Neuroimaging Advances in Deep Brain Stimulation: Review of Indications, Anatomy, and Brain Connectomics

E.H. Middlebrooks, R.A. Domingo, T. Vivas-Buitrago, L. Okromelidze, T. Tsuboi, J.K. Wong, R.S. Eisinger, L. Almeida, M.R. Burns, A. Horn, R.J. Uitti, R.E. Wharen Jr, V.M. Holanda, and S.S. Grewal

ABSTRACT

SUMMARY: Deep brain stimulation is an established therapy for multiple brain disorders, with rapidly expanding potential indications. Neuroimaging has advanced the field of deep brain stimulation through improvements in delineation of anatomy, and, more recently, application of brain connectomics. Older lesion-derived, localizationist theories of these conditions have evolved to newer, network-based “circuitopathies,” aided by the ability to directly assess these brain circuits in vivo through the use of advanced neuroimaging techniques, such as diffusion tractography and fMRI. In this review, we use a combination of ultra-high-field MR imaging and diffusion tractography to highlight relevant anatomy for the currently approved indications for deep brain stimulation in the United States: essential tremor, Parkinson disease, drug-resistant epilepsy, dystonia, and obsessive-compulsive disorder. We also review the literature regarding the use of fMRI and diffusion tractography in understanding the role of deep brain stimulation in these disorders, as well as their potential use in both surgical targeting and device programming.

ABBRVIATIONS: AL = ansa lenticularis; ALIC = anterior limb of the internal capsule; ANT = anterior nucleus of the thalamus; A5 = ansa subthalamica; ATR = anterior thalamic radiation; DBS = deep brain stimulation; DRTT = dentatorubrothalamic tract; ET = essential tremor; FGATIR = fast gray matter acquisition TI inversion recovery; FL = fasciculus lenticularis; FS = fasciculus subthalamicus; GP = globus pallidus externus; GPi = globus pallidus internus; MFB = medial forebrain bundle; MMT = mammillothalamic tract; OCD = obsessive-compulsive disorder; PD = Parkinson disease; slMFB = suprolateral branch of the medial forebrain bundle; STN = subthalamic; TF = thalamic fasciculus; VIM = ventral intermediate nucleus; VO = ventralis oralis; ZI = zona incerta

The use of deep brain stimulation (DBS) for treatment of multiple movement and psychiatric disorders has been both beneficial and safe. Currently, there are 5 indications for DBS recognized by the United States FDA: essential tremor (ET), Parkinson disease (PD), and drug-resistant epilepsy, with dystonia and obsessive-compulsive disorder (OCD) carrying a humanitarian device exemption. The relevant brain targets include the ventral intermediate nucleus (VIM) of the thalamus, subthalamic nucleus (STN), globus pallidus internus (GPi), anterior nucleus of the thalamus (ANT), and anterior limb of the internal capsule (ALIC). While their pathophysiology may be different, these disorders share 1 unifying feature: They represent brain network disorders, or “circuitopathies.” Additionally, no anatomic correlates (viewed on neuroimaging) can be found that code for various clinical signs of these conditions. Consequently, there has been a shift from traditional localizationist models of the brain to a “connectomic” approach (considering function more distributed within brain networks) to study mechanisms of and responses to DBS and other forms of functional neurosurgery. Reimagining the role of neuroimaging in directing such treatments is of paramount importance.

Historically, neurosurgical targeting was performed by use of a coordinate system referenced to readily identifiable landmarks (“indirect targeting”), for example, the anterior/posterior commissure line. Initial targeting was further refined during awake surgery by use of microelectrode neurophysiologic recordings and macrostimulation. Unfortunately, every pass of a microelectrode increases the risk of complication, as well as the possibility of inducing a transient “microlesion” effect that can further limit or complicate intraoperative testing and interpretation. Surgical targeting and stimulation programming rapidly evolved in conjunction with improvements in MR imaging technology. Improved direct visualization of targets with high-field MR imaging and volumetric, high-
resolution imaging allowed “direct targeting” of some structures. However, other targets remain poorly resolved, such as the nuclei of the thalamus. More recently, the field of brain connectomics (MRI and diffusion tractography) has shown great promise in elucidating the mechanisms of DBS and providing patient-specific functional targets that cannot otherwise be defined noninvasively.

In this review, we discuss the FDA-approved indications of DBS, including relevant connectomic and structural anatomy (summarized in the Table), as well as commonly employed MR imaging sequences. A combination of diffusion tractography and postmortem examination and an ultra-high-resolution 7T FLASH MR imaging open-source image set (https://datadryad.org/stash/dataset/doi:10.5061/dryad.119f80q) is used throughout to highlight relevant anatomy. For tractography, a group-averaged dataset based on 1021 subjects from the Human Connectome Project (https://www.humanconnectome.org) open-source data base, normalized to Montreal Neurological Institute template space and reconstructed by using a q-space diffeomorphic reconstruction, was utilized to obtain the spin distribution function. Tractography was then generated in DSI Studio (http://dsi-studio.labsolver.org) by using a combination of manual regions of interest, as well as from the DBS Intrinsic Template Atlas and Horn et al. Tractography was displayed in Lead-DBS software (http://www.lead-dbs.org). The generated tract atlas will be released as open-source data, and is currently available in the latest release of the Lead DBS software package.

**Essential Tremor**

ET was 1 of 2 initially approved indications for DBS in 1997 (along with severe tremor in PD), targeting the VIM nucleus of the thalamus. Multiple clinical trials have demonstrated the efficacy of VIM stimulation in the treatment of medical-refractory ET. Since the approval of VIM as a treatment target, more recent studies have questioned the ideal target location for treatment of tremor. In particular, there has been increasing interest in the posterior subthalamic area, which encompasses the caudal zona incerta (ZI).

Long-term studies, however, have shown that while there is a more pronounced improvement, initially, with caudal ZI stimulation, the VIM target has produced better long-term tremor relief. Last, the ventralis oralis (VO) nucleus of the thalamus has also been explored as a potential target for tremor, but has not been extensively studied.

**Anatomy.** The ventral thalamus contains multiple nuclei that function in the sensorimotor network. The ventral caudal nucleus, a relay nucleus for proprioception, vibration, and fine touch via the medial lemniscus pathway, lies in the posterior...
ventral thalamus.\textsuperscript{14} Anterior to the ventral caudal nucleus is the VIM (Fig 1A, -B; images without outlines in On-line Figure), and anterior to the VIM is the VO nucleus, which is divided into a posterior and anterior portion, which receives pallidofugal fibers from the pallidum (discussed later).\textsuperscript{15} The VIM and ventralis oralis posterior largely receive fibers of the dentatorubrothalamic tract (DRTT).\textsuperscript{14,16} The DRTT courses from the dentate nucleus of the cerebellum through the ipsilateral superior cerebellar peduncle and then partially decussates in the midbrain (Fig 1C, -D).\textsuperscript{17} Most fibers cross to the contralateral red nucleus and ascend through the posterior subthalamic area, VIM, and ventralis oralis posterior and finally terminate within the primary motor cortex. A small subset (20\%–30\%) does not decussate but rather courses to the ipsilateral red nucleus and follows a similar path to the ipsilateral primary motor cortex.\textsuperscript{17}

The outer boundaries of the thalamus are generally well-defined on high-resolution, T1-weighted gradient recalled-echo sequences (eg, MPRAGE). Contrast can be enhanced by application of 2 TIs in MPRAGE to create MP2RAGE images.\textsuperscript{18} The application of white matter suppression can also help delineate the thalamic boundaries and has the added advantage of revealing internal architecture of the thalamic nuclei (Fig 1B).\textsuperscript{19} Susceptibility-weighted imaging can also reveal internal details of the thalamic nuclei; however, this has been primarily shown at ultra-high-field (7T).\textsuperscript{20}

Connectomics. Multiple studies have examined the role of connectomics in the treatment of tremor targeting the VIM/ posterior subthalamic area region. Early studies examining the segmentation of the thalamus based on the diffusion tractography connectivity profile showed that diffusion tractography was an independent predictor of tremor improvement.\textsuperscript{21-25} Based on diffusion tractography results, a common hypothesis has emerged that both VIM and caudal ZI stimulation exert their effect through stimulation of the DRTT, which traverses both targets (Fig 1D).\textsuperscript{26}

Other studies examined segmentation of the thalamus using diffusion tractography, which revealed similar segregation of the ventral thalamus as described by histologic atlases.\textsuperscript{25,27} Using this approach, Middlebrooks et al\textsuperscript{28} showed substantial variability in structural connectivity in a cohort of subjects using a fixed anterior/posterior commissure targeting point, highlighting the need for more patient-specific, network-based targeting. By using this approach, several studies found that such segmentation was predictive of improvement in tremor, particularly, connectivity with nodes in the motor network.\textsuperscript{21-24}

More recent studies focused on the DRTT, with several showing improvement in tremor associated with overlap of stimulation volume with the DRTT.\textsuperscript{25,28} Al-Fatity et al\textsuperscript{29} used atlas-based connectivity measures, in contrast to previous studies using patient data,\textsuperscript{21,25} and found stimulation volumes in the posterior subthalamic area closely associated with the DRTT correlated with greater tremor control. Importantly, many European datasets have focused more on the posterior subthalamic area region compared with United States datasets targeting the ventral thalamus, which has led to difficulty in fully understanding the role of local structures (such as the VIM, ventralis oralis posterior, and caudal ZI) versus the white matter tracts traversing these regions.\textsuperscript{30} It is likely that influencing the DRTT plays a major role in tremor reduction, but the role of local stimulation effects in these different gray matter regions may be important given the variability in outcomes targeting the posterior subthalamic area versus the ventral thalamus, particularly the incidence of stimulation-induced adverse effects.

In control subjects, fMRI has been used to localize the thalamic region corresponding to the thalamic motor network by using resting-state connectivity.\textsuperscript{31,32} Unfortunately, lengthy acquisition times currently limit application to the clinical setting. Using group-averaged normative data, however, Al-Fatity et al\textsuperscript{29}
reported correlation between tremor improvement and functional connectivity similar to that seen with the structural connectivity, namely cerebellothalamocortical motor network connectivity. Gibson et al. used active VIM stimulation to assess blood oxygen level–dependent signal changes in a cohort of patients with ET. Activation in sensorimotor, supplementary motor area, cerebellar, brain stem, and thalamic regions correlated with greater improvement in tremor. Interestingly, stimulation-induced adverse effects were more associated with precentral, postcentral, and subcentral region activation, which could support the lower incidence of adverse effects, such as ataxia, with more anterior VIM/ventralis oralis posterior stimulation.

**Parkinson Disease**

Along with ET, the FDA approved VIM DBS for severe tremor in PD. In 2002, the FDA expanded its indications, approving DBS use in both the STN and GPI for advanced PD cases. Both targets have been shown as safe and effective, with comparable outcomes in motor symptom improvement. Both GPI and STN DBS have pros and cons, and target selection should be based on patient-by-patient considerations.

**Anatomy.** The STN is a small, almond-shaped subthalamic structure that lies anterolateral to the red nucleus, superior to the substancia nigra, and inferior to the ZI (Fig. 2). The STN is positioned in close proximity to multiple critical white matter tracts, including the corticospinal tract ventrolaterally, medial lemniscus postrolaterally, and the optic tract inferolaterally. The STN is considered to be functionally divided into 3 zones that do not have a clear anatomic distinction. This tripartite division consists of a posterolateral motor division, middle associative division, and anteromedial limbic division. These subdivisions are of critical importance when considering DBS programming due to the possibility of off-target adverse effects. Likely, the divisions are implemented as a gradient, rather than in the form of clear compartments. Given that the STN receives direct input from a wide array of frontal regions, this gradient is largely informed by a similar functional gradient in the frontal cortex. Thus, functional zones of the nucleus can be defined by their structural and functional connectivity, as described next.

The STN has broad cortical and subcortical connections, including the caudate, putamen, pedunculopontine nucleus, globus pallidus externus (GPe), GPI, substantia nigra, substantia innominata, hypothalamus, olfactory tubercle, and mammillary body. These broad connections follow the tripartite function in motor, associative, and limbic processes, e.g., limbic regions predominantly interact with limbic regions of the striatum or thalamus (Fig 3A). With regard to DBS, several key tracts warrant discussion. The fasciculus subthalamicus (FS) and ansa subthalamica (AS) are 2 of the 4 primary pallidofugal tracts (passing out of the pallidum) and connect the GPe and the GPI with the STN, respectively (Figs 3B–C). The FS courses from the GPe lateral to the genu and ALIC to insert along the anterolateral aspect of the STN. The AS is a less described pathway that courses from the anteroventral pole of the globus pallidus internus (green region) and curving into the anterior pole of the limbic division of the STN (yellow region), while the AS traverses the Edinger comb system extending from the globus pallidus externus (light blue region) to the middle associative STN (cyan).
connecting cells related to the nucleus basalis has been shown to project diffusely to neocortex. This could mean that direct connections between cortex and GPi, as seen in diffusion tractography, are projections to the cortex that originate from a peripallidal cell mass, or even false-positive connections, isolated due to the close proximity of the GPi to the internal capsule.

Of primary importance to DBS, the pallidofugal pathways are generally divided into the AL, fasciculus lenticularis (FL), FS, and AS (Fig 4B, -C). The FS and AS have been discussed above. The FL and AL, or pallidothalamic connections, ultimately join together with the cerebellothalamic fibers (DRTT) to form the thalamic fasciculus (TF) before inserting in the ventral thalamus (Fig 4D). The pallidofugal fibers of the FS and FL traverse the internal capsule at a perpendicular angle, creating the Edinger comb system, which can be readily seen on susceptibility-weighted imaging (Fig 2C). The AL courses from the inferomedial border along the anterior pole of the GPi, extends anteriorly and medially to cross the internal capsule, passes anteriorly to the STN, and then joins the FL. The FL extends from the GPi medial border, extends directly through the internal capsule, and then lies dorsal to the STN and ventral to the ZI, separating these 2 structures before joining the AL to form the TF (Fig 2A). The TF then courses dorsal to the ZI and inserts into the ventral thalamus with most fibers from the DRTT entering the VIM, the AL into the ventralis oralis posterior, and the FL into the ventralis oralis anterior (Fig 4D). The ZI is bordered inferiorly by the FL and superiorly by the TF. The relationship of these tracts is crucial, as they likely serve a major therapeutic role in DBS for movement disorders, for instance, DRTT/TF stimulation in alleviating tremor in caudal ZI DBS and reduction of dyskinesia with more dorsal STN stimulation (likely affecting the AL). 

Connectomics. Support for the functional zones of the STN has been illustrated by several studies. Using diffusion tractography data with local field potential recordings in the STN, high connectivity to the motor and premotor cortices was found in the dorsolateral STN, while the ventral STN showed connectivity to limbic regions, such as the amygdala, hippocampus, and medial temporal regions. Connectivity profiles have illustrated the variability in brain networks affected by DBS in treating specific symptoms of PD. Akram et al used stimulation modeling combined with diffusion tractography in patients with STN DBS with PD to explore structural connectivity patterns associated with improvement in bradykinesia, rigidity, and tremor. Greater connectivity to the prefrontal cortex and supplemental motor area.
were more beneficial for rigidity, while connectivity to the supplemental motor area only was associated with improved bradykinesia. As may be expected from previously discussed tremor networks, connectivity to the primary motor cortex was associated with greatest benefit in tremor.

To determine if connectivity measures alone could be used to predict improvement across a cohort, Horn et al. used group-level resting-state fMRI and diffusion tractography data from existing cohorts to predict improvement in Unified Parkinson’s Disease Rating Scale Part III motor scores in a group of patients with PD. By employing a group of stimulation volumes to generate structural and functional connectivity maps associated with Unified Parkinson’s Disease Rating Scale Part III outcomes, models were formulated to predict individual patient outcomes. On the basis of solely connectivity data, they were able to predict postoperative motor scores within 15%, highlighting the potential power of connectomics in predicting patient outcomes associated with specific DBS programming settings.

Similarly, Lin et al. used machine learning to examine connectivity profiles associated with effective-versus-ineffective electrode contacts and predicted, with 84.9% accuracy, which electrode contacts would be effective in reducing motor symptoms. Additionally, their study illustrated the potential of connectomics to reduce the burden on DBS programmers in the performance of tedious permutation surveys of multiple DBS contacts to determine optimal effectiveness.

The role of connectomics in GPI DBS has been less explored; however, it could potentially offer even greater benefit to programming and targeting than the STN due to the larger size of the GPI. Middlebrooks et al. evaluated the role of diffusion tractography in predicting outcomes from GPI DBS and found that the changes in Unified Parkinson’s Disease Rating Scale Part III motor scores in PD correlated primarily with connectivity to the M1 region, followed by the supplemental motor area/premotor cortex.

**Dystonia**

Dystonia manifests in the form of muscle contractions that can be intermittent or sustained, resulting in phasic or repetitive movements and/or abnormal posture. DBS has been used to treat various forms of dystonia, from focal (predominantly cervical) to generalized dystonia. DBS for dystonia targeting the bilateral GPIs received a humanitarian device exemption by the FDA in 2003. Multiple clinical trials have established the efficacy of GPI DBS in primary generalized dystonia, finding that those having the **DYT1** gene mutation have a better response to DBS.

**Anatomy.** Relevant anatomy and imaging considerations of the sensorimotor portion of the GPIs have been previously discussed (see PD section).

**Connectomics.** Connectivity in DBS for dystonia has not been extensively studied. Okromelidze et al. have recently shown that stimulation volumes with structural and functional connectivity to motor regions of the cerebellum, thalamus, and sensorimotor cortex were correlated with greater improvement in primary generalized dystonia. Similarly, by using diffusion tractography analysis of ventral and dorsal contacts in focal dystonia, Rozanski et al. found that connections from the more efficacious ventral contacts had greater connectivity to the primary sensorimotor regions, while less efficacious dorsal contacts had greater connectivity to premotor and supplementary motor areas.

Unfortunately, the combination of the heterogeneity of patients with dystonia as well as the relatively low number of patients treated with DBS compared with PD and ET has resulted in greater gaps in understanding connectivity in DBS for dystonia. However, connectomics stands to potentially benefit dystonia more than ET or PD given the lack of reliable, immediate (at the time of stimulation onset) clinical or physiologic markers, which limits confidence in both targeting and subsequent programming. As opposed to the near-immediate change in motor symptoms seen with ET and PD DBS, the effect of DBS in dystonia may take days to weeks to manifest and may change from month to month, resulting in frustrating, unpredictable, and suboptimal clinical outcomes. An imaging biomarker, therefore, may result in more successful targeting and programming, greatly benefiting dystonia DBS outcomes.

**OCD**

The last target to receive humanitarian device exemption by the FDA was the ALIC for treatment of OCD in 2009. A multinational, multicenter study by Greenberg et al. reported symptom reduction and functional improvement in >60% of the patient population, with overall reduction of illness changing from severe at baseline to moderate with DBS treatment. Furthermore, 38% showed clinical remission, according to their Yale-Brown Obsessive Compulsive Scale score. Like dystonia, the lack of an immediate biophysical marker of treatment effect makes DBS targeting and programming challenging; therefore, identifying useful imaging biomarkers stands to benefit OCD outcomes.

**Anatomy.** Underlying pathophysiology of OCD is commonly thought to involve frontostriatal dysfunction and abnormal cortico-striato-thalamo-cortical tracts. As such, multiple DBS targets have been utilized, including the nucleus accumbens, ventral striatum, and ALIC. Within the FDA-approved target of the ALIC, 2 primary fiber tracts have been discussed with regard to OCD DBS, the anterior thalamic radiations (ATR) and the medial forebrain bundle (MFB), namely what has been described as the superolateral branch (sMFB). The ATR connects the thalamus to the frontal lobe, particularly to the dorsolateral prefrontal cortex (Fig 5). The classic MFB connects the ventral tegmental area to the nucleus accumbens and olfactory cortex and does not lie within the ALIC but is more ventral in location. The sMFB DBS target, as described by Coenen et al., connects the dentate nucleus, ventral tegmental areas, superior and middle frontal gyri, and lateral orbitofrontal cortex. However, this tract has only been described by DTI, and no other confirmation of its existence has been found (see Discussion below). Anatomically, the ATR is described as lying medial to sMFB within ALIC.

**Connectomics.** One of the first DBS connectivity studies in OCD showed that connectivity to the right middle frontal gyrus (dorsolateral prefrontal cortex) was greater in positive responders, whereas connectivity to the lateral orbitofrontal cortex and
ventrolateral prefrontal cortex was associated with nonresponse.\(^6^0\)
Similarly, Baldermann et al\(^6^1\) found stimulation of the ATR region, with connection to the medial and lateral prefrontal cortex and right middle frontal gyrus to correlate with greater improvement. Their results showed connectivity with the anatomic description of MFB to be associated with nonresponse. Together, these studies suggest the ATR as a stimulation target within the ALIC.

Others, however, have reported seemingly contradictory findings. Coenen et al\(^6^2\) performed an observational study of direct targeting of the slMFB, employing diffusion tractography in 2 patients, and both showed some benefit with DBS, but this study did not compare stimulation of the ATR. Liebrand et al\(^6^3\) used diffusion tractography of the slMFB and ATR to show greater symptom improvement with stimulation closer to the slMFB. The authors reported “a distinct media-lateral organization of, respectively, the ATR and MFB within the vALIC [ventral ALIC]”; however, the MFB does not traverse the ALIC and is ventral to ATR, not lateral (Fig 5).\(^6^3,6^4\) Given the described anatomy of the slMFB and DBS response, it is possible that these fibers within the ALIC and lateral to the ATR represent connections of the anteromedial STN, which has also been shown to be an effective DBS target for OCD.\(^6^5\) Here, we show that these fibers of the anteromedial STN that connect the STN to the anterior cingulate cortex, lateral orbitofrontal cortex, and dorsolateral prefrontal cortex\(^6^6\) share a similar course to what has been described as the slMFB (Fig 5).\(^6^2\)

In summary, the effect of ALIC DBS in OCD is likely mediated through the ATR or connections of the anteromedial STN to the frontal lobe. There is limited anatomic evidence of the slMFB, short of diffusion tractography, but the anatomic description of this fiber tract, seemingly, corresponds to connections between the anteromedial STN and frontal lobe. Because the MFB does not traverse within the ALIC, it is likely that studies reporting stimulation of the slMFB in ALIC DBS are not utilizing accepted anatomic structures or nomenclature. Due to this conflicting nomenclature, the slMFB fibers have more recently been referred to as the projection pathway from the ventral tegmental area; however, further studies are needed to demonstrate these as a novel pathway versus misidentification of normal anteromedial STN cortical connections.

**Epilepsy**
Epilepsy is a common disorder (> 1% prevalence in most populations) with drug-resistant epilepsy cases comprising approximately 20%–40% of all patients with epilepsy. Patients who are not candidates for surgical resection or lesioning, such as those with generalized onset, poor localization, or eloquent brain onset, previously had limited treatment options. More recently, several forms of neuro-modulation have provided new treatment options, including vagus nerve stimulation, responsive neural stimulation, and DBS. Unfortunately, these technologies are in their infancy, and a thorough understanding of their mechanism and ideal patient selection is not well-known. The most recent of these to be approved by the FDA (in 2018) is bilateral DBS of the ANT. Efficacy and safety of ANT DBS was shown in the Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial, which found a 68% responder rate at 5 years.\(^6^6\) While effective in many patients, substantial variability in outcomes was reported.\(^6^6\) Also of note, stimulation-induced adverse effects, including depression and memory impairment, were found, the mechanism of which is not entirely understood.\(^6^6\) Outcome variability was likely related to multiple factors, including differing surgical approaches; variation in patient population; lack of reliable, direct targeting; and challenges in identifying the optimal stimulation settings, because epilepsy DBS lacks an immediate physiologic biomarker seen in other applications (eg, immediate cessation of tremor in movement disorders).

**Anatomy.** Much like other applications in DBS, indirect targeting of the ANT was the most widely used method in early studies. Unfortunately, epilepsy is known to be associated with regional thalamic atrophy,\(^7^1\) which questions the utility of employing such indirect targeting in the brain of a patient with long-standing epilepsy. Grewal et al\(^7^2\) have shown that indirect targeting of the ANT produced a wide range of inaccuracies compared with direct ANT targeting in a cohort of patients with epilepsy, which was dependent on the degree of thalamic atrophy. Grewal et al\(^7^3\) showed the utility of fast gray matter acquisition T1 inversion recovery (FGATIR) MR imaging in direct visualization of the ANT.
responders. Additionally, they showed that anticorrelation of connectivity between multiple nodes of the default mode network compared with nonresponders via the MMT and exits the anterior pole of the ANT as the bioelectric circuit that enters this region, which suggests modulation of this circuit that enters the anterior cingulate cortex, traditionally thought to course through the ALIC, but more recent evidence suggests connections extending through the stria terminalis, septal area, and subgenual cingulate (Fig 6C). Importantly, recent studies have shown that the greatest response to ANT DBS was with stimulation volumes near the termination of the MMT and into the anterior ANT, which suggests modulation of this circuit that enters via the MMT and exits the anterior pole of the ANT as the biologic basis of seizures.

Connectomics. Diffusion tractography of MMT has been previously reported. An initial study utilized lengthy diffusion acquisition, replicated with >50% reduction in time in a subsequent study. Nevertheless, given the acquisition times, postprocessing, technical knowledge, and management of substantial distortions present in echo-planar imaging, diffusion tractography has not been shown to be of added value to the clear visualization of the MMT present on FGATIR imaging.

The mechanism of ANT DBS is not understood, but fMRI provides valuable insights into the connectivity pattern associated with ANT DBS response. Middlebrooks et al used atlas-based resting-state fMRI to show that responders had greater connectivity to multiple nodes of the default mode network compared with nonresponders. Additionally, they showed that anticorrelation of connectivity to the hippocampus was greater in DBS responders. These findings are in line with prior animal studies that revealed elevated γ-aminobutyric acid levels in the hippocampus after ANT stimulation, supporting the inhibitory nature of anticorrelated resting-state connectivity. If such connectivity is a predictor of ANT DBS response, this could aid in understanding treatment failure in some patients—for instance, in a small cohort, patients with mesial temporal sclerosis were shown to have impairment of evoked potentials in the hippocampus after ANT stimulation and were all nonresponders. If network damage due to epilepsy limits transmission of DBS stimulus within these networks identified by fMRI, treatment may, therefore, be ineffective.

Last, the lack of timely, reliable, clinical biophysical markers of optimal DBS programming may give fMRI the potential to provide a useful in vivo biomarker for device programming. The feasibility of using fMRI to directly visualize areas of the brain affected by stimulation, by using a block design fMRI under the conditions of DBS ON versus DBS OFF, as has been recently shown, produced similar activation patterns within the default mode network and several other areas of the brain. While more studies are required to understand the ideal patterns of activation associated with optimal clinical outcomes, fMRI has the potential to be used as a patient-specific in vivo biomarker to select optimal stimulation settings.

CONCLUSIONS

Brain connectomics has led to advances in the understanding of DBS and will continue to shape surgical targeting and programming. The potential for improvements in patient safety and treatment outcomes suggests that the role of neuroimaging in DBS management will only continue to increase. A thorough understanding of relevant functional and structural anatomy is critical to providing neuroradiologic guidance for DBS.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of Lucy Bahn, PhD, in the preparation of this article.

REFERENCES

1. Franzini A, Cordella R, Messina G, et al. Targeting the brain: considerations in 332 consecutive patients treated by deep brain stimulation.
(DBS) for severe neurological diseases. Neuro Sci 2012;33:1285–1303 CrossRef Medline
2. DeLong MR, Wichmann T. Basal ganglia circuits as targets for neuromodulation in Parkinson’s disease. JAMA Neurol 2015;72:1354–60 CrossRef Medline
3. Edlow BL, Mareyam A, Horn A, et al. 7 Tesla MRI of the ex vivo human brain at 100 micron resolution. Sci Data 2019;6:244 CrossRef Medline
4. Yeh FC, Panesar S, Fernandes D, et al. Population-averaged atlas of the macroscale human structural connectome and its network topology. Neuroimage 2018;178:57–68 CrossRef Medline
5. Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. Neuroimage 2011;58:91–99 CrossRef Medline
6. Yeh FC, Wedeen VJ, Tseng WY. Generalized q-sampling imaging. IEEE Trans Med Imaging 2010;29:1626–35 CrossRef Medline
7. Ewert S, Plettig P, Li N, et al. Toward defining deep brain stimulation targets in MNI space: a subcortical atlas based on multimodal MRI, histology and structural connectivity. Neuroimage 2018;170:271–82 CrossRef Medline
8. Horn A, Wenzel G, Irmen F, et al. Deep brain stimulation induced normalization of the human functional connectome in Parkinson’s disease. Brain 2019;142:3129–43 CrossRef Medline
9. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. Neuroimage 2019;184:293–316 CrossRef Medline
10. Flora ED, Perera CL, Cameron AL, et al. Deep brain stimulation for essential tremor: a systematic review. Mov Disord 2010;25:1550–59 CrossRef Medline
11. Blomstedt P, Stenmark Persson R, Hariz GM, et al. Deep brain stimulation in the caudal zona incerta versus best medical treatment in patients with Parkinson’s disease: a randomised blinded evaluation. J Neurol Neurosurg Psychiatry 2018;89:710–16 CrossRef Medline
12. Eisinger RS, Wong J, Almeida D, et al. Ventral intermediate nucleus versus zona incerta region deep brain stimulation in essential tremor. Mov Disord Clin Pract 2018;5:75–82 CrossRef Medline
13. Foote KD, Okun MS. Ventralis intermedialis plus ventralis oralis anterior and posterior deep brain stimulation for posttraumatic Holmes tremor: two leads may be better than one: technical note. Neurosurgery 2005;56:E445 CrossRef Medline
14. Sammartino F, Krishna V, King NK, et al. Tractography-based ventral intermediate nucleus targeting: novel methodology and intraoperative validation. Mov Disord 2016;31:1217–25 CrossRef Medline
15. Middlebrooks E, Tuna I, Grewal S, et al.Segmentation of the globus pallidus internus using probabilistic diffusion tractography for deep brain stimulation targeting in Parkinson’s disease. AJNR Am J Neuroradiol 2018;39:127–34 CrossRef Medline
16. Schlaier J, Anthofer J, Steib K, et al. Deep brain stimulation for essential tremor: targeting the dentato-rubro-thalamic tract? Neuromodulation 2015;18:105–12 CrossRef Medline
17. Meola A, Comert A, Yeh FC, et al. The nondecussating pathway of the dentatorubrothalamic tract in humans: human connectome-based tractographic study and microdissection validation. J Neurol 2016;124:1406–12 CrossRef Medline
18. Marques JP, Kober T, Krueger G, et al. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. Neuroimage 2010;49:1271–81 CrossRef Medline
19. Tourdias T, Saranathan M, Levesque IR, et al. Visualization of intrathalamic nuclei with optimized white-matter-nulled MP-RAGE at 7T. Neuroimage 2014;84:534–45 CrossRef Medline
20. Jorge J, Gretsch F, Najdenovska E, et al. Improved susceptibility-weighted imaging for high contrast and resolution thalamic nuclei mapping at 7T. Magn Reson Med 2020;84:1218–34 CrossRef Medline
21. Middlebrooks EH, Tuna I, Almeida D, et al. Structural connectivity-based segmentation of the thalamus and prediction of tremor improvement following thalamic deep brain stimulation of the ventral intermediate nucleus. Neuroimage Clin 2018;20:1266–73 CrossRef Medline
22. Kim W, Shariim J, Tenn S, et al. Diffusion tractography imaging-guided frameless linear accelerator stereotactic radiosurgical thalamotomy for tremor: case report. J Neurosurg 2018;128:215–21 CrossRef Medline
23. Pouratian N, Zheng Z, Bari AA, et al. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation. J Neurosurg 2011;115:995–1004 CrossRef Medline
24. Tsolaki E, Downes A, Speier W, et al. The potential value of probabilistic tractography-based for MR-guided focused ultrasound thalamotomy for essential tremor. Neuroimage Clin 2018;17:1019–27 CrossRef Medline
25. Akram H, Dayal V, Mahlknecht P, et al. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. Neuroimage Clin 2018;18:130–42 CrossRef Medline
26. Calabrese E, Hickey P, Hulette C, et al. Postmortem diffusion MRI of the human brainstem and thalamus for deep brain stimulator electrode localization. Hum Brain Mapp 2015;36:3167–78 CrossRef Medline
27. Behrens TE, Johansen-Berg H, Woolrich MW, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 2003;6:750–57 CrossRef Medline
28. Middlebrooks EH, Holanda VM, Tuna I, et al. A method for preoperative single-subject thalamic segmentation based on probabilistic tractography for essential tremor deep brain stimulation. Neuroradiology 2018;60:303–09 CrossRef Medline
29. Al-Fatly B, Ewert S, Kubler D, et al. Connectivity profile of thalamic deep brain stimulation to effectively treat essential tremor. Brain 2019;142:3086–98 CrossRef Medline
30. Middlebrooks EH, Grewal SS, Holanda VM. Complexities of connectivity-based DBS targeting: rebirth of the debate on thalamic and subthalamic treatment of tremor. Neuroimage Clin 2019;22:101761 CrossRef Medline
31. Anderson JS, Dhatt HS, Ferguson MA, et al. Functional connectivity targeting for deep brain stimulation in essential tremor. AJNR Am J Neuroradiol 2011;32:1963–68 CrossRef Medline
32. Greene DJ, Marek S, Gordon EM, et al. Integrative and network-specific connectivity of the basal ganglia and thalamus defined in individuals. Neuron 2020;105:742–58 CrossRef Medline
33. Gibson WS, Jo HJ, Testini P, et al. Functional correlates of the therapeutic and adverse effects evoked by thalamic stimulation for essential tremor. Brain 2016;139:2198–210 CrossRef Medline
34. Ramirez-Zamora A, Ostrem JL. Globus pallidus interna or subthalamic nucleus deep brain stimulation for Parkinson’s disease: a review. JAMA Neurol 2018;75:367–72 CrossRef Medline
35. Holanda VM, Okun MS, Middlebrooks EH, et al. Postmortem dissections of common targets for lesion and deep brain stimulation surgeries. Neurosurgery 2020;86:860–72 CrossRef Medline
36. Parent A, Hazrati L-N. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Rev 1995;20:128–54 CrossRef Medline
37. Alho EJL, Alho A, Horn A, et al. The ansa subthalamica: a neglected fiber tract. Mov Disord 2020;35:75–80 CrossRef Medline
38. Petersen MV, Mlakar J, Haber SN, et al. Holographic reconstruction of axonal pathways in the human brain. Neuron 2019;104:1056–64 CrossRef Medline
39. Eisinger RS, Cernera S, Gittis A, et al. The potential value of probabilistic tractography-based guided frameless ultrasound thalamotomy for essential tremor. Neuroimage Clin 2018;20:1266–73 CrossRef Medline
40. Kim W, Shariim J, Tenn S, et al. Diffusion tractography imaging-guided frameless linear accelerator stereotactic radiosurgical thalamotomy for tremor: case report. J Neurosurg 2018;128:215–21 CrossRef Medline
41. Pouratian N, Zheng Z, Bari AA, et al. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation. J Neurosurg 2011;115:995–1004 CrossRef Medline
42. Tsolaki E, Downes A, Speier W, et al. The potential value of probabilistic tractography-based for MR-guided focused ultrasound thalamotomy for essential tremor. Neuroimage Clin 2018;17:1019–27 CrossRef Medline
43. Akram H, Dayal V, Mahlknecht P, et al. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. Neuroimage Clin 2018;18:130–42 CrossRef Medline
44. Calabrese E, Hickey P, Hulette C, et al. Postmortem diffusion MRI of the human brainstem and thalamus for deep brain stimulator electrode localization. Hum Brain Mapp 2015;36:3167–78 CrossRef Medline
45. Behrens TE, Johansen-Berg H, Woolrich MW, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 2003;6:750–57 CrossRef Medline
41. Parent A, De Bellefeuille L. Organization of eff erent projections from the internal segment of globus pallidus in primate as revealed by fl ourescence retrograde labeling method. Brain Res 1982;245:201–13 CrossRef Medline
42. Maier-Hein KH, Neher PF, Houde JC, et al. The challenge of mapping the human connectome based on diffusion tractography. Nat Commun 2017;8:1349 CrossRef Medline
43. Aquino CC, Duffyg G, Hedges DM, et al. Interleaved deep brain stimulation for dyskinesia management in Parkinson’s disease. Mov Disord 2019;34:1722–27 CrossRef Medline
44. Accolla EA, Herrojo Ruiz M, Horn A, et al. Brain networks modulated by subthalamic nucleus deep brain stimulation. Brain 2016;139:2503–15 CrossRef Medline
45. Akram H, Sotiropoulos SN, Jbabdi S, et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson’s disease. Neuroimage 2017;158:332–45 CrossRef Medline
46. Horn A, Reich M, Vorwerk J, et al. Connectivity predicts deep brain stimulation outcome in Parkinson disease. Ann Neurol 2017;82:87–78 CrossRef Medline
47. Lin H, Na P, Zhang D, et al. Brain connectivity markers for the identifi cation of effective contacts in subthalamic nucleus deep brain stimulation. Hum Brain Mapp 2020;41:2028–36 CrossRef Medline
48. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classifi cation of dystonia: a consensus update. Mov Disord 2013;28:863–73 CrossRef Medline
49. Vidalhbet M, Vercuel L, Houeto JL, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 2005;352:459–67 CrossRef Medline
50. Vidalhbet M, French SPIDY Study Group, Vercuel L, Houeto JL, et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. Lancet Neurol 2007;6:223–29 CrossRef Medline
51. Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;355:1978–90 CrossRef Medline
52. Artusi CA, Dwoi A, Romagnolo A, et al. Differential response to pallidal deep brain stimulation among monogenic dystonias: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2020;91:426–33 CrossRef Medline
53. Oskomelidze L, Tsouki T, Eisinger RS, et al. Functional and structural connectivity patterns associated with clinical outcomes in deep brain stimulation of the globus pallidus internus for generalized dystonia. AJNR Am J Neuroradiol 2020;41:508–14 CrossRef Medline
54. Rozanski VE, Vollmar C, Cunha JP, et al. Connectivity patterns of pallidal DBS electrodes in focal dystonia: a diffusion tensor tractography study. Neuroimage 2014;84:435–42 CrossRef Medline
55. Reese R, Vollmann J. Deep brain stimulation for the dystonias: evidence, knowledge gaps, and practical considerations. Mov Disord Clin Pract 2017;4:486–94 CrossRef Medline
56. Tastevin M, Spataola G, Régis J, et al. Deep brain stimulation in the treatment of obsessive-compulsive disorder: current perspectives. Neuropsychiatr Dis Treat 2019;15:1259–72 CrossRef Medline
57. Greenberg BD, Gabriels LA, Malone DA, Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry 2010;15:64–79 CrossRef Medline
58. Almari SE, Spellman T, Douglass NL, et al. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science 2013;340:1234–39 CrossRef Medline
59. Coenen VA, Pankepp J, Hurwitz TA, et al. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci 2012;24:223–36 CrossRef Medline
60. Hartmann CJ, Lujan JL, Chaturvedi A, et al. Tractography activation patterns in dorsolateral prefrontal cortex suggest better clinical responses in OCD DBS. Front Neurosci 2015;9:519 CrossRef Medline
61. Balderman J, Mezler C, Zapf A, et al. Connectivity profile predictive of effective deep brain stimulation in obsessive-compulsive disorder. Biol Psychiatry 2019;85:735–43 CrossRef Medline
62. Coenen VA, Schlaepfer TE, Goll P, et al. The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder. CNS Spectr 2017;22:282–89 CrossRef Medline
63. Liebrand LC, Caan MWA, Schuurman PR, et al. Individual white matter bundle trajectories are associated with deep brain stimulation response in obsessive-compulsive disorder. Brain Stimul 2019;12:353–60 CrossRef Medline
64. Ding SL, Royall JJ, Sunkin SM, et al. Comprehensive cellular-resolution atlas of the adult human brain. J Comp Neurol 2016;524:3127–481 CrossRef Medline
65. Tyagi H, Apergis-Schoute AM, Akram H, et al. A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: clinical and imaging evidence for dissociable effects. Biol Psychiatry 2019;85:726–34 CrossRef Medline
66. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84:1017–25 CrossRef Medline
67. Lehtimaki K, Coenen VA, Goncalves Ferreira A, et al. The surgical approach to the anterior nucleus of thalamus in patients with refractory epilepsy: experience from the international multicenter registry (MORE). Neurosurgery 2019;84:141–50 CrossRef Medline
68. Wu C, D’Haese P-F, Pallavaram S, et al. Variations in thalamic anatomy affect targeting in deep brain stimulation for epilepsy. Stereotact Funct Neurosurg 2016;94:387–96 CrossRef Medline
69. Grewal SS, Middlebrooks EH, Kaufmann TJ, et al. Fast gray matter acquisition T1 inversion recovery MRI to delineate the mammillothalamic tract for preoperative direct targeting of the anterior nucleus of the thalamus for deep brain stimulation in epilepsy. Neurosurg Focus 2018;45:E6 CrossRef Medline
70. Wang YC, Grewal SS, Middlebrooks EH, et al. Targeting analysis of a novel parietal approach for deep brain stimulation of the anterior nucleus of the thalamus for epilepsy. Epilepsia Res 2019;153:1–6 CrossRef Medline
71. Yang L, Li H, Zhu L, et al. Localized shape abnormalities in the thalamus and pallidum are associated with secondarily generalized seizures in mesial temporal lobe epilepsy. Epilepsy Behav 2017;70:259–64 CrossRef Medline
72. Grewal SS, Middlebrooks EH, Okromelidze L, et al. Variability between direct and indirect targeting of the anterior nucleus of the thalamus. World Neurosurg 2020 Apr 14. [Epub ahead of print] CrossRef Medline
73. Baydin S, Gungor A, Tanriover N, et al. Fiber tracts of the medial and inferior surfaces of the cerebrum. World Neurosurg 2017;98:34–49 CrossRef Medline
74. Choi SH, Kim YB, Paek SH, et al. Papez circuit observed by in vivo human brain with 7.0T MRI super-resolution track density imaging and track tracing. Front Neuroanat 2019;13:17 CrossRef Medline
75. Gao W, Koo BB, Kim JH, et al. Defining the optimal target for anterior thalamic deep brain stimulation in patients with drug-refractory epilepsy. J Neurosurg 2020;1–10 CrossRef Medline
76. Schaper F, Plantinga BR, Colon AJ, et al. Deep brain stimulation in epilepsy: a role for modulation of the mammillothalamic tract in seizure control? Neurosurgery 2020 May 18. [Epub ahead of print] CrossRef Medline
77. Kamali A, Zhang CC, Riascos RF, et al. Diffusion tensor tractography of the mammillothalamic tract in the human brain using
78. Middlebrooks EH, Grewal SS, Stead M, et al. Differences in functional connectivity profiles as a predictor of response to anterior thalamic nucleus deep brain stimulation for epilepsy: a hypothesis for the mechanism of action and a potential biomarker for outcomes. *Neurosurg Focus* 2018;45:E7 CrossRef Medline

79. Wang YC, Kremen V, Brinkmann BH, et al. Probing circuit of Papez with stimulation of anterior nucleus of the thalamus and hippocampal evoked potentials. *Epilepsy Res* 2020;159:106248 CrossRef Medline

80. Middlebrooks EH, Lin C, Okromelidze L, et al. Functional activation patterns of deep brain stimulation of the anterior nucleus of the thalamus. *World Neurosurg* 2020;136:357–63 CrossRef Medline