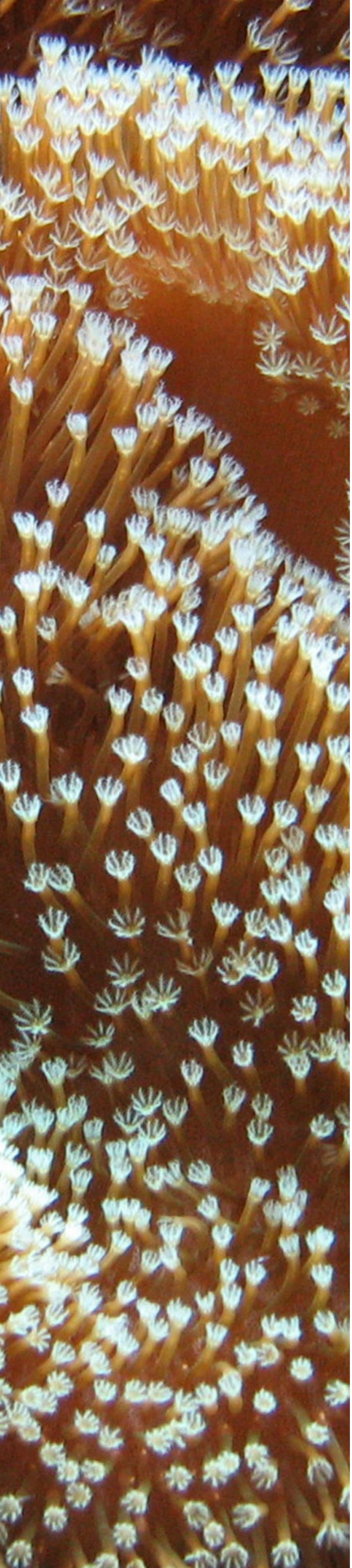

PERSONALIZING NEUROSURGERY: HOW UNDERSTANDING BRAIN NETWORKS AIDS THE SURGICAL APPROACH

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Key Takeaways

- To achieve optimal "onco-functional balance" in neurosurgery, a more comprehensive appreciation of brain anatomy and function is paramount.
- Brain networks underpin a swathe of human functions, many of which overlap with deficits observed following neurosurgery.
- Personalized brain mapping visualizes functional brain networks and associated tract bundles in individual patients, providing a practical solution for intraoperative navigation and formulating pre-surgical approaches.

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Introduction

The absolute goal of intracerebral neurosurgery is to provide optimal treatment whilst preserving patient quality-of-life[1,2]. This equation is often referred to as “onco-functional balance”, and in the case of tumor resection, this balance is represented as how aggressive surgical approaches can be in completely removing or reducing tumor volume, without heavily compromising regular functions like movement, cognition, or emotion[3]. Reaching this onco-functional balance requires an understanding of an individual patient’s anatomical and functional brain states before surgery – a requirement met by personalized brain mapping[4].

Indeed, it is widely accepted that maximal resection of tumor-affected regions ensures the greatest chance of extending life in most patients[3,5]. However, mounting evidence confirms that such an approach can lead to devastating and unpredicted consequences post-surgery – impacting not only the patient, but their family, career, and broader support network too[6–9]. These consequences, while not always avoidable, can be explained by incidental or necessary damage to brain networks: connected, distributed groups of functional brain regions. Personalized brain mapping is a technique that can locate these networks prior to surgery, and assess their damage post-surgery to better understand and avoid the varied states of recovery surgeons observe in their unique patients[10–12].

The concept of a brain network is not new, originating in academia over 20 years ago with a groundbreaking observation by Marcus Raichle, who defined the Default Mode Network – a series of brain regions activated when a person is at rest[13]. Since then, the number of brain networks has expanded and become more defined. Collectively, brain networks control a range of executive functions, including movement (sensorimotor network), cognition (central executive network), and language (language system), among others. Table 1 summarizes each functional network within the brain and their respective major tract bundles that connect them. Despite a lengthy history in academia, understanding of brain networks has seen limited translation into the surgical suite – mostly due to the inability to reliably define their location in an individual patient. Personalized brain mapping removes this barrier, for the first time bringing the modern academic understanding of brain networks into a clinically relevant landscape.

NETWORK	MAJOR BRAIN LOBES	MAJOR TRACT BUNDLE	ROLE	COMMON DEFICIT
Sensorimotor Network	Parietal Lobe	Corticospinal Tract	Sensory and motor function	Hemiparesis (unilateral paralysis)[46]
Central Executive Network (CEN)	Frontal, parietal, temporal lobes	Arcuate and superior longitudinal fasciculus	Task- and decision-making	Aphasia (speaking and understanding language)[47]
Default Mode Network (DMN)	Frontal, parietal, temporal lobes	Uncinate fasciculus	Idle thought and remembering	Autobiographical memory[48]
Salience Network (SN)	Frontal lobe	Inferior fronto-occipital fasciculus	Mediating the CEN and DMN	Mild Cognitive Impairment (MCI)[49]
Limbic System	Temporal lobe, subcortical components	Uncinate and Inferior fronto-occipital fasciculus	Emotional regulation and expression	Learning impairment[50]
Visual System	Occipital lobe	Optic radiations	Vision	Visual disability[51]
Auditory System	Frontal, parietal, temporal lobes	Middle longitudinal fasciculus	Hearing	Sensorineural deafness, Vertigo[52]
Language System	Frontal, parietal, temporal lobes	Arcuate and superior longitudinal fasciculus	Language speaking and comprehension	Global Aphasia[53]
Dorsal Attention Network (DAN)	Frontal, parietal, occipital lobes	Superior longitudinal fasciculus	Focused and goal-directed attention	Working memory[54]
Ventral Attention Network (VAN)	Frontal, parietal, temporal lobes	Superior longitudinal fasciculus	Task switching and reorientation	Spatial neglect[55]

Table 1. *Major brain networks, their location, major white matter connections, and roles in human processes.*

What makes Personalized Brain Mapping "Personalized"?

In the past, brain regions were considered either “eloquent” or “non-eloquent”, acting as a guide for surgeons as to which tissue could be sacrificed to aggressively manage the growth of tumors and surgical pathology[14]. However, through the field of connectomics, the study of how the brain is connected and communicates with itself, we now know that the human brain is vastly more complex. Much of this information has been elucidated through the work performed by the Human Connectome Project and continued by Baker, Briggs, and Sughrue in their “Connectomic Atlas of the Human Cerebrum”.

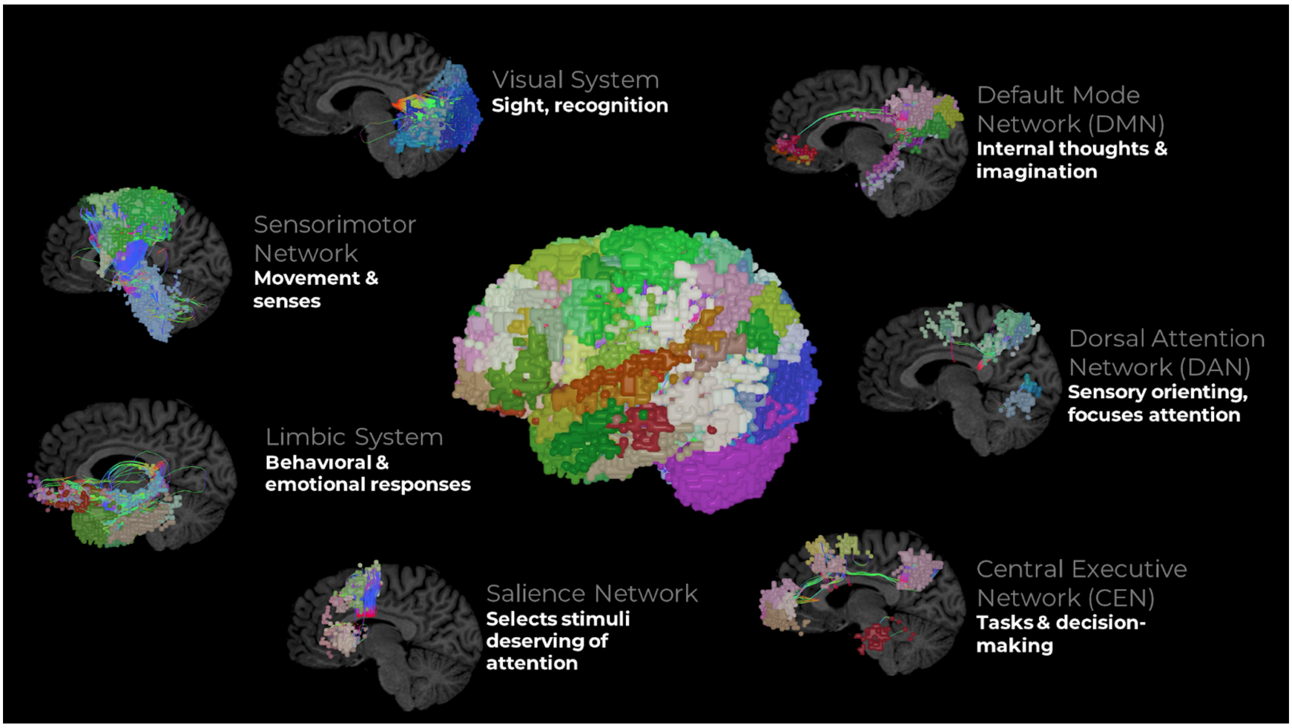

Figure 1. *The brain’s major networks. Distributed around the cortex and connected by tract bundles, brain networks co-ordinate human functions such as movement, audition, and cognitive processing.*

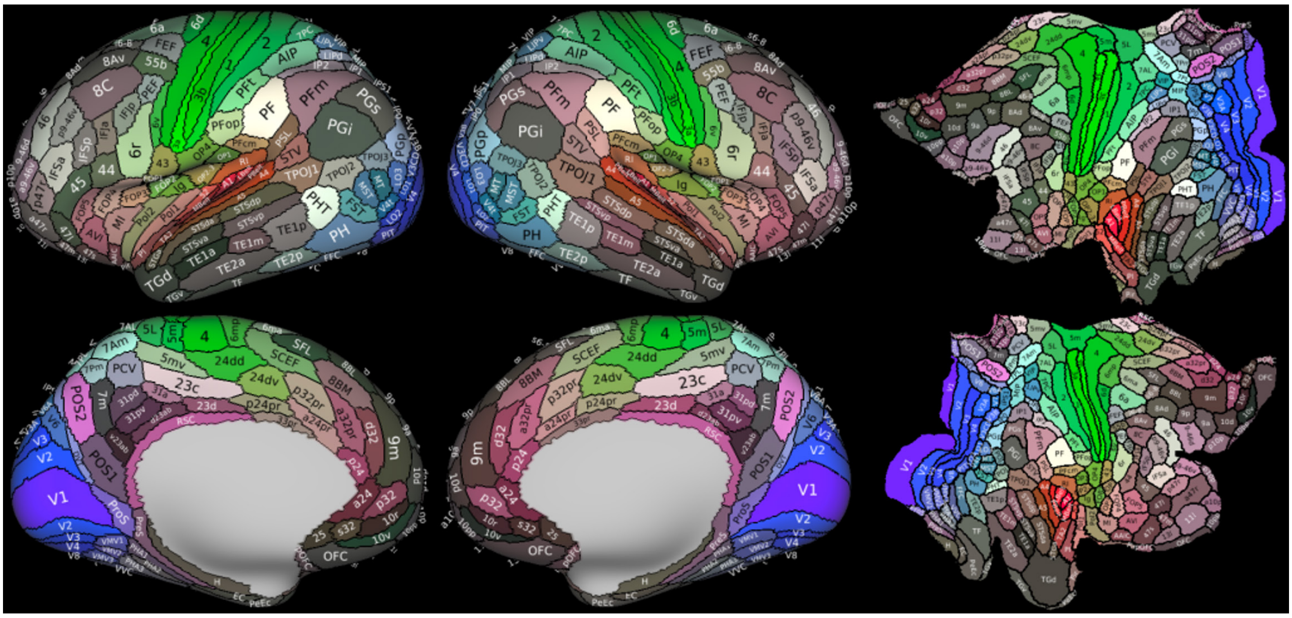

***Figure 2.** The Human Connectome Project (HCP) Atlas.* *Through resolving the topology, function, and connectivity between cortical gray matter, Glasser et al. delineated 360 independent regions (parcels) that comprise the human brain.*

In short, they describe that each hemisphere of the human cortex consists of 180 independent regions, or parcels, distinguishable by their function and the brain networks they form[15,16]. From this work, a standard template or "atlas" for modeling the human brain was developed: one granular enough to discern the discrete function of each brain area, yet simple enough to be discussed and universally understood in research settings.

This atlas held limited applicability in clinical settings however, as the brain data needed to be shifted in space to match this template in order to generate any real anatomical or functional inferences, restricting its use in intraoperative guidance[17].

Personalized brain mapping seeks to visualize where these functional areas lie in each individual, rather than assuming that a single archetypal atlas is applicable in every case. By employing and training a machine-learning algorithm to process brain data, personalized brain mapping generates a unique anatomical map of each functional brain area and the tracts which connect them. In practice, by utilizing standard Magnetic Resonance Imaging (MRI), personalized brain mapping informs the location of each of

these atlas regions in a single patient, with consideration for variations in gyral folding patterns, intracranial volume, or structural pathology. An in-depth description of one method for conducting personalized brain mapping has been described in the work of Doyen et al. and their Structural Connectivity Atlas (SCA)[18], and can be summarized as:

1. *Generating Connectivity Profiles:* Train a machine-learning algorithm using Diffusion Weighted Imaging (DWI) data to identify how white matter tracts connect each atlas region in a healthy individual (structural connectivity).

2. *Collecting Patient Data*: Collect and process patient DWI data, tracing out the location, distribution, and termination points of their individual white matter tracts.

3. *Model application*: Enter patient DWI data into the algorithm trained in (1.), which recreates the atlas in patient space, marking out region locations based on how a patient's white matter tracts are distributed and connected.

How Personalized Brain Mapping informs Neurosurgical Decision Making

Personalized brain mapping can be particularly useful in surgical settings. Beyond segmenting and naming individual brain networks and their associated tract bundles, it also includes considerations that are beneficial for neurosurgical applications. Firstly, if white matter tracts have shifted in location due to the physical mass effect of a tumor, the resulting personalized brain map will robustly define these shifted tracts. This allows the surgeon to segment tracts of interest and visualize their new locations to plan their approach. Additionally, in areas where no white matter tracts terminate (for example, where a tumor is located or has been resected), no atlas region will be mapped. This accounts for areas wholly or partially destroyed due to structural pathology. In sum, the aggressiveness of surgical approaches can be informed by which brain regions or tract

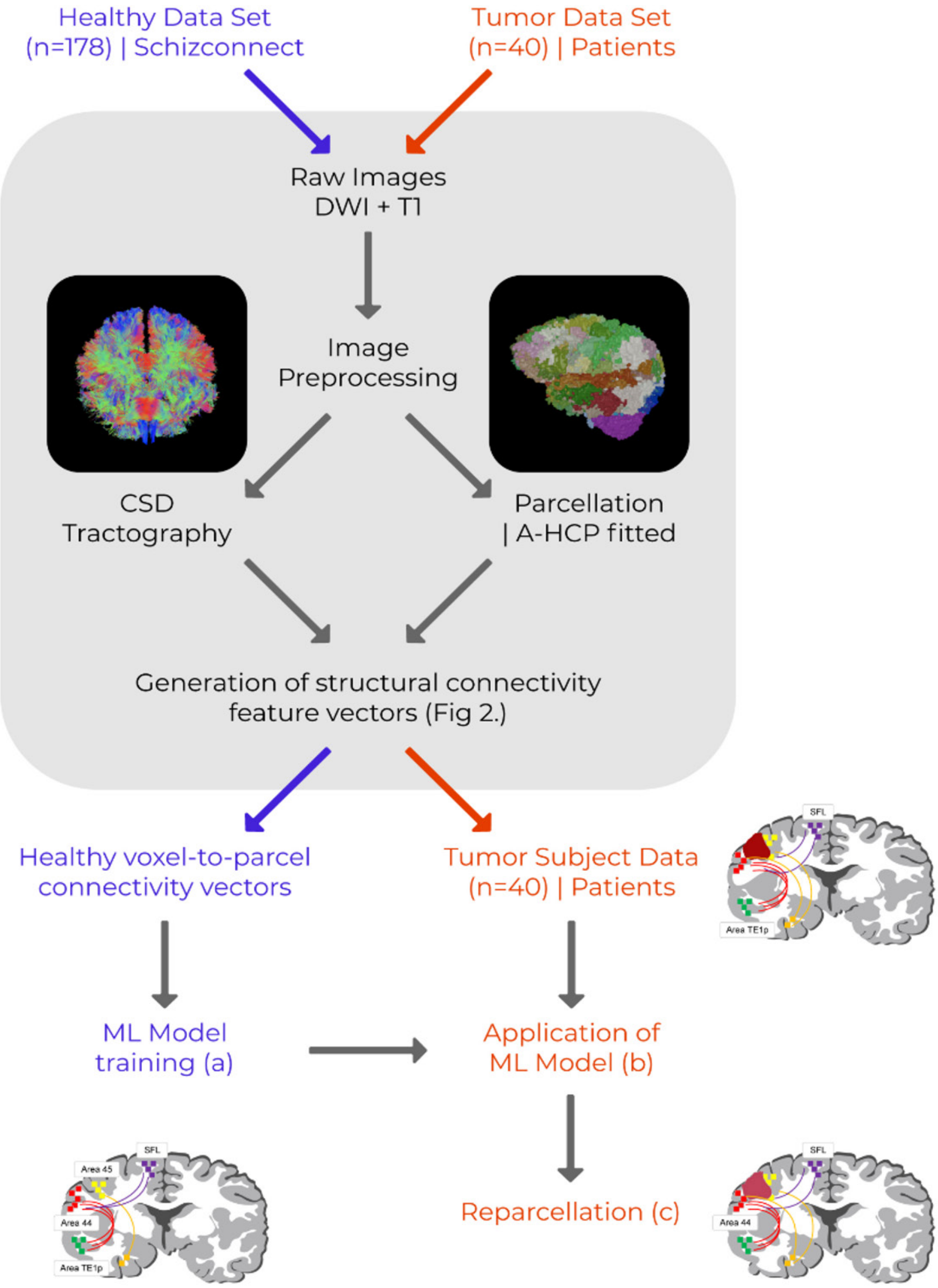

Figure 3. *Schematic description of a personalized brain mapping method (Structural Connectivity Atlas / SCA). By generating a machine learning algorithm using healthy brain data, personalized brain mapping seeks to create patient-specific representations of complex brain atlases. This method utilizes a modified version of the Human Connectome Project (HCP) atlas, and re-parcellates this atlas on a patient's brain, as informed by underlying structural connectivity.*

bundles have already become compromised by the presence of a tumor. Combined, these two considerations enable the integration of the most-recent academic understanding of brain structure and function into neurosurgical settings. An example of a brain atlas generated through personalized brain mapping is shown in figure 4.

What Personalized Brain Mapping means to a Surgeon

For a neurosurgeon utilizing personalized brain mapping, four key applications emerge as the most critical. These are: 1) attaining a greater preoperative understanding of brain network involvement in surgical pathology, 2) structurally informing maximal safe resection intraoperatively, 3) optimizing hospital cost per patient, so that as many patients can be treated within annual budgets, and most importantly, 4) enhancing understanding of potential postoperative consequences, giving patients more complete context prior to informed consent.

Brain Network involvement

Pre-operative assessment of a patient's brain networks gives surgeons an understanding of how pathology may have impacted functional brain tissue. As stated previously, brain networks, their regions, and connections underpin several human cognitive and executive functions. Damage to these networks can cause deficits in these same functions or manifest entirely new cognitive or neuropsychiatric disturbances.

Take, for example, the three main cognitive brain networks – the Central Executive (CEN), Default Mode (DMN), and Salience Networks (SN). Together, these networks provide an

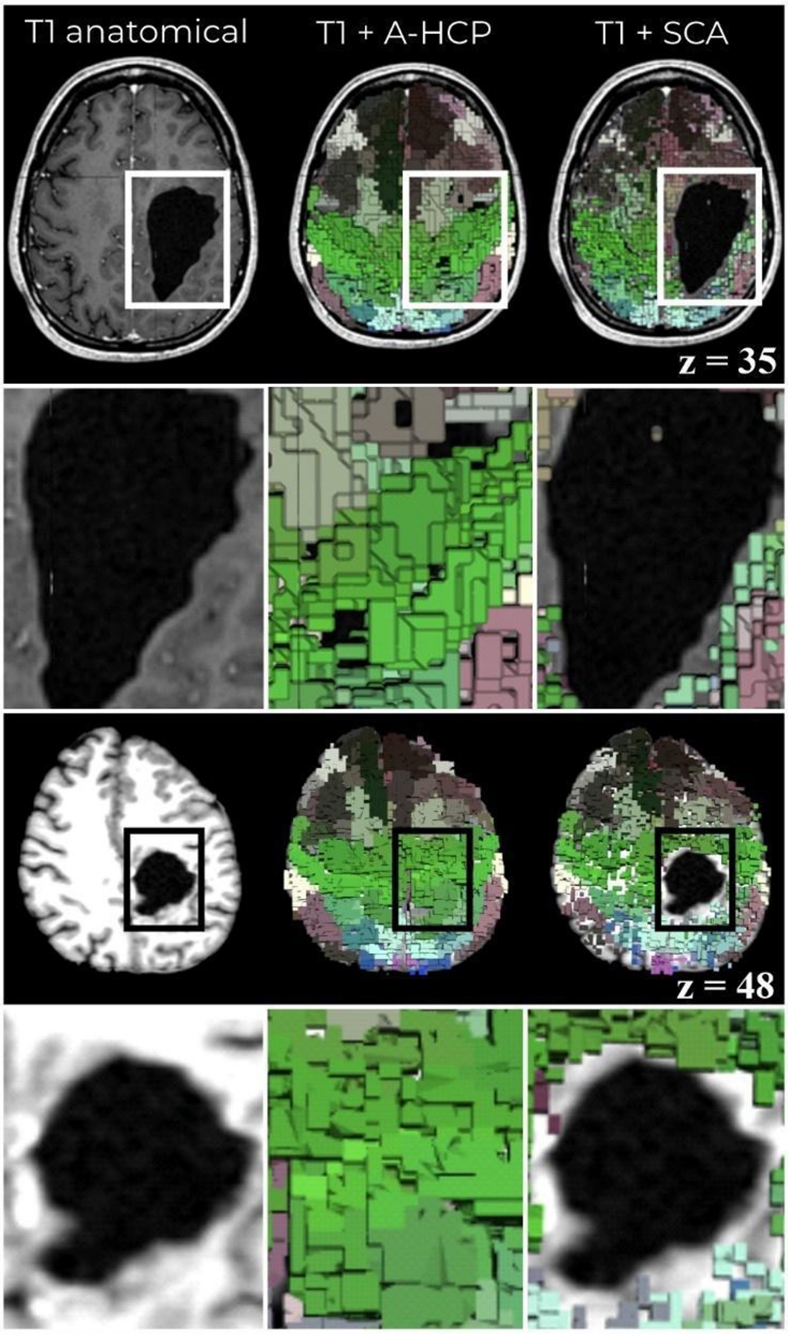

Figure 4. ***Personalized brain mapping resolving functional areas around structural pathology***. *Left column: a T1-weighted image showing the location and extent of structural damage. Middle column: a typical brain atlas overlayed on the T1 image, demonstrating an inability to account for structural damage. Right column: The Structural Connectivity Atlas (SCA) personalized brain mapping technique, showing that brain regions are mapped in accordance and surrounding structural damage.*

axis around which other networks align[19]. The CEN drives goal-directed behavior, and the DMN activates during passive states of mind and at rest[20,21]. Balancing and alternating between these two networks during daily life is mediated by the SN[22]. Unsurprisingly, damage to or disconnection of the tracts between these major networks can cause impairments to higher-order cognitive abilities and cause symptoms associated with schizophrenia, depression, and anxiety[23-25]. Leveraging personalized brain mapping preoperatively informs neurosurgeons about the precise location and involvement of these networks, among others, in their patient's pathology. This context allows them to plan accordingly to avoid and navigate these networks during surgery[26–28].

Maximal safe resection

In modern neurosurgery, the gold-standard approach aims to achieve a maximal resection volume of tumor-affected tissue whilst inducing a minimal risk of functional deficit[29,30]. These approaches, however, carry a greater risk of compromising nearby tracts and networks of the brain. With personalized brain mapping, a neurosurgeon can generate a visualization showing not only if a tumor site is entangled with a functioning region or tract bundle, but also if the regions surrounding a tumor site have already been compromised. In either case, a visualization afforded by personalized brain mapping empowers approaches seeking maximal resection, informing surgeons about the still-functioning tracts and networks to avoid in their approach and what tissue is already compromised and can be resected without potentially worse postoperative outcomes[31-33].

Alleviating financial burden

A retrospective investigation conducted by Mission and Bekelis of 36,000 glioma patients undergoing Neurosurgical intervention between 2005-2010 revealed that post-surgical neurologic complication broadly mediated a 10.3% increase in costs in addition to costs

incurred due to longer lengths of stay. At a median cost of $24,503 USD, complications increase average costs by $2,524 per case and an additional $2,303 for each additional day of stay[34]. This represents a significant financial burden on annual hospital budgets.

While personalized brain mapping does not directly relate to a shorter length of stay, various individual accounts from practicing neurosurgeons assert that the information provided by analogous techniques promote positive surgical outcomes[35-37]. As such, the enhanced guidance offered by Personalized Brain Mapping may aid in alleviating the costs associated with post-surgical complications.

Improved patient consent

Since the early 20th century, United States consent laws have been in place surrounding neurosurgical practice to ensure that, when possible, patients are made fully aware of the potential risk factors of intracranial procedures[38]. In line with these laws, knowing which brain networks may be involved or surrounding a particular pathology helps identify the risk factors that may be associated with necessary surgical action. Personalized brain mapping, that in nature displays and visualizes brain networks and connections, enables a neurosurgeon to not only convey, but for the first time, visually demonstrate to their patient where and why performing the elected surgical strategy could potentially result in postsurgical deficits[1,4]. Countless instances exist where a patient has awoken from a surgery with an unexplained deficit such as neurologic dysfunction or short-lasting apraxia. These scenarios possibly result from the path of the surgical approach or resection cutting through components of core brain networks[39-43]. What is of paramount importance in cases such as these is that patients are made aware of any potential consequences of surgery, which is eloquently offered by personalized brain mapping[44,45].

Omniscient Neurotechnology's Quicktome software enables a personalized brain mapping solution accessible by collecting basic MRI scanning sequences. By loading an anatomical and diffusion weighted imaging scan into Quicktome, neurosurgeons can view and segment individual brain network templates, regions, and tracts associated with their patients' structural pathology or symptom profiles, or utilize the inbuilt pre-selection tools for investigation of tractography and network damage isolated to any major lobe of the brain. In addition, the personalized brain maps generated by Quicktome can be integrated with modern PACS systems, providing neurosurgeons with actionable insights throughout the continuum of care.

Conclusion

The role of a neurosurgeon can never be overstated – they carry with them what few will ever achieve, the capacity to change and save a human life. Because of this, neurosurgeons must be armed with the best available tools to both prolong the lives of their patients without compromising their quality of life. Personalized brain mapping brings decades of research into the anatomy and function of the human brain into the hands of a neurosurgeon, helping to guide their approach towards maximal safe resection and away from major brain networks and tracts, all while keeping their patients informed of any potential surgical consequences.

References

1. Dadario NB, Brahimaj B, Yeung J, Sughrue ME. Reducing the Cognitive Footprint of Brain Tumor Surgery. Frontiers in Neurology. 2021;0:1342. doi:10.3389/FNEUR.2021.711646

2. Almeida JP, Chaichana KL, Rincon-Torroella J, Quinones-Hinojosa A. The Value of Extent of Resection of Glioblastomas: Clinical Evidence and Current Approach. Current Neurology and Neuroscience Reports. 2015;15(2):1-13. doi:10.1007/S11910-014-0517-X/FIGURES/4

3. Molinaro AM, Hervey-Jumper S, Morshed RA, et al. Association of Maximal Extent of Resection of Contrast-Enhanced and Non-Contrast-Enhanced Tumor With Survival Within Molecular Subgroups of Patients With Newly Diagnosed Glioblastoma. JAMA Oncol. 2020;6(4):495-503. doi:10.1001/JAMAONCOL.2019.6143

4. Yeung JT, Taylor HM, Nicholas PJ, et al. Using Quicktome for intracerebral surgery: early retrospective study and proof of concept. World Neurosurgery. Published online August 3, 2021. doi:10.1016/j.wneu.2021.07.127

5. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? Journal of Neurosurgery. 2016;124(4):977-988. doi:10.3171/2015.5.JNS142087

6. Herbet G, Moritz-Gasser S. Beyond Language: Mapping Cognition and Emotion. Neurosurgery Clinics of North America. 2019;30(1):75-83. doi:10.1016/J.NEC.2018.08.004

7. Drewes C, Sagberg LM, Jakola AS, Solheim O. Perioperative and Post-operative Quality of Life in Patients with Glioma–A Longitudinal Cohort Study. World Neurosurgery. 2018;117:e465-e474. doi:10.1016/J.WNEU.2018.06.052

8. Rijnen SJM, Kaya G, Gehring K, et al. Cognitive functioning in patients with low-grade glioma: effects of hemispheric tumor location and surgical procedure. Journal of Neurosurgery. 2019;133(6):1671-1682. doi:10.3171/2019.8.JNS191667

9. Starnoni D, Berthiller J, Idriceanu TM, et al. Returning to work after multimodal treatment in glioblastoma patients. Neurosurgical Focus. 2018;44(6):E17. doi:10.3171/2018.3.FOCUS1819

10. Noll KR, Sullaway CM, Wefel JS. Depressive symptoms and executive function in relation to survival in patients with glioblastoma. Journal of Neuro-Oncology. 2019;142(1):183-191. doi:10.1007/S11060-018-03081-Z/TABLES/4

11. Vassal M, Charroud C, Deverdun J, et al. Recovery of functional connectivity of the sensorimotor network after surgery for diffuse low-grade gliomas involving the supplementary motor area. Journal of Neurosurgery. 2017;126(4):1181-1190. doi:10.3171/2016.4.JNS152484

12. Carbo EWS, Hillebrand A, van Dellen E, et al. Dynamic hub load predicts cognitive decline after resective neurosurgery. Scientific Reports 2017 7:1. 2017;7(1):1-10. doi:10.1038/srep42117

13. Raichle ME, Macleod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. National Academy of Sciences. Published online 1996. Accessed April 18, 2022. www.pnas.org

14. Yong RL, Lonser RR. Surgery for Glioblastoma Multiforme: Striking a Balance. World Neurosurgery. 2011;76(6):528-530. doi:10.1016/J.WNEU.2011.06.053

15. Baker CM, Burks JD, Briggs RG, et al. A Connectomic Atlas of the Human Cerebrum—Chapter 1: Introduction, Methods, and Significance. Operative Neurosurgery. 2018;15(Suppl 1):S1. doi:10.1093/ONS/OPY253

16. Glasser MF, Coalson TS, Robinson EC, et al. A multi-modal parcellation of human cerebral cortex. Nature 2016 536:7615. 2016;536(7615):171-178. doi:10.1038/nature18933

17. Nowinski WL. Towards an Architecture of a Multi-purpose, User-Extendable Reference Human Brain Atlas. Neuroinformatics. 2021;1:1-22. doi:10.1007/S12021-021-09555-2/FIGURES/2

18. Doyen S, Nicholas P, Poologaindran A, et al. Connectivity-based parcellation of normal and anatomically distorted human cerebral cortex. Hum Brain Mapp. Published online 2021. doi:10.1002/HBM.25728

19. Menon V. The Triple Network Model, Insight, and Large-Scale Brain Organization in Autism. Biological Psychiatry. 2018;84(4):236-238. doi:10.1016/J.BIOPSYCH.2018.06.012

20. Sandhu Z, Tanglay O, Young IM, et al. Parcellation-based anatomic modeling of the default mode network. Brain and Behavior. 2021;11(2):e01976. doi:10.1002/BRB3.1976

21. Cao W, Cao X, Hou C, et al. Effects of cognitive training on resting-state functional connectivity of default mode, salience, and central executive networks. Frontiers in Aging Neuroscience. 2016;8(APR):70. doi:10.3389/FNAGI.2016.00070/BIBTEX

22. Goulden N, Khusnulina A, Davis NJ, et al. The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM. Neuroimage. 2014;99:180-190. doi:10.1016/J.NEUROIMAGE.2014.05.052

23. Chen H, Li Y, Liu Q, et al. Abnormal interactions of the salience network, central executive network, and default-mode network in patients with different cognitive impairment loads caused by leukoaraiosis. Frontiers in Neural Circuits. 2019;13:42. doi:10.3389/FNCIR.2019.00042/BIBTEX

24. Mohan A, Roberto AJ, Mohan A, et al. Focus: The Aging Brain: The Significance of the Default Mode Network (DMN) in Neurological and Neuropsychiatric Disorders: A Review. The Yale Journal of Biology and Medicine. 2016;89(1):49. Accessed April 3, 2022. /pmc/articles/PMC4797836/

25. Pannekoek JN, van der Werff SJ, Meens PH, et al. Aberrant resting-state functional connectivity in limbic and salience networks in treatment--naïve clinically depressed adolescents. J Child Psychol Psychiatry. 2014;55(12):1317-1327. doi:10.1111/jcpp.12266

26. Beevers CG. Cognitive vulnerability to depression: A dual process model. Clinical Psychology Review. 2005;25(7):975-1002. doi:10.1016/J.CPR.2005.03.003

27. Ren H, Zhu J, Su X, et al. Application of Structural and Functional Connectome Mismatch for Classification and Individualized Therapy in Alzheimer Disease. Frontiers in Public Health. 2020;8:720. doi:10.3389/FPUBH.2020.584430/BIBTEX

28. Zhou L, Pu W, Wang J, et al. Inefficient DMN Suppression in Schizophrenia Patients with Impaired Cognitive Function but not Patients with Preserved Cognitive Function. Scientific Reports 2016 6:1. 2016;6(1):1-10. doi:10.1038/srep21657

29. maximal_safe_resection [Operative Neurosurgery]. Accessed April 3, 2022. https://operativeneurosurgery.com/doku.php?id=maximal_safe_resection

30. Patel CK, Vemaraju R, Glasby J, et al. Trends in peri-operative performance status following resection of high grade glioma and brain metastases: The impact on survival. Clinical Neurology and Neurosurgery. 2018;164:67-71. doi:10.1016/j.clineuro.2017.11.016

31. Dubey A, Kataria R, Sinha VD. Role of Diffusion Tensor Imaging in Brain Tumor Surgery. Asian J Neurosurg. 2018;13(2):302-306. doi:10.4103/ajns.AJNS_226_16

32. Sparacia G, Parla G, Lo Re V, et al. Resting-State Functional Connectome in Patients with Brain Tumors Before and After Surgical Resection. World Neurosurg. 2020;141:e182-e194. doi:10.1016/j.wneu.2020.05.054

33. Morales H. Current and Future Challenges of Functional MRI and Diffusion Tractography in the Surgical Setting: From Eloquent Brain Mapping to Neural Plasticity. Semin Ultrasound CT MR. 2021;42(5):474-489. doi:10.1053/j.sult.2021.07.005

34. Missios S, Bekelis K. Drivers of hospitalization cost after craniotomy for tumor resection: creation and validation of a predictive model. BMC Health Serv Res. 2015;15:85. Published 2015 Mar 4. doi:10.1186/s12913-015-0742-2

35. Panigrahi M, Chandrasekhar YB, Vooturi S, Ram GA, Rammohan VS. Surgical Resection of Insular Gliomas and Roles of Functional Magnetic Resonance Imaging and Diffusion Tensor Imaging Tractography-Single Surgeon Experience. World Neurosurg. 2017;98:587-593. doi:10.1016/j.wneu.2016.11.001

36. Ung N, Pelargos PE, Mozaffari K, et al. Accuracy and outcomes of diffusion tensor imaging tractography in resection for vestibular schwannoma for facial nerve preservation. J Neurol Sci. 2021;430:120006. doi:10.1016/j.jns.2021.120006

37. Spena G, Nava A, Cassini F, et al. Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes. Acta Neurochir (Wien). 2010;152(11):1835-1846. doi:10.1007/s00701-010-0764-9

38. Ammar A, Bernstein M. Neurosurgical Ethics in Practice: Value-based Medicine 123.

39. Martin HC, Sethi J, Lang D, Neil-Dwyer G, Lutman ME, Yardley L. Patient-assessed outcomes after excision of acoustic neuroma: postoperative symptoms and quality of life. J Neurosurg. 2001;94(2):211-216. doi:10.3171/jns.2001.94.2.0211

40. Lopez Ramos C, Brandel MG, Rennert RC, et al. Clinical Risk Factors and Postoperative Complications Associated with Unplanned Hospital Readmissions After Cranial Neurosurgery. World Neurosurg. 2018;119:e294-e300. doi:10.1016/j.wneu.2018.07.136

41. Daabiss M. American Society of Anaesthesiologists physical status classification. Indian J Anaesth. 2011;55(2):111-115. doi:10.4103/0019-5049.79879

42. Campanella F, Fabbro F, Ius T, Shallice T, Skrap M. Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. Neuro Oncol. 2015;17(8):1121-1131. doi:10.1093/neuonc/nov065

43. Campanella F, Shallice T, Ius T, Fabbro F, Skrap M. Impact of brain tumour location on emotion and personality: a voxel-based lesion-symptom mapping study on mentalization processes. Brain. 2014;137(Pt 9):2532-2545. doi:10.1093/brain/awu183

44. Briggs RG, Allan PG, Poologaindran A, et al. The Frontal Aslant Tract and Supplementary Motor Area Syndrome: Moving towards a Connectomic Initiation Axis. Cancers 2021, Vol 13, Page 1116. 2021;13(5):1116. doi:10.3390/CANCERS13051116

45. Baker CM, Burks JD, Briggs RG, et al. The crossed frontal aslant tract: A possible pathway involved in the recovery of supplementary motor area syndrome. Brain and Behavior. 2018;8(3):e00926. doi:10.1002/BRB3.926

46. Kushner DS, Amidei C. Rehabilitation of motor dysfunction in primary brain tumor patients. Neuro-Oncology Practice. 2015;2(4):185-191. doi:10.1093/NOP/NPV019

47. Fridriksson J, Guo D, Fillmore P, Holland A, Rorden C. Damage to the anterior arcuate fasciculus predicts non-fluent speech production in aphasia. Brain. 2013;136(11):3451. doi:10.1093/BRAIN/AWT267

48. Philippi CL, Tranel D, Duff M, Rudrauf D. Damage to the default mode network disrupts autobiographical memory retrieval. Soc Cogn Affect Neurosci. 2015;10(3):318-326. doi:10.1093/SCAN/NSU070

49. Chand GB, Wu J, Hajjar I, Qiu D. Interactions of the Salience Network and Its Subsystems with the Default-Mode and the Central-Executive Networks in Normal Aging and Mild Cognitive Impairment. Brain Connectivity. 2017;7(7):401-412.

50. Isaacson RL, Kimble DP. Lesions of the limbic system: Their effects upon hypotheses and frustration. Behavioral Biology. 1972;7(6):767-793. doi:10.1016/S0091-6773(72)80170-6

51. Reich DS, Smith SA, Gordon-Lipkin EM, et al. Damage to the Optic Radiation in Multiple Sclerosis Is Associated With Retinal Injury and Visual Disability. Archives of Neurology. 2009;66(8):998-1006. doi:10.1001/ARCHNEUROL.2009.107

52. Acoustic neuroma - Symptoms and causes - Mayo Clinic. Accessed May 17, 2022. https://www.mayoclinic.org/diseases-conditions/acoustic-neuroma/symptoms-causes/syc-20356127

53. Kümmerer D, Hartwigsen G, Kellmeyer P, et al. Damage to ventral and dorsal language pathways in acute aphasia. Brain. 2013;136(2):619-629. doi:10.1093/BRAIN/AWS354

54. Müller NG, Knight RT. The functional neuroanatomy of working memory: Contributions of human brain lesion studies. Neuroscience. 2006;139(1):51-58. doi:10.1016/J.NEUROSCIENCE.2005.09.018

55. Corbetta M, Shulman GL. Spatial Neglect and Attention Networks. http://dx.doi.org/101146/annurev-neuro-061010-113731. 2011;34:569-599. doi:10.1146/ANNUREV-NEURO-061010-11373

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