Check for updates

Practical Application of Networks in Neurosurgery: Combined 3-Dimensional Printing, Neuronavigation, and Preoperative Surgical Planning

Rafael Romero-Garcia[1,3], Yaara Erez[4], Geoffrey Oliver[2], Mallory Owen[1], Sakinah Merali[3], Anujan Poologaindran[3], Robert C. Morris[1], Stephen J. Price[1], Thomas Santarius[1], John Suckling[3], Michael G. Hart[1]

■ BACKGROUND: **A plethora of cutting-edge neuroimaging analyses have been developed and published, yet they have not hitherto been realized as improvements in neurosurgical outcomes. In this paper we propose a novel interface between neuroimaging and neurosurgery for aiding translational research. Our objective is to create a method for applying advanced neuroimaging and network analysis findings to neurosurgery and illustrate its application through the presentation of 2 detailed case vignettes.**

■ METHODS: **This interface comprises a combination of network visualization, 3-dimensional printing, and ex-vivo neuronavigation to enable preoperative planning according to functional neuroanatomy. Clinical cases were selected from a prospective cohort study.**

■ RESULTS: **The first case vignette describes a low-grade glioma with potential language and executive function network involvement that underwent a successful complete resection of the lesion with preservation of network features. The second case describes a low-grade glioma in an apparently noneloquent location that underwent a subtotal resection but demonstrated unexpected and significant impairment in executive function postoperatively that subsequently abated during follow-up. In both examples the neuroimaging and network data highlight the complexity of the surrounding functional neuroanatomy at the individual level, beyond that which can be perceived on standard structural sequences.**

■ CONCLUSIONS: **The described interface has widespread applications for translational research including preoperative planning, neurosurgical training, and detailed patient counseling. A protocol for assessing its effectiveness and safety is proposed. Finally, recommendations for effective translation of findings from neuroimaging to neurosurgery are discussed, with the aim of making clinically meaningful improvements to neurosurgical practice.**

INTRODUCTION

The advent of magnetic resonance imaging (MRI) in the 1980s has created a wealth of neuroimaging data that describes cognition in health and disease. Growth in neuroimaging data has been prolific, encompassing a vast array of techniques such as mapping gray and white matter tissue characteristics, myelin maps, cortical and subcortical morphology, and connectomics.[1] Pleasingly, the field has been a leader in making multiple big data analyses freely available.[2] With such a prolific, long-standing, and important field, one would expect the applications to neurosurgery to be numerous and profound. However, this is not the case.

Reasons for this lack of translation from neuroimaging to neurosurgery are readily apparent. Publishing data on a significant effect at the group level does not necessarily mean an analogous effect can be found or applied at the individual level.[3] Neurosurgical interventions are by necessity physical, yet

Key words
- Connectome
- Functional connectivity
- Imaging
- Networks
- Tractography

Abbreviations and Acronyms
3D: 3-Dimensional
ANT: Advanced normalization tool
MPRAGE: Magnetization prepared rapid-acquisition gradient echo
MRI: Magnetic resonance imaging
rs-fMRI: Resting-state functional MRI
TE: Time to echo
TR: Time to repetition

From the [1]Division of Neurosurgery, Department of Clinical Neurosciences, and [2]Media Studio, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus; [3]Brain Mapping Unit, Department of Psychiatry, Herchel Smith Building for Brain and Mind Sciences, Robinson Way; and [4]MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, England, United Kingdom

To whom correspondence should be addressed: Michael G. Hart, Ph.D. [E-mail: mgh40@cam.ac.uk]

Citation: World Neurosurg. (2020) 137:e126-e137. https://doi.org/10.1016/j.wneu.2020.01.085

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/$ - see front matter © 2020 Elsevier Inc. All rights reserved.

neuroimaging findings are essentially visual and statistical, which necessitates an interface between the published data and operative application. A meaningful change to neurosurgical interventions must also be defined a priori (i.e., what does one wish to change during surgery, how does neuroimaging satisfy this requirement, and will this make a difference to an individual?). Finally, there need to be suitable tools that provide neuroimaging data in a way that is accessible, relevant, and easily interpretable in order to gain confidence in its ability to support clinical decisions.

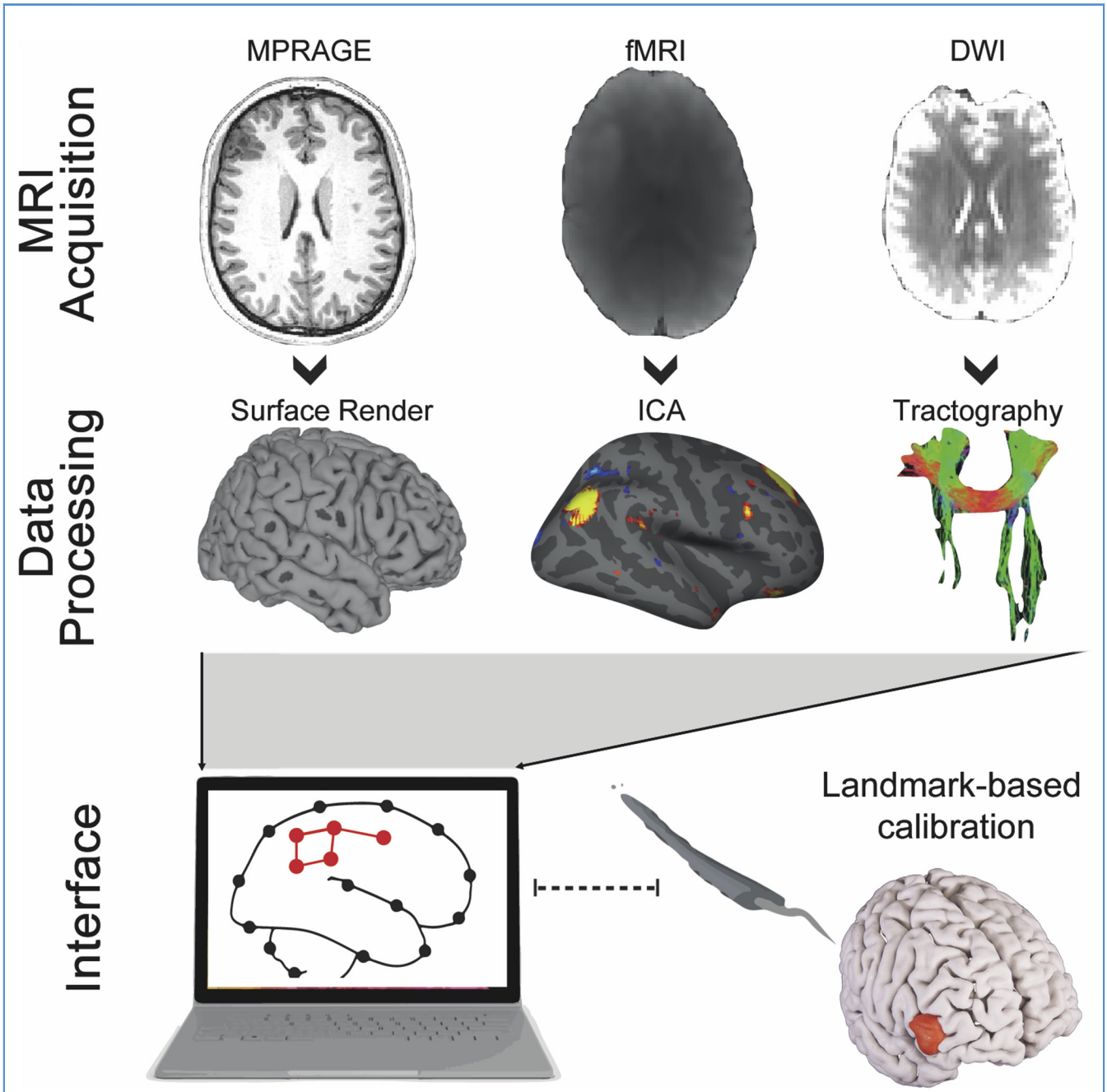

Figure 1. Analysis pipeline. To perform network navigation with the interface described herein, it is first necessary to acquire magnetic resonance imaging data, either using the sequences described in the paper or others. Subsequently these data are processed, and network analysis is performed to be used for later visualization. The processed structural data are used to create the 3-dimensional printed model that forms the core physical interaction point of the interface. Subsequently, the interface between the tracker system (e.g., the Polhemus Patriot system (Polhemus, Colchester, Vermont, USA) and a personal computer is initiated. Registration of the 3-dimensional brain to the network data to be visualized is then performed. Finally, the series of coordinates from navigation is used to display the network data. DWI, diffusion weighted imaging; fMRI, functional MRI; ICA, independent component analysis; MPRAGE, magnetization-prepared rapid gradient-echo.

We introduce a novel interface that enables the use of neuroimaging data for neurosurgical applications at the individual patient level. This interface comprises an advanced and customizable visualization platform of individual neuroimaging data, in our case networks and connectomics; a 3-dimensional (3D) printout of an individual patient's brain and tumor; and a trackable "wand" used to navigate and display the pertinent network features on the viewer for any specific point on the 3D brain. The interaction with the physical model is designed to provide a realistic approximation of operating and allow the tracker to act as a virtual scalpel for modeling the predicted in silico effects of surgery, and it will be familiar to anyone having used a neuronavigation system. The main differences are application ex vivo in a simulation setting; navigation on a high-resolution cortical reconstruction at high accuracy; and visualization of novel network and connectomic imaging data using our custom viewing platform.

Given the quantity, complexity, and need for scientific validation of neuroimaging data, the natural timing to use such an interface is preoperatively in an exploratory manner. This will allow one to see the pertinent network and connectomic features that could be relevant to the chosen surgical approach. Furthermore, it can be used to plan out areas to investigate for either clinical or research testing a priori. To illustrate this application, 2 case vignettes are presented to test and challenge contemporary surgical approaches in functional brain mapping and neurooncology. Finally, a means to evaluate the potential of this method in a subsequent clinical trial are described. We believe that such an interface will be key in bridging the aforementioned gap between scientific data and clinical applications.

Video available at www.sciencedirect.com

METHODS

A summary of the interface and analysis pipeline is presented in **Figure 1**.

Study Design

This study is a single-center prospective cohort design and was approved by the Local Regional Ethics Committee (protocol 16/EE/0151). All participants provided written informed consent. Inclusion criteria were an MRI appearance of a nonenhancing diffuse tumor consistent with a low-grade glioma and planned to undergo awake brain surgery. Two patients were selected to form a prospective cohort that presented different clinical conundrums in order to identify potential variability in the chosen surgical approach that could be aided by the proposed pipeline. The proposed trial is registered at the Open Science Framework managed by the Centre for Open Science (https://osf.io/p5eg6).

Imaging Data Acquisition

Our MRI data acquisition and processing are discussed in supplementary information 1. Note that the visualization interface has the flexibility to include a variety of neuroimaging analyses. The analyses presented herein are provided as examples to illustrate the potential for incorporating network and connectomic approaches.

Construction of 3-Dimensional Models

Cortical and tumor surface meshes are required to be in a suitable file formatted for 3D printing (**Figure 2**). Standard pipelines for 3D printing using MRI data are available,[4-6] but these require modification when a tumor is present. All codes for developing 3D brain and connectome models in patients with brain tumors have been made available online (http://github.com/jazzmanmike/braintumor_3D). Detailed instructions are presented in supplementary information 1.

Polhemus Interface and Neuronavigation

MATLAB 2016a (The MathWorks, Natick, Massachusetts, USA) was used to create a graphical user interface to control and interconnect the neuroimaging data with the Polhemus Patriot (Polhemus, Colchester, Vermont, USA) tracking system and the 3D printed brain. The printed brain was registered to the magnetization prepared rapid-acquisition gradient echo (MPRAGE) data. Static accuracy of the Polhemus tracking system is 2 mm root mean square of the XYZ position. Note that this is a direct registration between the 3D and neuroimaging cortical surfaces, thereby minimizing registration error. Correspondence between the space on the 3D brain and the structural MRI coordinate is thus created to view the relevant registered neuroimaging data using our custom viewer (**Figure 3**).

Network Visualization

Once data have been processed and the 3D brain has been registered to the navigation software, one can begin to view and interact with the chosen neuroimaging data (**Figure 4**; Supplemental Digital Content **Videos 1** and **2**, which illustrates interaction and outputs of the network visualization interface). In theory, any neuroimaging data could be displayed and not just restricted to that acquired by MRI including, for example, magnetoencephalography and transcranial magnetic stimulation. For the purposes of the current study, exemplar network visualizations include:

- Tractography visualized with MRTrix.[7]
- Resting state networks were binarized, converted to surface meshes, and labeled using cross-correlation of their surface topology with that of a series of canonical networks.[8]
- Connectomics and focused attack is performed by highlighting the top-weighted connections of a selected node as a means of capturing the functional associations that would be lost on removal of that region.

Costs vary depending on local economic factors. Once the interface has been established (depending on individual user preference), the per-patient costs will be limited to <1 hour of time in the MRI scanner and the price of 3D printing, which in turn will depend on the weight (and size) of the model required.

RESULTS

Two participants were chosen for their nontrivial brain mapping requirements and potential variability in surgical approaches. Note

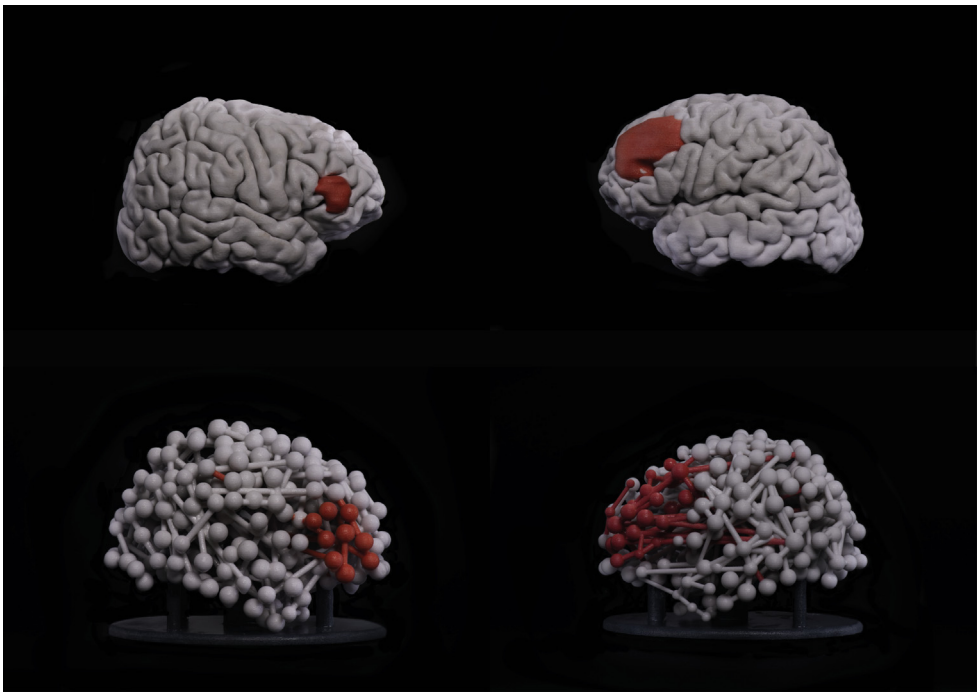

Figure 2. 3-Dimensional (3D) printing. Examples of 3D-printed brain models that can be used for network navigation. Each column refers to a specific participant. In this paper participant 1 is on the left and participant 2 is on the right. The top row represents a 3D-printed gray matter/pial surface rendering with the tumor volume colored in red. The lower row represents an example connectome with nodes overlapping the tumor in red.

that both patients were operated on and managed according to their clinical data: The network interface was used for research purposes and not for clinical care.

Participant 1

A 22-year-old, left-handed female presented with recurrent nocturnal seizures subsequently controlled with levetiracetam. An MRI scan demonstrated a focal cortical nonenhancing tumor of the right middle and inferior frontal gyrus reported to likely represent a low-grade glioma (Figure 5). Preoperative neuropsychologic assessment revealed only a mild reduction in scores on a single task of attention and scoring in the mild range for anxiety.

Awake brain surgery was performed with neuronavigation (StealthStation S7 System, Medtronic, Inc., Louisville, Colorado, USA) and mapping goals of language, but no sensitive areas were identified intraoperatively. Structural imaging revealed no evidence of residual disease on T2, fluid-attenuated inversion recovery, or T1 pregadolinium and postgadolinium sequences at 3 months postoperatively. Histology revealed a World Health Organization grade I ganglioglioma. Follow-up management consisted of regular imaging and clinical assessment without further treatment. Postoperatively there was initially a period of fatigue that resolved within 7 days. Formal neuropsychologic assessment 2 weeks after surgery noted improved scores in mood and no new deficits. The patient was notably quick in responses and demonstrated sustained attention with no evidence of fatigue.

Network data revealed an executive function network and putative language networks in close proximity to the tumor,

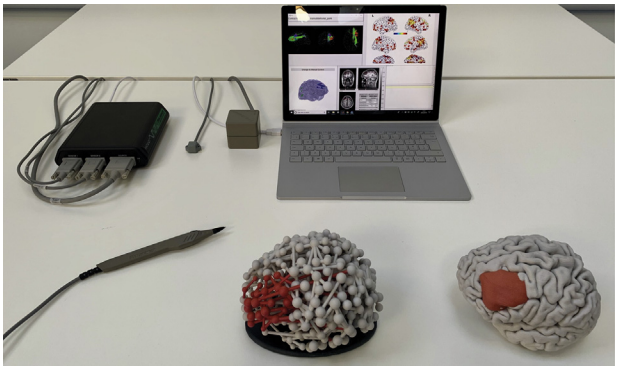

Figure 3. Network interface; practical visualization of the network simulation setup. The 3-dimensional brains from each participant are seen with tracker wand adjacent, electromagnetic field generator in black, connected to a personal computer with network visualization software running.

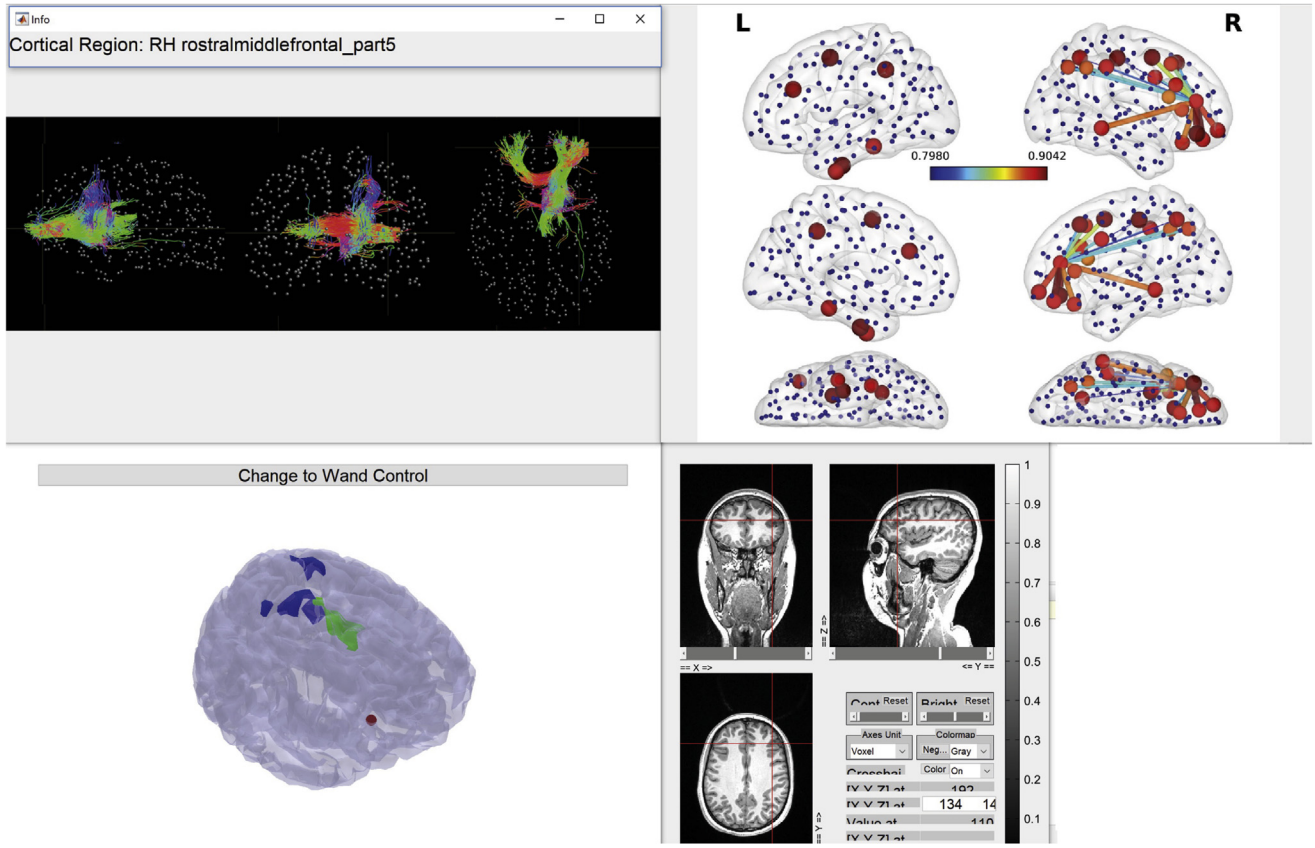

Figure 4. Network simulation visualization; screenshot of the network simulation software. This offers multimodal network representations to be viewed and coupled to either a tracker wand, neuronavigation interface, or using the touchscreen. In this example 4 views are offered: standard structural magnetic resonance imaging (sagittal, axial, and coronal axes); tractography; resting state networks on a cortical mesh; and focal lesioning of connectomic data.

particularly posteriorly. Both of these remained present at 3 months. Tractography revealed the majority of tracts to be deep to the lesion. Connectomics suggested network hubs adjacent to the tumor with modest intrahemispheric and interhemispheric connectivity. Overall, the preoperative network data suggested that this was a highly eloquent area for both language and executive function, possibly reflected by the subtle impairment in attention on neuropsychology testing. Complete resection of the lesion was performed without encroachment on these surrounding cortical networks or tracts, hence preserving connectome features and functional boundaries.

Preoperative planning for this lesion requires consideration of an approach to identify language function. Task-based functional MRI or resting-state networks could be used to localize presumed language areas, but these techniques do not exclude codominance or necessarily predict postoperative function. Our approach was to perform awake surgery with brain stimulation to maximize the potential of preserving language function. Furthermore, we could identify periregional tracts (inferior frontooccipital fasciculus), higher cognitive function (e.g., executive function) networks, and association cortex hubs surrounding the lesion that we would want to study in detail intraoperatively to be sure of our functional boundaries. For research purposes one could identify putative language networks for further testing during surgery with advanced neuropsychology paradigms or on assessment of executive function and attention.

Participant 2

A 29-year-old, right-handed male presented with a single nocturnal seizure and was placed on levetiracetam. An MRI scan demonstrated an infiltrating nonenhancing tumor of the left anterior superior frontal gyrus reported as a low-grade glioma (Figure 6). Preoperative neuropsychologic assessment revealed minor reduction in scores with tests of story recall, word cognition, and verbal memory but otherwise high cognitive function.

Awake brain surgery was performed with neuronavigation and mapping goals of language and motor control, but no sensitive areas were identified. Resection of the lesion was performed without complication with only a small possible residual of nonenhancing tumor at the deep margins. Histology revealed a World Health Organization grade II astrocytoma (isocitrate

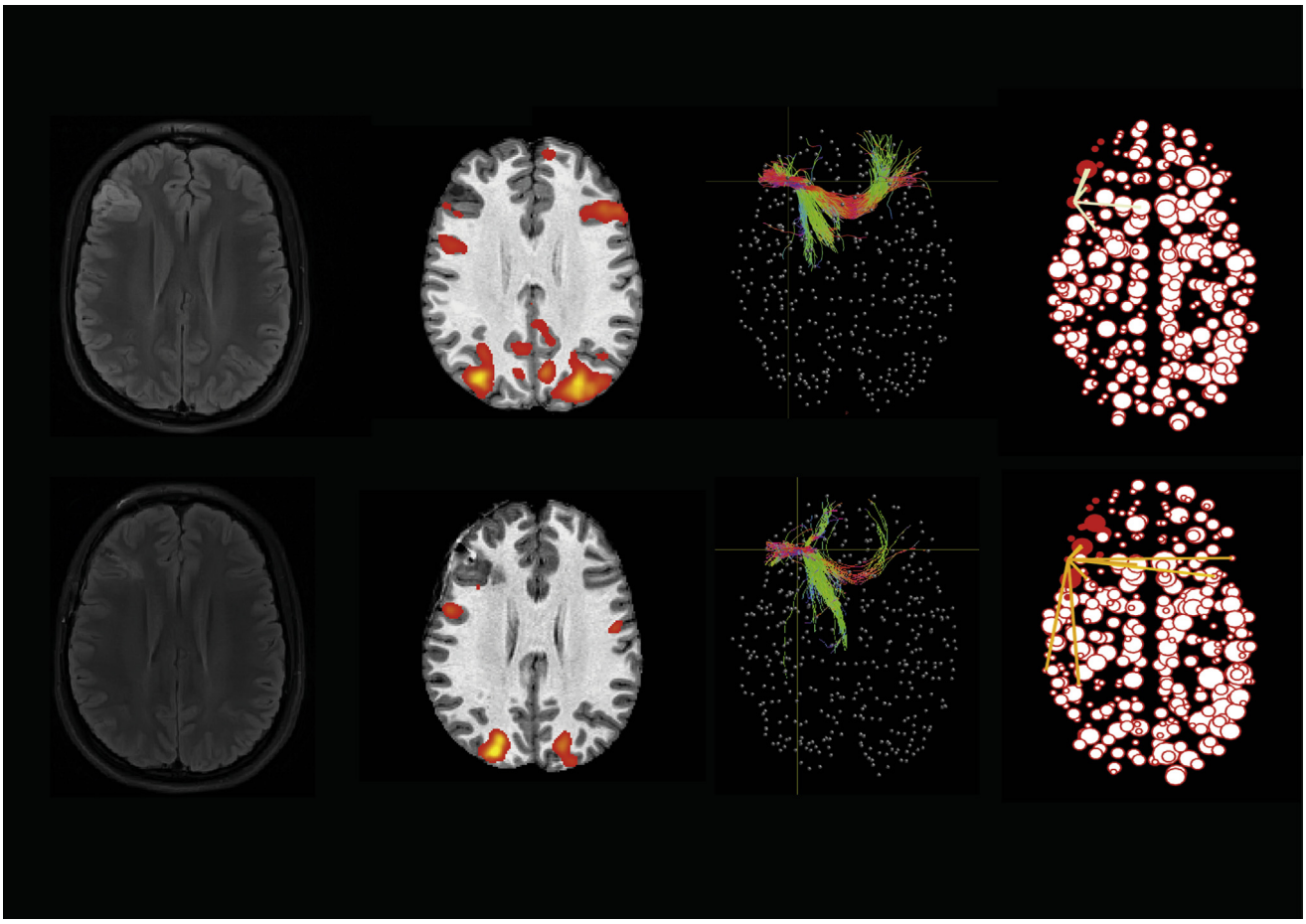

Figure 5. Participant 1 network data. Top row: preoperative data. Lower row: corresponding data from month 3 follow-up. Images are (from left to right, both rows): fluid-attenuated inversion recovery, resting state networks in Montreal Neurological Institute space with underlying magnetization prepared rapid-acquisition gradient echo underlay, tractography, and virtual lesioning ('focused attack') of connectomic data.

dehydrogenase-1 mutated, alpha thalassemia mental retardation [ATRX] mutated, 1p/19q co-deletion negative). Follow-up management consisted of regular imaging and clinical assessment without further treatment.

Postoperatively there was a period of initial fatigue that had resolved within 5 days. Neuropsychologic examination initially revealed a mixed picture at 2 weeks postoperatively. There were improvements in initiation and in a task of nonverbal memory without a timed component. However, there were also lower scores in design learning, design recall, immediate verbal recall, list recognition, inhibition timing, and inhibition scores. By 12 months his performance had returned to be consistent with his presurgical baseline.

Network data revealed multiple typically demarcated executive function and attention networks in the vicinity of the tumor. Tractography demonstrated significant intrahemispheric local and long-range connectivity immediately adjacent to the tumor. Postoperatively, resting state network topology and connectivity were markedly reduced. Connectomics revealed a similar picture with hub reorganization to the contralateral homologous region from the tumor and a reduction in connectivity of adjacent hubs, particularly involving intrahemispheric connections. Overall these disrupted connectome features are consistent with ongoing clinical recovery and in keeping with the neuropsychologic examination. Notably, major adjacent tracts such as the superior longitudinal fasciculus were preserved.

In terms of preoperative planning, surgical approaches to this lesion would largely be concerned with avoiding the supplementary motor area more posteriorly. In our case we were also interested in networks related to adjacent tracts such as the frontal-aslant and frontostriatal tracts, which highlights the importance of not just mapping the cortex but also the deep boundaries in the white matter. From a research perspective, numerous networks and hubs can be identified adjacent to the lesion that one might suppose to be involved in executive function, which could be used

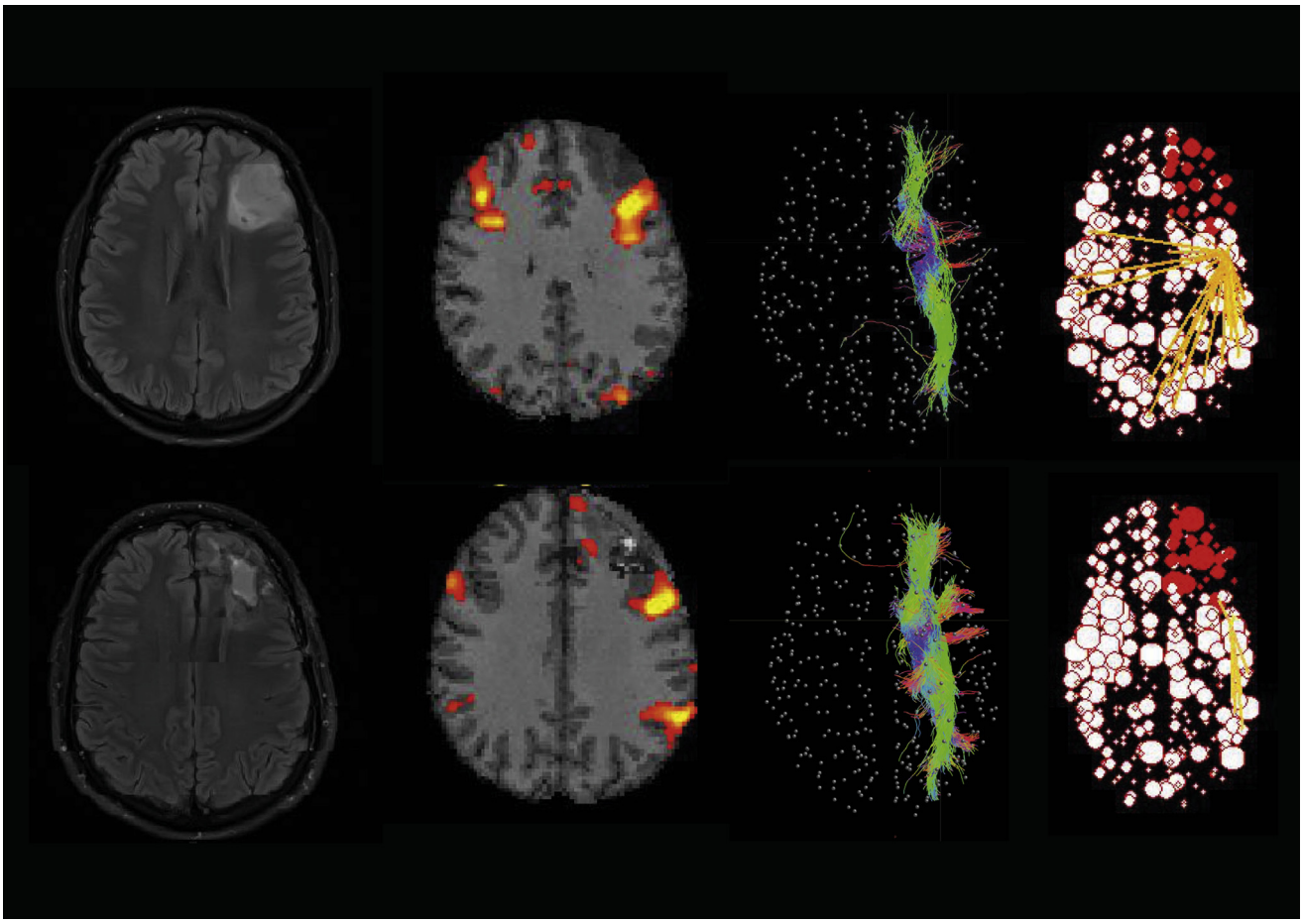

Figure 6. Participant 2 network data. Top row: preoperative data. Lower row: corresponding data from month 3 follow-up. Images are (from left to right, both rows): fluid-attenuated inversion recovery, resting state networks in Montreal Neurological Institute space with underlying magnetization prepared rapid-acquisition gradient echo underlay, tractography, and virtual lesioning ('focused attack') of connectomic data.

as a basis for more extensive intraoperative testing or rehabilitation perioperatively.

DISCUSSION

We presented a rapid, cost-effective, and generalizable interface for application of neuroimaging data with neurosurgery. Benefits of the approach include its customizability and generalizability to multiple forms of neuroimaging data. Furthermore, it could be expanded to the intraoperative situation, used preoperatively and postoperatively for educational purposes, as well as in clinic to counsel patients about the proposed surgery.

The case examples are presented to illustrate the application of neuroimaging data to neurosurgery and in particular where it could make a difference in clinical practice. The first participant had a right inferior frontal low-grade glioma that was complicated by the patient being left-handed and potential involvement of language and executive function networks. A surgical approach that focused on complete resection while also being mindful of preserving this surrounding highly eloquent brain corresponded with the excellent neuropsychologic outcome with improvement in many domains, as well as largely untouched brain network imaging results. The second participant had a left frontal low-grade glioma just anterior to the supplementary motor area, which involved several higher cognitive function networks well recognized to potentially have profound, albeit often temporary, postoperative deficits. In this instance, additional executive function networks were found adjacent to the tumor, with transient impairment in the corresponding networking imaging results that corresponded with the long-term neuropsychologic recovery. One could predict that a more aggressive strategy here would have potentially disastrous long-term consequences.

The value of the interface in both these circumstances is in further delineating the functional and structural anatomy before

performing the surgery. That is, the interface is not necessarily designed to change actions during surgery per se, but rather it is designed to change one's approach to surgery (e.g., awake or asleep) and consequently the resection that is performed (e.g., conservative, total, or supratotal resection of the lesion). This paper provides the necessary premise for understanding this approach, while we have developed plans to test its effectiveness in a subsequent cohort study.

Using neuroimaging at the individual level highlights several crucial methodologic issues that need to be resolved. Regarding resting state networks, there are issues regarding naming of individual networks, thresholding, and viewing multiple networks in a convenient manner (both the cases viewed a single network, but this ignored other potential networks in the vicinity). Tractography has its own set of issues that are well described in the literature including resolving complex tract trajectories, identifying long-range tracts, and determining the site of cortical termination.[9] Additional issues include determining the function of an individual tract and predicting the functional sequel to tract disruption in terms of plasticity (e.g., networks can restore structural function through degeneracy and redundancy without requiring new tracts to be generated). Issues with connectomics essentially relate to visualization and interpretation. Connectomes, particularly functional, often contain many more connections than can be easily viewed, and the effect on network measures of in vivo lesioning is not readily apparent. Finally, brain shift itself is an important problem if network data are to be used intraoperatively. This problem in itself should be tractable to solutions involving reregistration based on surface morphology intraoperatively or using suitably trained surface deformation models. However, it may be that neuroimaging data are best used preoperatively for planning purposes and that additional navigation intraoperatively is likely to obfuscate accurate surgery. Despite these limitations, the data provide a valuable additional tier of information to neurosurgeons, when interpreted appropriately.

Research on the technical aspects of 3D printing are also required to create more realistic, deformable models that mimic in vivo brain tactility and appearance. One approach has been to use the 3D-printed brain as a template in a molding-casting process using a silicone mixture. The resultant model achieved a high degree of satisfaction in a questionnaire survey across multiple domains.[10] Experience of 3D printing in neurosurgery is still in its infancy, with a review in 2015 identifying 16 eligible papers.[11] Applications have been varied, but in general studies tend to focus on stand-alone models, whereas for realistic simulation 3D printing will likely need to be combined with other modalities. The authors of this review also highlight the limited number of studies, difficulties in obtaining objective outcome measures of intervention effectiveness, and technical barriers to introducing 3D printing outside of research settings that will need to be overcome.

Prospectively and objectively assessing the effectiveness and safety of any new intervention is of paramount importance, especially with regards to new surgical technology. With this interface there are clearly multiple steps that require evaluation, such as the visualization of the data, the validity of the data, and how it affects the surgical approach. Clearly with such a complex intervention, clinical trials should be designed toward a process of repeated assessment and refinement, analogous to beta testing in software design, rather than a single definitive test. Therefore in the first instance we propose to assess how individual surgeons approach the resection of lesions in individual patients and how this can be affected by 3D printing and our interface. A preprint of our planned questionnaire, study design, and statistical analysis is available in supplementary information 4 and 5, as well as being registered online (https://osf.io/p5eg6).

CONCLUSIONS

Ultimately the challenge is to translate basic science research for real patient benefit. This requires appreciation of available approaches and their meaning, data to highlight their usefulness, and a means of translating studies from interesting papers to a practical application at the individual patient level. The interface described within is but 1 possible solution, and it is proposed partly to stimulate research and open the door to further studies rather than represent the single best solution. Strengths include the physical interaction, portability, cost-effectiveness, and flexibility. Potential roles are proposed in presurgical planning, intraoperative mapping, academic research, training, and patient counseling. Further characterization of its role in preoperative planning, optimal visualization of data, and characterization of what scenarios it is of most benefit in is required. It is hoped that presenting this interface will generate discussion and engagement with the neurosurgical community, which will be essential in translating neuroimaging data to any discernable benefit to patient care.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Rafael Romero-Garcia: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Visualization. **Yaara Erez:** Conceptualization, Investigation, Resources, Data curation, Writing - original draft, Visualization, Project administration, Funding acquisition. **Geoffrey Oliver:** Methodology, Software, Writing - review & editing, Visualization. **Mallory Owen:** Software, Formal analysis, Writing - review & editing. **Sakinah Merali:** Software, Formal analysis, Writing - review & editing. **Anujan Poologaindran:** Software, Formal analysis, Writing - review & editing. **Robert C. Morris:** Investigation, Resources, Writing - review & editing. **Stephen J. Price:** Investigation, Resources, Writing - review & editing. **Thomas Santarius:** Conceptualization, Investigation, Resources, Writing - original draft, Supervision, Funding acquisition. **John Suckling:** Resources, Writing - review & editing. **Michael G. Hart:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition.

ACKNOWLEDGMENT

The authors would like to acknowledge the work of Grace Winn in producing photos of the 3D models.

REFERENCES

1. Kim H, Yoon D, Kim E, Lee K, Bae J, Lee JH. The 100 most-cited articles in neuroimaging: a bibliometric analysis. *NeuroImage*. 2016;139:149-156.

2. Smith S, Nichols TE. Statistical challenges in "big data" human neuroimaging. *Neuron*. 2018;97:263-268.

3. Price CJ, Hope TM, Seghier ML. Ten problems and solutions when predicting individual outcome from lesion site after stroke. *NeuroImage*. 2017;145:200-208.

4. Madan C. Improved understanding of brain morphology through 3D printing: a brief guide. *Res Ideas Outcomes*. 2016;2:e10266.

5. Madan CR. Creating 3D visualizations of MRI data: a brief guide. *F1000Research*. 2015;4:466.

6. Notter M. 3dprintyourbrain: miykael/3dprintyourbrain. Available at: https://github.com/miykael/3dprintyourbrain. Accessed February 12, 2020.

7. Tournier DJ, Calamante F, Connelly A. MRtrix: diffusion tractography in crossing fiber regions. *Int J Imag Sys Tech*. 2012;22:53-66.

8. Smith S, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci USA*. 2009;106:13040-13045.

9. Sotiropoulos SN, Zalesky A. Building connectomes using diffusion MRI: why, how and but. *NMR Biomed*. 2019;32:e3752.

10. Ploch CC, Mansi CS, Jayamohan J, Kuhl E. Using 3D printing to create personalized brain models for neurosurgical training and preoperative planning. *World Neurosurg*. 2016;90:668-674.

11. Vakharia VN, Vakharia NN, Hill CS. Review of 3-dimensional printing on cranial neurosurgery simulation training. *World Neurosurg*. 2016;88:188-198.

Conflict of interest statement: RRG is funded by a Guarantors of Brain Post-Doctoral Fellowship award. YE is funded by a Royal Society Dorothy Hodgkin Research Fellowship. AP is funded by an Alan Turing Institute Doctoral Scholarship. SJP received funding through a National Institute for Health Research (NIHR) (UK)—Clinician Scientist Award (ref: NIHR/CS/009/011). MGH received an award from The Brain Tumour Charity (ref: RG86218) to fund this work.

Received 16 November 2019; accepted 11 January 2020

Citation: World Neurosurg. (2020) 137:e126-e137. https://doi.org/10.1016/j.wneu.2020.01.085

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

1878-8750/$ - see front matter © 2020 Elsevier Inc. All rights reserved.

SUPPLEMENTARY INFORMATION 1: METHODS

Neuroimaging Data Acquisition

Magnetic resonance imaging (MRI) data were acquired using a Siemens Magnetom Prisma-fit 3 Tesla MRI scanner and 16-channel receive-only head coil (Siemens AG, Erlangen, Germany). Total acquisition time was MPRAGE—9 minutes and 14 seconds, resting-state functional MRI—9 minutes and 10 seconds; neurite orientation dispersion and density imaging—15 minutes and 19 seconds.

Structural. Anatomic images were acquired using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (FOV 256 mm × 240 mm × 176 mm; voxel size 1 mm isotropic; time to repetition [TR] 2300 ms; time to echo [TE] 2.98 ms; flip angle 9 degrees).

Resting-State Functional Magnetic Resonance Imaging. Functional images were acquired using single-echo echo planar imaging (EPI) sequence (FOV 192 mm × 192 mm × 112 mm; voxel size 2-mm isotropic; TR 1060 ms; TE 30 ms; flip angle 74 degrees) generating 512 three-dimensional volumes of the supratentorial compartment.

Neurite Orientation Dispersion and Density Imaging. Diffusion-weighted images were acquired using Neurite Orientation Dispersion and Density Imaging with 2 different B values (800 & 2000) and both 32 and 64 directions (FOV 240 mm × 240 mm × 150 mm; voxel size 2.5 mm isotropic; TR 8200 ms; TE 95 ms) and GRAPPA acceleration.

Neuroimaging Data Processing

Structural. Advanced Normalization Tools (ANTs) cortical thickness pipelines were used for structural analysis (htpo://stnava.github.io). Data were intensity normalized, brain extracted, and nonlinearly mapped to the template of the Montreal Neurological Institute (MNI152) at 2-mm resolution using symmetric diffeomorphic registration. A hand-drawn mask of the tumor was used to exclude this region from the cost function during registration.

Resting-State Functional Magnetic Resonance Imaging. Resting-state networks were based on independent component analysis performed with MELODIC[1,2] with de-noising using FMRIB's independent component analysis-based Xnoiseifier with training specific to this dataset.[3,4] Data were preprocessed with rigid body motion correction, coarse brain extraction, normalized by a single scaling factor, smoothing to 5-mm fixed-width, half-maximum, and high-pass temporal filtering. Linear registration (6 degrees of freedom) was performed to the corresponding MPRAGE using ANTs.

Connectomes were constructed in functional space using an anatomically principled template subsequently random subdivided into 318 symmetric, equally sized (500 mm^2) cortical and 16 subcortical regions.[5] Links were determined by the Pearson correlations of processed rs-fMRI time series.

Neurite Orientation Dispersion and Density Imaging. Whole brain tractography was performed with BedPostX and ProbTrackX (FSL version 5.0, www.fsl.fmrib.ox.ac.uk). Complementarily, direction-encoded colored tractograms were generated for visualization purposes using constrained spherical deconvolution and probabilistic streamlines algorithm implemented in MRTrix.[6] Connectomes were constructed in diffusion space using the same template as for rs-fMRI with weighted links determined by the number of streamlines between parcels.

Construction of 3D Models. Cortical surface reconstructions, a necessary first step in generating a cortical mesh, are based on identifying the gray-white matter interface: the presence of a lesion can obscure this boundary and cause standard algorithms to fail. To obviate this issue the tumor region was removed and replaced with homologous cortex to reconstitute the gray-white matter interface in a process known as *enantiomorphic filling*.[7,8]

Tumor segmentation masks were initially drawn manually using FMRIB Software Library version 5.0 (www.fsl.fmrib.ox.ac.uk), following which the subsequent mask was refined using semi-automated pipelines (Unified Segmentation with Lesion toolbox, https://github.com/CyclotronResearchCentre/USwithLesion, unpublished observations). Brain extraction of the MPRAGE volume is performed using a template-based method with ANTs.[9] The extracted brain then underwent enantiomorphic filling of the tumor region following a cortical reconstruction using FreeSurfer (version 6.0 for Linux, www.surfer.nmr.mgh.harvard.edu).[10] Cortical surface ribbons were converted to a surface mesh, and stereolithography files then viewed on MeshLab 2016 (IST-CNR, www.github.com/cnr-isti-vclab/meshlab),[11] where they underwent final preprocessing with scale-dependent Laplacian smoothing. Tumor masks were tessellated to create a surface mesh and then processed in the same manner as cortical surface ribbons.

Resulting stereolithography files were scaled and printed at Addenbrooke's Media Studio (Addenbrooke's Hospital, Cambridge, UK) for 3-dimensional (3D) printing (process: 3D ColorJet Printing Technology, machine specification: Projet 660 Pro [3D Systems, Rock Hill, South Carolina, USA]), materials specification: VisiJet PXL (plaster powder, 3D Systems) and ColorBond (cyanoacrylate) infiltrant (3D Systems), machine parameters and settings: full resolution full color print mode.

NETWORK SIMULATION SOFTWARE BETA-TEST: METHODS AND ANALYSIS PREPRINT

Hypotheses

What is the variability in surgical approaches to the resection of low-grade gliomas?

What potential is there to alter a planned surgical approach based on additional information?

How does information from 3D models and network data affect neurosurgical planning?

Study Design

Neurosurgeons are asked to plan their surgical approach on 5 distinct clinical scenarios involving low-grade gliomas. For each scenario they will be asked the same questions in 3 stages:

Stage 1: Plan resection based on standard clinical MRI scans: "normal" approach

Stage 2: Plan resection based on standard clinical MRI scans plus 3D model

Stage 3: Plan resection based on standard clinical MRI scans plus 3D model plus network simulation software (including Polhemus wand interface)

Questions

At each stage the same questions will be asked:

Stage 1: "Normal" MRI

1. What is the predicted extent of resection?
2. What would be your surgical approach (i.e., awake/asleep, advanced imaging [task fMRI, tractography, other], ECoG)

Additionally

- What functional questions do you wish to know?

Stage 2: 3D Model

1. What is the predicted extent of resection?
2. What would be your surgical approach (i.e., awake/asleep, advanced imaging [task fMRI, tractography, other], ECoG)

Additionally

- What would be your margins?
- What functional questions do you wish to know?
- Would you resect more or less than the tumor?

Additionally for 3D

- Does the 3D model help with planning?
- Would you use it intraoperatively?

Stage 3: 3D Model Plus Network Visualization Interface

1 What is the predicted extent of resection?

2. What would be your surgical approach (i.e., awake/asleep, advanced imaging [task fMRI, tractography, other], ECoG)

Additionally

- What would be your margins?
- What functional questions do you wish to know?
- Would you resect more or less than the tumor?

For 3D & network visualization:

- Would you use it intraoperatively?
- What data were useful?
- What data weren't?
- Was the display helpful?

Scenarios

A repertoire of 5 example scenarios have been prepared (see **Table S1**, Supplemental Content, which illustrates the scenario, expected questions that will be generated, and predicted effects on surgical approach and extent of resection). Note that the first 2 cases have been described in detail in the main manuscript.

Statistical Analysis

Paired contingency test analysis (McNemar's test)
Correction (Bonferroni) for multiple comparisons
Predicted effect size

- 50% of surgeons change their operative approach based on additional information (3D *or* 3D + network visualization)
- Change in approach defined as different aim (subtotal vs. total vs. supratotal resection) or different method (awake vs. asleep or additional monitoring/imaging intraoperative/perioperative)

Power calculation:

- Single paired study group
- Binomial outcome (change in approach)
- Varies with initial
- Alpha = 0.05
- Power = 80%
- Sample size = 28
- Subgroups: analysis of different aims and methods separately (including subgroups of each, e.g., change from awake to asleep only)

Table S1. Brain Tumor Example Scenarios

Scenario	Tumor Location	Question for 3D/ Network Data	Predicted Effect on Surgical Approach	Predicted Effect on Extent of Resection
1. Unresectable tumor	Insula glioma	Will this become more resectable?	Nil (awake)	More extensive but subtotal
2. Eloquent: motor	Precentral gyrus	Will there be a move to a more extensive resection?	Nil (awake)	More extensive but subtotal
3. Eloquent: language	Right inferior frontal (left-handed patient)	Will there be more concern over functional boundaries?	Move to awake mapping from asleep	More extensive/ supramarginal
4. SMA syndrome	Left SMA	Will there be a change to the surgical approach?	Move to awake mapping from asleep	More conservative
5. "Non"eloquent	Left frontal pole	Change in consideration of eloquence?	Move to awake mapping from asleep	More conservative

SMA, supplementary motor area.

REFERENCES

1. Beckmann CF, DeLuca M, Devlin JT, Smith S. Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci*. 2005;360:1001-1013.

2. Beckmann CF, Smith S. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging*. 2004; 23:137-152.

3. Griffanti L, Douaud G, Bijsterbosch J, et al. Hand classification of fMRI ICA noise components. *NeuroImage*. 2017;154:188-205.

4. Salimi-Khorshidi G, Douaud G, Beckmann CF, Glasser MF, Griffanti L, Smith S. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. *NeuroImage*. 2014;90:449-468.

5. Romero-Garcia R, Atienza M, Clemmensen LH, Cantero JL. Effects of network resolution on topological properties of human neocortex. *NeuroImage*. 2012;59:3522-3532.

6. Tournier DJ, Calamante F, Connelly A. MRtrix: diffusion tractography in crossing fiber regions. *Int J Sys Tech*. 2012;22:53-66.

7. Solodkin A, Hasson U, Siugzdaite R, et al. Virtual brain transplantation (VBT): a method for accurate image registration and parcellation in large cortical stroke. *Arch Italiennes de Biol*. 2010;148:219-241.

8. Nachev P, Coulthard E, Jäger RH, Kennard C, Husain M. Enantiomorphic normalization of focally lesioned brains. *NeuroImage*. 2008;39:1215-1226.

9. Tustison N, ants B, Cook P. The ANTs cortical thickness processing pipeline. *SPIE Med*. 2013;8672: 86720K-86722K.

10. Fischl B. *FreeSurfer*. *NeuroImage*. 2012;62:774-781.

11. Cignoni P, Callieri M, Italian CM. Meshlab: an open-source mesh processing tool. Available at: academia.edu; 2008. Accessed February 12, 2020.