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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.

ABBREVIATIONS: AL = ansa lenticularis; ALIC = anterior limb of the internal capsule; ANT = anterior nucleus of the thalamus; AS = ansa subthalamica; ATR = anterior thalamic radiations; DBS = deep brain stimulation; DRTT = dentatorubrothalamic tract; ET = essential tremor; FGATIR = fast gray matter acquisition T1 inversion recovery; FL = fasciculus lenticularis; FS = fasciculus subthalamicus; GPe = globus pallidus externus; GPi = globus pallidus internus; MFB = medial forebrain bundle; MMT = mammillothalamic tract; OCD = obsessive-compulsive disorder; PD = Parkinson disease; slMFB = superolateral branch of the medial forebrain bundle; STN = subthalamic; TF = thalamic fasciculus; VIM = ventral intermedius 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.[1] 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 intermedius 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."[2] 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-

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Summary of key anatomic tracts and structures

Structure	Figure	Regions Connected	Relevant Disorders	Hypothesized Effects of Stimulation
AL	Fig 4*B*, *-D* (yellow)	GPi, VOa	PD and dystonia	Improve dystonia and dyskinesia
AS	Fig 4*B*, *-C* (purple); Fig 3*B*, *-C* (blue)	STN, GPi	PD and dystonia	Direct stimulation effect unknown
ATR	Fig 5*A*, *-B* (red)	Thalamus, prefrontal cortex	OCD	Improve OCD
DRTT	Fig 1*C*, *-D* (red and green); Fig 4*D* (green)	DN, RN, VIM/VOp, M1	ET and tremor-predominant PD	Improve tremor, worsen ataxia
FL	Fig 2*A*; Fig 4*D* (red)	GPi, VOa	PD and dystonia	Improve dystonia and parkinsonism
FS	Fig 3*B*, *-C* (Pink); Fig 4*B*, *-C* (red)	STN, GPe	PD and dystonia	Direct stimulation effect unknown
Hyperdirect pathway (limbic/associative)	Fig 3*A* (cyan, yellow)	STN, broad limbic and associative regions	OCD	Improve OCD
Hyperdirect pathway (motor)	Fig 3*A* (orange)	STN, motor cortex	PD	Improve parkinsonism
MMT	Fig 6*C* (green)	Mammillary body, ANT	Epilepsy	Decrease seizures
MFB	Fig 5*A*, *-B* (cyan)	VTA, nucleus accumbens and olfactory cortex	Depression (off-label use)	Possibly worsens OCD
TF	Fig 2*A*	Combination of FL, AL, and DRTT, thalamus	PD, dystonia, ET	Improve tremor
vtaPP (formerly slMFB)[a]	Fig 5*A*, *-B* (green)	DN, VTA, SFG, MFG, and lateral OFC	OCD	Possibly improve OCD
ANT	Fig 6*A*–*C*		Epilepsy	Decrease seizures
VIM	Fig 1*A*–*C*; Fig 4*D*		ET and tremor-predominant PD	Improve tremor, worsen ataxia, dysarthria
VOa/VOp	Fig 1*A*, *-B*; Fig 4*D*		ET and tremor-predominant PD	Improve tremor, dystonia, worsen ataxia
ZI	Fig 1*C*; Fig 2*A*		ET and tremor-predominant PD	Improve tremor, worsen ataxia

Note:—DN indicates dentate nucleus; M1, primary motor cortex; MFG, middle frontal gyrus; OFC, orbitofrontal cortex; RN, red nucleus; SFG, superior frontal gyrus; VOa, ventralis oralis anterior; VOp, ventralis oralis posterior; VTA, ventral tegmental area; vtaPP, projection pathway from the ventral tegmental area.
[a] vtaPP (slMFB) likely represents misidentification of the limbic/associative hyperdirect pathway.

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 (fMRI 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[3] 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[4] 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,[5] was utilized to obtain the spin distribution function.[6] 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[7] and Horn et al.[8] Tractography was displayed in Lead-DBS software (http://www.lead-dbs.org).[9] 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.[10] 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).[11] 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.[12] 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.[13]

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

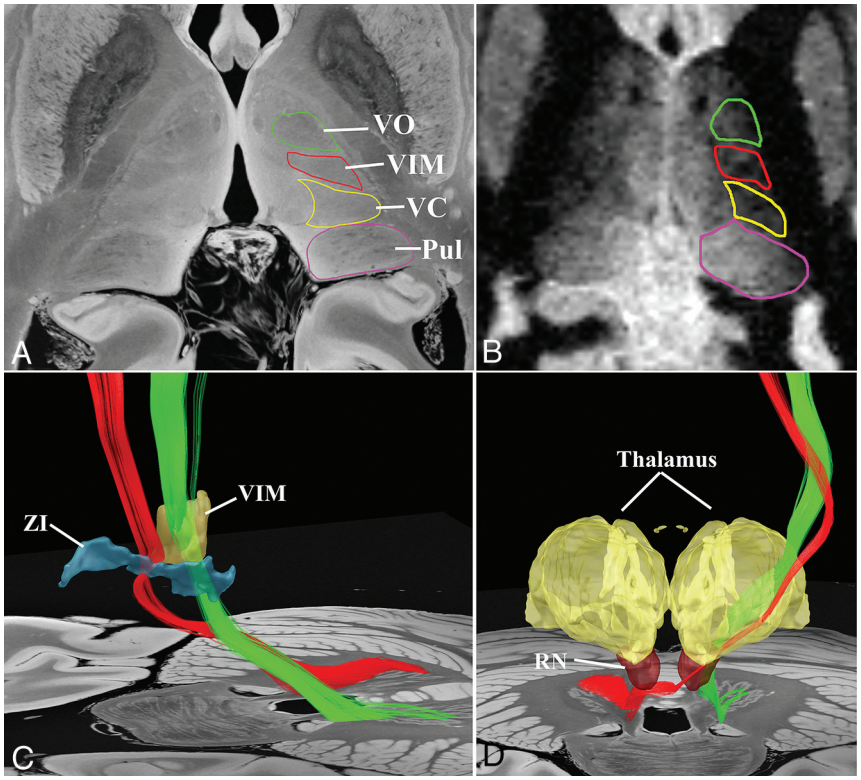

FIG 1. Axial 7T image (*A*) and axial 3T FGATIR image (*B*) illustrating the internal architecture of the ventral thalamus with key ventral nuclei outlined, including the ventral caudal (VC), VIM, and VO nuclei lying anterior to the pulvinar (Pul). Sagittal oblique (*C*) and coronal (*D*) images showing the relationship of the decussating (red) and nondecussating (green) tracts of the left DRTT and their relationship to the VIM nucleus and ZI (blue). The decussating fibers can be seen along the anterior border of the VIM in the location of the posterior VO. The DRTT extends from the dentate nucleus through the superior cerebellar peduncle, with part of the tract decussating in the midbrain and part continuing ipsilateral to the level of the red nucleus (RN), through the posterior subthalamic region and ZI, thalamus, and terminating in the primary motor cortex.

ventral thalamus.[14] Anterior to the ventral caudal nucleus is the VIM (Fig 1*A*, -*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).[15] The VIM and ventralis oralis posterior largely receive fibers of the dentatorubrothalamic tract (DRTT).[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 1*C*, -*D*).[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.[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.[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 1*B*).[19] Susceptibility-weighted imaging can also reveal internal details of the thalamic nuclei; however, this has been primarily shown at ultra-high-field (7T).[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.[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 1*D*).[26]

Other studies examined segmentation of the thalamus using diffusion tractography, which revealed similar segregation of the ventral thalamus as described by histologic atlases.[25,27] Using this approach, Middlebrooks et al[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.[21-24]

More recent studies focused on the DRTT, with several showing improvement in tremor associated with overlap of stimulation volume with the DRTT.[25,29] Al-Fatly et al[29] used atlas-based connectivity measures, in contrast to previous studies using patient data,[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.[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.[31,32] Unfortunately, lengthy acquisition times currently limit application to the clinical setting. Using group-averaged normative data, however, Al-Fatly et al[29]

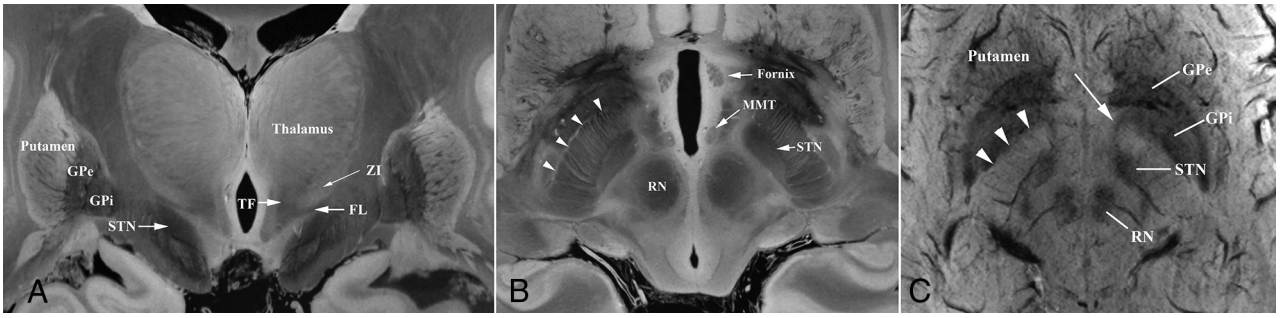

FIG 2. Coronal (*A*) and axial 7T MR imaging (*B*) showing the relationship of structures of the basal ganglia and subthalamic area. The ZI is bordered inferiorly by the FL and superiorly by the TF as it inserts into the thalamus. The Edinger comb system can be seen as *dark lines* traversing the internal capsule perpendicularly (*arrowheads*) composed of the pallidofugal tracts, fasciculus subthalamicus, and FL. Axial susceptibility-weighted MR imaging (*C*) shows similar anatomy including the Edinger comb (*arrowheads*) and the ansa subthalamica (*arrow*). RN indicates red nucleus.

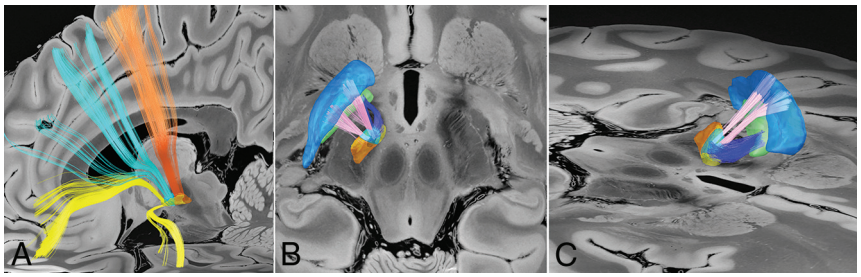

FIG 3. Sagittal view of the tripartite division of the STN (*A*) and corresponding hyperdirect fibers (orange = posterolateral sensorimotor STN; cyan = middle associative STN; yellow = anteromedial limbic STN). Axial (*B*) and oblique coronal views (*C*) show the course of the AS (blue fibers) extending 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 FS (pink fibers) traverses the Edinger comb system extending from the globus pallidus externus (light blue region) to the middle associative STN (cyan).

reported correlation between tremor improvement and functional connectivity similar to that seen with the structural connectivity, namely cerebellothalamocortical motor network connectivity. Gibson et al[33] 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.[21,30,33]

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.[34] Both GPi and STN DBS have pros and cons, and target selection should be based on patient-by-patient considerations.[34]

Anatomy. The STN is a small, almond-shaped subthalamic structure that lies anterolateral to the red nucleus, superior to the substantia nigra, and inferior to the ZI (Fig 2).[35] The STN is positioned in close proximity to multiple critical white matter tracts, including the corticospinal tract ventrolaterally, medial lemniscus posterolaterally, and the optic tract inferolaterally.[35] 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.[36] 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 mamillary body.[35] These broad connections follow the tripartite function in motor, associative, and limbic processes, eg, limbic regions predominantly interact with limbic regions of the striatum or thalamus (Fig 3*A*). 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 3*B*-, *C*).[35,37] The FS courses from the GPe lateral to the genu and ALIC to insert along the anterolateral aspect of the STN.[35] The AS is a less described pathway that courses from the anteroventral pole of the GPi, intimately associated with the ansa lenticularis (AL), tracking anteriorly to curve around the internal capsule, and descend inferiorly to the anterovental STN (both limbic).[37] Both connections likely contribute to the effect of STN DBS, in particular in treatment of dystonia.[35]

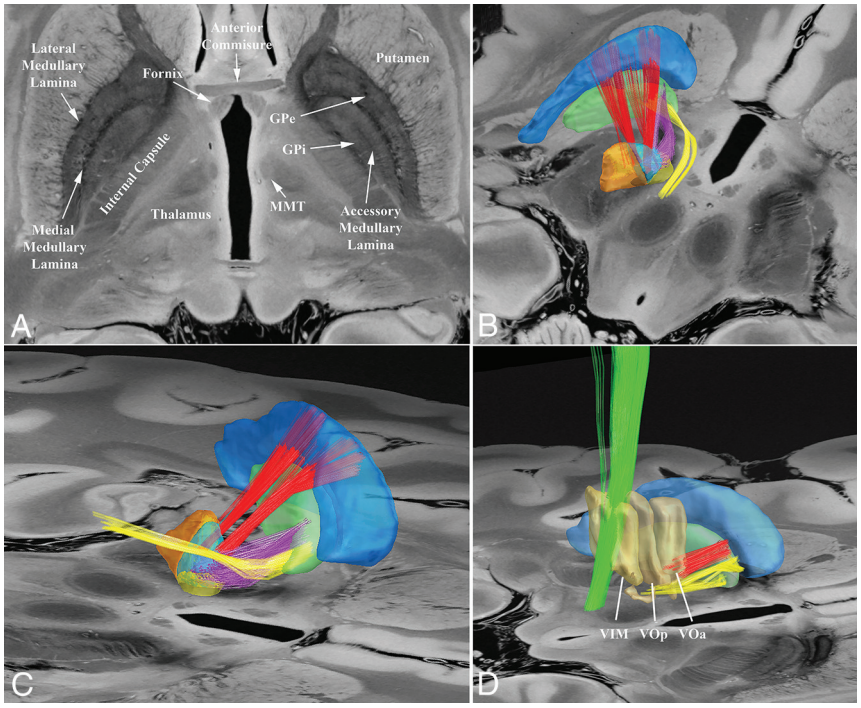

FIG 4. Axial 7T MR imaging (*A*) showing the anatomy of the pallidum and adjacent structures. Posterior oblique (*B*) and anterior oblique views (*C*) highlight the relationship of the AL (yellow fibers) that originates from the anteroventral pole of the globus pallidus internus near the origin of the AS (purple fibers) but courses more dorsal to the AS. The FS is shown as red fibers. Sagittal view (*D*) shows the components of the thalamic fasciculus: dentatorubrothalamic tract (green), AL (yellow), and FL (red) associated with the VIM, ventralis oralis posterior (VOp), and ventralis oralis anterior (VOa) nuclei, respectively.

Although it is not part of the original rate model of the basal ganglia, the more recently described hyperdirect pathway consists of direct connections from the cortex to the STN (Fig 3*A*).[38,39] In keeping with the tripartite division of the STN, hyperdirect connections extend to the motor cortex from the posterior STN, associative cortex from the mid-STN, and limbic regions from the anterior STN. The hyperdirect pathway has been implicated in symptomatology of PD and associated with motor improvement seen with STN DBS in PD using diffusion tractography.[35]

The dorsal pallidum consists of the GPi and GPe, which are separated by the thin internal medial medullary lamina (Fig 4*A*). The external lateral medullary lamina separates the GPe from the adjacent putamen. An accessory lamina further subdivides the GPi into medial and lateral subcomponents. The internal capsule forms the medial border of the globus pallidus. The dorsal pallidum plays a major role in the motor network and is a common treatment target for multiple movement disorders. Similar to the STN, the pallidum has also been described as having a tripartite division.[40]

The GPi primarily connects to the thalamus, putamen, pedunculopontine nucleus, GPe, STN, substantia nigra, habenula, and amygdala.[35] Also reported are direct corticopallidal connections to both GPi and GPe using diffusion tractography,[16,40] but the existence and role of these fibers are yet to be fully elucidated. Further complicating the issue, in the macaque, a peripallidal neuronal network composed of large acetylcholinesterase-containing cells related to the nucleus basalis has been shown to project diffusely to neocortex.[41] 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.[42]

Of primary importance to DBS, the pallidofugal pathways are generally divided into the AL, fasciculus lenticularis (FL), FS, and AS (Fig 4*B*, -*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 4*D*).[35] 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 2*C*). 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.[35] 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 2*A*).[35] 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 4*D*). 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).[43]

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.[44] Connectivity profiles have illustrated the variability in brain networks affected by DBS in treating specific symptoms of PD. Akram et al[45] 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.[45] As may be expected from previously discussed tremor networks, connectivity to the primary motor cortex was associated with greatest benefit in tremor.[45]

To determine if connectivity measures alone could be used to predict improvement across a cohort, Horn et al[46] 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.[46] 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.[46] Similarly, Lin et al[47] 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[15] 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.[48] DBS has been used to treat various forms of dystonia, from focal (predominantly cervical) to generalized dystonia. DBS for dystonia targeting the bilateral GPi received a humanitarian device exemption by the FDA in 2003. Multiple clinical trials[49–51] 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.[52]

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

Connectomics. Connectivity in DBS for dystonia has not been extensively studied. Okromelidze et al[53] 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[54] 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.[55] 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.[56] A multinational, multicenter study by Greenberg et al[57] 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.[57] 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.[58] 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 (slMFB). 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 slMFB DBS target, as described by Coenen et al,[59] 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 slMFB within ALIC.[59]

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

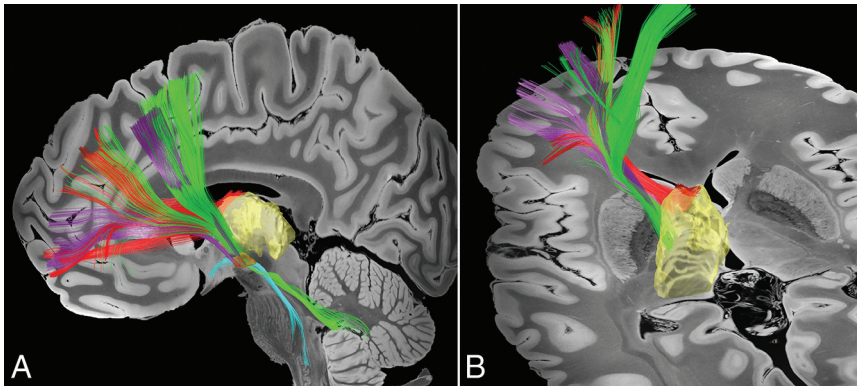

FIG 5. Sagittal (*A*) and posterior oblique views (*B*) showing the relationship of tracts associated with deep brain stimulation of the ALIC for treatment of OCD. The ATR (Red) extend anteriorly from the thalamus (yellow). The MFB (cyan) connects the ventral tegmental area with the nucleus accumbens and olfactory cortex. The MFB does not traverse the ALIC, but, rather, lies ventral and medial to ALIC. The tracts described as a superolateral branch of the MFB (green) mirror the position of the frontal connections of the anteromedial subthalamic nucleus (purple fibers) within the ALIC—both lying lateral to the ATR. These fibers of the subthalamic nucleus may account for the tractography findings previously reported as the superolateral branch of the MFB (more recently referred to as the projection pathway from the ventral tegmental [vtaPP] area). The subthalamic nucleus is shown in orange.

ventrolateral prefrontal cortex was associated with nonresponse.[60] Similarly, Baldermann et al[61] 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 anatomically correct 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[62] 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[63] 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).[63,64] 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.[65] 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[65] share a similar course to what has been described as the slMFB (Fig 5).[62]

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 neuromodulation 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.[66] While effective in many patients, substantial variability in outcomes was reported.[66] Also of note, stimulation-induced adverse effects, including depression and memory impairment, were found, the mechanism of which is not entirely understood.[66] 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).[67-70]

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,[71] which questions the utility of employing such indirect targeting in the brain of a patient with long-standing epilepsy. Grewal et al[72] 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[69] showed the utility of fast gray matter acquisition T1 inversion recovery (FGATIR) MR imaging in direct visualization of the ANT

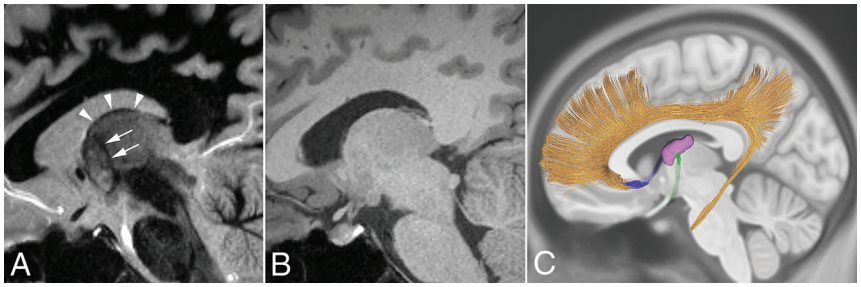

FIG 6. Sagittal 3T FGATIR MR imaging (*A*) compared with MPRAGE (*B*) in the same patient. The FGATIR more clearly highlights the course of the mammillothalamic tract (*arrow*) seen as a dark band extending from the mammillary body, through the thalamus, and terminating at the base of the anterior ANT (*outlined by arrowheads*). Sagittal view of the main connections of the ANT (purple region) (*C*). The mammillothalamic tract (green) connects the mamillary body to the ANT. Tracts (blue) then connect the ANT (through the stria terminalis) with the anterior cingulate and cingulate bundle (orange).

(Fig 6*A*, -*B*), which is currently the most utilized sequence for direct targeting of ANT.

The mammillothalamic tract (MMT) is a component of the limbic circuit that connects the mammillary body to the ANT (Fig 6*C*).[73] MMT arises from the anteromedial mammillary body traversing posterior to the insertion of the fornix and extending superiorly within the substance of the thalamus.[69,73] The termination of the MMT corresponds to the inferior boundary of the ANT. The continuation of the limbic circuit connects the ANT to 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 6*C*).[74] 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 seizure control.[75,76]

Connectomics. Diffusion tractography of MMT has been previously reported. An initial study[77] utilized lengthy diffusion acquisition, replicated with >50% reduction in time in a subsequent study.[69] 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[78] 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.[78] 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.[79] 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.[80] 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.

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