Development of an educational method to rethink and learn oncological brain surgery in an "a la carte" connectome-based perspective

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Title: DEVELOPMENT OF AN EDUCATIONAL METHOD TO RETHINK AND LEARN ONCOLOGICAL BRAIN SURGERY IN AN 'A LA CARTE' CONNECTOME-BASED PERSPECTIVE

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Compliance with Ethical Standards:

1) Conflicts of Interest: PAV is a consultant for an unrelated fluorescence guided surgery study for NX Development Corp. JDB has an equity position in Treovir LLC, an oHSV clinical stage company and is a member of the POCKiT Diagnostics Board of Scientific Advisors.

2) Ethics Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the (place name of institution and/or national research committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided informed consent to participate under a study protocol approved by the institutional review board of the Montpellier University Medical Center (#202000557).

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Abbreviations and acronyms:

WMT	white matter tracts
MRI	magnetic resonance imaging
DTI	diffusion tensor imaging
SMA	supplementary motor area
DICOM	Digital Imaging and Communications in Medicine
T1W	T1-weighted
FLAIR	fluid attenuation inversion recovery
NIFTI	neuroimaging informatics technology initiative
MNI	Montreal Neurological Institute
3D	3-dimensional
2D	2-dimensional
CST	corticospinal tract
NMN	negative motor network
FAT	fronto aslant tract
FST	fronto striatal tract
DES	direct electrical stimulation
VPMC	ventral premotor cortex
PrG	precentral gyrus
SLF-III	superior longitudinal fasciculus III
AF	arcuate fasciculus
IFOF	inferior fronto-occipital fasciculus
MFG	middle frontal gyrus
DLPFC	dorsolateral prefrontal cortex
PPTT	pyramids palm trees test
ILF	inferior longitudinal fasciculus
STG	superior temporal gyrus
MTG	middle temporal gyrus
ITG	inferior temporal gyrus
TR	thalamic radiations

Abstract

Background
Understanding the structural connectivity of white matter tracts (WMT) and their related functions is a prerequisite to implementing an 'a la carte' 'connectomic approach' to glioma surgery. However, accessible resources facilitating such an approach are lacking. Here we present an educational method that is readily accessible, simple, and reproducible, that enables the visualization of WMTs on individual patient images via an atlas-based approach.

Methods
Our method uses the patient's own magnetic resonance imaging (MRI) images and consists of three main steps: data conversion, normalization, and visualization; these are accomplished using accessible software packages and WMT atlases. We implement our method on three common cases encountered in glioma surgery: a right supplementary motor area tumor, a left insular tumor, and a left temporal tumor.

Results
Using patient-specific perioperative MRIs with open-sourced and co-registered atlas-derived WMTs, we highlight the critical subnetworks requiring specific surgical monitoring identified intraoperatively using direct electrostimulation mapping with cognitive monitoring. The aim of this didactic method is to provide the neurosurgical oncology community with an accessible and ready-to-use educational tool, enabling neurosurgeons to improve their knowledge of WMTs and to better learn their oncologic cases, especially in glioma surgery using awake mapping.

Conclusions
Taking no more than 3-5 minutes per patient and irrespective of their resource settings, we believe that this method will enable junior surgeons to develop an intuition, and a robust 3-dimensional imagery of WMT by regularly applying it to their cases both before and after surgery to develop an "a la carte" connectome-based perspective to glioma surgery.

Key Words: glioma; brain tumor; white matter tracts; brain mapping; connectome; awake surgery

Short Title: Didactic Method for Connectomic Glioma Surgery

Introduction:

Proper functioning of the human connectome depends on the integrity of the brain's cortical hubs and subcortical deep white matter tracts (WMT)[30]. Awake cortical[61] and subcortical mapping[15] are the gold standard approach in glioma surgery[11] as they allow one to maximize extent of tumor resection while concurrently reducing the rates of postoperative deficit(s)[21]. Such an approach has shown benefits on postoperative cognitive[50,42,48] and socioprofessional[49] outcomes, and overall survival[11,16,55]. Intraoperative cognitive mapping requires the execution of intraoperative tasks tailored to the patient's needs, preoperative neuropsychological examination, tumor location and connectomic constraints[66,33,13,12,15,10]. Patients undergo the selected tasks in a combined manner[23] (e.g., including movement, naming task[34], line bisection task[31], reading task[51], picture association task[47], or mentalizing task[82,32] and so forth) depending on the expected relation(s) to specific cortical hubs WMTs[19,66].

To successfully implement such 'connectomic approach' to glioma surgery, the surgeon needs to have a firm understanding of the underlying functional connectomics, i.e., have a working knowledge of the anatomy of the WMTs and functional network(s) involved[66,14,15,13,12]. To achieve this, studies centered on cadaveric brain dissections to visualize cortical and subcortical structures provide detailed descriptions of these WMTs; in doing so, their relative locations in relation to key anatomical landmarks (e.g., ventricles), and other WMTs and their cortical terminations have also been defined[45,44,28,41,25]. Further, diffusion tensor imaging (DTI) databanks are publicly available, providing information on the average patterns of structural connectivity and underlying WMTs at the population level[79,83,72,8,7].

However, cadaveric dissections and population level DTI studies do not allow surgeons to visualize the WMT of patients in relation to their pathology. While the acquisition of patient-specific DTI images might overcome this problem[29,9,4], creation of individual patient WMT reconstructions for accurate and daily use in glioma surgeries faces several challenges: not all patients receive a DTI acquisition; WMT reconstructions have severe reproducibility limitations with important rates of false positives and negatives; disagreement between expert teams using the same data; and pathology specific artifacts negatively impact the accuracy of reconstructions (e.g., brain edema in tumors)[24,74,27,70,5,69,43,38,56,78]. From a global perspective it is important to highlight that access may be a limitation, as there are institutions including in low- and middle-income countries, where trainees/surgeons may have no access to the appropriate software for reproducible and accurate WMT reconstruction.

Given the importance of WMT connectivity and the challenges of visualizing the patient specific pathology in relation to critical WMT, here we present a method that is readily accessible, simple, and reproducible, enabling visualization of the WMT connectivity for individual patient images using an atlas-based approach. We implement our method on three of the most common cases in glioma surgery: a right supplementary motor area (SMA) tumor, a left insular tumor, and a left temporal tumor. We use our method on the individual patient images to discuss the critical deep connectivity in relation to the tumor, the expected functional responses as well as the actual responses found during awake surgery, and the anatomofunctional correlates on post-operative imaging. We hope that by enabling an improved understanding of the human connectome in their daily clinical practice, surgeons will be able to maximize the advantages of awake mapping surgery to achieve the oncofunctional balance[22].

Methods:

1. Data Acquisition and Conversion

The patient's clinical MRIs are provided in Digital Imaging and Communications in Medicine (DICOM) format (Fig. 1a). Input images should include a high-resolution T1-weighted (T1W) image. Additional MRI sequences can be used, such as fluid attenuation inversion recovery (FLAIR) images, for visualizing non-enhancing tumors, edema, and infiltrative tumor margins.

The next step is to convert the DICOM data into a format compatible with subsequent steps, i.e., the neuroimaging informatics technology initiative (NIFTI) format, which contains all the relevant spatial information for visualization and image processing. We use one of two open-source software packages for this conversion, MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) or MRIcroGL (https://www.nitrc.org/projects/mricrogl), which enable importing of DICOM images, anonymization, and conversion to NIFTI. This is accomplished via the <Import> function to select the DICOM data folder, or by a 'drag and drop' approach, 'dragging' the folder with DICOM files and 'dropping' into the MRIcron/MRIcroGL window (Suppl. Methods).

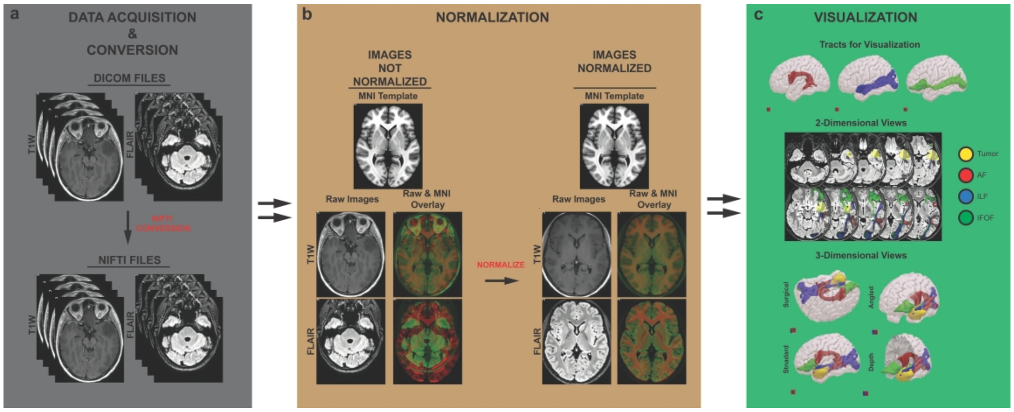

Fig. 1 Method Workflow. Our readily accessible method consists of three steps. (Data Acquisition and Conversion) The surgeon collects the DICOM formatted MRIs form their hospital system and converts them to NIFTI format using MRIcron/MRIcroGL. (Normalization) The surgeon uses the T1W images and FLAIR images in SPM12 to implement a normalization algorithm to register the patient MRIs to a MNI template. (Visualization) The surgeon loads the white matter tracts of interest and can interactively visualization in 2-dimensional cross-sectional view or 3-dimensional views the MRI, tumor, and white matters tracts

2. Normalization

Clinical MRIs exists in 'space and coordinates' specific to the patient (Fig. 1b). To enable use of clinical images with an atlas-based approach, the patient's MRI needs to be registered unto a template MRI that is commonly defined as the Montreal Neurological Institute (MNI) space[33,31]. This process is called 'normalization'. All open-sourced subcortical atlas used hereafter are provided in the MNI space, by convention.

We describe two normalization techniques, although different techniques are used in neuroimaging studies. We use the open-source toolbox from SPM12[60] (https://www.fil.ion.ucl.ac.uk/spm/software/download/) implemented in the software package MATLAB. Using a graphical user interface, the user can select the high resolution image as well as a second image to visualize non-enhancing tumor (Suppl. Methods). Once the NIFTI images are normalized, the user can proceed to visualize their normalized clinical MRI with any pertinent WMT atlas.

3. Visualization

A subcortical atlas is a 3-dimensional (3D) volume(s) that contains the volume occupied by a WMT(s) (e.g., left arcuate fasciculus) averaged from a population. Here we use the HCP1065 atlas derived from the largest cohort of normal brains[79] (http://brain.labsolver.org/diffusion-mri-templates/tractography) (Suppl. Table 1 with list of WMTs).

While atlases are population-averaged (derived from 1065 subjects as in the HCP1065 atlas), numerous studies have shown that they are in fact useful for drawing conclusions across large patient cohorts[79,72,7,37]. Accordingly, here we describe two approaches that enable one to produce 2-dimensional (2D) and 3D views of WMTs on patient specific clinical MRIs (Fig. 1c). To visualize in 2D, we open the NIFTI volume with MRIcron or MRIcroGL. Then, using the <Overlay> function, we open the WMT volume of interest, and finally, the selected tracts(s) are overlayed on the clinical MRI, with the user adjusting the colors for visualization. The user can also segment the tumor to create a tumor volume using MRIcron (Suppl. Methods 1).

To visualize in 3D, we use Surf Ice. Unlike MRIcron/MRIcroGL, the volumes in Surf Ice exist as a 'volume mesh'. As such, to visualize tracts in Surf Ice, the user needs to convert the NIFTI volumes into a Surf Ice 'volume mesh'. Then, they can load the segmented tumor volume and tract(s) of interest as overlays. The corresponding author can provide the NIFTI volumes and volume meshes for all tracts in the HCP1065 atlas as well as an MNI152 template and whole brain meshes for 2D and 3D visualization. Thus, the surgeon can collect their MRI DICOM data from their hospital, convert to NIFTI, and visualize in 2D and/or 3D.

Results:

1. Case number. 1 - right supplementary motor area (SMA) low grade glioma

Here we present the case of a 31 year-old right-handed female with an incidental discovery of a 59 cm^3 lesion with hyperintense FLAIR signal in the right SMA/pre-SMA regions (Fig. 2a). We applied our method on the patient's preoperative images to visualize three WMTs likely to be encountered during surgery in 2D (Fig. 2a) and 3D (Fig. 2b). First, the corticospinal tract (CST) was noted to be ~1 cm posterior to the tumor. Second, two tracts of the 'negative motor network' (NMN), the frontal aslant tract (FAT) and the fronto striatal tract (FST)[39], were posterior medial, posterior lateral and at the depth of the tumor. As was evident upon review of the perioperative MRI/overlayed WMTs, the anterior component of the FST and the medial component of the FAT were likely infiltrated and/or displaced by the tumor. At this stage, by understanding the relevant WMT anatomy, the surgeon can plan intraoperative tasks and possible intraoperative findings during surgery. For example, stimulation of the FST at the posterior medial aspect of tumor resection location would cause a NMN functional response including movement arrest and possible difficulty with bimanual coordination[57].

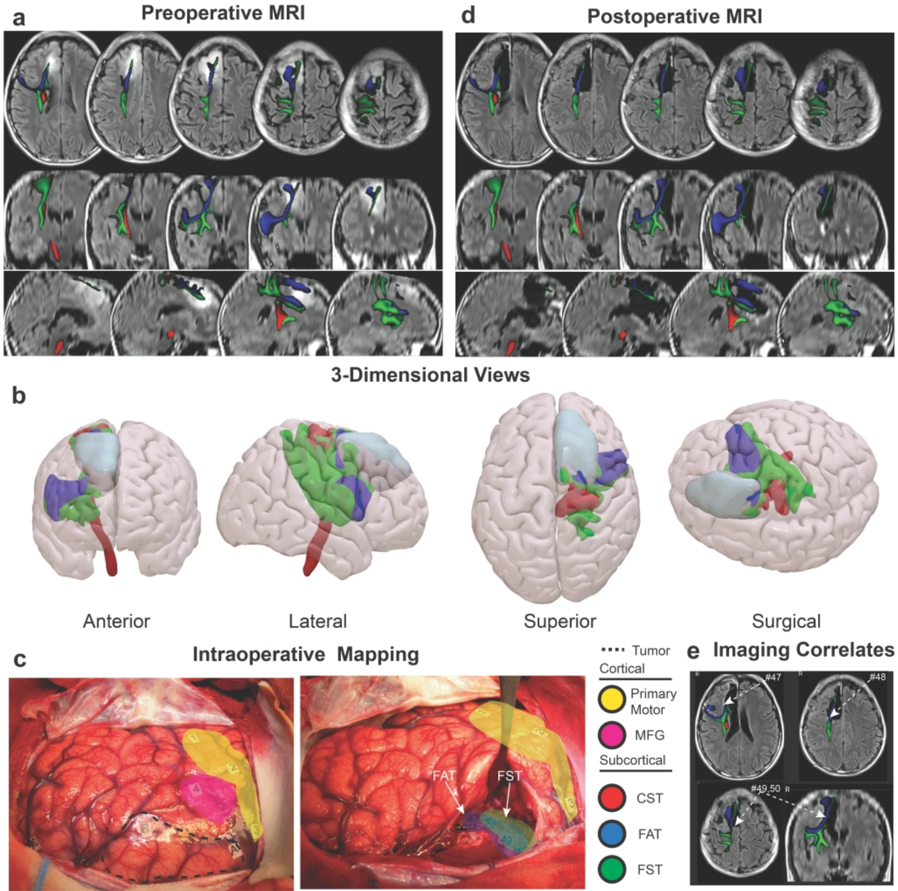

Fig. 2 Case #1: Right SMA/pre-SMA tumor. (a) Preoperative MRI images notable for a hyperintense FLAIR mass in the right SMA/pre-SMA region, with 2D overlays of the FAT (blue), FST (green) and CST (red) following data acquisition, normalization, and visualization. (b) 3D views showing relation of FAT, FST and CST and the tumor (gray). (c) Intraoperative images showing tags found to have a functional response (tag# on brain, with color coded legend for all images on the right) at the beginning (left) and end (right) of surgery. White arrows point to locations mapped for FAT and FST. (d) Postoperative MRI with surgical cavity and FAT, FST, and CST overlay as in (a). (E) MRI images with location of functional tags and their relation to the deep connectivity

The patient underwent a right sided awake craniotomy, and direct electrostimulation (DES) was used to identify the ventral premotor cortex ([VPMC]; response: anarthria; tag #1) at the lateral aspect of the precentral gyrus (PrG) (Fig. 2c). The frontal and Rolandic cortex were mapped to identify the primary motor area (response: involuntary movements, face and upper limb; tags #2 and 3, respectively).

The tumor was resected up to the FAT and FST, which were the functional boundaries identified by DES. The patient experienced left upper limb movement arrest and articulatory disorders with interruption in naming and counting (tag #47) at the posterior lateral depth; left upper limb movement arrest as well as inhibition of bimanual coordination when asked to perform simultaneous tasks with both upper limbs (tag #48) at the posterior medial depth; movement arrest of the left lower limb and inhibition of bimanual coordination (tag# 49) at the posterior medial surface; and arrest of the upper and lower limbs on the left with intact right sided movements and intact language (tag #50) at the most posterior medial aspect.

Postoperative MRI images (Fig. 2d) show the surgical cavity in relation to the FAT, FST, and CST. In relation to the surgical cavity: the FAT courses along the lateral and posterior aspect; the FST is observed at the medial and posterior aspect, with anterior terminations included within the resection however with preservation of its posterior terminations; and the CST is located ~1 cm posterior, explaining why no involuntary movements were elicited by DES. Thus, postoperative images correlate the intraoperative functional responses to their respective WMT and location relative to the resection cavity (Fig. 2e), following the expected subcortical somatotopy of the NMN[58], and allowing the patient to have no seizures and no deficits at 3-month follow-up with a return to normal activities.

2. Case number 2 - left insular low grade glioma

Next, we present the case of a 26 year-old right-handed male with seizures who was found to have a 43 cm^3 lesion with hyperintense FLAIR signal in the left insula (Fig. 3a). As was done with the case above, we used the patient's preoperative images to visualize four WMT likely to be encountered during surgery in 2D (Fig. 3a) and 3D (Fig. 3b). The CST was noted to be at the posterior, superior and medial aspect of the tumor at the level of the posterior limb of the internal capsule. Second, we identified two tracts of the 'dorsal system': the superior longitudinal fasciculus-III (SLF-III) at the lateral and superior aspect of the tumor and the arcuate fasciculus (AF) immediately adjacent and medial to the SLF-III on the periphery of the superior circular sulcus along the superior aspect of the tumor. Finally, the inferior fronto-occipital fasciculus (IFOF) was identified at the anterior boundary of the tumor; coursing along the temporal stem at the medial aspect of the tumor; and lateral to the putamen towards the occipital lobe at the posterior and medial aspect of the tumor. By learning the deep connectivity, the surgeon can plan their surgical approach, prepare cognitive tasks and understand expected functional findings. For example, while operating at the superior and lateral aspect of the tumor, we could expect articulatory disorders due to the SLF-III, whereas at the superior aspect of the tumor, along the superior circular sulcus, we could expect language disorders such as anomia and phonological paraphasias due to the AF located medial to the SLF-III[18].

The patient underwent an awake left sided craniotomy for tumor resection, and DES identified the negative motor areas (response: cessation of fluency and right upper limb movement; tag # 1-2) and the VPMC (response: articulatory arrest; tag# 3) (Fig. **3c**). The posterolateral MFG with the dorsolateral prefrontal cortex (DLPFC), demonstrated disorders on the pyramids palm trees test ([PPTT]; tag #4). A frontal transopercular approach was used to expose the insular surface, disconnect the insula, and resect the tumor[20,18,62].

Preoperative images predicted four tracts that were identified intraoperatively as the functional boundaries of the lesion. In line with this the patient experienced right upper limb involuntary movements during DES (no tag although positive identification intraoperatively) at the posterior superior depth (CST); articulatory disorders and anomia (no tag) at the posterior lateral depth (SLF-III and AF); and semantic paraphasias as well as repeated hesitations during the PPTT (tags# 49-50) at the level of the inferior insular sulcus, temporal stem and lateral aspect of the frontal horn (IFOF).

Postoperative images (Fig. 3d) show the surgical cavity in relation to these four WMTs. The CST is shown with decreased displacement from mass effect. The SLF-III and AF are shown at the superior aspect of the tumor from lateral to medial, respectively. The IFOF bordered the cavity at the inferior frontal region, temporal stem and towards the sagittal striatum. Therefore, critical WMTs of the dorsal and ventral systems and their expected 3D anatomofunctional relationships were identified and preserved intraoperatively (Fig. 3e), allowing the patient to have no seizures and no deficits including normal language evaluation at 3-month follow-up.

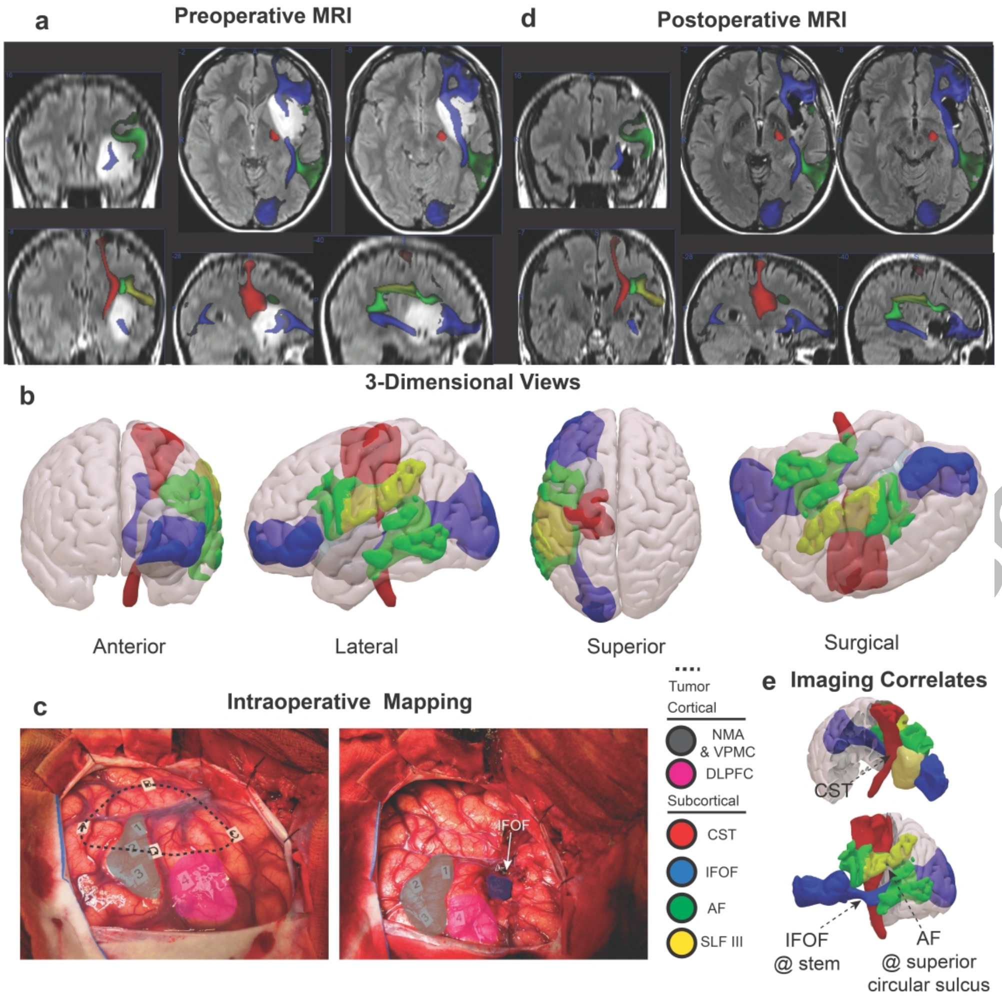

Fig. 3 Case #2: Left insular tumor. (a) Preoperative MRI images notable for a hyperintense FLAIR lesion in the left insula. The SLF III (yellow), AF (green), IFOF (blue), and CST (red) are overlayed following data acquisition, normalization, and visualization with atlas-based tracts. (b) 3-Dimensional views showing relation of SLF III, AF, IFOF, and CST and the tumor (gray). (c) Intraoperative images showing tags found to have a functional response (tag# on brain, and color coded on the right) at the beginning (left) and end (right) of surgery. Given the limited surgical corridor, no tags are visualized for SLF III, AF, and CST. (d) Postoperative MRI with surgical cavity and SLF III, AF, IFOF, and CST overlay as in (a) notable for a significant decrease in mass effect. (e) 3-Dimensional views with and without tumor volume and SLF III, AF, IFOF, and CST overlay correlating location of intraoperative functional responses and deep connectivity

3. Case number 3 - left anterior temporal low grade glioma

Next, we present the case of a 26 year-old right-handed female with partial seizures and language difficulties with a 20 cm^3 hyperintense FLAIR lesion located primarily in the left anterior temporal region with partial extension into the insula (Fig. 4a). Our method visualized four main WMTs likely to be encountered in surgery in 2D (Fig. 4a) and 3D (Fig. 4b). Tumor was noted to infiltrate the inferior longitudinal fasciculus (ILF) at the lateral and basal aspect of the anterior temporal lobe. The IFOF was shown along the medial aspect of the tumor along the temporal stem and along the superior lateral aspect of the temporal horn. The AF had terminations at the superior, middle and inferior temporal gyri (STG, MTG, and ITG, respectively) at the posterior boundary of the tumor. The somatosensory pathways (thalamic radiations [TR]) and CST were noted at the posterior, superior and medial depth of the tumor at the level of the posterior limb of the internal capsule.

The patient underwent an awake left sided craniotomy, and DES identified the VPMC (response: articulatory arrest; tags# 1-2) (Fig. 4c). As in Cases #1 and 2, preoperative MRI images revealed tracts that were in fact identified intraoperatively at the functional boundaries of the resection (Fig. 4c). The patient experienced semantic paraphasias during DES (tag# 50) at the temporal stem in the deep part of the temporal resection (IFOF)[26]; right upper limb dysesthesias in the posterior aspect of the insula near the internal capsule (tag# 47) (TR adjacent to the CST); jargonaphasia at the posterior border of the resection (tag# 48) (temporal terminations of the AF as it crosses the IFOF); and missing words (tag# 49) at the most posterior and basal aspect of the resection ~3.0-3.5 cm from the temporal pole (posterior functional component of the ILF)[34] (Fig. 4c).

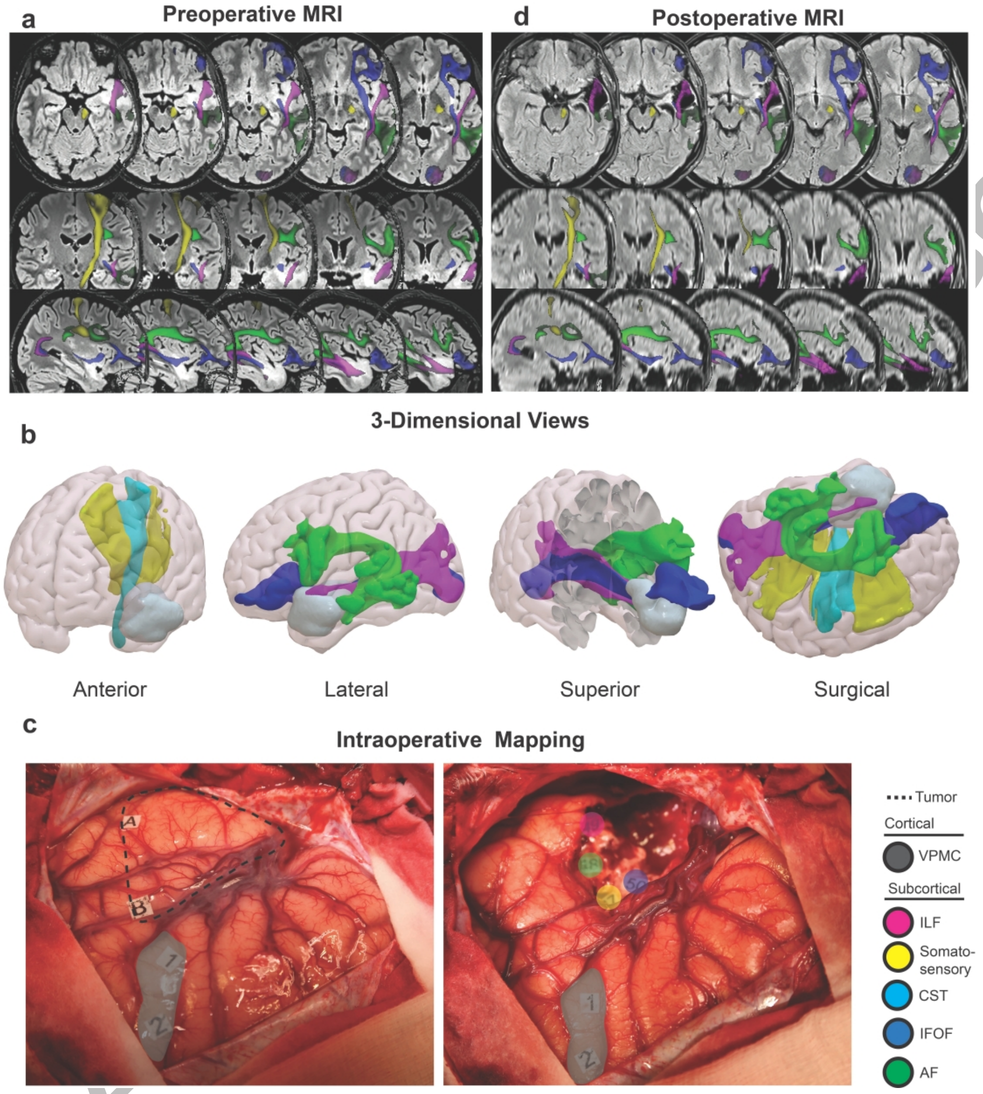

Fig. 4 Case #3: Left anterior temporal-insular tumor. (a) Preoperative MRI images notable for a hyperintense FLAIR mass in the left anterior temporal lobe with infiltration of the insula, with 2D overlays of the ILF (magenta), IFOF (blue), AF (green) TR (yellow), and CST (cyan) following data acquisition, normalization, and visualization. (b) 3D views showing relation of ILF, IFOF, AF, TR, CST, and the tumor (gray). (c) Intraoperative images showing tags found to have a functional response (tag# on brain, and color coded on the bottom right) at the beginning (left) and end (right) of surgery. (d) Postoperative MRI with surgical cavity and the ILF, IFOF, AF, TR, and CST overlay as in (a)

Postoperative images (Fig. 4d) show the ILF partially included within the surgical cavity, with its posterior portion at the posterior and basal aspect of the surgical cavity consistent with intraoperative difficulties with lexical access. The AF terminations are seen at and in proximity to the IFOF at the posterior aspect of the surgical cavity. Thus, our method confirmed the intraoperative DES findings, enabling a maximally safe resection and the patient showing no deficits and partial improvement in neuropsychological scores at 3-month follow-up.

Discussion:

Understanding the structural connectivity of WMTs and their related functions is critical in glioma surgery. Here we present a method that is readily accessible, simple, and reproducible that enables the visualization of WMTs in the context of a patient's unique pathology to help neurosurgeons learn the connectomic constraints in glioma surgery, and ultimately facilitate maximal safe surgical resections.

This method has several advantages for use on glioma cases. First, it is readily accessible irrespective of the surgeon's resource setting (e.g., not requiring preoperative DTI or expensive clinical software for WMT reconstruction and visualization). Second, it is simple and requires only three steps: data acquisition, normalization, and visualization. Third, it is reproducible, enabling surgeons at all levels to apply this method for learning, teaching, and/or planning. Fourth, it is fast, allowing surgeons to produce 2D or 3D visualization(s) in 3-5 minutes.

A 'connectomic approach' to glioma surgery requires the surgeon to have a mental imagery of the underlying deep connectivity for each patient. Only then can the surgeon make pre-operative plans that will positively impact post-operative functional outcomes. In line with this, our group applies an 'a la carte' approach to brain tumor patients, which takes into consideration the patient specific wishes, sociocultural and emotional needs, and functional requirements for a return to work and to continue to live a normal life[19,66,22,13,12]. However, to implement this 'a la carte' approach, the surgeon requires foundational knowledge about how the deep connectivity and its functional brain networks are related to the patient's pathology[66,65,63,13,12].

Here we show how our method can help surgeons develop the mental imagery of the deep connectivity with patient-specific MRIs harboring gliomas. Here we made use of three representative cases to demonstrate the utility of our method. First, we discussed a case of a patient with a right SMA/pre-SMA tumor. Of note, resection of these tumors can lead to contralateral akinesia of the hemibody and/or mutism (i.e., SMA syndrome). SMA syndrome, although reversible, is regularly followed by permanent deficit in bimanual coordination and fine motor skills even with intact motor mapping of the CST[39,40]. In **Case #1**, we visualized these WMTs with DES confirmation of the NMN somatotopy. Recent advances demonstrate the importance of the FAT and FST of the NMN[6,59], such that preservation of NMN deep connectivity has been shown to decrease the risk of SMA syndrome and permanent deficit in bimanual coordination and fine motor skills[59,57]. Thus, by understanding the WMTs of the NMN in relation to the CST in SMA and Rolandic tumors, the surgeon can perform an 'a la carte' surgery that would be particularly relevant in, for example, a concert pianist wishing to preserve bimanual and fine motor skills.

Case #2 presented a patient with a left insular tumor; such lesions require the surgeon to understand and visualize the complex anatomofunctional relationships of the dorsal (AF, SLF-III), ventral (IFOF, ILF, UF), motor (CST), NMN (FAT, FST), and somatosensory (TR) networks. Our method can help neurosurgeons visualize key relationships such as the proximity between the AF and SLF at the posterior, superior and lateral aspects of the resection, which explains how anomia, phonologic, and/or articulatory disorders can occur[44,75,67,68,26,30]; visualize the displacement and infiltration of the IFOF in the depths of the resection, which is imperative to avoid significant semantic language disorders[2,30,64]; and localize the motor and somatosensory pathways in an effort to ensure no transgression into the posterior limb of the internal capsule. Thus, we visualized all five major pathways in relation to this patient's anatomy, which would be impossible with ex vivo dissections, and prohibitively challenging in everyday use with DTI reconstructions.

Finally, **Case #3** presented a left temporal glioma with extension into the insula. While teaching within the neurosurgical community would posit that anterior temporal lobe resections ranging from 3-6 cm posterior from the temporal pole in dominant or non-dominant hemispheres are typically safe[76,71,1], our method shows the terminations of the AF in the STG, MTG, and ITG as well as the posterior portion of the ILF ~2.5-3.5 cm from the temporal pole and just posterior to the tumor. Intraoperatively, this was confirmed when we observed language disorders during DES of the AF and the ILF[34,35,26,36]. Had surgery proceeded anatomically, without understanding the WMTs and intraoperative DES, the patient would have suffered significant language disorders of lexical access including possible anomic aphasia as well as phonological disorders[34,35,26,36].

In all three cases, our method allowed us to critically evaluate an 'a la carte' connectomic approach[30,18] to glioma cases, and by performing cognitive assessments during awake surgery, enable patients to preserve function and return to a normal life. Importantly, other pre-planning tools aiming at assessing functional and structural connectomics exist (e.g., Quicktome, Omniscient neurotechnology, Sydney, Australia)[81,46,80], but neuroimaging technologies remain limited in providing enough sensitivity and specificity to accurately predict awake-guided DES results [3,24,74,27,70,5,69,43,38,77,73,53,54,52]. However, broad accessibility is limited given the costs associated with user fees; for example, this phenomenon is more pronounced in low-and middle-income countries. Therefore, it is important to understand that we do not intend for our method to predict the exact location of WMTs, since it is based on population-averaged diffusion measures[79]. As such, the information is not patient-specific with respect to the WMTs, since interindividual anatomofunctional variability is well demonstrated in glioma patients[17]. We do however contend that such an imaging tool is a powerful adjuvant to awake surgery and when used in conjunction with DES, can be leveraged by a surgeon who has used the tool to understand the WMTs and their approximate relationship to the pathology at hand. Further, our method complements the method by Sarubbo et al, in which they overlay probabilistic maps of cortical and subcortical functional responses to a patient's preoperative MRI[63], whereas we visualize the anatomofunctional subcortical basis for these probabilistic functional response maps.

Conclusions:

We present a method to help neurosurgeons learn the connectome in a simple, affordable, and reproducible manner. By learning the connectome, they will develop an understanding of the deep connectivity and its anatomofunctional relationships. Once they have the necessary mental imagery, they can perform 'a la carte connectomic' surgeries to tailor resections and achieve the optimal oncofunctional balance for a patient's individual needs and desires.

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