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Using machine learning to evaluate large-scale brain networks in patients with brain tumors: Traditional and non-traditional eloquent areas

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Abstract

Background. Large-scale brain networks and higher cognitive functions are frequently altered in neuro-oncology patients, but comprehensive non-invasive brain mapping is difficult to achieve in the clinical setting. The objective of our study is to evaluate traditional and non-traditional eloquent areas in brain tumor patients using a machine-learning platform.

Methods. We retrospectively included patients who underwent surgery for brain tumor resection at our Institution. Preoperative MRI with T1-weighted and DTI sequences were uploaded into the Quicktome platform. We categorized the integrity of nine large-scale brain networks: language, sensorimotor, visual, ventral attention, central executive, default mode, dorsal attention, salience and limbic. Network integrity was correlated with preoperative clinical data.

Results. One-hundred patients were included in the study. The most affected network was the central executive network (49%), followed by the default mode network (43%) and dorsal attention network (32%). Patients with preoperative deficits showed a significantly higher number of altered networks before the surgery (3.42 vs 2.19, $P < .001$), compared to patients without deficits. Furthermore, we found that patients without neurologic deficits had an average 2.19 networks affected and 1.51 networks at-risk, with most of them being related to non-traditional eloquent areas ($P < .001$).

Conclusion. Our results show that large-scale brain networks are frequently affected in patients with brain tumors, even when presenting without evident neurologic deficits. In our study, the most commonly affected brain networks were related to non-traditional eloquent areas. Integrating non-invasive brain mapping machine-learning techniques into the clinical setting may help elucidate how to preserve higher-order cognitive functions associated with those networks.

Key Points

- Brain networks are frequently altered in patients with brain tumors.
- These alterations are even present in patients with normal standard neurologic examination.
- Affected brain networks are regularly associated with non-traditional eloquent areas.

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Importance of the Study

Large-scale brain networks and higher cognitive functions are frequently altered in neuro-oncology patients, but comprehensive non-invasive brain mapping is difficult to achieve in the clinical setting. We conducted the first reported large-scale brain network analysis using a non-supervised machine-learning platform in patients with brain tumors. Our results show that the most commonly affected brain networks were related to non-traditional eloquent areas, including the central executive, dorsal attention, and default mode networks. Furthermore, we found that patients with neurologic deficits had a significantly higher number of altered brain networks, compared to patients without deficits. Finally, we discovered that non-traditional eloquent areas were frequently affected in patients found to be neurologically intact on a standard neurologic exam. Integrating non-invasive brain mapping machine-learning techniques into the clinical setting may help elucidate how to preserve higher-order cognitive functions associated with those networks.

The main objective of brain tumor surgery is to provide the best oncologic surgical treatment along with the best possible neurological outcome. While increasing tumor volume resection improves survival, new postoperative neurological deficits are associated with a decreased quality of life and overall survival.[1,2] Several methods for the preoperative mapping of traditional eloquent areas comprising the language,[3–5] visual[6] and sensorimotor[7–9] networks are routinely used for preoperative surgical planning. Imaging techniques such as diffusion tensor imaging (DTI), repetitive navigated transcranial magnetic stimulation (rTMS), and resting-state or task-based functional MRI are the most common modalities used, but they require expert personnel and logistics that are not available at many institutions.

Furthermore, patients' quality of life can be affected by postoperative deficits in other areas, affecting their personality,[10] executive,[11] visuospatial,[12] metacognition,[13] semantic,[14] memory,[15] or other cognitive functions.[16,17] Preserving these functions requires a deeper understanding of the "non-traditional" eloquent areas such as those that comprise the salience, default mode, limbic, central executive, and dorsal attention networks.[18–21] When non-traditional eloquent areas are damaged, less objectively obvious neurologic deficits or cognitive impairments can occur, which may nonetheless be devastating to the patient's quality of life. To address this, we must look beyond the traditional localizationist concept,[22] and towards a connectome-based preoperative assessment. In the localizationist paradigm,[23] function has been historically attributed to specific anatomical areas, such as Broca's area for speech articulation or Wernicke's area for language comprehension. Our current understanding of the complex map of the structures and connections that form the "brain connectome",[24] allows the construction of a contemporary brain mapping paradigm that recognizes function as part of the role of large-scale brain networks and subnetworks,[25] instead of fixed anatomical areas.

Developing mapping tools that allow identification of traditional or non-traditional eloquent areas is necessary to minimize the risk of neurologic deficits. To achieve that goal, new technologies allowing automated reconstruction of white matter tracts, cortical parcellations and ultimately, brain networks, are being developed. Most rely on the positions of functional areas in relation to a normal brain atlas, and thus are often unable to map significantly abnormal brain shapes, such as those with brain tumors. Quicktome™ is a novel cloud-based platform that uses machine-learning and reparcellation techniques to accurately map brain networks in brains with anomalous anatomy. The objective of this study is to use the Quicktome platform to identify how brain tumors affect large-scale networks, as well as traditional and non-traditional eloquent areas.

Methods

Patient Selection

After institutional review board approval was obtained, we retrospectively included all consecutive adult patients with primary or secondary intra-axial brain tumors who were treated at our Institution between the 16th of February and the 15th of October of 2021. Additional inclusion criteria included patients with available preoperative contrast-enhanced MRI with T1-weighted and high-resolution Diffusion Tensor Imaging (DTI) sequences.

Exclusion criteria included skull lesions, pituitary tumors, skull base tumors, meningiomas and infratentorial lesions.

MRI Acquisition

Preoperative MRI images were obtained in a 3 T scanner (Siemens Magnetom Vida, Germany). The acquisition of the preoperative contrast-enhanced MRI was performed the day prior to surgery, as part our institutional imaging protocol. The MRI protocol can be found in Supplementary material.

Data Processing and Evaluation

Pre- and post-operative contrast-enhanced MRI images containing T1-weighted and high-resolution DTI

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sequences were uploaded into the Quicktome (Omniscient Neurotechnology, Sydney, Australia) platform, an FDA-approved software for network analysis. An overview of the data transmission between our Institution and the Quicktome platform can be found in Figure 1. Data was uploaded in a HIPAA-compliant fashion.

As previously described,[26] Quicktome (Omniscient Neurotechnology, Sydney, Australia) is a machine learning

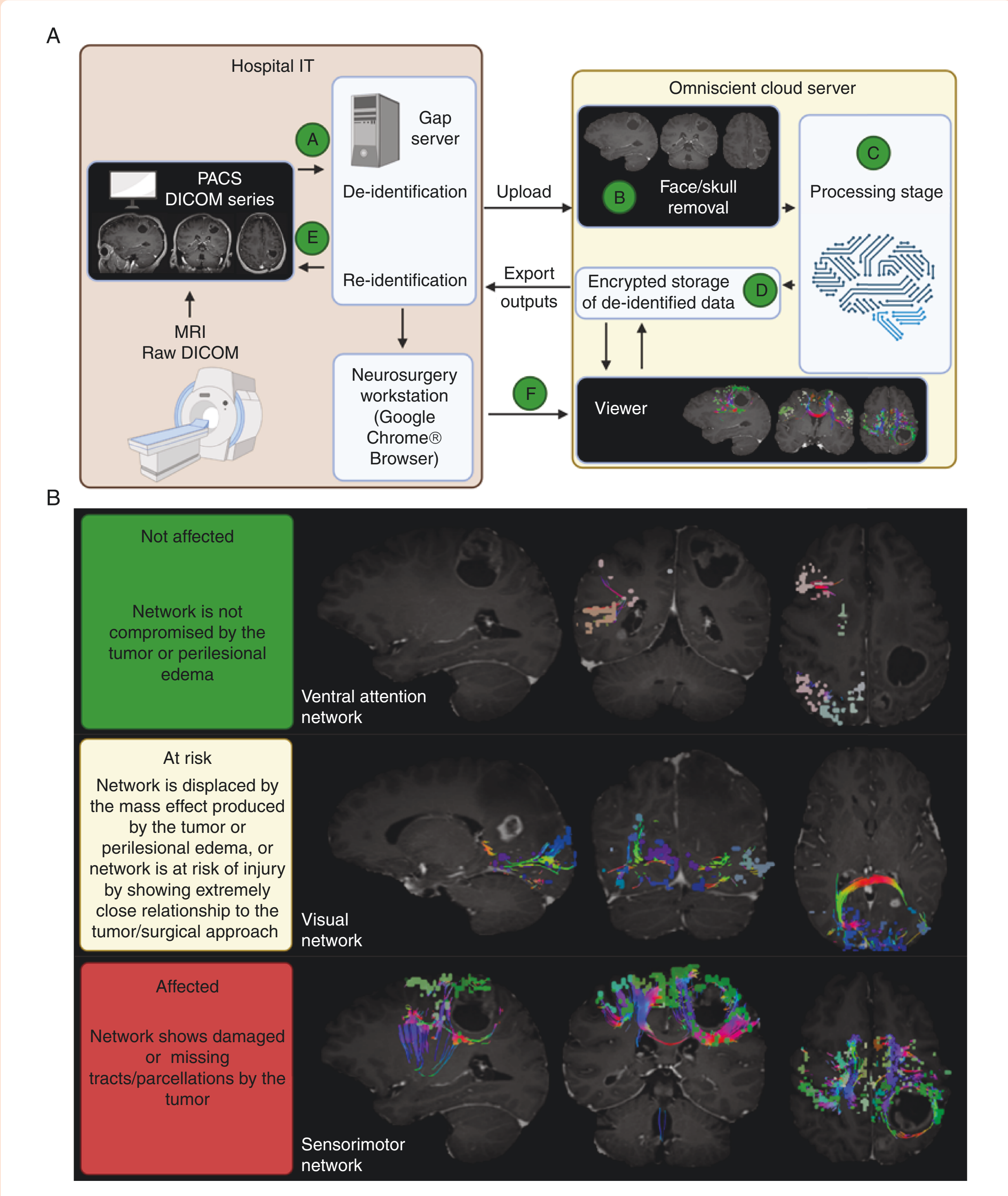

Figure 1. (A) Schematic diagram showing the workflow of the Quicktome Platform. Only points A (exporting dataset) and F (accessing the platform using an internet browser) require manual input. All other steps (B, C, D and E) are automated do not require human interaction. (B) Qualitative network analysis of large-scale networks. White matter tracts are represented as multicolored lines, and cortical parcellations are visualized as groups of dots with the same color.

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based software that creates a subject-specific version of the Human Connectome Project (HCP)[24] Multi-Model parcellation atlas. This is performed by using reparcellation based on structural connectivity instead of anatomic-based methods, which is more accurate in patients with a distorted anatomy, as those with brain tumors. It requires two MRI sequences: a high-resolution Diffusion Tensor Imaging (DTI) scan, and T1-weighted contrast-enhanced anatomical scan. The software's algorithm uses three steps to generate a subject-specific atlas:

a) Preprocessing step: to filter for distortion and motion in the underlying Diffusion Tensor Images.
b) Initial processing step: to register the HCP atlas to the patient's brain images.
c) Refinement step: reviews the connectivity between parcellations using the DTI sequence and adjusts parcellations accordingly.

Automated, unsupervised rendering of the brain networks, tracts and parcellations is accessible on demand through an internet browser (Google Chrome® Version 91.0, Google LLC, Mountain View, California). The platform allows to visualize large-scale brain networks, all the HCP Atlas parcellations segmented into the subject's brain, and most tractography bundles. An example of Quicktome's rendering of large-scale brain networks can be found on Figure 3, and the complete imaging protocol with specifications can be found as the Supplementary Data.

After the data was processed, we evaluated nine large-scale brain networks[21]: language, sensorimotor, visual, central executive, default mode, dorsal attention, ventral attention, salience, and limbic. We classified areas involving language, sensory, motor, and visual functions, as traditional eloquent areas, as these have been ubiquitously considered as eloquent in the literature. The ventral attention network, generally damaged in patients with spatial neglect, was also included as a traditional eloquent area.[27] We classified areas implicated in several other cognitive domains such as as attention, executive, and visuospatial functions,[12] personality,[10] theory of mind,[28] memory,[15] or emotional recognition[29] as non-traditional eloquent areas.

All networks, tractography bundles, and parcellations were reviewed by a board-certified neurosurgeon, recording severe tract misalignments or incorrect positioning of the parcellations.

Processing Speed of the Platform

To evaluate the role of the platform in our daily surgical setting, we collected processing time of the Omniscient cloud server in all the datasets uploaded to the Quicktome platform during the period of the study (point C in Figure 1A.). We decided to include all datasets to avoid re-identification of the patients in the Omniscient server and remain compliant with our IT protocols.

Clinical and Radiographic Assessment

Relevant clinical data as demographics, tumor size and location, pre-operative and post-operative deficits were assessed using electronic medical records. The integrity of each network was analyzed in the Quicktome platform and they were classified in three categories: (Figure 1B):

a) Affected: Network had missing cortical regions (parcellations) or white matter fibers by the presence of the tumor.
b) At-risk: Network had parcellations or white matter fibers displaced by the mass effect of the tumor, or networks had parcellations or white matter fibers that may be damaged during the surgery due to proximity to the tumor and/or planned transcortical trajectory.
c) Not affected: Network had no damaged or displaced parcellations or white matter fibers because of the tumor.

This qualitative analysis was performed by two board-certified neurosurgeons and was achieved by visually inspecting the white matter tracts and parcellations (cortical and sub-cortical) of each network. Both neurosurgeons were blinded to the history of the patient, included neurologic deficits. Networks or tractography bundles affected were correlated with preoperative focal neurologic deficits.

Statistical Analysis

Statistical Analysis was performed with SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY) and GraphPad Prism version 8.0.0, (GraphPad Software, San Diego, California, USA). Means in normally and non-normally distributed variables were compared by the Student's *T*-test, and Kruskal–Wallis test respectively. Categorical variables were assessed using χ^2. Figures were created with BioRender.com.

Results

One hundred patients were included in the study, of which 45% were female and 55% were males. The most common predominant tumor locations were temporal (n = 37) and frontal (n = 32) (Table 1). In 20 patients, the tumors were predominantly located in the parietal lobe, and the other seven patients presented with occipital tumors. Preoperative neurologic deficits were observed in 38% of patients (n = 38).

Quicktome Platform Analysis

All datasets (n = 100) were successfully uploaded into the Quicktome platform (Version 1.1.1, Omniscient Neurotechnology, o8t™). After individual visual inspection, no severe misalignments were found in any of the patients. Average processing time was 52 min (SD 10.82, range 17–81) (Figure 2).

Preoperative MRI and Large-Scale Network Analysis

Eighty-seven of 100 (87%) patients had at least one large-scale network affected, and 98% of them had at least one network at-risk or affected.

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Table 1. Patient demographics and tumor characteristics

Variable	No. (%)
Total no. of patients	100 (100%)
Female	45 (45%)
Male	55 (55%)
Median age in years, range	
All patients	61.06, 27–96
Female	62.50, 27–96
Male	61.87, 32–87
Predominant tumor location	
Temporal	37 (37%)
Frontal	32 (32%)
Parietal	20 (20%)
Occipital	7 (7%)
Other/multifocal	4 (4%)
Diagnosis	
Glioblastoma	45 (45%)
Metastatic disease	28 (28%)
Low grade glioma	16 (16%)
High grade glioma	11 (11%)
Preoperative deficits	
Yes	38 (38%)
No	62 (62%)

The most affected network was the central executive network (n = 49), followed by the default mode networks (n = 43), and the dorsal attention network (n = 32), while the least affected were the visual (n = 15), ventral attention (n = 21), and language (n = 23) networks. Furthermore, the most frequent network at-risk was the dorsal attention network (n = 23), followed by the central executive network (n = 21) (Table 2). A heatmap figure containing all patients and networks can in found in Figure 3.

Preoperative Focal Neurological Deficits

Patients with preoperative focal neurological deficits showed a significantly higher number of altered networks before the surgery compared to patients without focal neurologic deficits (3.42 vs 2.19 networks, P < .001). Furthermore, we found that patients without neurologic deficits had an average 2.19 networks affected and 1.51 networks at-risk, with most of them being related to non-traditional eloquent areas (P < .001).

Traditional vs Non-traditional Eloquent Areas

When we analyzed networks with traditional regions of eloquence, we found that they were affected at least once in 61% (n = 61) of the patients, and affected or at-risk in 82% of them (n = 82). Conversely, we found that networks involving non-traditional regions of eloquence were affected in 81% (n = 81) of the patients, and affected or at-risk in 93% (n = 93) of them (Figure 3).

Discussion

In the current era, we have an unprecedented understanding of the brain connectome, leading to the identification of cerebral networks that are associated with specific neurologic functions. The Human Connectome Project (HCP), launched in 2010 and funded by the National Institutes of Health, aimed to characterize human brain connectivity and develop improved neuroimaging methods.[30] By acquiring a dataset of unprecedented size, quality, resolution and diversity of imaging modalities, this project enabled the creation of a novel multimodal parcellation scheme of the human cerebral cortex. A machine-learning classifier was trained to recognize each cortical area, detecting 96.6% of the cortical areas in new individuals.[24] As has previously been published,[31,32] preoperative assessment of the connectome in patients with brain tumors may predict important clinical variables as survival or performance status. When we adopt a "connectomics" perspective,[33] we are able see beyond the tumor and the surgical approach, evaluating the whole brain and it's networks (Figure 4). While recognizing how parcellations are connected creating large-scale networks is paramount in patient with brain tumors, translating these concepts into the neurosurgical practice has been difficult.

In our study, we used a machine learning based platform that creates a subject-specific version of the HCP atlas,[24] using diffusion tractography structural connectivity and machine learning algorithms to construct models of known large-scale brain networks,[21,26,34] allowing for unsupervised visualization of brain networks in patients with brain tumors. This automated method was incorporated into our clinical setting with relative ease, as the only steps that required manual interaction were exporting the dataset and accessing the browser to visualize the studies (Figure 1). Processing time was on average 52.4 min, with most patients being processed in less than 1 h. While the processing time itself was rather short, we discovered that the automated nature of the platform allowed us to maintain our tight surgical workflow without spending extra time on processing the datasets.

One of the main findings in the studied cohort, including 100 consecutive patients with intra-axial lesions, was that most patients (89%) had at least one affected large-scale network. Networks involved in traditional regions of eloquence, such as the language, visual, VAN (associated with neglect syndromes) and sensorimotor networks, were found to be affected or at-risk in most patients (82%). On the other hand, networks involved in non-traditional regions of eloquence, were found to be affected or at-risk almost all patients (93%). This can be explained in part by the slightly higher number of networks in the latter group, but it remains clear that patients with brain tumors possess a very high chance of having non-traditional eloquent networks affected. These networks are commonly involved in higher cognitive functions, so their correct preoperative assessment generally involved specific tests and neuropsychological expertise.[35] While traditional eloquent

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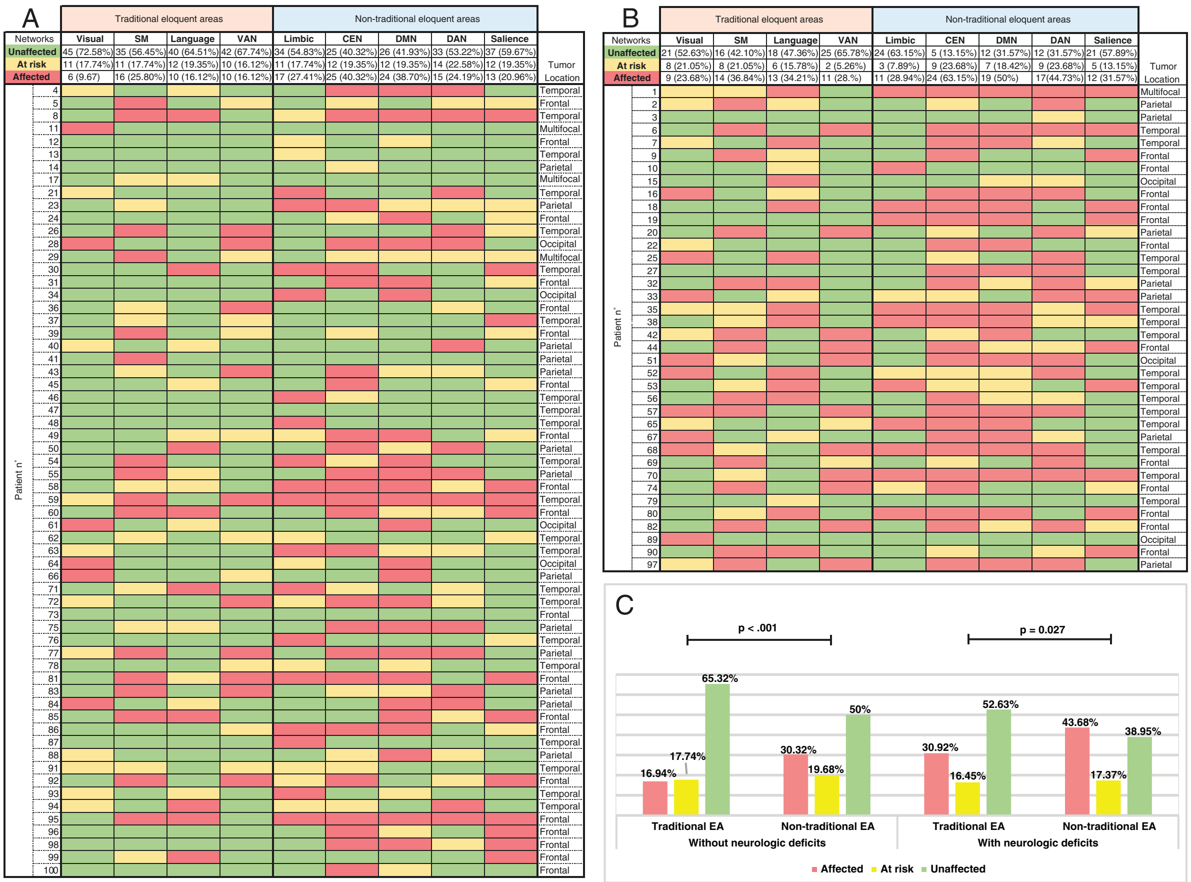

Figure 2. (A) and (B) Heatmap describing tumor location and large-scale network analysis in patients with (A) and without (B) neurological deficits. Data is presented as *n* (%). (C): comparison of affected brain networks between traditional and non-traditional areas. We found a statistically significant difference in patients without neurologic deficits ($P = .014$), with a higher amount of affected networks related to non-traditional eloquent areas. That finding was not present in the cohort of patients with neurologic deficits ($P = .868$). SM, sensorimotor; VAN, ventral attention network; CEN, central executive network; DMN, default mode network; DAN, dorsal attention network. Data is presented as percentage of networks affected, at-risk or unaffected.

networks as the VAN, sensorimotor, language and visual systems have been damaged in 15–30% of the patients included in our study, we would like to focus our discussion on the non-traditional eloquence areas.

Non-traditional Eloquent Networks

Deficits in higher cognitive functions such as visuospatial ability, metacognition, or theory of mind can profoundly impact the quality of life of our patients. For instance, the processes that allow to understand and predict the emotions and mental states of others,[36,37] known as mentalizing and theory of mind, are crucial to preserving social wellbeing in patients with brain tumors.[38,39] These processes are closely related to the default mode network and include brain areas as the medial prefrontal cortex and the lateral parietal lobe, not traditionally labeled as "eloquent". As it happens with other high-level cognitive functions, patients may recover totally or partially after surgery, but recognizing this potential postoperative deficit is a necessary element to include in the preoperative discussion with patients and their families. In our study, we found that the default mode network was the second most affected (43%) and considered at-risk in 19% of our patients.

The most affected network was the Central Executive Network, damaged in 49% of the patients and at-risk in 21% of them. This network is associated to goal-oriented attention and other higher cognitive functions as general intelligence and executive functioning.[40] In humans, it is specially involved in fluid cognition.[41,42] This type of cognition is responsible for critical domains such as processing speed, quantitative reasoning, problem-solving skills, and adequate adaptation to new environments.[43,44] Conversely, crystallized cognition refers to the knowledge and skills acquired through education and cultural background and is associated with long-term memory.[45] The former type of cognition is more labile in patients with brain tumors, and has been described by Lang et al.[46] as impaired in almost 40% of patients with diffuse gliomas in the frontal, temporal or parietal lobes. In that study, crystallized cognition was affected in only 7% of the patients before the surgery, while 78% of the total cohort ($n = 18$) demonstrated a significant deficit on one or more of the cognitive tests.

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Table 2. Brain network analysis in the total cohort (n = 100)

Brain network	Affected	At-risk	Unaffected	Total
Traditional eloquent areas				
Visual	15	19	66	100
SM	30	19	51	100
Language	23	19	58	100
VAN	21	12	67	100
Non-traditional eloquent areas				
Limbic	28	14	58	100
CEN	49	21	30	100
DMN	43	19	38	100
DAN	32	23	45	100
Salience	25	17	58	100
Statistical analysis Mean (SD) [Median, IQR]				
All patients	2.66 (1.81) [3,3]	1.44 (1.26) [1,2]	4.90 (1.84) [5,2.75]	
Without neurological deficits	2.19 (1.76) [2,2]	1.51 (1.36) [1,1.25]	5.29 (1.81) [5,2.25]	
With neurologic deficits	3.42 (1.63) [3,2]	1.31 (0.96) [1,1.25]	4.26 (1.73) [4,2)	

SM, sensorimotor; VAN, ventral attention network; CEN, central executive network; DMN, default mode network; DAN, dorsal attention network; SD, standard deviation; IQR, interquartile range.

The Dorsal Attention Network (DAN) presented a similar damage prevalence compared to the DMN affected in 32% of the patients and at-risk in 23% of them. The former is a bilateral network that is responsible for the voluntary orientation of attention and externally-directed cognition, while the DMN sub-serves internal cognition and is most active during task-negative processes as resting states or mind-wandering. Surprisingly, these two networks present apparent antagonistic features, and they are "modulated" by the previously mentioned CEN and the Salience network. In our study, the salience network was affected in 25% of patients.

The last evaluated network was the limbic system. This network includes structures as the hippocampus, amygdala, posterior cingulate gyrus, temporal pole, medial and lateral orbitofrontal cortex and the parahypocampal gyrus. It was affected in 28% of the patients, and it's dysfunction has been associated with socio-emotional behavior problems or memory loss.[38]

Networks and Neurologic Deficits

In our study, more than half of the cohort presented with neurologic deficits. As neuropsychological testing was not considered for this study, we only included deficits evident in a complete neurological physical examination. Patients with neurologic deficits had a significantly higher number of networks affected (3.42 vs 2.19 networks, $P < .001$), as may be expected. However, one of the major findings is that those patients who presented "neurologically intact", had an average of 2.19 large-scale networks with evident alterations. Historically, the term neurologic deficit in neurosurgery has been associated with the concept of *focal* neurologic deficit, defined as "a set of symptoms or signs in which causation can be localized to an anatomic site in the central nervous system".[47] When a neurologic function is altered, but the cause cannot be localized to a specific anatomic site, we generally use the term non-focal neurologic deficit (i.e. altered mental status, confusion).[48] In this context, one of the first thoughts that comes into our minds is that the new advances in neuroscience (including connectomics) challenge the historic definition of focal neurological deficits. As it has been published, a more accurate and contemporary onco-functional balance should be pursued by acknowledging higher cognitive functions in the management of brain tumors. Although more studies are needed to compare the accuracy and reliability of the Quicktome platform to current intra-operative mapping techniques, we expect that machine-learning techniques may provide a seamless method to incorporate highly efficient network analysis at the patient's bedside.

Limitations

Our study has several limitations that needs to be discussed. The first is its retrospective design, which makes the study susceptible to a patient selection bias. We tried to mitigate that bias by including one-hundred consecutive patients that met the inclusion criteria in a high-volume brain tumor practice. Secondly, a standardized preoperative neuropsychological assessment was not used, limiting the accuracy of the neurological examination. Albeit many neuropsychological domains have been described thoroughly in the literature, the complexity of the involved neural circuits and peri-operative assessments remain a challenge in neuro-oncology, and are not routinely evaluated in many centers.[29,49] Third, qualitative assessment can

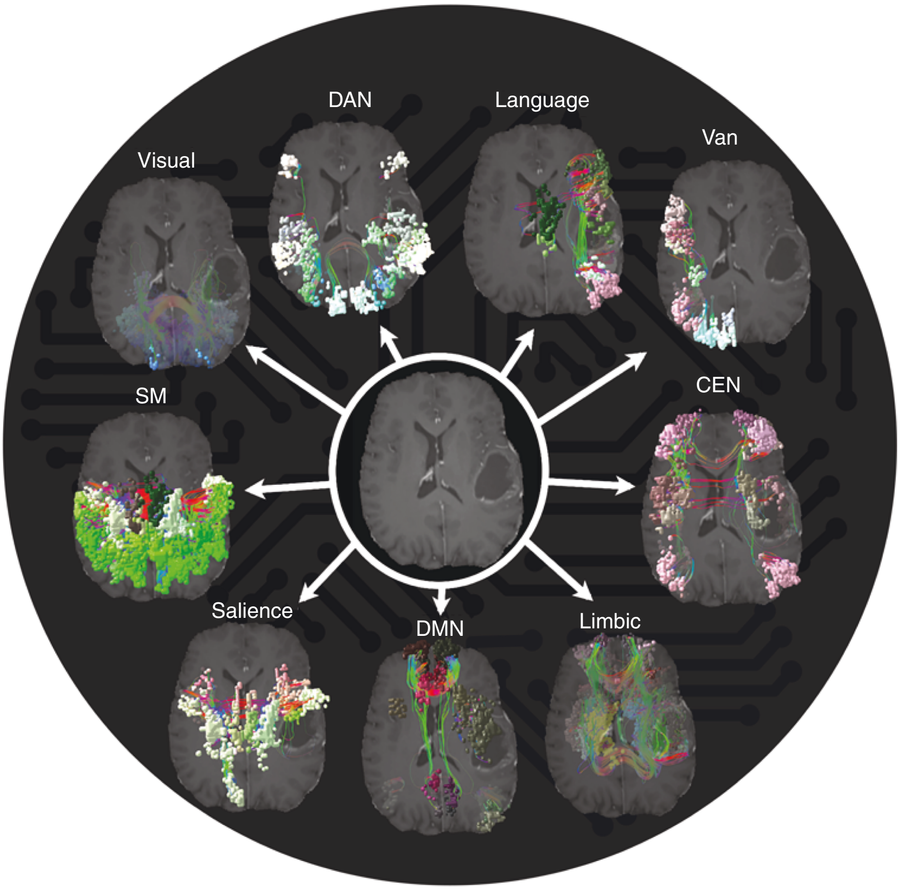

Figure 3. Example of patient with a left temporal glioblastoma who underwent large-scale network analysis using the Quicktome platform. Language, visual and sensorimotor networks are frequently considered in patients with tumors located in the dominant temporal lobe, but we can see in the images that additional networks may be damaged or at-risk in this case (CEN, Limbic, DMN, Salience, DAN). Visualization of the networks is represented on the same axial cut for comparison purposes, but the assessment was done inspecting each parcellation and white matter tract in the three-dimensional space. SM, sensorimotor; VAN, ventral attention network; CEN, central executive network; DMN, default mode network; DAN, dorsal attention network. White matter tracts are represented as multicolored lines, and cortical parcellations are visualized as groups of dots with the same color.

be subjective and difficult to validate in similar studies. We tried to mitigate this limitation by including two board-certified neurosurgeons who completed all assessments and were blinded to each other and the history of the patients. Currently, there are no available FDA-approved software tools that are able to analyze brain networks and retrieve metrics on damage to cortical or sub-cortical structures. Hopefully, as machine learning techniques grow in neurosurgery, we will count with more robust quantitative analysis in the near future. Forth, there are likely inherent differences between infiltrating primary brain tumors and metastases on network integrity. This limits the interpretation of our findings, and we expect to see studies performed on specific tumor types in the near future.

Future Directions

A better understanding of the human connectome and its peri-operative adaptations carries important implications in the management of brain tumors. Accessible brain network analysis at the bedside enhances the concept of precise, minimally invasive surgery. Moreover, it can generate data beyond the narrow setting of clinical trials, leveraging machine-learning models. We expect that the empirically validated concept of eloquence will be reappraised including new perspectives such as hubness,[26] PageRank centrality[50] and/or meta-networks.[25] The future applications of these concepts extend beyond the field of neuro-oncology, including vascular, degenerative, and traumatic pathologies, as well as neuro-rehabilitation.

Conclusions

Large-scale brain networks are frequently affected in patients with brain tumors, even when presenting without evident neurologic deficits. In our series, the most commonly affected brain networks were related to non-traditional

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eloquent areas. Although further studies are needed comparing novel machine-learning platforms to gold-standard brain mapping techniques, integrating them into the clinical setting can help us elucidate how to preserve higher-order cognitive functions associated with these networks.

Supplementary material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

brain network | eloquent areas | machine-learning | neuro-oncology.

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