Deep Brain Stimulation: Expanding Applications

Anand TEKRIWAL^{1,2} and Gordon BALTUCH¹

¹University of Pennsylvania, Department of Neurosurgery, Philadelphia, USA;

²University of Colorado School of Medicine and Graduate School of Neuroscience, MSTP, Colorado, USA (current affiliation)

Abstract

For over two decades, deep brain stimulation (DBS) has shown significant efficacy in treatment for refractory cases of dyskinesia, specifically in cases of Parkinson's disease and dystonia. DBS offers potential alleviation from symptoms through a well-tolerated procedure that allows personalized modulation of targeted neuroanatomical regions and related circuitries. For clinicians contending with how to provide patients with meaningful alleviation from often debilitating intractable disorders, DBSs titratability and reversibility make it an attractive treatment option for indications ranging from traumatic brain injury to progressive epileptic supra-synchrony. The expansion of our collective knowledge of pathologic brain circuitries, as well as advances in imaging capabilities, electrophysiology techniques, and material sciences have contributed to the expanding application of DBS. This review will examine the potential efficacy of DBS for neurologic and psychiatric disorders currently under clinical investigation and will summarize findings from recent animal models.

Key words: neurosurgery, deep brain stimulation, Parkinson's disease, epilepsy, neuromodulation

Introduction

Deep brain stimulation (DBS) is acknowledged to be effective at modulating dysfunctional neural circuits that can be either hypo or hyperactive as seen in Parkinson's disease (PD) and dystonia, respectively. This treatment necessitates the placement of image-guided electrode that leads into discrete regions of patients' neuroanatomy. This is followed by titration of current through the leads, allowing for refinement of stimulatory parameters; please refer to previously published works for reference regarding implantation methodology.^{1–7)} The Food and Drug Administration (FDA) first approved thalamic DBS in 1997 for tremor, and globus pallidus internus (GPi) as well as subthalamic nucleus (STN) by 2003 for PD. In part, because of demonstrated tolerability as well as encouraging clinical outcomes, DBS has qualified under the FDA's Humanitarian Device Exception (HDE) for a number of neurologically rooted disorders including stimulation of GPi and STN for dystonia in 2003,⁸⁾ stimulation of the anterior limb of the internal capsule for obsessive compulsive disorder (OCD) in 2009,⁹⁾ and closed-loop stimulation for epileptic indications in 2013.¹⁰⁾ The pipeline for

evaluating the use of DBS for novel indications begins with animal models or encouraging findings in case studies, progressing to small randomized trials, and culminating in large, multi-site, double-blinded clinical trial like the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trials backed by Medtronic. Advances in surgical techniques, clinical needs, and basic science findings also contribute to the fluctuating levels of interest a given innovative procedure receives. Often these variables necessitate the re-evaluation of DBS for indications formerly investigated such as depression as well as for novel indications like traumatic brain injury.^{11,12)}

As a tool to treat refractory cases of neurologically based disorders, DBS has noteworthy potential because of the scope of disorders it has the capacity to address. Results from the 2008–2012 Mental Health Surveillance Study indicated that among adults aged 18 and older, approximately 22.5% of the population had at least one diagnoses of a mental disorder when including adjustment disorder and substance abuse disorder.¹³⁾ Of these 51.2 million people, an estimated 9.6 million adults suffer from severe mental illness characterized as resulting in serious functional impairment, which significantly interferes with or limits one or more

major life activity. When added to the millions of people suffering from Alzheimer's disease (AD) induced dementia, intractable neuropathic pain, and movement disorders like PD, a very sizeable patient population are realized.

With the majority of patients clinically classified as under-treated and conventional neuropsychiatric drug discovery routes proving inefficient, adjunctive treatments have been increasingly utilized to augment conventional care. Such treatments range in approach as well as clinical clout; these include lifestyle modifications such as ketogenic diets, talk or physical therapy like Tai chi, off-label prescription of pharmaceuticals, and neuromodulatory techniques.¹⁴⁾ The latter category comprises a significant and growing number of adjunctive treatments with a mixed history of effectiveness dating back to the 1900s. DBS, which demonstrates the greatest level of treatment versatility as well as clinical confidence, along with vagus nerve stimulation (VNS), electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and recently developed optogenetic methods comprise this growing neuromodulatory armamentarium.

DBS for PD

The principal reason why DBS is held with high regard by clinicians and researchers is because of its demonstrated efficacy for treatment of PD and its related indications. A progressive motor system disorder resulting from degradation of dopamine-producing cells originating from the substantia nigra pars compacta; current treatments for PD can address dopaminergically related symptoms of the disease on the order of years but they do not cure the degeneration itself.^{15–17)} Routinely diagnosed in patients over 50, PD often presents as asymmetric tremor in the distal portion of the limbs but can also appear as stiffness or rigidity, primarily in the face and upper limbs. Disabilities associated with PD also include soft voice, masked face, shuffling gait, disequilibrium, constipation, and orthostatic hypotension as well as nonmotor symptoms such as apathy, depression, and cognitive decline.^{18–20)} In the United States, medication cost for PD patients is from \$1,000 to \$6,000 per year with annual risk of hospitalization exceeding 30%, contributing to a national burden of approximately \$23,000 per patient.^{18,21)} As one in three patients will be unemployed within a year of diagnosis these financial burdens can vary significantly and affect the quality of life and will exert a progressively greater economic impact as the age distribution in America approaches that of countries like Japan.^{18,22)}

Early diagnosis of PD is challenging, and although longitudinal disease models indicate a prodromal dementia stage characterized by declines in working memory, visuospatial processing, and bradyphrenia beginning about 5 years prior to motor deterioration, can often be confused with effects of aging.²⁰⁾ Without the ability to look for revealing biomarkers that clinicians could otherwise use to generate robust diagnostic measures, these relatively ambiguous cognitive deficits are our best indicators of PD onset. Although a traditional diagnostic blood test may not be available for PD, novel measures like olfactory ability as well as tone in vocal cords and tremor detected by smart phone software applications may elucidate clinically useful, non-invasively gathered diagnostic data.²³⁾ When needed, cerebrospinal fluid analysis and positron emission tomography (PET) scans can elucidate more detailed information concerning pathology.^{24,25)}

Patients' best treatment course is levodopa taken in conjuncture with a decarboxylase inhibitor; the combination of which confines the conversion of levodopa to dopamine within the blood brain barrier. Unfortunately, this treatment produces significant dyskinesia in 5 to 10 years when patients' tolerance to the medication necessitates relatively high doses. Whether from the symptoms of PD or adverse effects of their levodopa treatments, patients in the advanced stages of the disease can experience significantly impaired quality of life. Fortunately, DBS has been shown to attenuate this pharmacologically induced dyskinesia as well as tremor seen in pronounced PD, making it very appealing as an intervention for advanced cases.²⁶⁾ Primary neuroanatomical targets for PD DBS are the STN and GPi, which can both be implanted unilaterally or bilaterally. The majority of medical institutions have traditionally favored the STN over the GPi, resulting in bilateral implantation of the STN being the most commonly performed procedure. Recent findings from randomized trials indicate that a consensus on which target is most efficacious is still being formed, and will likely not result in one becoming the overwhelming standard. Rather, different permutations of DBS procedures will likely be best suited for different types of PD cases.

Published in 2012, a large US Veteran's Affairs multi-site randomized trial followed outcomes of 89 GPi patients and 70 STN patients for 36 months, showing both targets to have similar motor function outcomes relative to patients' baselines.²⁷⁾ Quality of life measures also showed similar significant improvements following stimulation, but the STN group did report slightly worse scores on the Mattis Dementia Scale at 6 months than the GPi group ($p = 0.03$). In 2013, a Dutch group announced results

from a double-blinded comparison of 65 GPi and 63 STN patients, also finding no significant differences in primary outcomes. Interestingly, they reported no large differences in effect on mood and cognition, but did observe a meaningful difference in the off-drug phase of the experiment in which the STN group displayed a markedly greater improvement. In line with these findings, a substantial meta-analysis by a group from the Second Affiliated Hospital of Chongqing Medical University reported on 563 patients across six trials. Data mining work published prior to April 1, 2013, broadly supports the claims that both targets significantly improve motor function, both improve quality of life measures, the STN allows for great reduction in dose of medication, and the GPi is the preferred target for those with cognitive function concerns.²⁸⁾

The unilateral vs. bilateral treatment choice is another judgment being debated and has been more poignantly assessed in a group of recent literature. Hershey et al. found similar outcomes on motor function and working memory for bilateral stimulation and unilateral stimulation of the more affected brain region.²⁹⁾ In findings published in 2010 from the National Institutes of Health (NIH) COMPARE cohort, 52 patients were randomized between STN and GPi unilateral implantation, with the opportunity to have their contralateral side similarly addressed 6 months later. Outcomes indicate that unilateral DBS was efficacious for a subset of patients who had especially pronounced asymmetric PD symptoms. Additionally, the majority of such cases were GPi targets; patients implanted in the STN were 5.2 times more likely to undergo bilateral implantation than their GPi counterparts, with the most common reason for undergoing bilateral implantation being poor control of symptoms with one lead.³⁰⁾ If unilateral implantation in the GPi were therapeutically equivalent to bilateral STN or GPi in certain PD subpopulations, it would be of great value in identifying them and limiting the surgical exposure that patients needed to sustain.

Although these results do indicate that additional refinement of patient selection criteria is needed, the consensus continues to be supportive of the overall efficacy of DBS for PD. Crucially, recent long-term studies also support the efficacy of DBS, but are limited in that they largely report on solely bilateral STN patients. A Rush University group published preliminary data from a proposed 100 patients cohort in which long-term outcomes of bilateral STN implantation are being measured with the unified Parkinson's disease rating scale (UPDRS) as well as measures of patient satisfaction and quality of life. Eleven patients' responses indicated

satisfaction was maintained at an average of 10 years after surgery with higher quality of life at time of survey despite progressive disability. Patients also indicated that they would undergo the surgery again, at a younger age if possible.¹⁹⁾ A similar, larger study was carried out in China surveying 195 bilaterally implanted STN patients using the UPDRS at 1 year, 3 years, and 5 years after surgery—both on and off medication. Patients indicated significant improvements ($p < 0.001$) in tremor, rigidity, akinesia, postural stability, gait, and cumulative score in the motor examination portion of the UPDRS as well as in the writing, freezing of gait, and overall score in the activity of daily living portion of the UPDRS, both 3 years and 5 years after surgery vs. baseline.³¹⁾ The survey also reported one fatality due to an intraoperative intracerebral hemorrhage, as well as 26 hardware-related complications affecting 20 patients. Notably, 12 complications were erosions and/or infections, 7 of which occurred beyond 12 months after implantation.³¹⁾

Cumulatively, these reports indicate some ambiguity for how a given patient may respond to a particular set of treatment parameters; but in general for patients with cognitive concerns, the GPi is likely the more efficacious target, while for patients who do not tolerate levodopa treatment well, the STN may be preferred. Patient outcomes and satisfaction are broadly positive with regard to control of dopaminergically related symptoms and can be extended for over a decade. For treatment of axial impairments and cognitive decline seen in advanced PD, however, modulation of these nuclei do not meet patients' needs. This has prompted investigation of novel targets such as the pedunculopontine tegmental nucleus (PPTg), caudal zona incerta, and substantia nigra pars reticulata (SNr). However, recent evidence indicates these nuclei to be too heterogeneous to effectively target and our understanding of exactly how these regions contribute to axial dysfunction to be too primitive.^{32–34)} It is possible that future procedures will incorporate multi-site modulation to address the full gamut of dopaminergic, axial, and cognitive impairments advanced PD patients endure.^{11,32,35–39)} It is certain that clinicians will need to keenly match patients' symptoms with known outcomes of a number of neuroanatomic targets, unilateral and bilateral stimulation, as well as various stimulatory parameters including frequency, intensity, pulse width, and constant-current vs. voltage-controlled stimulation.^{40–43)}

I. DBS in essential tremor (ET)

DBS has also demonstrated an effective relief from ET, the first indication that the Food and Drug

Administration (FDA) approved the procedure in 1997. The NIH broadly defines tremor as a type of rhythmic shaking movement that is not necessarily specific to a given body part. ET is the most common type of tremor with an estimated prevalence of up to 5%.^{44–46)} ET is a neurologically a rooted condition characterized by its lack of an identifiable cause as well as its progressive disease course.^{47–49)} Diagnostic criteria for the disorder include bilateral, often symmetrical tremor of the hands, forearms, voice, head, and leg tremor.⁵⁰⁾

Some cases of ET can be treated pharmacologically with off label prescription of beta blockers, tranquilizers, anti-seizure medication, or even Botox injections for certain cases of head and voice tremors.^{51,52)} These medications offer some relief of symptoms but only reduce tremor by approximately 60%.^{53,54)} DBS is significantly more effective than medicinal treatments of ET, reducing tremor on average by 90% although some studies report over 7% complication rate within the first 90 days.^{56–57)} Interesting, Verla et al. found that the rates of complication for severe complications like hemorrhage and infection did not significantly increase with age indicating that perhaps patients currently thought to be outside the therapeutic window will tolerate the procedure well.⁵⁷⁾

Surgeons generally target the ventral intermediate nucleus (Vim) of the thalamus for ET treatment.⁵⁶⁾ Vim DBS in ET was first performed in 1991 and has been quite successful in many studies, reducing tremor and providing long-term relief in some patients.⁵⁸⁾ However, recent research shows that the Vim might be a less optimal target than the posterior subthalamic area (PSA), especially for patients who do not respond well to Vim thalatomy.^{59,60)} A review of the literature performed by Chopra et al. from the Mayo Clinic found both targets appear to be efficacious and well tolerated, but also indicated that long-term follow-up work on PSA patients is necessary to assess its merit.⁶¹⁾ For Vim implantation, studies have shown that more than 70% of ET patients experienced waning benefits of DBS at around 56 months after initial implantation.⁶²⁾ However, reports have also shown that DBS in the Vim can be an effective way of reducing tremor even 12 years after implantation.⁶³⁾

Another novel target, the dentato-rubro-thalamic tract (DRTT) was assessed with the aid of diffusion tensor imaging but results from the small cohort of five patients were not encouraging.⁶⁴⁾ Essential voice tremor (EVT), an indication closely related to ET, was recently treated with DBS by a Stanford group pioneering a comprehensive intraoperative voice evaluation approach which may lead the establishment

of a new approach for subtypes of ET.⁶⁵⁾ Patients suffering from EVT display a pronounced tremulous voice often associated with social embarrassment and loss of quality of life.

II. DBS in dystonia

DBS has also been approved in the treatment of dystonia. Dystonia is an often refractive, heterogeneous neuromuscular disorder characterized by abnormal muscle contractions causing repetitive involuntary movements or irregular postures. The majority of dystonia cases have unknown causes, but some are known to be genetic in origin. First used to treat dystonia in 1977, the procedure became widespread by the turn of the century. DBS targeting the GPi is most common in the treatment of dystonia, and has repeatedly shown efficacy over the years.^{66–70)} A recent meta-analysis of the literature found strong evidence supporting the use of DBS for cervical, primary, or segmental dystonia, especially when symptoms can be traced to mutations of the DYT1 gene.⁷¹⁾ Long-term GPi-DBS is effective in patients presenting with DYT6 and non-DYT dystonia as well, but the effect of DBS is more variable in patients with DYT6.⁷²⁾ In a study of 22 young adult dystonia patients, Haridas et al. showed that DBS in dystonia patients under the age of 21 is a safe method of treatment.⁷³⁾ This is particularly important for the viability of DBS-treated dystonia, as childhood and young adulthood onset is common for dystonia patients. Other clinical trials show that DBS is more effective in children than in adults.⁷⁴⁾ Although modulation of the GPi is efficacious, the treatment brings with it a risk for mild yet significant impairment of speech.⁷⁵⁾ DBS offers a safe and effective way of reducing dystonia symptoms in cases that do not respond to medicinal treatments.

III. DBS for epilepsy

Because of the ability of DBS to modulate electrical activity it would seem to be uniquely suited to address cases of refractory epilepsy. In 2013, closed loop stimulation was approved as an HDE by the FDA to treat intractable cases of epilepsy with expanding approval expected in the near future. Epilepsy as a clinical diagnosis generally describes chronic, spontaneous seizures, which can be further classified based on how the epileptic activity arises, spreads, and extinguishes for a given patient. Causes of epilepsy include genetic predisposition, pharmacologically induced neurological adaptations, mechanical injuries as seen in traumatic brain injury (TBI), and deleterious developmental events. Even with the best clinical care, about a third of all epileptics will receive insufficient care. Prior to

the use of DBS as a treatment, surgical intervention entailed resective brain surgery until the turn of the 20th century.⁷⁶⁾ In 1997, VNS was approved by the FDA for the treatment of epilepsy, but with this treatment seizure freedom is rare and 25% of patients receive no benefit from the procedure.⁷⁷⁾

The anterior nucleus of the thalamus (ANT) is a particularly interesting target, and as such was the focus of the Medtronic Inc. that sponsored Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trials. Out of 157 patients, 110 qualified to undergo bilateral stimulation of the ANT at 1 of the 17 facilities in the United States.⁷⁸⁾ The study reported a 56% reduction in seizure frequency 2 years after implantation and although approval was granted in Europe and Canada, the FDA did not. Despite the shortfall of the SANTE trials in the eyes of the FDA, the ANT continues to be a target of interest for treatment of epilepsy, and Medtronic continues to support clinical trials in the international market. Advances in intraoperative electrode positioning using computed tomography provided by devices like Medtronic's O-arm and novel electrode implant trajectories may be techniques that assist in bringing the effectiveness of ANT DBS up to the required levels.^{79,80)} These new techniques may be especially effective for targeting the ANT because of the sequestered location of the nucleus and heterogenic local cellular composition.

Although ANT has garnered the most attention in the last decade; there are other strong candidates as well. Medtronic and George Washington University are currently sponsoring a trial to evaluate the effect of stimulation of the fornix in intractable mesial temporal lobe epilepsy. The hippocampus (HC) and related projections like the fornix are the primary regions of interests for temporal lobe epilepsy (TLE).^{81–83)} Because TLE accounts for the greatest number of epileptic diagnoses, the HC has long been known to be implicated in this subset of disorders.⁸⁴⁾ As a result, resective surgery of this region has historically been relatively common and is still carried out in some cases.⁷⁶⁾ Compared to resection, DBS places minimal additional risk to the patient's health as resective surgery candidates often undergo electrode placement in the HC as a means to evaluate seizure localization. Significant challenges exist to develop the HC as a viable surgical target due to its notably heterogeneous composition and recruitment into most major neurologic functions. Likely because of this anatomic complexity, clinical trials have reported mixed findings.

Another target of interest, the centromedian nucleus of the thalamus (CMN), is known to be integral to neurologic gate-keeping which is hypothesized to be

altered in epileptics. Small-scale clinical trials have yielded encouraging results of reducing generalized seizures by > 50% up to a year after implant.^{85,86)} However, results have not been uniformly encouraging, indicating necessary refinement in stimulatory parameters and/or superior patient selection criteria. Interestingly, for the CMN as well as ANT there is a therapeutic effect of lead placement without current that often lasts for several months.^{78,86)}

IV. DBS for Gilles de la Tourette (GTS)

Patients diagnosed with Tourette's syndrome (TS) display repetitive motor and vocal behaviors on a broad spectrum.^{87,88)} Often in proportion to the severity of their symptoms, patients respond to conventional care including relatively new treatments such as intramuscular injections of botulinum toxin. Patients who present with TS as well as other comorbidities, "TS plus", are the population most likely to benefit from DBS as they are often refractory to care. Although much remains unknown concerning the causes of the disorder, genetic predisposition has been known to play a role in some cases. What is known about the etiology of TS comes from imaging studies that have elucidated the likely role of impaired thalamic, dopaminergic system, and basal ganglia function. However, it is challenging to separate which factors contribute to comorbidities and which to TS itself.^{89,90)}

Although the number of implanted patients is only around 100, most of these cases have been reported to respond well to DBS.^{87,91,92)} Based on these studies, the regions of the thalamus, globus pallidus, and nucleus accumbens (NAc) have received the most clinical attention. Among the many case reports, an Italian group headed by Dr. Servello has crucially published sizeable patient cohorts of bilateral thalamic intralaminar/ventralis oralis complex implants with follow-up data acquired at 6 years post surgery.^{93,94)}

The findings of Servello et al. are nearly uniformly encouraging, and they are not the only team whose work is indicating such. An Australian group evaluating the anteromedial globus pallidus interna published that 10 of their 11 patients reported improvement in tic severity while 6 of these patients had more than 50% overall reduction in tics for at least a 3-month period.⁹⁵⁾ In line with these findings, a Mayo Clinic group targeting the bilateral thalamic centromedian/parafascicular complex found a 60%–80% mean reduction in tics as measured by the Yale Global Tic Severity Scale at the 1 year follow-up point in their three-patient study.⁹⁶⁾

Smith and Spindler from the Perelman School of Medicine recently conducted a review of case

studies and small trials for hyperkinetic movement disorders and found that for treatment of GTS and tardive syndromes, the literature supported the efficacy of DBS.⁹⁷⁾ Evaluation of GTS was aided by two randomized, double-blind studies that cumulatively assessed 11 patients.^{98,99)} Due to these promising findings, there are currently at least five clinical trials expected to report on the efficacy of DBS for GTS in the next year with several others evaluating TMS and tDCS to the same end, but significant challenges remain in addressing the true efficacy of DBS for GTS as evidenced by disappointing results from a randomized trial utilizing Neuropace's responsive neurostimulation system reported in 2013.¹⁰⁰⁾

These encouraging findings would indicate that DBS for TS seems to be effective for over 90% of patients to varying degrees.¹⁰¹⁾ When considering that most of these data come from case reports or small cohorts being implanted in different targets by different clinicians, it is especially impressive. Work showing the potential for amelioration of "TS plus" cases should be the focus of future study as these cases are in particularly dire need of adequate care.^{102,103)} Overall, TS is one of the most promising rising indications for DBS.^{101,102)} Clinical trials are currently recruiting participants at the University of Western Australia, University of Florida, and John Hopkins while results from trials carried out at University College London are forthcoming.

V. DBS for depression

The World Health Organization estimates that over 350 million people suffer from major depressive disorder (MDD). In Japan, a top-down costing approach estimated the national burden of depression to be \$11 billion in 2008.¹⁰⁴⁾ In America, over 2% of adults will suffer from severe depression in a given 12-month period.¹⁰⁵⁾ Like most psychiatric disorders, MDD is challenging to treat due to lack of treatment options as well as complex social stigmas and complicating comorbidities. Because of need, DBS has been increasingly assessed as a potential option for patients afflicted with refractory disease courses.

The first wave of trials evaluated the anterior limb of the capsula interna (ALIC), anterior cingulate cortex (Cg25), ventral striatum, medial forebrain bundle (mFB), and subcallosal cingulate gyrus (SCG).¹⁰⁶⁾ The ALIC, mFB, and SCG are especially deserving attention as long-term data is available for analysis.¹⁰⁷⁾ The SCG was targeted in 17 patients with refractory MDD by Holtzheimer et al., and showed reduction in reported levels of depression in 92% of patients. Impressively, these results are

2 years post implantation.¹⁰⁸⁾ This finding supports Mayberg's proposed circuitry for depression, as well as pharmacologic and imaging studies that indicate hypermetabolism of the SCG is at work behind MDD.^{77,109,110)} The ventral striatum and related reward centers have been another focus for researchers. Ten patients implanted in the NAc reported improved cognition and vision in 1 year after treatment.¹¹¹⁾

Encouraged by these and related findings, Medtronic sponsored a 30-patient, multi-site randomized sham-controlled trial evaluating the effect of ventral capsule/ventral striatum DBS on refractory MDD.¹¹²⁾ In the first such randomized controlled trial for MDD published in 2014, patients were blinded to their treatment for 16 weeks, followed by open-label treatment. Although the desired 50% improvement in Montgomery-Åsberg Depression Rating Scale was not achieved, patients did report a range of 20–26.7% improvement in the open-label continuation phase. These findings would indicate that additional randomized controlled trials evaluating other anatomic targets or incorporating alternate surgical approaches and stimulatory parameters will be likely best suited for the treatment of MDD. The medial forebrain bundle, may be such a target.¹¹³⁾

Addiction

Addiction describes a pattern of ingrained, repetitive behavior that is engaged despite risks or deleterious consequences. The DSM V includes gambling and substance abuse as examples of specific addictions. Proposing adjunctive use of DBS for refractory cases of neuropsychiatric disorders is always a complicated undertaking, but with addiction there are additional ethical questions and concerns over patient's ability to cohere to a regular treatment regimen. Additionally, it is not clear whether deleterious drug-induced neurologic changes contribute as greatly to uncontrolled substance use as environmental or social factors. For these reasons patient selection is crucial.

Proposals for use of DBS to treat addiction have drawn evidence from animal models and imaging studies in conjunction with clinical observation of unintended effects of NAc stimulation. Changes in several brain regions have been correlated to addictive behaviors, but it is the dopaminergic pathways incorporating the NAc and related structures that have received the most attention.^{114–116)} Implanted in the NAc for the purpose of addressing anxiety and depression, a 54-year-old patient was able to significantly reduce the amount of alcohol he was consuming.¹¹⁷⁾ The treatment did not affect his

intended behavioral outcome but the effect on the patient's long-standing alcoholism was significant itself.

A group headed by the same researchers who noticed this unintended effect tracked the smoking behavior of 10 patients after they began receiving NAc DBS for refractory anxiety, OCD, or TS in 2011. While receiving stimulation, 30% enrolled reported cessation of smoking. The most damaging substance addictions such as alcohol, nicotine, and heroine have all been reported to respond positively to stimulation in some cases.^{118,119)} In Germany, a recent five patient trial attempted to treat severe alcoholism with off-label bilateral NAc DBS and found encouraging results. All patients reported immediate cessation of cravings following stimulation.¹²⁰⁾ Two patients were abstinent from alcohol for over 4 years, while for the three cases where stress was heavily implicated in alcohol abuse, the frequency and intensity of relapses was heavily attenuated. Additionally, one patient suffered broken electrode leads, following replacement and reported a therapeutic effect equal to what was initially felt following surgery. No adverse effects of surgery were reported, and although one patient exhibited a transient episode of hypomania, adjustment of stimulation settings resulted in symptoms abating. Although overall very positive, findings from this study cannot be analyzed with a high level of confidence because patients were not blinded to their treatment. It is encouraging to see that in the case of the patient with broken leads, reported therapeutic effects were in line with whether or not current was effectively being delivered.¹²⁰⁾

With data accumulation in the early stages, it is difficult to know how much promising modulation of the reward the circuitry holds for treatment of addiction, but with the economic and disease burden of addiction being so and preliminary results, it appears to be worth further investigation. Several clinical trials are recruiting opioid or alcohol dependent patients for NAc DBS on the international stage, but at the time of writing results are forthcoming. Of particular interest will be two trials being carried out by the German Research Foundation in response to positive findings by Voges et al. Additionally, promising optogenetic work carried out in animal models has indicated that activation of metabotropic glutamate receptors may normalize drug-adaptive behavior. In 2015 a Swiss group reported that such an effect could also be elicited by low-frequency DBS and selective blocking of D1 receptors.¹²¹⁾ Such findings will likely result in optimized clinical trial stimulation parameters and improved outcomes.

DBS for Obesity

Obesity presents some of the same challenges as addiction to clinicians who must gauge whether a given patient would truly benefit from neurologic intervention as well as whether they could adhere to a larger treatment plan including lifestyle modifications. Worldwide obesity is a growing epidemic with the WHO estimating 600 million people have a BMI > 30 kg/m². This disease state is strongly linked to cardiovascular disease, diabetes, and stroke. Perhaps even more poignantly, obese individuals suffer from a significantly reduced quality of life.¹²²⁾ Nonetheless it can seem like an overstep to address a metabolic imbalance with neurosurgical measures, but when considering the rates that patients opt for often ineffective bariatric surgery it does not seem like a radical treatment.^{123,124)}

In a review by Halpern et al., several targets of interest are outlined that are largely supported by case reports as well as known neurologic functions.^{116,125,126)} One such region is the hypothalamus, which regulates feeding behavior through the endocrine system. The ventromedial hypothalamus (VMH) is a specific subregion being investigated, but current evidence links stimulation of this region with adverse behavioral reactions linked to anxiety and fear response.¹²⁷⁾ In 2008, Hamani et al. carried out bilateral implantation of the VMH in a morbidly obese individual resulting in feelings of déjà vu and related phenomena but had no effect on hedonia.¹²⁸⁾ Another region of the hypothalamus, the lateral hypothalamus (LH), is also under investigation as modulation of its activity may lead to increased metabolic rate itself.¹²⁹⁾ To assess the viability of DBS, a human pilot study was conducted out of the Allegheny General Hospital in Pittsburgh, PA. In 2013, they reported three intractable obese patients who were implanted in an effort to see how safely such a procedure could be done in this patient population.¹³⁰⁾ During the 3-year follow-up period no serious adverse effects were reported. DBS was programmed using standard parameters from movement disorder work, so no significant weight loss was observed, but promising data showing increased resting metabolic rate indicate such a result is a real possibility.

Animal Models

Findings from animal models inform future clinical investigations, but due to the number of such studies it can be challenging to keep informed on promising work. Grouped by indications of interest, recent work in rodents and higher mammals is summarized in Table 1.^{121,131–149)}

Table 1

Indication(s)	Treatment modality	Model organism	Outcome measures	Findings	Journal	Research group
PD	rTMS	Mouse - MPTP model	Resting motor threshold, locomotion measures, high performance liquid chromatography-electrochemical detection	Low frequency rTMS (< 1 Hz) improved motor coordination, resting motor threshold was significantly decreased, and greater levels of BDNF and glial cell line derived neurotrophic factor	Parkinson's Disease, 2015	Dong et al. ¹³¹⁾
Parkinson's disease (PD)	DBS in pedunculopontine tegmental nucleus (PPTg)	Rat – lesions in PPTg and DA depletion through 6-OHDA-hydrobromide	Locomotion measures, histological analysis	Stimulation of the anterior PPTg exaggerated freezing behavior while stimulation of the posterior PPTg ameliorated gate deficits in capitated PD modeled mice	Journal of Neuroscience, 2015	Gut and Winn ¹³²⁾
PD	DBS of the STN	Macaques – reaction time for reaching movements in choice task with concurrent single unit recordings	Gross motor abnormalities, single unit recordings in GPI, immunohistochemistry to confirm placement of probes	No motor differences, STN-DBS caused short-latency and longer latency phasic increases in firing probability resulting in effect of DBS as “information filter” or desynchronizing force as opposed to a informational lesion	Journal of Neuroscience, 2015	Zimnik et al. ¹³³⁾
PD	Epidural SCS at high thoracic level (T3–T4)	Marmosets – Injections of 6-OHDA into the medial forebrain bundle to capitate dopaminergic degeneration	Cortical microelectrode recordings, freezing, hypokinesia, bradykinesia, coordination, gait, posture, fine motor skills	SCS significantly alleviated motor deficits at 4–300 Hz, disrupted synchronization of oscillatory activity associated with PD symptoms	Neuron, 2014	Santana et al. ¹³⁴⁾
PD	Computational modeling	Model based on macaque recordings	Complex network analysis	Current DBS targets are notable in that they share relatively low centrality values while drifting with PD	Neuroscience, 2015	Lei et al. ¹³⁵⁾
Epilepsy	DBS of the STN	Macaque - focal motor seizures induced by intracortical injection of penicillin	Seizure onset, duration, and total length, ictal spike frequency	Stimulation at 130 Hz and 60 us pulse width slightly delayed the occurrence of the first seizure and significantly decreased the total number or duration of seizures	Brain Stimulation, 2015	Prabhu et al. ¹³⁶⁾
Epilepsy	DBS of the hippocampus	Macaque – spontaneous recurrent seizures for at least 2 years prior to experiment	Chronic electrographic recordings, acute stimulation, seizure classification	Characterization of effects of long term stimulation was accomplished in non-human primate	Journal of Neurophysiology, 2015	Lipski et al. ¹³⁷⁾

(Continued)

Table 1 (Continued)

Indication(s)	Treatment modality	Model organism	Outcome measures	Findings	Journal	Research group
Epilepsy	Closed loop DBS with concurrent LFP recording	Sheep	Electrophysiological analysis of hippocampal LFP, animal behavior	LFP suppression can be produced in the hippocampus through hippocampal or thalamic stimulation at certain parameters	Neurosurgery, 2015	Cheng and Anderson ¹³⁸⁾
Epilepsy	DBS of the right basolateral amygdala	Rat – pilocarpine animal model of temporal lobe epilepsy	Characterization of seizure activity using Racine's scale, immunohistochemistry	Nonperiodic stimulation of the basolateral amygdala showed significantly reduced number and duration of seizures, whereas periodic stimulation had no effect	Epilepsy & Behavior, 2014	de Oliveira et al. ¹³⁹⁾
Addiction	DBS of the STN	Rat - self administration of sucrose pellets and cocaine injections	Number of pellets/injections obtained, last ratio reached, cumulative lever presses	STN DBS increased motivation for "natural" rewards like food but decreased it for cocaine in a progressive ratio task, but had no effect on consummatory patterns in a fixed ratio 1 task	Proceedings of the National Academy of Sciences, 2010	Rouaud et al. ¹⁴⁰⁾
Addiction	DBS in accumbens shell	Rats – cue-induced reinstatement of cocaine seeking	Lever presses for self administration of cocaine and sucrose pellets	Bilateral stimulation of the accumbens shell at 150 Hz attenuates cue-induced reinstatement of cocaine and sucrose seeking	Behavioral Brain Research, 2015	Guercio et al. ¹⁴¹⁾
Addiction	DBS in accumbens shell	Rats – chronic cocaine self-administration and subsequent withdrawal	Drug seeking behavior following removal of cocaine self-administration at 1 day, 15 days, and 30 days	Unilateral stimulation at both 20 Hz and 160 Hz attenuated drug seeking behavior when measured 15 days after withdrawal onset	Brain Stimulation, 2015	Hamilton et al. ¹⁴²⁾
Addiction	DBS in accumbens shell, accumbens core, and mPFC	Mice – locomotor sensitization through intraperitoneally injected cocaine	Cocaine challenge test 10 days following withdrawal of cocaine administration	DBS at 130 Hz, 90 us, suppressed sensitization during the cocaine challenge as well as when applied 60 min leading up to challenge	Science, 2015	Creed et al. ¹²¹⁾
Gilles de la Tourette (GTS)	Axonal tracing	Macaque – microinjections of bicuculine to stimulate GTS-like symptoms	Axonal tracers injected into striatum following provoked GTS-like symptoms, behavioral analysis of animals, neuronal labeling	Tic-like movements associated with labeling within sensorimotor network, while neuronal labeling in the PFC and basal ganglia was related to hyperactivity	Cortex, 2013	Worbe et al. ¹⁴³⁾
Major depressive disorder	DBS of the ventromedial prefrontal cortex (vmPFC), rodent correlate of subgenual cingulate (Cg25)	Rat – Flinders sensitive line (FSL), rat genetic model of depression	Forced swim test (FST), sucrose consumption test (SCT), intracranial self-stimulation (ICSS)	vmPFC-DBS at 130 Hz, 100 us, pulse width, 300 uA current intensity showed a significant main effect of stimulation in the FST and SCT	Brain Stimulation, 2014	Rea et al. ¹⁴⁴⁾

(Continued)

Table 1 (Continued)

Indication(s)	Treatment modality	Model organism	Outcome measures	Findings	Journal	Research group
Major depressive disorder	DBS for many targets	Rat – chronic unpredictable stress model	Forced-swim test, sucrose intake, extracellular single-unit recordings in Dorsal Raphe Nuclei	Stimulation at 100 Hz, 100 uA, 100 us pulse width in vmPFC produced decreased forced swim immobility, reduced anxiety, enhanced hedonia	Translational Psychiatry, 2015	Lim et al. ¹⁴⁵⁾
Stroke recovery, plasticity	DBS of the cerebellar output	Rats – focal cortical ischemia on animals pre-trained in a pasta matrix retrieval task	Pasta retrieval, intracortical microstimulation motor mapping, 3D electron microscopy, and Western blot analysis	DBS administered for 5 weeks in either regular or burst at 30 Hz resulted in greater pasta retrieval in the 5th week of testing, enhanced cortical plasticity, greater synaptic density, and increased expression of synaptophysin, NMDAR1, CAMKII, and PSD95	Journal of Neuroscience, 2014	Cooperrider et al. ¹⁴⁶⁾
OCD	DBS in ventral striatum	Rats – auditory fear conditioning with subsequent extinction training	Freezing behavior on open field, spontaneous lever pressing, and expression of phosphorylated extracellular signal-regulated kinase	DBS for 3 hours at 130 Hz, 100–200 uA, 0.1 ms pulse duration delivered prior to extinction training reduced fear expression and strengthened extinction memory	PNAS, 2012	Rodriguez-Romaguera et al. ¹⁴⁷⁾
Neuropathic pain	DBS in ventral posterolateral nucleus (VPL)	Rats – tibial and sural nerve transection (TST) model	Hind limb withdrawal	Stimulation of VPL was effective at reducing both magnitude and duration of pain response	Journal of Korean Neurosurgical Society, 2015	Kim et al. ¹⁴⁸⁾
Traumatic Brain Injury	DBS of the central thalamus	Mice - multiple weight-drop model, simulating moderate closed head injury	Neurological severity screen (NSS), parental care assay, elevated plus maze, light-dark transition assay, pheromonal spatial learning, partition test, social discrimination	DBS at 125 Hz, 150 uA, and 200 us pulse width increased the motor component of arousal. Additionally, the temporal pattern of DBS can effect the magnitude of effect	Behavioral Brain Research, 2014	Tabansky et al. ¹⁴⁹⁾

DA: dopamine, DBS: deep brain stimulation, GPe: globus pallidus internus, LPF: local field potential, mPFC: medial prefrontal cortex, rTMS: repetitive transcranial magnetic stimulation, SCS: spinal cord stimulation, STN: subthalamic nucleus, 3D: three-dimensional.

Conclusion

With over 700,000 stimulation devices in use, internationally ranging from sacral nerve stimulators for urinary incontinence to cochlear implants for hearing loss, and with revenue nearing three billion dollars it is clear that technologies like DBS are disrupting conventional treatment options.¹⁵⁰⁾ DARPA's recently disclosed \$70 million Brain Research through Advancing Innovative Neurotechnologies specifically addresses the development of novel, wireless devices like DBS hardware, further highlighting the attention modulatory devices are receiving from the larger academic community.¹⁵¹⁾ Miniaturization of scopes that can be used intraoperatively as well as advances in DBS hardware will continue to make therapeutically powerful but technically difficult targets like the HC or ANT more easily.^{10,32,83,152)} The coming decades will see a proliferation of DBS procedures, with the major limitations continuing to be acquiring resources to pursue double blinded clinical trials as well as long-term monitoring.

Conflicts of Interest Disclosure

The authors, Anand Tekriwal and Dr. Gordon Baltuch, declare no conflicts of interest.

References

- Connolly PJ, Halpern CH, Baltuch GH, Danish SF, Jaggi JL: Implications for programming strategy of the location of the active contact in subthalamic nucleus deep brain stimulation. *J Clin Neurosci* 19: 1029–1031, 2012
- Connolly PJ, Kilpatrick M, Jaggi JL, Church E, Baltuch GH: Feasibility of an operational standardized checklist for movement disorder surgery. A pilot study. *Stereotact Funct Neurosurg* 87: 94–100, 2009
- Halpern C, Hurtig H, Jaggi J, Grossman M, Won M, Baltuch G: Deep brain stimulation in neurologic disorders. *Parkinsonism Relat Disord* 13: 1–16, 2007
- Kramer DR, Halpern CH, Buonacore DL, McGill KR, Hurtig HI, Jaggi JL, Baltuch GH: Best surgical practices: a stepwise approach to the University of Pennsylvania deep brain stimulation protocol. *Neurosurg Focus* 29: E3, 2010
- Kramer DR, Halpern CH, Connolly PJ, Jaggi JL, Baltuch GH: Error reduction with routine checklist use during deep brain stimulation surgery. *Stereotact Funct Neurosurg* 90: 255–259, 2012
- Kramer DR, Halpern CH, Danish SF, Jaggi JL, Baltuch GH: The effect of intraventricular trajectory on brain shift in deep brain stimulation. *Stereotact Funct Neurosurg* 90: 20–24, 2012
- Syre P, Bohman LE, Baltuch G, Roux PL, Welch WC: CSF leaks and their management following anterior cervical discectomy and fusion: a report of 13 cases and a review of the literature. *Spine (Phila Pa 1976)* 2014 [Epub ahead of print]
- Schultz DG: Medtronic Activa® Dystonia Therapy in: F.a.D. Administration (Ed.), Rockville MD, 2003
- Tillman D-B: Reclaim Deep Brain Stimulation for Obsessive Compulsive Disorder (OCD) Therapy in: F.a.D. Administration (Ed.), Food and Drug Administration, Rockville MD, 2009
- Foreman C: RNS® System, in: F.a.D. Administration (Ed.), Silver Spring, MD, 2013
- Deco G, Kringelbach ML: Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. *Neuron* 84: 892–905, 2014
- Shin SS, Dixon CE, Okonkwo DO, Richardson RM: Neurostimulation for traumatic brain injury. *J Neurosurg* 121: 1219–1231, 2014
- Rhonda S Karg, Jonaki B, Kathryn R. Batts, Valerie L. Forman-Hoffman, Dan Liao, Erica Hirsch, Michael R. Pemberton, Lisa J. Colpe, Sarra L Hedden: Past year mental disorders among adults in the United States: results from the 2008–2012 Mental Health Surveillance Study. *CBHSQ Data Review* 2014
- Liu T, Lao L: Tai chi for patients with Parkinson's disease. *N Engl J Med* 366: 1737; author reply 1738, 2012
- Yasuhara T, Kameda M, Agari T, Date I: Regenerative medicine for Parkinson's disease. *Neurol Med Chir (Tokyo)* 55(Suppl 1): 113–123, 2015
- Fischbach GD, McKhann GM: Cell therapy for Parkinson's disease. *N Engl J Med* 344: 763–765, 2001
- Calne DB: Progress in Parkinson's disease. *N Engl J Med* 310: 523–524, 1984
- Okun MS: Deep-brain stimulation—entering the era of human neural-network modulation. *N Engl J Med* 371: 1369–1373, 2014
- Jessica K, Bichum O, Leonard VM: Patient-centered outcomes of deep brain stimulation in parkinson's disease. (P1.174). *Neurology* 84(Supplement P1.174): 2015
- Johnson DK, Langford Z, Garnier-Villarreal M, Morris JC, Galvin JE: Onset of mild cognitive impairment in parkinson disease. *Alzheimer Dis Assoc Disord* 2015 [Epub ahead of print]
- Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A: The current and projected economic burden of Parkinson's disease in the United States. *Mov Disord* 28: 311–318, 2013
- Rodriguez-Violante M, Camacho-Ordoñez A, Cervantes-Arriaga A, González-Latapí P, Velázquez-Osuna S: Factors associated with the quality of life of subjects with Parkinson's disease and burden on their caregivers. *Neurologia* 30: 257–263, 2015
- Arora S, Venkataraman V, Zhan A, Donohue S, Biglan KM, Dorsey ER, Little MA: Detecting and monitoring the symptoms of Parkinson's disease using smartphones: a pilot study. *Parkinsonism Relat Disord* 21: 650–653, 2015

- 24) Sako W, Murakami N, Izumi Y, Kaji R: Neurofilament light chain level in cerebrospinal fluid can differentiate Parkinson's disease from atypical parkinsonism: evidence from a meta-analysis. *J Neurol Sci* 352: 84–87, 2015
- 25) Suwijn SR, van Boheemen CJ, de Haan RJ, Tissingh G, Booij J, de Bie RM: The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review. *EJNMMI Res* 5: 12, 2015
- 26) Chiken S, Nambu A: Mechanism of deep brain stimulation: inhibition, excitation, or disruption? *Neuroscientist* 2015 [Epub ahead of print]
- 27) Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, Marks WJ, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ; CSP 468 Study Group: Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 79: 55–65, 2012
- 28) Liu Y, Li W, Tan C, Liu X, Wang X, Gui Y, Qin L, Deng F, Hu C, Chen L: Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease. *J Neurosurg* 121: 709–718, 2014
- 29) Hershey T, Wu J, Weaver PM, Perantie DC, Karimi M, Tabbal SD, Perlmuter JS: Unilateral vs. bilateral STN DBS effects on working memory and motor function in Parkinson disease. *Exp Neurol* 210: 402–408, 2008
- 30) Taba HA, Wu SS, Foote KD, Hass CJ, Fernandez HH, Malaty IA, Rodriguez RL, Dai Y, Zeilman PR, Jacobson CE, Okun MS: A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. *J Neurosurg* 113: 1224–1229, 2010
- 31) Li J, Zhang Y, Li Y: Long-term follow-up of bilateral subthalamic nucleus stimulation in Chinese Parkinson's disease patients. *Br J Neurosurg* 29: 329–333, 2015
- 32) Castrioto A, Moro E: New targets for deep brain stimulation treatment of Parkinson's disease. *Expert Rev Neurother* 13: 1319–1328, 2013
- 33) Blomstedt P, Fytagoridis A, Åström M, Linder J, Forsgren L, Hariz MI: Unilateral caudal zona incerta deep brain stimulation for Parkinsonian tremor. *Parkinsonism Relat Disord* 18: 1062–1066, 2012
- 34) Moro E, Hamani C, Poon YY, Al-Khairallah T, Dostrovsky JO, Hutchison WD, Lozano AM: Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain* 133: 215–224, 2010
- 35) De Rose M, Guzzi G, Bosco D, Romano M, Lavano SM, Plastino M, Volpentesta G, Marotta R, Lavano A: Motor cortex stimulation in Parkinson's disease. *Neurol Res Int* 2012: 7, 2012
- 36) Khan S, Gill SS, Mooney L, White P, Whone A, Brooks DJ, Pavese N: Combined pedunculopontine-subthalamic stimulation in Parkinson disease. *Neurology* 78: 1090–1095, 2012
- 37) Lavano A, Guzzi G, De Rose M, Romano M, Della Torre A, Vescio G, Deodato F, Lavano F, Volpentesta G: Minimally invasive motor cortex stimulation for parkinson's disease: a review of literature. *J Neurosurg Sci* 2015 [Epub ahead of print]
- 38) Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM: A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol* 68: 521–534, 2010
- 39) Weiss D, Breit S, Wächter T, Plewnia C, Gharabaghi A, Krüger R: Combined stimulation of the substantia nigra pars reticulata and the subthalamic nucleus is effective in hypokinetic gait disturbance in Parkinson's disease. *J Neurol* 258: 1183–1185, 2011
- 40) Sugiyama K, Nozaki T, Asakawa T, Koizumi S, Saitoh O, Namba H: The present indication and future of deep brain stimulation. *Neurol Med Chir (Tokyo)* 55: 416–421, 2015
- 41) Lyons MK: Deep brain stimulation: current and future clinical applications. *Mayo Clin Proc* 86: 662–672, 2011
- 42) Fukaya C, Yamamoto T: Deep brain stimulation for Parkinson's disease: recent trends and future direction. *Neurol Med Chir (Tokyo)* 55: 422–431, 2015
- 43) Okun MS, Gallo BV, Mandybur G, Jagid J, Foote KD, Revilla FJ, Alterman R, Jankovic J, Simpson R, Junn F, Verhagen L, Arle JE, Ford B, Goodman RR, Stewart RM, Horn S, Baltuch GH, Kopell BH, Marshall F, Peichel D, Pahwa R, Lyons KE, Tröster AI, Vitek JL, Tagliati M; SJM DBS Study Group: Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol* 11: 140–149, 2012
- 44) Tallón-Barranco A, Vázquez A, Javier Jiménez-Jiménez F, Ortí-Pareja M, Gasalla T, Cabrera-Valdivia F, Benito-León J, Molina JA: Clinical features of essential tremor seen in neurology practice: a study of 357 patients. *Parkinsonism Relat Disord* 3: 187–190, 1997
- 45) Louis ED: Clinical practice. Essential tremor. *N Engl J Med* 345: 887–891, 2001
- 46) Louis ED, Ferreira JJ: How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 25: 534–541, 2010
- 47) Zhang K, Bhatia S, Oh MY, Cohen D, Angle C, Whiting D: Long-term results of thalamic deep brain stimulation for essential tremor. *J Neurosurg* 112: 1271–1276, 2010
- 48) Hubble JP, Busenbark KL, Wilkinson S, Penn RD, Lyons K, Koller WC: Deep brain stimulation for essential tremor. *Neurology* 46: 1150–1153, 1996
- 49) Boockvar JA, Telfeian A, Baltuch GH, Skolnick B, Simuni T, Stern M, Schmidt ML, Trojanowski JQ: Long-term deep brain stimulation in a patient with

- essential tremor: clinical response and postmortem correlation with stimulator termination sites in ventral thalamus. Case report. *J Neurosurg* 93: 140–144, 2000
- 50) Kestenbaum M, Michalec M, Yu Q, Pullman SL, Louis ED: Intention tremor of the legs in essential tremor: prevalence and clinical correlates. *Mov Disord Clin Pract (Hoboken)* 2: 24–28, 2015
 - 51) Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, Jankovic J, Karp B, Ludlow CL, Miyasaki JM, Naumann M, So Y; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 70: 1699–1706, 2008
 - 52) Hallett M, Albanese A, Dressler D, Segal KR, Simpson DM, Truong D, Jankovic J: Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. *Toxicon* 67: 94–114, 2013
 - 53) Warren JB, O'Brien M, Dalton N, Turner CT: Sympathetic activity in benign familial tremor. *Lancet* 1: 461–462, 1984
 - 54) O'Brien MD, Upton AR, Toseland PA: Benign familial tremor treated with primidone. *Br Med J (Clin Res Ed)* 282: 178–180, 1981
 - 55) Kalakoti P, Ahmed O, Bollam P, Missios S, Wilden J, Nanda A: Predictors of unfavorable outcomes following deep brain stimulation for movement disorders and the effect of hospital case volume on outcomes: an analysis of 33,642 patients across 234 US hospitals using the National (Nationwide) Inpatient Sample from 2002 to 2011. *Neurosurg Focus* 38: E4, 2015
 - 56) Deuschl G, Raethjen J, Hellriegel H, Elble R: Treatment of patients with essential tremor. *Lancet Neurol* 10: 148–161, 2011
 - 57) Verla T, Marky A, Farber H, Petraglia FW, Gallis J, Lokhnygina Y, Parente B, Hickey P, Turner DA, Lad SP: Impact of advancing age on post-operative complications of deep brain stimulation surgery for essential tremor. *J Clin Neurosci* 22: 872–876, 2015
 - 58) Blomstedt P, Hariz GM, Hariz MI, Koskinen LO: Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up. *Br J Neurosurg* 21: 504–509, 2007
 - 59) Blomstedt P, Sandvik U, Tisch S: Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. *Mov Disord* 25: 1350–1356, 2010
 - 60) Sandvik U, Koskinen LO, Lundquist A, Blomstedt P: Thalamic and subthalamic deep brain stimulation for essential tremor: where is the optimal target? *Neurosurgery* 70: 840–845; discussion 845–846, 2012
 - 61) Chopra A, Klassen BT, Stead M: Current clinical application of deep-brain stimulation for essential tremor. *Neuropsychiatr Dis Treat* 9: 1859–1865, 2013
 - 62) Shih LC, LaFaver K, Lim C, Papavassiliou E, Tarsy D: Loss of benefit in VIM thalamic deep brain stimulation (DBS) for essential tremor (ET): how prevalent is it? *Parkinsonism Relat Disord* 19: 676–679, 2013
 - 63) DiLorenzo DJ, Jankovic J, Simpson RK, Takei H, Powell SZ: Long-term deep brain stimulation for essential tremor: 12-year clinicopathologic follow-up. *Mov Disord* 25: 232–238, 2010
 - 64) Schlaier J, Anthofer J, Steib K, Fellner C, Rothenfusser E, Brawanski A, Lange M: Deep brain stimulation for essential tremor: targeting the dentato-rubro-thalamic tract? *Neuromodulation* 18: 105–112, 2015
 - 65) Ho AL, Erickson-Direnzo E, Pendharkar AV, Sung CK, Halpern CH: Deep brain stimulation for vocal tremor: a comprehensive, multidisciplinary methodology. *Neurosurg Focus* 38: E6, 2015
 - 66) Vitek JL: Long-term benefit from deep brain stimulation of the subthalamic nucleus: is it for everyone? *Alzheimers Res Ther* 4: 13, 2012
 - 67) Tagliati M, Krack P, Volkmann J, Aziz T, Krauss JK, Kupsch A, Vidailhet AM: Long-term management of DBS in dystonia: response to stimulation, adverse events, battery changes, and special considerations. *Mov Disord* 26(Suppl 1): S54–S62, 2011
 - 68) Starr PA, Bejjani P, Lozano AM, Metman LV, Hariz MI: Stereotactic techniques and perioperative management of DBS in dystonia. *Mov Disord* 26(Suppl 1): S23–S30, 2011
 - 69) Okun MS, Foote KD: Setting realistic expectations for DBS in dystonia. *Lancet Neurol* 11: 1014–1015, 2012
 - 70) Jahanshahi M, Czernecki V, Zurowski AM: Neuropsychological, neuropsychiatric, and quality of life issues in DBS for dystonia. *Mov Disord* 26(Suppl 1): S63–S78, 2011
 - 71) Fox MD, Alterman RL: Brain stimulation for torsion dystonia. *JAMA Neurol* 72: 713–719, 2015
 - 72) Brüggemann N, Kühn A, Schneider SA, Kamm C, Wolters A, Krause P, Moro E, Steigerwald F, Wittstock M, Tronnier V, Lozano AM, Hamani C, Poon YY, Zittel S, Wächter T, Deuschl G, Krüger R, Kupsch A, Münchau A, Lohmann K, Volkmann J, Klein C: Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. *Neurology* 84: 895–903, 2015
 - 73) Haridas A, Tagliati M, Osborn I, Isaias I, Gologorsky Y, Bressman SB, Weisz D, Alterman RL: Pallidal deep brain stimulation for primary dystonia in children. *Neurosurgery* 68: 738–743; discussion 743, 2011
 - 74) Coubes P, Cif L, El Fertit H, Hemm S, Vayssiére N, Serrat S, Picot MC, Tuffery S, Claustres M, Echenne B, Frerebeau P: Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. *J Neurosurg* 101: 189–194, 2004
 - 75) Risch V, Staiger A, Ziegler W, Ott K, Scholderle T, Pelykh O, Bötzel K: How does GPi-DBS affect speech in primary dystonia? *Brain Stimul* 2015 [Epub ahead of print]

- 76) Kunieda T, Kikuchi T, Miyamoto S: Epilepsy surgery: surgical aspects. *Curr Opin Anaesthesiol* 25: 533–539, 2012
- 77) Kocabicak E, Temel Y, Höllig A, Falkenburger B, Tan SKh: Current perspectives on deep brain stimulation for severe neurological and psychiatric disorders. *Neuropsychiatr Dis Treat* 11: 1051–1066, 2015
- 78) Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C, Pollard J, Tonder L, Grebin J, Coffey R, Graves N; SANTE Study Group: Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51: 899–908, 2010
- 79) Lee DJ, Zwienenberg-Lee M, Seyal M, Shahlaie K: Intraoperative computed tomography for intracranial electrode implantation surgery in medically refractory epilepsy. *J Neurosurg* 122: 526–531, 2015
- 80) Van Gompel JJ, Klassen BT, Worrell GA, Lee KH, Shin C, Zhao CZ, Brown DA, Goerss SJ, Kall BA, Stead M: Anterior nuclear deep brain stimulation guided by concordant hippocampal recording. *Neurosurg Focus* 38: E9, 2015
- 81) Hsiao FJ, Yu HY, Chen WT, Kwan SY, Chen C, Yen DJ, Yiu CH, Shih YH, Lin YY: Increased Intrinsic Connectivity of the Default Mode Network in Temporal Lobe Epilepsy: Evidence from Resting-State MEG Recordings. *PLoS ONE* 10: e0128787, 2015
- 82) Eryurt B, Oner AY, Ucar M, Capraz I, Kurt G, Bilir E, Tali ET: Presurgical evaluation of mesial temporal lobe epilepsy with multiple advanced MR techniques at 3T. *J Neuroradiol* 2015 [Epub ahead of print]
- 83) Chang EF, Englot DJ, Vadera S: Minimally invasive surgical approaches for temporal lobe epilepsy. *Epilepsy Behav* 47: 24–33, 2015
- 84) Taylor DC, Marsh SM: Hughlings Jackson's Dr Z: the paradigm of temporal lobe epilepsy revealed. *J Neurol Neurosurg Psychiatr* 43: 758–767, 1980
- 85) Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M: Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia* 33: 841–851, 1992
- 86) Valentín A, García Navarrete E, Chelvarajah R, Torres C, Navas M, Vico L, Torres N, Pastor J, Selway R, Sola RG, Alarcon G: Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. *Epilepsia* 54: 1823–1833, 2013
- 87) Scharf JM, Miller LL, Gauvin CA, Alabiso J, Mathews CA, Ben-Shlomo Y: Population prevalence of Tourette syndrome: a systematic review and meta-analysis. *Mov Disord* 30: 221–228, 2015
- 88) Mink JW: Clinical review of DBS for Tourette Syndrome. *Front Biosci (Elite Ed)* 1: 72–76, 2009
- 89) Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, Ben-Pazi H, Varadkar S, Aumann TD, Horne MK, Church AJ, Fath T, Brilot F: Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain* 135: 3453–3468, 2012
- 90) Worbe Y, Malherbe C, Hartmann A, Pélérini-Issac M, Messé A, Vidailhet M, Lehericy S, Benali H: Functional immaturity of cortico-basal ganglia networks in Gilles de la Tourette syndrome. *Brain* 135: 1937–1946, 2012
- 91) Yasmeen S, Melchior L, Bertelsen B, Skov L, Mol Debes N, Tümer Z: Sequence analysis of SLITRK1 for var321 in Danish patients with Tourette syndrome and review of the literature. *Psychiatr Genet* 23: 130–133, 2013
- 92) Schrock LE, Mink JW, Woods DW, Porta M, Servello D, Visser-Vandewalle V, Silburn PA, Foltynie T, Walker HC, Shahed-Jimenez J, Savica R, Klassen BT, Machado AG, Foote KD, Zhang JG, Hu W, Ackermans L, Temel Y, Mari Z, Changizi BK, Lozano A, Auyeung M, Kaido T, Agid Y, Welter ML, Khandhar SM, Mogilner AY, Pourfar MH, Walter BL, Juncos JL, Gross RE, Kuhn J, Leckman JF, Neimat JA, Okun MS; Tourette Syndrome Association International Deep Brain Stimulation (DBS) Database and Registry Study Group: Tourette syndrome deep brain stimulation: a review and updated recommendations. *Mov Disord* 30: 448–471, 2015
- 93) Porta M, Servello D, Zanaboni C, Anasetti F, Menghetti C, Sassi M, Robertson MM: Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. *Acta Neurochir (Wien)* 154: 2029–2041, 2012
- 94) Servello D, Sassi M, Brambilla A, Defendi S, Porta M: Long-term, post-deep brain stimulation management of a series of 36 patients affected with refractory gilles de la tourette syndrome. *Neuromodulation* 13: 187–194, 2010
- 95) Cannon E, Silburn P, Coyne T, O'Maley K, Crawford JD, Sachdev PS: Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome. *Am J Psychiatry* 169: 860–866, 2012
- 96) Savica R, Stead M, Mack KJ, Lee KH, Klassen BT: Deep brain stimulation in tourette syndrome: a description of 3 patients with excellent outcome. *Mayo Clin Proc* 87: 59–62, 2012
- 97) Smith KM, Spindler MA: Uncommon applications of deep brain stimulation in hyperkinetic movement disorders. *Tremor Other Hyperkinet Mov (N Y)* 5: 278, 2015
- 98) Maciunas RJ, Maddux BN, Riley DE, Whitney CM, Schoenberg MR, Ogrocki PJ, Albert JM, Gould DJ: Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. *J Neurosurg* 107: 1004–1014, 2007
- 99) Ackermans L, Duits A, van der Linden C, Tijssen M, Schruers K, Temel Y, Kleijer M, Nederveen P, Bruggeman R, Tromp S, van Kranen-Mastenbroek V, Kingma H, Cath D, Visser-Vandewalle V: Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain* 134: 832–844, 2011

- 100) Okun MS, Foote KD, Wu SS, Ward HE, Bowers D, Rodriguez RL, Malaty IA, Goodman WK, Gilbert DM, Walker HC, Mink JW, Merritt S, Morishita T, Sanchez JC: A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. *JAMA Neurol* 70: 85–94, 2013
- 101) Müller-Vahl KR: Surgical treatment of Tourette syndrome. *Neurosci Biobehav Rev* 37: 1178–1185, 2013
- 102) Velasco AL, Velasco F, Jiménez F, Velasco M, Castro G, Carrillo-Ruiz JD, Fanghanel G, Boleaga B: Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. *Epilepsia* 47: 1203–1212, 2006
- 103) Viswanathan A, Jimenez-Shahed J, Baizabal Carvallo JF, Jankovic J: Deep brain stimulation for Tourette syndrome: target selection. *Stereotact Funct Neurosurg* 90: 213–224, 2012
- 104) Okumura Y, Higuchi T: Cost of depression among adults in Japan. *Prim Care Companion CNS Disord* 13: pii, 2011
- 105) Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC: Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62: 629–640, 2005
- 106) Schlaepfer TE, Bewernick BH: Deep brain stimulation for major depression. *Handbook Clin Neurol* 116: 235–243, 2013
- 107) Merkl A, Schneider GH, Schönecker T, Aust S, Köhl KP, Kupsch A, Kühn AA, Bajbouj M: Antidepressant effects after short-term and chronic stimulation of the subgenual cingulate gyrus in treatment-resistant depression. *Exp Neurol* 249: 160–168, 2013
- 108) Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, Wint D, Craighead MC, Kozarsky J, Chismar R, Moreines JL, Mewes K, Posse PR, Gutman DA, Mayberg HS: Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry* 69: 150–158, 2012
- 109) Awan NR, Lozano A, Hamani C: Deep brain stimulation: current and future perspectives. *Neurosurg Focus* 27: E2, 2009
- 110) Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwab JM, Kennedy SH: Deep brain stimulation for treatment-resistant depression. *Neuron* 45: 651–660, 2005
- 111) Grubert C, Hurlmann R, Bewernick BH, Kayser S, Hadrysiewicz B, Axmacher N, Sturm V, Schlaepfer TE: Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. *World J Biol Psychiatry* 12: 516–527, 2011
- 112) Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, Eskandar EN, Baltuch GH, Machado AD, Kondziolka D, Cusin C, Evans KC, Price LH, Jacobs K, Pandya M, Denko T, Tyrka AR, Brelje T, Deckersbach T, Kubu C, Malone DA Jr: A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biol Psychiatry* 78: 240–248, 2015
- 113) Mavridis IN: Deep brain stimulation for psychiatric disorders: are nucleus accumbens and medial forebrain bundle two branches of the same tree? *Neurosci Biobehav Rev* pii: S0149–S7634(15)00089-5, 2015
- 114) Luijckes J, van den Brink W, Feenstra M, van den Munckhof P, Schuurman PR, Schippers R, Mazaheri A, De Vries TJ, Denys D: Deep brain stimulation in addiction: a review of potential brain targets. *Mol Psychiatry* 17: 572–583, 2012
- 115) Hall W, Carter A: Is deep brain stimulation a prospective “cure” for addiction? *F1000 Med Rep* 3: 4, 2011
- 116) Halpern CH, Torres N, Hurtig HI, Wolf JA, Stephen J, Oh MY, Williams NN, Dichter MA, Jaggi JL, Caplan AL, Kampman KM, Wadden TA, Whiting DM, Baltuch GH: Expanding applications of deep brain stimulation: a potential therapeutic role in obesity and addiction management. *Acta Neurochir (Wien)* 153: 2293–2306, 2011
- 117) Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, Sturm V: Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? *J Neurol Neurosurg Psychiatr* 78: 1152–1153, 2007
- 118) Müller UJ, Sturm V, Voges J, Heinze HJ, Galazky I, Heldmann M, Scheich H, Bogerts B: Successful treatment of chronic resistant alcoholism by deep brain stimulation of nucleus accumbens: first experience with three cases. *Pharmacopsychiatry* 42: 288–291, 2009
- 119) Kuhn J, Moller M, Treppmann JF, Bartsch C, Lenartz D, Gruendler TO, Maarouf M, Brosig A, Barnikol UB, Klosterkötter J, Sturm V: Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction. *Mol Psychiatry* 19: 145–146, 2014
- 120) Voges J, Müller U, Bogerts B, Münte T, Heinze HJ: Deep brain stimulation surgery for alcohol addiction. *World Neurosurg* 80: S28 e21–31, 2013
- 121) Creed M, Pascoli VJ, Lüscher C: Addiction therapy. Refining deep brain stimulation to emulate optogenetic treatment of synaptic pathology. *Science* 347: 659–664, 2015
- 122) Murray CJ, Lopez AD: Measuring the global burden of disease. *N Engl J Med* 369: 448–457, 2013
- 123) Joshi GP, Ahmad S, Riad W, Eckert S, Chung F: Selection of obese patients undergoing ambulatory surgery: a systematic review of the literature. *Anesth Analg* 117: 1082–1091, 2013

- 124) Pisapia JM, Halpern CH, Williams NN, Wadden TA, Baltuch GH, Stein SC: Deep brain stimulation compared with bariatric surgery for the treatment of morbid obesity: a decision analysis study. *Neurosurg Focus* 29: E15, 2010
- 125) Halpern CH, Wolf JA, Bale TL, Stunkard AJ, Danish SF, Grossman M, Jaggi JL, Grady MS, Baltuch GH: Deep brain stimulation in the treatment of obesity. *J Neurosurg* 109: 625–634, 2008
- 126) Ho AL, Sussman ES, Pendharkar AV, Azagury DE, Bohon C, Halpern CH: Deep brain stimulation for obesity: rationale and approach to trial design. *Neurosurg Focus* 38: E8, 2015
- 127) Melega WP, Lacan G, Gorgulho AA, Behnke EJ, De Salles AA: Hypothalamic deep brain stimulation reduces weight gain in an obesity-animal model. *PLoS ONE* 7: e30672, 2012
- 128) Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, Wennberg RA, Lozano AM: Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann Neurol* 63: 119–123, 2008
- 129) Jennings JH, Rizzi G, Stamatakis AM, Ung RL, Stuber GD: The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding. *Science* 341: 1517–1521, 2013
- 130) Whiting DM, Tomycz ND, Bailes J, de Jonge L, Lecoultre V, Wilent B, Alcindor D, Prostko ER, Cheng BC, Angle C, Cantella D, Whiting BB, Mizes JS, Finnis KW, Ravussin E, Oh MY: Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism. *J Neurosurg* 119: 56–63, 2013
- 131) Dong Q, Wang Y, Gu P, Shao R, Zhao L, Liu X, Wang Z, Wang M: The neuroprotective mechanism of low-frequency rTMS on nigral dopaminergic neurons of Parkinson's disease model mice. *Parkinsons Dis* 2015: 564095, 2015
- 132) Gut NK, Winn P: Deep brain stimulation of different pedunculopontine targets in a novel rodent model of parkinsonism. *J Neurosci* 35: 4792–4803, 2015
- 133) Zimnik AJ, Nora GJ, Desmurget M, Turner RS: Movement-related discharge in the macaque globus pallidus during high-frequency stimulation of the subthalamic nucleus. *J Neurosci* 35: 3978–3989, 2015
- 134) Santana MB, Halje P, Simplício H, Richter U, Freire MA, Petersson P, Fuentes R, Nicolelis MA: Spinal cord stimulation alleviates motor deficits in a primate model of Parkinson disease. *Neuron* 84: 716–722, 2014
- 135) Lei X, Huang B, Li H, Jiang H, Hu X, Zhang B: Drift in centrality of different brain regions in an anatomical neural network with Parkinson's disease: a view from complex network analysis. *Neuroscience* 299: 107–124, 2015
- 136) Prabhu S, Chabardès S, Sherdil A, Devergnas A, Michallat S, Bhattacharjee M, Mathieu H, David O, Piallat B: Effect of subthalamic nucleus stimulation on penicillin induced focal motor seizures in primate. *Brain Stimul* 8: 177–184, 2015
- 137) Lipski WJ, DeStefino VJ, Stanslaski SR, Antony AR, Crammond DJ, Cameron JL, Richardson RM: Sensing-enabled hippocampal deep brain stimulation in idiopathic nonhuman primate epilepsy. *J Neurophysiol* 113: 1051–1062, 2015
- 138) Cheng JJ, Anderson WS: Closed-loop deep brain stimulation successfully modulates hippocampal activity in an animal model. *Neurosurgery* 76: N13–N15, 2015
- 139) de Oliveira JC, Medeiros Dde C, de Souza E Rezende GH, Moraes MF, Cota VR: Temporally unstructured electrical stimulation to the amygdala suppresses behavioral chronic seizures of the pilocarpine animal model. *Epilepsy Behav* 36: 159–164, 2014
- 140) Rouaud T, Lardeux S, Panayotis N, Paleressompoulle D, Cador M, Baunez C: Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. *Proc Natl Acad Sci USA* 107: 1196–1200, 2010
- 141) Guercio LA, Schmidt HD, Pierce RC: Deep brain stimulation of the nucleus accumbens shell attenuates cue-induced reinstatement of both cocaine and sucrose seeking in rats. *Behav Brain Res* 281: 125–130, 2015
- 142) Hamilton J, Lee J, Canales JJ: Chronic unilateral stimulation of the nucleus accumbens at high or low frequencies attenuates relapse to cocaine seeking in an animal model. *Brain Stimul* 8: 57–63, 2015
- 143) Worbe Y, Sgambato-Faure V, Epinat J, Chaigneau M, Tandé D, François C, Féger J, Tremblay L: Towards a primate model of Gilles de la Tourette syndrome: anatomo-behavioural correlation of disorders induced by striatal dysfunction. *Cortex* 49: 1126–1140, 2013
- 144) Rea E, Rummel J, Schmidt TT, Hadar R, Heinz A, Mathé AA, Winter C: Anti-anhedonic effect of deep brain stimulation of the prefrontal cortex and the dopaminergic reward system in a genetic rat model of depression: an intracranial self-stimulation paradigm study. *Brain Stimul* 7: 21–28, 2014
- 145) Lim LW, Prickaerts J, Huguet G, Kadar E, Hartung H, Sharp T, Temel Y: Electrical stimulation alleviates depressive-like behaviors of rats: investigation of brain targets and potential mechanisms. *Transl Psychiatry* 5: e535, 2015
- 146) Cooperrider J, Furmaga H, Plow E, Park HJ, Chen Z, Kidd G, Baker KB, Gale JT, Machado AG: Chronic deep cerebellar stimulation promotes long-term potentiation, microstructural plasticity, and reorganization of perilesional cortical representation in a rodent model. *J Neurosci* 34: 9040–9050, 2014
- 147) Rodriguez-Romaguera J, Do Monte FH, Quirk GJ: Deep brain stimulation of the ventral striatum

- enhances extinction of conditioned fear. *Proc Natl Acad Sci USA* 109: 8764–8769, 2012
- 148) Kim J, Lee SE, Shin J, Jung HH, Kim SJ, Chang JW: The neuromodulation of neuropathic pain by measuring pain response rate and pain response duration in animal. *J Korean Neurosurg Soc* 57: 6–11, 2015
 - 149) Tabansky I, Quinkert AW, Rahman N, Muller SZ, Lofgren J, Rudling J, Goodman A, Wang Y, Pfaff DW: Temporally-patterned deep brain stimulation in a mouse model of multiple traumatic brain injury. *Behav Brain Res* 273: 123–132, 2014
 - 150) Lane E: Neuroscience. Will brain stimulation technology lead to “neuroenhancement”? *Science* 342: 438, 2013
 - 151) Ling G: Newsmaker interview: Geoffrey Ling. DARPA aims to rebuild brains. Interview by Emily Underwood. *Science* 342: 1029–1030, 2013
 - 152) Ozbay BN, Losacco JT, Cormack R, Weir R, Bright VM, Gopinath JT, Restrepo D, Gibson EA: Miniaturized fiber-coupled confocal fluorescence microscope with an electrowetting variable focus lens using no moving parts. *Optics Lett* 40: 2553–2556, 2015

Address reprint requests to: Anand Tekriwal, MD, PhD,
Candidate at the University of Colorado Anschutz
School of Medicine, Colorado, USA.
e-mail: tekriwal@sas.upenn.edu