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A Connectomic Atlas of the Human Cerebrum—Chapter 18: The Connectional Anatomy of Human Brain Networks

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BACKGROUND: It is widely understood that cortical functions are mediated by complex, interdependent brain networks. These networks have been identified and studied using novel technologies such as functional magnetic resonance imaging under both resting-state and task-based conditions. However, no one has attempted to describe these networks in terms of their cortical parcellations.

OBJECTIVE: To describe our approach to network modeling and discuss its significance for the future of neuronavigation in brain surgery using the cortical parcellation scheme detailed within this supplement.

METHODS: Using network models previously elucidated by our group using coordinate-based meta-analytic techniques, we show the anatomic position and underlying white matter tracts of the cortical regions comprising 8 functional networks of the human cerebrum. These network models are displayed using Synaptive's clinically available BrightMatter tractography software (Synaptive Medical, Toronto, Canada).

RESULTS: The relevant cortical parcellations of 8 different cerebral networks have been identified. The fiber tracts between these regions were used to construct anatomically precise models of the networks. Models are described for the dorsal attention, ventral attention, semantic, auditory, supplementary motor, ventral premotor, default mode, and salience networks.

CONCLUSION: Our goal is to move towards more precise, anatomically specific models of brain networks that can be constructed for individual patients and utilized in navigational platforms during brain surgery. We believe network modeling and future advances in navigation technology can provide a foundation for improving neurosurgical outcomes by allowing us to preserve complex brain networks.

KEY WORDS: Connectivity, Tractography, DTI, Anatomy, Functional connectivity, Cerebrum, Human, Parcellations

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In the first 9 chapters of this supplement, we cataloged the structural and functional connectivity of all 180 cortical regions delineated under the Human Connectome Project (HCP).[1] We then used these data to summarize the subcortical anatomy of 8 large white matter tracts in the brain. These preceding chapters raise more questions about the human connectome than we are able to answer here. However, one of the most critical questions to us is how this new model of the cerebral cortex and the data presented in this supplement can be integrated into the neurosurgical clinic or operating room. This chapter serves, in part, to answer that question.

While it is obvious that imaging such as diffusion tractography and resting state functional magnetic resonance imaging (fMRI) have the potential to provide new insights into brain anatomy not previously possible, adoption into mainstream neurosurgery has been slower than ideal, especially given the profound potential this knowledge has to radically change how we plan cerebral surgery.

ABBREVIATIONS: ALE, anatomic likelihood estimation; **DTI,** diffusion tensor imaging; **fMRI,** functional magnetic resonance imaging; **MNI,** montreal neuroimaging institute; **MRI,** magnetic resonance imaging; **ROIs,** region of interest

In our opinion, the principle barriers presently preventing widespread adoption of connectomic imaging in brain surgery are (1) the relative difficulty of postprocessing magnetic resonance imaging (MRI) images to provide clinically useful data that can be used for intraoperative navigation and planning, (2) a relative lack of knowledge about the anatomy of brain networks and tracts, (3) difficulty linking connectomic anatomy to clinical phenotypes and functional significance. The first problem is beginning to be addressed within the medical technology industry, but will not be financially viable until it is demanded by all neurosurgeons who perform brain operations. Addressing the second problem is the principle motivation for the previous 17 chapters of this supplement.

As for the third barrier, it is more difficult to address, in large part because it involves many key aspects of neuroscience that are still in evolution. Ultimately, this is a big data problem. However, we would argue that few problems are more interesting or important that solving where in the brain we can and cannot cut without lasting consequence. While tract anatomy gives us some sense of the likely architecture of the brain networks they involve, ultimately no one is as much concerned with preservation of the arcuate fasciculus as they are with preservation of language functions. Thus, linking functions to anatomy is an essential step in making these technologies clinically useful.

It is clear that cerebral regions that are often separated in space have activity time sequences that are correlated, suggesting that they activate together more often than they activate with other cerebral regions.[2] This has led to the concept of these areas being termed "large-scale functional networks".[3] It is clear that given some of these networks show strong correlations between areas well known to be involved in specific functions such as motor, vision, and language, that it is likely that these networks represent a major building block of human cognition, though many higher cognitive functions may arise from interactions between these networks. At minimum, providing visual depiction of the anatomy of these networks seems an appropriate place to start.

One limitation of the existing literature about the organizational scheme of large-scale brain networks is that they are not written as anatomy texts that would be useful to neurosurgeons. More specifically, they usually lack the precision needed to compare between patients, and to plan an actual surgery in an actual person. Instead, they usually localize key hubs of the networks to gross brain regions,[4] which means that they do not provide enough detail to make the finer distinctions necessary in neurosurgery.

In the final chapter of this supplement, we outline models of large-scale brain networks using a combination of coordinate based meta-analysis combined with diffusion tractography. To show that this is not far from present reality, we collaborated with Synaptive (Synaptive Medical, Toronto, Canada) to demonstrate the future capabilities of clinically available connectomic software packages. This software can be used to visualize large-scale cerebral brain networks for patients undergoing brain surgery. We used Synaptive's BrightMatter fiber tracking program (Synaptive Medical) in conjunction with our network schema to show the cortical and subcortical anatomy of 8 cerebral networks, including dorsal and ventral attention, semantic, auditory, supplementary and ventral premotor motor, default mode, and salience. All network schema were initially derived using coordinate-based meta-analytic techniques and deterministic tractography, and are based on the (HCP) cortical parcellation model presented throughout this supplement.

METHODS

Derivation of Network Parcellation Schema

Literature Searches

Literature searches for all relevant coordinate-based fMRI studies related to attention, language, auditory, motor processing, and the default mode and salience networks were completed using BrainMap Sleuth 2.4,[5-7] as well as PubMed and Google Scholar if no fMRI studies were identified in the Sleuth fMRI database. Studies were included in our analysis if they met the following criteria: (1) peer-reviewed publication, (2) task-based fMRI study related to attention, language, auditory, or motor functioning, (3) based on whole-brain, voxel-wise imaging, (4) including standardized coordinate-based results in the Talairach or Montreal Neuroimaging Institute (MNI) coordinate space, and (5) including at least 1 healthy human control cohort. Only coordinates from healthy subjects were utilized to construct network models.

ALE Generation and Identification of Relevant Cortical Regions

We used BrainMap Ginger anatomic likelihood estimation (ALE) 2.3.6 to extract the relevant fMRI coordinate data to create an ALE based on the literature for each network.[8-10] All coordinates were exported to Ginger ALE in the MNI coordinate space. We subsequently performed a Single Study analysis using Cluster-Level Interference (cluster level of 0.05, threshold permutations of 1000, uncorrected p-value of 0.001). The ALE coordinate data were displayed on an MNI-normalized template brain using the Multi-image Analysis GUI (Mango) 4.0.1 (ric.uthscsa.edu/mango). Using the parcellation region of interests (ROIs) constructed in the Connectome Workbench command line interface, we assessed parcellations for inclusion in each network if the parcellation and ALE data overlapped.

Tractography

After determining the parcellations overlapping the ALE of a particular network, we proceeded to assess the fiber tracts between parcellations underlying each network using deterministic tractography. All fiber tractography was done in diffusion spectrum imaging Studio (http://dsi-studio.labsolver.org) using publicly available brain imaging from the Human Connectome Project (http://humanconnectome.org, release Q3). Tractography was performed individually with 10 randomly chosen adult subjects. A multishell diffusion scheme was used, with b-values of 990, 1985, and 2980 s/mm^2. Each b-value was sampled in 90 directions. The in-plane resolution was 1.25 mm. The slice thickness was 1.25 mm. The diffusion data were reconstructed using generalized q-sampling imaging.[11] The diffusion sampling length ratio was 1.25.

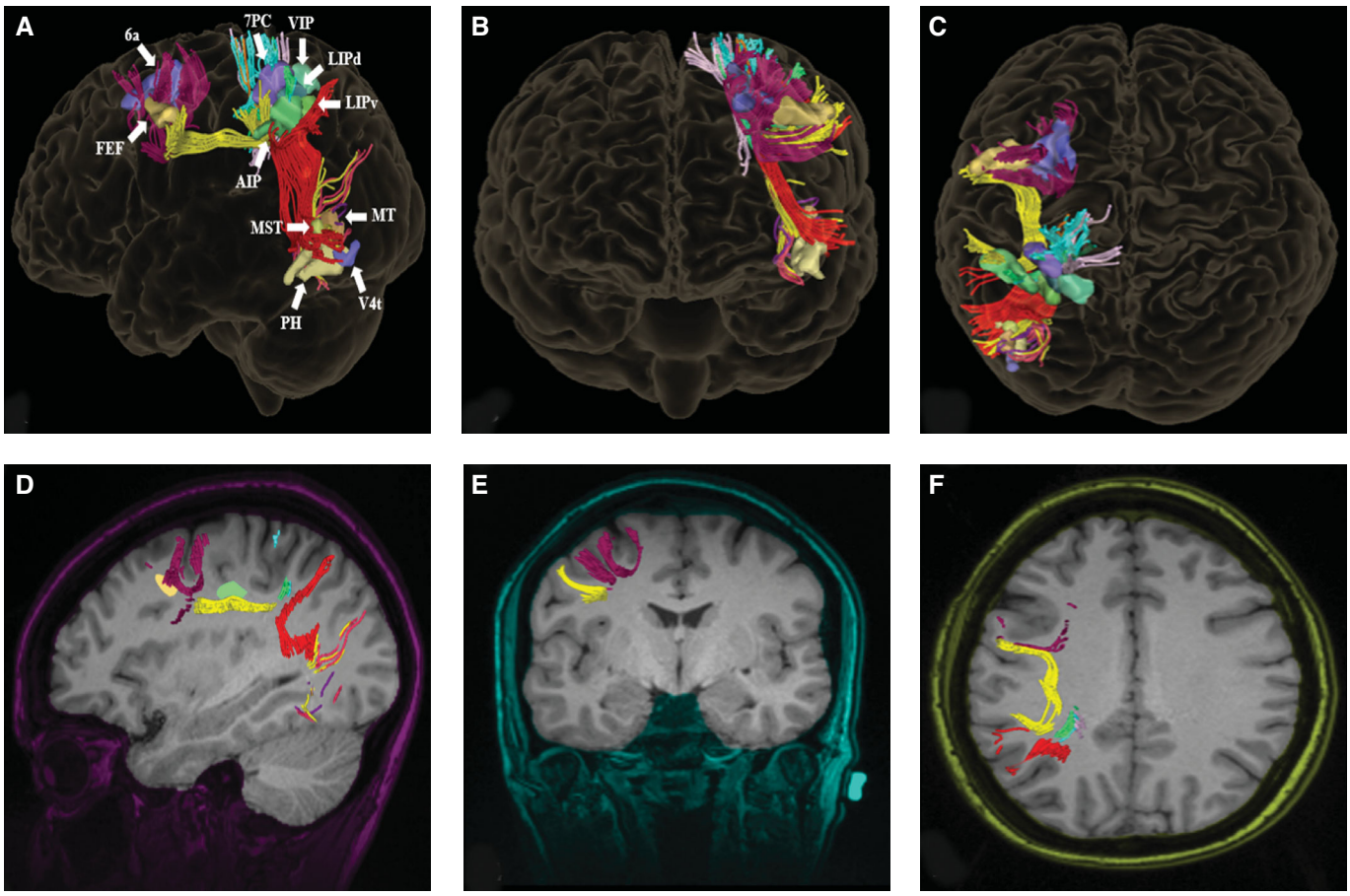

FIGURE 1. *The dorsal attention network is displayed using Synaptive's BrightMatter fiber tracking software. Individual parcellations are labeled and identified with arrows in* **A**. *The dorsal attention network is shown in the left cerebral hemisphere on a 3D-rendered brain mask in* **A**, *medial-lateral view,* **B**, *anterior-posterior view, and* **C**, *superior-inferior view. The fiber tracts of the network are readily identified in the sagittal plane. Corresponding T1-weighted MR images in the* **D**, *sagittal,* **E**, *coronal, and* **F**, *axial planes show the fiber connections of the network in this particular patient.*

All reconstructions were performed in MNI space using a ROI approach to initiate fiber tracking from a seeded region. Voxels within each ROI were automatically traced with a maximum angular threshold of 45°. When a voxel was approached with no tract direction or a direction greater than 45°, the tract was halted. Tracks with length shorter than 10 mm or longer than 800 mm were discarded. In some instances, exclusion ROIs were placed to exclude spurious tracts or tracts inconsistently represented across individuals. Tracts were considered real between parcellations if they could be identified consistently across multiple subjects.

BrightMatter Fiber Tractography

DTI Postprocessing

Imaging was acquired for a healthy control using a clinical protocol on a 3T Siemens MRI scanner. Automated postprocessing was performed in the clinically available software program, BrightMatter Plan (Synaptive Medical): a 30 direction, 5 min diffusion tensor imaging (DTI) scan was used to generate tractography using whole brain seeding and a deterministic streamline algorithm following motion, eddy current, and field inhomogeneity correction. DTI scans were subsequently co-registered to the corresponding T1-weighted anatomic MRI.

Network Generation

The 3-dimensional parcellation files generated through the Connectome Workbench command line interface were loaded into the BrightMatter software platform using a tool in development and were manually placed in the appropriate subject-specific anatomic position. The white matter tracts between parcellations were isolated and identified based on the network schema. This was performed using a clinically available region intersection tool that allows for filtering of tracts that interconnect regions. This exercise was performed for each of the 8 networks.

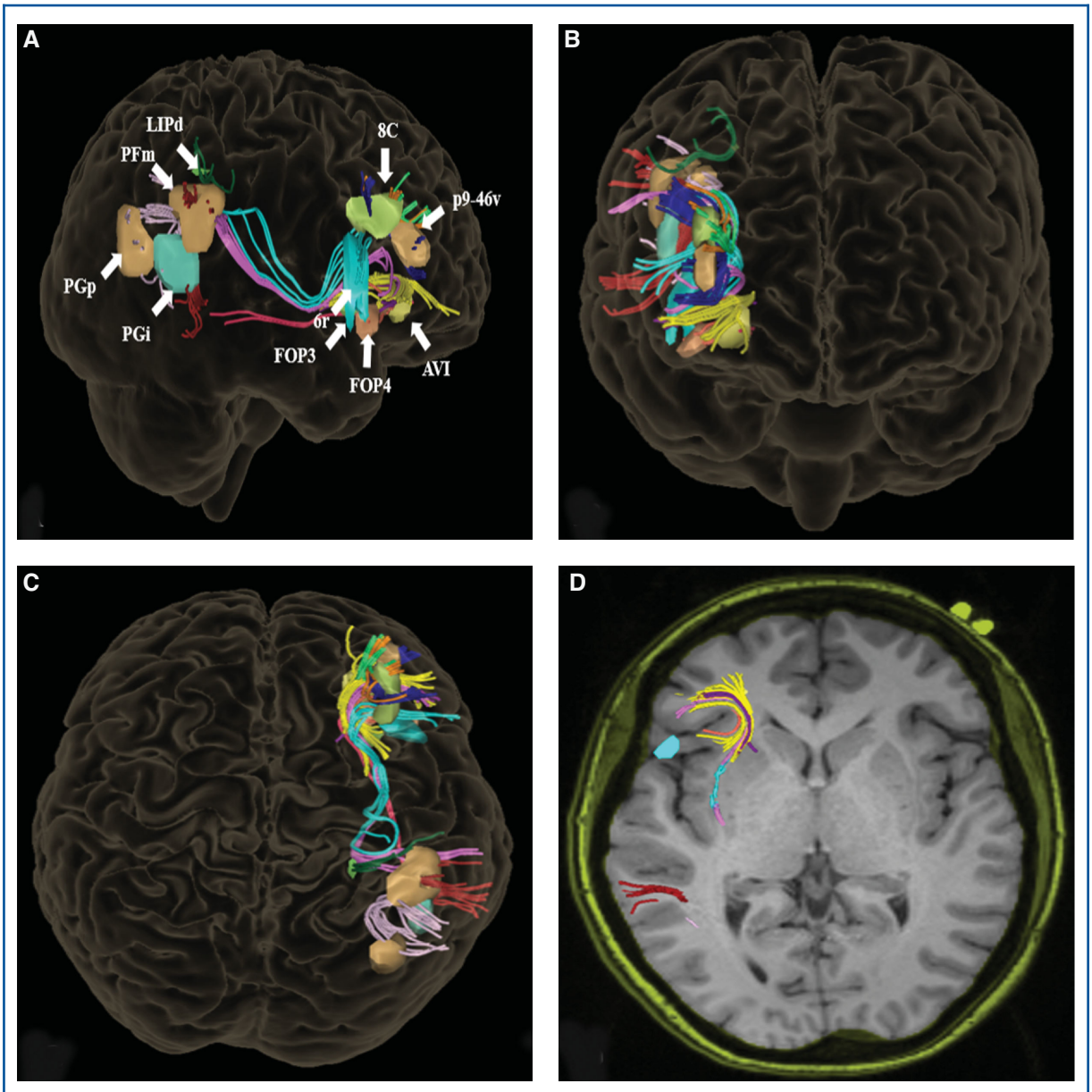

FIGURE 2. *The ventral attention network is displayed using Synaptive's BrightMatter fiber tracking software. Individual parcellations are labeled and identified with arrows in* **A**. *The ventral attention network is shown in the right cerebral hemisphere on a 3D-rendered brain mask in multiple views in* **A**, *medial-lateral view,* **B**, *anterior-posterior view,* **C**, *superior-inferior view, and* **D**, *axial view.*

RESULTS

Figures 1-7 demonstrate the anatomic position and fiber tractography between the ROI comprising the 8 networks considered in this study, including dorsal and ventral attention (Figures 1 and 2), semantic (Figure 3), auditory (Figure 4), supplementary and ventral premotor (Figure 5), default mode (Figure 6), and salience (Figure 7). A description of the parcellations and white matter tracts comprising these networks follows:

The Dorsal Attention Network

Twelve cortical regions in the left cerebral hemisphere comprise the dorsal attention network: 6a, 7AM, 7PC, AIP, FEF, LIPd, LIPv, MST, MT, PH, V4t, and VIP. These regions demonstrated consistent interconnections between adjacent parcellations. The

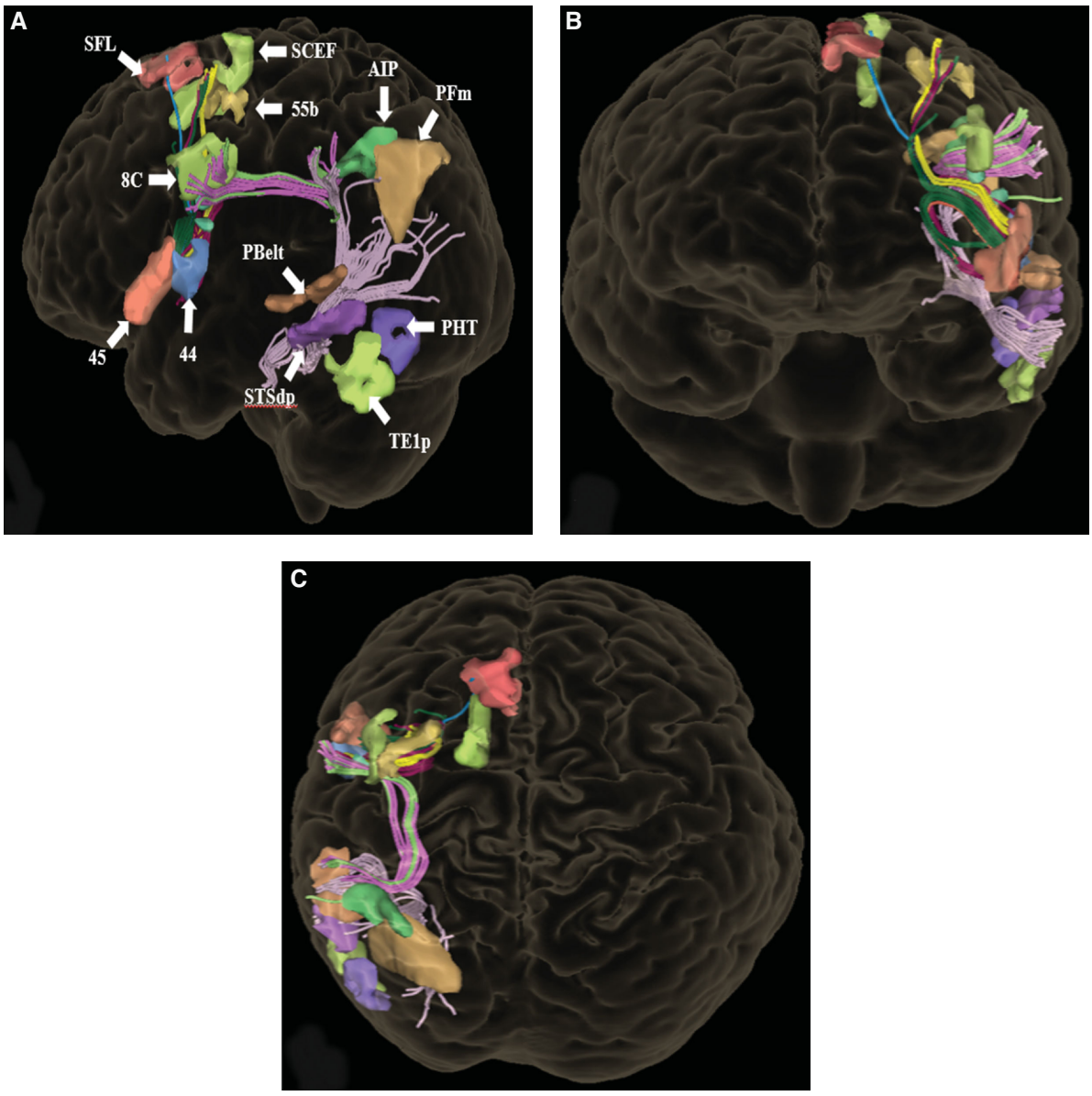

FIGURE 3. *The semantic network is displayed using Synaptive's BrightMatter fiber tracking software. Individual parcellations are labeled and identified with arrows in* **A**. *The semantic network is shown in the left cerebral hemisphere on a 3D-rendered brain mask in multiple views:* **A**, *medial-lateral view,* **B**, *anterior-posterior view, and* **C**, *superior-inferior view. The fiber tracts of the network are readily identified in the sagittal plane.*

superior longitudinal fasciculus connects AIP, FEF, LIPd, and PH. (P.G. Allan, et al., Unpublished Data, December 2017)

The Ventral Attention Network

Ten cortical regions in the right cerebral hemisphere comprise the ventral attention network: 6r, 8C, AVI, FOP3, FOP4, LIPd, p9–46v, PFm, PGi, and PGp. These regions demonstrated consistent interconnections between adjacent parcellations. The superior longitudinal fasciculus connects 6r, 8C, PFm, and LIPd. (P.G. Allan, et al., Unpublished Data, December 2017)

The Semantic Language Network

Fifteen cortical regions in the left cerebral hemisphere comprise the semantic network: 44, 45, 55b, IFJA, 8C, SFL, SCEF,

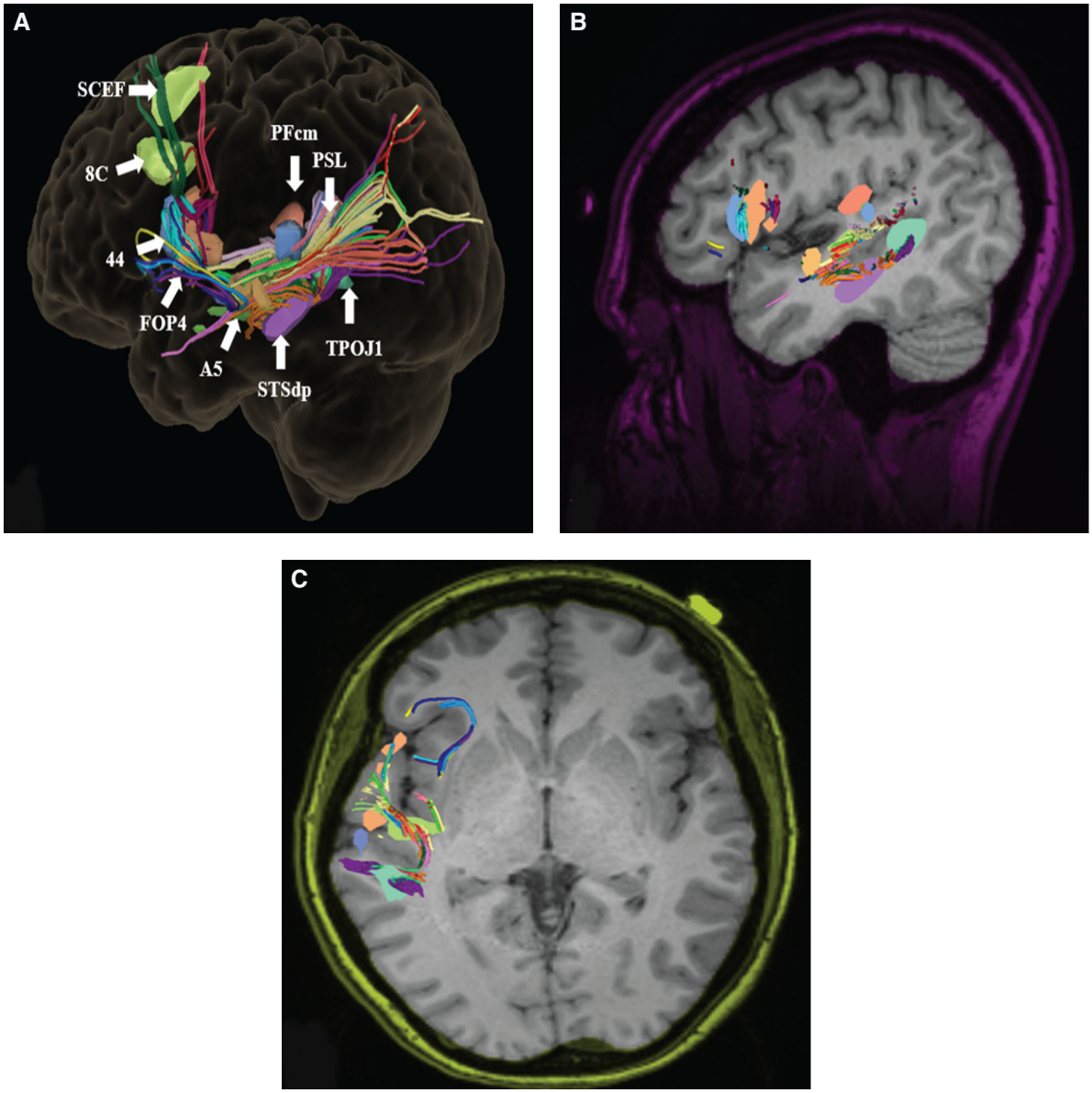

FIGURE 4. *The auditory network is displayed using Synaptive's BrightMatter fiber tracking software. Individual parcellations are labeled and identified with arrows in* **A**. *The auditory is shown in the left cerebral hemisphere on a 3D-rendered brain mask in multiple views:* **A**, *medial-lateral view. Corresponding T1-weighted MR images in the* **B**, *sagittal, and* **C**, *axial planes show the fiber connections of the network for this particular patient.*

8BM, STSdp, STSvp, AIP, PFM, TE1P, PHT, and P-Belt. These regions demonstrated consistent interconnections between parcellations. The superior longitudinal fasciculus connects areas 44, STSdp, STSvp, PHT, and TE1p, as well as areas 55b, AIP, PFm, and PHT. The frontal aslant tract connects area 44 to SFL and SCEF. (C.M. Milton et al., Unpublished Data, January 2018)

The Auditory Network

Fifteen cortical regions in the left cerebral hemisphere comprise the auditory network: A1, A4, A5, LBelt, MBelt, PBelt, PFcm, PSL, RI, STSdp, TPOJ1, 44, FOP4, 8C, and SCEF. These regions demonstrated consistent interconnections between adjacent parcellations. The superior longitudinal fasciculus connects regions 44, A4, PBelt, and RI to other parcellations

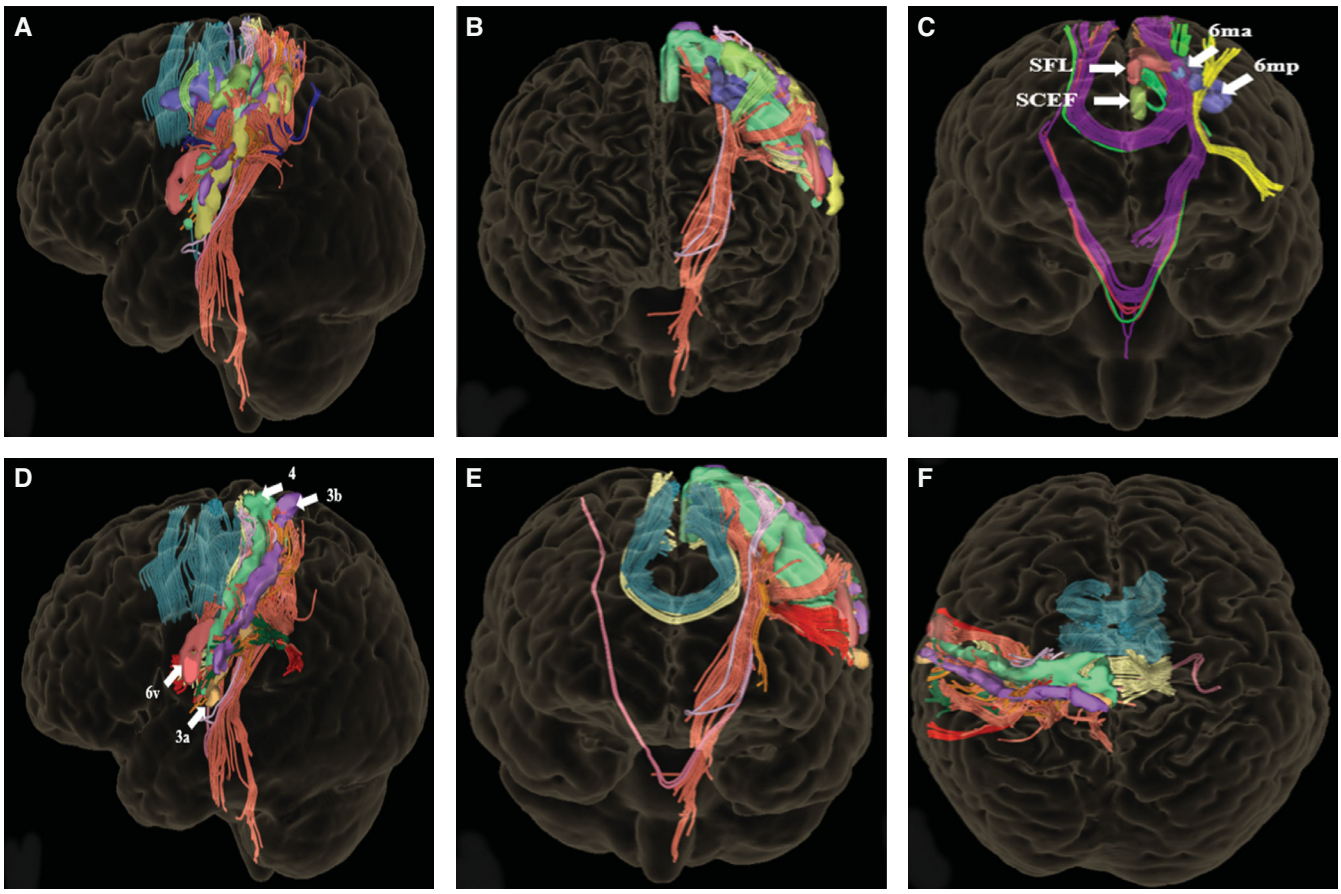

FIGURE 5. **A** *and* **B**, *Composite images of the supplementary motor and ventral premotor networks. The supplementary motor network is shown isolated in* **C**, *and includes four parcellations: 6ma, 6mp, SFL, and SCEF (arrows). The ventral premotor network is shown isolated in* **D**, **E**, *and* **F** *and includes four parcellations: 3a, 3b, 4, and 6v (arrows). Motor network tractography is displayed using Synaptive's BrightMatter fiber tracking software on a 3D-rendered brain mask.*

in the network. (J Kuiper et al, Unpublished Data, December 2017)

Motor Networks

Four left hemisphere parcellations were found to comprise the supplementary motor network: SFL, SCEF, 6ma, and 6mp. Four parcellations were also identified as part of the ventral premotor network: 3a, 3b, 4, and 6v. These areas showed consistent interconnections between each other. Tracts were also identified to ipsilateral parcellations in the primary motor cortex, inferior and middle frontal gyri, the anterior cingulate cortex, and insula. Fiber tracking analysis revealed connections to the contralateral SMA, anterior cingulate cortex, lateral premotor region, and inferior frontal gyrus. (J.R. Sheets et al., Unpublished Data, February 2018)

The Default Mode Network

Eighteen cortical regions in the left cerebral hemisphere comprise the default mode network: 10r, a24, p32, s32, 31a, 31pd, 31pv, 7m, POS1, POS2, d23ab, v23ab, RSC, IP1, PFm, PGs, PGi, and TPOJ3. These regions showed consistent interconnections between adjacent parcellations. The cingulum connects regions in the anterior and posterior cingulate cortices. No connection was identified from the anterior or posterior cingulate regions to the lateral parietal areas. (Briggs et al, Unpublished Data, March 2018)

The Salience Network

Eight cortical regions in the left cerebral hemisphere comprise the salience network: a24pr, a32pr, AVI, FOP4, FOP5, MI, p32pr, and SCEF. These regions showed consistent interconnections between adjacent parcellations. The frontal aslant tract

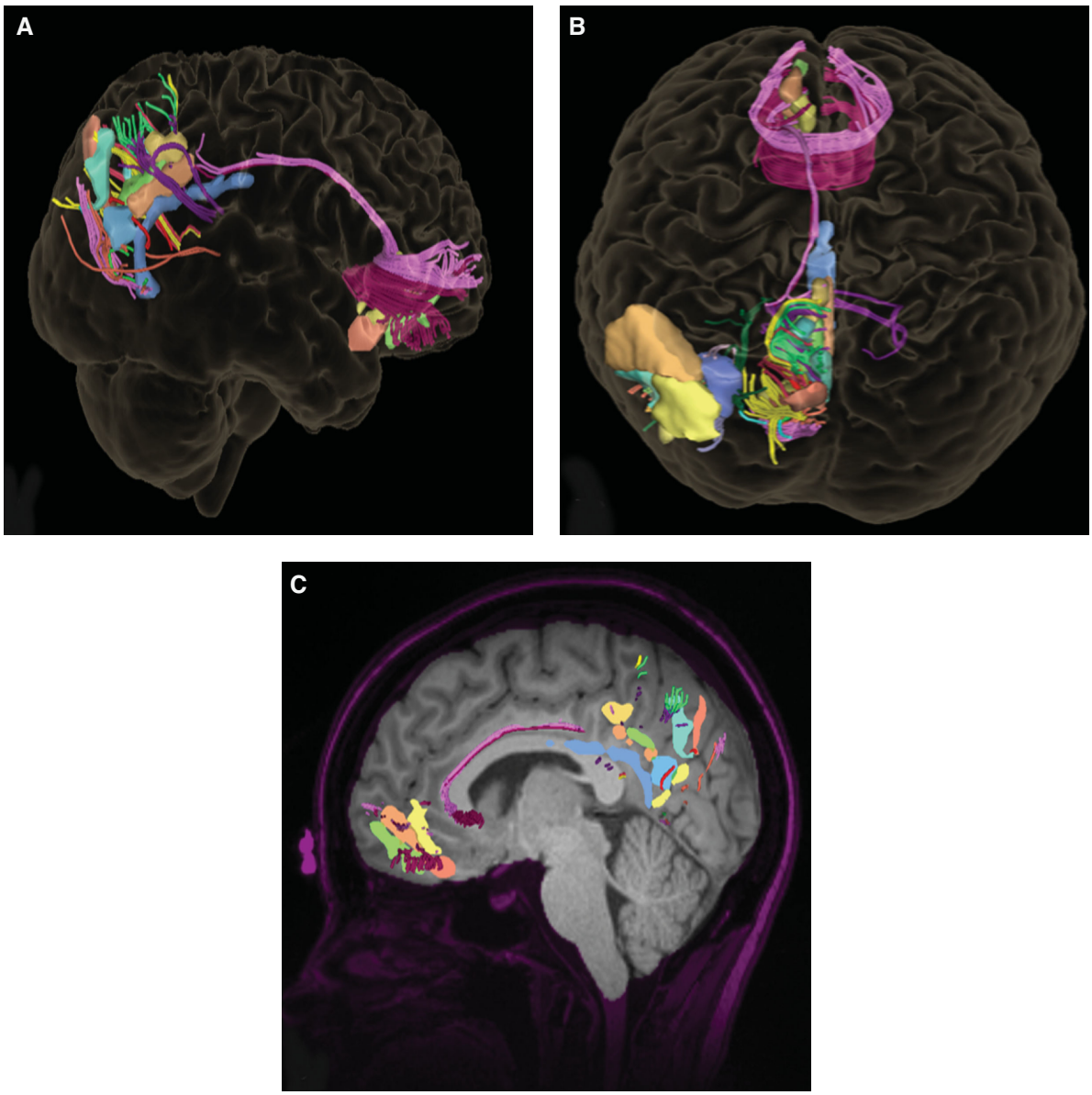

FIGURE 6. *The default mode network is displayed using Synaptive's BrightMatter fiber tracking software. The default mode network is shown in the left cerebral hemisphere on a 3D-rendered brain mask in multiple views:* **A**, *medial-lateral view and* **B**, *superior-inferior view. The fiber tracts of the network are readily identified in the sagittal plane.* **C**, *Corresponding T1-weighted MR imaging in the sagittal plane demonstrates the fiber connections of the network for this particular patient.*

connects SCEF to FOP4 and MI. (Briggs et al, Unpublished Data, March 2018)

DISCUSSION

This chapter aims at providing a look at what we believe is the future of operative navigation and planning for brain surgery, namely a visual depiction of large scale brain networks. Using a clinically available navigation and planning platform, Synaptive's BrightMatter fiber tracking program (Synaptive Medical), we demonstrate the anatomy of these networks using the connectomic scheme we have elaborated in previous chapters.

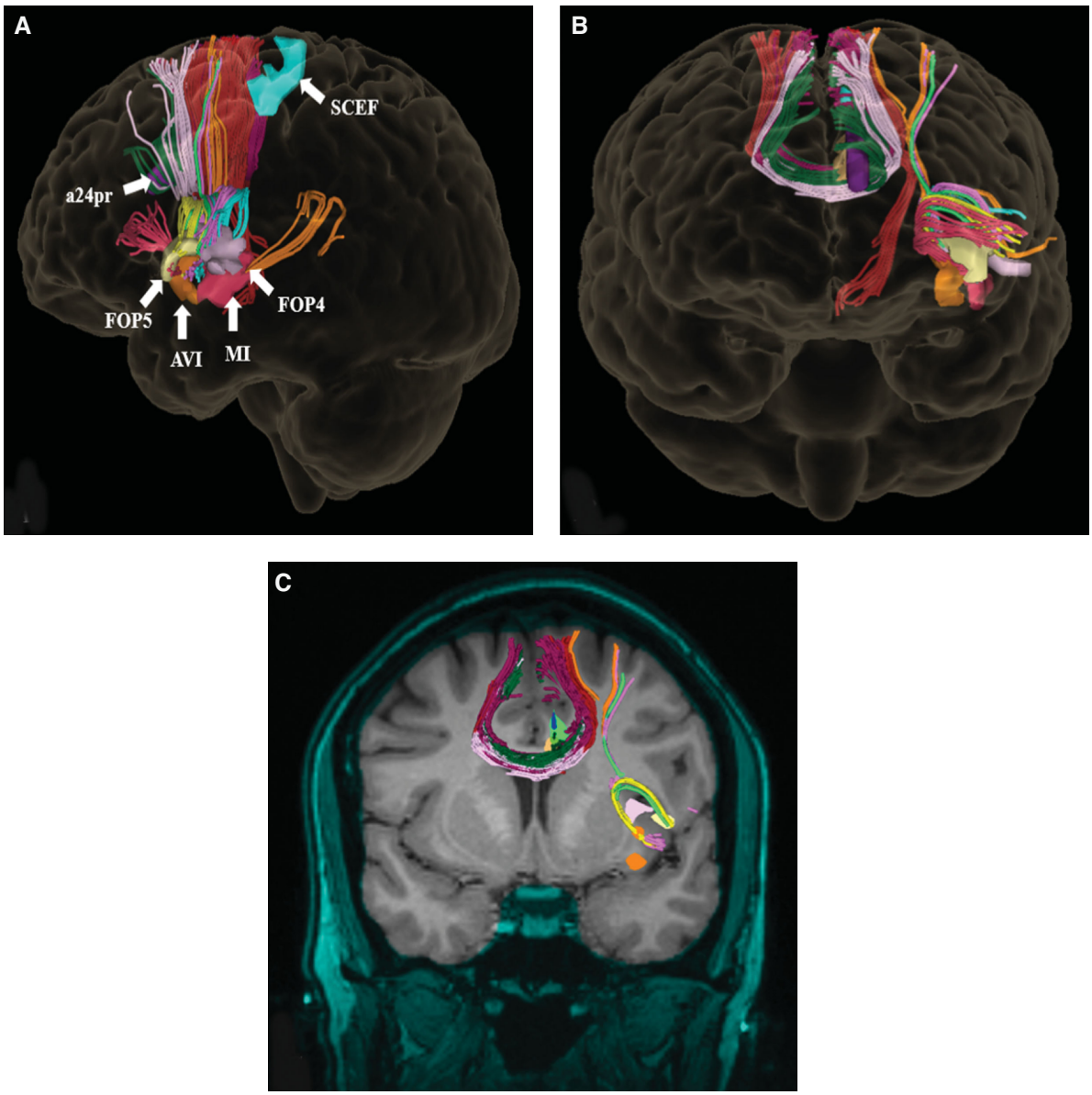

FIGURE 7. *The salience network is displayed using Synaptive's BrightMatter fiber tracking software. Individual parcellations are labeled and identified with arrows in* **A**. *The salience network is shown in the left cerebral hemisphere on a 3D-rendered brain mask in multiple views:* **A**, *medial-lateral view and* **B**, *anterior-posterior view. The fiber tracts of the network are readily identified in the sagittal and coronal planes.* **C**, *Corresponding T1-weighted MR imaging in the coronal plane shows the fiber connections of the network for this particular patient.*

Implications of Network Modeling

First, these models highlight the central significance of the superior longitudinal fasciculus in network connectivity. It was identified in the semantic, dorsal attention, and ventral attention networks. Given the number of networks with projections in this white matter bundle, we would argue that cutting across this white matt tract during brain surgery is undesirable, and that preservation of the superior longitudinal fasciculus (SLF) when possible should be a priority.

There are also several advantages to the network modeling approach we delineate here. First, it allows for a more detailed and accurate depiction of brain function than Brodmann's areas are able to provide.[12,13] Instead of attributing functions to particular sulci and gyri, network modeling allows us to

visualize different parts of the cortex and their relevant subcortical white matter connections together. Related to this are higher cognitive functions such as judgment, self-identification, and human awareness. Modeling of such functions is beyond our current capability. However, as neuroscientists work to better understand these cognitive domains and the parts of the cortex involved in these processes, neurosurgeons will be better equipped to model these networks in greater detail, thereby allowing for their preservation.

Finally, it is important to note that our data reflects network topology in healthy individuals with normal brain structure. Patients with brain tumors are known to have unusual tumor-related networks in which the neoplastic masses distort network architecture.[14,15] For example, white matter bundles may shift from mass effect or edema,[16-18] or network reorganization may occur.[15,19] The significance of our approach is that it provides a framework to begin testing how the anatomic structures of networks change under different experimental and clinical conditions. Modeling these networks provides a template for future studies to refine and modify our models, and to test how cortical injury and pathology may alter the underlying human connectome and its subnetworks.

A Look to the Future

It seems probable that future generations of neurosurgeons will look back at a time when we made serious decisions about surgical planning in the cerebrum without the benefit of knowing the organization of the patient's brain with the same stunned faces as we do when shown old, premicrosurgical diagrams of finger sweeping of tumors near the brainstem, or when we hear of tales of the precomputed tomography and MRI days of neurosurgery. We all know that anatomic MRI does not provide every critical fact about the patient's brain, and we will not improve our surgical outcomes by using better aspirators or having a better microscope if we continue to think about the brain in terms of "eloquent" and "noneloquent" areas alone.[20]

Not only can connectomic-type imaging, processed to its present limits, provide new insights into the exact anatomy of human brain networks, but it will likely be able to allow us to study the potential consequences of our actions prior to cutting into the brain. It is likely that understanding the dynamics of these networks and their interactions will also be necessary,[21] but these ideas are not as well understood at present. Nevertheless, it is important to understand that doing cerebral surgery means cutting in and around brain networks. While we cannot be certain that our network models will withstand future scientific scrutiny (we expect that the models will be refined through future studies), it is important to begin the discussion concerning the development and refinement of network models and their clinical application.

A Look into the Present

Setting future predictions aside, what is presently available in practice is DTI-based processing software that is able to demonstrate the approximate location of major white matter tracts in a stereotactic navigation platform.[18,22] While DTI is widely available in commercial platforms for image guidance and surgical planning, this imaging platform does not provide a full connectomic view of network anatomy to the degree we would like. It does, however, offer some insight into the basic architecture of the networks when combined with our understanding of the anatomy of their subcortical connections. Network maps and knowledge of network architecture informs us of the connections that likely matter most, allowing us to plan cuts into the brain that can minimize damage to these networks.

In most cases, network architecture can be explained as collections of locally connected areas joined by U-shaped fibers, with distant modules linked by major white matter pathways. Sometimes the interaction is more complex than this, but most of the time the parts of the cortex that are activated simultaneously over similar time courses are directly linked through structural connections in the brain.[23-25] For example, knowing the position of the SLF/arcuate complex and its rami does not tell us the exact position of the cortical areas involved in language or speech production, however it gives us an idea of where the networks are located, and provides us a mental framework for our efforts to avoid destroying the network.

Not all networks can be saved, particularly in cases where they have already been distorted, destroyed or invaded. Connectomic imaging does not necessarily tell us what to do in such cases, rather it gives us the data to make better decisions, and to reduce the risk of causing additional, unintended deficits. It is one thing to remove an area of cortex, however when we damage the adjacent white matter tracts, we alter or disrupt the functional connectome for areas unrelated to the region being resected. Thus, while there is much to be improved upon regarding our imaging and neuronavigation technology, knowing the position of major white matter tracts, combined with a knowledge of what they are doing, improves our safety and efficacy in the operating room.

CONCLUSION

While we would argue the future of neurosurgery lies in parcellated human brains, network modeling, and advanced neuronavigation techniques, this supplement fundamentally serves as a guide to the human connectome. We hope this series of publications will serve as a starting point for the avid learner, be they a neurosurgeon or neuroscientist, to begin studying brain structure and function.

Disclosures

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