Combining nTMS and Tractography for Language Mapping: An Integrated Paradigm for Neurosurgical Planning

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Introduction

In the intricate tapestry of the human brain, the white matter tracts serve as high-speed communication networks, facilitating the complex interplay between different regions. Tractography, a remarkable neuroimaging technique, leverages the diffusion of water molecules to visualize and map these pathways, offering us a glimpse into the structural highways of neural communication. By tracking the movement of water along axons, tractography provides us with the unique ability to delineate the course of white matter tracts within the living brain, a feat unattainable by traditional imaging methods.

As we navigate deeper into neurosurgery, the role of tractography becomes particularly pivotal when focusing on function of language — a fundamentally human domain. Language tractography reveals the architecture underlying our verbal and written communication and is a critical guide in neurosurgical planning and intervention. The nuanced understanding of language pathways helps avoid functional compromise during surgery, thereby preserving the essence of human interaction postoperatively.

Enter the domain of navigated Transcranial Magnetic Stimulation (nTMS) — a technology that marries the anatomical insights gained from tractography with functional localization. nTMS for language mapping is a non-invasive, patient-specific approach allowing us to 'navigate' the cortical surface precisely. By combining subcortical anatomical white matter mapping derived from tractography with surface functional probing of nTMS, neurosurgeons can tailor their approach to each patient's unique neural landscape.

In this chapter, we will discuss the foundational principles of tractography to the cutting-edge applications of nTMS in language mapping. We will explore how the synergy of these two technologies is revolutionizing preoperative planning and maximizing surgical outcomes while safeguarding the quintessential human capacity for language.

Part 1: The Methods

Navigated Transcranial Magnetic Stimulation (nTMS)

Navigated Transcranial Magnetic Stimulation (nTMS) has emerged as a critical instrument in delineating cortical regions implicated in functional processes, particularly in motor and language mapping. The efficacy of TMS has been significantly enhanced by integrating MRI-based navigation systems. These systems allow for the concurrent visualization of an individual's structural brain scan, providing a real-time guide to target and precisely navigate the stimulation across the cortical landscape. This advancement marks a transformative step from the earlier, less precise techniques, enabling a tailored and patient-specific approach to brain mapping and standing in contrast to earlier mapping techniques, which often involved somewhat indiscriminate stimulation of the cortex without imaging support, or relied on standardized brain models (Krings et al. 2001; Rotenberg, Horvath, and Pascual-Leone 2014; Ruohonen and Karhu 2010). The necessity for individualized imaging becomes especially critical in cases involving brain tumor patients, where significant anatomical changes occur due to the presence and growth of a tumor. This individualized approach ensures a more accurate and safe intervention, accounting for the unique anatomical variations present in each patient.

The setup for nTMS for language mapping involves a series of coordinated steps and equipment, designed to accurately stimulate specific cortical regions involved in language processing (CROSS REF: chapter 10 “Basic principles and clinical use”). Here is an outline of the typical setup:

1. Patient Preparation and MRI Scanning: Before the nTMS procedure, the patient undergoes an MRI scan. This scan provides detailed images of the patient's brain structure, which are crucial for the navigation during the TMS procedure. The MRI data, commonly in DICOM format, is used to create a 3D model of the patient’s brain. Additional sequences can be simultaneously acquired for later processing steps, including diffusion weighted imaging (DWI).

2. Integration of MRI Data with nTMS System: The MRI images are uploaded into the nTMS system. Advanced software integrates these images with the nTMS navigation system, allowing for real-time guidance and precise targeting of specific brain areas.

3. Positioning of the Patient: The patient is seated comfortably in a chair or lies on a bed. Their head is positioned to ensure optimal access for the TMS coil and patient comfort.

4. Aligning of MRI with Patient’s Head: By means of neuronavigation including an infrared camera, several markers on the patient's head are recorded and aligned on screen with the 3D image of the patient's brain, based on the individual MRI.

5. Setting Up the nTMS Equipment: The nTMS machine, equipped with a stimulation coil, is brought near the patient. The coil is positioned over the patient’s scalp, targeting specific predefined brain areas. The position and orientation of the coil are guided by the navigational software, visualized on screen.

6. Language Task Execution: The patient is typically asked to perform language tasks during the stimulation. These tasks may involve naming objects and/or actions, or reading. The task items are timely aligned with the stimulation targeting the cortex.

7. Stimulation and Mapping: The TMS coil delivers magnetic pulses to the targeted brain areas. The responses and effects of these stimulations on the patient's language capabilities are monitored and recorded. This helps to identify language processing areas by observing any disruptions or changes in the patient's ability to perform these tasks when different brain regions are stimulated.

8. Data Analysis and Interpretation: The data collected from the nTMS session is analyzed to identify the brain regions essential for language function. All areas that were found to be involved in language, i.e. showing disruptions in performing the designated task, are marked as a positive language map in the MRI.

9. Integration with Surgical Planning: The language map obtained from nTMS is burned into the DICOM that can further be integrated into the surgical planning process.

The nTMS setup for language mapping is depicted in *Figure 1*.

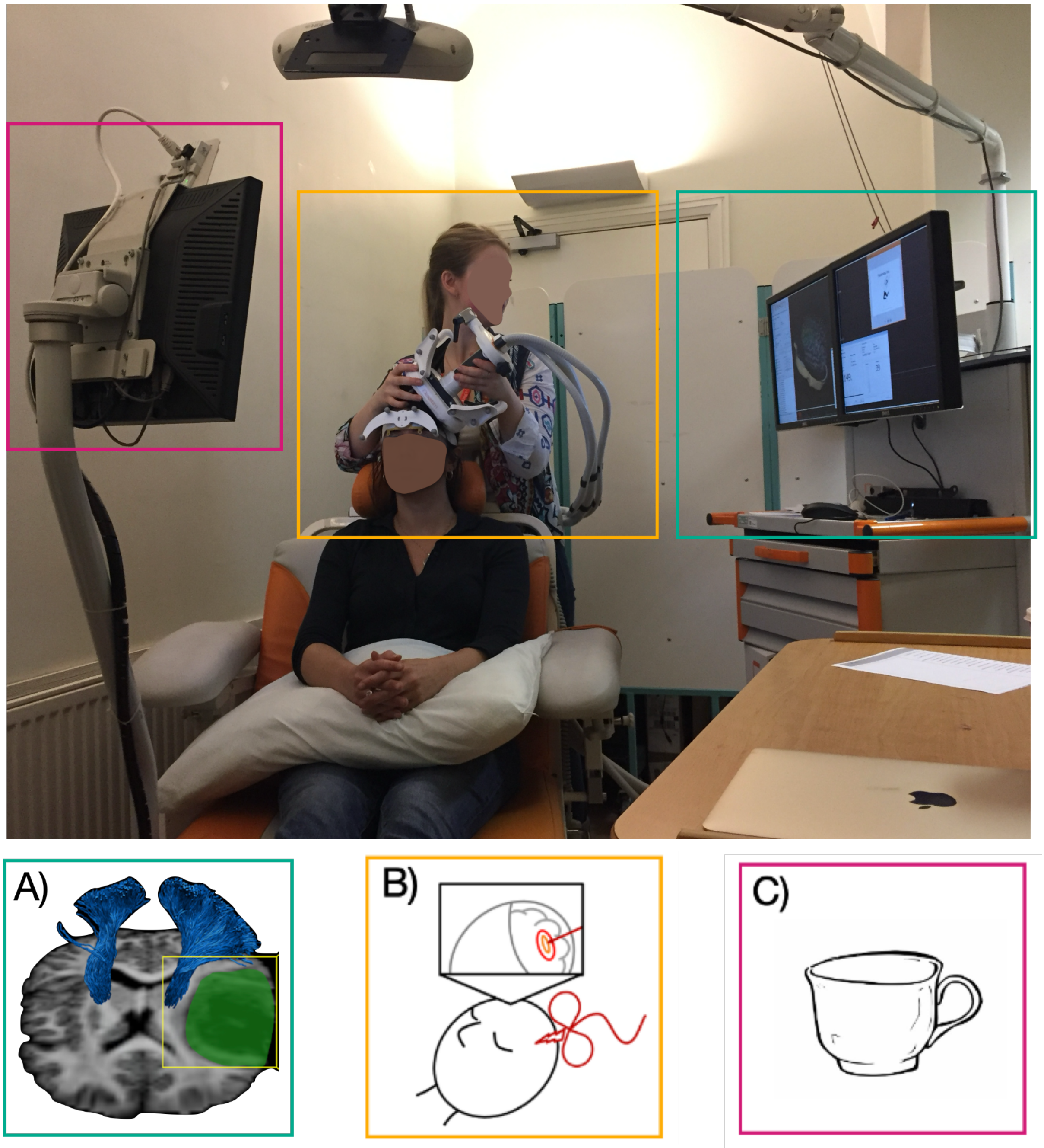

Figure 1. *The clinical setup for presurgical language mapping using tractography and TMS. A) 3D-model of patient's neuroanatomy based on pre-TMS MRI scanning (including tumor entity) to aid coil placement and thereby TMS pulse on cortex, with the possibility to visualize a priori segmented tractography results. B) The experimenter places the stimulation coil on the head of the patient, guided by A). C) Patients view a screen where picture stimuli of a language task are presented (original artwork by Victor Xandri Antolin; © University of Groningen).*

Although nTMS provides a reasonably good understanding of the cortical regions crucial for language, it cannot currently map the subcortical language network. This limitation includes the inability to effectively reach subcortical gray and white matter (WM) structures. There is no dependable method for nTMS to target the subcortex directly. This is in contrast to direct electrical stimulation (DES) used intraoperatively, which can be applied directly to the exposed brain tissues. In the case of nTMS, the magnetic pulses need to traverse not only the scalp and skull but also various layers of potentially relevant cortical gray matter, as well as other cellular and white matter structures, before they can reach the deeper subcortical areas of interest (CROSSREF: chapter 1 “Basic principles of nTMS”). As a result, this can give rise to a situation where a region of interest might be falsely identified as relevant (a false positive). This occurs when the observed effects are due to the stimulation and disturbance of lateral structures surrounding the intended target areas, rather than the target areas themselves.

Diffusion-weighted data acquisition

In response to these challenges, significant strides have been made in reconstructing individual white matter (WM) bundles in the brain using diffusion-weighted imaging techniques. These methods track the diffusion pathways of water molecules, enabling the reconstruction of presumed white matter tracts where these molecules are present. Among the various algorithms available for reconstructing the brain’s connective tissues, deterministic tractography, mainly based on diffusion tensor imaging, has become a standard and widely-used approach in neurosurgical settings (CROSSREF: chapter 27 “Advanced Tractography”).

We provide a brief overview of optimizing diffusion protocol for presurgical planning in this book’s chapter on *Advanced Tractography* under *Acquiring clinically suitable DWI data* (CROSSREF: chapter 27 “Advanced Tractography”). When preparing for the surgical treatment of language-related brain tumors, the implementation of an effective diffusion protocol for tractography is crucial. The protocol's nuances significantly influence the quality and utility of the resulting data for presurgical planning. The data is primed for processing using various algorithmic models with these acquisition parameters set. In the clinical setting, the FACT algorithm is the most common, which makes a single fibre orientation decision per voxel allowing to propagate from voxel to voxel following the primary orientation of the diffusion tensor in each voxel, hence diffusion tensor imaging (DTI). More advanced models would also account for the diffusion patterns in neighbouring voxels and integrate this information.

Tractography Parameters and Algorithms

Once the data is acquired and preprocessed for tractography reconstructions (CROSSREF: chapter 27 “Advanced Tractography”), one can reconstruct the whole connectome (i.e. all connections) or segment out individual connections of interest. The segmentation method choice depends on the preprocessing and the tracking algorithm used. Broadly speaking two methods are used: 1) virtually segmenting a pathway from a whole brain connectome based on anatomical regions and 2) Tracking individual pathways based on anatomical or functional seed and target regions. A concrete example would be delineating the language network by placing an anatomical region of interest (ROI) into *a priori*-defined brain areas (e.g. inferior frontal gyrus, IFG). This approach will visualize all streamlines passing through this region. For the second example, a seed ROI can be placed in the IFG to initiate repeated tracking from this part of the brain. Both these methods can be used with nTMS positive and negative points serving as ROIs.

Anatomical placement of ROIs

Anatomical (ROIs) are a pivotal component in tractography, offering a tailored approach to mapping brain connections. They can be defined manually, typically preferred in clinical settings, or based on established brain atlases. ROIs are strategically placed in critical "bottleneck" areas, acting as essential passageways for white matter tracts (Catani et al. 2002; Hau et al. 2016).

Consider the inferior fronto-occipital fasciculus (IFOF), which spreads across the frontal and occipital lobes but narrows significantly as it traverses the external capsule. Placing an ROI in this narrow region effectively captures most of the IFOF's streamlines. However, for more nuanced dissection, such as differentiating the IFOF in the context of the ventral triade alongside the uncinate fasciculus and the inferior longitudinal fasciculus, employing three ROIs is advisable. Similarly, the arcuate fasciculus, connecting the frontal and temporal lobes, can be segmented by placing an ROI in the converging zone within the inferior parietal white matter (referenced in (Catani, Jones, and Ffytche 2005)).

Not all connections, however, converge into bottlenecks. In such instances, employing multiple ROIs helps define connections as traversing between distinct brain regions, like the superior longitudinal fasciculi linking the frontal and parietal lobes (Thiebaut de Schotten et al. 2011). When multiple ROIs are used, each can act as a filter, including or excluding streamlines based on Boolean logic ('AND', 'OR', 'NOT').

Moreover, the function of an ROI can vary: a 'waypoint' ROI captures or excludes streamlines passing through it, while an 'endpoint' ROI focuses on streamlines that start or finish within it. This distinction is crucial for accurately mapping different types of fibers, such as short U-shaped fibers connecting adjacent gyri, where the 'both ends' endpoint criterion is particularly effective. Utilizing these ROI rules and configurations, exploring almost every white matter connection in the brain becomes feasible, providing a comprehensive and precise understanding of its intricate network. Examples of this approach as applied to the language networks are provided in *Figure 2*.

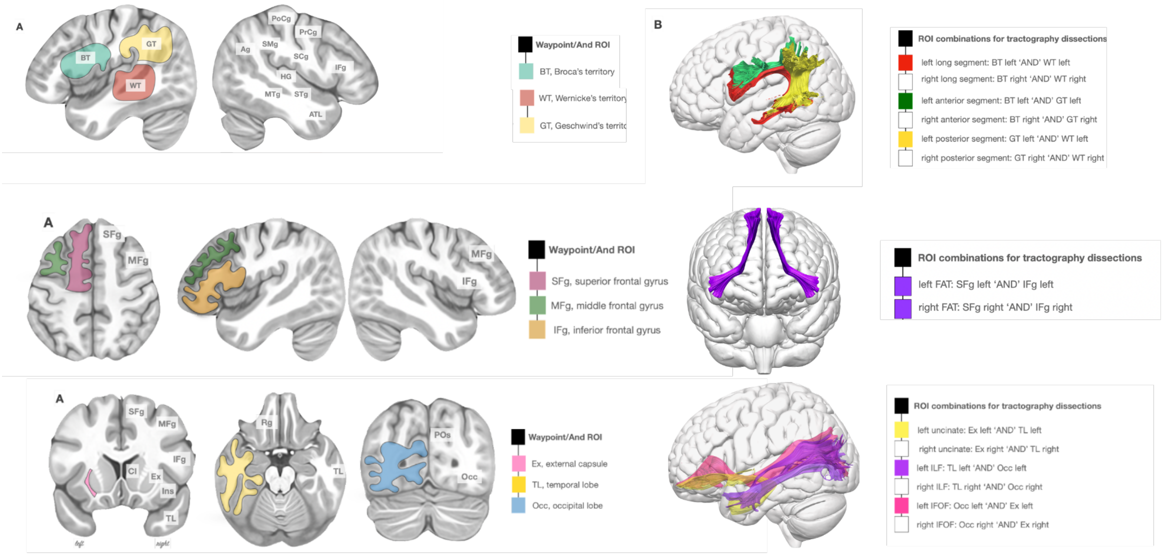

Figure 2. *Manuel delineation of the language network with tractography. A.1.) Waypoints for AF A.2.) Visualization of three segments of AF based on waypoints B.1.) Waypoints for FAT, B.2.) Visualization of FAT in both hemispheres C.1.) Waypoints for UF, ILF and IFOF C.2.) Visualization of UF (magenta fibers), ILF (yellow fibers) and IFOF (purple fibers) based on waypoints Figure permission: Amended from Forkel, S., Bortolami, C., Dulyan, L., Barrett, R. L., & Beyh, A. (2023). Dissecting white matter pathways: A neuroanatomical approach.*

Functional ROIs

In contrast to anatomical ROI creation, functional ROI creation begins with identifying areas of functional involvement specific to the individual. These could be areas delineated using functional magnetic resonance imaging readouts (fMRI; for more information, see (Kleiser et al. 2010)) or can be based on nTMS mapping results.

While fMRI is widely available in most medical institutions, its alignment with TMS-positive sites presents limitations, as the correlation is not always direct. Moreover, fMRI typically offers lower spatial resolution, which can be challenging when dealing with brain tumor patients (Giussani et al. 2010; Ille et al. 2015; Babajani-Feremi et al. 2016).

TMS, on the other hand, can be directly employed for functional-based mapping. If the ROIs originate from nTMS, they were typically conducted a few days before surgery for high-grade lesions or at a longer interval for lower-grade lesions. This mapping provides an up-to-date representation of the patient's functional cortical hubs for language.

In short, this involves targeting predefined cortical areas across most of the left hemisphere with nTMS pulses synchronously with a language task (for detailed description, see chapter XX, and for a commonly applied protocol (Krieg et al. 2017)). Any stimulations that cause disruption in the patient’s language output, such as difficulties in correctly and fluently naming a picture, are identified. These disruptions are marked and are later transformed into cortical spots (sphere of 1-2mm^2), that are used as seed ROIs or objects within the imaging data. This is achieved by enlarging their size to a 5mm radius to create an ROI of sufficient size to encompass white matter areas. Fibers originating from these cortical nTMS hubs can then be reconstructed and visualized in 3D. Finally, the data are co-registered and ideally placed onto the neuronavigation system in the OR, ensuring precise alignment and integration of functional data for surgical planning (see *Figure 3*).

However, it is essential to note that this method primarily identifies functionally relevant components of neural networks rather than mapping the entire anatomical network. Studies such as Negwer and colleagues have demonstrated that this approach can effectively reveal white matter connections critical for cognitive functions, and their disruption could lead to significant cognitive deficits (Negwer et al. 2018).

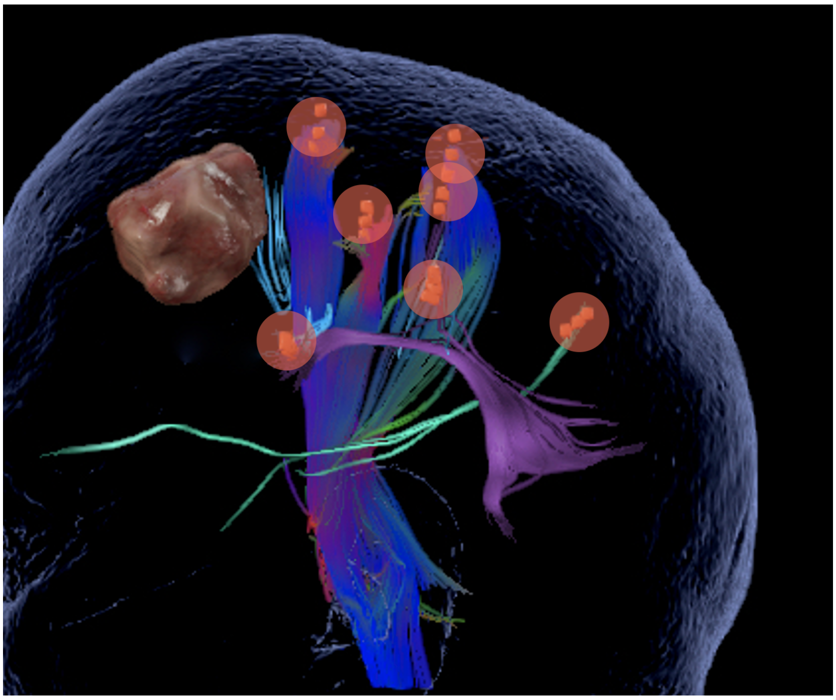

***Figure 3**: DTI fiber tracking on the basis of nTMS positive spots for language in relation to tumour mass (here in brown). All areas that, due to stimulation, resulted in a disruption of speech and language are marked as orange spheres of 1-2mm. The spheres' diameter is increased to 5mm to enlarge the region of interest (ROI) in order to mimic the size of focal stimulation and reach subcortical white matter. Fibers originating from these ROIs are then visualized and colour-coded: CST (blue), arcuate (purple), MdLF (greeen), callosal fibers (light blue)).*

How to integrate TMS and tractography for language

Three main approaches have been described on the integration of TMS and tractography to preoperatively define the language network of the individual patient:

1.TMS-informed Tractography (Sollmann, Negwer, et al. 2016; Negwer, Ille, et al. 2017): In contrast to the anatomical ROI creation, with this approach no *a priori* tracts are selected, but only those tracts that surpass, end or start in the created nTMS sphere ROIs on the cortex are visualized (Giovanni Raffa et al. 2016, 2022; Silva et al. 2021; Sollmann, Negwer, et al. 2016; Ohlerth et al. 2022). While this certainly limits white matter presentation to functionally relevant tracts, cortical ROI placement entails drawbacks as well: it often produces aberrant fibre representations that do not align with anatomically nor functionally plausible structures and hence requires postprocessing of the tractogram before clinical use

(Giovanni Raffa et al. 2022; Silva et al. 2021). This is due to false positive responses with TMS for language.

2.Tractography-informed TMS (Reisch et al. 2022). In this approach, the subcortical anatomical information guides the TMS cortical mapping to decrease the false positive rate. A TMS response cannot be considered if there is no subcortical tract whereby that stimulation can influence the subcortical network.

3. Independently-performed TMS and Tractography (Lucena et al. 2023; Hazem et al. 2021). In this approach, tractography and TMS are performed independently (using anatomical and functional ROIs) and the results are merged. This method tries to minimize one technique's false positive and false negative responses over the other. It aims for a probability approach given by the degree of overlap of the two techniques.

Different studies have compared the above methods and how they correlate with DES mapping in the OR. Whilst some reports mention that TMS-informed tractography did not improve the intraoperative identification of positive sites for language when compared with TMS-only approach (Sollmann, Kubitscheck, et al. 2016), others support better outcomes with TMS-based tractography when compared with DES-based tractography when the quality of tract reconstruction is considered (S. Li et al. 2023). Conflicting results emerge when comparing TMS-based tractography versus anatomy-based tractography supporting either a superiority of one method or the other when comparing visualization of tracts involved in the subcortical language network (Negwer, Sollmann, et al. 2017; Silva et al. 2021). Therefore, a standardized approach is still lacking and open to discussion within the neurosurgical community. A combined tractogram, employing both subcortical hand-drawn ROIs and nTMS-based functional information holds potential in visualizing specific pathways of the major language tracts more accurately (Silva et al. 2021). This avenue demands further attention and calls for prospective, large cohort investigations, as it can overcome both shortcomings of the single approaches, if done correctly.

Part 2: The Applications

Functional Mapping of Language

Language is a highly intricate cognitive function, spanning two modalities (expressive and receptive) and encompassing several forms of communication (spoken; written; gestures…). It is broadly based on three subskills in all these modalities, entailing *meaning building* (conceptual and semantic processing, thereby selecting the correct meaning leading to lexical retrieval of words in the mind), *structure building* (morphological and syntactic processes of putting elements together to form more complex words and later sentences) and *sound building* (phonological encoding and finally phonetic-articulatory motor processes by assigning sounds to elements and initiating motor movements of speech articulators). Inversely, an equally complex chain of processes is in place during receptive language, namely comprehension, of dissecting strings of sound waves into elements, words, and sentences and correctly inferring meaning to the entire utterance.

As it is the ultimate goal in neurosurgical and neuro-oncological care to preserve as many of these subskills as possible, a line of research has been dedicated to how best to elicit and evaluate language skills during mapping techniques. In the search for designing and validating linguistic tasks covering the above-mentioned processes most comprehensively, the recent decades have brought about several available protocols of intraoperative tasks to be used with DES (for a review, see (Papatzalas 2021)). These language test batteries exist in several languages (such as the DULIP, the ECCO, the VAN-POP and the MULTIMAP) and allow for task selection based on the patient's profile and preoperative status. Moreover, the respective tests are then used intraoperatively to identify positive areas relevant for language skills while approaching brain tumours (Alves et al. 2021; De Witte et al. 2015; Ohlerth et al. 2020; Gisbert-Muñoz et al. 2021; Dragoy et al. 2016).

Language mapping tasks for nTMS are not as vast compared to mapping with the gold standard DES. The highly restricted time frame of roughly 1 sec of stimulation duration during nTMS compared to up to 4 sec in DES precludes an adaptation of the extensive intraoperative DES tasks to the preoperative setting with nTMS. Faced with this limitation, most institutions at present opt for an expressive task (Natalizi et al. 2022; Jeltema et al. 2021) that prompts a short verbal output to a visual stimulus, is easily disrupted by nTMS interference and can be thereby straightforward to evaluate.

This is most commonly done with the picture naming variant *object naming*. Depicting an object as an easy-to-decipher, black-and-white drawing triggers the patient or participant to recognize the concept and produce it as a noun. In addition to being the most established task and facilitating comparisons with earlier work, accurately naming an object can engage various stages of language function, ranging from conceptual retrieval to articulation. While a robust tool, this task alone does not do justice to the complexity of language in general (Bastiaanse and Ohlerth 2023). This shortcoming has been addressed recently by studies adding more depth to the production paradigm in the form of verb tasks and by venturing into possibilities of adding comprehension tasks: To incorporate a second, crucial word class of verbs to the paradigm and to trigger grammatical skills, so-called *action naming* can be employed under nTMS (Ohlerth et al. 2020). Eliciting verb retrieval and encoding, and later employing it in mapping cortical representation, reveals cortical hubs for verb knowledge that can then be considered for the preservation of function (Ohlerth et al. 2021a, [b] 2021, 2022).

On top of that, utilizing *comprehension tasks* under nTMS could potentially not only aid in uncovering hubs for this modality but also enable the inclusion of individuals with highly impaired production of language: In these patients, picture naming, hence expressive language, might be impossible to administer, but a receptive task might render mapping viable after all: Hearing a noun label, matching it with visually presented options of object drawings and answering with a button press circumvents verbal response and enables mapping (Kram et al. 2023).

More data is needed to manifest the added benefit of the newly proposed tasks. Only case reports or small groups of patients have been presented piloting these approaches in brain tumor patients (Ohlerth et al. 2022; Kram et al. 2023). Nonetheless, evidence from other demographics (e.g. stroke) and methodologies (DES, fMRI, MEG) give rise to the assumption that a variety of tasks might be beneficial over single tasks (Hillis, Tuffiash, and Caramazza 2002; Mätzig et al. 2009; Miceli et al. 1984; Zingeser and Berndt 1988; Rofes et al. 2017). Object naming remains the most used and validated variant for task choice in nTMS mapping (Natalizi et al. 2022).

Tractography and prediction of outcome

In neuro-oncology, tractography has become a valuable tool for predicting surgical outcomes, particularly in cases involving tumors located in brain regions crucial for language. The technique is used preoperatively to assess the extent to which language-related tracts, such as the Inferior Fronto-Occipital Fasciculus (IFOF), have been infiltrated or displaced by the tumor. When a brain mass, such as a glioma, exerts pressure on the surrounding tissue, it can cause significant deviation in the shape and location of adjacent white matter fibers from their typical anatomy. For instance, a tumor in the lateral frontal lobe may compress and shift a segment of the corticospinal tract (CST) towards the medial wall. This displacement, however, usually affects only the CST portion close to the tumor, altering its path when compared to a white matter atlas (S. Forkel et al. 2023). Crucially, these alterations are unique to each individual, making it impossible to predict the precise configuration of the white matter without employing tractography for each specific case. It is also crucial to consider the hemispheric asymmetries in the anatomy of white matter, which complicates using the contralesional hemisphere as a reference point (Satoer, Dulyan, and Forkel n.d.). This inherent variability between the two hemispheres means that relying on the unaffected side as a mirror image for surgical planning or tractography interpretation in the affected hemisphere may lead to inaccuracies. Understanding these asymmetries is vital for accurate mapping and surgical intervention strategies.

The indispensability of tractography in accounting for such patient-specific anatomical variations has cemented its role as a vital instrument in neurosurgical procedures. Its clinical utility has been extensively documented and advocated in numerous studies and publications, including those by (Cochereau et al. 2020; Dragoy et al. 2020; Duffau 2008; Kemerdere et al. 2016; Leclercq et al. 2010; Mirchandani et al. 2020; Sollmann et al. 2020; Teichmann et al. 2015; Thiebaut de Schotten et al. 2005). These works highlight the pivotal role of tractography in enhancing the precision and safety of neurosurgical interventions, particularly in cases where normal anatomical landmarks are distorted by pathological processes.

Furthermore, the preoperative involvement of specific tracts has been linked to a heightened risk of transient and permanent postoperative cognitive and linguistic deficits (Kinoshita et al. 2014; Castellano et al. 2017; Bello et al. 2010). These findings underscore the importance of detailed tract mapping in surgical planning to minimize the risk of functional impairment.

Tractography offers a nuanced means of evaluating surgical risks by measuring the lesion-to-tract distance (LTD), which is the proximity between a specific brain tract and a tumor. This metric has been instrumental in predicting language outcomes through anatomical ROIs (Tuncer et al. 2021) and functional ROIs derived from TMS data (Sollmann et al. 2020). In cases where preoperative infiltration of tracts is observed, specific LTD thresholds have been linked to language outcomes. For instance, an LTD of 16 mm or less for the Arcuate Fasciculus (AF), or 25 mm or less for other language tracts like the IFOF, Uncinate Fasciculus (UF), Frontal Aslant Tract (FAT), and Inferior Longitudinal Fasciculus (ILF) have been associated with an increased risk of poor language outcomes post-surgery (Sollmann et al. 2020). Additionally, Sollmann N. (2020) proposed safety cutoffs for language-sparing resections: LTDs of at least 8 mm for the AF and 11 mm for the SLF, ILF, UF, and IFOF.

However, it is absolutely crucial to acknowledge the inherent variability in tractography results based on the acquisition, preprocessing and processing parameters (CROSSREF: chapter 27 “Advanced Tractography”). Different tractography algorithms and parameters can significantly alter the estimates of tract dimensions, extensions, and proximity to the surgical target. This variation underscores a significant caveat in applying LTD measurements during surgery: the accuracy and reliability of the language tract reconstruction heavily depend on the specific algorithm and parameters used. Thus, careful consideration and standardization of these factors are essential for effectively utilizing LTD in surgical planning.

Surgical anatomy of language

Moving beyond the localizationist perspectives of language prevalent in the 19th and 20th centuries, contemporary research increasingly supports the view that language relies on a widespread network involving multiple regions and white matter tracts (Thiebaut de Schotten and Forkel 2022). This perspective contrasts with the more focal and clearly defined networks associated with primary functions, such as those seen in the motor system. The language network is thought to be more expansive and includes diverse areas and tracts. Recent studies have also highlighted that variability in anatomy is associated with variability in cognitive profiles, including language functions (Croxson et al. 2018; S. Forkel et al. 2023) for more details).

This complexity and variability underscore the critical need for individualized mapping of the language network in the preoperative stages of neurosurgical interventions. This need is further emphasized by the fact that damage to white matter structures is often less reversible than damage to cortical hubs (as discussed by (Duffau 2014; Trinh et al. 2013)). While cortical neuroplasticity allows for functional shifting to new cortical areas – a phenomenon observed over time in brains infiltrated by tumors (Rösler et al. 2014; G. Raffa et al. 2018) – white matter pathways cannot regrow over time. Therefore, a thorough understanding of their location and function is essential to prevent additional damage through disconnection. It makes precise white matter mapping indispensable in preserving language function during neurosurgical procedures.

Apart from more recent discoveries, like the middle longitudinal fascicle (MdLF), whose role is not yet understood and the corticospinal tract (CST) for motor speech articulation, the contemporary understanding of the language network encompasses the following key pathways:

The arcuate fasciculus is a key interlobar (fronto-parietal-temporal) association tract connecting the inferior frontal gyrus, inferior parietal lobe (SMg, Ag), and posterior temporal lobe (STg, MTg). This fasciculus can be viewed as a singular fronto-temporal pathway or as a structure comprising multiple branches (e.g. (Catani, Jones, and Ffytche 2005)). The nomenclature for its components varies across studies. Generally, there is agreement that the arcuate fasciculus includes additional segments that are more lateral compared to the primary fronto-temporal pathway: a fronto-parietal segment (sometimes called the horizontal or anterior component) and a parietal-temporal segment (often referred to as the vertical or posterior segment) ((Catani, Jones, and Ffytche 2005; S. J. Forkel, Friedrich, et al. 2022; Frey et al. 2008; Giampiccolo and Duffau 2022; Kaplan et al. 2010)). However, the exact endpoints of these components remain a topic of ongoing discussion and vary with different methodologies (Giampiccolo and Duffau 2022).

Functionally, the subsegments of the Arcuate Fasciculus (AF), primarily play a role in phonological processing and encoding, which involves the association of sounds with their respective meanings (Catani, Jones, and Ffytche 2005; Catani et al. 2007; Duffau et al. 2002; Mandonnet et al. 2007; Sierpowska et al. 2017). Additionally, the AF's involvement in semantic processing, which relates to the construction of meaning, as well as its role in syntactic processes, or the organization of sentence structure, have been increasingly recognized (Friederici 2015; Papoutsi et al. 2011; Blecher et al. 2019; Flöel et al. 2009; Vidorreta et al. 2011; Anderson et al. 1999; Duffau et al. 2002). This multifaceted functionality positions the AF as a critical network component supporting a variety of linguistic subskills, as highlighted in studies by (Turken and Dronkers 2011; Ivanova et al. 2021), also see (Vavassori et al. 2023) for a recent study in neurosurgery). Damage to the AF has a detrimental role to language, leading to deficits in expressive and receptive language abilities (Geva, Correia, and Warburton 2011; Hillis et al. 2018; Hosomi et al. 2009; Kim and Jang 2013; Rosso et al. 2015; S. J. Forkel, Thiebaut de Schotten, Dell'Acqua, et al. 2014).

Historically, and still prevalent in some literature, the terms 'superior longitudinal fasciculus' (SLF) and 'arcuate fasciculus' have been used interchangeably. While there is an overlap between the networks, such as between the SLF-III and the anterior segment of the arcuate fasciculus, other branches and segments are distinct. From anatomical and etymological standpoints, the superior longitudinal fasciculus should be defined as the fibers connecting frontal and parietal regions, aligning with its descriptor 'superior and longitudinal' (Thiebaut de Schotten et al. 2011). In contrast, the arcuate fasciculus is appropriately characterized as the fronto-temporal connection, with 'arcuatus' meaning 'arching' around the Sylvian fissure (Dulyan & Forkel, submitted).

The Frontal Aslant Tract (FAT) represents an intralobar connection within the frontal lobe, linking the inferior frontal gyrus to the superior frontal gyrus (Thiebaut de Schotten et al. 2011; Vergani et al. 2014). The FAT can be effectively delineated using a method involving two ROIs. It is believed to play a crucial role in facilitating fluent speech and aiding in speech initiation (Catani et al. 2012; Dick et al. 2019; Vergani et al. 2014). Damage to the FAT has been associated with various speech impairments, including stuttering, speech arrests, and in less severe cases, a reduction in speech rate (F. Vassal et al. 2014; Kemerdere et al. 2016; M. Li et al. 2017; Dragoy et al. 2020). This highlights the FAT's significance in the neural network governing speech production and execution.

The uncinate fasciculus (UF) forms a crucial fronto-temporal association connection and is recognized as a component of both the limbic network and the language system (Catani, Dell'acqua, and Thiebaut de Schotten 2013; S. J. Forkel, Friedrich, et al. 2022)). The uncinate fasciculus converges in the ventral portion of the external capsule and extends into the orbitofrontal and anterior temporal lobes. The functional significance of the UF remains debated within the neurological community. The inconsistency in deficit patterns arising from damage or virtual lesions to the UF, induced through stimulation, further complicates our understanding. These deficits encompass a range of disturbances, from phonological and phonemic to semantic (Giovanni Raffa et al. 2016; Mandonnet, Gatignol, and Duffau 2009; Papagno et al. 2011, 2016). Such varied outcomes mirror the observations from neurological pathologies, suggesting a complex and multifaceted role of the UF in cognitive processing. These findings, collated from clinical interventions and pathological studies in patients with primary progressive aphasia (Mesulam et al. 2009; D’Anna et al. 2016), highlight the need for a more nuanced understanding of the UF's contribution to brain function.

The inferior longitudinal fasciculus (ILF) is an association tract linking the occipital and ventral temporal lobes. It comprises both long-range medial connections and shorter lateral ones, bridging early and late visual cortices and extending into the occipital and temporal lobes (Catani et al. 2003). The ILF plays a role in connecting the occipital visual areas with the amygdala and hippocampus and higher-order visual areas within the temporal lobe. The role of the Inferior Longitudinal Fasciculus (ILF) in cognitive functions related to literacy and visual object recognition is more clearly established and substantiated in the literature. Notably, damage to the ILF frequently results in consistent deficits in semantic processing, reading, and writing. However, these impairments are not always irreversible, suggesting potential for recovery or neuroplastic adaptation (Mandonnet et al. 2007; Ortibus et al. 2012; Sarubbo et al. 2015; Gil-Robles et al. 2013). Further expanding on this, research has indicated that the ILF is crucial in integrating visual information with linguistic processing, linking visual cortex areas to language processing centers. This connection is vital for comprehending and interpreting written language and recognising objects and faces, an essential aspect of visual cognition (Catani and Thiebaut de Schotten 2008; Mandonnet, Gatignol, and Duffau 2009; Mandonnet et al. 2007; Martino and De Lucas 2014).

The inferior fronto-occipital fasciculus (IFOF) is a white matter tract that facilitates connections between the occipital and frontal cortices. It originates from the cuneus, lingual gyrus, posterior fusiform gyrus, and occipital pole in the posterior region. As it progresses from the occipital lobe into the temporal stem, its fibers converge at the level of the external/extreme capsule, just above the uncinate fasciculus. In the frontal lobe, these fibers form a thin sheet that extends towards the inferior frontal gyrus, medial orbitofrontal region, and frontal pole. The IFOF's complex history can be reviewed in works by (S. J. Forkel, Thiebaut de Schotten, Kawadler, et al. 2014; Schmahmann and Pandya 2007; Türe, Yaşargil, and Pait 1997). Its nomenclature, with the term 'inferior' suggesting the existence of a 'superior' fronto-occipital fasciculus, is a remnant of its historical interpretation. While this term persists in some atlases, such as the John Hopkins University (JHU) atlas (Mori et al. 2005), several studies using diverse methodologies have questioned the existence of a 'superior' counterpart (see (S. J. Forkel, Thiebaut de Schotten, Kawadler, et al. 2014; Liu et al. 2020; Meola et al. 2015)).

The IFOF plays a key role in assigning meaning to visual inputs. Disruptions to the IFOF, particularly during surgical procedures, have frequently been observed to result in semantic deficits. This correlation has been extensively documented in various studies, including those by (Jarret et al. 2022; Duffau et al. 2005; Leclercq et al. 2010; Maldonado et al. 2011; Botha et al. 2015; Ivanova et al. 2016; Bello et al. 2007, 2008; De Witt Hamer et al. 2011). These findings underscore the IFOF’s significant role in the neural processing of semantic information, highlighting its importance in the cognitive network of language and visual processing.

The Vertical Occipital Fasciculus (VOF) forms connections between the dorsolateral and ventrolateral visual cortex. This pathway includes the Visual Word Form Area (VWFA), located in the ventral occipitotemporal cortex, which specializes in the visual processing of words and reading (Dehaene et al. 2002; S. J. Forkel, Labache, et al. 2022; Wandell, Rauschecker, and Yeatman 2012). This area is significant for its role in reading and word recognition. The earliest detailed account of the occipital lobe's white matter was provided by Heinrich Sachs in his atlas, ‘The white matter of the human cerebrum. Part 1. The Occipital Lobe’ (S. J. Forkel et al. 2015; S. J. Forkel 2015). Under the encouragement of his mentor Carl Wernicke, Sachs made significant contributions to our understanding of cerebral anatomy. The atlas was envisioned as part of a more extensive series exploring each tract's function and clinical relevance. With advancements in tractography and Klingler dissections, researchers have recently revisited and further elucidated the occipital white matter (Bugain et al. 2021; Vergani et al. 2014). To accurately identify the VOF, two Regions of Interest (ROIs) are placed—one in the ventral and another in the dorsal occipital lobe. These ROIs are outlined on axial slides to be perpendicular to the vertical fiber system. The dorsal ROI is posterior to the parieto-occipital sulcus (POS), while the ventral ROI is posterior to the occipital notch. The most lateral part of the occipital region, featuring the preoccipital (or temporo-occipital) notch, serves as a boundary between the inferior temporal gyrus and the ventral surface of the inferior occipital gyrus, sometimes continuing with the inferior temporal sulcus. The delineation of the occipital lobe's borders is based on landmarks between the POS and the notch, distinguishing the occipital lobe from the adjacent temporal and parietal lobes.

Figure 4 summarises the language-related network in the left hemisphere (LH), outlining their presumed functions based on current research. This overview illustrates the specific contributions of tracts like the ILF and the interconnected nature of these pathways in supporting the broader network of language processing and cognitive functions in the brain.

The traditional viewpoint in neuroscience has long emphasized the dominance of the left hemisphere (LH) in language functions, leading clinical research to concentrate primarily on LH regions. However, this perspective is being reevaluated due to emerging evidence and clinical observations. Notably, in cases involving slow-growing tumor masses, neuroplasticity can lead to the right hemisphere (RH) assuming more significant roles in language processes, traditionally attributed to the LH. Recent studies are increasingly questioning the notion of the RH playing only a secondary role in language (Sarubbo et al. 2020; Vilasboas, Herbet, and Duffau 2017; Hartwigsen et al. 2010, 2013; Jung and Lambon Ralph 2016; Rice, Lambon Ralph, and Hoffman 2015).

Consequently, contemporary clinical methodologies advocate for mapping cortical and subcortical white matter (WM) areas in the RH. This approach aims to preserve these areas from potential damage during surgical resection. Intraoperative language mappings have highlighted the importance of networks in the RH, emphasizing its involvement in various linguistic processes, both verbal and non-verbal, that are crucial to preserving (Chang et al. 2011; Tate et al. 2014; M. Vassal et al. 2010; Vilasboas, Herbet, and Duffau 2017; Herbet, Moritz-Gasser, and Duffau 2017).

In recognition of the integral roles played by both hemispheres and encompassing all relevant lobes and tracts, the upcoming subsection will detail the methodologies for effectively capturing and visualizing individual language networks in a case report. This comprehensive approach highlights the importance of considering the entire cerebral landscape in the study and clinical treatment of language functions.

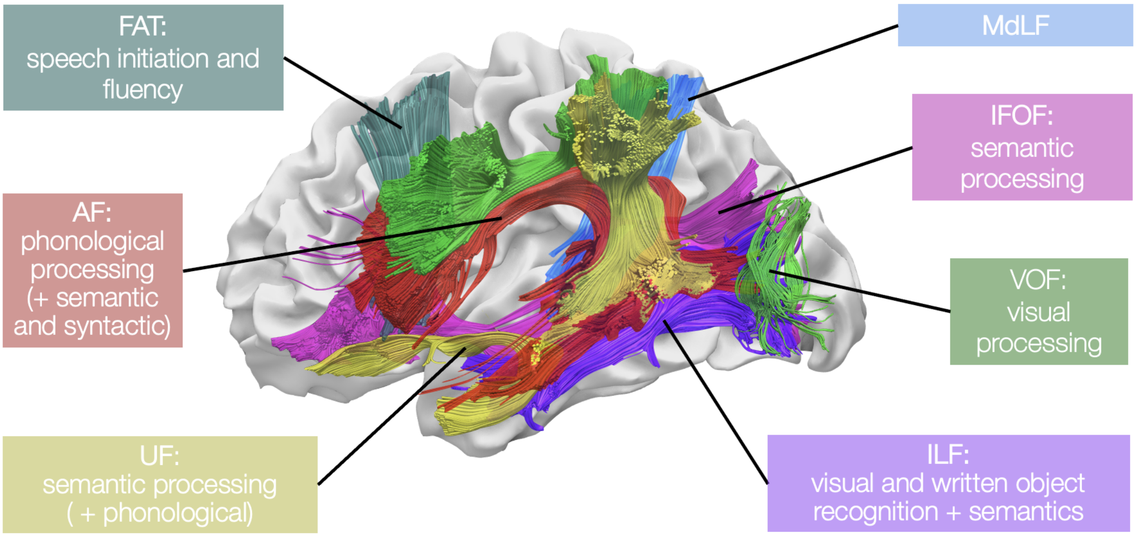

Figure 4: *Summary of language networks in the left hemisphere.*

Part 3: Illustrative case

In this section, we delve into a complex and instructive case of a 51-year-old patient presenting with language difficulties due to a brain lesion. The case highlights the intersection of advanced neuroimaging, meticulous surgical planning, and the critical role of neuromonitoring in managing brain pathologies located in functionally significant areas. Through this patient's journey, we explore how integrated approaches in neurosurgery, combining preoperative tractography, navigated Transcranial Magnetic Stimulation (nTMS), and minimally invasive surgical techniques, can effectively address challenging neuro-oncological cases while preserving essential cognitive and motor functions.

A 51-year-old individual with a history of lung sarcoidosis came to the hospital, experiencing newly developed difficulties in finding words and hesitancy in speech. Diagnostic imaging revealed a lesion in the anterior limb of the internal capsule, characterized by solid and cystic components, exerting a mass effect in the area (as shown in *Figure 5*). Following thorough discussions involving the patient and the neuro-oncology multidisciplinary team (MDT), it was decided to proceed with a maximal safe resection. This approach involved using a transsulcal minimally invasive parafascicular surgery (MIPS) technique, complemented by integrated neuromonitoring and mapping before and during the operation.

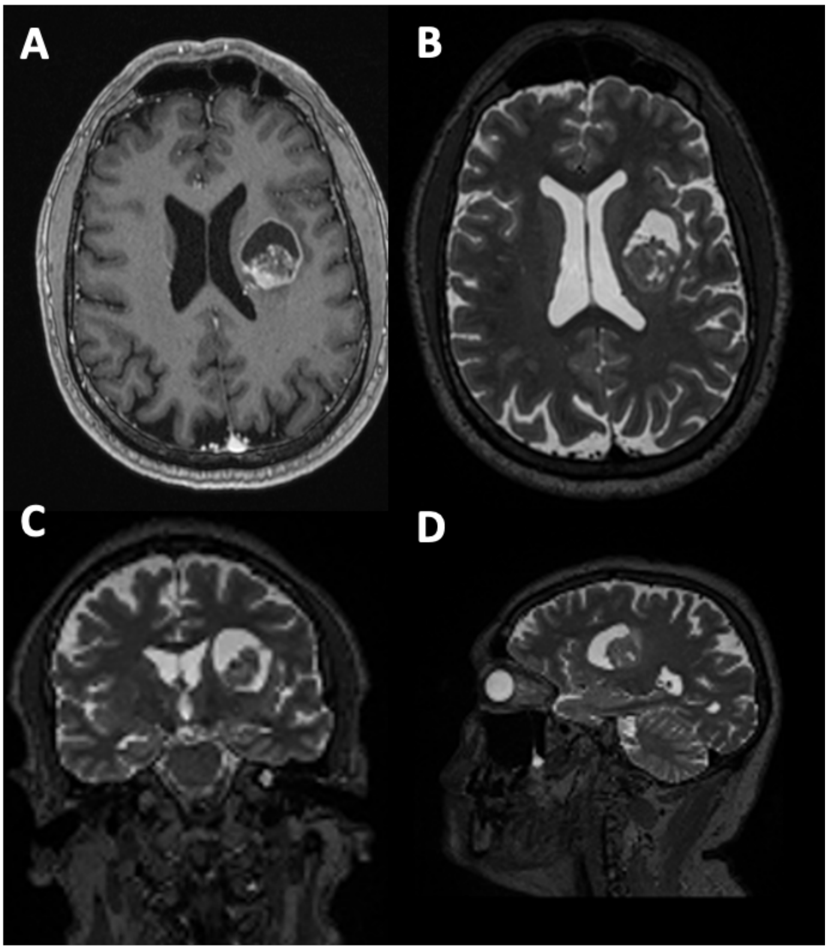

***Figure 5 – Diagnostic structural image** – Axial T1-weighted with gadolinium (A), T2-weighted axial (B), coronal (C) and sagittal (D) images showing an intrinsic lesion with mixed cystic-solid characteristics within the anterior limb of corona radiata (central core).*

Preoperative tractography targeting specific tracts of interest was conducted using an anatomically guided, manual segmentation approach. This method involved careful delineation based on anatomical landmarks to accurately identify and visualize the relevant neural pathways:

1. For the Corticospinal Tract (CST), ROIs were precisely placed in the pre-central gyrus and the ipsilateral cerebral peduncle to ensure accurate tract visualization.
2. For the Fronto-Aslant Tract (FAT), ROIs were established in the superior frontal gyrus and the ipsilateral frontal operculum for detailed mapping.
3. In the case of the Arcuate Fasciculus (AF), ROIs were placed in the frontal operculum and extended to the posterior temporal lobe, encompassing areas toward the angular and supramarginal gyri for comprehensive tract visualization.

4. The inferior fronto-occipital fasciculus (IFOF) was mapped with an ROI positioned in the frontal lobe, lateral to the frontal horn, and another ROI in the ipsilateral stratum sagittale to capture its full trajectory.

nTMS was carried out on the same side as the lesion (ipsilateral). For motor mapping of both upper and lower limbs, resting motor thresholds (RMT) were set at 25% for the upper limb and 65% for the lower limb, with positive responses defined by an amplitude threshold of 50 microvolts. Language mapping involved using repetitive nTMS at 7Hz, set to 110% of RMT, utilizing the VAN-POP Test (Ohlerth et al. 2020), which is tailored for native English speakers. Positive language responses were detected at the conjunction of the AF and FAT in the pars opercularis during object naming, and at most anterior and posterior superior frontal gyrus terminations of the FAT during past tense action naming tasks, as shown in *Figure 6*.

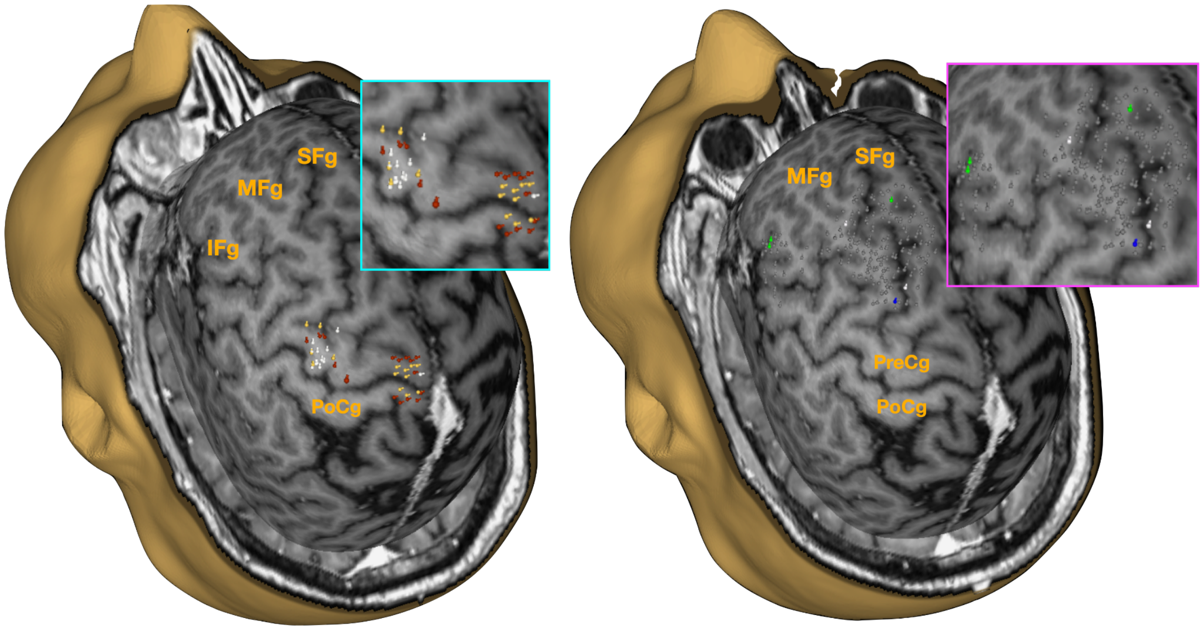

***Figure 6** – nTMS motor (left) and language (right) mapping. The motor mapping is visually represented using a color-coded voltage scale: red dots indicate responses within the 50-500 microvolts range, yellow dots for 500-1000 microvolts, and white dots for responses exceeding 1000 microvolts. In the language mapping panel, different colors denote various response types: grey dots represent negative responses, green dots indicate performance errors, white dots signify no response, and blue dots are used to mark semantic errors. This color-coding provides a clear and concise visual representation of the motor and language areas as identified by nTMS.*

A three-dimensional model of the tumor was created and seamlessly integrated with both cortical and subcortical mapping data. Utilizing this combined model, a transsulcal approach for brain cannulation was planned through the superior frontal sulcus. This carefully chosen surgical corridor ran parallel to the AF and the CST, and navigated through the middle third of the FAT, deliberately avoiding areas where the FAT terminates that showed positive responses in nTMS language mapping. Additionally, the cortical region surrounding the selected cannulation site showed no language-related activity in the nTMS mapping, as indicated in *Figure 7*.

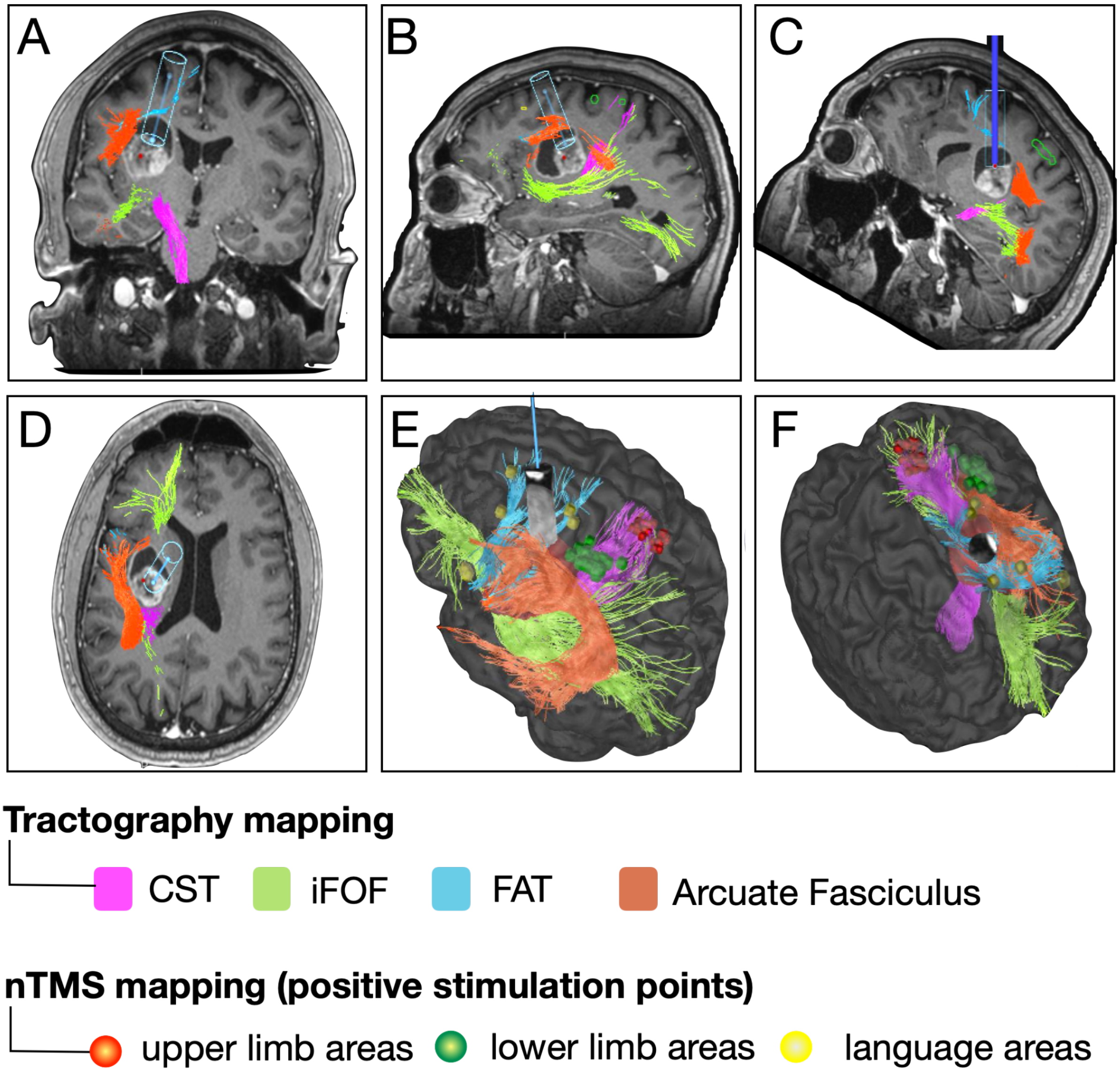

Figure 7 – Integrated Preoperative Cortical and Subcortical Mapping *This figure illustrates detailed motor and language mapping in various perspectives: coronal (A), sagittal (B), a trajectory view (C), axial (D), and a comprehensive 3D model (E-F).*

An awake craniotomy was conducted, allowing for real-time intraoperative monitoring and mapping. The frontal operculum remained unexposed due to the Minimally Invasive Parafascicular Surgery approach targeting the superior frontal gyrus. Owing to the absence of positive language responses in the nTMS mapping and the lack of speech arrest, cortical mapping was not deemed necessary. During the procedure, brain cannulation took place concurrently with VAN-POP testing, which did not reveal any language deficits. Throughout the tumor resection, continuous language and motor mapping were employed. This process was halted once functional margins were identified, marked by reversible language disturbances such as hesitations (laterally) and semantic errors (inferiorly), as well as corticospinal tract responses at 4mA with high-frequency stimulation. The details of this phase are depicted in Figure 8.

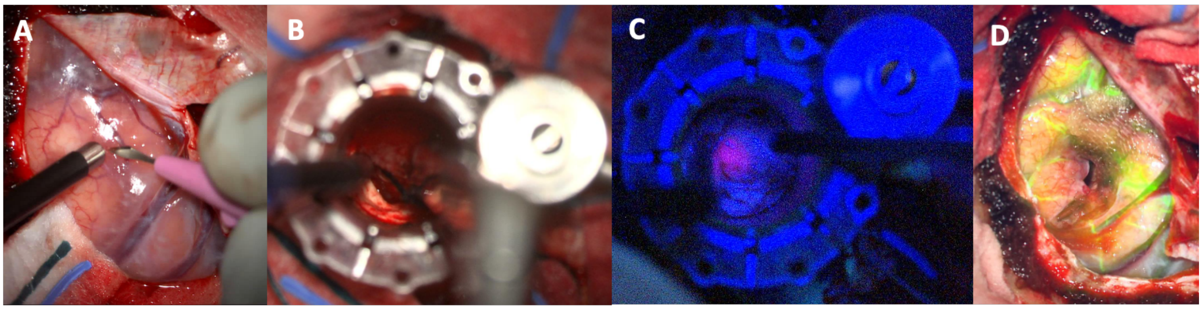

Figure 8 – Surgical Procedure – *It begins with a small craniotomy precisely centered over the superior frontal sulcus, followed by the opening of the overlying arachnoid membrane (Panel A). The process then proceeds to brain cannulation and the resection of a tumor that tested positive for 5-aminolevulinic acid (5-ALA), as shown in Panels B and C. Finally, Panel D illustrates the decannulation stage post-tumor resection, with use of indocyanine green to confirm the patency and integrity of the cortical vascular structures.*

Following the surgery, the patient successfully recovered without any language or motor impairments. Postoperative care included the continuation of oncological treatment (*Figure 9*).

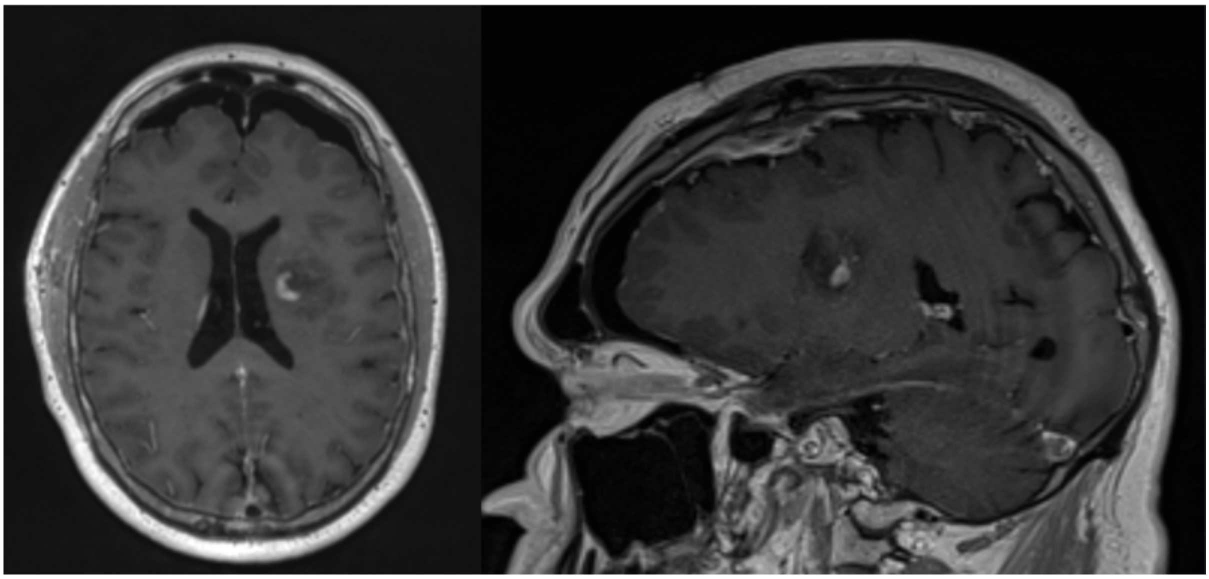

Figure 9 *– Postoperative Imaging– Axial (A) and Sagittal (B) views captured after the tumor resection. These images confirm the absence of complications and show the presence of hemostatic material at the surgery site, indicating a successful procedural outcome.*

Conclusion

In conclusion, this chapter has highlighted the critical importance of tractography and navigated Transcranial Magnetic Stimulation (nTMS) in neurosurgery, particularly for preserving language functions. Tractography provides invaluable insights into the intricate white matter tracts, while nTMS offers functional cortical localization. Their combined use in preoperative planning has revolutionized surgical approaches, maximizing outcomes and safeguarding vital human capabilities.

The presented case exemplifies the effectiveness of these techniques in managing complex brain lesions. Integrating advanced neuroimaging and neuromonitoring facilitated a tailored surgical intervention, successfully preserving the patient's cognitive and motor functions. This case underscores the transformative potential of combining anatomical and functional mapping in neurosurgery, paving the way for more personalized and precise treatments. As the field continues to evolve, such integrated approaches will undoubtedly play a pivotal role in enhancing patient care and outcomes in neurosurgery.

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