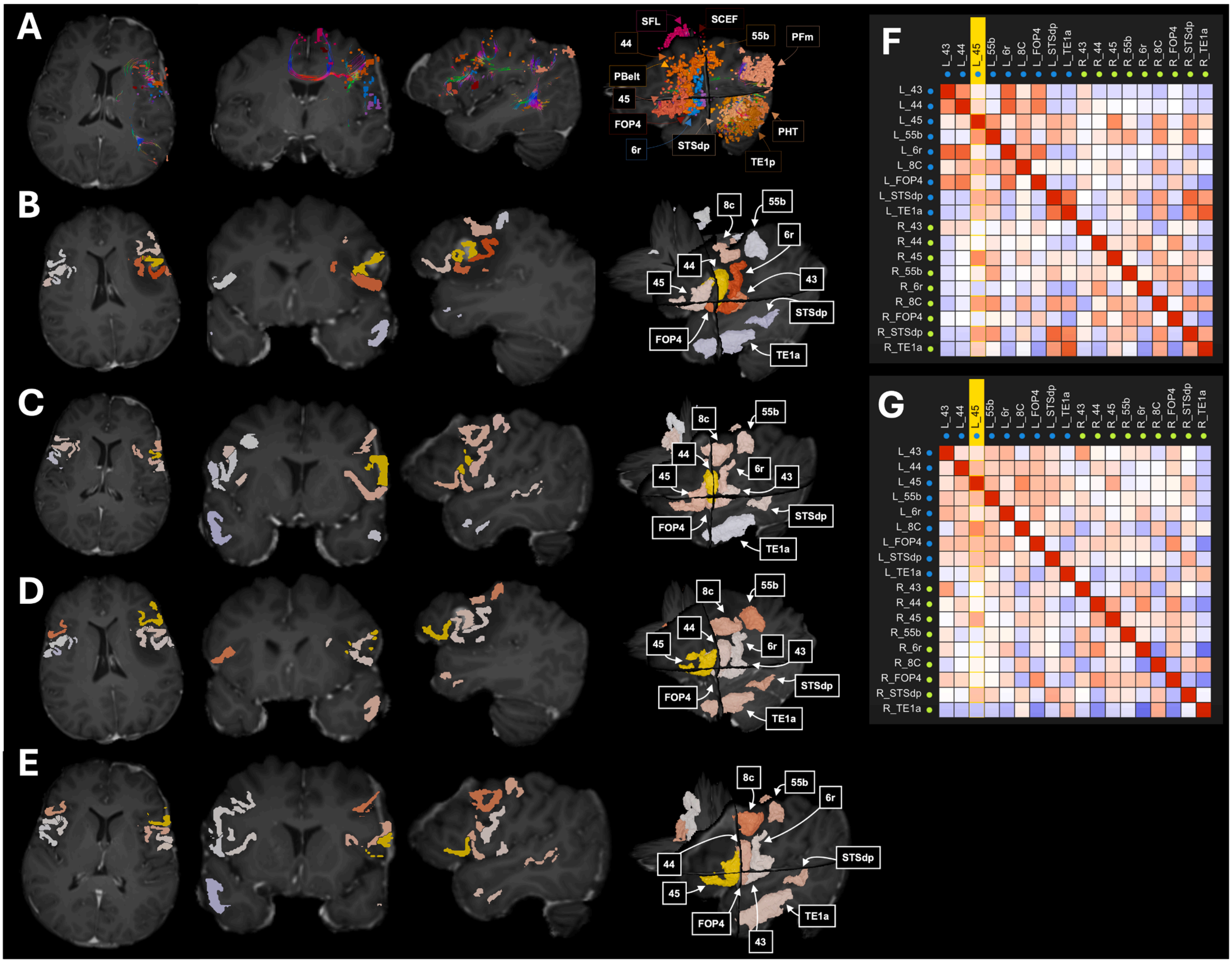

Fig. 2. Structural and functional connectome analysis identifies individual patterns of connectivity and unique changes postoperatively. (A) Preoperative structural connectome scan depicting axial, coronal, and oblique views. Parcellations of the language network adjacent to the tumor are highlighted and labelled, with Brodmann areas 44 and 45 at the anterior tumor border, and area 55b posterosuperiorly. (B) Preoperative seed-based functional connectivity analysis of area 44 with correlation and anomaly matrices identifying areas of functional connectivity to 6r, 43, and FOP4. (C) Postoperative seed-based functional connectivity analysis of area 44 demonstrating changes in correlativity with adjacent language parcellations (D) Preoperative seed-based functional connectivity analysis of area 45 with strong correlations to area 9a, area 55b, area PFm, the STSdp, and TE1p. (E) Postoperative seed-based functional connectivity analysis of area 45 showing unique patterns of correlativity change (F) Preoperative correlation matrix (blue indicates a correlation coefficient of −1, and red a coefficient of +1) between relevant language network parcellations (G) Postoperative correlation matrix demonstrating areas of connectivity (red) and hypoconnectivity (blue) within language network parcellations.

analysis of area 44 demonstrated reduced correlation to areas 6r and FOP4 compared to preoperative imaging. Analysis of area 45 showed continued strong connectivity with STSdp, though connectivity to areas 55b and FOP4 and other components of the language network appeared weakened. Additionally, the right hemisphere demonstrated increased functional correlativity with left hemispheric parcellations post-operatively (Fig. 5).

4. Discussion

This case series illustrates the value of incorporating structural and functional connectome imaging into the planning and execution of tumor resections in language-dominant regions, where precision is essential for balancing maximal resection with functional preservation and evaluating post-operative recovery. By integrating patient-specific connectivity data into neuronavigation, connectome imaging allows neurosurgeons to identify critical language pathways, assess the risk of injury, and tailor surgical approaches to avoid functional disruption. Additionally, postoperative, serial imaging can monitor structural and functional recovery, providing insights into neuroplasticity and informing prognoses. These cases highlight how a multimodal approach, combining connectome-guided imaging, enhances surgical planning in eloquent regions where traditional imaging and neuronavigation lack the specificity to define functional boundaries in highly variable language regions.

In both cases, connectome imaging enabled a more nuanced approach to surgical planning by providing detailed maps of structural and functional connectivity within language networks, specifically around Brodmann areas 44 and 45. This patient-specific mapping facilitated targeted resection strategies that reduced the risk of language deficits—a key consideration in frontal opercular tumors, where individual variability in language localization complicates intraoperative identification [14,26,27]. While advances in navigation have allowed the incorporation of DTI or task-based fMRI studies, to identify anatomical landmarks or structurally important regions, this is the first time structural and functional network visualization has been

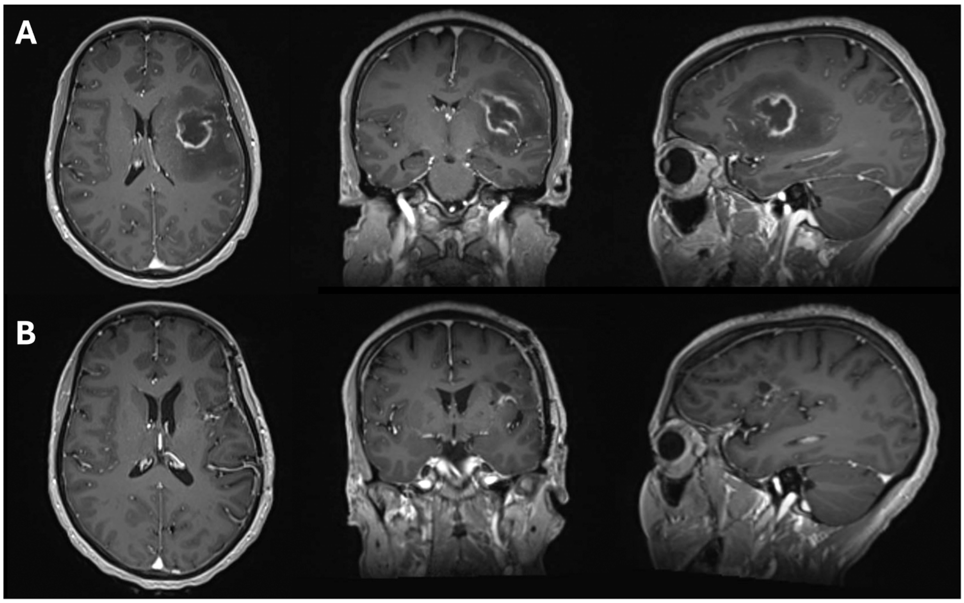

Fig. 3. T1 post-contrast MRI (A) Preoperative axial (left), coronal (middle), and sagittal (right) T1 post-contrast MRI depicting a left frontal lobe abscess. (B) 3-month postoperative axial (left), coronal (middle), and sagittal (right) T1 post-contrast MRI demonstrating resection of the left frontal lesion.

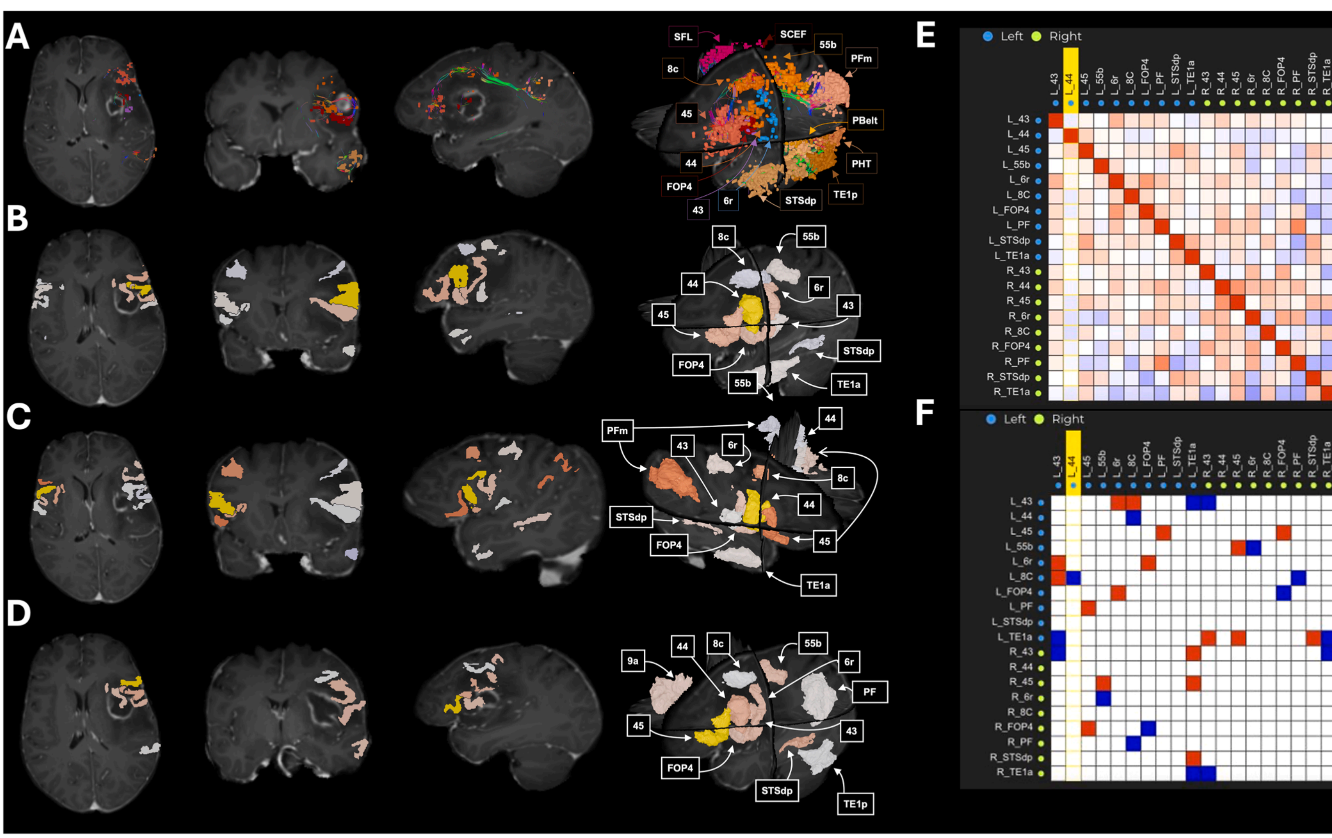

Fig. 4. Preoperative structural and functional connectomics analysis identifies unique patterns of functional connectivity. (A) Preoperative structural connectome scan demonstrates at-risk parcellations of the language network including Brodmann areas 44 and 45 anteriorly and superiorly. (B) Seed-based functional connectivity analysis of area 44 demonstrates functional connectivity with several adjacent parcellations including area 45, 6r, and FOP4. (C) Seed-based functional connectivity analysis of the right area 44 demonstrates limited functional connectivity to ipsilateral and contralateral language parcellations. (D) Seed-based functional connectivity analysis of the left area 45 demonstrates functional connectivity with area 44, area 55b, FOP4, STSdp, and 6r. (E) Correlation matrix (blue indicates a correlation coefficient of −1, and red a coefficient of +1) between relevant language network parcellations. (F) Anomaly matrix demonstrating areas of anomalous connectivity (red) and hypoconnectivity (blue).

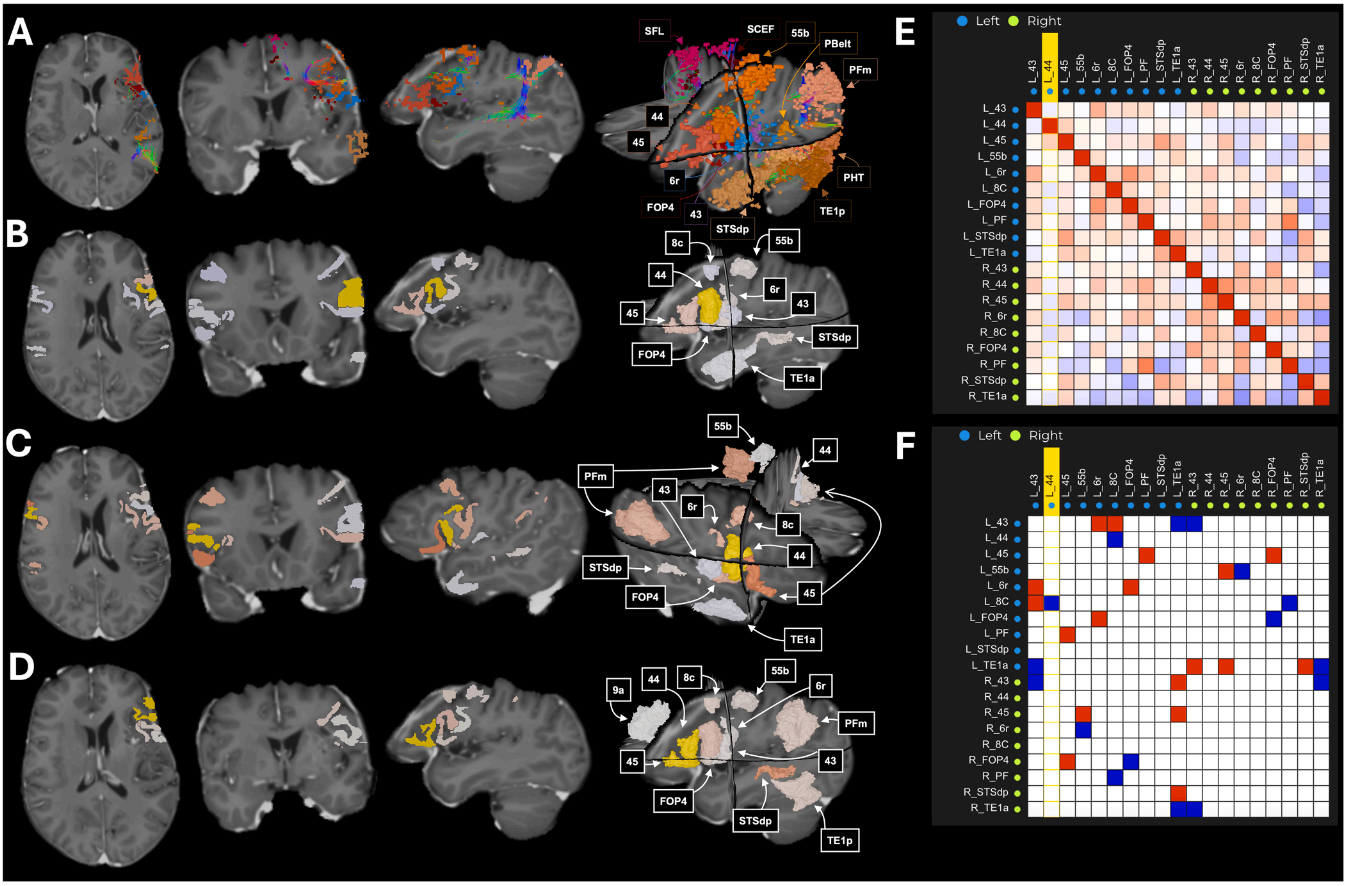

Fig. 5. Postoperative structural and functional connectomics identifies changes in functional connectivity. (A) 3-month postoperative structural connectome scan demonstrating gross preservation of parcellations adjacent to the patient's lesion. (B) Seed-based functional connectivity analysis of area 44 demonstrating reorganized functional connectivity to areas 6r, and FOP4. (C) Seed-based functional connectivity analysis of the right area 44 demonstrating areas of functional correlation and anticorrelation to ipsilateral and contralateral parcellations. (D) Seed-based functional connectivity analysis of area 45 demonstrating robust functional connectivity to STSdp, with weakening of connectivity to area 55b, and FOP4. (E) Correlation matrix (blue indicates a correlation coefficient of -1, and red a coefficient of $+1$) between relevant language network parcellations. (F) Anomaly matrix demonstrating areas of anomalous connectivity (red) and hypo-connectivity (blue).

incorporated into a multimodal approach to avoiding eloquent regions for surgical planning. Specifically, rs-fMRI addresses the functional heterogeneity within language areas, particularly in patients unable to perform task-based studies, making it a more versatile tool. This integration revealed differential functional connectivity patterns between Brodmann areas 44 and 45 in both patients, including connections to regions such as area 55b, STSdp, PFm, and TE1p, providing critical information to the surgical team and allowing resection through less connected areas to minimize functional impact.

Integrating connectome data into neuronavigation allowed for real-time, data-driven adjustments during surgery, minimizing disruption of functional networks. For example, connectivity data informed subcortical stimulation thresholds to identify motor pathways near the posterior tumor margins, ensuring both motor and language networks were preserved. Previous studies suggest that combining connectomic data with intraoperative monitoring yields superior outcomes, as it enables surgeons to target resection more accurately while preserving eloquent networks [28,29]. This approach is particularly valuable in cases where awake craniotomy is contraindicated, offering a safe alternative for identifying and sparing functional regions [4,30].

Postoperative imaging and neuropsychological outcomes in both patients indicated that preserving language network integrity contributed to stable or improving language function, with evidence of functional reorganization. The observed increased bilateral connectivity in patient 2 postoperatively (Fig. 5) suggests compensatory mechanisms, potentially reflecting neuroplasticity in response to structural changes. Research has shown that sparing key hubs within language networks is associated with better recovery trajectories and long-term outcomes in glioma patients [14,26–28,31]. Serial connectomic imaging has the potential to provide further insights into how functional reorganization occurs and may even provide targets for therapeutic interventions in the recovery phase.

Traditional neuronavigation and awake language mapping techniques alone may not adequately capture the full scope of language networks, as these functions are distributed across multiple, interconnected cortical and subcortical regions. Connectome imaging addresses this limitation by offering a network-based perspective, providing a nuanced understanding of language connectivity that traditional imaging lacks [5,32,33]. In these cases, connectome-guided imaging enabled the surgical team to plan resection pathways through areas with less critical or already compromised connectivity, thus mitigating functional impact. This aligns with recent studies suggesting that a network-based approach is instrumental in cases of high-risk language-area tumors, offering advantages in both precision and patient outcomes [28,29,34]. Our findings support the clinical utility of connectome-guided imaging as an adjunct to traditional mapping, with potential applications beyond language networks, to other eloquent brain regions. Future research should focus on standardizing connectome integration in surgical workflows and exploring its role in enhancing patient-specific neurosurgical strategies.

4.1. Limitations

While these cases demonstrate the benefits of connectome imaging, there are limitations to consider. The small sample size and the specific language lateralization and Western language backgrounds of these patients may limit the generalizability of our findings. Moreover, variability in language localization across languages and cultural backgrounds could impact how connectome imaging is applied and interpreted across diverse patient populations. Future studies with larger, more diverse cohorts will be necessary to validate connectome-guided surgical approaches in a wider range of patients. Additionally, technical limitations in connectome imaging warrant further investigation. The proprietary nature of connectome mapping software can introduce variability in the processing and interpretation of connectivity data, potentially affecting reproducibility. Advancements in real-time connectome integration and validation studies that assess connectomic accuracy and consistency across platforms could strengthen the reliability of this approach. Furthermore, research into the cost-effectiveness and practical accessibility of connectome imaging in clinical settings would provide valuable insights into its broader applicability.

5. Conclusion

Connectome-guided imaging provided critical insights for surgical planning and execution, allowing for safe and effective resections in patients with language-dominant lesions. By integrating structural and functional connectivity data, neurosurgeons can achieve a more personalized approach, supporting functional preservation and optimizing patient outcomes in challenging eloquent brain areas. The clinical value of connectome imaging lies in its ability to refine intraoperative decision-making, reduce the risk of functional deficits, and potentially support postoperative neuroplasticity, underscoring its potential as a valuable tool in the neurosurgical management of brain tumors.

CRediT authorship contribution statement

Shah Harshal: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Duehr James:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Silverstein Justin:** Project administration, Writing – original draft, Writing – review & editing. **D'Amico Randy:** Project administration, Writing – original draft, Writing – review & editing. **Abramyan Arevik:** Data curation, Writing – original draft, Writing – review & editing. **Mittelman Laura:** Data curation, Writing – original draft, Writing – review & editing. **Galvez Rosivel:** Writing – original draft, Writing – review & editing. **Winby Taylor:** Project administration, Writing – original draft, Writing – review & editing.

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