A Connectomic Atlas of the Human Cerebrum—Chapter 1: Introduction, Methods, and Significance

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BACKGROUND: As knowledge of the brain has increased, clinicians have learned that the cerebrum is composed of complex networks that interact to execute key functions. While neurosurgeons can typically predict and preserve primary cortical function through the primary visual and motor cortices, preservation of higher cognitive functions that are less well localized in regions previously deemed "silent" has proven more difficult. This suggests these silent cortical regions are more anatomically complex and redundant than our previous methods of inquiry can explain, and that progress in cerebral surgery will be made with an improved understanding of brain connectomics. Newly published parcellated cortex maps provide one avenue to study such connectomics in greater detail, and they provide a superior framework and nomenclature for studying cerebral function and anatomy.

OBJECTIVE: To describe the structural and functional aspects of the 180 distinct areas that comprise the human cortex model previously published under the Human Connectome Project (HCP).

METHODS: We divided the cerebrum into 8 macroregions: lateral frontal, motor/premotor, medial frontal, insular, temporal, lateral parietal, medial parietal, and occipital. These regions were further subdivided into their relevant parcellations based on the HCP cortical scheme. Connectome Workbench was used to localize parcellations anatomically and to demonstrate their functional connectivity. DSI studio was used to assess the structural connectivity for each parcellation.

RESULTS: The anatomy, functional connectivity, and structural connectivity of all 180 cortical parcellations identified in the HCP are compiled into a single atlas. Within each section of the atlas, we integrate this information, along with what is known about parcellation function to summarize the implications of these data on network connectivity.

CONCLUSION: This multipart supplement aims to build on the work of the HCP. We present this information in the hope that the complexity of cerebral connectomics will be conveyed in a more manageable format that will allow neurosurgeons and neuroscientists to accurately communicate and formulate hypotheses regarding cerebral anatomy and connectivity. We believe access to this information may provide a foundation for improving surgical outcomes by preserving lesser-known networks.

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

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Anyone with even moderate experience operating in the cerebrum understands that our present models of cerebral functional anatomy are inadequate. While neurosurgeons typically have the ability to predict the locations of primary cortices, such as speech and motor areas, it remains common for patients to note

ABBREVIATIONS: BALSA, Brain Analysis Library of Spatial Maps and Atlases; **GQI,** generalized q-sampling imaging; **HCP,** Human Connectome Project; **MNI,** montreal neurologic institute; **QSDR,** and q-space diffeomorphic reconstruction; **ROI,** region of interest; **rsfMRI,** resting state functional magnetic resonance imaging

unanticipated postoperative cognitive, judgment, or memory problems following seemingly successful surgery.[1] This suggests that many areas that we have traditionally deemed "silent" and therefore, dispensable, are more anatomically complex and redundant than our previous methods of inquiry have elucidated.[2]

The surgical appearance of the cut cerebrum largely comprises featureless anatomy; however, we know that contained within this dissected cerebrum is a complex neural framework that is responsible for making us human. This suggests that true progress in cerebral surgery will only be achieved when technology allows surgeons to overlay conceptual anatomy onto indiscrete cerebral regions that we are unable to differentiate with the naked eye. This technology is increasingly available in the form of high resolution white matter tractography and network-based imaging modalities such as resting state functional magnetic resonance imaging (rsfMRI), which have the ability to provide new insights into the organization of cerebral connectivity and the process by which it functions.[3-10] Presently, the greatest limitation in bringing these technologies into clinical practice is the overwhelming complexity of the brain, and the challenges inherent in understanding the data derived from a system that is as intricate and variable as the human brain.

The Human Connectome Project (HCP) is a large-scale, publicly funded, multi-institutional brain mapping effort whose goal is to publish data related to the cerebral connectivity of healthy individuals.[11] The most recent report derived from HCP data provided a revised map of cortical regions which reclassified the traditional Brodmann's areas based on functional connectivity, degree of myelination, cortical thickness, and cross-correlations with previously published cortical parcellation schemes.[12] This landmark effort increased the number of cortical regions from Brodmann's 47 areas to 180 distinct cortical parcellations.[12] The result is a superior framework and common nomenclature for studying cerebral function and anatomy.

The challenges for us when studying and attempting to utilize this landmark study have been its daunting complexity and inaccessibility. The supplementary data alone span 90 pages of text.[12] By necessity, the data are presented in flat maps and other unfamiliar formats which are nonanatomic, lack contextual cues, and as a result are confusing to surgeons. Many areas are small and tucked into clefts of the cerebrum we rarely notice. As a result, it took the senior author 2 mo to firmly understand where these areas actually are, let alone our continuing work trying to grasp the exact connectional anatomy of each of these areas. Despite these challenges, we would argue that moving toward a nomenclature and anatomy which simplify the cerebrum to more manageable, rationally defined subunits opens the possibility for surgical outcomes to be defined in a more precise manner than "frontal" vs "parietal," for cerebral anatomy to be studied and analyzed in the way skull base anatomy has been studied for decades, and for true technical advances to occur toward further reductions in cerebral morbidity as we begin to better elaborate on the underlying connectional anatomy of cortical networks.

This multipart supplement aims to build on the work of previous neuroscientists and neurosurgeons to define the anatomy of the cerebral cortex in a surgically useful, gross connectional framework based on this parcellation scheme. It will sequentially define these cortical areas and demonstrate where they are on the brain surface. This atlas will further provide detailed maps of the functional and structural connections of each area. Finally, where appropriate, we provide our own insights into the significance of some of the patterns which arise from this analysis. First, however, we define the methods we utilized to construct the images in this atlas and provide an overview of the parcellation scheme.

METHODS

Modeling Parcellation Location on Cadaver Brains

Approval for this study was granted via our home institution's Institutional Review Board (IRB #3199). Human specimens were obtained from our institution's Willed Body Program with approval of the state's anatomical board. The cadaver brains were fixed in 10% formalin for at least 3 mo after removal from the cranium. Until the time of dissection, the pia-arachnoid membrane was left attached. After fixation, the meninges were removed and the cortical anatomy, including gyri and sulci, was identified.

Photographs of brain regions were taken from multiple angles and when necessary, gyri were retracted to identify parcellations located deep in sulci. The location of each parcellation was determined by careful comparison with inflated computerized brain parcellations from the Brain Analysis Library of Spatial Maps and Atlases (BALSA) database (https://balsa.wustl.edu) and from written anatomical descriptions provided in the supplementary neuroanatomical results from the Glasser study.[12,13] Adobe Photoshop CC 2017 (Adobe Systems, San Jose, California) was used to overlay parcellations on cadaver brains.

Resting State Functional Connectivity Maps

In order to create functional connectivity maps, averaged rsfMRI data from the BALSA database was uploaded into Connectome Workbench and visualized on inflated brains.[11,13] The "HCP500" dataset (June 2014 Data Release) provided by the HCP was used to create the resting state BALSA files.[13-18] HCP MRI data acquisition has been described in detail in previous publications.[15,19,20] Detailed descriptions of the pre-processing pipelines utilized for analysis of resting state functional connectivity data and creation of a "group averaged" resting state functional connectivity dataset mapped in relation to parcellation boundaries is outlined in detail in the supplementary methods of the Glasser study.[12]

Figures of parcellation-specific resting state functional connectivity are shown with interactive scene files based on the newly created CIFTI file format.[12,21] Utilization of these files allows for regions of interest (ROIs) to be placed on 1 of 180 parcellations to show associated connectivity. A resting state functional connectivity matrix of the averaged dataset was also used to easily denote functionally connected parcellations.[12] In an attempt to show areas that are more significantly functionally connected than other parcellations, we used a Z-score threshold of $\geq$20. Yellow-shaded parcellations on inflated brains in Connectome Workbench represent regions that have cleared this threshold. For clarity, we present left-sided (dominant) hemisphere data in this initial survey of results.

Creation of Volumetric Parcellation ROI

In the Glasser study, parcellation data were analyzed in the CIFTI format. This is a surface-based coordinate system termed greyordinates, which localizes regions on inflated brains.[21] This is in contrast to traditional file formats, which denote regions based on volumetric dimensions.[22] As a result, it is difficult to perform tractography analysis using ROI in a CIFTI file format. To convert files to the appropriate format, we used Workbench Command, which is a set of command line tools used to perform simple and complex operations within Connectome Workbench.[15] This allowed us to convert all 180 parcellations from a surface coordinate system to volumetric coordinates.

In order to ensure that the newly created ROIs aligned accurately on the brains for which tractography analysis was being performed, we created an averaged diffusion MRI brain from the same "HCP500" dataset on which the parcellations were based.[14-18,23-26] This created an averaged diffusion brain from the 449 subjects from which the parcellations were created and supplemented the tractography results from individual subject brains. The averaged diffusion brain was constructed in DSI studio using the batch-processing tool.[27,28]

Tractography

Publicly available imaging data from the Human Connectome Project were obtained for this study (http://humanconnectome.org, release Q3).[14-18,23-26] Imaging was analyzed on an averaged brain of 449 subjects, and also from 10 unrelated, healthy adult subjects (HCP Subject IDs: 100307, 103414, 105115, 110411, 111312, 113619, 115320, 117122, 118730, 118932).[14] 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 (GQI) for individual brains and q-space diffeomorphic reconstruction (QSDR) for averaged brain (12).[28,29] The diffusion sampling length ratio was 1.25.

Following registration to montreal neurologic institute (MNI) space, tractography with GQI and QSDR (12) was performed in DSI studio (http://dsi-studio.labsolver.org) using an ROI approach to initiate the fiber tracking from a user-defined seed region.[28-30] A 2-ROI approach was used to isolate tracts when necessary and all were tested for reproducibility.[31] Dissecting in MNI space allowed for the assessment of variability among subjects. 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. Tractography was stopped after reaching a length of 450 mm. In some instances, exclusion ROIs were placed to exclude spurious tracts or tracts inconsistently represented across multiple brains.

We determined connectivity between parcellations and characterized connections from a given parcellation through detailed inspection of the tracts in the averaged and 10 individual subject brains. We reported connections between areas that were consistent in both individual subjects and the averaged brain. There were rare instances in which a tract was consistent across individual brains but not present on the averaged brain, in this situation the tract was reported as real. Comparison between averaged and individual brains was necessary as each imaging modality provided distinct but valuable information. The average brain represented a conservative method to analyze major white matter tracts from a given region but excluded smaller tracts that may be consistently present. Individual brains provided analysis of smaller tracts but also contained fibers that were unique to the individual. As such, we thought it beneficial to compare tractography results between all of these modalities with an emphasis placed on identifying the major white matter bundles connected with each parcellation.

Literature Review of Parcellation Functions

As one of the goals of this study was to provide a practical neuroanatomical reference for the neurosurgeon, we thought it necessary to provide a concise and simplified summary of what we know thus far regarding the function of all 180 cerebral parcellations. The hope was that this information would integrate neuroanatomy and connectivity with up-to-date information on the specific functions of particular regions. We searched PubMed and Google Scholar for peer-reviewed references of the functions of cortical regions. We also utilized references in the supplemental results section of the Glasser study for additional sources.[12] We searched for the exact parcellation name, and when applicable, the derivative region from which it was subdivided. For example, for area 6ma we looked for the terms "area 6ma", "area 6m," "area 6a," and "area 6." This technique was used as roughly half of the 180 parcellations are newly described, but are named based on the original Brodmann scheme. We focused our efforts on human functional imaging studies, and looked at relevant ROIs from these papers in comparison to parcellation regions to determine if the description of the function in that paper was relevant.

Many of these areas are described with new names that are unique to this parcellation scheme. In situations where the area was a subdivision from a previously described area, we present the overall function of that area, and also data from the supplemental anatomic results section of the Glasser study to provide the rationale for the division.[12] For example, area 8 was previously divided into areas 8A, 8B, and 8C; however, in the Glasser study, area 8 was further divided into regions 8Ad, 8Av, 8BL, 8BM, and 8C. We provide the previous data to describe the functions of region 8A as well as data from the Glasser study to describe why this area was divided into areas 8Av and 8Ad. In other words, some of the newly parcellated areas have functional descriptions that are similar or the same as their neighboring parcellations with the only differentiating description being task-based fMRI studies from the Glasser paper used for the division. In other cases, the area is entirely unique, and we describe the Glasser data primarily along with any information related to the area from which it was derived.

DISCUSSION

Why Study Cortical Anatomy in This Level of Detail?

Obviously, this submission is an in-depth study of cerebral anatomy which dives into a substantial degree of detail not possible with previous methods. The obvious question is what to do with these data? The most obvious reason for going into this detail is that it provides a framework for asking questions and testing hypotheses. It is probably impossible to determine all of the relevant functions for a tract like the superior longitudinal fasciculus by just staring at it, but it is reasonable to ask what is running through the pathway when we know which areas provide fibers to the tract. Furthermore, it is clear that some parcellations straddle systems and switch between networks depending on the cognitive context,[12] and identification of these cross roads provides new insight into how networks function and how to preserve them.

Most importantly, such detail provides us a common nomenclature. Calling a part of the cortex the "parietal lobe" or the "dorsolateral prefrontal cortex" does not allow us to compare results or to apply observations into clinical practice as precisely as studying region "8C" or "PGs." We would argue our work allows for a more focused analysis that better describes the brain and its organization as opposed to studying the brain in nondescript terms that refer to entire lobes or gyri.

An Introduction to Complexity Theory and Cerebral Networks

For over a century, neurosurgeons have been performing cerebral surgery with a model of the brain that cannot possibly encompass a correct view of cerebral function.[32] Localizationism, the idea that certain functions are performed by specific parts of the brain, like many outdated models, does not always lead to correct functional predictions. For example, primary motor functions are usually found in the precentral gyrus.[33] However, such a model fails when we operate in patients with reorganized cerebral circuitry,[34] and it cannot begin to explain how to avoid damaging higher cognitive functions, which are difficult to localize.[1] We argue that to improve surgical outcomes, we need to embrace complexity and begin to restructure our thinking around the idea that we are cutting functional networks when we operate in the cerebrum.

The term "complex" does not merely signify that a system has a lot of parts, that it is difficult to study, or that it is poorly understood. Instead, the term "complex systems" refers to large networks of diverse, interconnected, interdependent, and adaptive parts.[35] In other words, to be "complex" a system needs to have a network of interconnected entities which interact with each other, usually in nonlinear ways.

Complex systems display some unique properties not seen in linear, randomly connected, or regularly interconnected systems. Most notable, complex systems demonstrate a property called emergence,[35,36] which is when a complex network and its nonlinear dynamics demonstrate behavior on the macroscale which cannot possibly be predicted a priori by the simple sum of the network's parts and their individual interactions.[36] Most higher cognitive functions are likely emergent phenomena that cannot be predicted simply by looking at the activation patterns of individual neuron action potentials.[36]

Complex networks also demonstrate non-Gaussian power law mathematical distributions within their static and dynamic structures.[35,37] While many relationships between variables vary in normal or near normal distribution, complex systems often vary in a power law fashion,[38] meaning that the distribution curve has a very long, broad tail. Height is a variable influenced by numerous, mostly independent influences, and it is roughly normally distributed. This means that as we move several standard deviations away from mean height, that the probability of finding extreme outliers approaches zero. For example, there has never been a 10-foot-tall person in recorded history, and a 20-foot or 100-foot tall person would be unthinkable. If height were distributed as a power law, then 100-feet tall people would be rare, but occasionally they would be seen. This means that very extreme outliers are uncommon but possible in complex systems.

The degree of connectedness of brain nodes (ie, the number of other areas an area is connected to) does not perfectly conform to a power law distribution, but it is closer to a broad tailed distribution than a normal distribution.[35] This means that while most areas of the brain are mainly connected to immediate neighbors, a few areas (so called "hubs") are interconnected to a large number of areas of the brain.[35]

Finally, complex networks are robust, meaning that they can withstand deletion of nodes.[35,39] Deletion studies, where nodes are removed from a network to determine the organizational effect on the network, have shown that power law networks are highly resilient to random deletions, meaning that the path length is relatively unchanged due to the loss of individual nodes.[39] However, targeted attack on the most highly connected nodes causes the network to fragment after deleting only a few nodes.[39] Robustness may also explain the early recovery of some neurological problems as the network might reorganize to perform a cognitive task without the injured area; it might also be a key way gliomas cause the brain to reorganize.

Small World Networks

One of the most influential papers of the past 20 yr in science was published by Watts and Strogatz in 1998.[40] In this mathematical study, they analyzed completely regular, lattice graphs (graphs where every node was initially only connected to its neighbors), and used computer simulation to randomly rewire one connection at a time.[40] They found that the path length (meaning the distance between any 2 nodes in the graph) decreased in a steep nonlinear fashion, dropping substantially when only a small fraction of the connections were rewired.[40] They termed this the small world phenomenon, and it has been shown to be a common organizational scheme in diverse complex networks including the internet and social networks.[41] Fundamentally this means complexity is governed by common mathematical principles regardless of the area of study, and that these mathematics are heavily driven by small world topology. The evidence suggests that brain networks follow small-world patterns of organization as well.[35,42]

Complex networks have been found to be self-organizing, meaning that they usually do not have a leader which drives the activity or static organization of the network. The small world organization is a result of self-organization as it is a logical effect of the need for the brain to achieve its static and dynamic goals with a minimal energy consumption.[42,43] Statistically, it is most efficient for areas to make the shortest axons possible, and so most areas should be primarily connected to their neighbors. However, as Watts and Strogatz[40] demonstrated, path length drops substantially when making a few long-range connections. Path length in the brain equals the number of synapses, and the increasing

synapse number needed for 2 distant areas to communicate slows long-range conduction, increases noise, and increases energy costs. Small world networks are the result of self-organization driven around these competing demands.[42,43]

There are many ways to describe brain networks; however, the one most accessible to us for surgery focuses on the major white matter connections in the brain, as they are demonstrable and disproportionately central to the proper functioning of wide-scale brain networks. Given that these tracts are the principle method by which 2 groups of nodes interact with each other, it is reasonable to conclude that they play a significant role in proper cognitive functioning.

Static vs Dynamic Connectivity

It is tempting to look at brain networks and their architecture and try to deduce the direction of information flow related to brain function. The reality, as usual, is far more complicated than this. Structural connections are meaningless without understanding function, and studies of functional connectivity have taught us that the functional connections of the brain are changing constantly.[44,45] Beyond this, standard rsfMRI provides statistical evidence that 2 areas coactivate with each other more than chance, but more nuanced analyses of so-called dynamic functional connectivity have shown that this approach is akin to opening the camera shutter at an automobile race for a few minutes and then pointing to the strongest blurs.[46-48] The brain is constantly altering its activity pattern depending on the context and cognitive task, and while areas A and B may coactivate for some tasks, areas A, C, and D may need to co-activate for others.[46-48]

Sorting out an already complex static network is hard enough without accounting for the thousands of possible metastable states for all situations. This work requires supercomputers, and the mathematical tools for this processing are in development. It is critical to note that the dynamic configuration of brain activities is constrained by the possibilities of the static brain network. For example, areas A, B, and C cannot talk to each other if they are not connected in some way, either directly or indirectly. Therefore, until dynamic connectivity is better understood, it is at least a good idea not to disconnect key parts of important cortical networks when possible.

Nodes, Edges, Hubs, and Rich Clubs

Graph theoretical metrics are not currently accessible to brain surgeons for clinical use. However, we believe they will eventually be available as they have the promise to answer key clinical questions. A brain graph analysis reduces the connections of the brain to a ball-and-stick graphical format comprised of nodes, which signify specific brain regions and edges, which are the lines signifying the connections between them.[35] It does not take a high level of exposure to this field of study to recognize that nodes are gray matter structures and edges represent their underlying white matter connections. The concept of how to define discrete brain nodes is a contentious one, but in almost all systems, most of the nodes are parts of the cerebral cortex, with nodes in thalamic and other subcortical nuclei included in some graphs. Either way, while a graph does not necessarily reflect the nature of the transformations enacted by various nodes, it does allow some basic hypothesis testing on the overall organization of the connectome.

A key question in graph theory is the definition of a hub, in other words a node which is extensively connected to many areas, and thus assumed to be the pathway involved in numerous systems. There are several ways to define such a hub. Degree centrality refers to the number of other nodes which connect to a node.[49] While simple to understand, this measure does not take into account the fact that a connection to a highly connected node suggests a greater degree of connectivity than a connection to a peripheral or low-degree node. This is corrected by measures such as eigenvector centrality and page rank centrality which take connectivity of neighbors into account.[49] Closeness and betweenness centrality consider the number of shortest paths through the graph which traverse a node.[49] Furthermore, highly connected nodes which are highly connected to each other comprise a "rich club."[49]

Does "hubness" indicate parts of the brain we should avoid destroying, and if so which measure is best? The answers to these questions are unknown and require additional study. Of note, some of the more well-known primary cortices, such as the primary motor cortex are not clearly hubs or uniformely in rich clubs. Others, like area 44, almost certainly are. Based on mathematical measurements of random vs targeted attacks on broad-scale networks (such as in the brain), it is likely that preserving hubs is critical in preventing cognitive networks from collapsing.[39]

What Parts of the Brain Are Truly Eloquent?

For decades, neurosurgeons have divided the cerebral world into "eloquent" brain and "noneloquent" brain with the dividing line between the 2 representing clinically evident neurological deficits when cutting into brain.[2] In this conceptual model of cerebral function, areas such as the motor strip where an injury would cause a motor deficit are "eloquent," and thus best avoided, while other areas of the brain, such as the anterior right frontal lobe, were more "silent" and safe to cut.

This is a system for organizing brain function which is simple, easy to teach residents, and completely inconsistent with common sense and scientific studies. We would argue that there are probably no legitimately "silent" areas of the brain.[2] All parts of the brain probably did not evolve as a decoration, a cerebrospinal fluid sponge, or a shock absorber, but rather evolved to perform some neurological function.[2] Thus, all parts of the brain are eloquent in some way. If you are skeptical of this, spend some time talking to a family member of a patient who has had significant right frontal lobe damage, and you will probably become convinced that there are consequences to losing this part of your brain.[50] These consequences are not glaringly obvious immediately after surgery in the recovery room.

This is not to argue that brain function is randomly distributed, or that some parts of the cortex are not more tolerant of injury than others. It is just that the model we work under presently fails to prevent neurological problems, especially in the context of higher brain functions. We would argue a better way to preserve such functions comes from network and complexity science, with different cortical nodes serving to coordinate with different networks under different contexts in order to achieve specific goals and execute key functions.

How Is Brain Surgery Possible if Everything Is Doing Something All the Time?

We know from years of experience that not all cuts in the brain lead to clinically apparent problems. Additionally, given the potential that a brain area could be involved in the function of a network centered in a distant part of the brain, we would argue that the tradeoff should be based on a more nuanced appraisal of the exact organization of the functional network than what the "eloquent" vs "noneloquent" model can yield. In other words, if we have to remove a part of the brain to resect a glioma, we should base the decision regarding which part to remove on a realistic assessment of risks to the neighboring brain networks vs the relative benefit of cytoreduction in a specific brain area.

It is important to note that as our understanding of cerebral functional anatomy, network organization, and macroconnectomics becomes more sophisticated, the idea that some parts of the brain are completely without consequence or functional risk when operating will become more problematic. This idea should be replaced with a view that we are trying to minimize the functional consequences of surgery and to preserve functional networks as much as possible given the functional and oncological starting points of a specific patient.

General Observations About the Parcellation Map and Its Nomenclature

Prior to a detailed study of individual brain regions, it is worth discussing several interesting features of the HCP parcellation map which are not immediately obvious at a cursory glance.

Many Areas Are New

The new HCP parcellation map defined 97 new cortical areas not previously published prior to their work, in addition to redefining the boundaries of others.[12] Thus, over half of the areas in the HCP parcellation scheme are new.[12]

Those of us familiar with Brodmann's areas will note that this map has largely supplanted them.[32] Most of Brodmann's areas have not survived the transition to a connectomic-based model of the brain. This map only utilizes 23 of Brodmann's original 47 defined areas in any form: areas 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 23, 24, 25, 31, 32, 33, 43, 44, 45, 46, and 47.[12] Of these, only areas 1, 2, 4, 11, 13, 25, 33, 43, 44, and 45 remain basically intact as Brodmann originally described them.[12,32] Thus, 79% of Brodmann's areas no longer remain in the current anatomic nomenclature of the cerebral cortex as he described them.

In many cases, the original areas were subdivided, and the Brodmann's number was combined with a suffix to designate the relative location of subdivisions within a particular area. For example, area 9 is now 3 areas: 9m, 9a, and 9p. Area 8 is now 5 distinct areas: 8BM, 8BL, 8AD, 8AV, and 8C. The original area 6 now contains 9 areas: 6ma, 6mp, 6a, 6d, FEF, 55b, PEF, 6r, and 6v. Other areas were named based on subdivisions of previous nomenclatures. For example, area 24 has long been subdivided.[51-53] This parcellation scheme divides area 24 further, creating 2 parts of area 24 prime, a24prime and p24prime, in addition to the more anterior a24 and p24, and the more dorsal 24dd and 24dv. Finally, some of the areas are subdivisions of previously re-organized areas. For example, the dorsolateral prefrontal areas 9 and 46 have long been co-associated more than Brodmann's scheme suggested.[54] Now in addition to the subregions of area 9 described above, there are subdivisions of the border areas 9-46, including 9-46 dorsal, and anterior and posterior regions of 9-46 ventral, a9-46v and p9-46v. This is in addition to area 46 proper. These confusing distinctions are made clearer in the relevant sections which follow.

Far more common than subdivision of Brodmann's areas are entirely new areas. All of the insular regions are redefined, as are all of the temporal and occipital regions. Most of the parietal regions are not based on Brodmann's areas, with the exception of some of the medial parietal and posterior cingulate regions (areas 5, 7, 23, and 31). Taken altogether, these findings raise questions of the relevance of teaching Brodmann's areas to future trainees.

Functional Anatomy Is Not Constrained by Our Anatomic Distinctions

A first run through the anatomic parcellations reveals a number of regions which were challenging for us to understand fully. Many of these areas sit entirely within a sulcus or straddle a gyrus into a neighboring sulcus. Others are confined to a specific gyrus. In some cases, the upper bank of a sulcus is functionally distinct from the opposite side. This is notably true for the superior temporal sulcus which has 4 distinct areas within its cleft. In the extreme case of the intraparietal sulcus, 7 different functional regions lie along the banks of the sulcus. In other instances, areas ignore gyral distinctions altogether and cross between gyri and sulci. For example, areas 9-46d and 46 straddle portions of the superior frontal and middle frontal gyri, running perpendicular to the axis of these gyri and the superior frontal sulcus. The bottom line is that while some areas are easy to understand based on our understanding of gross cerebral anatomy, parsing through these areas requires thinking differently about the brain.

No Area Is Left Behind

In our training, we frequently spent time focusing on anatomically obvious parts of the cerebrum, like the central sulcus, the pars triangularis, and the cingulate gyrus. Studying an unfolded map of the cortex, then refolding it, teaches you how much of

the brain we do not consider, yet which contains functional brain areas. The most obvious example of this is how many functional areas lie within sulci. Most neurosurgeons do not map the sulci when performing awake brain surgery, and transsulcal approaches are often viewed as ideal routes to minimize brain transgression to deep targets.[55,56] The fact that the sulci can possess unique functional areas which differ from the abutting gyri should make us rethink the wisdom that sulci always represent a better route for tumor resection. This may or may not be the case depending on the sulcus in question. The most obvious such area is the undersurface of the frontal and parietal opercula, which contains 8 functionally distinguishable brain regions (FOP1, FOP2, FOP3, FOP4, FOP5, OP1, OP2-3, and OP4) which differ from the lateral surface of the same opercula. In the end, these maps highlight the limited way we as neurosurgeons think about what is important and what is not in the cerebral cortex.

Why Does Studying This Matter?

The idea that a large part of the brain is "noneloquent" has deep roots in neurosurgical thinking and guides how we plan our surgeries, study our outcomes, and counsel our patients.[57] However, it is improbable that millions of years of evolution did not drive brain development toward creating excessive padding so-called eloquent brain regions. It is beyond question that there are not electrically silent parts of the brain, and what we view as noneloquent is really either compensable or redundant to functional networks. Thus, the eloquent/noneloquent distinction involves parts of the brain for which it is easy to understand what they do vs those which have subtle effects when lost or which cause more subtle problems with more poorly measured negative consequences.

We are not the first neurosurgeons to make this observation regarding the limitations of the eloquence/noneloquence concept in neurosurgery.[2] However, it is important to note that the need for cerebral surgery often means we need to cut into the brain, and it is without question that some cuts are safer than others. Thus, it is critical to be both aware of but not overreact to the idea that all of the brain is potentially necessary. The idea, rather, is to make good choices with our plans, choices which are more nuanced than statements such as "stay out of the motor strip" and "the right frontal lobe is safe."

Further, we would note that complex functions, like higher cognition and emotion, likely have complex networks and involve several cross modal communications. The connectional anatomy of the cerebrum globally is extraordinarily complex, likely beyond what our brains are capable of processing. Regardless, we would suggest that this complexity does not excuse the postmodern view that because it is so complex there is no reason to try to reduce that complexity to manageable subunits to study and to integrate into our thinking. By adopting a well-justified nomenclature, we can begin to minimize the complexity of these networks to something that can be tested and cross-communicated in ways which are more repeatable than merely localizing something to the parietal lobe. Thus, these parcellations give us a framework for moving forward toward truly connectomic-based surgery.

How Does This Level of Detail Change What We Think About Cerebral Surgery?

The obvious answer is it creates the possibility of working toward mechanisms for doing surgery that minimize damage to brain networks that we do not currently understand. This is obviously a lifetime of work, and the answer is that we really do not know what new insights will impact the surgical techniques we presently use.

There are a few more practical observations to consider. First, it is clear that our ways of describing locations in the brain are outdated and are in need of refinement. For example, staying out of the motor strip has long implied staying out of the precentral gyrus, but this is not really accurate, as the primary motor area only comprises half of the gyrus with the anterior half of the gyrus containing other areas which likely perform related but different tasks.[12] In addition, the numerous areas which straddle sulci onto different portions of different gyri or wrap around an angle like the frontal pole or the interhemispheric cleft show us that describing function in terms of gyri and sulci is inadequate for describing where function is truly located. The entirety of the work in this atlas was performed for the sole purpose of moving toward a more precise, universal nomenclature.

Another point this raises is whether we should be focusing more attention toward looking for function in places we do not currently consider relevant. For example, most neurosurgeons performing awake brain surgery begin cortical mapping shortly after exposing the cortex and prior to any definitive dissection. The presence of many functional areas inside the depths of sulci, straddling sulci, and sitting on the underside of opercular cortices raises numerous questions about whether we are ignoring much of the brain when we plan our surgeries. The popularity of transsulcal approaches to deep-seated targets is conceptually pleasing, but counterproductive if the cortex at the depth of a sulcus is more critical to a functional network than the cortices at the surface. We have long ignored the idea that the sulci contain brain in the walls and floors. Perhaps brain mapping in certain areas might be best preceded by a sulcal dissection to better visualize the areas that matters.

Limitations

Like any effort to map the cerebrum, the limits of the technology utilized are a key factor in how definitive our conclusions can be. While brain mapping technologies have provided an unparalleled ability to define the wiring diagram of the brain, they are not infinitely applicable to all details of brain connectivity.

A Question of Scale

It is critical to acknowledge that this is a macroscale map of brain connectivity, and is focused solely on gross anatomy and large white matter bundles. It is not an exhaustive wiring diagram of the brain. Most of the axons in the cerebrum are

local and terminate in the same gyrus from which they originate. In using diffusion imaging, we are studying a small subset of fibers that are long range connections, which, while they may be the disproportionately important ones, are in the minority. Presently, techniques for mapping brain connections at the microscopic scale, such as with electron microscopy, take hundreds or thousands of work hours to delineate connections at the scale of cubic nanometers. Thus, they cannot realistically be used to map the brain on a large scale.

The Limits of Deterministic Tractography

In order to make sense of the movement patterns of water in the brain, diffusion weighted imaging programs process data to create maps of tracts in 2 steps. First, the fractional anisotropy map is decomposed into the eigenvector or eigenvectors within an individual voxel to create a map of direction or directions within each voxel. While earlier platforms like diffusion tensor imaging only modeled the dominant eigenvector in a voxel, newer generation models like diffusion spectral imaging collect diffusion plans in more than one direction.[28] Second, the tractography step needs to determine how to join the eigenvectors from various voxels into a series of vectors which align with a white matter tract. This can be done by probabilistic or deterministic methods, the latter of which (used in this study) joins the vectors sequentially from an ROI depending on thresholds for angular direction change and vector size.

The data we used from the Human Connectome project were collected using rigorous acquisition parameters, thereby allowing us to resolve crossing fibers to the best extent currently possible. Nevertheless, there are limitations. We cannot follow fibers to their cortical targets with extreme certainty: the fibers begin to spread out as they enter the gyrus and this prevents the tractography program from following them this far. Also, while DSI can resolve complex eigenvector combinations within a voxel, it is not infinitely able to distinguish all possible small fibers which may be crossing within a voxel. This may cause some small connections to fall out of our analysis. Whether tracts so small that they cannot influence the eigenvector complex within a voxel are clinically or neuropsychologically relevant is unclear, but worth asking. Either way, it is important to note that we cannot guarantee that our methods do not miss some small connections, or that if a connection was not found then no connection exists.

Modeling Functional Connectivity As an Average

By using an ROI method to summarize resting state connectivity based on a thresholded Z-score, we are following standard methods frequently published in the field; however, this is only a partial view of the patterns of connectivity in the brain, and it is important to be aware of what it is missing.

First, a threshold for a Z-score suggests that at a Z-score of 20.0, 2 areas are functionally connected in a meaningfully way, and that at 19.9 the coactivation between these areas is co-incidental noise. Common sense tells us that this is probably not true, and that functional connectivity strength lies along a spectrum. However, it is quite challenging to address this level of complexity in our initial analysis of the human connectome. Furthermore, by thresholding the data, some basic patterns can be identified, which can be clarified later in more detail. The critical point here is that it is important not to fixate too much on the lack of functional connectivity between 2 areas.

More importantly, brain connectivity does not work in an average fashion, and this is the method of data presentation. As described above, connectivity changes on a near continuous basis and a given area may change affiliations between networks fluidly depending on the cognitive context. Thus, dynamic connectivity is the reality, and our maps are providing average connectivity over the time period studied. This is analogous to leaving a video camera on in the operating room for a day and then looking at the video and listing the people most commonly in the room. This is better than no information, but does not give you a true sense of the flow of an operation. This is likely the mechanism of differing Z-scores between connectional pairs, and may be the reason why a connection with a lower Z-score may be more critical than a connection which cleared our threshold. The methods to deal with such complexity are in evolution, but this is the future. In the meantime, we are providing average connectional strengths over time.

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