Patterns of Traditional and Nontraditional Network Involvement in Insulo-Sylvian Gliomas: An Anatomic Study using the Quicktome Platform

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Abstract

Background

Neurosurgeons are increasingly capable of maintaining language and motor functions in glioma patients following surgery due to the ability to preserve traditionally "eloquent" structures. However, glioma patients continue to present with severe morbidity in cognitive functions due to the lack of familiarity in the neurosurgical community with non-traditionally "eloquent" brain networks. Therefore, the authors sought to identify and describe the frequency of invasion and/or proximity of Insulo-Sylvian gliomas to portions of non-traditional, large scale brain networks during surgery.

Methods

A retrospective analysis was completed of consecutive adult patients undergoing surgery for newly diagnosed glioma at a single center between 2017-2020 with WHO grade II-IV infiltrating gliomas centered in the insula, opercular cortices or temporal stem. Diffusion tensor imaging (DTI)-based tractography was completed by creating a personalized brain connectome atlas based on the Human Connectome parcellation scheme with Quicktome software. This algorithm utilizes an machine learning (ML)-approach to assign voxels of the cerebral cortex to various brain regions according to structural connectivity patterns of voxels in the brain region of interest utilizing neuroimaging data specifically from normal healthy adults. Insulo-Sylvian tumors were categorized based on their involvement with non-traditional cognitive networks versus traditionally eloquent structures.

Results

45 patients were included (47±15 years, 51% female) consisting of mostly high grade (IV)-gliomas (56%) compared WHO grade II (22%) or III (22% tumors). Ultimately, 44/45 (98%) patients demonstrated tumor involvement (<1cm proximity or invasion) to the cortical or subcortical components of a non-traditional, large scale brain network or major white matter pathway involved in cognition. In comparison, 35/45 (78%) patients demonstrated tumor involvement of traditionally considered "eloquent" structures like the corticospinal tract or language regions/tracts. The most common non-traditional cognitive networks involved in cases included the salience network (60%) followed by the central executive network (56%).

Conclusions

Non-traditionally "eloquent" brain networks are increasingly encountered during surgical resection of Insulo-Sylvian gliomas in both hemispheres and must be considered moving forward. Damage or dysfunction in these networks has been shown to result in severe cognitive morbidity and an improved understanding of their presence can allow for more informed surgical decisions based on patient onco-functional goals.

Introduction

It is well established that performing intra-axial tumor surgery around the Sylvian fissure, insula, and opercular cortices has a significant risk of causing new and permanent neurological deficits (1). A substantial body of literature has been dedicated to refining techniques for reducing this risk. Most work has principally focused on reducing risks of causing motor weakness, and aphasia with left sided lesions, where the anatomy has been known for some time. However, more recent efforts have focused on functional preservation techniques in less well-known anatomy, such as preservation of the inferior frontal-occipital fasciculus (IFOF) (2) and the frontal aslant tract (FAT) (3, 4). While it is generally wise to avoid cutting through the middle of white matter bundles, removing an intra-axial brain tumor always requires cutting some brain tissue, reflecting our constant need to make trade-offs in surgical choices. However, it remains clear that numerous glioma patients continue to present with severe post-operative morbidity in higher order functions (5–7), limiting their return back into society and the workplace(8). Given that neurological decline occurs after brain surgery in many cases (9), especially despite the fact that no serious transgressions of white matter bundles occurred, it is clear that additional information is necessary to define the anatomy at risk in these operations.

Recent work in neuroscience has clearly established the central role of large scale brain networks, such as the Central Executive Network (CEN) (10–13), Default Mode Network (DMN) (14–17), Salience network (SN) (12, 18–20), Dorsal Attention network (DAN) (10, 21, 22), and Ventral Attention network (VAN) (22), in numerous aspects of human cognition. These networks include spatially distant, but highly synchronized brain regions and their connecting white matter fibers which dynamically work together across the human cortex. While specific aspects of these networks when damaged by brain tumors or dysfunctional in neuropsychiatric illnesses have yet to be completely mapped to specific clinical symptoms, it is increasingly clear that inadvertently injuring these networks during surgery is a mechanism by which patients experience increased cognitive morbidity following surgery(23). To date, the large-scale brain networks have provided the best anatomic maps to make sense of traditionally less familiar anatomy responsible for cognitive functions. Therefore, the large-scale brain networks during glioma surgery is a topic which demands increased scrutiny moving forward.

For some time, progress in answering these kinds of questions has been held back by the substantial challenge of meaningfully mapping structural connections and making sense of them in cases where gliomas have distorted and/or invaded these connections. However, the Quicktome algorithm addresses these limitations by utilizing a machine learning (ML)-approach which assigns voxels of the cerebral cortex to various regions based on their similarity of structural connectivity patterns of voxels of this region seen in normal healthy adults. Therefore, in this study, we utilized Quicktome to characterize a cohort of patients with gliomas around the insula and sylvian fissure as it relates to traditional and non-traditional brain networks. While we expect that these cases will demonstrate that often these tumors are in areas well known to neurosurgeons to be “eloquent” structures, like the language system and sensorimotor cortices, our specific goal was to demonstrate the frequency of invasion and/or proximity to portions of non-traditional, large scale brain networks such as the CEN, DMN, SN, VAN and DAN.

Methods

Patient Cohort

The patients in this study were retrospectively analyzed from a consecutive series of adult patients undergoing surgery for newly diagnosed glioma at our center between 2017 and 2020 with WHO grade II to IV infiltrating gliomas centered in the insula, opercular cortices or temporal stem. While many of these tumors extend beyond these regions, we included only patients where the primary epicenter of the tumor was in the insulo-sylvian regions. This project was completed with Human Ethics Committee approval of the first affiliated hospital of Nanjing Medical University, and all patients provided informed consent to study participation and image publication.

Imaging protocol

All patients underwent a pretreatment standard structural T1 and T2 weighted images used for image guidance immediately prior to surgery. In addition, they underwent diffusion tractography imaging (DTI) with the following parameters: Siemens Skyra 3.0 MRI scanner, with 10 b=0 baseline image and a b=1000 shell with 64 direction acquisition, FOV=224mm*224mm, slice thickness 2mm, 0 mm gap between slices with no overlap, full brain coverage, isotropic voxels, square 112*112 matrix.

Diffusion tractography preprocessing steps

The DT images were processed using the Omniscient Quicktome software (24), which employs a standard processing steps in the Python language (25) which specifically include the following steps: 1) the diffusion image is resliced to ensure isotropic voxels, 2) motion correction is performed using a rigid body alignment, 2) slices with excess movement (defined as DVARS> 2 sigma from the mean slice) are eliminated, 3) the T1 image is skull stripped using a convolutional neural net (CNN), this is inverted and aligned to the DT image using a rigid alignment, which is then used as a mask to skull strip the DT, 4) gradient distortion correction is performed using a diffeomorphic warping method which aims to locally similarize the DT and T1 images, 5) eddy current correction is performed, 6) fiber response function is estimated and the diffusion tensors are calculated using constrained spherical deconvolution, 7) deterministic tractography is performed with random seeding, usually creating about 300,000 streamlines per brain.

C*reation of a personalized brain atlas using machine learning based parcellation*

The Quicktome algorithm creates a ML-based, subject specific version of the HCP-MMP1 (26) atlas based on diffusion tractography structural connectivity, which has been reported in previous studies (27). In short, this was created by training a ML-model on 200 normal adult subjects by first processing T1 and DT images as above. A HCP-MMP1 atlas in NIFTI MNI space is then warped onto each brain to assess structural connectivity between each parcellation pair of the atlas and a set of regions including 8 subcortical structures per hemisphere and the brainstem based on streamlines terminating in each region. This step both allows the generation of feature vectors (basically a 379 x 379 structural connectivity-based adjacency matrix), and generates a centroid of the parcellation which is utilized to constrain the voxels studied for assignment to a given parcellation to a plausible area in the vicinity of its typical position. These feature vectors for each region were then used as a training set and the data were modeled using the XGBoost method.

This model is then applied to the new subject by first warping the HCP-MMP1 atlas to the new brain and collecting a set of feature vectors of the connectivity of each voxel. The feature vectors are then used to determine if each voxel belongs to a parcellation or region or not, and if so to assign the voxel to that parcellation. This creates a version of the HCP-MMP1 atlas with subcortical components, which is not dependent on brain shape or pathologic distortion, and which is specific for this subject, but comparable between subjects.

Definition of tumor boundaries for purposes of this analysis

Tumor boundaries were defined using the preoperative postcontrast T1 and T2 images. For the purposes of this study, we used definitions of tumor boundaries to align with typical surgical goals as opposed to strict definition of all T2 changes in high grade gliomas being defined as tumor. Thus, the boundaries of enhancing high grade gliomas were defined solely as the contrast enhancing portion of the tumor, and the boundaries of low-grade gliomas were defined as the T2 hyperintense portion of the tumor. Of note, none of these patients received bevacizumab or other therapies which could change the imaging behavior in a clinically important way.

The rationale for limiting analysis of high-grade tumors to solely the contrast enhancing portions is two fold: First, the T2 changes in most Insulo-Sylvian high-grade gliomas are typically quite extensive, which would make this study biased towards overestimating the frequency of involvement of networks like CEN, DAN and SN in the surgical approach (they would be involved or near the T2 change in basically every case) and second, given the location of these tumors, it is unlikely that even advocates of supramaximal resectable surgery would recommend chasing T2 changes into the corticospinal tract, arcuate fasciculus and basal ganglia. Thus, we felt that given the goal of most neurosurgeons operating on a high-grade glioma centered in this region would be to remove as much contrast enhancing tumor as possible, we should perform our analysis in a way which aligned with the surgical goals of these cases to provide an accurate snapshot of the nature of nontraditional network involvement in a standard surgical neuro-oncology workflow.

The determination of network involvement in glioma cases

Quicktome defines networks as a set of cortical regions, defined using the machine learning based atlas described above, and the fiber bundles connecting the component regions. This structural connectivity-based approach to atlasing leverages the insight that specific cortical regions have been reproducibly and robustly demonstrated to have strong fMRI blood oxygen level dependent (BOLD) signal correlation with other regions in the brain, in patterns which are consistent across individuals. These correlation patterns form the basis of the concept of large-scale brain networks, for instance, regions of the brain which synchronize their activity because they serve a common function. The cortical regions used in Quicktome to select the anatomic components of these networks are determined from published meta-analyses which mapped the specific large scale brain networks to these specific regions (28–33).

We visually inspected the processed images to determine whether the boundary of the tumor was in close proximity to (defined by tumor extending to within 1cm of some portion of the tract or cortical region of a brain network template) or invaded various brain structures.

Results

Patient cohort and characteristics

A total of 45 patients met the inclusion criteria described above. The demographic data for these is outlined in Table 1. They had a median age at diagnosis of 47±15 years, with a male to female ratio of 22 to 23. There were 26 left sided tumors and 19 right sided tumors. There were 10 WHO grade II gliomas, 10 WHO grade III gliomas, and 25 WHO grade IV gliomas. While most of these tumors had some extension into the insula, and many were multilobular or large tumors, only 6/45 patients had a tumor largely focused in the insula, while 13 had tumors mostly focused in the frontal lobe and frontal opercula, 22 had primarily temporal tumors, and 4 tumors were mainly focused in the parietal opercula and inferior parietal lobule.

Table 1
Subject demographics.

Variable (n=45)	
Age (mean, SD, in years)	47 (15)
Gender	
Female (n, %)	22 (49%)
Ipsilesional side	
Left (n, %)	26 (58%)
WHO grade (n, %)	
Grade II gliomas	10 (22%)
Grade III gliomas	10 (22%)
Grade IV gliomas	25 (56)
Location of the tumor (n, %)	
Insula	6 (13)
Frontal Predominant	13 (29%)
Temporal Predominant	22 (49%)
Parietal Predominant	4 (9%)

Insulo-Sylvian gliomas usually involve both traditional and non-traditionally eloquent brain networks

We found that if we limited our analysis of whether an Insulo-Sylvian glioma was in close proximity to or invading a structure classically viewed as eloquent by neurosurgeons (specifically the corticospinal tract, the motor cortex, the language regions or tracts, the optic radiations, or the basal ganglia), around 77% of patients (35/45) demonstrated involvement of a traditional eloquent structure. Conversely 44/45 (98%) patients demonstrated involvement (proximity or invasion) of a non-traditionally eloquent brain network, such as the CEN, SN, DMN, DAN or VAN. Ultimately, only 1 patient in this series did not demonstrate a surgically relevant risk to some structure, network or tract associated with a known neurological, or cognitive function.

An overall summary of the patterns of network involvement with these Insulo-Sylvian tumors is displayed in Table 2. Notably, the SN and its associated tract (FAT) were frequently involved, being nearby or invaded in 60% of these cases, as were the other more laterally positioned networks, CEN (56% of cases) and VAN (63% of right sided cases as it is a right lateralized network). The more medial positioned DAN was affected slightly less often (47% of cases) and the DMN was relatively uncommon (18% of cases) with the involvement being most often due to proximity to the parietal component of the DMN with the medial frontal component invaded by tumor extension in one case.

Table 2
Overall summary of the patterns of network involvement with these Insulo-Sylvian tumors

		Uninvolved	Closer Than 1cm	Structure Invaded
Cognitive networks	Salience	18 (40%)	9 (20%)	18 (40%)
	CEN	20 (44%)	8 (18%)	17 (38%)
	DMN	37 (82%)	1 (2%)	7 (16%)
	DAN	24 (53%)	9 (20%)	12 (27%)
	VAN	32 (71%)	4 (9%)	9 (20%)
Traditional Eloquent Structures	Optic Radiations	16 (36%)	22 (49%)	7 (16%)
	Language	19 (42%)	7 (16%)	19 (42%)
	Motor Cortex	20 (44%)	10 (22%)	15 (33%)
	CST	10 (22%)	24 (53%)	11 (24%)
	Basal Ganglia	19 (42%)	20 (44%)	6 (13%)
White Matter Tracts	FAT	18 (40%)	12 (27%)	15 (33%)
	IFOF	14 (31%)	17 (38%)	14 (31%)
Analysis Limited to Relevant Hemisphere	Language	0 (0%)	7 (27%)	19 (73%)
	VAN	7 (37%)	4 (21%)	8 (42%)

Discussion

In this study, we evaluated a cohort of patients who presented to our center with insular and peri-Sylvian gliomas and utilized a machine learning based analytic tool to determine the frequency of involvement of large-scale brain networks and/or associated *en passage* white matter fiber bundles in these tumors. We found that in these patients, greater than 98% of these patients had tumors which had sub-centimeter distance to the cortical or subcortical components of a large-scale brain network or major white matter pathway (or it invaded these structures). Most of these patients had multiple structures at risk from their tumor. All of this highlights the challenges posed by these complex tumors, and suggests that these cases really seldom are no risk, even when on in right hemisphere.

Connectome-Based Neurosurgery

There are substantial advantages to reconsidering the deep white matter anatomy in terms of large-scale brain networks. Notably, many large white matter bundles are in fact numerous bundles connecting different areas, not all of which are necessary for human cognitive function. This is especially true for the superior longitudinal fasciculus (SLF)-arcuate fasciculus (AF) complex, which is a highly complex network of connections, of varying importance. Given that some parts of these bundles and their branches are more important than others, and we need to cut something in order to remove a glioma, network-based approaches provide the potential benefit for better defining which white fibers are more important than others. Ultimately, all of brain surgery involves accurately calculating risks vs rewards of our actions.

The Non-Traditional, Large Scale Brain Networks

1. Default Mode Network

The default mode network (DMN) serves a primary role in passive states of mind (29), like internal thought or contemplation, however, it is also active during some goal-oriented tasks. The DMN network is typically described as consisting of the anterior and posterior cingulate cortices, and the lateral parietal lobe bilaterally. DMN also plays an integral role in coordinating with other networks for passive sensory processing (30). These connections often include: visual system (31), language subnetwork (32), and limbic system (33). In Figure 1, we demonstrate a tumor invading the DMN.

2. Salience Network

The Salience Network (SN) is integral for sensorimotor processing, general cognition, and coordinating between emotion, pain, and physical action (34). As the mind's moderator, the SN constantly monitors the external environment and decides how other brain networks react to new information and stimuli, it also plays an essential role in switching between the internal and external processing (35) of the brain's two main control networks (36): the default mode network (DMN) and central executive network (CEN). The main functional areas of the salience network are located in the anterior cingulate, the anterior insula (37, 38) and the presupplementary motor areas (39). The SN also includes nodes in the amygdala, hypothalamus, ventral striatum, thalamus, and specific brainstem nuclei (37), anterior cingulate cortex (ACC), medial temporal network, parahippocampal gyrus, olfactory lobe, and the ventral tegmental area (VTA). In Figure 2, we demonstrate a tumor invading the SN.

3. Central Executive Network

The central executive network (CEN) exists as a superordinate control network (40). It uses input from other networks for task selection and executive function. By integrating with the other brain networks, the CEN processes a varied set of information, such as flexibility, working memory, initiation, and inhibition, all of which had previously been thought to be separate processes. Since its initial discovery in the anterior frontal lobe (41),the central executive network has been found to be functionally connected to regions in the anterior cingulate cortex, the inferior parietal lobe (42), and the posterior most portions of the middle and inferior temporal gyri (43, 44). In Figure 3, we demonstrate a tumor invading the CEN.

4. Dorsal Attention Network

The dorsal attention network (DAN) is an important mediator of goal-directed attentional processing (24), and it has many ways of contributing to intellectual capabilities. As a bilateral network, DAN demonstrates strong connectivity between areas in the lateral occipital lobe, the pre-central sulcus, the dorsal-most portion of the superior frontal sulcus considered to be the frontal eye fields (FEF), the ventral premotor cortex, superior parietal lobule, intraparietal sulcus, and motion-sensitive middle temporal area (45). In Figure 4, we demonstrate a tumor invading the DAN.

5. Ventral Attention Network

The ventral attention network (VAN) is one of two-network model of cortical attention (46, 47), which is involved in reorienting attention when a new, unexpected stimulus, like shock, frightening events, or “oddball” occurrences, is detected within the environment (47, 48). Multiple cortical areas, such as the middle and inferior frontal gyri, anterior insula, inferior parietal lobule, and temporo-parietal junction have been linked in this processing (25). In Figure 5, we demonstrate a tumor invading the VAN.

Limitations and Future Directions

The specific goal of this study was to estimate how often a surgeon performing surgery for infiltrating gliomas around the Sylvian fissure could reasonably expect that a network not normally addressed at surgery would be inside of the tumor, and this ultimately suggested that this was the expected nature of almost all of these tumors. This study is a survey of the insula-Sylvian region gliomas encountered in at a single center over a 3-year period. Ultimately, this study was not intended to be an exhaustive epidemiologic study of all patterns of glioma spread in cases around the Sylvian fissure, and it is possible that a different center may find different frequencies of network involvement with a similar cohort. We studied a consecutive series and generally aim to perform resectable surgery of some type for every case reasonable, even if not completely resected. Thus, there is not an obvious selection bias which skewed the results which is readily apparent to us other than the inherent referral patterns which route tumors around the Sylvian fissure frequently to university-based neuro-oncology programs. While it is possible that a cohort of gliomas seen over a large community cohort, with different complexity and disease severity from ours, might have different specific rates of involvement of the brain networks than our study, the fact remains that the rate of these networks being involved in these tumors is likely high. Therefore, they will continue to pose a risk of cognitive and emotional morbidity in the majority of patients if we continue to not address the situations where they cannot or should not be transgressed in the name of increasing the extent of resection a small amount.

Conclusions

In this study we demonstrate the extensive involvement of Insulo-Sylvian tumors with non-traditionally “eloquent” large-scale brain networks involved in cognition. While neurosurgeons have traditionally focused on eloquent structures related to language and motor activity, failure to consider the presence of non-traditional, large-scale brain networks will likely continue to exacerbate the cognitive and emotional disturbances documented in the majority of glioma patients after surgery. Brain network maps provide an improved understanding of the relationship between tumor and brain anatomy such that neurosurgeons can better understand the risks and benefits of certain surgical decisions for specific tumors.

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of the first affiliated hospital of Nanjing Medical University. Written informed consent was obtained from individual or guardian participants.

Consent for publication

Not applicable.

Availability of data and material

All deidentified data used in the current manuscript can be provided by the authors per the readers requests. No data spreadsheet has been made publicly available due to patient confidentiality.

Competing interests

Michael Sughrue is the Chief Medical Officer, co-founder and share-holder of Omniscient Neurotechnology. Yan Zheng is an employee of Omniscient Neurotechnology. Products related to these companies were only discussed in this paper for discussion of methodology or statistical analyses. No other authors report any conflict of interest.

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Author Contributions

JZ, ZZ, GH, ZW, XW, LZ, BW, NL, and YY contributed to the conception and design of the study, data curation, and wrote sections of the manuscript. ND, YZ, MS, and YY did the statistical analyses and data interpretation and wrote the first draft of the article. All authors contributed to manuscript revision, read, and approved the submitted version.

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Figures

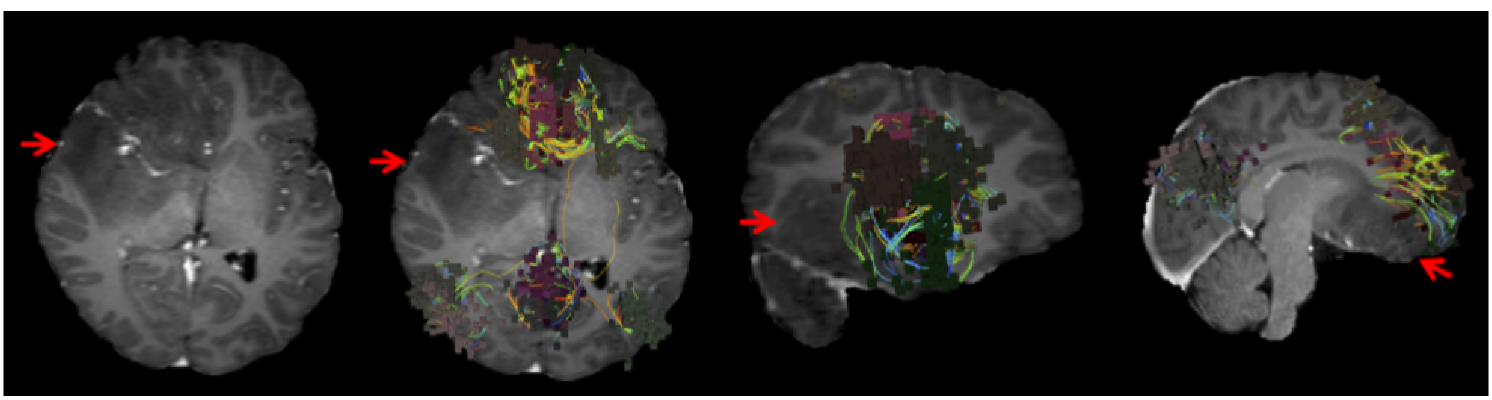

Figure 1

Default mode network (DMN) invaded by tumor

Figure 2

Salience network (SN) invaded by tumor

Figure 3

Central executive network (CEN) invaded by tumor

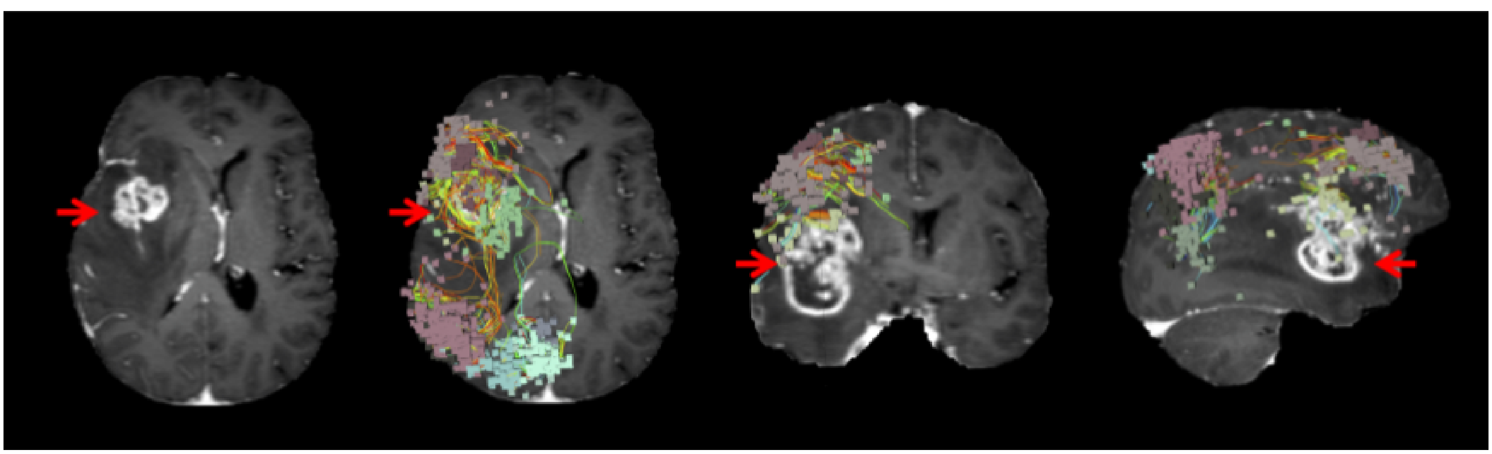

Figure 4

Ventral attention network (VAN) network invaded by tumor

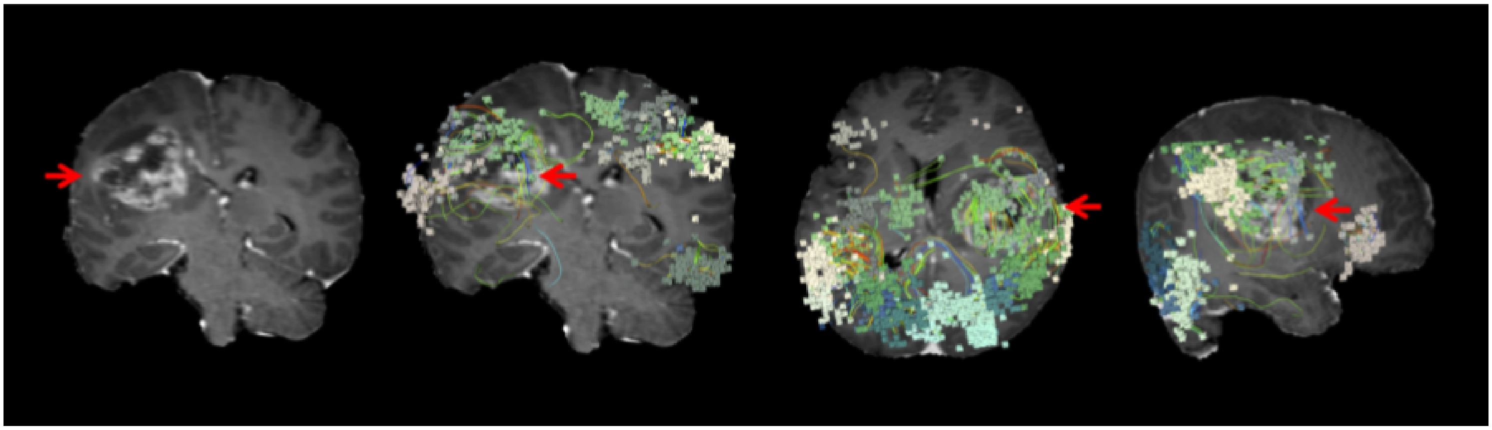

Figure 5

Dorsal attention network (DAN) network invaded by tumor