International Journal of Neuroscience, 2015; 125(7): 475–485
Copyright © 2015 Taylor and Francis
ISSN: 0020-7454 print / 1543-5245 online
DOI: 10.3109/00207454.2014.999268

Taylor & Francis
Taylor & Francis Group

REVIEW PAPER

Proceedings of the Second Annual Deep Brain Stimulation Think Tank: What's in the Pipeline

Aysegul Gunduz,[1] Hokuto Morita,[1] P. Justin Rossi,[1] William L. Allen,[1] Ron L. Alterman,[2] Helen Bronte-Stewart,[3] Christopher R. Butson,[4] David Charles,[5] Sjaak Deckers,[6] Coralie de Hemptinne,[7] Mahlon DeLong,[8] Darin Dougherty,[9] Jens Ellrich,[6] Kelly D. Foote,[1] James Giordano,[10] Wayne Goodman,[11] Benjamin D. Greenberg,[12] David Greene,[13] Robert Gross,[8] Jack W. Judy,[1] Edward Karst,[14] Alexander Kent,[15] Brian Kopell,[11] Anthony Lang,[16] Andres Lozano,[16] Codrin Lungu,[17] Kelly E. Lyons,[18] Andre Machado,[19] Hubert Martens,[6] Cameron McIntyre,[20] Hoon-Ki Min,[21] Joseph Neimat,[5] Jill Ostrem,[7] Sat Pannu,[22] Francisco Ponce,[23] Nader Pouratian,[24] Donnie Reymers,[25] Lauren Schrock,[4] Sameer Sheth,[26] Ludy Shih,[2] Scott Stanslaski,[27] G. Karl Steinke,[28] Paul Stypulkowski,[27] Alexander I. Tröster,[23] Leo Verhagen,[29] Harrison Walker,[30] and Michael S. Okun[1,*]

[1]University of Florida, Gainesville, FL, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Stanford University, Stanford, CA, USA; [4]University of Utah, Salt Lake City, UT, USA; [5]Vanderbilt University, Nashville, TN, USA; [6]Sapiens Steering Brain Stimulation, Eindhoven, The Netherlands; [7]University of California San Francisco, San Francisco, CA, USA; [8]Emory University, Atlanta, GA, USA; [9]Massachusetts General Hospital, Boston MA, USA; [10]Georgetown University Medical Center, Washington, DC, USA; [11]Mount Sinai Hospital, New York, NY, USA; [12]Brown University, Providence, RI, USA; [13]Neuropace University, Mountain View, CA, USA; [14]St. Jude Medical, Sylmar, CA, USA; [15]St. Jude Medical, Sunnyvale, CA, USA; [16]University of Toronto, Toronto, ON, Canada; [17]National Institutes of Health, Bethesda, MD, USA; [18]University of Kansas Medical Center, Kansas City, KS, USA; [19]Cleveland Clinic, Cleveland, OH, USA; [20]Case Western University, Cleveland, OH, USA; [21]Mayo Clinic, Rochester, MN, USA; [22]Lawrence Livermore National Laboratory, Livermore, CA, USA; [23]Barrow Neurological Institute, Phoenix, AZ, USA; [24]University of California Los Angeles, Los Angeles, CA, USA; [25]Functional Neuromodulation Ltd., Toronto, ON, Canada; [26]Columbia University, New York, NY, USA; [27]Medtronic, Minneapolis, MN, USA; [28]Boston Scientific Neuromodulation, Valencia, CA, USA; [29]Rush University Medical Center, Chicago, IL, USA; [30]University of Alabama, Birmingham, AL, USA

The proceedings of the 2nd Annual Deep Brain Stimulation Think Tank summarize the most contemporary clinical, electrophysiological, and computational work on DBS for the treatment of neurological and neuropsychiatric disease and represent the insights of a unique multidisciplinary ensemble of expert neurologists, neurosurgeons, neuropsychologists, psychiatrists, scientists, engineers and members of industry. Presentations and discussions covered a broad range of topics, including advocacy for DBS, improving clinical outcomes, innovations in computational models of DBS, understanding of the neurophysiology of Parkinson's disease (PD) and Tourette syndrome (TS) and evolving sensor and device technologies.

KEYWORDS: deep brain stimulation, Movement disorders, Neuroethics, Electrophysiology, neurotechnology

Introduction

The Second Annual Deep Brain Stimulation (DBS) Think Tank convened at the University of Florida Center for Movement Disorders and Neurorestoration in Gainesville, FL, on March 6–7, 2014. The enclosed proceedings provide a record of the conference, which

Received 29 October 2014; revised 13 December 2014; accepted 13 December 2014

Correspondence: Dr Michael S. Okun, Department of Neurology, University of Florida, Gainesville, FL, United States. Tel: 1-352-294-5400, Fax: 1-352-627-4373. E-mail: okun@neurology.ufl.edu

highlighted the most current and groundbreaking clinical, electrophysiological, and computational work on DBS for the treatment of neurological and neuropsychiatric disease. The DBS Think Tank represents an effort to bring together perspectives from the various disciplines that influence DBS research, including engineering and industry, and to facilitate a much-needed intellectual exchange on the key issues facing the field. These disciplines include, but are not limited to, clinical neurologists, neurosurgeons, neuropsychologists, psychiatrists, scientists, engineers and ethicists. Presentations and discussions covered a broad range of topics, including advocacy for DBS, improving clinical outcomes, innovations in computational models of DBS, increased understanding of neurophysiology of Parkinson's disease (PD) and TS, and evolving sensor and device technologies.

The field is advancing at an impressive rate, but many important issues remain unresolved. How does one best navigate the complex regulatory, economic, and ethical landscapes of DBS research? How can clinical outcome measures and study designs be improved to ensure the validity and clinical relevance of results? How can we improve upon DBS as it is currently practiced through the application of emerging methods in the convergent sciences of computational modeling, electrophysiology, neuroimaging and other disciplines? How do we best harness recent sensor and device developments and develop those on the horizon to improve clinical outcomes and expedite the use of DBS for emerging indications? The meeting sought to raise awareness of these critical issues among DBS researchers and practitioners and to initiate contemplation, discussion and ultimately action toward potential solutions and improvements for the field. To this end, the meeting was conducted in a think tank style; speakers presented their analysis of a critical issue so as to foster dialogue in a subsequent discussion session. The summary of the proceedings includes key points from the follow-up discussions as well as a review of the presentations.

Critical Needs for DBS Advocacy

The success of device-based research has overshadowed a critical and emerging problem in the biomedical research environment. Neurotechnologies such as DBS have been shown in humans to be promising for scientific exploration of neural pathways and as potentially powerful treatments. Large device companies have, over the past several decades, funded and developed major research programs. However, both the structure of clinical trial funding and the current regulation of investigator-initiated device research, particularly in the United States, have threatened academia-initiated investigative efforts for neurological disorders. The current atmosphere has dissuaded clinical investigators from pursuing formal and prospective research with novel devices or novel indications. In a recent paper, Kelly et al. [1] review and discuss their experience in conducting a federally-funded, investigator-initiated, device-based clinical trial that utilized DBS for central pain syndrome. The authors describe the barriers that clinical investigators face in conducting device-based clinical trials, particularly in early stage studies or in rare disease populations. Five specific areas for potential reform and integration were discussed:

i. An alternative pathway for device approval. Investigator initiated research and research into the treatment for rare disorders will likely need a separate regulatory pathway. While the Humanitarian Device Exemption (HDE) mechanism provides an important pathway for the use of medical devices in rare disorders that have been well studied, the regulatory burden for the research remains too high. This is particularly true for conducting academia-initiated research. Simple mechanisms that facilitate reasonable oversight and regulation and that will provide an assurance of patient safety are critically needed.
ii. Eliminating right of reference requirements; particularly for early-phase academia-initiated research. Right of reference refers to the authority to use an investigation for the purpose of obtaining FDA approval; this normally entails a Letter of Authorization (LOA) from the device manufacturer to provide investigators with critical information from existing FDA applications.
iii. Combining federal grant awards with regulatory approval. The NIH peer-review process already has a section for reviewing safety for human subjects. This section could be combined with an FDA review so in the event that if a grant is funded, the investigator would concomitantly receive U.S. federal regulatory approval. This would allow the investigators to focus resources on conducting the research rather than obtaining regulatory approval.
iv. Consolidation of oversight for human subjects research, so that local IRBs would follow federal regulatory recommendations.
v. Private insurance coverage for the patient care component of clinical trials, including coverage for managing complications that may arise during the clinical trial.

Careful reformulation of regulatory policy and funding mechanisms will be critical for expanding investigator-initiated device research. This type of research has the potential to benefit science, industry and especially, the patient.

Still, the field has a responsibility to foster realistic preparedness for possible contingencies arising from clinical applications as well as research involving DBS. The scope and conduct of DBS research and the surgical intervention itself necessitates the proper implementation of ethical obligations including (i) professional intellectual honesty regarding the extant knowns and unknowns (of neural structure and function, various pathologies, DBS technology and its effects); (ii) researcher and clinician veracity in communicating knowns and unknowns to research subjects and patients; and most importantly (iii) the provision of continued care to redress any and all adverse effects or manifestations that could be attributed to the DBS intervention [2].

Addressing neuroethical issues arising from DBS research and the translation of DBS research into clinical practice will be imperative, especially as the pace and extent of DBS use increases. Discussion and development of neuroethical guidelines will be of great value, yet articulating these ethical precepts in practice can be arduous and problematic. For example, extant constraints and alignment of economic resources required for the longitudinal study and care of DBS patients (in both translational research and clinical care) do little to uphold or advance neuroethical constructs. Economic considerations are axiomatic to both ethical discourse and to actualizing ethics-in-practice, as fiscal support will be required for ongoing research, and for the continuity of care that is necessary to uphold the principle of nonabandonment when employing nascent, novel technologies in clinical research [2]. The challenge will be to evoke change in the administrative and economic infrastructures of medical research and clinical care. These changes will be necessary to uphold the neuroethical integrity of DBS in practice [3, 4].

Advancing the DBS Procedure

Improving the interpretation of clinical outcomes: Placebo, lessebo and microlesion effects

Accurate appraisal of the benefits of DBS will require careful consideration of factors beyond the procedure itself, including *placebo*, *lessebo* (the expectation of a negative outcome associated with the possibility of assignment to the placebo group) and *microlesion effects*. Failure to consider these factors in interpreting data could lead to false conclusions and ultimately lead to unnecessary procedures, increased costs or even harm. To date, no clinical studies of surgical interventions for the treatment of PD have accounted for the lessebo effect. Another well-known phenomenon consistently found in studies of DBS is the microlesion effect, a benefit associated with the surgical placement of DBS leads, occurring independently of stimulation activation. Interestingly, the microlesion effect seems to correlate with the outcomes of DBS and in some cases has been shown to be equivalent to the benefits of stimulation in the short term [5]. Data suggest that the microlesion effects can persist beyond six months in select cases [6]. These placebo, lessebo and microlesion effects may warrant reevaluation of recent trials such as the EARLYSTIM trial [7] and should be considered in the design of future studies.

Previous double blind surgical studies offer an estimate of the magnitude of the placebo effect, which can be as high as 39% [8]. In PD surgery trials, limited evidence suggests that the placebo effect could be associated with ventral striatal dopamine release [9]. In a meta-analysis of active controlled trials of dopamine agonists, the lessebo effect was estimated as 1.6 units on the motor section of the Unified PD Rating Scale (mUPDRS). The lessebo effect was larger in short-term trials and larger in early PD [10]. In the EARLYSTIM trial, consistent with a large lessebo effect, patients in the best medical therapy arm showed no benefit in UPDRS at 6 months, which is counter to the findings of almost every placebo controlled trial to date conducted on early PD patients treated for the symptom of motor fluctuations [11]. Future consideration of adjustment for both placebo and lessebo effects in the EARLYSTIM trial should be considered [11]. Additional studies are needed to better understand the impact of DBS applied in earlier stages of PD and trials are needed to account for the placebo effect. It would be optimal if these trials were well-constructed randomized controlled studies. Addressing the lessebo effect will require more complex designs that may involve active deception of study participants regarding the treatment condition. Input from bioethicists will thus be critical in developing ethically sound study designs and informed consent protocols.

In summary, effects beyond those of treatment need to be accounted for in the design and interpretation of surgical trials for PD. Study designs that limit the effects of both patient and physician expectation are critical. These effects may be limited by: presenting equipoise, blinding evaluators and using longer-term endpoints, and/or sham programming. Studies are needed to identify patient subsets likely to reveal expectation effects [12].

Improving DBS outcome measures

Previous research in DBS has relied on a wide variety of outcomes, including motor function (as assessed by the mUPDRS-III), waking time in ON state without dyskinesia, levodopa equivalent dose reduction, medication-

induced complications, activities of daily living, health-related quality of life (QOL) and incidence of adverse events [13]. Patient-centered outcomes are important to consider for future studies [14]. Psychiatric and neuropsychological outcomes are particularly critical to measure, especially given reports of worsening in these domains after DBS intervention [15]. A sharper focus on functional ability would be desirable, rather than relying on clinical severity scores, as the two types of outcomes can prove divergent [16, 17], and the former is more relevant to patient well-being. Individualized and patient-centered outcomes should be a new focus for DBS research, and these outcomes should rely more on patient assessment or a mix of objective and subjective measures [18].

Advancing DBS through optimization of electrode placement: Where and when to target

Understanding the functional segmentation of cortico-basal ganglia circuits is requisite for targeting in DBS surgery. Studies using anterograde tracers and probabilistic tractography have shown functional segmentation of the subthalamic nucleus (STN) [19]. Pathways are not confined to the hyperdirect motor pathway from M1 to STN; there are likely parallel pathways from prefrontal and associative areas connected to STN [20]. Fibers of passage from other pathways traverse functional zones of interest and stimulation of these fibers may lead to undesirable or unpredictable effects. Hence, in addition to anatomical targeting based on imaging, intraoperative microelectrode recordings can be used to behaviorally map motor and nonmotor regions within the STN.

In PD, the use of local field potentials (LFPs) as an adjunct to microelectrode recordings in surgical targeting has shown great promise. Central to this strategy is the abnormal synchrony of neural activity in alpha-beta bands (8–35 Hz) during rest in STN and globus pallidus (GPi) in PD [21–28]. Recently, Bronte-Stewart (*in preparation*) demonstrated exaggerated beta-range peaks in STN in a cohort of 55 PD patients at rest (101 STN DBS leads). In cases with bilateral STN DBS leads, higher beta peaks were observed in the hemisphere contralateral to the side of the body that manifests most pathological symptoms. Beta synchrony also has implications for DBS treatment, as it was shown to attenuate with therapeutic doses of medication and with efficacious DBS treatment [29]. Mounting evidence suggests that DBS may exert its effects by suppression of beta synchrony (8–35 Hz) within cortical-basal ganglia circuits [30]. Other physiologic markers can also contribute to localization and treatment guidance; for example, phase-amplitude coupling (PAC) as an expression of cross-frequency interactions between beta and high frequency oscillations correlate with optimal response to therapy [31].

For purposes of targeting, the presence of beta peaks in LFPs during rest could be used as a feature to correlate motor behavior in STN in PD patients. There is, however, a pitfall when targeting the beta band, as both involuntary tremor and dyskinesia can mask beta rhythms intra-operatively, and result in the false impression that beta is absent or alternatively attenuated. Moreover, microlesioning effects of the macroelectrode implantation may suppress beta synchrony. Therefore, in its current form LFPs should not be used as a replacement for microelectrode recordings, but can be used as additional verification of macroelectrode placement.

In PD, a more tailored approach to selection of DBS targets should be sought and the decision to employ unilateral versus bilateral stimulation should be made based on the individualized PD patient profile. Several well-designed studies have addressed the question of outcomes with the traditional targets (STN and GPi) [32]. Historically, Benabid's work performed in the 1990s with bilateral STN DBS in PD patients had consistently better clinical outcomes when compared to his cohort of 15 patients treated with pallidal (GPi) stimulation and the use of bilateral STN DBS for the treatment of PD gained favor [33]. However, closer analysis of the original GPi patients later revealed that outcomes were more variable. This was due to wide variability in the location of GPi with respect to the midcommisural point (i.e., variability in lead placement), and the question of the optimal target was re-opened [34], leading to considerable re-evaluation of this issue through large well-designed trials [35, 36, 32].

In considering whether a unilateral or bilateral approach should be employed, it should be kept in mind that PD is generally an asymmetric syndrome, and 21 of 44 (48%) patients in the NIH COMPARE trial remained unilateral [37]. There was a surprising amount of satisfaction reported with the unilateral approach. In follow-up studies to the COMPARE trial, those that had unilateral GPi implants had greater QOL improvement compared to unilateral STN. Additionally, other studies cite differences such as Rocchi et al. [38] who suggested less decrement in ambulation with unilateral GPi when compared to unilateral STN. Thus, unilateral procedures remain an important treatment option, and when a patient may be at high need for a bilateral implantation, this scenario may favor GPi.

There has been considerable controversy in performing bilateral procedures, especially whether lead placement should be staged or performed simultaneously. There are currently insufficient data on this point; however, there are several factors to consider. The increased time of any surgical procedure is usually

associated with more adverse events. Many neurosurgeons commented that with simultaneous procedures there is an increased incidence of poor placement on the second side. This poor placement may reflect brain shift. In summary, tailored approaches based on patient characteristics and a thorough interdisciplinary evaluation should be utilized.

Trials of STN DBS in early stage PD patients merit serious consideration. One hypothesis, based on animal models of PD, is that bilateral STN DBS could have a neuroprotective effect [39, 40]. A pilot study of high frequency bilateral STN DBS in 30 early-stage PD patients demonstrated safety, tolerability and feasibility [41]. The FDA recently approved (G050016) a pivotal, phase III, double-blind, placebo controlled and multicenter study involving 350 patients with early stage PD and this study attempts to control for placebo and lessebo effects and may enlighten the field on any potential disease modifying effects of STN DBS. There is considerable debate on the subject of studying DBS in early stage PD but most experts concur that a controlled clinical trial should be conducted to evaluate whether DBS plus medication is superior to standard medical therapy, or if DBS in any way will modify disease progression, and potentially suppress the development of dyskinesia and medication induced fluctuations.

Tailoring DBS for nondopaminergic symptoms in Parkinson's disease

Addressing the nonmotor symptoms (NMS) of PD is a current critically unmet need. NMS are underrecognized, can often precede motor symptoms by years, and are a source of significant morbidity in PD. There are limited studies on the effect of DBS on NMS [42], but it has become increasingly clear that some NMS may benefit from DBS such as pain, sleep quality, orthostatic hypotension, urinary urgency and frequency, constipation, swallowing, drooling and smell identification [43–46]. There are, however, several challenges to the study of DBS effects on NMS. First, some NMS are closely related to motor symptoms; for example, pain due to dystonia. Second, medications may change after the DBS procedure, creating inconsistencies. Third, there are fewer scales for evaluating NMS [47].

Most of the data regarding the effect of DBS on NMS comes from STN DBS. The data are limited to small case series and there have been differences in the scales and questionnaires used. The development of adequate and standardized scales will be critical for the evaluation of the nonmotor effects of DBS. To date the best screening questionnaire for NMS has been the NMSQuest tool; a 30-item questionnaire developed by a multidisciplinary group, including patient group representatives [48]. This tool was initially validated in 123 PD patients compared to 96 controls. NMS were highly prevalent across all disease stages, and the number of symptoms correlated with the onset and duration of the disease.

To summarize, limited evidence prevents tailoring DBS specifically to target NMS. Barriers include the inadequacy of standardization of scales in previous studies. Data from these questionnaires should be collected from a large number of DBS patients and association studies should be performed examining changes resulting from differences in stimulation parameters and targeting. With this type of data, it may be possible to tailor DBS therapy for both motor and NMS.

Advancing DBS clinical programming through computational modeling

Current clinical practices for optimizing DBS therapy involve post-operative visits to adjust stimulation parameter settings. These decisions are based on observed behavior and input from patients to achieve desirable therapeutic effects and to minimize adverse effects. Given the vast number of stimulation parameter combinations (stimulation electrode, frequency, pulse width and amplitude) and the lack of scientific understanding of the neurophysiological responses to the electrical fields generated, clinical outcomes of DBS therapy have become highly reliant on the intuitive skill of the clinicians performing parameter selection. Standardization of clinical practices for DBS programming can also be highly challenging, as programming approaches vary widely on a case-by-case basis.

Computational models aimed at understanding neural activation patterns stimulated by DBS electrical fields and the relations to clinical outcome have the potential to innovate DBS parameter selection. Butson et al. [49] developed a methodology to predict the volume of tissue activated by DBS parameters on a patient-specific basis. The volume of tissue activation is based on incorporating 3-D anatomical models of subcortical structures (reconstructed from a pre-operative MRI scan) and can be predicted from the modeled response of tissue conductivity properties (derived from diffusion tensor imaging (DTI)) to the applied electric field. DBS settings programmed by a clinician and selected based on these computational models recently yielded similar clinical outcome measures in 10 patients with PD (mUPDRS) [50]. Moreover, the amount of power consumed with model-based settings was on average reduced by half, and this has the potential to increase the battery lifetime.

Computational models can possibly be used to investigate how LFPs are generated and how they differ in regions of the brain and across different disease states. To this end, Lempka and colleagues developed a

computational model coupling two components: a volume conduction model of the recording electrode and tissue interface and an electrical source model based on multicompartment cable models of neurons surrounding the DBS electrode [51]. They investigated the amplitude and temporal characteristics of LFPs that depended on recording configurations, such as recording sites, distance to and orientation with respect to a structure, and those that depend on neural activity, such as synchronization and oscillatory properties that would potentially be disease- or patient-specific [51]. Despite challenges to computational approaches, such as interpretability for clinicians, computational models have a great potential to shed light on the complexities of neural activity, neural architecture and network interactions.

Advancing the DBS procedure through electrophysiology

Traditional DBS systems are programmed to stimulate continuously in a feed-forward manner, with no modulation of stimulation in response to the underlying neurophysiological states of the disease, or to how neural activity is modulated by the electrical currents. DBS therapy may be improved by incorporation of feedback into the stimulation settings. For instance, an electrophysiological biomarker of the disease state could guide the timing of stimulation when symptoms are worsened, and could optimize the stimulation parameters and bring the brain closer to a healthy state. For PD, a potential biomarker is the exaggerated alpha-beta band (8–35 Hz) synchrony in STN LFPs. This synchrony appears to be modulated by therapeutic DBS in a manner that correlates with symptoms [52, 53]. However, one of the barriers to the use of this biomarker is its susceptibility to stimulation artifact and its attenuation during voluntary movements or tremor. An alternative approach involves utilizing cortical activity (electrocorticography, ECoG) as a feedback signal, which has the advantage of being less prone to stimulation artifacts given the large amplitude of the signals and greater distance from the stimulation site. Using ECoG strips placed over motor cortex of PD patients, two potential biomarkers to guide closed-loop DBS have been identified: beta band power [54] and coupling between beta band phase and amplitude of broadband gamma (50–200 Hz) [30]. PAC between beta and broadband gamma, thought to reflect the synchronization of population spiking, is a signature of healthy motor cortex [55] that is exaggerated in PD and which disappears during therapeutic DBS [30]. An electroencephalographic (EEG) study also demonstrated exaggerated phase-amplitude coupling patterns in PD off medication, which diminished when on medication [56]. Other studies explore techniques to remove stimulation artifact from EEG recordings, potentially allowing noninvasive measurement of the brain response to DBS in individual patients [57, 58]. Tethering stimulation to the timing of pathologic spike activity has been shown to modulate the electrical activity pattern rather than the rate, with better effects on symptom control [59]. These results suggest that PAC may be a good candidate for feedback signal in closed-loop DBS therapy.

TS is a suitable test bed for identifying electrophysiological markers and designing closed-loop stimulation paradigms, as it is a paroxysmal disorder that may manifest in involuntary motor tics. It is likely that a neural signature pattern will emerge before the manifestation of tics and that this pattern can be captured through electrophysiology. It may therefore be well-suited to responsive stimulation as well. Continuous approaches drain battery when the symptoms are absent and may induce adverse effects when stimulation parameters are not optimized. Okun et al. [60] recently demonstrated that scheduled stimulation had similar therapeutic outcomes as continuous stimulation. Maling et al. [61] showed that clinically efficacious DBS increased the gamma band (30–50 Hz) power in the centromedian complex of the thalamus, along with decreasing the alpha band (8–12 Hz) power. Thus a threshold on gamma and/or alpha power could possibly be used as biomarkers to trigger responsive stimulation.

It is quite likely that the advent of DBS systems capable of chronic recordings [62, 63] will lend enable identification of biomarkers for symptomatic and healthy brain states necessary for closed-loop stimulation.

Advancing DBS through neuroimaging and chemical sensing

Targeting methods have to date been limited by the resolution of traditional magnetic resonance imaging and the paradigm of targeting individual subcortical structures rather than cortical–subcortical circuits. The use of probabilistic tractography, or probabilistic connectivity based segmentation of the traditional subcortical DBS targets may overcome these limitations [64]. This methodology combines diffusion tensor imaging with probabilistic methods to segment subcortical structures based on the highest probability of a connection with predefined cortical areas. Essentially, a probability distribution function for the most likely fiber direction can be defined for each voxel within a subcortical structure and based on these functions the likelihood of connection with a predefined cortical target can be determined [64]. Data from the individual voxels can be used to segment the subcortical structure into distinct nuclei. Using these techniques, Elias et al. [65] suggested that targeting thalamic segments that have a high connectivity with premotor cortex, rather than motor

cortex corresponded with the location of the most efficacious DBS contact for the treatment of tremor. This technique has been validated within subjects by showing correspondence of the thalamic segmentation map with the results from thalamic SEP recordings. Moreover, fiber tracking techniques can be combined with the volume of activation techniques (previously discussed) to delineate functional mechanisms.

Another methodology to map cortical–subcortical circuits may employ functional magnetic resonance imaging (fMRI)-compatible DBS systems. These systems could potentially use a tracing DBS-induced global neuronal network activation technique by monitoring the blood oxygenation level-dependent (BOLD) response on fMRI. These fMRI activation patterns represent DBS contact [66], amplitude [67], and frequency dependent [68] DBS stimulation parameters. Min et al. studied the BOLD activations induced by DBS in STN [69, 70] and the centromedian-parafiscular complex (CM-Pf) of the thalamus [66] in large animals. STN DBS significantly increased BOLD activation in the ipsilateral motor cortex, as well as the thalamus, pontine areas and contralateral cerebellum. Comparing stimulation of the CM and Pf, at low amplitudes Pf showed decreased BOLD in the limbic and prefrontal association cortex, while CM exhibited decreased BOLD activity in the motor and premotor cortex. The decreased BOLD activity (negative BOLD) reflected GABAergic projections from CM-Pf to the cortex. At higher amplitudes the activation patterns of CM and Pf began to converge [66]. CM stimulation has been shown to elicit therapeutic effect for TS patients. Demonstrating that CM-Pf stimulation affects the aforementioned networks reinforces the notion that TS is a condition with both psychiatric and motor symptoms and strengthens the idea of CM-Pf DBS as a potentially effective tool for treating both types of symptoms. Overall, fMRI-compatible DBS systems could provide useful platforms for investigating the functional effects of DBS [71].

Studies using animal models suggest that therapeutic DBS coincides with changes in neurotransmitter release [72–74]. It might be possible to design a closed-loop DBS system based on neurochemical sensing of neurotransmitters. Implementation of neurochemically-driven closed-loop DBS strategies requires characterization of the relationship between electrical stimulation and neurochemical responses. To this end, Grahn et al. [75] captured stimulation-evoked dopamine levels using fast-scan cyclic voltammetry (FSCV) and fit them into models of DBS stimulation with constrained optimization for minimization of stimulation energy. The preliminary results in four anesthetized rats suggest that the relationships between stimulation-evoked dopamine responses and DBS parameters fit the trained models and this provided a proof-of-principle for closed-loop control based on DBS-evoked dopamine changes.

Advancing DBS through new DBS technology

Current DBS systems have remained mostly unchanged for decades, and there is interest in new technologies and engineering approaches. The approaches discussed included advanced DBS electrode designs, pulse generators and chronic recordings. The goal of DBS should be to bring about smaller, more energy-efficient units with reduced adverse effects and better clinical outcomes.

The intrinsic variability of electrode placement, in combination with the geometry of electrical fields generated by standard DBS leads, can result in stimulation-induced side effects [76]. Recently developed high-resolution DBS leads, provide for precise three-dimensional shaping of the electrical field when paired with appropriate implanted pulse generators (IPGs). The shaping DBS lead consists of up to 40 small disc electrodes arranged in 10 rows of 4 discs each with a size of 0.4 mm^2, as compared to a standard DBS lead with 4 ring electrodes of 6 mm^2 each. The lead has the capability for both high resolution intraoperative LFP recording and chronic stimulation. The first data in man recorded under intraoperative conditions demonstrated that this innovative DBS technique reduced stimulation-induced side effects and maintained therapeutic efficacy [77]. Intraoperative LFP recordings after different modes of stimulation showed suppression of STN oscillatory beta activity [78]. Future clinical trials will investigate the long-term clinical outcome of this unique DBS device that combines electrical stimulation and recording abilities in the same high-resolution DBS lead.

Further efforts should be aimed at designing pulse generators that can create stimulation patterns of non-periodic bursts. For instance, bradykinesia might be better treated with nonperiodic patterns of stimulation [79] and coordinated reset stimulation, in which temporal bursts of stimulation can be applied through multiple electrode contacts for de-synchronizing coupled oscillators [80]. Other efforts should focus on DBS systems with multiple independent current sources that can provide control over the shape and size of the stimulation volume. Although these new electrode and pulse generator designs bring more flexibility and more control over the shape of the electric field, they may come at the cost of increased parameter space, and this may further complicate programming at the bedside.

Proof of concept studies of closed-loop systems are now underway with the advancement in recording capabilities in DBS implants. Even in the first generation models, these approaches are opening up unparalleled avenues for human electrophysiological research and for improving DBS outcomes. The recording capabilities of

the devices in future generations are likely to increase in number of recording channels, device memory and data transfer speeds, and also with improvements in telemetry. Because of the increasing amount of human neurophysiological data generated with these devices, collaborations between clinicians, signal processing teams, and big data engineers will likely facilitate the analysis and interpretation of the data.

Conclusions

The critical issues affecting the progress of DBS are multifocal, ranging from regulatory and ethical issues to study design to harnessing advances in computational modeling, electrophysiology and sensor and electrode engineering. The specific advances discussed in the Think Tank demonstrate the potential for transformative, not just incremental change in DBS therapy. The future of DBS resides in converging these advances into new therapies while carefully considering clinical research concerns and methodology in the implementation of next generation technology.

Declaration of Interests

The authors alone are responsible for the content and writing of this paper.

AG: Grant support from Medtronic, Inc.; *HK:* None; *PJR:* None; *WLA:* None; *RLA:* Consultant for Medtronic, Inc.; *HB-S:* None; *CRB:* Consultant for St Jude Medical, Boston Scientific; IP related to DBS; *DC:* Vanderbilt receives income from grants or contracts from Allergan, Ipsen, Merz and Medtronic for research led by DC; DC receives income from Allergan, Ipsen, Medtronic and, the Alliance for Patient Access for education or consulting services; *SD:* Employee and shareholder of Sapiens Steering Brain Stimulation GmbH (Medtronic Eindhoven Design Center); *CDH:* None; *MDL:* None; *DD:* Grant support from Medtronic, Cyberonics, Eli Lilly, Roche, Honoraria from Medtronic, Insys, Johnson & Johnson; *JE:* Chief Medical Officer at Sapiens Steering Brain Stimulation GmbH; *KDF:* Grant support from Medtronic, St. Jude, Boston Scientific, Neuropace; Consultant for Medtronic, Neuropace; *JG:* None; *WG:* None; *BDG:* None; *DG:* Employee of Neuropace; *RG:* None; *JJ:* None; *EK:* Employee of St. Jude Medical; *AK:* Employee of St. Jude Medical; *BK:* Consultant for Medtronic, St Jude Neuromodulation, MRI Interventions; *ALang:* Consultant for Abbvie, Allon Therapeutics, Avanir Pharmaceuticals, Biogen Idec, Boerhinger-Ingelheim, Ceregene, Lilly, Medtronic, Merck, Novartis, NeuroPhage Pharmaceuticals, Teva, UCB; Honoraria from Medtronic, Teva, UCB, AbbVie; Grant support from Brain Canada, Canadian Institutes of Health Research, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, Tourette Syndrome Association, W. Garfield Weston Foundation; Publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, Cambridge University Press; *ALozano:* Consultant for Medtronic, St Jude and Boston Scientific, Co-Founder of Functional Neuromodulation; *CL:* None; *KL:* Consultant for Medtronic, St. Jude Medical; *AM:* IP in Enspire, ATI, Cardionomics, Grant support from Medtronic, Inc., Consultant for Functional Neuromodulation, Spinal Modulation; *HM:* Employee and shareholder of Sapiens Steering Brain Stimulation GmbH (Medtronic Eindhoven Design Center); *CM:* IP in Boston Scientific Neuromodulation; Consultant for Boston Scientific Neuromodulation; Shareholder in Autonomic Technologies, Inc., Cardionomics, Inc., Neuros Medical, Inc., Surgical Information Sciences, Inc.; *BM:* None; *HKM:* None; *JN:* Grant support from Medtronic, Inc.; Consultant for Medtronic, Inc., Monteris Inc.; *JO:* Grant support from Boston Scientific, MRI Interventions, St Jude Medical, Medtronic; *SP:* None; *FP:* Consultant for Medtronic, Inc; *NP:* None; *DR:* Employee of Neuromodulation, Inc; *LSchrock:* Site PI for the Boston Scientific INTREPID DBS trial; *SSheth:* None; *LShih:* None; *SStanslanski:* Employee of Medtronic, Inc.; *GKS:* Employee of Boston Scientific Neuromodulation; *PS:* Employee of Medtronic, Inc.; *AT:* Consultant for St Jude Medical, Boston Scientific, Theravance, Teva; Grant support from Glaxo Smith Kone, Speaker for Medtronic; Royalties from Oxford University Press; *LV:* None; *HW:* None; *MSO:* Consultant for National Parkinson Foundation; Grant support from NIH, NPF, Michael J. Fox Foundation, Parkinson Alliance, Smallwood Foundation, Bachmann-Strauss Foundation, Tourette Syndrome Association, UF Foundation.

References

1. Kelly ML, Malone D, Okun MS, et al. Barriers to investigator-initiated deep brain stimulation and device research. Neurology 2014;82(16):1465–73.
2. Rossi PJ, Okun MS, Giordano J. Translational imperatives in deep brain stimulation research: Addressing neuroethical issues of consequences and continuity of clinical care. AJOB-Neurosci 2014;5(1):46–8.
3. Giordano J, Hutchison P, Benedikter R. Regrounding medicine amidst a technological imperative and Post-Modern mindset. Int J Polit Cult Soc 2010;10(10).
4. Giordano J, Schatman ME. Pain medicine from "bench to bedside": Bridging the disconnect(s) between research and clinical care. J Humanities Sci Healthcare 2011;1(1):22–40.

5. Tykocki T, Nauman P, Koziara H, et al. Microlesion effect as a predictor of the effectiveness of subthalamic deep brain stimulation for Parkinson's disease. Stereotact Funct Neurosurg 2013;91(1):12–7.
6. Mann JM, Foote KD, Garvan CW, et al. Brain penetration effects of microelectrodes and DBS leads in STN or GPi. J Neurol, Neurosurg psych 2009;80(7):794–7. doi: 10.1136/jnnp.2008.159558. PubMed PMID: 19237386; PubMed Central PMCID: PMC3791596.
7. Deuschl G, Schüpbach M, Knudsen K, et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM-study. Parkinsonism Relat Disord 2013;19(1):56–61. doi: 10.1016/j.parkreldis.2012.07.004. PubMed PMID: 22841616.
8. McRae C, Cherin E, Yamazaki TG, et al. Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Heneral Psychiat 2004;61(4):412–20. doi: 10.1001/archpsyc.61.4.412. PubMed PMID: 15066900.
9. de la Fuente-Fernandez R. Uncovering the hidden placebo effect in deep-brain stimulation for Parkinson's disease. Parkinsonism & related disorders. 2004;10(3):125–7. doi: 10.1016/j.parkreldis.2003.10.003. PubMed PMID: 15036165.
10. Mestre TA, Shah P, Marras C, et al. Another face of placebo: the lessebo effect in Parkinson disease: meta-analyses. Neurology 2014;82(16):1402–9. doi: 10.1212/WNL.0000000000000340. PubMed PMID: 24658930; PubMed Central PMCID: PMC4001195.
11. Mestre TA, Espay AJ, Marras C, et al. Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease-the EARLYSTIM trial: Early is not always better. Mov Disord 2014;29(14):1751–56. doi: 10.1002/mds.26024. PubMed PMID: 25227325.
12. Ko JH, Feigin A, Mattis PJ, et al. Network modulation following sham surgery in Parkinson's disease. The Journal of clinical investigation. 2014;124(8):3656–66. doi: 10.1172/JCI75073. PubMed PMID: 25036712; PubMed Central PMCID: PMC4109544.
13. Perestelo-Perez L, Rivero-Santana A, Perez-Ramos J, et al. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. J Neurol 2014;261(11):2051–60. Epub 2014/02/04. doi: 10.1007/s00415-014-7254-6. PubMed PMID: 24487826.
14. Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. Jama 2012;307(15):1583–4. Epub 2012/04/19. doi: 307/15/1583 [pii], 10.1001/jama.2012.500. PubMed PMID: 22511682.
15. Voon V, Krack P, Lang AE, et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. Brain 2008;131(Pt 10):2720–8. Epub 2008/10/23. doi: awn214 [pii], 10.1093/brain/awn214. PubMed PMID: 18941146; PubMed Central PMCID: PMC2724899.
16. Air EL, Ostrem JL, Sanger TD, et al. Deep brain stimulation in children: experience and technical pearls. Journal of neurosurgery Pediatrics. 2011;8(6):566–74. doi: 10.3171/2011.8.PEDS11153. PubMed PMID: 22132914.
17. Gimeno H, Tustin K, Lumsden D, et al. Evaluation of functional goal outcomes using the Canadian Occupational Performance Measure (COPM) following Deep Brain Stimulation (DBS) in childhood dystonia. Eur J Paediatr Neurol 2014;18(3):308–16. Epub 2014/01/28. doi: S1090-3798(14)00005-1 [pii], 10.1016/j.ejpn.2013.12.010. PubMed PMID: 24461258.
18. Maier F, Lewis CJ, Horstkoetter N, et al. Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. J Neurol Neurosurg Psychiatry. 2013;84(11):1273–81. Epub 2013/05/30. doi: jnnp-2012-303670 [pii], 10.1136/jnnp-2012-303670. PubMed PMID: 23715910.
19. Lambert C, Zrinzo L, Nagy Z, et al. Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. NeuroImage 2012;60(1):83–94. doi: 10.1016/j.neuroimage.2011.11.082. PubMed PMID: 22173294; PubMed Central PMCID: PMCPMC3315017.
20. Haynes WI, Haber SN. The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for Basal Ganglia models and deep brain stimulation. J Neurosci 2013;33(11):4804–14. doi: 10.1523/jneurosci.4674-12.2013. PubMed PMID: 23486951; PubMed Central PMCID: PMCPMC3755746.
21. Nini A, Feingold A, Slovin H, et al. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophys 1995;74(4):1800–5. PubMed PMID: 8989416.
22. Brown P, Oliviero A, Mazzone P, et al. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosci 2001;21(3):1033–8. PubMed PMID: 11157088.
23. Bevan MD, Magill PJ, Terman D, et al. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. Trends Neurosci 2002;25(10):525–31. PubMed PMID: 12220881.
24. Levy R, Hutchison WD, Lozano AM, et al. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci. 2002;22(7):2855–61. doi: 20026193. PubMed PMID: 11923450.
25. Schnitzler A, Timmermann L, Gross J. Physiological and pathological oscillatory networks in the human motor system. J Physiol Paris 2006;99(1):3–7. doi: 10.1016/j.jphysparis.2005.06.010. PubMed PMID: 16054347.
26. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006;52(1):155–68. doi: 10.1016/j.neuron.2006.09.020. PubMed PMID: 17015233.
27. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 2007;30(7):357–64. doi: 10.1016/j.tins.2007.05.004. PubMed PMID: 17532060.
28. de Solages C, Hill BC, Koop MM, et al. Bilateral symmetry and coherence of subthalamic nuclei beta band activity in Parkinson's disease. Exper Neurol 2010;221(1):260–6. doi: 10.1016/j.expneurol.2009.11.012. PubMed PMID: 19944098.
29. Kuhn J, Gaebel W, Klosterkoetter J, et al. Deep brain stimulation as a new therapeutic approach in therapy-resistant mental disorders: ethical aspects of investigational treatment. Eur Arch Psychiatry Clin Neurosci 2009;259(Suppl 2):S135–41. Epub 2009/11/13. doi: 10.1007/s00406-009-0055-8. PubMed PMID: 19876671.
30. de Hemptinne C, Ryapolova-Webb ES, Air EL, et al. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci USA 2013;110(12):4780–5. doi: 10.1073/pnas.1214546110. PubMed PMID: 23471992; PubMed Central PMCID: PMC3606991.

31. Yang AI, Vanegas N, Lungu C, et al. Beta-coupled high-frequency activity and Beta-locked neuronal spiking in the subthalamic nucleus of Parkinson's disease. J Neurosci 2014;34(38):12816–27. doi: 10.1523/JNEUROSCI.1895-14.2014. PubMed PMID: 25232117; PubMed Central PMCID: PMC4166162.
32. Williams NR, Foote KD, Okun MS. STN vs. GPi Deep Brain Stimulation: Translating the Rematch into Clinical Practice. Mov Disord Clin Pract (Hoboken) 2014;1:24–35.
33. Krack P, Pollak P, Limousin P, et al. Inhibition of levodopa effects by internal pallidal stimulation. Movement Disorders 1998;13(4):648–52.
34. Nestor KA, Jones JD, Butson CR, et al. Coordinate-based lead location does not predict Parkinson's disease deep brain stimulation outcome. PloS one 2014;9(4):e93524. doi: 10.1371/journal.pone.0093524. PubMed PMID: 24691109; PubMed Central PMCID: PMC3972103.
35. Williams NR, Foote KD, Okun MS. STN vs. GPi deep brain stimulation: Translating the rematch into clinical practice. Mov Disord Clin Pract (Hoboken) 2014;1(1):24–35. doi: 10.1002/mdc3.12004. PubMed PMID: 24779023; PubMed Central PMCID: PMC4000041.
36. Rothlind JC, York MK, Carlson K, et al. Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy. J Neurol Neurosurg Psychiatry 2014. doi: 10.1136/jnnp-2014-308119. PubMed PMID: 25185211.
37. Taba HA, Wu SS, Foote KD, et al. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. J Neurosurg 2010;113(6):1224–9. Epub 2010/09/21. doi: 10.3171/2010.8.JNS10312. PubMed PMID: 20849215.
38. Rocchi L, Chiari L, Cappello A, et al. Comparison between subthalamic nucleus and globus pallidus internus stimulation for postural performance in Parkinson's disease. Gait Posture 2004;19(2):172–83. doi: 10.1016/s0966-6362(03)00059-6. PubMed PMID: 15013506.
39. Spieles-Engemann AL, Steece-Collier K, Behbehani MM, et al. Subthalamic nucleus stimulation increases brain derived neurotrophic factor in the nigrostriatal system and primary motor cortex. J Parkinson's Disease 2011;1(1):123–36. PubMed PMID: 22328911; PubMed Central PMCID: PMC3275429.
40. Charles PD, Gill CE, Davis TL, et al. Is deep brain stimulation neuroprotective if applied early in the course of PD? Nat Clin Pract Neuro 2008;4(8):424–6. doi: Doi 10.1038/Ncpneuro0848. PubMed PMID: WOS:000258106000008.
41. Kahn E, D'Haese PF, Dawant B, et al. Deep brain stimulation in early stage Parkinson's disease: operative experience from a prospective randomised clinical trial. J Neurol, Neurosurg, Psych 2012;83(2):164–70. doi: 10.1136/jnnp-2011-300008. PubMed PMID: 21890575; PubMed Central PMCID: PMC3733009.
42. Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. Lancet Neurol 2012;11(5):429–42. Epub 2012/04/21. doi: S1474-4422(12)70049-2 [pii], 10.1016/S1474-4422(12)70049-2. PubMed PMID: 22516078.
43. Zibetti M, Torre E, Cinquepalmi A, et al. Motor and non-motor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. Eur Neurol 2007;58(4):218–23. doi: 10.1159/000107943. PubMed PMID: 17823535.
44. Troche MS, Brandimore AE, Foote KD, et al. Swallowing and deep brain stimulation in Parkinson's disease: a systematic review. Parkinsonism Relat Disord 2013;19(9):783–8. doi: 10.1016/j.parkreldis.2013.05.001. PubMed PMID: 23726461; PubMed Central PMCID: PMCPMC3775508.
45. Fabbri M, Guedes LC, Coelho M, et al. Subthalamic deep brain stimulation effects on odor identification in Parkinson's disease. Eur J Neurol 2015;22(1):207–10. doi: 10.1111/ene.12396. PubMed PMID: 24602222.
46. Nazzaro JM, Pahwa R, Lyons KE. The impact of bilateral subthalamic stimulation on non-motor symptoms of Parkinson's disease. Parkinsonism Relat Disord 2011;17(8):606–9. doi: 10.1016/j.parkreldis.2011.05.009. PubMed PMID: 21669545.
47. Martinez-Martin P, Chaudhuri KR, Rojo-Abuin JM, et al. Assessing the non-motor symptoms of Parkinson's disease: MDS-UPDRS and NMS Scale. Eur J Neurol 2015;22(1):37–43. doi: 10.1111/ene.12165.
48. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 2006;21(7):916–23. Epub 2006/03/21. doi: 10.1002/mds.20844. PubMed PMID: 16547944.
49. Butson CR, Cooper SE, Henderson J, et al. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. NeuroImage 2007;34(2):661–70.
50. Frankemolle AMM, Wu J, Noecker AM, et al. Reversing cognitive–motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. Brain 2010;133:746–61.
51. Lempka SF, McIntyre CC. Theoretical analysis of the local field potential in deep brain stimulation applications. PloS one 2013;8(3):e59839.
52. Bronte-Stewart H, Barberini C, Koop MM, et al. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exper Neurol 2009;215:20–8.
53. Kuhn AA, Kempf F, Brucke C, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory activity in patients with Parkinson's disease in parallel with improvement in Motor performance. J Neuros 2008;28(24):6165–73.
54. Whitmer D, de Solages C, Hill BC, et al. High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. Frontiers Human Neurosci 2012; 6:155.
55. Miller KJ, Hermes D, HIne CJ, et al. Human motor cortical activity is selectively phase-entrained on underlying rhythms. PLoS Comput Biol 2012;8(9):e1002655.
56. López-Azcárate J, Tainta M, Rodríguez-Oroz MC, et al. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. J Neurosci 2010;30(19):6667–77. doi: 10.1523/jneurosci.5459-09.2010. PubMed PMID: 20463229.
57. Walker HC, Huang H, Gonzalez CL, et al. Short latency activation of cortex during clinically effective subthalamic deep brain stimulation for Parkinson's disease. Mov Disord 2012;27(7):864–73. doi: 10.1002/mds.25025. PubMed PMID: 22648508; PubMed Central PMCID: PMC3636546.
58. Walker HC, Huang H, Gonzalez CL, et al. Short latency activation of cortex by clinically effective thalamic brain stimulation for tremor. Mov Disord 2012;27(11):1404–12. doi: 10.1002/mds.25137. PubMed PMID: 22926754; PubMed Central PMCID: PMC3691999.
59. Rosin B, Slovik M, Mitelman R, et al. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. Neuron 2011;72(2):370–84. doi: 10.1016/j.neuron.2011.08.023. PubMed PMID: 22017994.

60. Okun MS, Foote KD, Wu SS, et al. A trial of scheduled deep brain stimulation for tourette syndrome: Moving away from continuous deep brain stimulation paradigms. Arch Neurol 2012:1–10. Epub 2012/10/10. doi: 10.1001/jamaneurol.2013.580. PubMed PMID: 23044532.
61. Maling N, Hashemiyoon R, Foote KD, et al. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette's syndrome. PloS One 2012;7(9):e44215. Epub 2012/09/13. doi: 10.1371/journal.pone.0044215. PubMed PMID: 22970181; PubMed Central PMCID: PMC3435399.
62. Afshar P, Khambhati A, Stanslaski S, et al. A translational platform for prototyping closed-loop neuromodulation systems. Frontiers Neural Circuits 2013;6:117.
63. Sun FT, Morrell MJ, Wharen RE. Responsive cortical stimulation for the treatment of epilepsy. Neurotherapeutics 2008;5:68–74.
64. Pouratian N, Zheng Z, Bari AA, et al. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation. J Neurosur 2011;115(5):995–1004. doi: 10.3171/2011.7.JNS11250. PubMed PMID: 21854118.
65. Elias WJ, Zheng ZA, Domer P, et al. Validation of connectivity-based thalamic segmentation with direct electrophysiologic recordings from human sensory thalamus. NeuroImage 2012;59(3):2025–34. doi: 10.1016/j.neuroimage.2011.10.049. PubMed PMID: 22036683.
66. Kim JP, Min HK, Knight EJ, et al. Centromedian-parafascicular deep brain stimulation induces differential functional inhibition of the motor, associative, and limbic circuits in large animals. Biol Psychiatry 2013;74(12):917–26. doi: 10.1016/j.biopsych.2013.06.024. PubMed PMID: 23993641; PubMed Central PMCID: PMC3910443.
67. Knight EJ, Min HK, Hwang SC, et al. Insular and prefrontal cortical activation during nucleus accumbens high frequency stimulation in a large animal model: A functional MRI atudy. PloS One 2013;8(2):e56640.
68. Paek SB, Min HK, Kim IY, et al. Frequency-dependent functional neuromodulatory effects on the motor network by ventral lateral thalamic deep brain stimulation in swine. NeuroImage 2015;105:181–8.
69. Min HK, Hwang SC, Marsh MP, et al. Deep brain stimulation induces BOLD activation in motor and non-motor networks: an fMRI comparison study of STN and EN/GPi DBS in large animals. NeuroImage 2012;63(3):1408–20. doi: 10.1016/j.neuroimage.2012.08.006. PubMed PMID: 22967832; PubMed Central PMCID: PMC3487590.
70. Min HK, Ross EK, Lee KH, et al. Subthalamic nucleus deep brain stimulation induces Motor network BOLD activation: Use of a high precision MRI guided stereotactic system for nonhuman primates. Brain Stimulat 2014;7(4):603–7. doi: Doi 10.1016/J.Brs.2014.04.007. PubMed PMID: WOS:000339984300015.
71. Gorny KR, Presti MF, Goerss SJ, et al. Measurements of RF heating during 3.0-T MRI of a pig implanted with deep brain stimulator. Magn Reson Imaging 2013;31(5):783–8. doi: Doi 10.1016/J.Mri.2012.11.005. PubMed PMID: WOS:000319103000021.
72. Lee KH, Chang S-Y, Roberts DW, et al. Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 2004;101:511–7.
73. Shon Y-M, Chang S-Y, Tye SJ, et al. Comonitoring of adenosine and dopamine using the wireless instantaneous neurotransmitter concentration system: Proof of principle. J Neurosurg 2010;112:539–48.
74. Shon Y-M, Lee KH, Goerss SJ, et al. High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery. Neurosci Lett 2010;475:136–40.
75. Grahn PJ, Mallory GW, Khurram OU, et al. A neurochemical closed-loop controller for deep brain stimulation: toward individualized smart neuromodulation therapies. Frontiers Neurosci 2014;8:169. doi: 10.3389/fnins.2014.00169. PubMed PMID: 25009455; PubMed Central PMCID: PMC4070176.
76. Marceglia S, Mrakic-Sposta S, Tommasi G, et al. Multicenter study report: electrophysiological monitoring procedures for subthalamic deep brain stimulation surgery in Parkinson's disease. Neurol Sci: Off J Italian Neurol Soc Italian Soc Clin Neurophys 2010;31(4):449–57. Epub 2010/04/24. doi: 10.1007/s10072-010-0254-0. PubMed PMID: 20414706.
77. Contarino MF, Bour LJ, de Bie RMA, et al. Steering deep brain stimulation: An exploratory study with a new 32-contact lead. Mov Disord 2013;28:S439–S40. PubMed PMID: WOS:000320940505143.
78. Bour LJ, Verhagen R, Contarino F, et al. A new DBS lead: Simultaneous 32-contact local field potential recording in the Parkinsonian STN. Mov Disord 2013;28:S445–S. PubMed PMID: WOS:000320940505155.
79. Brocker DT, Swan BD, Turner DA, et al. Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease. Exp Neurol 2013;239:60–7. doi: 10.1016/j.expneurol.2012.09.008. PubMed PMID: 23022917; PubMed Central PMCID: PMC3547657.
80. Tass PA, Qin L, Hauptmann C, et al. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. Ann Neurol 2012;72(5):816–20. doi: 10.1002/ana.23663. PubMed PMID: 23280797.