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A Comprehensive Review of Brain Connectomics and Imaging to Improve Deep Brain Stimulation Outcomes

Joshua K. Wong, MD[1,*], **Erik H. Middlebrooks, MD**[2], **Sanjeet S. Grewal, MD**[3], **Leonardo Almeida, MD**[1], **Christopher W. Hess, MD**[1], **Michael S. Okun, MD**[1]

[1]Fixel Institute for Neurological Diseases, University of Florida, Gainesville, Florida, USA

[2]Department of Radiology, Mayo Clinic, Jacksonville, Florida, USA

[3]Department of Neurosurgery, Mayo Clinic, Jacksonville, Florida, USA

Abstract

DBS is an effective neuromodulatory therapy that has been applied in various conditions, including PD, essential tremor, dystonia, Tourette syndrome, and other movement disorders. There have also been recent examples of applications in epilepsy, chronic pain, and neuropsychiatric conditions. Innovations in neuroimaging technology have been driving connectomics, an emerging whole-brain network approach to neuroscience. Two rising techniques are functional connectivity profiling and structural connectivity profiling. Functional connectivity profiling explores the operational relationships between multiple regions of the brain with respect to time and stimuli. Structural connectivity profiling approximates physical connections between different brain regions through reconstruction of axonal fibers. Through these techniques, complex relationships can be described in various disease states, such as PD, as well as in response to therapy, such as DBS. These advances have expanded our understanding of human brain function and have provided a partial in vivo glimpse into the underlying brain circuits underpinning movement and other disorders. This comprehensive review will highlight the contemporary concepts in brain connectivity as applied to DBS, as well as introduce emerging considerations in movement disorders.

[*]**Correspondence to**: Dr. Joshua K. Wong, Fixel Institute for Neurological Diseases, University of Florida, 3009 Williston Road, Gainesville, FL 32608, USA; joshua.wong@neurology.ufl.edu.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution;
(2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
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J.K.W.: 1A, 1B, 1C, 3A, 3B
E.H.M.: 3B
S.S.G.: 3B
L.A.: 3B
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DBS is an innovative therapy that can be applied for specific cases of movement disorders, but has been also used in epilepsy, chronic pain, and some neuropsychiatric conditions. Advances in biomedical technology have catalyzed the field of neuromodulation, particularly in movement disorders, and the field has evolved from the use of permanent ablative procedures to an approach utilizing neuromodulation-based strategies. DBS has emerged as a "less destructive, adaptable, and partially reversible" technique that can be applied to avoid the known complications following bilateral ablative procedures.[1] Recently, there has been an emergence of an ablative technique called focused ultrasound; however, we will not cover this topic.[2-4] Improvements in MRI technology have provided tools to characterize the complex basal ganglia and related circuitry. Collectively, many studies have suggested that a more wide-spread cortical and subcortical network may underpin much of the neuromodulatory effect. Herein, we review the potential role of MRI-based brain connectivity measures within the field of DBS. We focus much of the discussion on movement disorders given that this neuromodulation area is the most developed.

A Brief History

Historically, DBS has focused on modulation of the subcortical gray matter. This approach was partially based on early animal models of Parkinson's disease (PD) that revealed reduction of motor symptoms following lesioning of the STN, thalamus, and globus pallidus internus (GPi).[5] However, as technology has improved, our understanding of the pathophysiology underpinning neurological disorders and the mechanisms underpinning DBS has transitioned from a local target model to also include whole-brain network-based interactions. In 2005, Sporns and colleagues proposed a novel strategy to approach the analysis of whole-brain function.[6] Noting the increasing prevalence of large databases and computational bioinformatics, the researchers suggested examining the anatomical relationships across the brain rather than focusing solely on local regions. The term "connectome" was thus coined to convey the idea that comprehensive analysis of whole-brain data could provide insightful information to drive our understanding of the underlying brain circuitry. This paved the way toward utilizing "connectivity based" metrics as one of the major components within the connectome.

Expanding upon classical "localizationist" theories of brain function, modern neuroscience has begun to investigate a more complex, network-based hypothesis. The interest was fueled by the fact that many disconnection syndromes could not be explained solely by a localizationist approach. Although descriptions of elaborate anatomical pathways date back to the early 20th century, contemporary techniques have now introduced more sophisticated viewpoints.[7] Tract-tracing studies of a macaque, for example, facilitated many insights into the network theory. Anatomical connectivity data from macaque brains were organized into a digital repository known as the "collation of connectivity data on the macaque brain" (CoCoMac; http://www.cocomac.org). The CoCoMac database provided a vast directory for

computational neuroscience analysis and exploration. This CoCoMac approach discovered that cortical regions had unique "connectional fingerprints."[8] These fingerprints could be used to describe groups of neurons that shared similar functional properties or alternatively shared electrophysiological properties. Furthermore, all fundamental components within a fingerprint were also found to share similar degrees of connectivity with other, more distant regions of the brain. Early intraoperative electrophysiology studies also identified topographical differences in local field potential (LFP) activity within DBS targets, such as the STN, further supporting the notion of an intricate communication network.[9,10]

Analysis of these connectivity fingerprints was then correlated with functional activity. Whereas early studies relied on techniques such as single-photon emission computed tomography or PET, the discovery of blood-oxygen-level–dependent (BOLD) MRI was a precursor to the dawn of brain connectomics. BOLD MRI relies on the detection of regional increases in the concentration of oxygenated hemoglobin with respect to time and facilitates many advantages over older techniques, including ease of repeated measures, an improved safety profile, and better anatomical accuracy. Early functional MRI (fMRI) studies examined the task-dependent change in BOLD signal as a function of stimulus-based neuronal activity (i.e., task-based fMRI). Although spontaneous fluctuations in the BOLD signal at rest had been known for some time, they were largely considered to represent noise. It was not until 1995 when Biswal and colleagues published a landmark article showing synchrony in these spontaneous fluctuations between multiple brain regions, giving birth to the field of resting-state functional MRI (rs-fMRI).[11] Whereas task-based fMRI is a reliable tool for investigating neuronal response to various stimuli, rs-fMRI facilitates the exploration of baseline brain connectivity within numerous brain networks.

As we understand more about neurological and psychiatric diseases at the whole-brain-network level, our mindset for future therapeutic intervention has also slowly begun to shift. Several ideas have been proposed to adapt the existing approach toward functional stereotactic neurosurgery and neuromodulation. In 2012, Henderson framed the concept of "connectomic surgery," using a diffusion tensor imaging (DTI) tractography method for targeting in DBS for movement disorders surgery.[12] Similarly, Lozano and Lipsman suggested that many movement and other neurological diseases need to be reinterpreted as disorders of circuit function or disorders of the network— coining the term "circuitopathies."[13] We will briefly review the modern techniques used in connectomic surgery. A summary of these new approaches and the chronicle of events leading up to the modern era are illustrated in Figures 1 and 2.

Advanced Techniques

To date, the mechanism of action of DBS is not entirely understood. Initial research focused on the electrical field generated and how it interacted with surrounding brain tissue in patients. Early studies modeled a spherical electric field in a uniform biomaterial centered on the DBS contact and termed this the volume of tissue activation (VTA).[14] The VTA represented a biophysical estimation of brain tissue receiving electrical current.[14,15] VTA analyses quickly became the primary method to refine neurosurgical targeting in DBS. VTA maps were superimposed with neurosurgical atlases and led to the creation of probabilistic

brain atlases (PBAs).[16] PBAs mapped the most frequently stimulated brain regions and correlated them with clinical outcomes.

VTA analysis was further refined as diffusion MRI technology improved to incorporate electric field modeling in an anisotropic medium. Essentially, previous VTA models were created under the assumption that the DBS lead was surrounded by a homogeneous material with uniform, directionally independent electrophysiological properties. in vivo measurements have shown that this is not the case.[17] Current VTA analysis now involves the estimation of conductivity/resistivity of the gray and white matter tissue adjacent to the DBS lead. This approach paved the way to "patient-specific analysis." VTA models are now specific to the DBS programming parameters and gray/white matter orientation for individual patients.[18] Although these models still lack high precision because of oversimplification of the model, variability in the electrode localization process, and heterogenous parcellation schemes, they provide tremendous insights into the volume of tissue potentially affected by specific DBS settings and allow a crude comparison within and between patients. Importantly, these VTA models are largely meant to estimate the potential volume of tissue that is affected by the stimulation, but many questions remain about the physiological effect within the VTA that may vary significantly based on other parameters, such as frequency and pulse width.

"Functional connectivity" is a term that has emerged to describe the analysis of regions of the brain that collaborate to complete a similar objective. In the context of DBS, rs-fMRI has emerged as a popular tool to describe networks of various brain regions and how they are related with respect to a clinical phenotype. These profiles, for example, have identified networks that have been associated with various pathological conditions, such as PD, Alzheimer's disease, depression, and schizophrenia.[19] Several methods of rs-fMRI analysis exist (e.g., independent component analysis, seed-based correlation, etc.), but incorporation of VTA modeling has made seed-based approaches common by use of the VTA to serve as a seed region for correlation of connectivity with distant brain regions. It is important to remember that most studies using this approach are inferring that regions of the brain with functional connectivity to the region of stimulation are affected by the stimulation. This assumption may or may not be true. Additional studies are needed to understand the true stimulation effect on these distant brain regions.

"Structural connectivity" is a term that has emerged to describe the white matter axons that connect various brain regions to one another. With the development of DTI technology, advanced mathematical algorithms have been able to indirectly model axonal fibers from the passive diffusivity of water obtained during an MRI diffusion sequence. Prediction algorithms based on the direction of water flow from a voxel-to-voxel basis can then reconstruct axonal fibers throughout the entire brain. The structural connectivity data can then be used for DBS analysis, such as using the estimated VTA as a seed region to analyze white matter tracts that are potentially affected by the stimulation. The true effect on these fibers is speculative and may be influenced by numerous factors, such as frequency, pulse width, etc. These structural connectivity maps are becoming more commonly used in PD, essential tremor (ET), dystonia, and other movement disorders.

Recently, the field of DBS in movement and other disorders has shifted toward network-level analysis of DBS optimization. Calabrese and colleagues proposed in 2016 that patient outcomes and clinical efficacy could be improved by targeting the affected network circuitry, rather than focusing on specific individual structures.[20] A combination of functional and structural connectivity techniques has been used to identify profiles in patients undergoing DBS. The current review highlights connectivity profiling for various common applications of DBS, though, notably, most of the literature is in movement disorders. A graphical visualization of the applications is shown in Figure 3.

PD

There have been extensive studies in connectivity profiling for DBS in PD; we will highlight a few key studies and summarize additional representative studies in Tables 1 and 2. Our search strategy is available in the Supporting Information supplemental materials.

The STN is the most common target worldwide for PD DBS. Neurophysiological studies have suggested a tripartite functional organization of the STN in humans.[21] One study combined structural connectivity data with LFP recordings to map the structural organization of the STN.[22] Profile analysis found that the dorsolateral region had high connectivity to the motor cortex and premotor cortex (pMC), whereas the ventral region had strong connectivity to the amygdala, hippocampus, and other medial temporal structures. Although this finding did not entirely concur with previous anatomical literature, this study was limited to testing within the boundaries that could be reached by the DBS electrode trajectory. The researchers interpreted the electrophysiology in this study as an insight into the underlying and complex circuitry of the human STN.

A recent study used structural connectivity profiles to characterize the efficacy of STN DBS on motor symptoms in PD.[23] Patient-specific VTA models were created and combined with structural connectivity data into a connectivity matrix. The matrix represented connectivity strength of voxel groups given a set of DBS programming parameters. Analysis of this matrix found that there were certain stimulation connectivity profiles that were more effective for rigidity, bradykinesia, and tremor. For rigidity, the researchers observed that stronger connectivity to the supplemental motor area (SMA) and prefrontal cortex (PFC) provided greater clinical benefit. For bradykinesia, the researchers found that low-voltage stimulation (1–2 V) of tissue with strong connectivity to the SMA provided relief of clinical symptoms. For tremor, activation of brain regions with connectivity to the primary motor cortex (PMC) provided the greatest benefit. Overall, this study suggested that within the complex connectivity network of the basal ganglia, activation of different connectivity profiles led to varied benefits for individual PD motor symptoms.

Few studies have examined the connectivity associated with GPiDBS for PD. Middlebrooks and colleagues utilized a structural connectivity analysis to segment the GPi based on fiber pathways to 10 predefined targets—caudate, globus pallidus externa (GPe), PMC, pedunculopontine nucleus, PFC, putamen, SMA, STN, SN, and thalamus.[24] Probabilistic tractography estimated the connectivity of each voxel within the GPi with the predefined targets. The voxel data were averaged as a group and modeled to create a parcellation map.

This mapping was performed on 11 patients who underwent unilateral GPi DBS for PD. Patient-specific VTAs were also calculated based on programming parameters documented at the 6-month postoperative visit. When correlated with clinical data, activation of the GPi segments that were most connected to the PMC and SMA/pMC showed the greatest degree of improvement in the UPDRS Part III.

Akram and colleagues used structural connectivity profiles of ventralis intermedius nucleus (VIM) of the thalamus DBS to visualize the dentato-rubro-thalamo-cortical tract (DRTC) in PD patients with debilitating tremor.[25] Conventional MRI techniques lack the capability to delineate the subnuclei boundaries within the thalamus. By analyzing structural connectivity, the thalamus could be mapped to fit the connectivity relationships with the cerebral cortex and were found to correlate well with previously defined anatomical surgical atlases. When correlating with clinical outcomes, patients had the best response when the stimulated thalamic area had strong connectivity with the contralateral dentato-thalamic region—suggesting that modulation of the DRTC was important.

One limitation of connectomic analysis for DBS has been the availability of high-quality raw data. Patient-specific modeling studies published in the literature typically report on <50 patients. To address this concern, Horn and colleagues proposed using publicly available databases of healthy patients that contain large volumes of clinical data. In 2017, Horn and colleagues combined functional and structural connectivity data of open-sourced connectome databases to build a mathematical model that predicted STN-DBS response in a PD test population.[26] The model incorporated radiographic data from a healthy control population and a PD population with the Parkinson's Progression Markers Initiative (PPMI).[27] In the healthy control population, functional connectivity data from 1,000 subjects were acquired as part of the Brain Genomics Superstruct Project.[28] Structural connectivity data were acquired from 32 subjects as part of the Human Connectome Project at Massachusetts General Hospital.[29,30] In the PD population, both functional and structural data were acquired by the PPMI database. These data were combined to create a comprehensive connectivity profile by incorporating a patient-specific VTA and DBS lead location data of a completely different group of patients who underwent bilateral STN DBS in Germany. The connectivity profile was able to predict the post-DBS percent change of the UPDRS Part III within 15%. It was also able to identify 1 patient who had a suboptimal response (initially worsening of UPDRS-III), but was able to obtain predicted therapeutic benefit after treatment of concurrent depression. This study proposed several novel approaches to DBS management. First, functional and structural connectivity profiles have strong correlations with clinical outcomes, but both profiles were found to be independent predictors of response. Second, connectomic data could be taken from entirely unrelated populations to build clinically relevant connectivity profiles. This concept is particularly noteworthy in that DBS for rare or unique indications can utilize large, publicly available connectome data sets in prediction modeling rather than having to slowly accumulate data over time. Last, connectivity profiles built upon connectomic data from a healthy control population versus a disease-matched population had similar results in predicting the clinical response of DBS. The last point is under constant debate given that although clinical outcomes may appear similar, the analysis and inference of healthy control data clearly do not represent the

connectivity state of a specific disease state. Future studies will be needed to investigate this question.[31]

Bioinformatics and computational biology are increasingly being utilized in medicine. In one example, a study created a computational basal ganglia model that simulated thalamo-cortico interactions through the direct, indirect, and hyperdirect pathways.[32] This model mimicked the excitatory and inhibitory output in response to various input parameters. The model was combined with structural connectivity data and behavioral testing to clarify the role of the basal ganglia in motor control. Whole-brain structural connectivity was computed using the open-source PPMI database. Patient-specific VTA models were not used, but instead activated fiber tracts were defined as those traversing through the coordinates of the DBS contact within a 1-mm sphere. Lesions of the computation model were introduced as disruptions of signaling pathways between network nodes. Effects of STN DBS were introduced as a modulation of the firing rate of STN which led to modulation of GPi signal output to the cortex. Analysis of this model suggested that STN DBS had a strong effect on the hyper- and indirect pathways. Neuromodulation led to faster reaction times with modifications to the cognitive aspects of motor preparation and execution. There was also increased movement velocity, but with an associated increase in trajectory errors and erroneous movements. The findings in this study provide strong support for existing PD network models of motor control.[33-35]

ET

As biotechnology evolves, novel methods are emerging to advance our understanding of neuroanatomy and enhance our in vivo visualization techniques. This change in technology has driven the growth of structural connectivity-based segmentation of many deep gray nuclei. In 2011, one study examined 6 patients who underwent bilateral VIM DBS for ET.[36] Structural connectivity data were used to conduct “connectivity-based thalamic segmentation” based on connectivity to seven cortical targets—the PFC, pMC, PMC, primary sensory cortex, temporal cortex, posterior parietal cortex, and occipital cortex. This technique provided an alternative method to visualizing the thalamus rather than the use of the existing anatomical atlases. Connectivity profiles were created based upon the location of the most effective DBS contact with respect to the segmented thalamus. Profiles were correlated with clinical outcomes, and the data revealed that DBS contacts in the thalamic region that had the strongest connectivity to the pMC yielded the greatest degree of tremor suppression. The study, however, also revealed that the anatomical location of this thalamic region was highly variable. Variability between structural-connectivity–defined segmentation and a rigid anterior commissure/posterior commissure coordinate space between and within patients was also replicated and demonstrated by Middlebrooks and colleagues.[37]

A similar study utilized structural connectivity data to segment the thalamus into regions based on their connection to cortical regions. This study also updated the connectivity profile to include patient-specific VTA models.[38] The thalamus was divided into regions based on connectivity strength to the PMC, primary sensory cortex, SMA/pMC, PFC, occipital lobe, temporal lobe, and parietal lobe. DBS lead locations and patient-specific VTA

models were generated using the Lead-DBS MATLAB toolbox (The MathWorks, Inc., Natick, MA).[39] Profile analysis revealed that stimulation of thalamic regions with strong connectivity to the SMA/pMC was associated with greater tremor suppression.

Other studies have highlighted the tremor suppression associated with stimulation of the DRTC—a fiber tract that connects the dentate nucleus with the red nucleus, thalamus, and PMC.[25,40-42] Akram and colleagues found, in a small series of ET and PD patients, that greater VTA overlap with the DRTC was present in patients with better tremor control.[25] In contradiction, Nowacki and colleagues was unable to reproduce the findings of greater tremor improvement with DRTC stimulation using four different tractography methods.[41] As opposed to the previously discussed ET studies, which used patient-specific data, Al Fatly and colleagues found similar connectivity associated with VTAs in the posterior subthalamic area, and these VTAs correlated with greater improvement in tremor when using normative connectome data.[40]

The summation of these studies highlights the complexity of targeting within and around the thalamus for ET. Adding to the challenge, studies have used a variety of connectivity measures, including patient data of variable spatial and angular resolution, as well as normative connectome data. Beyond these technical differences, tremor benefit is likely multifactorial where variation in surgical technique, stimulation settings, and outcome variables have all contributed to the mixed findings. For instance, it has been suggested that greater tremor control with DRTC stimulation may also be accompanied by an increased incidence of stimulation-induced ataxia, a common side effect of VIM DBS that is less frequent with caudal zona incerta stimulation—and perhaps more anterior VIM/ventralis oralis stimulation.[43,44] Additionally, outcome endpoints within studies may be an additional confound given that most connectivity investigations in ET DBS unfortunately have very short follow-up intervals. To date, the evidence suggests that patients with more subthalamic VTA locations may fare worse than those with thalamic stimulation when followed beyond 3 years.[45] The field will benefit from larger studies with longer clinical follow-up periods.

Functional connectivity is less well studied than structural connectivity in ET DBS. In the Al Fatly and colleagues study, normative functional connectivity data consisting of rs-fMRI from 1,000 healthy subjects were combined with structural connectivity data to create a voxel-based statistical map which predicted optimal clinical outcomes. Functional connectivity profiles were largely concordant with structural connectivity data. The study highlights the importance of the pre- and postcentral gyri, as well as the superior and inferior cerebellar lobes, as targets of neuromodulation.[40] Rather than use normative connectome data, Gibson and colleagues assessed BOLD signal change during active VIM-DBS stimulation in a series of ET patients.[46] In line with other studies of structural and functional connectivity, stimulation-induced activation of cerebellar, sensorimotor, SMA, brainstem, and thalamic regions was present in patients with greater tremor improvement. Importantly, incidence of stimulation-induced side effects was correlated with activation in pre-, post-, and subcentral regions. These findings could potentially explain the more anterior stimulations uncovered in the Pouratian and colleagues and Middlebrooks and colleagues cohorts.[36,38]

Dystonia

A recent study used functional connectivity data to create profiles to characterize network-level differences between patients with dystonia and dystonic tremor (DT), ET, and healthy patients.[47] Tasked-based BOLD fMRI data were acquired during a force-grip task with low and high degrees of visual feedback. Change in BOLD ($BOLD_{\Delta}$) amplitude was calculated by examining the differences in signal intensity during the low- versus high-visual-feedback task. This difference was applied to network-wide voxel analysis of the fMRI data and used to compute functional connectivity. This study found that patients with dystonic tremor had decreased functional connectivity with the supplemental motor cortex, inferior parietal lobe, and cerebellum when compared to patients with ET. Functional connectivity was decreased between the GPi and premotor/supplemental motor cortices in both DT and ET; however, connectivity in DT was much more affected. This study suggested that distinct neural signatures could be identified in various movement disorders, and that connectivity profiles could potentially provide helpful information in differentiating the heterogeneous spectrum of tremor syndromes.

Obsessive-Compulsive Disorder

Efficacy of DBS in psychiatric conditions has been more variable than other neurological conditions. It is thought that the heterogeneity of psychiatric disease suggests a brain-wide network dysfunction for which there is no single universal target for modulation. One study investigated the effects of DBS on the anterior limb of the internal capsule in patients with obsessive-compulsive disorder (OCD).[48] The researchers created structural connectivity profiles of 22 patients and found that clinical improvement was associated with neuromodulation of tissue that had strong connectivity with the medial and lateral PFCs. Specifically, they found that connectivity to the right medial PFC predicted a good response and connectivity to the orbital frontal cortex predicted a poor response.

Another study examined a personalized technique for DBS targeting in OCD.[49] A prospective, randomized, double-blinded study was conducted of 7 patients who underwent bilateral DBS of the striatum to strategically reach projections from the PFC. Two DBS contacts were positioned in the nucleus accumbens and two were positioned within the caudate head. Before DBS implantation, patients underwent a task-based fMRI study in which they were shown images of common triggers to OCD symptoms. A connectivity profile was generated for each patient by combining fMRI provocation data, structural connectivity, and patient-specific VTA data. Analysis of the connectivity profiles revealed that patients achieved the greatest degree of symptomatic relief when stimulation regions defined by the VTA and structural connectivity matched the cortical regions activated during the provocation task. This study highlighted the value of identifying patient-specific connectivity profiles and the feasibility of personalized DBS targeting.

Tourette’s Syndrome

Tourette’s syndrome (TS) is a heterogenous disorder with a broad phenomenology of motor and vocal tics. It can similarly be painted as a complex global network dysfunction disorder

for which there may not be a universal target for modulation. TS is also associated with neuropsychiatric comorbidities and has critical dysfunction of frontal, limbic, and motor networks.[50-52] Jo and colleagues investigated the functional global connectivity of 5 TS patients in response to bilateral thalamic DBS of the centromedian and parafasicularis complex (CMPf).[53] The CMPf is a unique target in that its location allows connectivity into the sensory, motor, and limbic circuitries.[54] These 5 patients underwent intraoperative fMRI with simultaneous high-frequency bipolar stimulation of the most dorsal contact and most ventral contact. Patients were then evaluated 3 months postoperatively for tic suppression in three testing conditions: (1) sham stimulation, (2) dorsal stimulation, and (3) ventral stimulation. Correlation with fMRI data revealed a complex network pattern of activity corresponding to clinical symptoms. Several areas of increased and decreased BOLD activation in the basal ganglia/thalamocortico, cortical motor, and limbic networks were observed. Overall, modulation of the sensorimotor cortex, insula, and Brodmann's area 8 was associated with reduced motor tics whereas modulation of the anterior cingulate cortex, nucleus accumbens, and temporal lobe was associated with reduced vocal tics. Larger studies are underway utilizing the International Tourette DBS Registry and Database.

Epilepsy

DBS earned U.S. Food and Drug Administration approval for epilepsy in 2017. Given that the use of DBS within the field of epilepsy remains in the early stages, several targets for the neuromodulation of epilepsy have been proposed. Middlebrooks and colleagues investigated stimulation of the anterior nucleus of the thalamus for refractory epilepsy.[55] Whole-brain functional analysis by rs-fMRI and VTA analysis found that DBS patients who experienced >50% reduction of seizure frequency had distinctly different functional connectivity patterns than those who had <50% seizure reduction. Specifically, greater connectivity between the VTA and multiple nodes in the default mode network (DMN) was present in DBS responders. One prevailing feature among epilepsy patients was a decreased baseline DMN connectivity that is also correlated to seizure frequency.[56,57] Additionally, the DMN demonstrated a reactive property given that there have been observations of DMN node deactivation at seizure onset and reactivation at seizure termination.[58-61] This may suggest that this particular connectivity profile represents treatment resistant epilepsy, but further studies are required to fully characterize this network.

Chronic Pain

One small study examined 7 patients with refractory chronic cluster headache who underwent DBS in the ventral tegmental area.[62] Structural connectivity data were used to identify the optimal target for stimulation. Connectivity profiles were created to characterize the effect of DBS on headache load (HAL) over a 2-week period. VTA was estimated using methods described by Astrom and colleagues.[63] Response to DBS was defined as a sustained 30% decrease in HAL. The connectivity profile of responders suggested that neuromodulation of the trigeminohypothalamic tract was an important component in cluster headache relief. Although the exact pathophysiology of cluster headache remains unclear, this study was consistent with previous observations that characterized cluster headache by

the absence of structural lesions on MRI brain while having abnormal function in the hypothalamus on PET.[64]

Limitations and Pitfalls

Brain connectomics has provided an unparalleled in vivo glimpse into the function of the human brain. Although many questions remain to be answered, the potential impact in clinical medicine has only recently been materializing. There are many barriers that have limited the clinical translation of this technology to DBS, several of which merit discussion.

In DBS, millimeter-to-submillimeter accuracy may be needed to ensure clinical efficacy and prevent stimulation-induced side effects. Inherent distortion in MRI is amplified with echo-planar imaging sequences that commonly serve as the basis for DTI and BOLD imaging. Geometric distortions, such as stretching or compressing of the brain in the phase-encode direction, misregistration of voxel position, and signal dropout, can severely affect accuracy. Several methods have been developed to help mitigate these distortions, but such postprocessing methods are also subject to inaccuracy under certain conditions. Additionally, spatial resolution has traditionally been limited in fMRI and DTI. Historically, voxel volumes upwards of 15 mm^3 (2.5 × 2.5 × 2.5 mm) were commonly utilized, and this technique presents issues when assessing submillimeter-millimeter accuracy required for some DBS applications. The recent advent of two-dimensional acceleration techniques, such as simultaneous multislice acquisition, have improved spatial resolution (e.g., commonly on the order of 3–4 mm^3 [1.5 × 1.5 × 1.5 mm] in DTI) and reduced image acquisition time.

Patient motion is a well-known issue hampering DTI and fMRI imaging, and this problem can induce both false positives and false negatives. This problem is amplified in patients with movement disorders, adding to the difficulty with advanced imaging. In our experience, we have found that effective patient communication, careful head packing, and careful consideration of MRI acquisition and postprocessing methods can dramatically reduce the number of patients with unusable imaging data.

Another important consideration is the inherent limitations of fiber tracking. Many potential biases exist with commonly used tracking methods, such as gyral bias, where fiber tracking preferentially selects fibers inserting at the gyral apex rather than at the banks of the sulci. Various tracking methods also predispose to errors, such as a high rate of false positives with probabilistic methods and false negatives with deterministic methods. Examples of other issues affecting DTI include inaccuracies with crossing fibers and tracking within areas of low fractional anisotropy (e.g., tracking through gray matter nuclei). Newer acquisition schemes with higher angular resolution (e.g., high angular resolution diffusion-weighted imaging, generalized q-sampling imaging, or diffusion spectrum imaging) have improved tracking accuracy, but are associated with longer acquisitions and more complex postprocessing.

Conclusion

DBS for movement disorders is a rapidly evolving technique in the field of neurology. As technology advances, our ability to optimize and personalize neuromodulation for a variety

of neurological diseases will also mature. The growth of this field will likely be based on the premise that dysfunction of a complex brain network underlies the symptoms of a given disease. Exploration into these networks will likely manifest through various modalities, such as inspection of the physical connections between brain regions (e.g., structural connectivity profiling) and surveillance of metabolically synchronized brain regions (e.g., functional connectivity profiling). These techniques hold promise for improving DBS outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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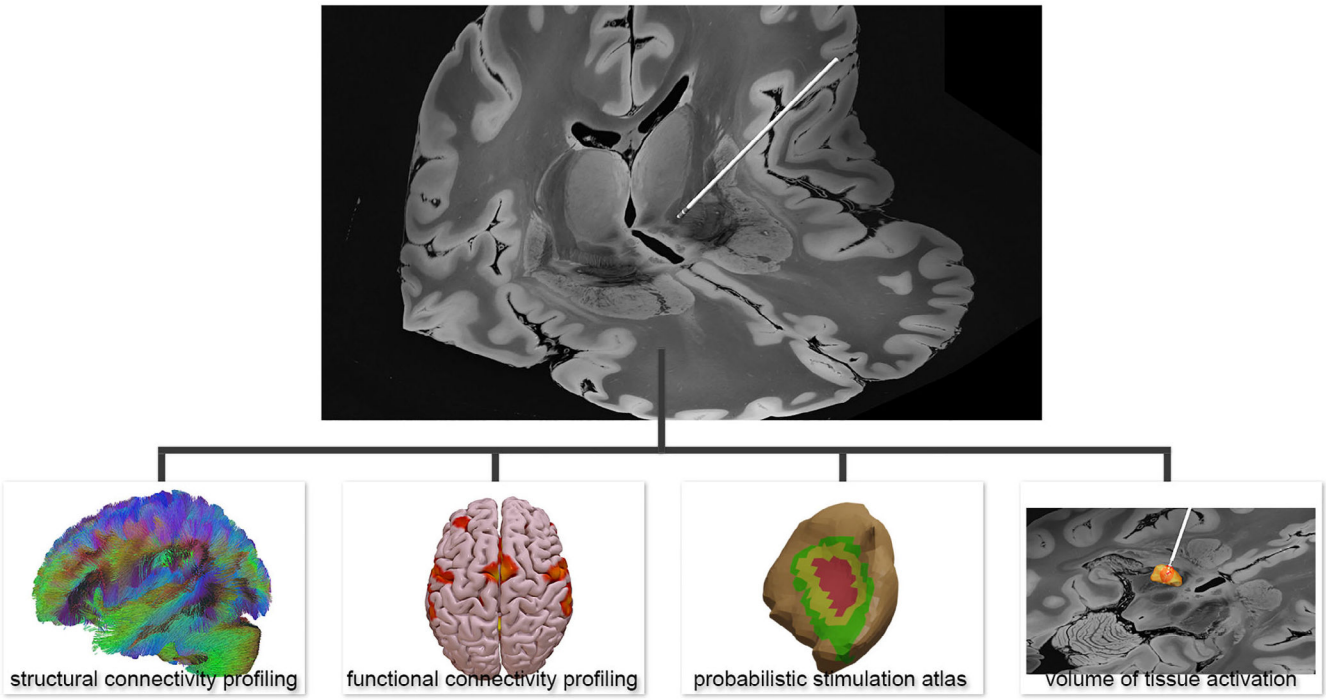

FIG. 1.

Modern DBS. The current approaches to DBS are illustrated from left to right: structural connectivity profiling, functional connectivity profiling, probabilistic stimulation atlases, and volume of tissue activation analyses. Images were rendered using the Lead-DBS advanced processing pipeline and DSI Studio.[39,78,79]

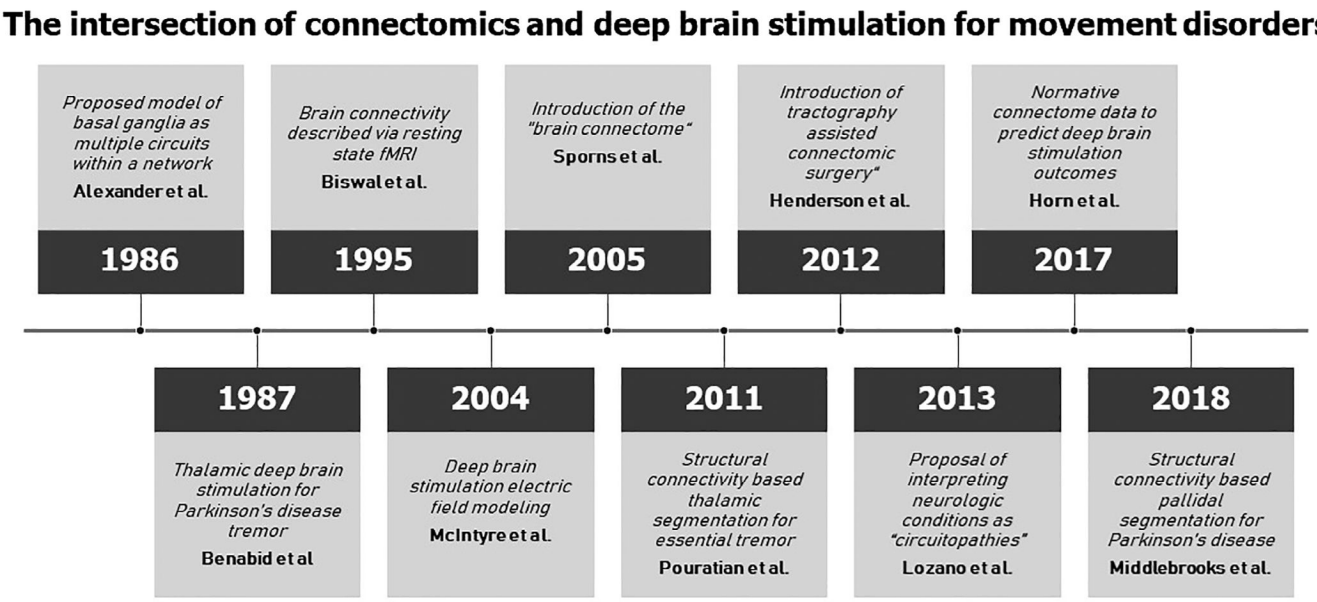

FIG. 2.

Intersection of connectomics and DBS for movement disorders. Landmark articles that highlight the adoption of network-based models in DBS research.

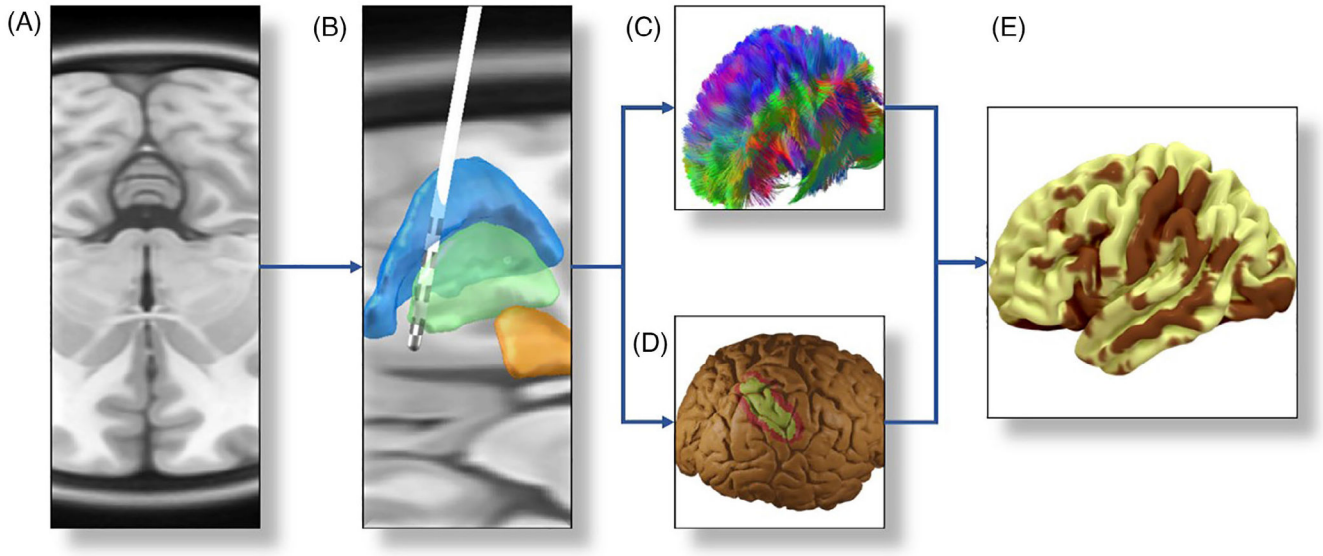

FIG. 3.

Application of structural and functional connectivity in DBS. DBS analysis begins with postoperative imaging (A) and lead localization (B). Neuroimaging techniques can then be used to compute patient-specific structural (C) and functional (D) connectivity. These data can be combined with clinical outcome data to create statistical brain-mapping images (E) to guide DBS optimization strategies. Images were rendered using the Lead-DBS advanced processing pipeline and DSI Studio.[39,78,79]

TABLE 1.

Structural connectivity profiling in DBS for PD

Author, Year	Main Findings
da Silva, 2017[65]	SC-based parcellation of the GPi into three clusters
Ewert, 2018[66]	SC data from high-resolution images of healthy patients were used to create a parcellation atlas of the STN, GPi, and RN.
Koirala, 2016[67]	SC-based connectivity profiling found that PMC and SMA fibers were the main bundles affected on a network level from STN DBS.
Pujol, 2017[68]	SC data were used to map white matter connectivity between STN and GPi. STN and GPi connectivity could reliably be identified, but STN to GPe connectivity had very complex fiber architecture with variable results.
Vanegas-Arroyave, 2016[69]	In STN DBS, strong connectivity to the SFG and thalamus was positively associated with clinical effectiveness.
Frankenmolle, 2010[70]	SC profiles of bilateral STN DBS found that current spread into nonmotor regions of the STN were associated with greater cognitive impairment.

SC, structural connectivity; RN, red nucleus; SFG, superior frontal gyrus.

TABLE 2.

Functional connectivity profiling in DBS for PD

Author, Year	Main Findings
Helmich, 2011[71]	TD PD had increased FC between GPi and putamen compared to non-TD PD and healthy controls.
Fling, 2014[72]	FOG in PD is associated with increased FC between SMA and MLR and CLR.
Tessitore, 2012[73]	FOG in PD was associated with decreased FC between “executive attention” network (RAG and MFG) as well as visual network (OTG).
Rektorova, 2012[74]	PDD was associated with decreased FC between posterior cingulate cortex and inferior frontal cortex.
Chen, 2018[75]	Whole-brain FC from local and public databases were combined to create a functional connectome neural network model to predict the best DBS target site with no a priori assumptions.
Kahan, 2014[76]	STN DBS reduced cortico-striatal, striato-thalamic, and thalamo-cortical FC while increasing cortico-STN and striato-STN FC.
Mueller, 2018[77]	Therapeutic effect of STN DBS was associated with increased FC of cerebello-thalamic-cortical network.

TD, tremor dominant; FC, functional connectivity; FOG, freezing of gait; MLR, mesencephalic locomotor region; CLR, cerebellar locomotor region; RAG, right angular gyrus; MFG, middle frontal gyrus; OTG, occipito-temporal gyrus; PDD, Parkinson’s disease dementia.