Connections, Tracts, Fractals, and the Rest: A Working Guide to Network and Connectivity Studies in Neurosurgery

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Brain mapping and connectomics can probe networks that span the entire brain, producing a diverse range of outputs for probing specific clinically relevant questions. The potential for understanding the effect of focal lesions on brain function, cognition, and plasticity abounds, any one of which would likely yield more effective and safer neurosurgical strategies. However, the possibilities of advanced magnetic resonance imaging and connectomics have been somewhat underused in neurosurgery, arising from actual or perceived difficulties in either application or analysis. The present review builds on previous work describing the theoretical attractions of connectomics to deliberate on the practical details of performing high-quality connectomics studies in neurosurgery. First, the data and methods involved in deriving connectomics models will be considered, specifically for the purpose of determining the nature of inferences that can be made subsequently. Next, a selection of key analysis methods will be explored using practical examples that illustrate their effective implementation and the insights that can be gleaned. The principles of study design will be introduced, including analysis tips and methods for making efficient use of available resources. Finally, a review of the best research practices for neuroimaging studies will be discussed, including principles of open access data sharing, study preregistration, and methods for improving replicability. Ultimately, we hope readers will be better placed to appraise the current connectomics studies in neurosurgery and empowered to develop their own high-quality studies, both of which are key steps in realizing the true potential of connectomics and advanced neuroimaging analyses in general.

INTRODUCTION

> There is nothing either good or bad, but thinking makes it so
>
> Shakespeare, Hamlet, II, ii, 249

The adoption of new methods and techniques is often polemic, and none more so than when applied within medicine. Neuroimaging analyses can often be particularly contentious owing to the frequent development of new methods, perceived complexity of analyses, and the nontrivial demand to consolidate findings with ground truth data. However, in the present review, we argue that the fundamental relationship between neurosurgery and neuroanatomy demands a critical appreciation of contemporary brain mapping strategies to properly apply them in a nuanced manner to specific clinical scenarios. Through a series of practical illustrations, we will demonstrate how a judicious application of new brain mapping techniques—specifically connectomics and network analysis—together with a careful study design can enhance our understanding of neuroanatomy to answer clinically meaningful questions.

The applications of an accurate map of functional neuroanatomy to neurosurgery are myriad. Neuro-oncology, epilepsy, deep brain stimulation (DBS), and understanding symptoms

Key words
- Connectome
- Fractal
- Functional connectivity
- Structural connectivity
- Tractography

Abbreviations and Acronyms
BOLD: Blood oxygen level-dependent
DBS: Deep brain stimulation
fMRI: Functional magnetic resonance imaging
MRI: Magnetic resonance imaging
rs-fMRI: Resting state fMRI
RSN: Resting state network

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Table 1. Glossary

Term	Definition
Amplitude of low frequency fluctuations (ALFF)	Fourier transform of underlying resting state BOLD time series with analysis of subsequent low frequency component's (e.g., 0.02—0.0Hz) amplitude
Connectome	A brain wiring diagram, whereby regions are defined as nodes (or vertices) and connected by links (or edges), creating a graph
Centrality	A graph theory measure of a node property pertaining to a key ("central") role within the network
Edge	A link (connection) between 2 nodes in a connectome
Functional connectivity (FC)	Statistical dependency (e.g., Pearson correlation) between BOLD time series (e.g., from resting state analyses)
Fractal	Self-similarity property of an object (i.e., no preferential scale for viewing its property)
Hub	A node in a connectome that plays a key role in network function, often related to a high centrality score
Independent component analysis (ICA)	A machine learning-based data dimensionality reducing technique of reducing a source to its underlying components (e.g., solving the "cocktail party" problem)
Node	A brain region in connectome analysis, usually defined based on a template parcel
Motif	A specific pattern of localized and directed connections that is repeated in the brain architecture
Parcellation	A method of decomposing the brain into discrete regions (e.g., spatially), usually for connectome analysis
Regional homogeneity (ReHo)	The similarity in a region's time series properties compared with its nearest neighbors
Resting state network (RSN)	A spatially distinct group of brain regions defined on the basis of their functional connectivity (SCA) or independence from other networks (ICA)
Seed connectivity analysis (SCA)	A means of forming an RSN based on functional connectivity of a given region (seed) with all other brain regions (mass univariate analysis)

BOLD, blood oxygen level-dependent; SCA, seed connectivity analysis; ICA, independent component analysis; RSN, resting state network.

relating to focal lesions from a variety of causes (e.g., trauma, vascular) are but a few. Historically, neurosurgery has contributed many revealing findings to our understanding of functional neuroanatomy[1,2] owing to its unique ability to contribute to the characterization of lesions, how they induce plasticity, and postoperative changes. Furthermore, specific complementary mapping techniques are available that can only be practically applied in neurosurgery (in humans at least), such as electrocorticography and awake brain stimulation.[3,4] Building on these foundations and linking direct measures of brain activity with neuroimaging and connectomics are 2 key steps to maximizing the scientific potential of experimental studies involving neurosurgical patients for an understanding of brain function.

Modern approaches to understanding functional neuroanatomy have focused on the paradigms of activity at rest and neuronal connectivity (Table 1). Traditional brain mapping focused on localization of task-based activations; however, changing the focus to the baseline activity (previously considered "noise") opened a previously unrealized opportunity for understanding brain function.[5] The emergent view is that brain function is already well organized at rest—with much of the task-based functional architecture already present[6]—and also encompassing "task-negative" networks that are deactivated during a directed mental task.[7] Synonymous with this newfound understanding of brain function at rest has been the emergence of resting state (rs) functional magnetic resonance imaging (fMRI), although other methods are available to study the brain at rest. Connectomics is a related discipline that developed in parallel that seeks to explain brain function in terms of connectivity and distributed processing, drawing on specific aspects of network analysis and graph theory (throughout the present review, connectomics and network analysis have, therefore, been used synonymously).[8] Confidence in these data has been bolstered by experimental replicability, intermodality concordance, and a robust basis in physical and neurobiological principles.

Designed for neurosurgeons who wish to take these ideas forward and design their own connectomics studies, the present review used a novel problem-based approach to demystify connectomics analyses. In doing so, the principles of data acquisition, study design, and research practice have been covered. For those who wish to understand the more fundamental aspects of connectomics and network theory in general, multiple primers are available both in general and specific to neurosurgery.[8-10] Many of the examples and learning points covered are based on our own practical experience with performing connectomics studies in neuro-oncology and functional neurosurgery.[11] Ultimately, we hope that by presenting these data, we will aid in the development of high-quality connectomics research studies that will not only benefit patients but will also provide neuroscientific

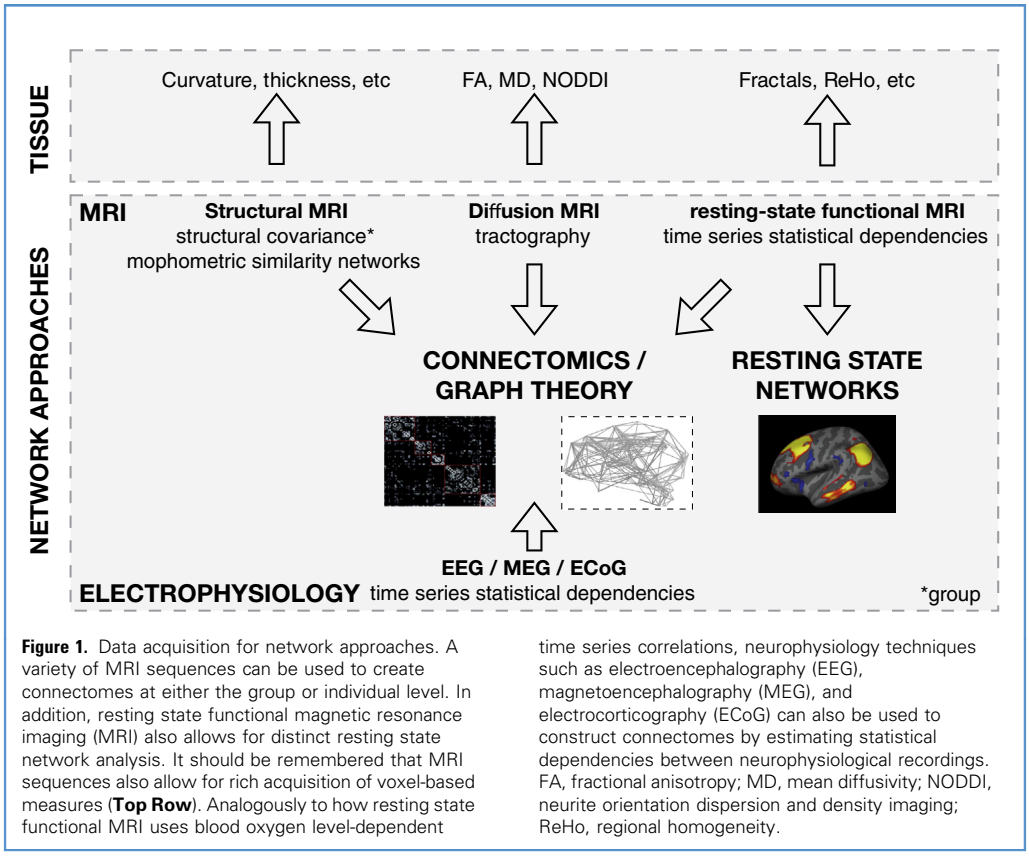

Figure 1. Data acquisition for network approaches. A variety of MRI sequences can be used to create connectomes at either the group or individual level. In addition, resting state functional magnetic resonance imaging (MRI) also allows for distinct resting state network analysis. It should be remembered that MRI sequences also allow for rich acquisition of voxel-based measures (**Top Row**). Analogously to how resting state functional MRI uses blood oxygen level-dependent time series correlations, neurophysiology techniques such as electroencephalography (EEG), magnetoencephalography (MEG), and electrocorticography (ECoG) can also be used to construct connectomes by estimating statistical dependencies between neurophysiological recordings. FA, fractional anisotropy; MD, mean diffusivity; NODDI, neurite orientation dispersion and density imaging; ReHo, regional homogeneity.

insights into the many fascinating observations that can be made in everyday neurosurgical practice.

WHAT SIGNALS DOES THE CONNECTOME COMPRISE?

Connectomes can be made using a wide variety of neuroimaging and neurophysiological methods (Figure 1). Once the data have been acquired, the actual connectomics methods (also known as network analysis) are broadly conserved between modalities, and comparisons between imaging acquisitions are a fertile field of research.[12-14] However, to make useful inferences regarding the constructed networks, it is important to appreciate what the raw data means and how the data are affected by previous processing.

White Matter and Structural Connectomes

Structural connectivity is intended to represent a direct physical connection between regions such as an axonal fiber or tract. Such models are typically based on tractography algorithms using diffusion-weighted MRI data[15,16] but can also be based on structural covariance networks using variation in cortical morphological features at the group level.[17] Important considerations to remember include the following: what is being measured (each tract is composed of an axon, myelin, and connective tissue), how it is being measured (various models of this structure inferred by loss of signal from water movement determined by time-delayed resonance pulses), and, again, the volume of connections measured in each voxel (~400 m/mm^3 and ~4 km/mm^3 of dendrites and axons, respectively). Issues with tractography can arise in estimating complex tract geometry (e.g., crossing, branching, or bending patterns), determining the site of termination in the gray matter, and modeling fibers over long ranges. These issues have resulted in myriad approaches to analysis without consensus reached for a single reference standard.[5,18] Although a high degree of subjective validation exists in terms of tract plausibility and correspondence with anatomical tract-tracing methods, quantitative validation has revealed a more concerning picture regarding false-positive results and replicability.[19] In terms of connectomics, however, the reproducibility, sensitivity, and correspondence for tract-based models have been high, confirming an important role for their use in network analyses.[20]

Connectivity and Functional Connectomes

Analysis of rs-fMRI is based on low-frequency fluctuations in blood oxygen level-dependent (BOLD) contrast believed to represent physiologically meaningful information and closely related to the underlying neural activity.[21] Overall, the emergent hypothesis is one of connectivity through coherence (i.e., synchronized activity reflects a connection between regions).[22] Whether this connection reflects a direct axonal link, shared inputs, or some other modulation of activity as a part of a larger network is not implicit in the model and is the subject of ongoing research. Important considerations are the temporal resolution (in the order of seconds), spatial resolution (a single 1-mm isotropic voxel will contain the signal of 10^5 neurons), and the indirect

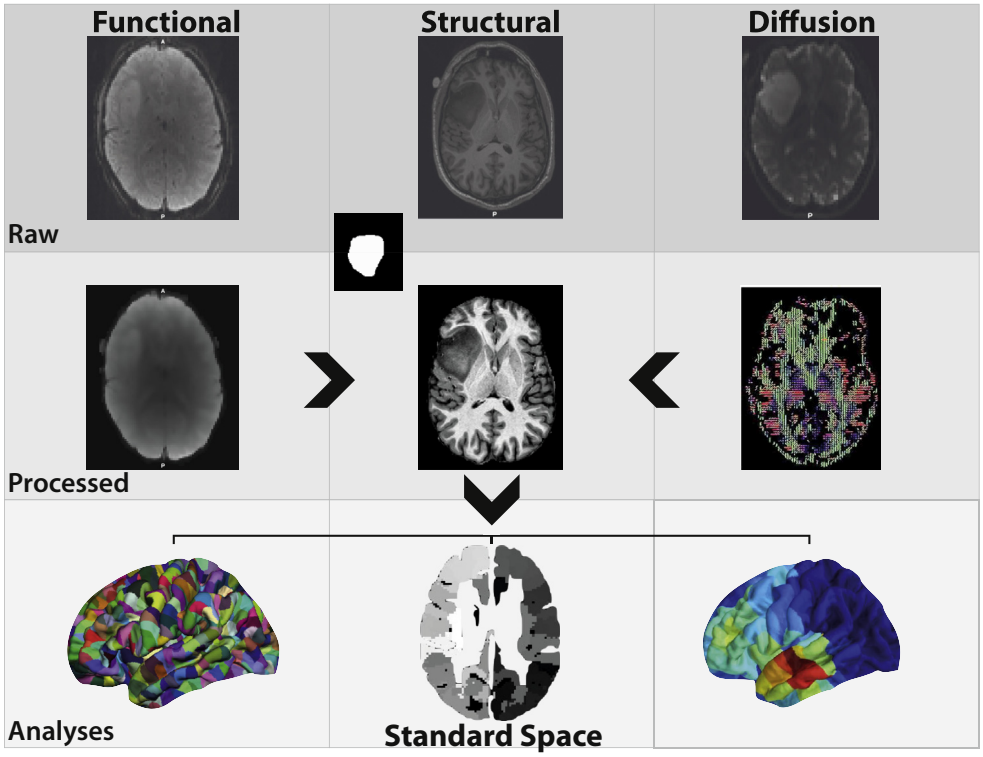

Figure 2. Neuroimaging data processing. A neuroimaging processing pipeline matrix. (**Top Row,** *Left to Right*) Resting state functional magnetic resonance imaging (rs-fMRI), magnetization-prepared rapid acquisition with gradient echo (MPRAGE), diffusion imaging data for tractography are acquired in their raw format. (**Middle Row,** *Left to Right*) The raw data have been processed in preparation for analysis and modeling. Potential steps for structural imaging include the following: lesion segmentation; intensity normalization; and brain extraction. Optionally, further segmentation (e.g., into gray and white matter) and cortical surface reconstruction can be performed. For rs-fMRI, the options include the following: rigid-body motion correction; bandpass filtering; B0 correction; brain extraction; and smoothing. For diffusion imaging, the options include the following: reorientation; brain extraction; and eddy current correction. Finally, registrations can be performed from either functional or diffusion space to structural (MPRAGE) space using linear algorithms and from structural to standard space using nonlinear registration. Once standard space mapping has been performed, one can use parcellation templates to perform connectomics or analyze group lesion effects (e.g., voxel-based lesion-symptom mapping or resection-probability maps). Note that analysis of rs-fMRI and diffusion data is often performed in the subject's native space using an inverse mapping of the template from standard space. BBR, boundary-based registration; SyN, symmetrical diffeomorphic registration with advanced normalization tools.

relationship between BOLD contrast and neuronal activity. Finally, functional connectivity is one of many approaches used to map brain activity. However, perfect concordance between methods (e.g., rs-fMRI and cortical stimulation) should not be expected and will not necessarily reflect methodological failure. Rather, each technique has its own principles that should be considered for the chosen study design and inference of interest.

Structural and Functional Network Relations

A dichotomous definition of connectomes, based on either structural or functional connections, inevitably leads to questions pertaining to their relationship in vivo. Early studies had formed the hypothesis that structure constrains function, with structural connectomes containing the wiring backbone that functional connectomes use.[13] More recent studies have suggested that this relationship is more complex.[23,24] Related to this is the issue of information transfer and how networks choose a particular route for communication.[25] Overall, the emerging viewpoint is that although structural connectomes provide the available routes for neurons to exchange data, functional connectomes also reflect additional features such as indirect connections, shared inputs, and/or synaptic changes.[26] Therefore, it is clear that both approaches are required, as is an understanding of their limitations, complementarity, and synergism.

Considerations in Networks Construction

Connectome analysis itself, regardless of whether based on structural or functional data, also contains methodological

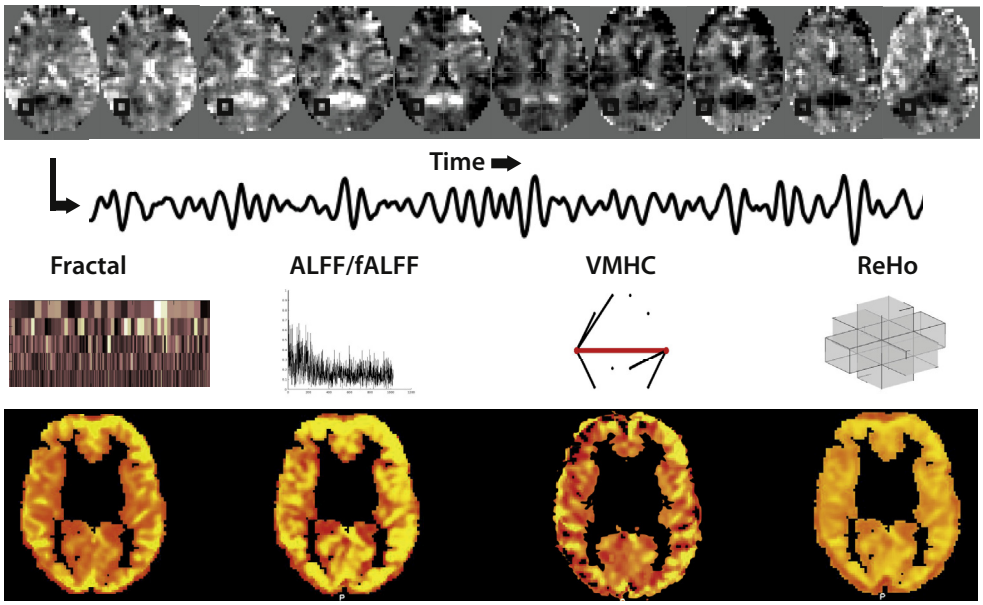

Figure 3. Voxel-based measures. A blood oxygen level-dependent time series is generated through the acquisition of a series of whole brain 3-dimensional volumes at rest. The time series relates to the region within the *black square*. Once this time series has been acquired (and appropriately processed), a variety of analyses can be directly performed at the voxel level. These include a maximal overlap discrete wavelet transform (MODWT), which allows for calculation of the Hurst component and fractal analysis; Fourier decomposition and analysis of the amplitude of low frequency fluctuations (ALFF); a comparison with homotopic areas in terms of symmetry of voxel-measured homotopic connectivity (VMHC); and a comparison of the time series with spatially adjacent neighbors for regional homogeneity (ReHo).

characteristics that will influence subsequent inferences. Effective connectivity defines causal patterns of neuronal activations or repeating patterns of neural organization (motifs) but neither of the aforementioned MRI techniques allow for this analysis approach.[27] Network density has historically been believed to be sparse; however, contemporary tract-tracing studies in mice have suggested a more densely connected network.[28] Typically, functional connectivity networks have connections for every pair of regions (often known as fully connected and subsequently thresholded to reduce this density), and tractography-based structural networks are relatively sparse (most pairs of regions will not have a connection between them). Finally, multiple models (or layers) of connectivity can be present within a single brain that vary across time and are determined by other factors such as genetics, development, environment, and disease.[29]

In summary, we should consider connectomics as a model to allow new insights into meaningful clinical questions but with its own unique set of challenges that must be addressed during this process. Some considerations are related to the underlying data, with others distinct from the specific data acquisition method used and related to the network analysis itself.

Table 2. Analysis Comparisons

Methods	Basis	Strengths	Weaknesses	Examples
Voxel based	Properties of underlying de-noised time series	Physically principled; interpretation of network level effects	Local; difficult to interpret	Distance-related effects, hemispheric asymmetries, statistical parametric maps
Resting state networks	Collections of brain regions with synchronized functional activity	Close to data; intuitive; correspondence with task-based architecture	Need for thresholding; mass univariate approach	Connectivity of specific regions (e.g., peritumoral)
Connectomics	Relationship between time series of different brain regions	Whole brain mapping; wide approach to analysis	Highest level analysis (most distant to the data)	Cognitive eloquence

How to Process Connectomics Data?

Neuroimaging data require processing before the data will be suitable for connectomics (Figure 2). In brief, these steps aim to reduce and quantify artifacts and thereby increase the signal/noise ratio. No universally agreed pipeline is available; therefore, the following guidelines are based on the principle of minimal preprocessing, in keeping with other recent datasets.[30] Because the present review has focused on the principles underlying study design, the actual acquisition of sequences has not be covered in lieu of the many excellent resources available to those interested.[30,31]

For rs-fMRI, the main aim is to reduce or quantify motion-related and other artifacts and to focus on the underlying low-frequency fluctuations of BOLD contrast in the gray matter. In addition, some form of de-noising is required to remove artifacts. Note that de-noising and motion correction are complex fields with extensive existing data reported.[32] The decisions required for sequence acquisition include determining the repetition time and sequence duration (which, in turn, will determine the number of volumes available), resolution and field of view (which will affect the repetition time), and whether any de-noising strategies are required to be built in at this stage.

Diffusion imaging also aims to reduce errors due to movement, in addition to those due to current-induced distortions. After this initial processing, one can either analyze the underlying voxel-based diffusion data (e.g., fractional anisotropy or mean diffusivity maps) or perform tractography. This latter step involves creating a model of the underlying fiber direction or directions in each voxel and then propagating this to generate a streamline, ideally from seed to gray matter termination. Similar to rs-fMRI, vast and contentious reported studies are available on the methods and validity of applying any specific model.[19] Sequences available for performing tractography are increasing, in addition to the historical diffusion tensor imaging and have now focused on improved resolution of fiber orientations[33,34] and tissue parameterization.[35]

Video available at www.sciencedirect.com

APPROACHES TO NETWORK ANALYSIS

Many different techniques or approaches can be used for connectivity analyses. The following examples illustrate how distinct network analysis approaches can be used to provide insight into clinically meaningful neurosurgical questions. Therefore, the following subsections are not intended to be exhaustive nor prescriptive in the analyses that can or cannot be performed, and interested readers are directed to other comprehensive studies focused specifically in this area.[36,37]

Peritumoral Region and Local Functional Capacity

An appropriate start to analyzing fMRI data acquired at rest is using voxel-based (point estimate) methods that characterize the underlying BOLD time series (Figure 3), creating a variety of maps (Table 2).[38-41] Such methods directly measure the properties of the low frequency (~0.5 Hz) fluctuations in the BOLD signal believed to contain physiologically meaningful information.[21] These maps lend themselves to understanding the spatial distribution of any subsequently observed network changes and are often related to fundamental components of the underlying neural processes.

Fractals are one such feature reflecting the complexity of the acquired signal; increased complexity is believed to convey a physiological advantage in information processing capacity[42-46] (as an analogy, consider bandwidth and internet speed). In patients with glioblastoma, a penumbra of reduced cortical complexity was found adjacent to the lesion that with increasing distance increased above baseline before returning to baseline. These findings disprove a purely localizationist approach to understanding the functional effects of focal lesions and suggest that subsequent analyses should consider global effects in their approach.

In summary, voxel-based measures of BOLD signals offer insight into the complexity that, as we have explored later in the present report, complements the spatially diverse approaches of functional networks at rest and the mathematical properties of graph theory connectomics. Determining what these measures probe in individual patients requires cross-referencing with neurocognitive data; however, the information might reflect the underlying neurophysiological function rather than a detectable phenotypic change. Overall, voxel-based measures are often an appropriate place to start an analysis and can be used to help understand the local basis of more global changes. Furthermore, they are especially attractive for testing selected topological hypotheses related to distance or asymmetries.

Higher Cognitive Function Mapping and Resting State Networks

Resting state networks (RSNs) were one of the early findings that led to appreciation of the significance represented by brain activity at rest (Figure 4 and Video 1).[5,47] Template RSNs derived from groups of healthy participants have been identified that correspond to task performance,[6] healthy development,[48] and disease.[49] These networks cover a wide constellation of both primary cortex functions (visual, sensorimotor, auditory) and higher cognitive function networks such as attention, salience, executive function, accessory visual areas, and, potentially, language (Video 1). It is this ready access to multiple readily defined network topologies that makes RSN analysis so attractive to neurosurgery, for example, in investigating the functional effects of surgery, increasing our understanding of disease pathophysiology, and developing novel biomarkers of treatment response.

One use of RSNs could be in developing a more holistic view of brain function and how function can be affected by neurosurgery. In an early exploratory analysis of a homogeneous cohort of patients with right parietal glioblastoma, numerous qualitative changes were described in multiple higher cognitive function networks but especially in the default mode network, a region believed to be involved in automated information processing and cognitive flexibility.[50] This insight allows one to go beyond understanding the typical focal deficits that might be expected for lesions in this location (e.g., those related to apraxia, hemianopia, and hemisensory changes) and to develop novel neuropsychology paradigms for testing hypotheses related to the higher cognitive function networks that might be involved (e.g., with novel intraoperative tasks during awake brain stimulation or focused postoperative rehabilitation).

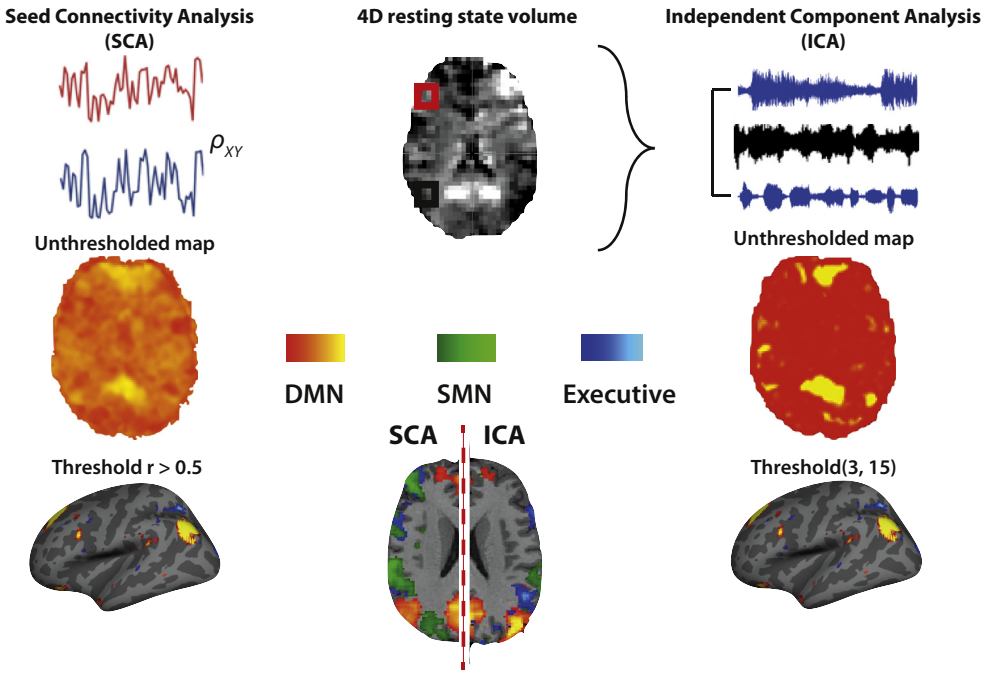

Figure 4. Resting state network (RSN) analysis. RSNs can be identified using 2 main approaches. Seed connectivity analysis (SCA) sets a region of interest (seed), isolates its representative time series, and performs a mass univariate analysis of all other voxel's time series to create a whole brain map. Independent component analysis (ICA) considers the whole brain signal and decomposes this into independent components that represent the underlying sources (as an analogy, consider the colloquial "cocktail party" problem, whereby one filters out the background noise and multiple other conversations from the specific conversation of interest). Note only a selection of RSNs are shown for clarity but multiple RSNs will be generated. Both these techniques create whole brain maps that are often subsequently thresholded for viewing as either a volume or surface. Note the concordance between both techniques and sensitivity to a variety of spatially distinct or overlapping RSNs. 4D, 4-dimensional; DMN, default mode network; SMN, sensorimotor network.

RSNs can also be used as objective biomarkers of treatment response and to study the effects of neurosurgical intervention on higher cognitive function. In a landmark report investigating the role of nucleus accumbens DBS for obsessive compulsive disorder, the connectivity between the nucleus accumbens and prefrontal cortex using rs-fMRI demonstrated a linear correlation with treatment response.[51] Thus, the investigators were able to demonstrate nonlocal effects of DBS and alteration of disease pathophysiology and to suggest a novel biomarker of treatment effectiveness.

In summary, RSNs demonstrate how one can move beyond localization and achieve a more holistic insight into a patient's higher cognitive function using a relatively straightforward analysis. Clinical translation opportunities are myriad and include tailored rehabilitation, detailed preoperative counseling, and objective biomarkers of treatment response (e.g., titrating parameters of DBS during follow-up). Ongoing research into understanding the underlying biological mechanisms involved in RSN dynamics such as developing methods for statistical comparisons at the individual subject level[52] and optimizing acquisition and analysis strategies to maximize intra- and intersubject reliability[53] is only likely to increase the applicability of these analysis methods.

Distributed Effects of Empirical and In Silico Lesions with Connectomics

The connectome is a term coined >1 decade ago that encapsulated the search for the "wiring diagram" of the brain (**Figure 5**).[54,55] Viewing the brain in this manner considers the brain to be a small world[56,57]—whereby segregated local communities are married together and complemented by long distance links and short cuts—forming a complex network topology (along with other key organizational principles such as scale-free degree distribution, hubs, community architecture, rich clubs, and weak links). Connectome analysis is attractive to neurosurgeons for this holistic model of brain connectivity, its novel mathematical vocabulary for describing brain function, and the manner in which it lends itself to intuitive modeling strategies, such as the effects of focal lesions and plasticity.

The case of Phineas Gage is a landmark example illustrating the effects of focal frontal lobe lesions that is particularly applicable to neurosurgery. In an elegant and multifaceted reappraisal of the case, the effects of the sustained focal lesion were modeled using a computational simulation of the original penetrating injury and accurate mapping of this injury onto a standard template brain.

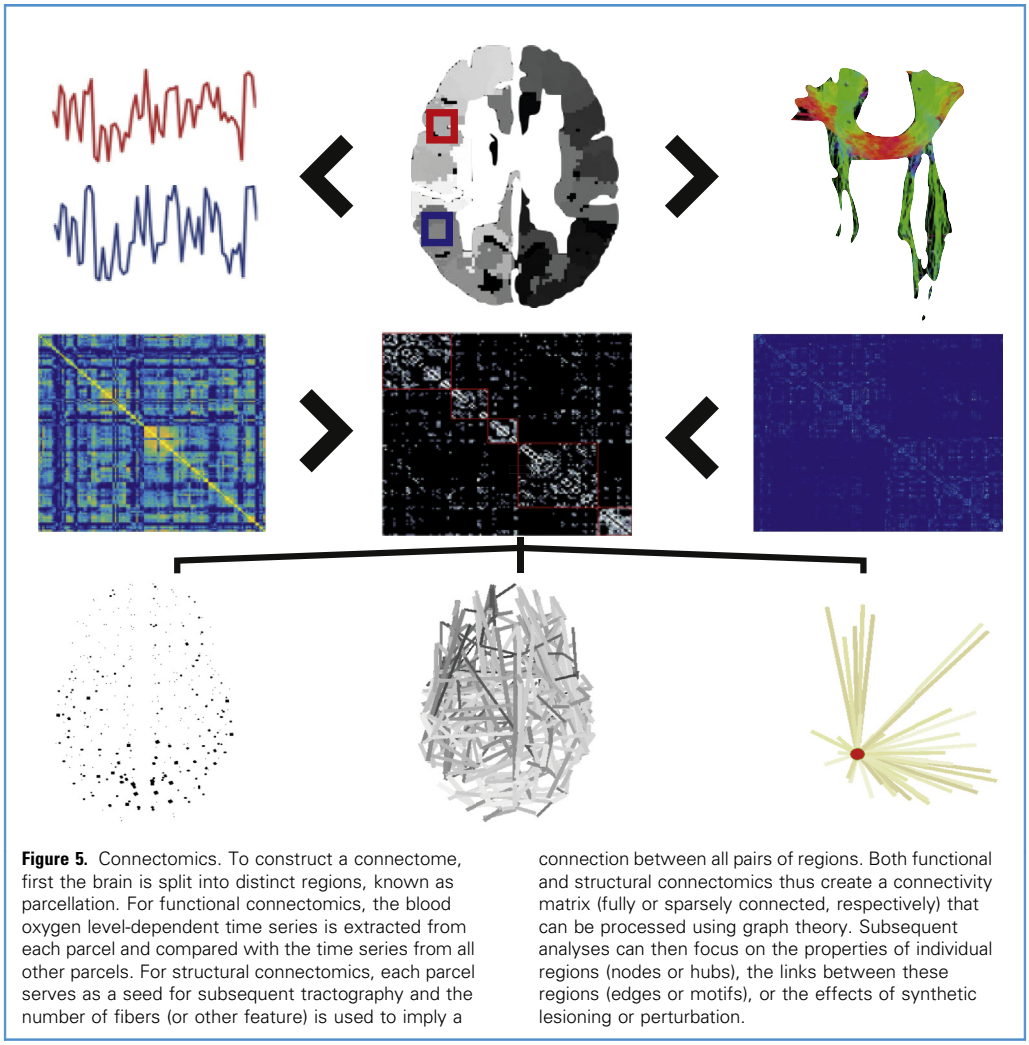

Figure 5. Connectomics. To construct a connectome, first the brain is split into distinct regions, known as parcellation. For functional connectomics, the blood oxygen level-dependent time series is extracted from each parcel and compared with the time series from all other parcels. For structural connectomics, each parcel serves as a seed for subsequent tractography and the number of fibers (or other feature) is used to imply a connection between all pairs of regions. Both functional and structural connectomics thus create a connectivity matrix (fully or sparsely connected, respectively) that can be processed using graph theory. Subsequent analyses can then focus on the properties of individual regions (nodes or hubs), the links between these regions (edges or motifs), or the effects of synthetic lesioning or perturbation.

Next, this lesion was used as an in silico structural lesion onto a control connectome generated from healthy individuals to simulate its potential functional effects.[58] This allows one to see that what was originally believed to be a focal lesion with effects localized to the nondominant frontal lobe was actually a diffuse injury involving long-range inter- and intrahemispheric connections. Opportunities for further work abound, including how to model the effects of recovery or plasticity, determining the secondary insults such as infection believed to have occurred, and defining how the network topology was related to seizure generation (which eventually led to his demise).

Developing this concept of nonlocal effects of focal lesions, an empirical dataset of patients with glioblastoma with connectomes generated from their own rs-fMRI data was studied.[59] In that study, virtual or in silico lesioning was used to develop "connectomics signatures" predicted to be at risk from surgery, highlighting individual phenotypes and connectivity beyond that encompassed by standard structural imaging. An additional benefit of their study was the confirmation that individual connectomes could be created using a variety of both simple and more sophisticated methods in patients with empirical lesions, requiring only minor adjustment to pipelines used in otherwise healthy individuals (Figure 5).

Understanding the complex nonlinear dynamics of lesions was performed using a "virtual brain" simulator based on empirical lesions.[60] In that study, a cohort of patients with gliomas and meningiomas underwent diffusion tensor imaging and rs-fMRI. However, in addition, a computational model of neural dynamics was used combined with the underlying empirical tractography data to create individualized virtual brains that mirrored the empirical rs-fMRI data.[60] Distinct individual signatures were identified that described whether the brain regions had been directly affected by a tumor or not. These results suggest that personalized virtual brain models will contribute additional information to our understanding of the effects of focal lesions and have the potential to be used for individualized brain mapping.

Expanding on this understanding of the static effects of focal lesions, a longitudinal study was performed to characterize lesion-related plasticity and reorganization after surgery.[61] In that study,

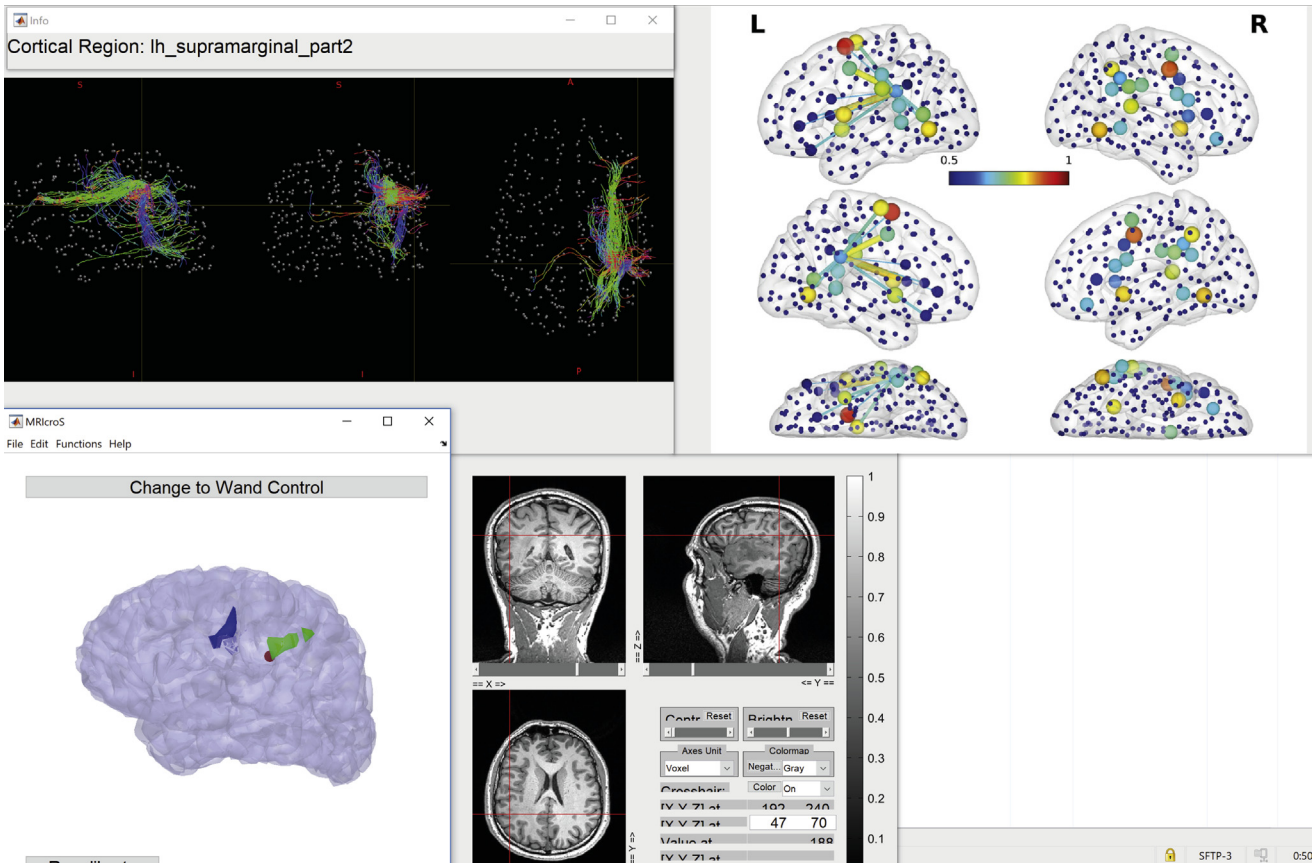

Figure 6. Individual language network mapping. Application of connectomics and network mapping at the individual level to study language networks. Preoperative planning of a patient with a diffuse low-grade glioma of the left superior temporal lobe involving dominant hemisphere language pathways. Views include (**Lower Middle**) standard structural magnetic resonance imaging scans, (**Lower Left**) resting state networks corresponding to the canonical Wernicke-Lichtheim-Geschwind language network, and (**Upper Right**) connectomics and (**Upper Left**) tractography analyses based on a seed in the left supramarginal gyrus. Complex data are presented, highlighting the classical tracts (e.g., the arcuate fasciculus), and more provocative findings, including interhemispheric networks and global connectivity. This example illustrates some of the difficulties in applying connectomics at the individual level in clinical scenarios and should serve as motivation for the further work required to translate the neuroscientific advances to benefits in patient treatment. The visualization screenshot was taken from the NetSym network navigation interface for applying connectomics to neurosurgery.[67]

a cohort of 6 participants with transient supplementary motor area syndrome after awake brain surgery for diffuse low-grade glioma was studied longitudinally at baseline, postoperatively, and at the 3-month follow-up examination.[61] This highlighted the interhemispheric dynamic changes relating to connectivity between the contralateral supplementary motor area and ipsilateral sensory–motor regions that mirrored the patients' clinical recovery. Whether these promising results can be used to create a novel noninvasive biomarker of lesion-related plasticity remains to be seen and will naturally require participants with less than complete recovery to also be included.

In summary, connectomics has established itself at the forefront in the modern brain mapping era and is conceptually appealing while offering a novel global mathematical approach to functional neuroanatomy. Studies have already shown the promise of connectomics for understanding the nonlocal effects of lesions, studying the nonlinear dynamics of empirical lesions, and developing biomarkers of plasticity to predict postoperative outcomes. Terms such as cognitive eloquence, hubs, and weak links have been quickly establishing themselves in the modern lexicon of brain mapping (Table 1); however, whether they can be defined as markers used in neurosurgery will depend on whether the appropriately designed studies can prove their worth at the individual level (Figure 6).

STATISTICAL AND METHODOLOGICAL CONSIDERATIONS IN DESIGNING CONNECTOMICS STUDIES

First and foremost, one must have a clear and meaningful research question with objective aims for the study. Dependent on this will be the study design, analysis strategy, and, indeed, whether it is even tractable with currently available methods. For certain

questions, pursuing a group-based comparison might be most appropriate; therefore, consideration of what comprises a relevant control population is paramount. However, for other questions, individual predications might be more relevant. Therefore, a challenge for this design will be the requirement for a sufficient density of data (e.g., through multimodal sampling and longitudinal study designs). Connectomics research from its inception has been multidisciplinary, involving the fields of mathematics, computer science, engineering, neuroimaging, neuropsychology, and social science, to name a few. Taking the time to engage and involve experts from such diverse fields early on, will not only lead to unique opportunities within the study, but will also leverage this key advantage of the field.

Also, important "traps" exist that one should be careful not to fall into when designing studies. Exploratory studies are fundamentally different from what have often been termed in the vernacular as "fishing" strategies. Therefore, one must be clear from the start whether the future study will be a hypothesis-generating study or whether a clear hypothesis will be tested a priori. One must also avoid circular analysis strategies whereby the same data are used to define and test models of function counteracted.[62] Finally, robust consideration should be given to the sample size early in the design to prevent studies that are either underpowered from the outset or overambitious and subsequently transpire to capture insufficient data.

Finally, one must consider the necessary financial, logistical, and technical resources and address any discordance if these are not available. Thus, one should invest properly in high-quality data because its lack cannot be compensated for subsequently, such as by using sophisticated analyses (including machine learning techniques). One method to manage this would be to foster collaborations between groups with complementary skillsets or shared computational resources. Multinational initiatives to foster collaborations already exist in neurosurgery (e.g., the successful global neurotrauma program), and a role might exist for similar resources to support neuroimaging and connectomics research in neurosurgery. Another approach would be to use freely available datasets to complement clinical data, such as the Human Connectome Project or OpenfMRI (now OpenNeuro) repository. Although these issues might not initially appear to be a priority, post hoc compromise resulting from inaccurate appreciation of the available or required resources can usurp a hitherto robust study design, leading to underpowered studies without reproducible findings.

DISCUSSION

Application of advanced neuroimaging and connectivity analyses to neurosurgery has much to offer in terms of providing insight to fundamental neuroscience, biomarkers of disease, and understanding cognitive outcomes. We hope that the present report will act as a primer for developing high-quality individual network studies. For further development of these ideas and more detailed discussion of the imaging and network processing methods, diverse and detailed reports are available.[10,31,36,37,63]

When reflecting on the principles of study design, it is also worth considering the other desirable features of research practice in general that can be implemented. Open access and data sharing are not just important for the validity of research but will also allow one to learn about analysis strategies and the development of new analysis tools.[64,65] Nevertheless, although data sharing is common within neuroimaging, it has remained something of a rarity in neurosurgery. Finally, research should be affordable, not just to allow value for money for the funding organizations and charities, but also to allow for the use of the research output and establishment of the research itself in lower income countries.

One notable issue for neuroimaging and cognitive research in general is the generalizability and replicability of the findings.[66] Data sharing and open access will help in this regard, because independent groups can perform their own analyses of the same data, which could either enhance the legitimacy of the findings if consistent or caution against errors or overinterpretation otherwise.

Preregistration is another helpful method that has been underused. All these approaches should be seen as positive and necessary challenges to overcome for generating robust scientific findings that minimize the number of false trails that occur and facilitate our understanding of the neuroscientific basis of the data more efficiently.

CONCLUSIONS

> There is nothing either good or bad, but thinking makes it so
>
> Shakespeare, Hamlet, II, ii, 249

Although Shakespeare used this quotation to highlight Hamlet's toying with his old friends Rosencrantz and Guildenstern, in the present report, we have used it in a contemporary and more philosophical context, suggesting that, fundamentally, analysis techniques are neither good nor bad but rather are dependent on the manner in which a specific study was designed. Thus, the thinking (or art) is in choosing an interesting study question and designing the experiment in such a manner to appropriately answer it, rather than in the use (or not) of any given technology. Connectomics, like any other research field, requires due care and thought at the study design phase to harness its power. It is not a panacea that will produce relevant results regardless of the study design. We hope the readers will now be better placed to understand the potential attractions and benefits of advanced neuroimaging and connectomics analyses and also be in a position to translate this knowledge into effective research studies. Carefully designed and analyzed studies are not only necessary, but also a priority, for the field to grow and improve the treatments we offer our patients.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Michael G. Hart: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition. **Rafael Romero-Garcia:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Visualization. **Stephen J. Price:** Investigation, Resources, Writing - review & editing. **Thomas Santarius:** Conceptualization, Writing - original draft, Supervision, Funding acquisition. **John Suckling:** Resources, Writing - review & editing.

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