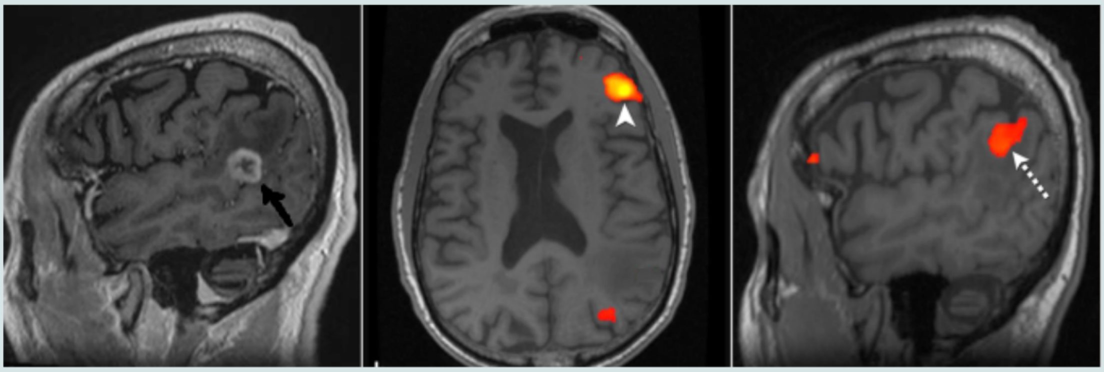
BrainSightAI

VoxelBox+ Glioma V4

Advancing the pre-surgical planning and survival analysis of Glioma



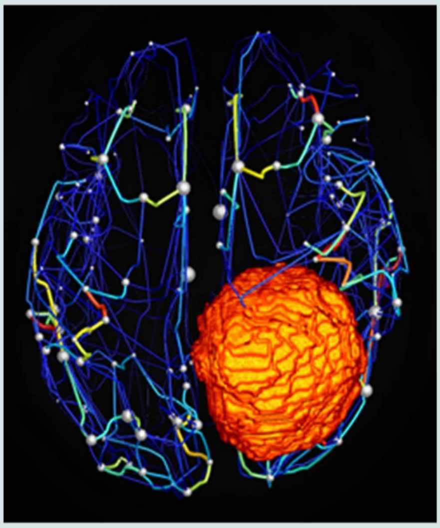


Image Credit: Aerts et al, 2018

Abstract

Glioma is a common type of CNS tumor and has a poor survival rate. Accurate detection and classification of the tumor is crucial to improve treatment outcomes among patients. Tools that can aid neurosurgeons in crucial tasks such as eloquent cortex mapping and predicting the tumor dynamics can significantly improve the quality of surgical treatment. Task-based fMRI and sMRI, the current modalities to perform these critical tasks, suffer from various drawbacks. To address these challenges, BrainSightAI is building a suite of advanced computational neuroscience tools, called VoxelBox and VoxelBox+ Glioma, to aid in more personalized presurgical planning. VoxelBox analyzes the functional activity and connectivity patterns and anatomical details from resting-state functional MRI, structural MRI, and DTI, whereas VoxelBox+ Glioma overlays it with artificial intelligence and 3D technology. These analyses enable investigation into several use-cases, such as mapping of functional networks, fiber tracts, segmentation of tumor, and classification of tumor grade and subtype. The details of these use-cases are discussed in this paper.

1. Glioma- The Fatal Disease

Glioma is the most common primary CNS tumor and a difficult form of tumor to treat with a low 5-year relative survival rate [1]. Recurrence of high grade Glioma like Glioblastoma is often inevitable [2] and exhibits intra-tumor heterogeneity making the design of the treatment regime more difficult [3][4][5].

Diagnostic tests are critical for developing treatment plans and also to inform prognosis, prediction, and assessment of treatment response, disease progression, and recurrence. However, it is difficult to precisely classify Glioma from other types of CNS tumors such as meningioma, pituitary adenoma, and metastatic tumors like metastatic bronchogenic carcinoma due to the lack of distinct characteristics in MRI scans. This might lead to misdiagnosis or late diagnosis affecting the overall survival of the patient.

2. Challenges faced by Clinicians

2.1 Challenges faced by Neurosurgeons

The mode of treatment of Glioma is greatly dependent on prognosis of the tumor which in turn is dependent on tumor properties like location, type, grade, and direction of growth. Although the histopathological characteristics of glioma studied from a post-operative pathological sample is considered as the gold standard biomarker for grading the tumor and predicting patient survival, it suffers from significant limitations. It gives crucial information about the tumor properties and dynamics after the surgery leading to a non-timely report which cannot be used

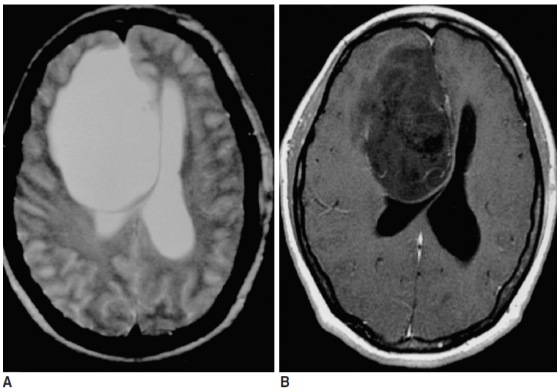


Figure 1- *Low-grade astrocytoma A:T2-weighted MR image B: Enhanced T1-weighted showing no contrast enhancement [6]*

in early prognosis and pre-surgical planning. Also, histopathology is often unable to pick on the tumor heterogeneity thereby greatly affecting the treatment course.

With an intention to get more information about the tumor dynamics before the surgery, MRI sequences like T1w, FLAIR, T2w gradient echo and post-contrast T1w images are commonly used. Although these sequences provide details on the anatomical location and detection of compromised blood-brain barriers using gadolinium-based contrast agents, it is difficult or sometimes impossible, to distinguish the histological type and grade of the glioma (e.g.: grade II versus grade III tumors, or oligodendroglioma versus astrocytoma)[6][8] as shown in Figure 1. Sometimes, what appears to be low grade gliomas are in fact grade III or grade IV tumours [7]. It is also difficult to predict the direction of tumor growth by just looking at MRI sequences.

Combination of different neuroimaging techniques like DTI, DWI, PWI, MRS and PET can be used to get more insights about the tumor but it is difficult to interpret these multimodal scans[6][8] in conjunction.

Along with tumor dynamics, the identification of important functional areas close to the tumor is crucial for planning the surgery to ensure maximal resection of tumor and minimal functional loss. Imaging techniques such as task based-fMRI is used to identify the functionality (motor, language, and visual networks) around the pathological area but suffers from various challenges. It needs specific hardware and software for delivery of the task-related stimuli, different scans must be performed for each network, a dedicated personnel for evaluating patient's cognitive status, selecting the tasks, and assessing task performance. Also, it cannot be performed on nonresponsive patients (e.g., coma or vegetative state). Moreover, it doesn't give information on other crucial networks, such as default mode network, frontoparietal network and salience network, which greatly dictates an individual's cognition and emotions.

Despite these challenges, task based-fMRI can help in identifying the brain networks for responsive patients. However, it can't be used for higher level analysis - as it is difficult to predict the post-surgical functional outcomes due to complex non-linear dynamics of the brain and the modifications of brain activity due to the surgery.

Thus, it is difficult for a neurosurgeon to do pre-surgical and prognostic planning due to limited available information on tumor dynamics and its impact on functional connectivity.

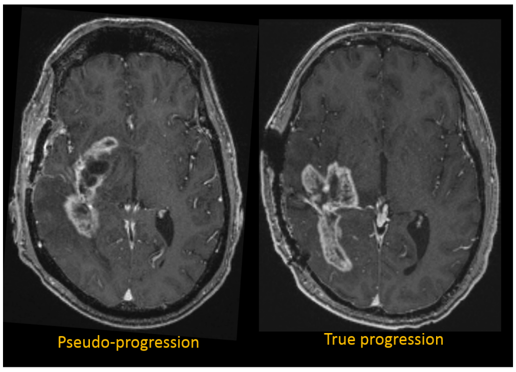


Figure 2- *Treatment effect and True progression*
Image:https://consultqd.clevelandclinic.org/using-machine-learning-to-distinguish-brain-tumor-progression-from-pseudoprogression-on-routine-mri/

2.2. Challenges faced by Neuro-Radiologists

During follow-up, new lesions may be seen as adverse effects of the radiotherapy and chemotherapy. These may mimic tumor progression or recurrence in post contrast MRI as shown in Figure 2, making it very challenging for the radiologist to distinguish between these. The treatment effect, labeled "pseudoprogression," is seen in approximately 20–30% of patients within 3 months of combined chemotherapy (temozolomide) and radiotherapy.

Further, radiation necrosis typically occurs within a year but cases have been reported as late as 6 years to 7 years after radiation treatment. Advanced imaging techniques such as Dynamic susceptibility contrast (DSC), Dynamic contrast-enhanced (DCE) MRI or PET/SPECT can be used but have shown mixed results[9][10][11].

These challenges faced by neurosurgeons and radiologists have a significant impact on the patients and may lead to multiple surgeries and higher expenses.

3. BrainSightAI Engine

BrainSightAI aims to combine the functional architecture of the brain through analysis of resting-state fMRI, with the anatomical details obtained through sMRI and DTI. It further aims to add advanced machine learning and 3D simulation models to it to answer crucial clinical questions around it.

BrainSightAI's advanced computational neuroscience tools aim to empower doctors to do a functional and structural investigation of the brain, thereby enabling appropriate prognosis and individualized pre-surgical planning thus improving patient outcome.

Pre-processing of rs-fMRI gives functional connectivity and activity patterns of the brain. By adding AI models to the mix, the BrainSightAI engine will help in answering a wider range of questions and as data gathering increases, provide predictive capabilities.
For example, the powerful AI engine will provide a quantitative estimate of the probability of overall survival of the patient by extracting critical tumor properties like type, subtype, grade and direction of tumor growth from neuroimaging before the surgery.

For familiar visualisation of results of BrainSightAI engine, these AI outcomes will be mapped back to the MRI space, using the 3D visualization tools of Dassault Systemes.

Apart from the AI engine, BrainSightAI will also provide a 3D simulation engine for understanding, designing and parametrizing real-world surgical decisions.

Thus, BrainSightAI's VoxelBox can serve as a great tool to improve the treatment workflow, as shown in Figure 3, which helps the doctors in making more evidence-based decisions using risk-based cutoff points.

Below we provide a few of the use-cases that our technology can be proved useful for.

3.1. Mapping of eloquent cortex

3.1.1. Pre-surgical mapping using rs-fMRI and AI

Surgical treatment of tumors in close proximity to eloquent areas remains a challenge, and eloquent location is a risk factor for disease progression and poor overall survival [34][32]. Determining the anatomical location is not enough to determine resectability of a tumor because it does not represent functional activity and connectivity with its inter-individual variations. Thus, functional patterns as well as anatomical locations are required to elevate the risk of surgery-related deficits[32]. Megan et al. [33] have shown the potential of rs-fMRI in determining the functional activity and connectivity of the eloquent location. Multiple studies [28][29][30] have also shown good overlap between the networks exhibited in rs-fMRI and the areas of task based-fMRI activation (elicited by motor, language, and visual tasks) . Domenico et al. [31] have worked on evaluation of the spatial agreement between rs-fMRI networks and localization of activation with intraoperative direct electrical stimulation (DES) on 6 patients and have achieved promising results, as shown in Figure 4.

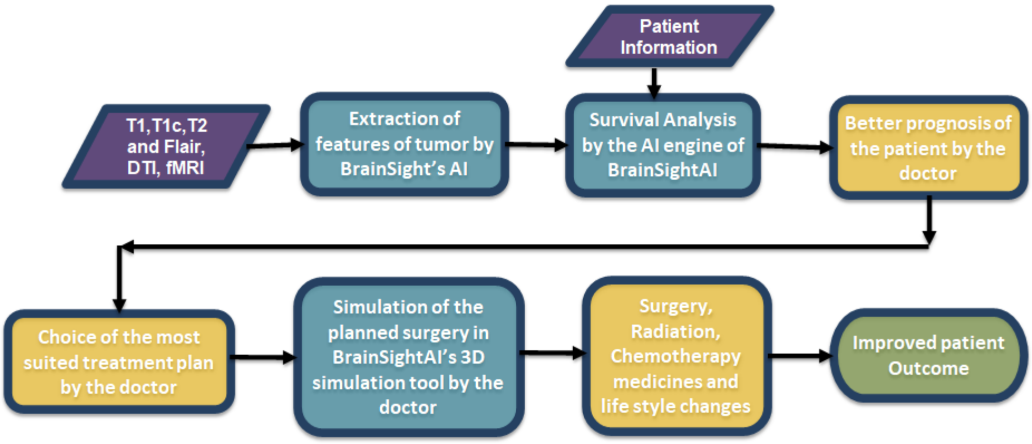


Figure 3- *Diagnosis and treatment Workflow*

BrainSightAI has corroborated this by performing independent component analysis (ICA) on rs-fMRI data to extract eloquent cortex mapping (Motor, Language, and Visual Mapping) for right temporal lobe High Grade glioma,as shown in Figure 5. The accuracy of the mapping will improve further by clinical collaborations.

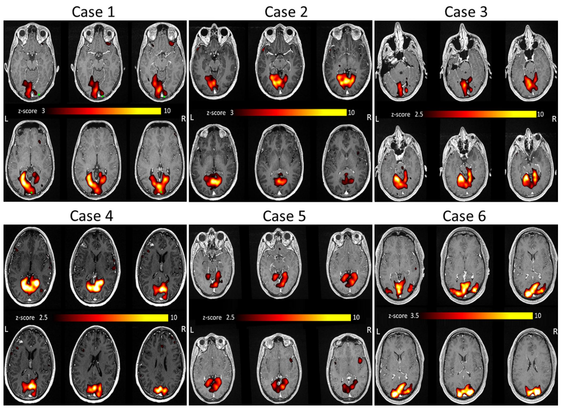
These studies show that rs-fMRI can be used as an eloquent cortex mapping tool in supplement to other imaging modalities such as task-based fMRI, and in cases where it is not possible to get other modalities, resting-state fMRI can provide valuable presurgical information.

3.1.1.1. 3D Visualization and Simulation

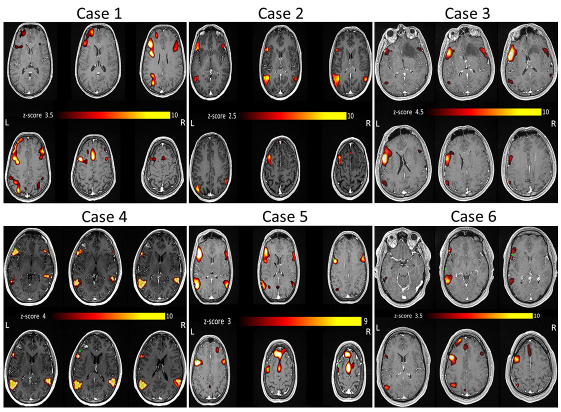
BrainSightAI will also develop neurosurgeon-friendly 3-d models of the brain in partnership with Dassault systemes and General Electric (GE). The computational neuroscience (AI) results will be mapped back to the MRI space as 3D models to enable the neurosurgeon to envision the planned surgery around the operative region.

The fact that we are able to map back the AI results to the MRI space, is due to the fact that we use a subset of algorithms called Traceable AI. We believe that for wide adoption of innovative technology, it's important to build interfaces that put the power back in the hands of their human users. Black box AI algorithms make users feel powerless, as doctors are not able to question the results. Our focus at BrainSightAI is on algorithms which expose the black box working and can be mapped to the 3D space.

We aim to build 2 types of 3-D models. One is an atlas-based 3-D model as shown in Figure 6(a). The other is based on a 3D imaging fabric, depicted in Figure 6(b), helping the neurosurgeons to map the AI results to the physiology of the brain.



(a)



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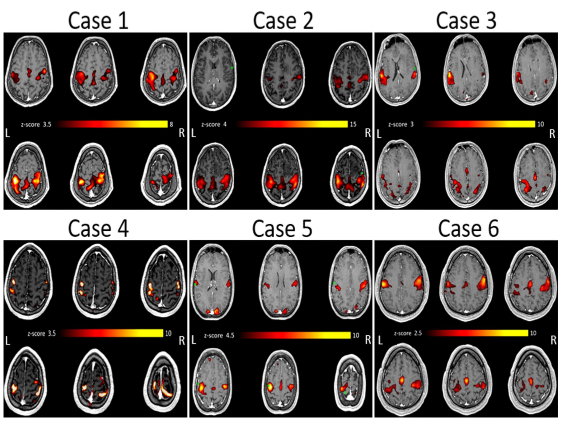
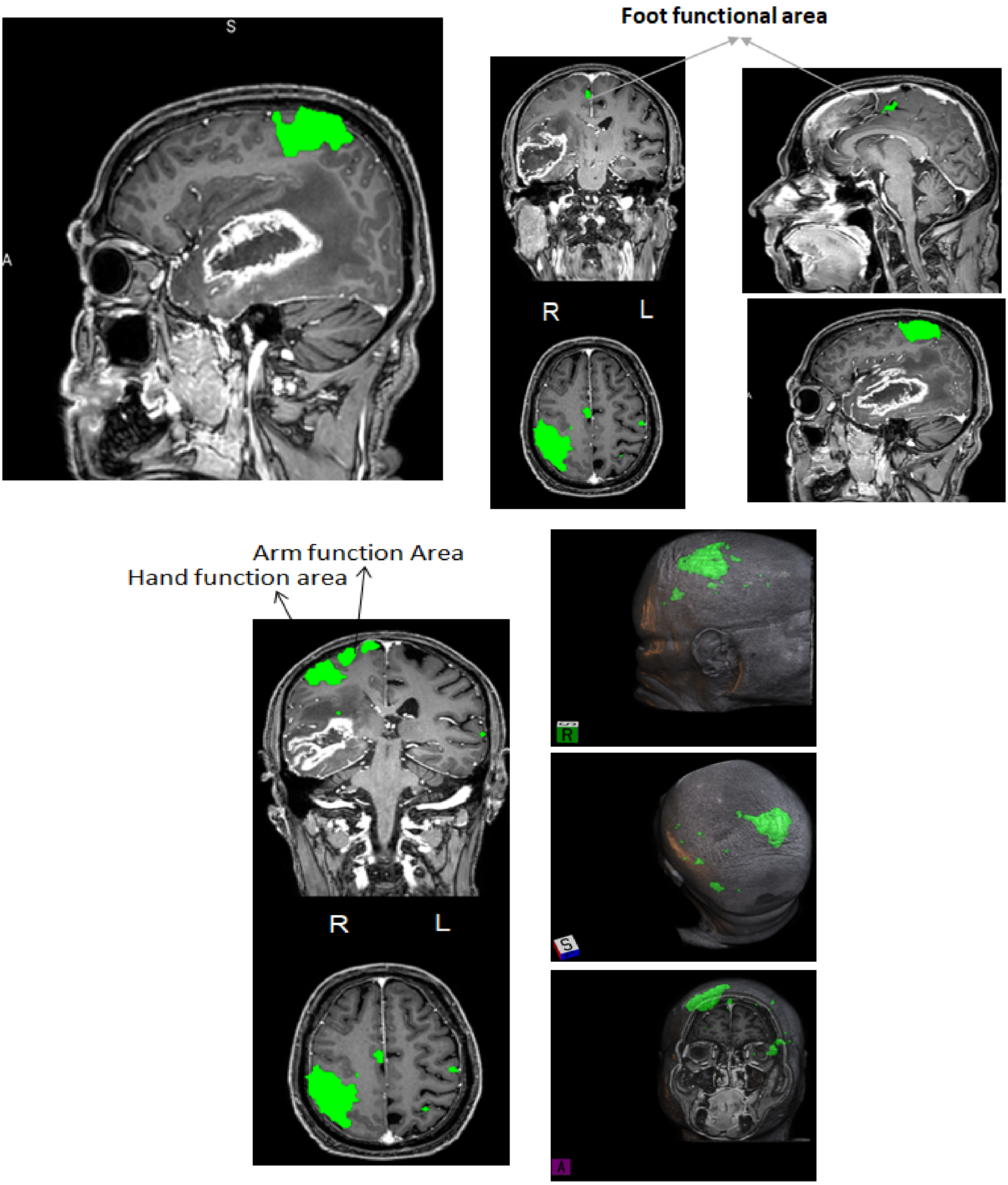


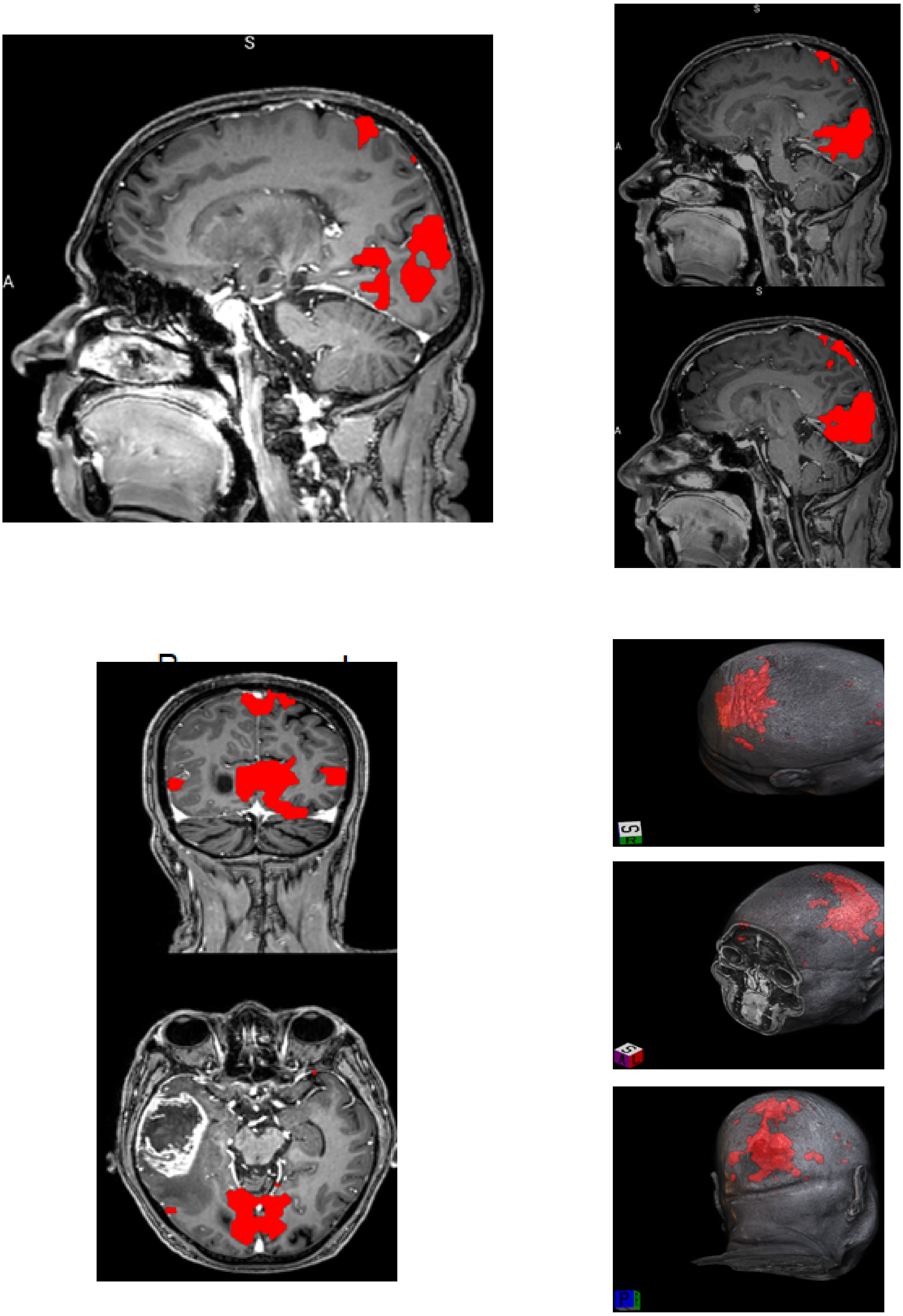
(c)

Figure 4: *(a) Visual mapping (b) Language mapping (C) Motor mapping [31]*

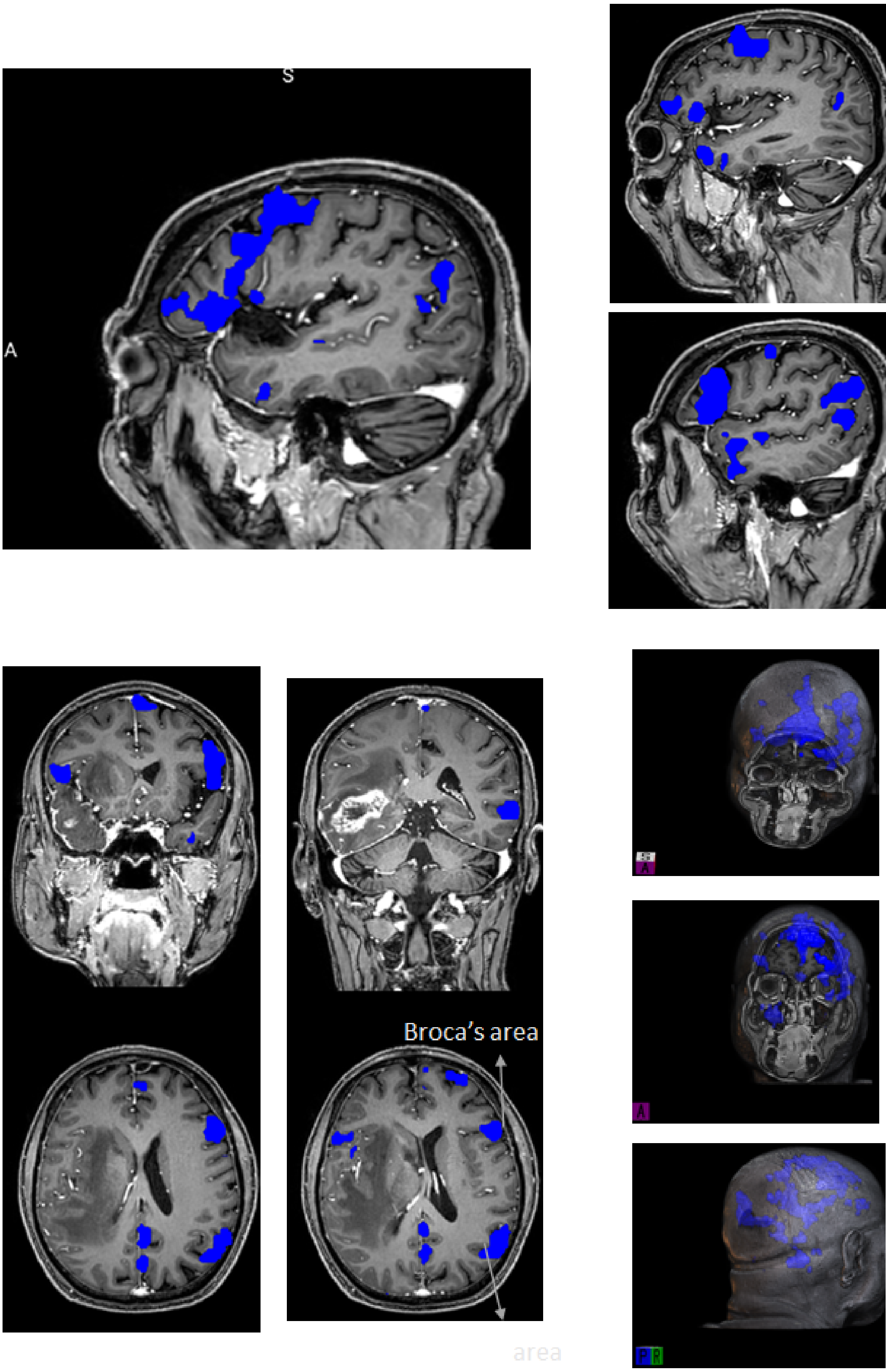
Figure 5: Presurgical Brain Network MappingI for Right temporal lobe High Grade glioma by BrainSightAI



(a) Motor mapping



(b) Visual mapping



(c) Language mapping

Furthermore, using physics-based simulation tools provided by Dassault Systemes in combination with our neuroimaging data, BrainSightAI will develop a 3-D simulation tool to simulate the impact on the functionality of the brain due to structural and connectivity changes as per the planned surgery.Thus, it will allow neurosurgeons to simulate the outcomes of various procedures preoperatively, guiding the surgical plan.

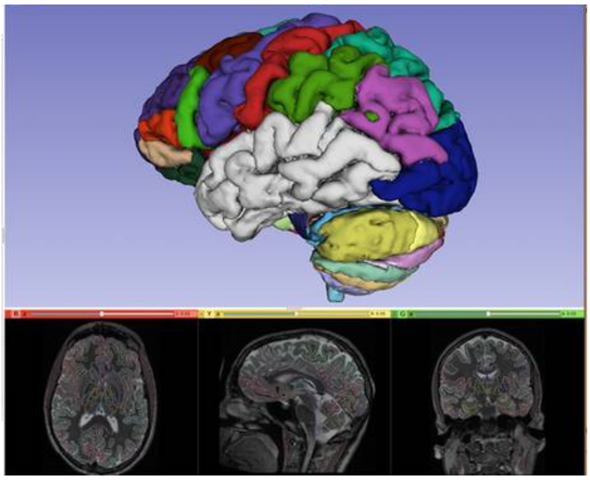


Figure 6(a): *Atlas-based 3-D model of brain [50]*

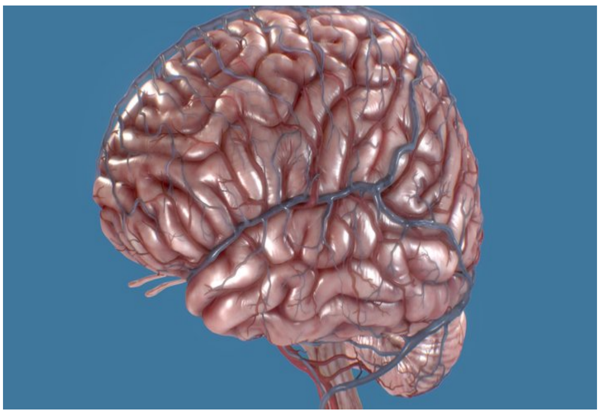


Figure 6(b): *3-D model of the brain [51]*

3.1.2. Intraoperative mapping

It takes multiple attempts and time by technicians to locate intra-operative eloquent cortex locations by direct electrical stimulation (DES), which also dictates the accuracy of mapping.

Rs-fMRI can be used as a complementary tool to solve this challenge. Domenico et al. [31] show a good correlation between eloquent cortex mapping results of pre-surgical rs-fmri and intra-operative DES. Thus, the mapping results from pre-surgical rs-fMRI can guide the technician to perform intra-operative electrical stimulation reducing the time, number of cortical DES attempts (especially speech arrest or motor) as well as improving the accuracy of localization of eloquent areas.

3.1.3. Eloquent cortex mapping at Follow-up after the surgery-Postoperative mapping

Surgery carries its own risks and complications that can give rise to additional functional deficits such as Prosopagnosia [35][36]. The degree of such deficits depends upon the spatial proximity of the area of resection to the important functional areas of the brain. Postoperative eloquent cortex mapping using rs-fMRI can be very beneficial to track these changes that have occurred in the functional and connectivity patterns of the brain after the surgery.

This postoperative mapping can be beneficial in two ways:

1. It can highlight the success rate of the surgery.

2. The deficit areas indicated by it can be used to plan the neurorehabilitation and monitor the progress [53].

3.2. Mapping of “Non-Eloquent” Networks

Over the past decade, anatomical understanding of brain function has evolved from a purely localizationist perspective to a network-based approach, for which rs-fMRI has been gaining popularity[40]. While the eloquent cortex is the most commonly mapped network, there is an increasing focus on preserving other networks such as default mode, frontoparietal, salience, attention (dorsal and ventral), memory, and emotional networks. These networks, though not considered “eloquent”, are associated with important brain functions such as self-awareness, cognition, executive function, and social behavior. Hence, mapping of these networks can also be of paramount importance during the presurgical planning to ensure minimal functional deficit with maximal tumor removal.

Michael et al. [40] reviewed the methods for mapping cognitive and emotional networks using rs-fMRI and discussed possible applications in neurosurgical patients. They generated all four RSNs (Default Mode Network, Frontoparietal Network, Salience Network, Dorsal Attention Network) using seed-based correlation analysis of rs-fMRI as shown in Figure 7(a).

Maxime et al. [49] present an interactive method to generate and visualize tractography-driven resting-state functional connectivity, which reduces the bias introduced by seed size, shape and position. Figure 7(b) depicts the tractography-driven reconstruction of the default mode network applied to a neurosurgical case.

Thus, rs-fMRI can greatly help in gaining holistic information about the various brain networks and their associated functions [43]. It can not only help doctors make more informed decisions about whether or not to opt for surgery but also can aid the development of comprehensive rehabilitation plans significantly improving quality of life.

Based on these proof of concepts, BrainSightAI can also generate the resting state networks along with Eloquent cortex mapping.

3.3 DTI Fiber tracts-

Diffusion tensor imaging (DTI) is also increasingly being used in the tumor surgery to ensure minimal functional loss. Whereas sMRI techniques provide only anatomical information, DTI gives crucial data on the connecting fibre tracts allowing neurosurgeons to better guide their surgical approach and resection.

Kalil et al.[41] highlight important clinical studies on the application of DTI in preoperative planning for glioma resection, preoperative diagnosis, and postoperative outcomes. In the review, They discuss the study by Lorenzo et al. [42] which did the study on 234 Glioma patients using DTI, task-based fMRI and DES. They show the location and relation between the functional sites at a cortical level, the course or modification of subcortical tracts and the tumor, as shown in Figure 8[41][42], particularly stressing the importance of integrating functional information and anatomical tracts. Similar study has been done by Hacker et al. [43] using rs-fMRI for network mapping and DTI, as shown in Figure 9.

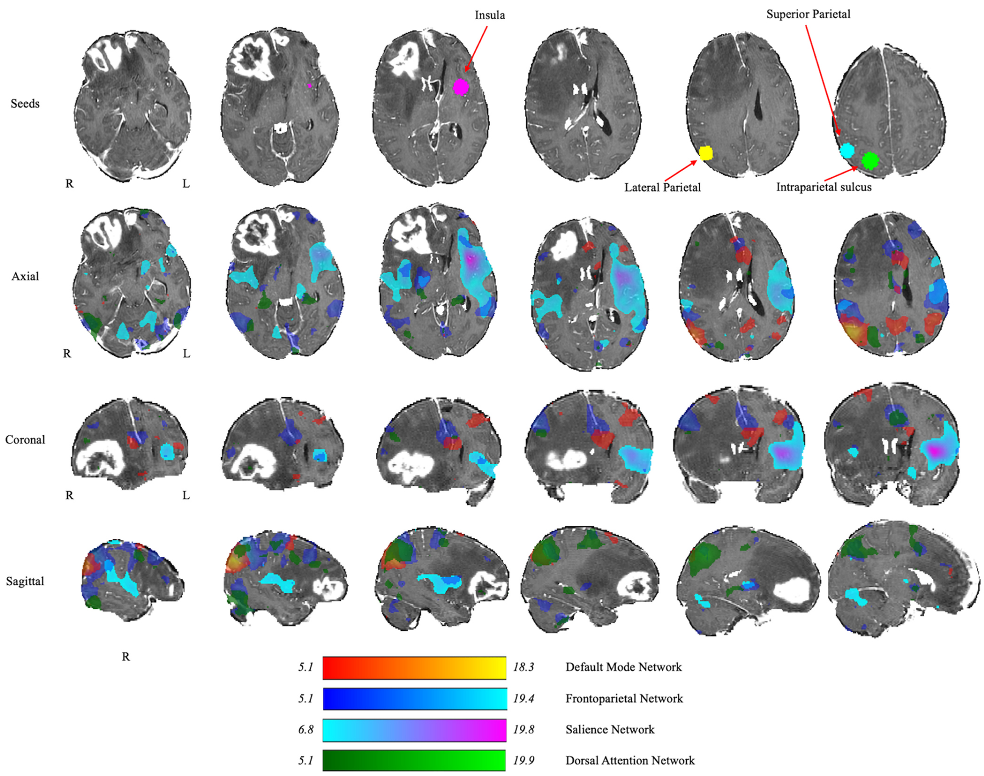


Figure 7(a): *Orthogonal views of the cognitive and emotional networks in a patient with a right frontal glioblastoma overlapped onto the post contrast T1-weighted image [40]*

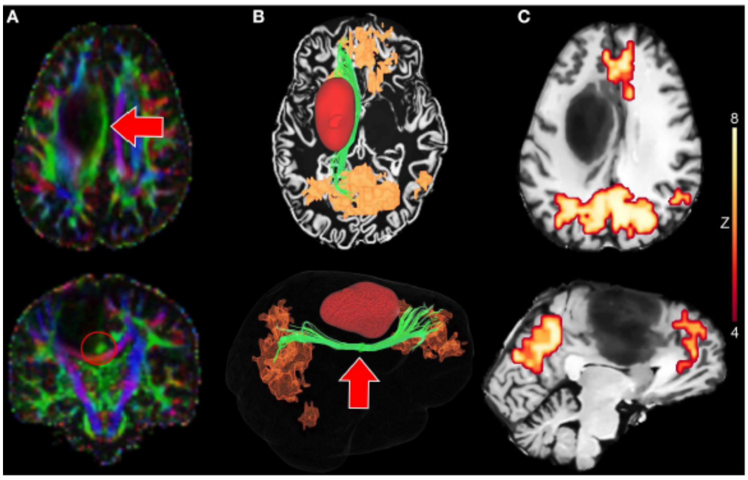


Figure 7(b): *Tractography-driven reconstruction of the DMN applied to a neurosurgical case.(A) Axial and coronal views of RGB map showing the deviated Cg (red arrows) induced by the mass effect of the tumor. (B) 3D Reconstruction of the Cg(green),the tumor(red) and the DMN (orange) based tractography-driven resting-state. Seed-region was positioned at the mid-body of eCg (redcircle). (C) 2D axial and sagittal views of DMN-overlayedT1map showing functional connectivity near the tumor (mPFC) [49]*

Although DTI offers great value, it suffers from several critical limitations. These include an inability to replicate crossing fibers and a low angular-resolution, affecting quality of results. Advanced, non-tensor methods have been devised to address DTI's shortcomings, but they remain clinically underutilized due to logistical issues such as the need for expert processing and interpretation, high time-consumption by preprocessing and cost [44]. To address this issue of DTI, Nath et al. [45] described a method of

Figure 8(a): *Preoperative DTI with corticospinal tract mapping in the case of a thalamic GBM [41][42]*

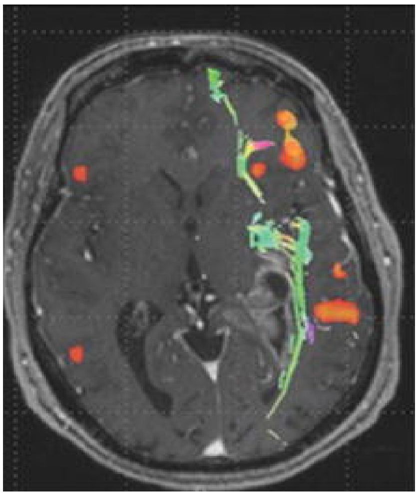


Figure 8(b):*Preoperative DTI of the superior longitudinal (arcuate) fasciculus (SLF) and superimposed fMRI in a temporal lobe GBM. [41][42]*

transforming DTI data into non-tensor high-resolution data, suitable for tractography, using a deep learning technique. The deep learning model utilizes a residual convolutional neural network architecture (Deep Machine Learning Method) to yield a spherical harmonic representation of the diffusion-weighted MR signal, as depicted by Figure 10 and 11- A,B,C- DTI. D,E,F- Deep Learning Algorithm (DLA). Similarly, Qiyuan et al. [46] have worked on DeepDTI which minimizes the data requirement of DTI to one and six DWI volumes.

Based on these proof of concepts, BrainSightAI will develop its own system which will use deep learning to pre-process DTI to generate high-resolution data of relevant association fibers, projection fibers that connect cortical areas to the deep nuclei, brainstem, cerebellum, and spinal cord (depending on the region of interest) and commissural fibers. On top of it, it will also automatically delineate these major fibers and quantify the tissue properties within the tracts. Further, these AI-based results of fiber tracts will also be mapped to the 3-D model of the brain.

3.4. Using AI to understand Tumor Dynamics and Enable Better Pre-Surgical Planning for Optimizing Tumor Resection

BrainSightAI aims to develop an AI powered engine based on imaging modalities to improve prediction of the tumor dynamics before the surgery.

3.4.1 Demarcation and Segmentation of the tumor

The understanding of the tumor dynamics starts with tumor demarcation and segmentation. BrainSightAI will develop machine learning algorithms which demarcate the tumor and perform intra-tumor segmentation. Deep learning methods, such as Convolutional Neural

Networks (CNN) can be used to segment the tumor into- edema, necrosis, nonenhancing tumor, and enhancing tumor[47[48], as shown in Figure 12[47].

It will not only save the time of the radiologist but also give insightful relation, such as proximity, between tumor and crucial cortical areas. Data set required to perform demarcation and segmentation are- T1w, T1w contrast, T2w, and FLAIR MRI.

3.4.2. Type of Brain Tumor

The AI engine will perform the differential diagnosis between the following types of brain tumors- Gliomas, meningioma, pituitary adenoma, and metastatic tumor (metastatic bronchogenic carcinoma) as shown in Figure 13[16][17]. Deepak et al. [16] have proposed a classification system which adopts the concept of artificial intelligence (deep transfer learning and uses a pre-trained GoogLeNet) to extract features from brain MRI images to differentiate between the type of tumor. This work acts as a proof of concept for BrainSightAI to develop an intelligent engine.

MRI data Required for training the AI algorithm are - T1w, T1w post contrast (T1c), T2w. The FLAIR and rs-fMRI data will further improve the accuracy.

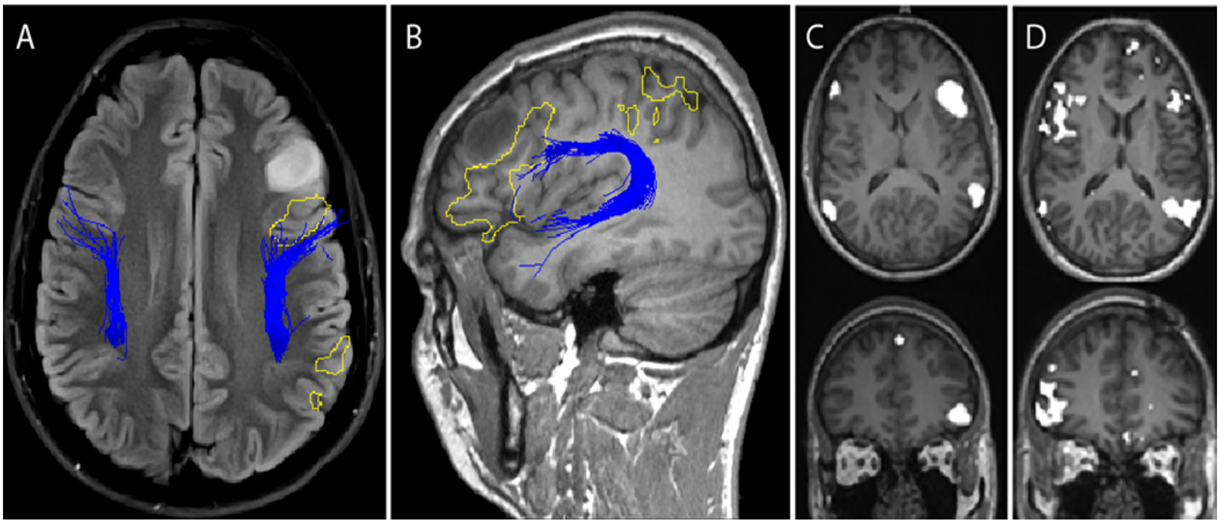


Figure 9: *Left frontal glioma. FLAIR image (A) and T1-weighted MR image (B) demonstrating a left frontal lesion. Resting state language network regions (yellow outlined regions) are seen in proximity to the T1 signal hypodense lesion. Tractography of the arcuate fasciculus (blue lines) colocalizes to language regions in the frontal lobe, posterior to the tumor. Language mapping (C) initially demonstrated a left-sided predominance. On repeat imaging at 3 years (D), the resting state demonstrates remapping of language network regions, contralateral to the tumor [43]*

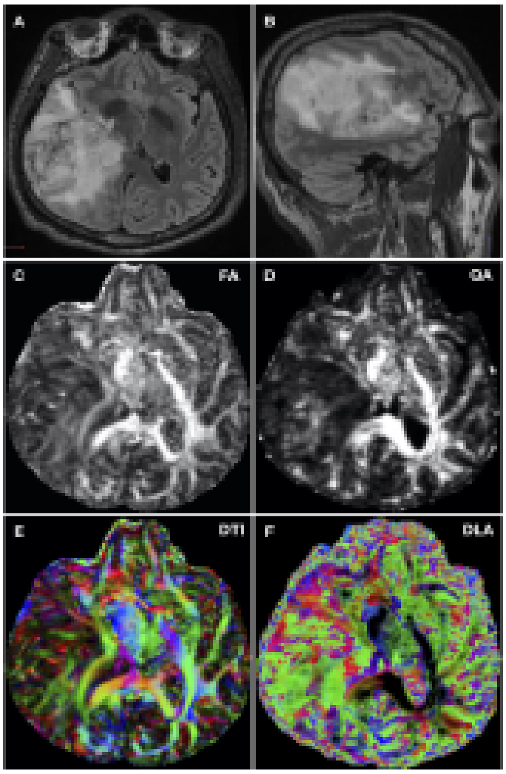


Figure 10[45]: *A – Axial FLAIR sequence demonstrating large right sided parietal mass. The tumor is surrounded with substantial edema, and is causing a degree of midline shift.*
B – Sagittal FLAIR sequence demonstrating the parietal lobe. Edema extends into the upper parietal lobe, the occipital lobe and the upper temporal lobe.
C – Fractional anisotropy (FA) map, visible is a loss of white matter architectural integrity in the area of the tumor.
D – Quantitative anisotropy (QA) map. The tumor region appears darker compared to the corresponding FA map.
E – Color diffusion tensor map produced by diffusion tensor imaging (DTI) sequence. Green – anteroposteriorly travelling fibers; Blue- superoinferiorly travelling fibers; Red – laterally travelling fibers.
F – Color orientation distribution function map produced by deep learning algorithm (DLA) processing demonstrating. Green – anteroposteriorly travelling fibers; Blue- superoinferiorly travelling fibers; Red – laterally travelling fibers.

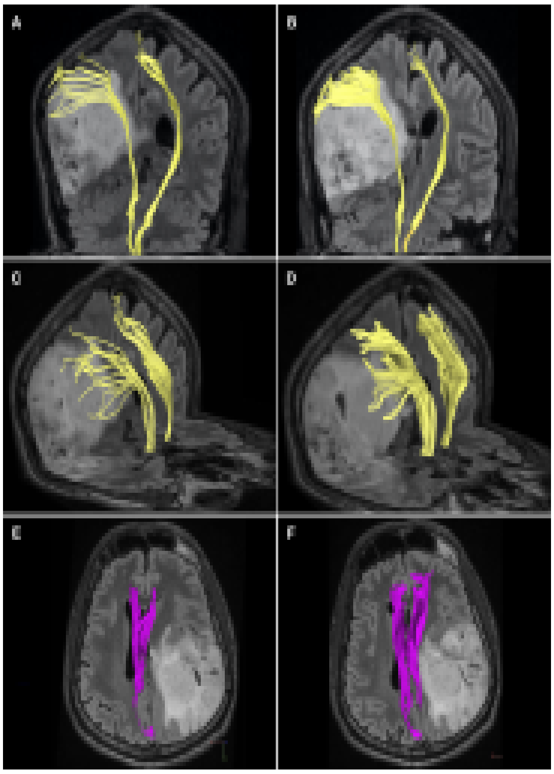


Figure 11[45]: *A – Coronal view of the DTI-generated CSTs in subject 1. Apparent is the degree of medial deviation of the right CST produced by the tumor mass effect.*
B – Coronal view of the deep learning algorithm generated CSTs in subject 1. Compared to 3A,the tracts appear more robust, especially the laterally extending fibers of the corona radiata.
C – An oblique-anterior view of the DTI CSTs in subject 1, here the shape of the tumor/edema has created an according deviation of the laterally-travelling CST fibers.
D - An oblique-anterior view of the deep learning algorithm CSTs in subject 1. Compared to figure 3C, the tracts appear more robust along their entire course, which is especially apparent when comparing the laterally-travelling fibers of the corona radiata.
E – Axial (supero-inferior) view of the DTI cingulum tracts in subject 1. Though the length of the left cingulum has been produced, only a portion of the right has, which is substantially deviated to the contralateral hemisphere.
F – Axial (supero-inferior) view of the bilateral cingulum tracts created using the deep learning algorithm. Compared to 3E, not only has a much larger portion of the deviated right cingulum been reproduced, both bundles appear more robust.

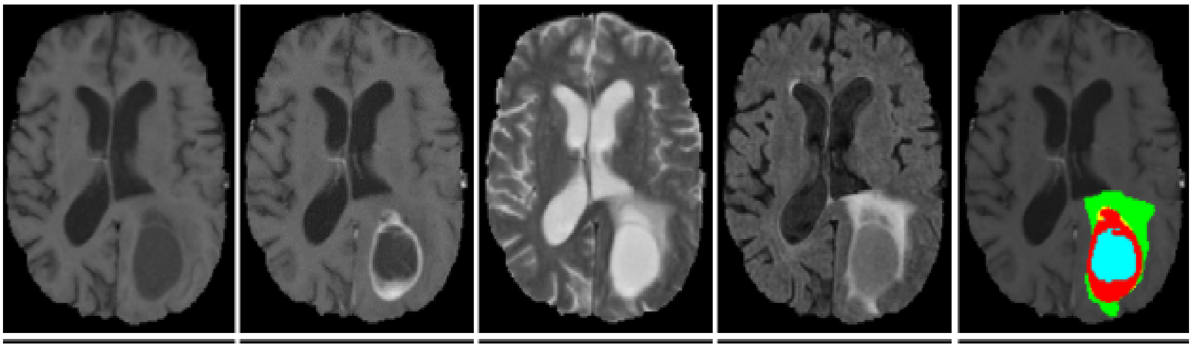


Figure 12: *Segmentations of a HGG. From left to right: T1,T1c, T2, FLAIR, and the segmentation. Each color represents a tumor class: green – edema, blue – necrosis, yellow – nonenhancing tumor, and red – enhancing tumor [47]*

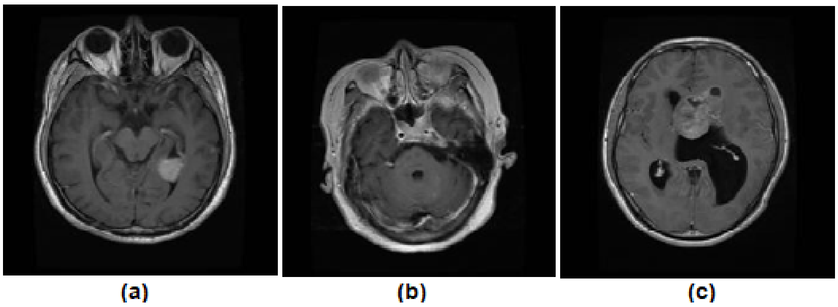


Figure 13 *-Types of Brain Tumor[17]*
(a) Meningioma (b)Pituitary Tumor (c)GliomaTypes of Brain Tumor
Image:https://www.sciencedirect.com/science/article/abs/pii/S0010482519302148

3.4.3. Subtype of Glioma

As the prognosis greatly depends on the subtype of the Glioma, BrainSightAI will develop Deep Learning algorithms on multimodal MR scans and radiomics features to characterize the IDH and 1p/19q status of Glioma, which will do the classification as per "The 2016 World Health Organization Classification of Tumors [52]" [18][19].

MR scans required for conducting this type of analysis are T1w, T1w post contrast (T1c), T2w. The FLAIR and rs-fMRI will further improve the accuracy. Histopathological reports of the tumor will also be needed to train the algorithm.

3.4.4. Grade of the tumor

The proliferation rate of the tumor and survival of the patient majorly depends on the tumor grade. Prediction of the tumor grade prior to the surgery can help the doctor to decide on the extent of resection of the tumor.

Roberto et al. [37] have done a study on 24 non-aphasic patients with non-operated left frontal and/or temporo-parietal lobe brain glioma (histologically confirmed as 10 WHO grade II (low-grade) and 14 WHO grade IV (high-grade) gliomas) to study the correlation between connectivity modifications in the Default Mode Network (DMN) and the tumor characteristics. Based on the group-level analysis, they qualitatively observed a larger correspondence of the DMN spatial pattern between controls and high-grade tumor patients, whereas larger differences were detected in low-grade tumor patients as shown in Figure 14. They also did the evaluation with a one-way analysis of variance which facilitated direct comparison of the spatial patterns for the high-grade and low grade tumor patients. An increased integration of the hippocampus and the posterior cingulate within the DMN, and a reduced integration of the left inferior parietal lobule and the left medial prefrontal cortex was found, as shown in Figure 15.

This result suggested that DMN could be more right-lateralized in the low-grade than in the high-grade patients. Thus, modifications in DMN can be exploited to predict the grade of the tumor. Jiangfen et al. [38] have used the parameters of rs-fMRI (signal intensity difference ratio, signal intensity correlation (SIC), fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo)) to classify the tumor grade. Chung-Ming et. al [20] have used Deep Learning Algorithms to use the MRI Radiomic Features to predict the tumor grade. Other studies using MRI to evaluate the characteristics of the tumor are exhibited in [21][22].

These studies are significant proof of concepts to evaluate the tumor grading based on neuroimaging modalities before the surgery.

BrainSightAI will need the following MR scans to train the AI algorithm- rs-fMRI, T1w, T1w post contrast (T1c), T2w, FLAIR.

3.4.5. Direction of Tumor growth

BrainSightAI aims to help the doctors by predicting the direction of tumor growth to ensure maximal removal of the tumor. Nico et al. [39] have found tumors have a high tendency to recur towards the motor cortex. Hence, the potential of rs-fMRI can be exploited to predict the direction.
The regrowth direction is also correlated with radiomic features of the tumor [23] and the pattern of displacement of white matter by Tumor[24] , as shown in Figure 16.

Using these studies as the basis, BrainSightAI will need the following MR scans to train the AI algorithm - T1, T1c, T2, DTI and rs-fMRI are required to work on this.

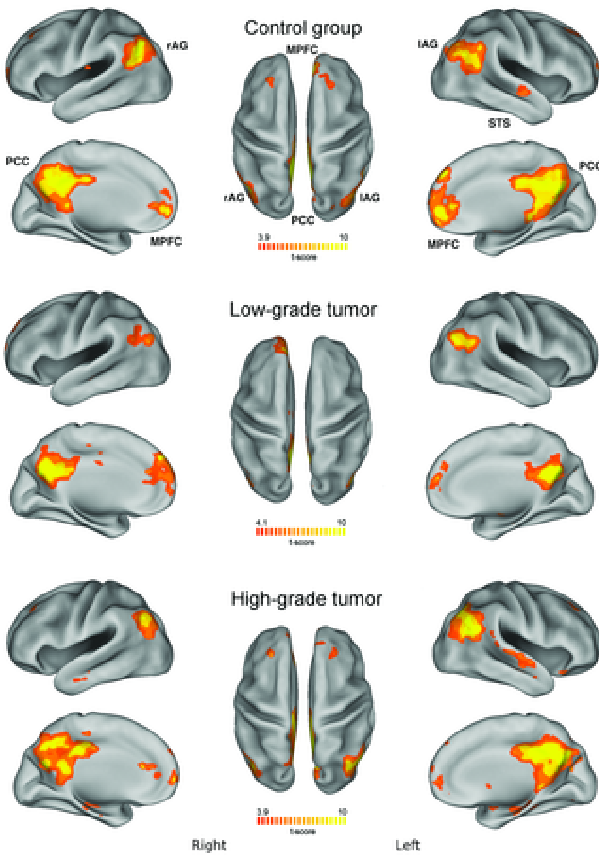


Figure 14 *- Group-level default mode network (DMN) maps for healthy controls, patients with low-grade and high-grade glioma [37]*

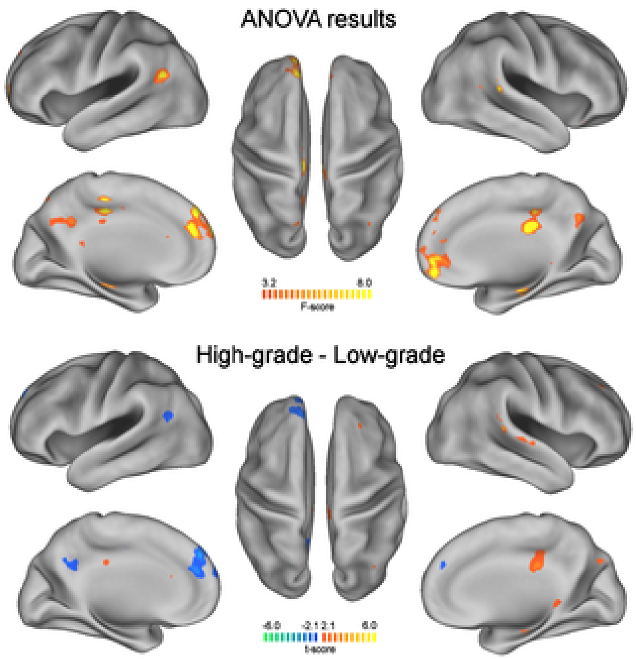


Figure 15*- Differences in the DMN for healthy controls, patients with low-grade and high-grade glioma [37]*

3.5. Using AI for Survival Analysis

Survival analysis is very critical for the doctor to do prognosis and largely depends on tumor dynamics (tumor type, sub-type, grade, direction of tumor) and the effect on the eloquent cortex due to tumor resection.
Using the data of tumor dynamics, eloquent cortex mapping (generated by BrainSightAI as mentioned in the previous sections) and patient history an AI-powered engine will be developed to predict the survival of the patient [12][13]. Data required to train the AI model and predict the survival rate is depicted in Table 1. The result of the survival analysis (overall survival and progression free survival) will be presented in the form of a graph with probability of survival being the Y-axis. The representation of the scan and graph is shown in Figure 17[12].

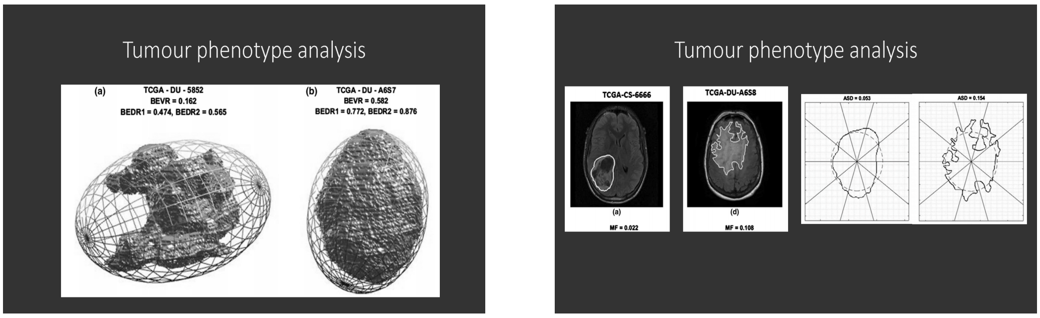


Figure 16(a) - *Tumour phenotype analysis to predict direction of tumor growth*
Image:https://pubmed.ncbi.nlm.nih.gov/28470431/

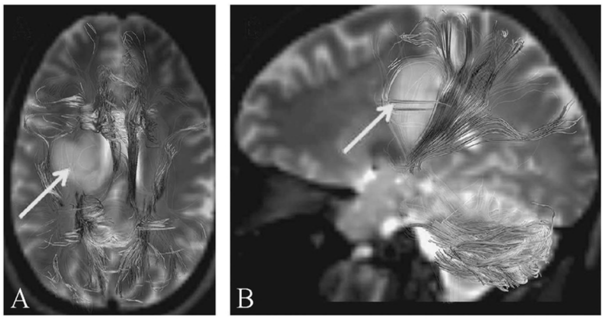
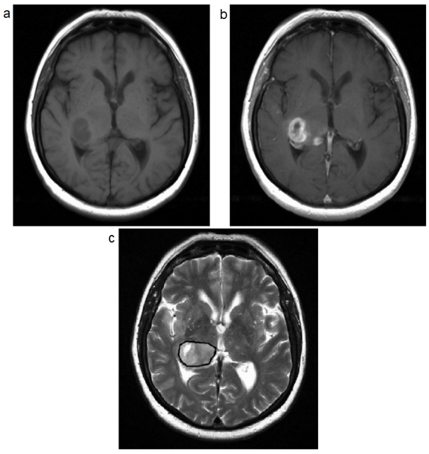


Figure 16(b)- *Axial (A) and sagittal (B). T2-weighted images of the brain with superimposed DTI-derived tractographic images showing the displacement of fiber tracts by the tumor.*
Image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6123261

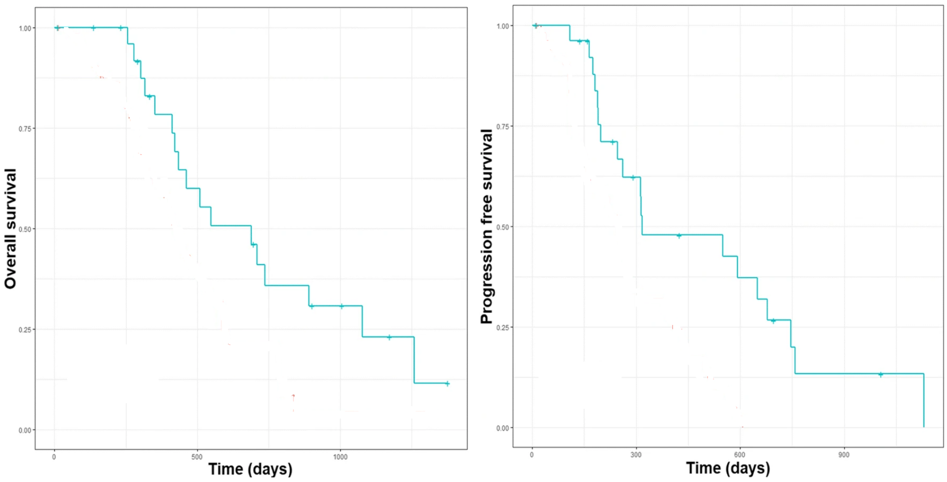
Data needed to train the AI model to investigate critical tumor features and predict Overall Survival	
Patient Information	Age, Sex, symptoms, underlying comorbidities, Overall survival time, progression free survival time
NeuroImaging	T1,T1c,T2 and Flair, DTI, rs-fMRI
Treatment Regime	Chemotherapy, radiation , medications

Data needed once the model is created	
Patient Information	Age, Sex, symptoms, underlying comorbidities, Overall survival time, progression free survival time
NeuroImaging	T1,T1c,T2 and Flair, DTI, rs-fMRI

Table 1: *Data required for Survival Analysis*



(a) Axial T1-weighted pre-contrast scan, (b) T1 post-contrast scan, (c) T2-weighted scan showing the tumor
Image:https://journals.sagepub.com/doi/10.1258/AR.2011.100510



Graph showing Survival Analysis. Y-axis- probability (1-0) [13]
Image:https://link.springer.com/article/10.1007/s00330-018-5984-z

Figure 17: *MR scans and Graph of Survival Analysis for Glioblastoma*

3.6. Guiding the Treatment- Predicting the deficits and surgical outcomes

3.6.1. Networks and fiber tracts with respect to tumor

With recent advancements in surgery, the major focus is on maximal tumor resection along with minimal functional loss to maintain a good quality of life. Thus, during pre-surgical planning and the surgery, precise information on the proximity of the tumor to the network and fiber tracts holds paramount importance.

Along with the rich information on networks, fiber tracts and tumor dynamics, BrainSightAI will also provide a neuroradiologist-friendly neuroimaging viewer to enable them to quantify the crucial data for neurosurgeons. The neuroradiologists will be able to measure the distance between the tumor and the nearby networks and fiber tracts, as shown in Figure 18. To give a sense of direction, the relation between the tumor and other areas will be presented in terms of the clock-faced approach to empower the pre-surgical planning and surgery with very familiar data.

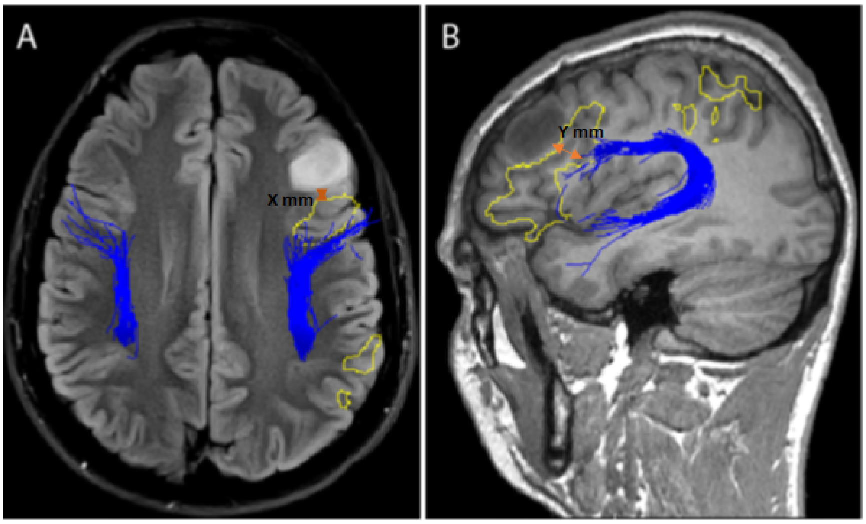


Figure 18(a): *Resting state language network regions (yellow outlined regions) are seen in proximity to the T1 signal hypodense lesion. Tractography of the arcuate fasciculus (blue lines) colocalizes to language regions in the frontal lobe, posterior to the tumor [43]*

Distance and Clock-faced information: In the axial plan, the closest edge of the tumor is at 1 O'clock and X mm distance (arrow-orange color) to the language network (yellow color). In sagittal view, the closest edge of the tumor is at 10 O'clock and Y mm distance (arrow-orange color) to the arcuate fasciculus fiber tracts (blue color)

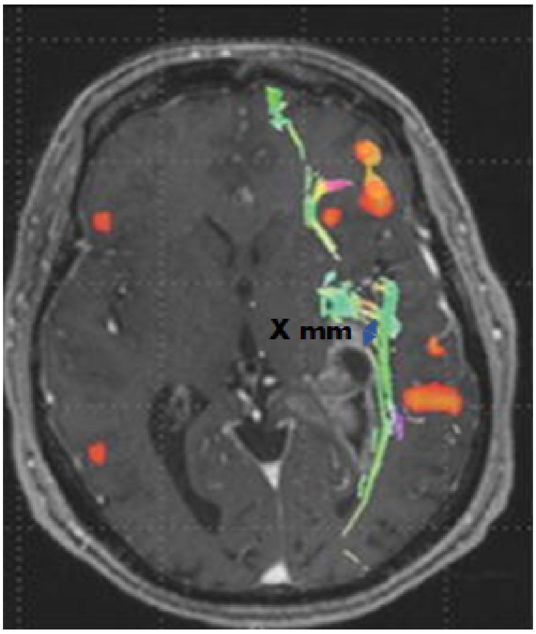


Figure 18(b): *Preoperative DTI of the superior longitudinal (arcuate) fasciculus (SLF) and superimposed fMRI in a temporal lobe GBM*

Distance and Clock-faced information: In the axial plan, the closest edge of the tumor is at 7 O'clock and X mm distance (arrow-blue color) to the superior longitudinal (arcuate) fasciculus (SLF).

Neuronavigation systems are generally equipped with dicom coordinate systems, which can only be used during the surgery. To introduce these in pre-surgical discussions, the BrainSightAI will also provide the dicom coordinate systems such as, LPS (left-posterior-superior),RAS (right-anterior-superior) in the neuroimaging viewer, to view the pre-surgical (X,Y,Z) position of any ROI (region of interest). For the familiarity of the neurosurgeons, it will also have an option to represent the data in neurosurgeon's convention along with neuroradiologist's convention.

Further, the AI-based results and the annotations by the neuro-radiologists, can be viewed in a 3-D model of the brain by the neurosurgeon, to carry out the pre-surgical planning.

3.6.2. 3-D simulation tool for prediction of alteration in eloquent cortex due to the planned surgery

Using the functional connectivity-activity patterns and tumor dynamics, BrainSightAI will develop a 3-D simulation tool to simulate the impact on the functionality of the brain due to structural and connectivity changes as per the planned surgery. Hannelore Aerts et al.[14][15] have built a computational model, using DTI and rs-fMRI, as shown in Figure 19. They simulated large-scale brain dynamics in 25 human brain tumor patients and 11 human control participants and found promising results. This study shows the potential of developing an unique predictive tool to investigate the impact of diverse structural connectivity alterations due to the planned surgery on brain functioning, in order to, minimize the chances of any unknown post-surgical functional loss.

BrainSightAI will require the following Imaging data to build this simulation tool- T1,T1c,T2 and Flair, DTI, rs-fMRI.

3.7. Using AI for evaluating the effect of radiation and chemotherapy on Tumor

The flow diagram, depicted in Figure 20, shows the goal of BrainSightAI to make treatment follow ups more informed and effective. AI algorithms will be developed to evaluate the effect of radiation and chemotherapy on tumor by distinguishing between

I. True progression vs Pseudo-progression
II. True progression vs Tumor necrosis, shown in Figure 21

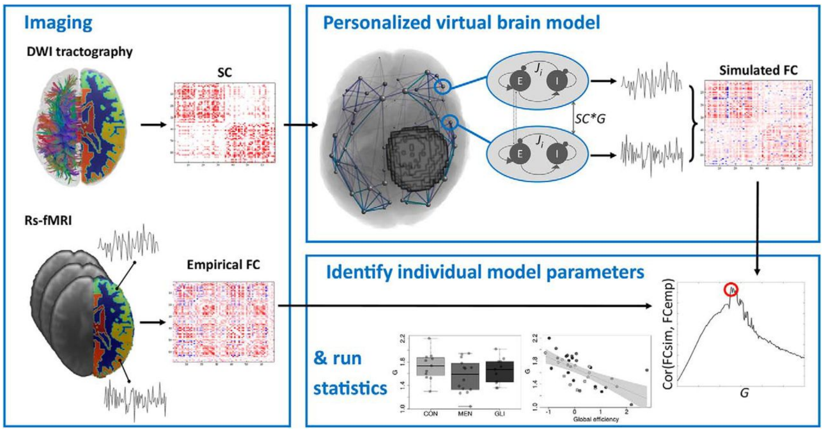
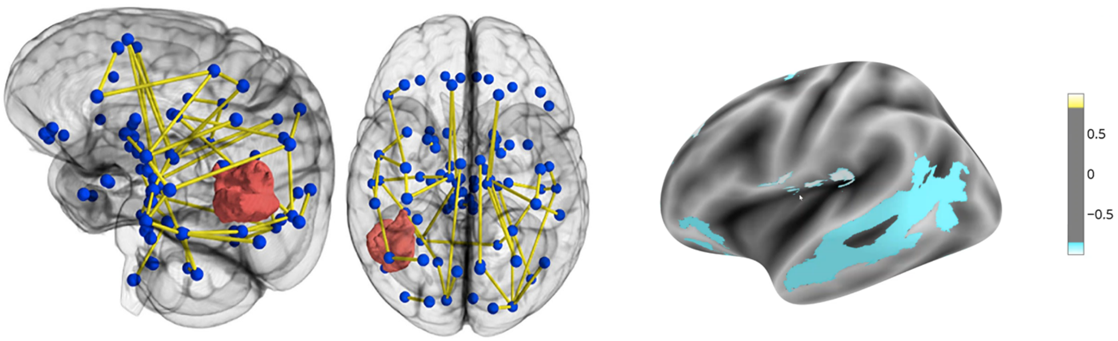


Figure 19(a) *-Summary of computational modeling workflow*
Image:https://www.eneuro.org/content/5/3/ENEURO.0083-18.2018



Connectivity patterns around the tumor

Regional patterns around the tumor
(for representation purpose only)

Figure 19(b) *-Representation of Connectomics of White matter networks - output of modelling*
Image:https://thejns.org/focus/view/journals/neurosurg-focus/48/2/article-pE6.xml

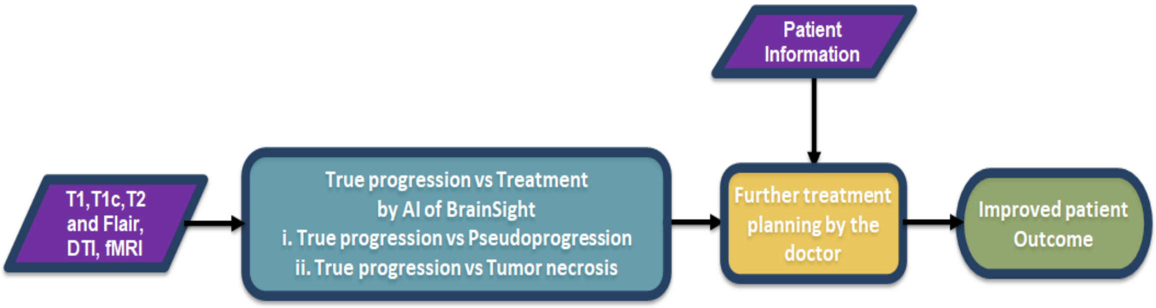


Figure 20- *Clinical Workflow of Follow-ups*

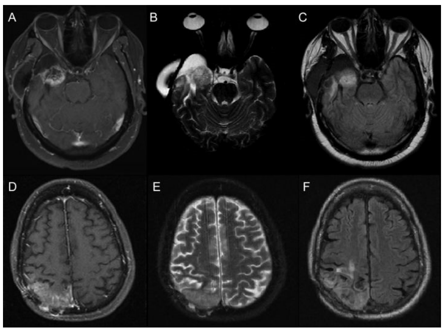


Figure 21 *- A,B,C-glioblastoma recurrence; D,E,F- Tumor Necrosis*
Image Source:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3635510/

Prager *et al.* [26] demonstrates a model using diffusion and perfusion MRI which help to distinguish between treatment related changes and recurrent tumor. Jang et al. [27] have developed an Machine Learning algorithm using contrast T1-weighted images on a small sample set.
BrainSightAI aims to develop AI models using T1, T1c, T2, Flair, DTI, Perfusion MRI and information about the treatment regime to differentiate between the treatment effect and recurrent tumor. Further, rs-fMRI will be required to provide the eloquent cortex mapping of the patient to assess the effect of the radiation.

3.8. Reports and Software Interface

The user-friendly imaging viewer will also enable the neuroradiologists to provide

BT-RADS (Brain Tumor Reporting and Data System) [25] based pdf report. They can select the relevant neuroimages with annotations to add to the report. The AI-based findings and inputs by the neuroradiologists will be summarized in the clinical indications and impression section of the report as shown in Figure 22.

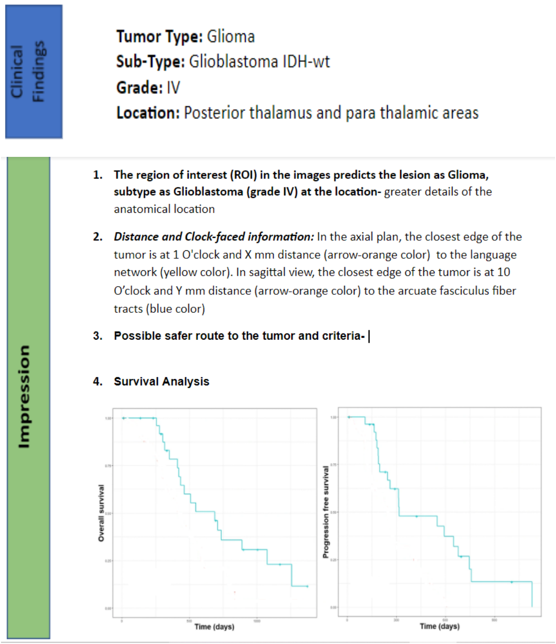


Figure 22- *Clinical Findings and Impression part of BrainSightAI's report*

4. Conclusion

The VoxelBox suite of tools can guide the treatment of glioma by helping clinicians understand the important characteristics of the individual patient's brain as well as the pathology. Research suggests that rs-fMRI is a powerful tool that can aid in all phases of surgical treatment, such as ECM, mapping of non-eloquent networks, tumor demarcation, gradation, and classification, and survival analysis. When used in conjunction with structural MRI and DTI, rs-fMRI can help neurosurgeons gain a holistic understanding of the patient's condition. VoxelBox further optimizes this data with the use of artificial intelligence, 3D visualization, and 3D simulation. These advanced technologies allow neurosurgeons to perform complex analyses such as predicting surgical outcomes and analyzing direction of tumor growth. These analyses are provided on a user-friendly 3D interface, enabling clinicians to have an immersive experience during their treatment planning.

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