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Case Report

# Connectome imaging to facilitate preservation of the frontal aslant tract

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ABSTRACT

Supplementary motor area (SMA) syndrome is characterized by contralateral akinesia and mutism, and frequently occurs following resection of tumors involving the superior frontal gyrus. The frontal aslant tract (FAT), involved in functional connectivity of the supplementary area and other related large-scale brain networks, is implicated in the pathogenesis of, and recovery from, SMA syndrome. However, intraoperative neuromonitoring of the FAT is inconsistent and poorly reproducible, leading to a high rate of postoperative SMA syndrome. We report the cases of two patients harboring lesions of the superior frontal gyrus: one cavernoma and one low grade glioma. Connectome imaging revealed involvement of functional networks implicated in SMA syndrome, as well as displacement of the FAT. A connectome-guided awake craniotomy was performed in both cases, and a combinatorial approach using awake language mapping and connectome-imaging guidance facilitated gross total resection of both patient's lesions without inducing SMA syndrome postoperatively. Functional and structural connectivity imaging through connectomics allows the identification of areas not traditionally considered eloquent, such as the SMA and FAT, and can help facilitate their preservation. Conserving the functional and structural connectivity of broader brain regions that are not traditionally deemed eloquent can improve patient outcomes.

## 1. Introduction

Brain tumor surgery has witnessed significant advancements, primarily aimed at maximizing the extent of resection (EOR) to improve overall survival (OS) [1]. However, resecting brain tumors located in or near eloquent regions carries a significant risk of iatrogenic injury, potentially leading to neurologic deficits that profoundly impact patient quality of life and prognosis [2]. While the overarching surgical goal remains safe maximal resection, accurately assessing the balance between oncological and functional outcomes preoperatively, intraoperatively, and postoperatively continues to be a vital and evolving aspect of glioma surgery.

Traditionally, brain eloquence has been understood in terms of region-specific functions, primarily related to language and motor skills [3]. Recent advances in understanding the brain's functional and anatomic interconnectedness, termed the connectome, have revealed a more diffuse functional integration than previously recognized [4–6]. This has enabled neurosurgeons to redefine 'eloquence', using connectome imaging to guide tumor resection to minimize the cognitive impacts of glioma surgery [4]. While traditional anatomic resection, supported by intraoperative neuromonitoring and image guidance, has enabled surgeries with a high degree of safety and preservation of language and motor skills, it often does not sufficiently preserve higher-order cognitive functions [7,8]. Even with awake craniotomies, mapping regions responsible for complex cognitive and psychomotor functions is challenging [9,10]. The introduction of functional-structural connectomic imaging for identifying networks at risk from tumor pathology and resection allows for customized surgical planning, particularly in lesions within or near traditionally and non-traditionally eloquent areas [11].

Although not a traditionally eloquent region, the supplementary motor area (SMA) is frequently affected by gliomas and other brain lesions [12,13]. Surgical interference within the SMA can lead to SMA syndrome (SMAS), characterized by contralateral akinesia, motor weakness, and significant speech disturbances when the language-dominant hemisphere is affected [13,14]. Although typically

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self-resolving, SMAS can profoundly impact patients' quality of life with deficits that may last from weeks to months, affecting daily activities and delaying rehabilitation [13]. The frontal aslant tract (FAT), a white matter pathway that connects the SMA and pre-SMA to the inferior frontal gyrus and anterior insula, is involved with initiating and controlling speech and movement [13]. Damage to the FAT has been implicated in the development of SMAS, and its preservation is thought to facilitate recovery [12,15]. However, intraoperative neuromonitoring of the FAT is less reliable compared to motor, or speech mapping, complicating the ability to preserve this non-canonically eloquent pathway [13]. As such, SMAS occurs in about 60 % of surgeries involving superior frontal gyrus (SFG) tumors [13].

Despite the importance of the FAT, there is a lack of effective intraoperative mapping techniques to reliably identify and preserve this tract. The integration of connectomic imaging into surgical planning presents a potential solution, but its practical application in preserving the FAT during tumor resection has been underreported in the literature. By providing a detailed map of individual patients' neural networks, connectomic imaging allows for the identification of critical but non-traditionally eloquent pathways like the FAT [15]. This methodology not only facilitates the preservation of these networks during resection but also lays the foundation for future studies aiming to utilize connectomics in preserving other non-canonical networks.

Here we report two illustrative cases highlighting the practical application of connectomic imaging in preserving the FAT during tumor resection near the SMA and highlight the use of connectomics-guided strategies in surgical planning.

### 1.1. Case reports

Case 1: Patient 1 was a 31-year-old, right-handed, English-speaking woman who presented with increasing sporadic episodes of vertigo and disorientation over a year, concerning epileptiform activity. Imaging revealed a non-enhancing mass arising within the left superior frontal gyrus just anterior to the premotor gyrus (Fig. 1), later found to be an IDH-mutant WHO Grade II astrocytoma. Preoperative neuropsychological testing demonstrated evidence of mild frontal subcortical inefficiencies. On connectome imaging (Fig. 2), the lesion was near parcellations of the language network including the superior frontal language area (SFL), part of the supplementary motor regions, central executive network (CEN), and sensorimotor network, with the FAT compressed medially by the tumor.

The patient underwent an awake tumor resection with language and motor mapping. Preoperative connectome imaging was integrated into the neuronavigation software (Fig. 3). Intraoperatively, a 1 × 8 strip electrode was placed in the subdural space, and motor and sensory cortices were identified using the phase reversal technique. Language evaluation included open conversation in English and standardized testing including auditory comprehension and naming. Negative language and motor mapping in conjunction with connectome-integrated neuronavigation was used to plan the site of corticectomy. Cortical language mapping was performed using the Penfield method, consisting of 60 Hz low-frequency stimulation at 5 mA for 5-second intervals using a handheld bipolar probe [16]. Subcortical stimulation utilized a combination of dynamic Penfield stimulation at a continuous current of 5 mA for the anterior and medial portions of the FAT, as based on navigation guidance, and dynamic monopolar continuous Taniguchi stimulation (high-frequency, short-train, multipulse stimulation) for the posterior, deep, and lateral aspects along the corticospinal tract (CST) as denoted on connectome imaging. The awake craniotomy facilitated the precise delineation of regions associated with speech and language, and neuronavigation integrated with connectome imaging guided stimulation and ensured the anatomical preservation of at-risk connectome networks.

Postoperatively, gross total resection was achieved, and the patient recovered well with intact sensory-motor and language functions on postoperative day (POD) 1. Neuropsychological evaluation performed 5 months postoperatively demonstrated stable frontal-subcortical inefficiencies to baseline, with a subtle decline in processing speed. Her Karnofsky Performance Status (KPS) was 100 and her Eastern Cooperative Oncology Group (ECOG) Performance Status was 0.

Case 2: Patient 2 was a 21-year-old, right-handed, bilingual woman

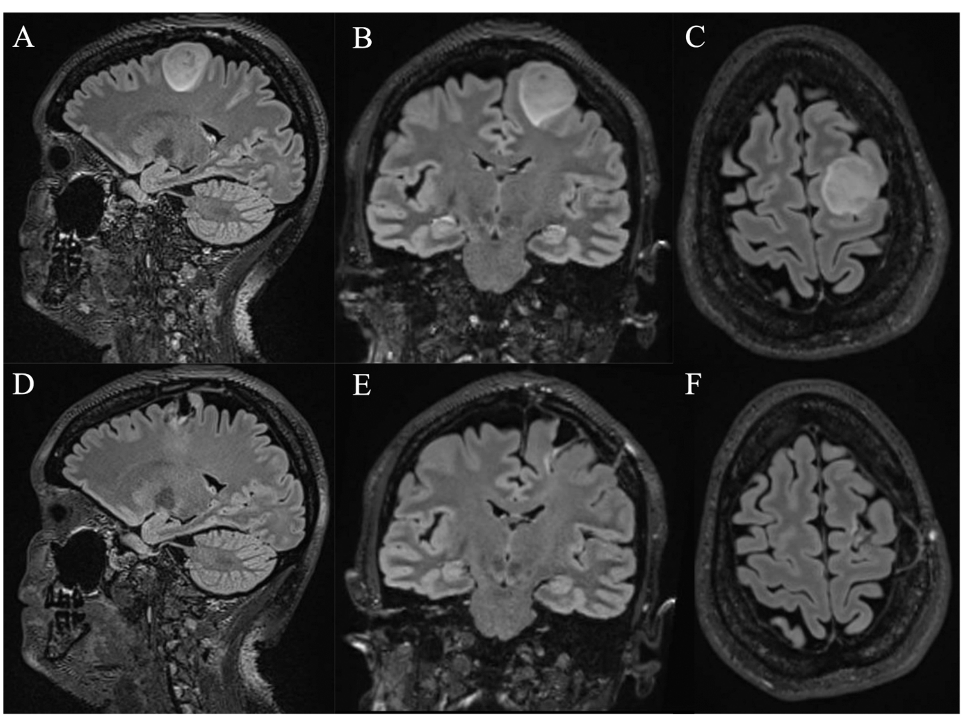


**Fig. 1.** Preoperative (A) sagittal, (B) coronal, and (C) axial T2 fluid attenuated inversion recovery (FLAIR) MRI demonstrating a low grade glioma located in the left superior frontal gyrus. Postoperative (D) sagittal, (E) coronal, and (F) axial T2 FLAIR MRI demonstrating gross total resection of the lesion.

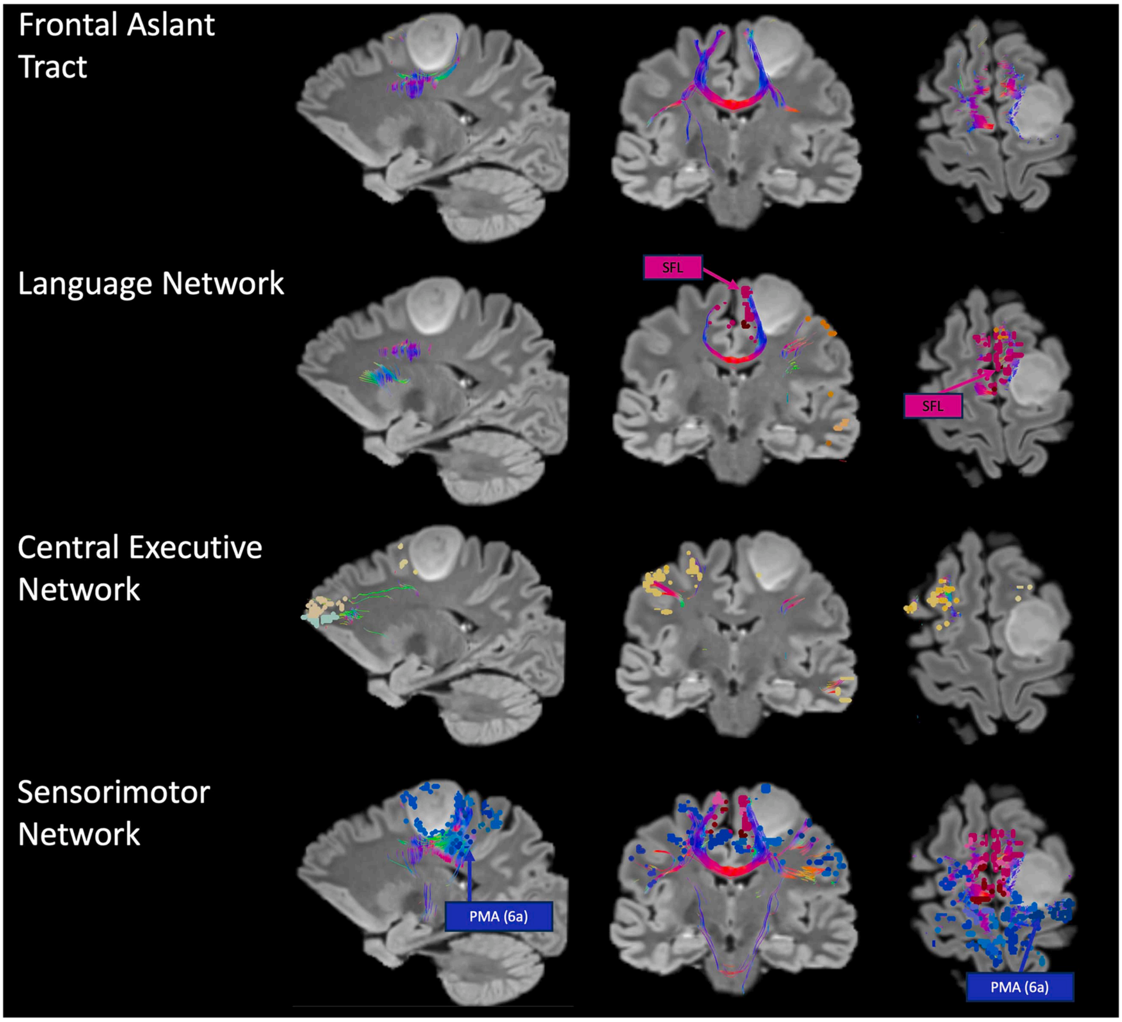


**Fig. 2.** Preoperative connectome imaging demonstrating sagittal, coronal, and axial views of relevant tracts and network parcellations of including the frontal aslant tract, language network, central executive network, and sensorimotor network. Parcellations deemed at risk are denoted, including the SFL of the language network, and area 6 A of the premotor area.

who presented after a brief loss of consciousness following a motor vehicle accident and a history of right-sided weakness and language deficits. Imaging revealed a left frontal cavernoma (Fig. 4). Preoperative connectomics imaging revealed a laterally displaced FAT, proximity to the central executive network (CEN) at the postero-inferior margin of the tumor, and the salience network and corticospinal tract (CST) near the postero-medial, lateral, and posterior margins of the lesion (Fig. 5).

Intraoperative neuromonitoring followed the same protocol as detailed earlier. Penfield cortical and subcortical simulation was targeted at the anterior and lateral portions of the lesion-brain interface where the FAT was identified on connectome imaging, and dynamic subcortical motor evoked potentials were targeted along the posterior, lateral and deep margins of the lesion. Subcortical motor stimulation was initiated at 20 mA and resection proceeded until a threshold of 5 mA was reached. During the surgery, the patient maintained intact expressive and receptive language with no changes in speech output or comprehension. Language evaluation, motor mapping, and neuromonitoring revealed no new disturbances, and subcortical motor mapping did not encounter the CST at 20 mA. Intraoperative language evaluation included open conversation in both English and Spanish and standardized testing including auditory comprehension and naming. Open conversation with the patient revealed intact receptive and expressive language throughout the procedure.

Postoperatively, the patient had an uneventful recovery and imaging confirmed gross total resection of the lesion. She was discharged on POD 2 without any deficits. Final histopathology confirmed the lesion as a cavernoma. She was ECOG 0, and KPS 100 at her last follow-up 4 months postoperatively.

### 1.2. *Connectome generation*

Neuroimaging was acquired using a 3.0 T Siemens MAGNETOM Vida MRI machine (Siemens Medical Solutions USA Inc., Malvern, PA, USA). A T1-weighted anatomical scan (Magnetization-prepared rapid gradient echo, TR/TE: shortest, FOV: 256 mm, slice thickness: 1.00 mm, 190 slices, no slice gap) and a 30-direction diffusion weighted scan (TE/TR: shortest, FOV: 240 mm, voxel size: 2.00 $mm^3$ isotropic, slice thickness: 2.00 mm, slices: 90, no slice gap, diffusion scheme: bipolar, b-values: 0, 1000) were obtained.

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 [17]. Briefly, MRIs were preprocessed by Quicktome's cloud-based software. Using a constrained spherical deconvolution (CSD)-based tractography algorithm, streamlines were automatically generated from structural scans using random seeding. Personalized-connectome images were then generated by reparcellating the Human Connectome Project Multi-Modal Parcellation (HCP-MMP)

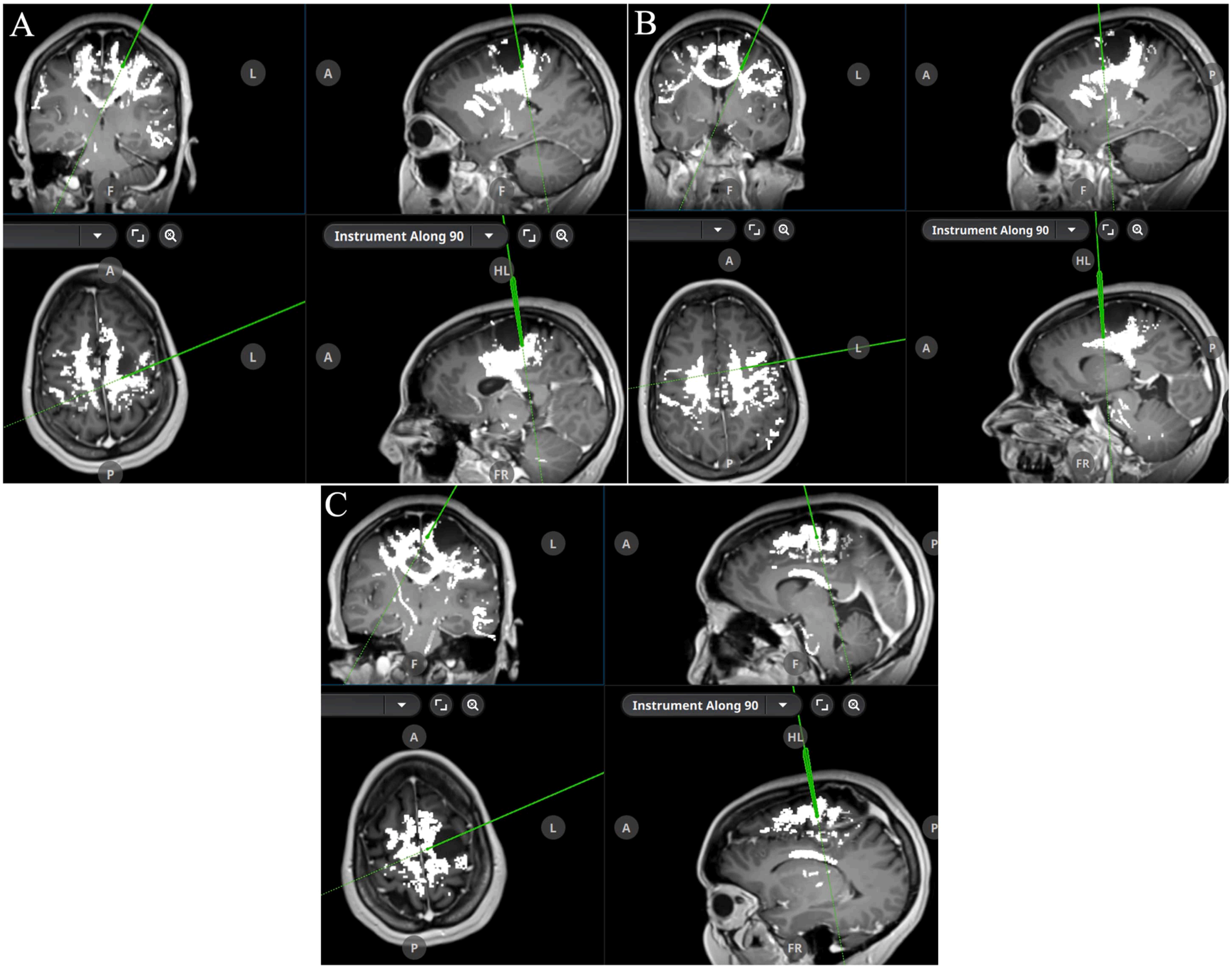


**Fig. 3.** Intraoperative neuronavigation demonstrating stimulation locations during awake craniotomy language mapping at the (A) posterior, (B) anterior, and (C) medial tumor borders.

atlas based on patient-specific connectivity.

## 2. Discussion

The cases presented in this study underscore the practical utility of connectomic imaging in the surgical management of brain lesions adjacent to non-canonical eloquent networks, specifically the SMA and FAT. By integrating patient-specific connectome data into preoperative planning and intraoperative navigation, we were able to identify and preserve critical cortical regions and subcortical white matter pathways—namely the FAT— that are not reliably monitored using traditional intraoperative techniques [18,19]. This approach facilitated maximal safe resection of tumors located near the SMA without inducing SMAS, thereby maintaining patients' motor and cognitive functions postoperatively. The FAT has traditionally been difficult to monitor intraoperatively, leading to rates of SMAS approaching 60 % following resection of lesions in the SFG [13]. The multimodal connectome imaging modality implemented provided structural information regarding the location of FAT fibers relative to patients' lesions – in one case medial to the tumor, and in the other case lateral to the tumor – and additionally provided functional information about the location of relevant network parcellations of large-scale brain networks contributing to higher-order cognitive functions. The integration of this information with neuronavigation provided surgeons the ability to avoid these critical structures and nodes during tumor resection, sparing the patients deficits associated with SMAS.

There is a paucity of literature on the use of multimodal connectomic imaging for the preservation of the FAT during tumor resection, and there are limitations in the existing anatomic imaging modalities and intraoperative identification techniques implemented [20,21]. Traditionally, fiber tractography through diffusion tensor imaging has been used to characterize the FAT preoperatively [21,22]. However, this imaging modality is limited in its ability to account for functional brain regions. Additionally, functional neuroimaging including resting-state and tasked-based functional MRI have been used to characterize SMA functionality preoperatively and postoperatively, however, these imaging modalities have limited utility in preventing SMA syndrome likely due to their inability to delineate tracts [22–24]. Multimodal connectome imaging, as performed in the highlighted cases, reveals functional tracts as well as functional network parcellations at risk of damage during tumor resection. Specifically, we identified parcellations of the language network (SFL), central executive network, sensorimotor network, and salience network to be at risk between the two patients included. Among these networks, the salience network is thought to be modulated by the FAT through a cingulo-insular-opercular axis that, when impaired in patients with SMAS, impairs the ability to initiate desired actions [25]. Intraoperative navigation of the connectome imaging facilitate guidance to preserve parcellations adjacent to the

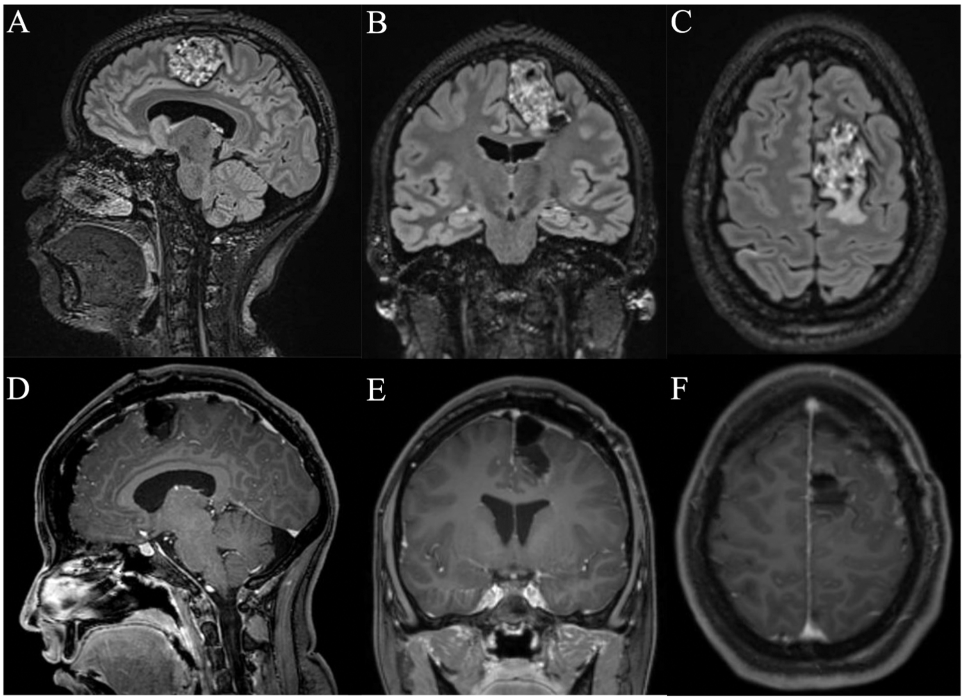


**Fig. 4.** Preoperative (A) sagittal, (B) coronal, and (C) axial T2 FLAIR MRI demonstrating a cavernoma located in the left superior frontal gyrus. Postoperative (D) sagittal, (E) coronal, and (F) axial T1 post-contrast MRI demonstrating gross total resection of the lesion.

patients' tumors, and we observed no instances of postoperative SMAS. The use of connectome imaging for the prevention of SMAS has been previously reported on by Molina et al., in a patient with a recurrent oligodendroglioma resected supramaximally [26]. They observed transient akinetic mutism postoperatively, consistent with SMAS lasting 3 days, despite intact connectome imaging postoperatively. This could be attributed to tumor pathology as oligodendrogliomas tend to invade the FAT more than astrocytomas (such as in Patient 1), which are more likely to displace the FAT [27].

The SMA and FAT serve as models for the challenges associated with non-canonical network preservation. The FAT, a white matter pathway connecting the SMA to the inferior frontal gyrus and anterior insula, is essential for higher-order functions such as movement planning and execution [28,29]. Intraoperative stimulation of the FAT in the language-dominant hemisphere has been shown to evoke speech disturbances, linking it to language deficits seen in SMA damage [30,31]. However, traditional mapping methods, such as direct cortical and subcortical stimulation, have limited reliability in identifying the FAT intraoperatively, often leading to the high incidence of SMAS in surgeries involving the SFG [32]. The SMA and FAT represent a model for the challenges associated with preserving non-canonical networks during neurosurgical procedures. Their unique features—including the inability to consistently monitor them intraoperatively and the significant clinical symptoms that result from their damage—highlight the limitations of traditional mapping techniques and consequences of these limitations and underscore the need for alternative approaches to minimize postoperative deficits. Studies by Vassal et al. demonstrated that damage to the FAT correlates with speech initiation disorders in patients undergoing glioma surgery, highlighting the challenges in intraoperative identification and preservation of the FAT using standard mapping techniques [32]. Our cases support these assertions, as both patients exhibited preserved motor and language functions postoperatively, with no occurrence of SMAS. While intraoperative adjuncts like direct cortical and subcortical stimulation remain the gold standard to localize and avoid critical networks, our cases demonstrate that connectomic imaging can augment these techniques, especially when traditional mapping is unreliable. The role of awake mapping in these cases remains a topic for further research, but our findings suggest that combining connectomic imaging with intraoperative monitoring can enhance surgical precision and patient outcomes.

## 3. Conclusions

These illustrative cases demonstrate the potential of connectomic imaging to enhance neurosurgical precision and patient outcomes by facilitating the preservation of critical neural pathways beyond traditionally eloquent regions. As we advance toward more extensive tumor resections, shifting from traditional anatomical definitions of eloquence to a better understanding of functional connectivity will be necessary to accurately assess the safety of surgery and the feasibility of preserving cognitive outcomes. Future research should focus on larger, multicenter studies to assess the effectiveness of connectomic imaging in preserving non-canonical networks like the FAT. The development of standardized protocols for the integration of connectomic data into surgical planning and intraoperative navigation would facilitate broader adoption of this methodology. Advancements in imaging technology could enhance the resolution and reliability of connectomic maps, making them more accessible and practical for routine use. Furthermore, exploring the use of connectomic imaging in other non-canonical networks could expand its application and improve surgical outcomes across a variety of neurosurgical procedures.

## CRediT authorship contribution statement

**Harshal A. Shah:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Souvik Singha:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Laura Mittelman:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Julianna Cavallaro:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Rosivel Galvez:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Grace Huang:** Methodology, Project administration, Writing – original draft, Writing –

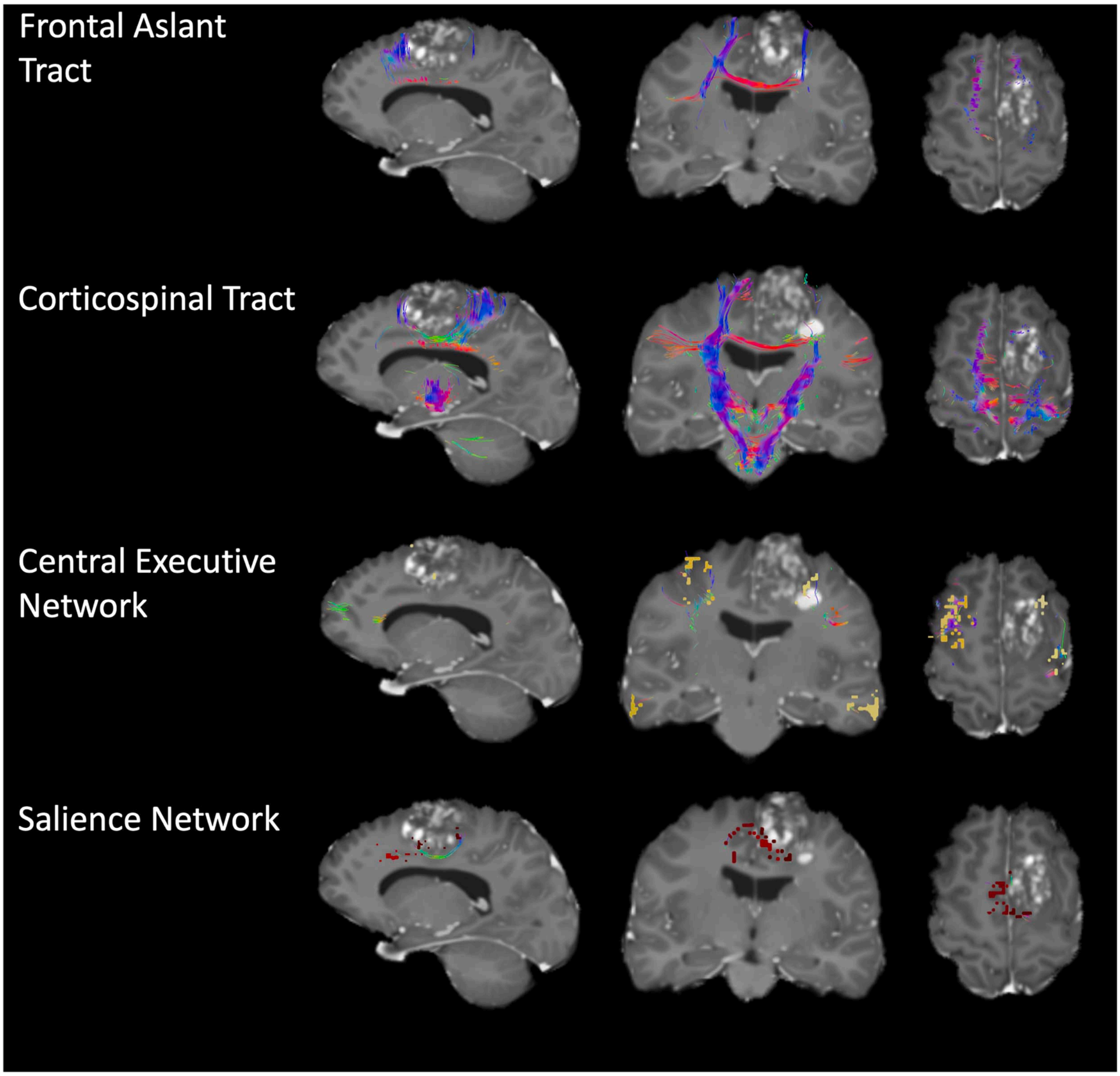


**Fig. 5.** Preoperative connectome imaging demonstrating sagittal, coronal, and axial views of relevant tracts and network parcellations of including the frontal aslant tract, corticospinal tract, central executive network, and salience network.

review & editing. **Beril Yaffe:** Methodology, Supervision, Writing – review & editing. **Randy S. D′Amico:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Justin W. Silverstein:** Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

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