Advances and Future Directions of Neuromodulation in Neurologic Disorders

Matthew R. Burns, MD, PhD, Shannon Y. Chiu, MD, Bhavana Patel, DO, Sotiris G. Mitropanopoulos, MD, Joshua K. Wong, MD, Adolfo Ramirez-Zamora, MD*

KEYWORDS

• Deep brain stimulation • Epilepsy • Chronic pain • Dystonia • Chorea • Tourette syndrome • Essential tremor • Parkinson disease

KEY POINTS

- Deep brain stimulation is a safe and effective therapy for a growing number of neurologic conditions.
- Neuromodulation advances include the development of directional leads, new programming and stimulation paradigms, closed loop capabilities, as well as an increasing number of controllable variables.
- New anatomic targets for neuromodulation are being explored for the treatment of complex neuropsychiatric conditions.

INTRODUCTION

Deep brain stimulation (DBS) is a safe and innovative neuromodulatory therapy applied in multiple neurologic disorders including movement disorders, dementia, epilepsy, neuropsychiatric conditions, and pain.[1] Although the mechanism of action of DBS is not entirely understood, advances in biomedical technology, neuroimaging, neuroanatomy, and neurophysiology have propelled research and adoption of neuromodulation in other conditions. Historically, DBS emerged as an alternative therapy to traditional neurosurgical lesioning treatments based on improved safety with bilateral procedures and reversible side effects.[2,3] In this review, the authors highlight some of the most current insights and advances in this rapidly evolving field.

The Fixel Institute for Neurological Diseases, Department of Neurology, The University of Florida, 3009 Williston Road, Gainesville, FL 32608, USA
* Corresponding author.
E-mail address: Adolfo.Ramirez-Zamora@neurology.ufl.edu

Neurol Clin 39 (2021) 71–85
https://doi.org/10.1016/j.ncl.2020.09.004
neurologic.theclinics.com

ADVANCES IN UNDERSTANDING OF MECHANISM OF ACTION

Since the introduction of DBS, a complete understanding of mechanisms of action has been elusive. Several hypotheses have been proposed despite our incomplete knowledge of related brain physiology.[4,5] The "inhibition" hypothesis proposes that DBS exerts a dampening effect on overactive neurons in the basal ganglia. DBS is thought to decouple local cell body activity from downstream axonal activity via a "functional lesion,"[6] and computational models reveal that DBS exerts local neuronal suppression as previously observed but also results in increased action potential propagation to downstream axons.[7] These ideas are based on animal studies showing excessive inhibition of the pallidum in Parkinson disease (PD) and a decrease in neuronal firing of the subthalamic (STN) nucleus with high-frequency stimulation (HFS),[8] leading to improvements in bradykinesia and rigidity.[9–12] The "jamming" hypothesis suggests that DBS disrupts the normal communication pathways of the basal ganglia, extending its effect beyond the regions immediately adjacent to the lead contacts. Observations on the physiologic responses to DBS over various stimulation frequencies, effects on neighboring neurons, and complex interactions based on physiologic recordings at multiple locations serve as the foundation for this hypothesis.[11,13–15]

In addition, recent studies of STN DBS in PD animal models have detected high-fidelity antidromic action potentials to the cortex along with preserved downstream activation of the globus pallidus (GPi).[16,17] Updates in computational modeling have led to an increase in model components, and the complexity of interactions between them suggests that DBS alters the real-time dynamics of neurotransmitter flow in the form of synaptic suppression at different brain network levels. As our understanding of these complex mechanisms continues to evolve, direct application in clinical practice or development of newer technology is expected.

PARKINSON DISEASE

PD is a progressive neurodegenerative disorder characterized by resting tremor, rigidity, bradykinesia, and postural instability. DBS has emerged as an effective therapy in PD for symptomatic management of medically refractory tremor, motor fluctuations, and/or troublesome dyskinesia superior to medical therapy alone.[18–20]

Briefly, suitable candidates include patients with diagnosis of idiopathic PD of at least 5 years, clear motor fluctuations with robust levodopa response without prominent cognitive impairment or neuropsychiatric symptoms.[21] DBS target selection should be individualized for every patient,[21,22] and several comparative, prospective, randomized studies have shown comparable motor benefit and quality of life between Gpi and STN targets.[22] Nonetheless, a variety of new therapeutic targets are currently under investigation in PD for treatment of freezing of gait, refractory tremor, or associated nonmotor symptoms (**Table 1**).

Recent technological advances in DBS include the development of DBS leads capable of current shaping or steering. DBS side effects occur when undesired tissues/pathways are stimulated (eg, muscle pulling from internal capsule stimulation or sensory changes related to stimulation of medial lemniscus). With traditional leads, complex programming strategies including bipolar or interleaving settings are used to minimize stimulation-induced side effects but may provide suboptimal symptomatic control. Newer DBS leads offer directional stimulation, avoiding undesired tissues/pathways while directing stimulation toward therapeutic regions. In addition, newer devices provide an expanded range of features to reduce side effects including lower pulse widths, shaping of stimulation using multiple independent current control,

Table 1
Emerging neuromodulation targets in Parkinson disease

Target	Indication
Centromedian and parafascicular thalamic complex	Refractory tremor[91]
Nucleus basalis of Meynert	PD dementia[92]
Pedunculopontine nucleus (PPN)	Freezing of gait,[93] sleep[94,95]
Substantia nigra pars reticulate (SNr)	Freezing of gait[96]
Spinal cord stimulation	Freezing of gait[97]
Caudal zona incerta	Refractory tremor[98]
Combined subthalamic nucleus and SNr	Freezing of gait[99]

anodic stimulation, newer leads designs, and programming using constant current versus voltage (**Table 2**).

New research shows promise improving motor outcomes using alternative pulse shapes such as patterned stimulation algorithms (eg, bursts of 0.1-s duration repeated at 5 Hz with an impulse width of 60 μs[23]) or square biphasic pulses to enhance the therapeutic window.[24,25] In addition, the development of adaptive closed-loop DBS has emerged as a promising new tool for motor and paroxysmal symptoms in PD.[4] Adaptive closed-loop approaches use individual patient's electrophysiological signature and pathology status to delivering customized stimulation, providing therapeutic benefit with fewer side effects and prolonging battery life. Research has identified abnormal brain coupling in the phase of activity in beta-frequency band (13–35 Hz) as a physiologic biomarker in PD that correlates with parkinsonian symptoms, and it is modulated by either dopaminergic treatment or DBS. Additional electrophysiologic biomarkers currently being investigated include narrowband gamma oscillation in the motor cortex between 60 and 90 Hz associated with dyskinesia,[5] the use of patterned stimulation using neural activity phase rather than just local field potentials (LFP),[8] or disruption of longer bursts of hypersynchronized beta activity (more pervasive oscillatory synchronization within the neural circuit).[9] Biomarker detection using machine learning control algorithms might be required and may need to adapt over time to compensate for neuroplasticity seen with disease progression. Development of external sensing devices and algorithms for tremor control[10] or freezing of gait and using stimulation-induced signals such as evoked resonant neural activity in STN DBS for programming and placement of DBS leads are under investigation as well.[10] Short-term studies of adaptive DBS in PD are promising thus far[7,26,27]; however, more studies are needed to evaluate long-term efficacy of adaptive DBS in PD, particularly addressing additional treatment-refractory symptoms such as postural instability, dysarthria, cognitive, and mood dysfunction.

ESSENTIAL TREMOR

Essential tremor (ET) is one of the most common adult-onset movement disorders, affecting nearly 10 million Americans.[28] ET classically involves postural and kinetic tremors of the hands and arms but can involve the head, voice, trunk, or legs. Approximately 50% of patients develop medication-refractory tremor and/or intolerable side effects from medications. For these patients, surgical therapy, primarily DBS of the ventral intermediate (VIM) nucleus of the thalamus, is an effective option.[11,29,30]

Table 2
Comparison of commercially available deep brain stimulation systems in the United States

System Features	Boston Scientific	Medtronic	Abbott
Number of lead contacts	1-3-3-1 segmented with current steering and multiple independent current control; 8 contacts/lead	1-1-1-1 segmented not available; 4 contacts/lead	1-3-3-1 segmented current shaping lead; 8 contacts/lead
Programming platform	Bionic Navigator software on touch screen interface with tissue activation, volume visualization, multiple independent current control, anodic stimulation	Samsung Galaxy tablet	iOS software wireless platform with Apple mobile digital devices as programming platforms
Programming features	Programmer connects through a wireless IR link	Wireless through Medtronic wireless close-range communicator	Wireless through Apple devices
Parameter control	2–250 Hz; 20–450 PW; 12.7 mA/contact max or 20 mA total max; up to 4 independent freq. ctrl/program	2–250 Hz; 60–450 PW; 10.5 V/25.5 mA max. No independent freq. ctrl	2–240 Hz; 20–500 PW, 12.75 mA max. up to 2 independent freq. ctrl
Battery	Dual-chamber Vercise primary cell and rechargeable Vercise Gevia	Single-chamber Activa SC and dual-chamber PC; rechargeable activa RC	Dual-chamber Abbott Infinity
Sensing	Not commercially available	NEXUS, PRECEPT, advanced sensing platform in development	Not commercially available
Wireless capability	3 feet	Not available	3–6 feet
MRI compatibility	Unavailable	Conditionally compatible	Conditionally compatible

Abbreviation: PW, pulse width.

Although some studies report decrease in tremor benefit over time, it remains unclear whether these longitudinal changes are due to disease progression, effects of atrophy, side effects from long-term stimulation, and/or due to disruption of neuronal oscillatory pathways within the tremor network.[12,13]

Although VIM DBS remains the primary target for ET, the posterior subthalamic area/caudal zona incerta (PSA/cZI) region has been proposed as an alternative target for stimulation in ET.[14] Few studies, however, have directly compared the efficacy of VIM versus PSA/cZI.[15,26,31] The proposed advantage of PSA/cZI stimulation relies on the notion that more effective stimulation can be delivered to compact, bundled white matter projections from the cerebellum before reaching the VIM, potentially improving axial symptoms as well.[27] Alternative surgical targets for neuromodulation of both ET and other complex, refractorytremor syndromes include dual lead placement in VIM and thalamic ventralis oralis anterior and posterior (Voa/Vop), STN, and GPi.[7] As a pallidal receiving area, Voa/Vop stimulation in conjunction with VIM has been used in the treatment of postural-action tremors alone or as a rescue lead for severe, refractory tremor.[16]

Newer technology including segmented electrodes may improve steering of current away from unintended tissue/pathways in the thalamus and toward VIM efferent and afferent projections for tremor suppression.[17] Meanwhile, the application of closed-loop DBS has been used in conjunction with central or peripheral sensors that detect abnormal brain activity during tremor states, thus delivering customized stimulation only at tremor onset.[6,32] Thalamic DBS for tremor has seen marked advances in technology with new methods to direct lead placement and connectivity assessments including anatomic (diffusion tensor imaging and tractography) and functional techniques (electrocardiogram, functional MRI, and invasive neurophysiological techniques including microelectrode recordings, LFPs, and electrocorticography). A combination of advances in both technology and lead localization has the potential to translate into further improvements in clinical outcomes.[33]

DYSTONIA

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Several randomized blinded sham-controlled studies have demonstrated safety and efficacy of pallidal DBS in focal and segmental dystonia in children and adults.[34–36] The extent of benefit from DBS may depend on an individual's unique genetic background and phenotype.[37] Although posteroventral lateral GPi is currently the most common DBS target,[38] recent evidence supports efficacy in STN,[39–41] along with early reports stimulating the sensorimotor thalamus.[42] At present time, there are no comparative studies available, and unique side effects have been reported with evolving targets such as generalized dyskinesia with STN DBS and gait difficulties or weight gain with thalamic stimulation. There is enormous interest in identifying specific neurophysiological biomarkers for dystonia to aid with DBS programming and implantation, as programming is challenging, slow, and not standardized. A few series and reports point to possible abnormal electrophysiologic signals, primarily a high theta band activity in both deep basal ganglia structures and cortex.[43,44] Given the delayed but sustainable effects of long-term DBS stimulation in dystonia, even when DBS is turned off, the field has begun to examine the potential symptomatic and disease-modifying effect of earlier DBS intervention for dystonia. More research is needed in all these areas of dystonia research.

TOURETTE SYNDROME

Tourette syndrome (TS) is characterized by motor and phonic tics often associated with comorbid obsessive-compulsive disorder, attention-deficit hyperactivity disorder, impulsivity, depression, and anxiety.[45] Most of the individuals with TS experience an improvement in tics during late adolescence; however, tics may persist or become debilitating in about 20% of individuals.[46] For refractory, severe, or disabling tics DBS can be an effective treatment option. Thalamic DBS was first introduced as a treatment option for TS in 1999, and various targets have since been proposed and evaluated by expert centers worldwide with promising outcomes.[47,48] The most commonly used target is the medial thalamus (centromedian nucleus, parafascicular nucleus, ventralis oralis nucleus), but additional targets include anteromedial or posterior ventrolateral GPi, anterior internal capsule, nucleus accumbens, subthalamic nucleus, fields of Forel (H1), and globus pallidus externus.[49–57] A recent meta-analysis revealed decreased tic severity among all thalamic and pallidal targets, with a greater than 20% improvement in YGTSS scores. A greater than 50% improvement in tic severity scores was observed in 64% of individuals. Traditionally, DBS therapy for TS delivers continuous stimulation; however, adaptive DBS is of particular interest in disorders with paroxysmal symptoms such as TS. Newer technology might be needed to successfully deliver adaptive stimulation in TS; improved sensing capabilities, biomarkers, real-timer recording, and signal synchronization of DBS devices would be essential. In 2012 the International TS DBS Registry and Database was launched in association with the Tourette Association of America to create a worldwide registry to help answer these questions.[48,58] Currently there are 33 participating centers with 277 individuals with DBS for TS registered [https://tourettedeepbrainstimulationregistry.ese.ufhealth.org].

TARDIVE DYSKINESIA AND CHOREA

Chorea is defined as an irregular, nonstereotyped, involuntary movement that flow to adjacent body regions and is caused by a variety of neurodegenerative, drug-induced, autoimmune, vascular, and metabolic causes.[59–61] Medically refractory chorea has been managed primarily with pallidal DBS stimulation, although there are few reports of thalamic stimulation as well.[59] In Huntington disease, long-term benefit (up to 4 years) in chorea has been reported with a mean improvement in the Unified Huntington's Disease Rating Scale chorea subscore of 59.8% in single-case reports.[62,63] Additional case reports and small open-label studies suggest sustained and marked efficacy with pallidal DBS in chorea with DBS in other neurodegenerative conditions causing refractory chorea including neuroacanthocytosis.[64,65] Prolonged use of dopamine receptor-blocking agents can produce a variable syndrome of chorea, dystonia, and parkinsonism called tardive dyskinesia (TD). DBS has been evaluated in patients with refractory TD in a prospective, multicenter, double-blind, study showing adequate safety, tolerability, and efficacy using pallidal DBS in 10 patients with severe TD.[66] Long-term outcomes of the original cohort with the addition of 10 more cases were recently reported showing persistent safety and efficacy.[66]

DEMENTIA

Alzheimer disease (AD) is a neurodegenerative cognitive and memory disorder characterized by progressive pathologic accumulation of beta-amyloid plaques, neurofibrillary tangles of tau proteins, and neuronal cell death. Evidence implicates disruption of neural networks in the pathophysiology of disease,[67,68] and as a result,

research efforts have begun to focus on DBS applications in AD attempting to modulate and disrupt aberrant signals that might contribute to neurodegeneration. Anatomic targets currently in clinical trials include the Fornix,[69,70] nucleus basalis of Meynert,[71,72] and ventral capsule/ventral striatum.[73] Preliminary evidence has shown that DBS of the fornix has possible benefit in patients older than 65 years in early stages, and new clinical trials are undergoing ADVANCE-2 (NCT03622905). Early, preliminary studies are investigating the role of DBS in other dementias.

EPILEPSY

Neurostimulation is primarily indicated in epilepsy when the patient meets criteria for drug-resistant epilepsy, defined by failure of rational polytherapy of at least 2 well-tolerated and appropriately chosen antiseizures drugs, and is a poor candidate for traditional surgical treatments.[74] There are a variety of neuromodulatory approaches to epilepsy, but the main modalities include DBS, responsive neurostimulation, and vagal nerve stimulation. Other emerging modalities for the treatment of epilepsy include repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and external trigeminal nerve stimulation.

In the Electrical Stimulation of the Anterior Nucleus of Thalamus for treatment of refractory Epilepsy (SANTE) trial, the anterior nuclei (AN) of the thalami were selected as targets based on data showing at least a 50% reduction in seizure frequency.[75] The AN connect to the superior frontal and temporal lobe structures, which are areas involved in seizure onset and propagation. At 3 months, the stimulated group had a 29% reduction in seizure frequency over the control group (40.4% vs 14.5%).[75] At 2 years, 102 participants remained in the study and had a 56% median percent reduction in seizure frequency, of which 54% had at least a 50% reduction. The procedure was safe with no intracranial bleeding or infection, but the treatment arm included complaints of decreased mood and memory issues. At 5 years postimplantation, 75 participants remained active in the study, and the median improvement was 69%.[76] Eleven subjects reported seizure-free intervals of 6 months. Subgroup analysis based on seizure onset zone yielded a 76%, 59%, and 68% reduction in seizures from temporal lobe, frontal lobe, and other onset locations, respectively, at 5 years.[75] Other targets in DBS for epilepsy include the centromedian nucleus of the thalamus, the subthalamic nucleus, the hippocampus, and the cerebellum showing potential benefit with modulation of different nodes in the epileptic network; however, most studies were small with uncontrolled designs.[77]

PAIN

DBS has been applied to a variety of pain syndromes ranging from poststroke pain, spinal cord injury, brachial plexus injury, and headache.[78] There are 3 commonly targeted structures for neuromodulation of pain: (1) the thalamus, specifically the ventral posterolateral nucleus and ventral posteromedial nucleus (VPL/VPM), (2) the periventricular and periaqueductal gray (PVG/PAG), and (3) the anterior cingulate cortex (ACC). Neuromodulation of the VPL/VPM and PVG/PAG have been the most well established in the literature.[79–81] One longitudinal study of VPL/VPM and PVG/PAG DBS for various pain conditions revealed 59% of patients experienced significant acute pain relief.[81] After approximately 80 months of follow-up, 31% of patients continued to experience pain relief. In another study with up to 15 years of follow-up after VPL/VPM or PVG/PAG DBS for various pain syndromes, 62% of patients continued to experience adequate pain relief.[82] A meta-analysis of DBS for pain reported that modulation of the PVG/PAG alone or PVG/PAG with VPL/VPM or internal

capsule was more effective than VPL/VPM alone. In addition, overall 58% of patients achieved pain relief. DBS was most effective in treating intractable low back pain and least successful in treating central thalamic pain/poststroke pain. Although central thalamic pain syndrome has historically been difficult to treat, Franzini and colleagues[83] recently investigated DBS of the posterior limb of the internal capsule in 4 patients. Three of four patients achieved long-term pain relief post-DBS. After a mean follow-up of 5.88 years, the average reduction in pain was 38% based on the 10-point visual analog scale.

Inspired by lesional therapies for cancer-related pain, ACC DBS has emerged as the newest potential target for pain.[84,85] Spooner and colleagues[86] published the first

Table 3
Other neurologic and psychiatric disorders managed with neuromodulation under investigation

Indication	Potential DBS Target	Trial[a]
Tinnitus	Auditory pathways Area LC VIM	Phase I–II
Major depression	SCC NAc Habenula Medial forebrain bundle VC/VS ITP BNST	Phase I–III
Obsessive-compulsive disorder	NAc STN BNST ITP ALIC VC/VS	Phase I–IV
Schizophrenia	Temporal cortex NAc VTA SCC	Preclinical/Phase I
Addiction	NAc STN	Phase I–III
Anorexia nervosa	SCC NAc ALIC	Phase I
Obesity	Lateral hypothalamus NAc	Phase I

This table lists some additional indications and targets not previously mentioned in this review.

Abbreviations: ALIC, anterior limb of the capsula interna; Area LC, locus of caudate neurons; BNST, bed nucleus of stria terminalis; ITP, inferior thalamic peduncle; NAc nucleus accumbens; VC/VS, ventral capsule/ventral striatum; VIM, ventral intermediate nucleus of the thalamus; SCC, subgenual cingulate cortex; STN, subthalamic nucleus; VTA, ventral tegmental area.

[a] Refer to clinicaltrials.gov for more details.

Data from Clinicaltrials.gov; and Budman et al. Potential Indications for Deep Brain Stimulation in Neurological Disorders: An Evolving Field. Eur J Neurol. 2018 Mar;25(3):434-e30; and Lee et al. Current and Future Directions of Deep Brain Stimulation for Neurological and Psychiatric Disorders. J Neurosurg. 2019 Aug 1;131(2):333-342; and Lozano et al. Deep Brain Stimulation: Current Challenges and Future Directions. Nat Rev Neurol. 2019 Mar;15(3):148-160.

case report of ACC DBS in 2007 in a patient with medically refractory neuropathic pain from a complete C4 spinal cord injury. At 3 months post-DBS implantation, the patient reported a 3 out of 10 on the pain visual analog scale compared with 10 out of 10 with DBS off. Since then, several other case reports have described success in ACC DBS for medically refractory neuropathic pain.[87–89] One recent study has showed some efficacy of ACC DBS for central thalamic pain.[90] In this study, 5 patients with medically refractory central thalamic pain syndrome underwent simultaneous bilateral ACC DBS. The investigators reported an average of 38% and 35% improvement of pain at 6- and 18-months post-DBS implantation, respectively.

DISCUSSION AND FUTURE DIRECTIONS

Recent advances in our understanding of brain neurophysiology in neurologic disorders, coupled with improved signal acquisition and delivery of neurostimulation, have propelled growing interest in the study and use of neuromodulation in neurologic and psychiatric conditions (**Table 3**). As detailed in previous sections, new research continues to shape the practice and future of neuromodulation in neurology. Collaborative, long-term, controlled trials are necessary to establish long-term safety, define appropriate candidates, and persistent efficacy. In response to issues arising from the development and application of DBS and other neurotechnologies, incorporating ethical principles and guidelines to research will continue to be crucial. The future is bright, and neuromodulation techniques will continue to increase our understating of pathologic brain states while helping patients around the globe.

ACKNOWLEDGMENTS

MRB acknowledges salary and research support from the Parkinson's; BP acknowledges salary and research support from the American Academy of Neurology. Also JKW's research is supported by R25 NS108939.

DISCLOSURE

There are no disclosures relevant to the content of this paper. Unrelated to the content of the paper, in the past year.

REFERENCES

1. Budman E, Deeb W, Martinez-Ramirez D, et al. Potential indications for deep brain stimulation in neurological disorders: an evolving field. Eur J Neurol 2018; 25(3):434–434.e30.
2. Hariz MI, Hariz GM. Therapeutic stimulation versus ablation. Handb Clin Neurol 2013;116:63–71.
3. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 1992;76(1):53–61.
4. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. Ann Neurol 2013;74(3):449–57.
5. Swann NC, de Hemptinne C, Miocinovic S, et al. Gamma Oscillations in the Hyperkinetic State Detected with Chronic Human Brain Recordings in Parkinson's Disease. J Neurosci 2016;36(24):6445–58.
6. Herron JA, Thompson MC, Brown T, et al. Chronic electrocorticography for sensing movement intention and closed-loop deep brain stimulation with wearable sensors in an essential tremor patient. J Neurosurg 2017;127(3):580–7.

7. Ramirez-Zamora A, Okun MS. Deep brain stimulation for the treatment of uncommon tremor syndromes. Expert Rev Neurother 2016;16(8):983–97.
8. Pina-Fuentes D, van Dijk JMC, Drost G, et al. Direct comparison of oscillatory activity in the motor system of Parkinson's disease and dystonia: A review of the literature and meta-analysis. Clin Neurophysiol 2019;130(6):917–24.
9. Tinkhauser G, Pogosyan A, Little S, et al. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. Brain 2017;140(4):1053–67.
10. Ramirez-Zamora A, Giordano JJ, Gunduz A, et al. Evolving Applications, Technological Challenges and Future Opportunities in Neuromodulation: Proceedings of the Fifth Annual Deep Brain Stimulation Think Tank. Front Neurosci 2017;11:734.
11. Baizabal-Carvallo JF, Kagnoff MN, Jimenez-Shahed J, et al. The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. J Neurol Neurosurg Psychiatry 2014;85(5):567–72.
12. Favilla CG, Ullman D, Wagle Shukla A, et al. Worsening essential tremor following deep brain stimulation: disease progression versus tolerance. Brain 2012;135(Pt 5):1455–62.
13. Martinez-Ramirez D, Morishita T, Zeilman PR, et al. Atrophy and other potential factors affecting long term deep brain stimulation response: a case series. PLoS One 2014;9(10):e111561.
14. Blomstedt P, Sandvik U, Fytagoridis A, et al. The posterior subthalamic area in the treatment of movement disorders: past, present, and future. Neurosurgery 2009;64(6):1029–38 [discussion: 1038–42].
15. Hamel W, Herzog J, Kopper F, et al. Deep brain stimulation in the subthalamic area is more effective than nucleus ventralis intermedius stimulation for bilateral intention tremor. Acta Neurochir (Wien) 2007;149(8):749–58 [discussion: 758].
16. Yamamoto T, Katayama Y, Kano T, et al. Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. J Neurosurg 2004;101(2):201–9.
17. Keane M, Deyo S, Abosch A, et al. Improved spatial targeting with directionally segmented deep brain stimulation leads for treating essential tremor. J Neural Eng 2012;9(4):046005.
18. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991;337(8738):403–6.
19. Pollak P, Benabid AL, Gross C, et al. [Effects of the stimulation of the subthalamic nucleus in Parkinson disease]. Rev Neurol (Paris) 1993;149(3):175–6.
20. Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 1994;35(6):1126–9 [discussion: 1129–30].
21. Almeida L, Deeb W, Spears C, et al. Current Practice and the Future of Deep Brain Stimulation Therapy in Parkinson's Disease. Semin Neurol 2017;37(2):205–14.
22. Ramirez-Zamora A, Ostrem JL. Globus Pallidus Interna or Subthalamic Nucleus Deep Brain Stimulation for Parkinson Disease: A Review. JAMA Neurol 2018;75(3):367–72.
23. Horn MA, Gulberti A, Gülke E, et al. A New Stimulation Mode for Deep Brain Stimulation in Parkinson's Disease: Theta Burst Stimulation. Mov Disord 2020;35(8):1471.

24. De Jesus S, Almeida L, Shahgholi L, et al. Square biphasic pulse deep brain stimulation for essential tremor: The BiP tremor study. Parkinsonism Relat Disord 2018;46:41–6.
25. Akbar U, Raike RS, Hack N, et al. Randomized, Blinded Pilot Testing of Nonconventional Stimulation Patterns and Shapes in Parkinson's Disease and Essential Tremor: Evidence for Further Evaluating Narrow and Biphasic Pulses. Neuromodulation 2016;19(4):343–56.
26. Barbe MT, Reker P, Hamacher S, et al. DBS of the PSA and the VIM in essential tremor: A randomized, double-blind, crossover trial. Neurology 2018;91(6): e543–50.
27. Ramirez-Zamora A, Smith H, Kumar V, et al. Evolving Concepts in Posterior Subthalamic Area Deep Brain Stimulation for Treatment of Tremor: Surgical Neuroanatomy and Practical Considerations. Stereotact Funct Neurosurg 2016;94(5): 283–97.
28. Louis ED, Ottman R. How many people in the USA have essential tremor? Deriving a population estimate based on epidemiological data. Tremor Other Hyperkinet Mov (N Y) 2014;4:259.
29. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. J Neurosurg 2006;104(4):506–12.
30. Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84(2):203–14.
31. Eisinger RS, Wong J, Almeida L, et al. Ventral Intermediate Nucleus Versus Zona Incerta Region Deep Brain Stimulation in Essential Tremor. Mov Disord Clin Pract 2018;5(1):75–82.
32. Tan H, Debarros J, He S, et al. Decoding voluntary movements and postural tremor based on thalamic LFPs as a basis for closed-loop stimulation for essential tremor. Brain Stimul 2019;12(4):858–67.
33. Ramirez-Zamora A, Giordano J, Boyden ES, et al. Proceedings of the Sixth Deep Brain Stimulation Think Tank Modulation of Brain Networks and Application of Advanced Neuroimaging, Neurophysiology, and Optogenetics. Front Neurosci 2019;13:936.
34. Krauss JK, Pohle T, Weber S, et al. Bilateral stimulation of globus pallidus internus for treatment of cervical dystonia. Lancet 1999;354(9181):837–8.
35. Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. Lancet Neurol 2014;13(9):875–84.
36. Kupsch A, Benecke R, Müller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;355(19):1978–90.
37. Jinnah HA, Alterman R, Klein C, et al. Deep brain stimulation for dystonia: a novel perspective on the value of genetic testing. J Neural Transm (Vienna) 2017; 124(4):417–30.
38. Moro E, LeReun C, Krauss JK, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. Eur J Neurol 2017;24(4):552–60.
39. Ostrem JL, Racine CA, Glass GA, et al. Subthalamic nucleus deep brain stimulation in primary cervical dystonia. Neurology 2011;76(10):870–8.
40. Gupta A. Subthalamic stimulation for cervical dystonia. Acta Neurochir 2020; 162(8):1879.
41. Hua X, Zhang B, Zheng Z, et al. Predictive factors of outcome in cervical dystonia following deep brain stimulation: an individual patient data meta-analysis. J Neurol 2020. https://doi.org/10.1007/s00415-020-09765-9.

42. Pauls KA, Hammesfahr S, Moro E, et al. Deep brain stimulation in the ventrolateral thalamus/subthalamic area in dystonia with head tremor. Mov Disord 2014;29(7):953–9.
43. Miocinovic S, de Hemptinne C, Qasim S, et al. Patterns of Cortical Synchronization in Isolated Dystonia Compared With Parkinson Disease. JAMA Neurol 2015;72(11):1244–51.
44. Miocinovic S, Swann NC, de Hemptinne C, et al. Cortical gamma oscillations in isolated dystonia. Parkinsonism Relat Disord 2018;49:104–5.
45. Robertson MM. The Gilles de la Tourette syndrome: the current status. Br J Psychiatry 1989;154:147–69.
46. Cath DC, Hedderly T, Ludolph AG, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part I: assessment. Eur Child Adolesc Psychiatry 2011;20:155–71.
47. Vandewalle V, van der Linden C, Groenewegen HJ, et al. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet 1999;353:724.
48. Deeb W, Rossi PJ, Porta M, et al. The International Deep Brain Stimulation Registry and Database for Gilles de la Tourette Syndrome: How Does It Work? Front Neurosci 2016;10:170.
49. Cavanna AE, Eddy CM, Mitchell R, et al. An approach to deep brain stimulation for severe treatment-refractory Tourette syndrome: the UK perspective. Br J Neurosurg 2011;25:38–44.
50. Dehning S, Mehrkens JH, Muller N, et al. Therapy-refractory Tourette syndrome: beneficial outcome with globus pallidus internus deep brain stimulation. Mov Disord 2008;23:1300–2.
51. Massano J, Sousa C, Foltynie T, et al. Successful pallidal deep brain stimulation in 15-year-old with Tourette syndrome: 2-year follow-up. J Neurol 2013;260:2417–9.
52. Flaherty AW, Williams ZM, Amirnovin R, et al. Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: technical case report. Neurosurgery 2005;57:E403 [discussion: E403].
53. Kuhn J, Lenartz D, Mai JK, et al. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. J Neurol 2007;254:963–5.
54. Martinez-Torres I, Hariz MI, Zrinzo L, et al. Improvement of tics after subthalamic nucleus deep brain stimulation. Neurology 2009;72:1787–9.
55. Piedimonte F, Andreani JC, Piedimonte L, et al. Behavioral and motor improvement after deep brain stimulation of the globus pallidus externus in a case of Tourette's syndrome. Neuromodulation 2013;16:55–8 [discussion: 58].
56. Maciunas RJ, Maddux BN, Riley DE, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. J Neurosurg 2007;107:1004–14.
57. Neudorfer C, El Majdoub F, Hunsche S, et al. Deep Brain Stimulation of the H Fields of Forel Alleviates Tics in Tourette Syndrome. Front Hum Neurosci 2017;11:308.
58. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, et al. Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome: The International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. JAMA Neurol 2018;75(3):353–9.
59. Edwards TC, Zrinzo L, Limousin P, et al. Deep brain stimulation in the treatment of chorea. Mov Disord 2012;27:357–63.

60. Barton B, Zauber SE, Goetz CG. Movement disorders caused by medical disease. Semin Neurol 2009;29(2):97–110.
61. Bhidayasiri R, Truong DD. Chorea and related disorders. Postgrad Med J 2004; 80:527–34.
62. Gonzalez V, Cif L, Biolsi B, et al. Deep brain stimulation for Huntington's disease: long-term results of a prospective open-label study. J Neurosurg 2014;121(1): 114–22.
63. Biolsi B, Cif L, Fertit HE, et al. Long-term follow-up of Huntington disease treated by bilateral deep brain stimulation of the internal globus pallidus. J Neurosurg 2008;109:130–2.
64. Li P, Huang R, Song W, et al. Deep brain stimulation of the globus pallidus internal improves symptoms of chorea-acanthocytosis. Neurol Sci 2012;33(2):269–74.
65. Wang KL, Hess CW, Xu D, et al. High Frequency Bilateral Globus Pallidus Interna Deep Brain Stimulation Can Improve Both Chorea and Dysarthria in Chorea-acanthocytosis. Parkinsonism Relat Disord 2019;62:248–50.
66. Pouclet-Courtemanche H, Rouaud T, Thobois S, et al. Long-term efficacy and tolerability of bilateral pallidal stimulation to treat tardive dyskinesia. Neurology 2016;86:651–9.
67. Greicius MD, Srivastava G, Reiss AL, et al. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A 2004;101(13):4637–42.
68. Sperling RA, Dickerson BC, Pihlajamaki M, et al. Functional alterations in memory networks in early Alzheimer's disease. Neuromolecular Med 2010;12:27–43.
69. Laxton AW, Tang-Wai DF, McAndrews MP, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010;68:521–34.
70. Lozano AM, Fosdick L, Chakravarty MM, et al. A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer's Disease. J Alzheimers Dis 2016;54:777–87.
71. Hardenacke K, Hashemiyoon R, Visser-Vandewalle V, et al. Deep Brain Stimulation of the Nucleus Basalis of Meynert in Alzheimer's Dementia: Potential Predictors of Cognitive Change and Results of a Long-Term Follow-Up in Eight Patients. Brain Stimul 2016;9:799–800.
72. Kuhn J, Hardenacke K, Shubina E, et al. Deep Brain Stimulation of the Nucleus Basalis of Meynert in Early Stage of Alzheimer's Dementia. Brain Stimul 2015;8: 838–9.
73. Bittlinger M, Muller S. Opening the debate on deep brain stimulation for Alzheimer disease - a critical evaluation of rationale, shortcomings, and ethical justification. BMC Med Ethics 2018;19:41.
74. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
75. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899–908.
76. 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.
77. Klinger N, Mittal S. Deep brain stimulation for seizure control in drug-resistant epilepsy. Neurosurg Focus 2018;45:E4.
78. Farrell SM, Green A, Aziz T. The Current State of Deep Brain Stimulation for Chronic Pain and Its Context in Other Forms of Neuromodulation. Brain Sci 2018;8. https://doi.org/10.3390/brainsci8080158.

79. Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. J Neurosurg 1977;47:178–83.
80. Mazars G, Roge R, Mazars Y. [Results of the stimulation of the spinothalamic fasciculus and their bearing on the physiopathology of pain]. Rev Neurol (Paris) 1960;103:136–8.
81. Levy RM, Lamb S, Adams JE. Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. Neurosurgery 1987;21:885–93.
82. Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery 1997;40:736–46 [discussion: 746–7].
83. Franzini A, Messina G, Levi V, et al. Deep brain stimulation of the posterior limb of the internal capsule in the treatment of central poststroke neuropathic pain of the lower limb: case series with long-term follow-up and literature review. J Neurosurg 2019;1–9. https://doi.org/10.3171/2019.5.JNS19227.
84. Viswanathan A, Harsh V, Pereira EA, et al. Cingulotomy for medically refractory cancer pain. Neurosurg Focus 2013;35(3):E1.
85. Pereira EA, Paranathala M, Hyam JA, et al. Anterior cingulotomy improves malignant mesothelioma pain and dyspnoea. Br J Neurosurg 2014;28(4):471–4.
86. Spooner J, Yu H, Kao C, et al. Neuromodulation of the cingulum for neuropathic pain after spinal cord injury. Case report. J Neurosurg 2007;107(1):169–72.
87. Boccard SGJ, Prangnell SJ, Pycroft L, et al. Long-Term Results of Deep Brain Stimulation of the Anterior Cingulate Cortex for Neuropathic Pain. World Neurosurg 2017;106:625–37.
88. Boccard SG, Pereira EA, Moir L, et al. Deep brain stimulation of the anterior cingulate cortex: targeting the affective component of chronic pain. Neuroreport 2014;25:83–8.
89. Boccard SG, Fitzgerald JJ, Pereira EA, et al. Targeting the affective component of chronic pain: a case series of deep brain stimulation of the anterior cingulate cortex. Neurosurgery 2014;74:628–35 [discussion: 635–7].
90. Levi V, Cordella R, D'Ammando A, et al. Dorsal anterior cingulate cortex (ACC) deep brain stimulation (DBS): a promising surgical option for the treatment of refractory thalamic pain syndrome (TPS). Acta Neurochir (Wien) 2019;161:1579–88.
91. Mazzone P, Stocchi F, Galati S, et al. Bilateral Implantation of Centromedian-Parafascicularis Complex and GPi: A New Combination of Unconventional Targets for Deep Brain Stimulation in Severe Parkinson Disease. Neuromodulation 2006;9(3):221–8.
92. Freund H-J, Kuhn J, Lenartz D, et al. Cognitive Functions in a Patient With Parkinson-Dementia Syndrome Undergoing Deep Brain Stimulation. Arch Neurol 2009;66(6):781–5.
93. Thevathasan W, Debu B, Aziz T, et al. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: A clinical review. Mov Disord 2018;33(1):10–20.
94. Romigi A, Placidi F, Peppe A, et al. Pedunculopontine nucleus stimulation influences REM sleep in Parkinson's disease. Eur J Neurol 2008;15(7):e64–5.
95. Lim AS, Moro E, Lozano AM, et al. Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. Ann Neurol 2009;66(1):110–4.

96. Weiss D, Walach M, Meisner C, et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. Brain 2013; 136(7):2098–108.
97. Samotus O, Parrent A, Jog M. Spinal Cord Stimulation Therapy for Gait Dysfunction in Advanced Parkinson's Disease Patients. Mov Disord 2018;33(5):783–92.
98. Plaha P, Ben-Shlomo Y, Patel NK, et al. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. Brain 2006;129(Pt 7):1732–47.
99. Valldeoriola F, Muñoz E, Rumià J, et al. Simultaneous low-frequency deep brain stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the subthalamic nucleus to treat levodopa unresponsive freezing of gait in Parkinson's disease: A pilot study. Parkinsonism Relat Disord 2019;60:153–7.