# Deep Brain Stimulation: Expanding Applications

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## 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 FDAs 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 reticulate (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 off 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 havebeen 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 capitulated 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 | Epideural SCS at high thoracic level (T3–T4) | Marmosets – Injections of 6-OHDA into the medial forebrain bundle to capitulate 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 LPF recording | Sheep | Electrophysiological analysis of hippocampal LPF, 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 1day, 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 – Flingers 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 usec 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, GPi: 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 dollarsit 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 easilyy.[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.

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