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Novel applications of deep brain stimulation

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Abstract

The success of deep brain stimulation (DBS) surgery in treating medically refractory symptoms of some movement disorders has inspired further investigation into a wide variety of other treatment-resistant conditions. These range from disorders of gait, mood, and memory to problems as diverse as obesity, consciousness, and addiction. We review the emerging indications, rationale, and outcomes for some of the most promising new applications of DBS in the treatment of postural instability associated with Parkinson's disease, depression, obsessive–compulsive disorder, obesity, substance abuse, epilepsy, Alzheimer's-type dementia, and traumatic brain injury. These studies reveal some of the excitement in a field at the edge of a rapidly expanding frontier. Much work still remains to be done on basic mechanism of DBS, optimal target and patient selection, and long-term durability of this technology in treating new indications.

Key Words: Alzheimer's disease, deep brain stimulation, depression, epilepsy, movement disorders, psychiatry

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INTRODUCTION

The modern application of deep brain stimulation (DBS) to the treatment of neurological illness began in the late 1980s with the pioneering work of Benabid and colleagues,[10,11] who successfully treated patients with Parkinsonian and essential tremor by high-frequency electrical stimulation of the thalamus. With its obvious advantages over traditional ablative neurosurgical procedures including reversibility, adjustability, and titratability, DBS quickly established itself as a mainstay of the therapeutic armamentarium in functional neurosurgery. In particular, DBS has proven its safety and efficacy in the management of patients with Parkinson's disease (PD), tremor, and dystonia. While the precise mechanisms of action of DBS are still being elucidated, its unquestioned efficacy in treating movement disorders has stimulated interest in its application to debilitating diseases previously considered outside the realm of neurosurgical intervention. This search for emerging applications of DBS has also been aided by progress in our understanding of the pathophysiological basis of refractory disease in neurology and psychiatry. We review here recent and promising novel applications of DBS reported in preliminary clinical trials.

GAIT IMPAIRMENT AND POSTURAL INSTABILITY IN PD

A number of recent studies have provided convincing evidence that both pallidal (globus pallidus internus or GPi) and subthalamic nucleus (STN) DBS are highly effective in treating PD. DBS improves the cardinal motor symptoms of PD including tremor,[13,25,49] rigidity,[105,113] and bradykinesia.[19,113,116] It is also effective against some

of the dose-limiting side effects of prolonged levodopa therapy, namely, motor fluctuations and disabling dykinesias.[44,84] In fact, there is now class I evidence from large randomized, controlled trials that DBS is superior to the best medical management in patients with moderate to severe PD.[24,131,133] Unfortunately, advanced PD patients suffer from a large burden of non-motor symptoms which respond poorly both to medication and to DBS at the standard GPi or STN targets. These so-called non-levodopa responsive symptoms can be significant drivers of disability, and include disorders of cognition, mood, olfaction, sleep, gait, and posture.[1,102,115] Gait impairment and postural instability, in particular, account for considerable morbidity: at 10 years after the initial diagnosis of PD, approximately 50% of patients are falling, and at 20 years, a substantial proportion have sustained a fracture as a direct consequence of their falls.[52]

As a result, there has been renewed interest in understanding the neuroanatomical substrates of locomotion and their relevance in PD. Early work on decerebrate cats first suggested that electrical stimulation in the brainstem could initiate or enhance locomotive behavior.[92,106] This work led to the subsequent discovery of a midbrain locomotor region in mammals,[37,38] a region that would also encompass the pedunculopontine nucleus (PPN).[93] Several groups have now performed DBS of the PPN region to address the gait and postural disturbances associated with PD.[30,81,83,94,96,109] Initial reports of efficacy are promising, particularly for the treatment of freezing of gait and falls.[83] The enthusiasm generated by the early results of PPN DBS must be tempered by several unresolved issues associated with this novel target. For one, it is unknown which neural structures within or around the PPN mediate therapeutic effect, though some evidence has emerged implicating cholinergic neurons within the nucleus in non-human primates.[60] In addition, the impact of PPN stimulation on functions unrelated to gait, such as sleep and cognition,[8,47,69,98,110,111] remains to be worked out. Larger controlled trials will be necessary to establish criteria for optimal patient selection as well as the durability of the therapy.

TREATMENT RESISTANT DEPRESSION

The notion of neurosurgery for psychiatric disorders evokes memories of a troubled past. The misguided and indiscriminant application of lobotomy with its unacceptable rate of morbidity, coupled with the development of effective psychotropic medications nearly led to the demise of psychiatric surgical procedures by the 1960s.[134] While a few neurosurgical centers have continued to perform stereotactic ablative procedures for patients with intractable psychiatric conditions, it was not until the last decade, with the emergence of DBS as an accepted therapeutic modality, that psychiatric surgery underwent a resurrection. Much of the renewed enthusiasm in the field has recently been focused on using DBS to manage refractory depression.[53]

Major depressive disorder (MDD) is a prevalent and costly illness. Recent data suggest that it afflicts more than 121 million people worldwide.[91] By 2020, MDD is projected to become the second leading cause of disease burden worldwide with profound public health consequences.[70] Despite the availability of several new classes of anti-depressant medications, evidence-based psychotherapy, and electroconvulsive therapy (ECT), relapse is very common.[40] In all, 10–20% patients respond poorly to the existing therapies and are classified as having treatment-resistant depression (TRD).[29] For these patients, there is a considerable and urgent need for new and effective treatment options.

DBS is now being used to target nodes within dysregulated mood circuits. Among these, a commonly studied region is the subcallosal cingulate gyrus (SCG). Functional imaging studies demonstrate SCG overactivity in depressed patients, accompanied by corresponding reductions in activity in associated prefrontal and premotor cortical areas (areas 9 and 46).[79,80] This pattern of activation is reversed in patients successfully treated with antidepressant medications, cognitive behavioral therapy, or ECT.[28,41,78,86] These findings prompted the conduction of a pilot trial on SCG DBS in TRD patients.[80] At 6 months following implantation, four of six patients were responders (defined by >50% reduction in the Hamilton Rating Scale for Depression-17) and two patients had achieved remission. Furthermore, positron emission tomography (PET) imaging showed a reversal of SCG overactivity and impaired frontal cortex metabolism. No patients suffered neurological or cognitive side effects attributable to DBS in this pilot study, although two patients ultimately required electrode explantation owing to infection.

Long-term follow-up data from an extended cohort of 20 patients treated with SCG DBS have now been published.[61,71] At 3–6 years following implantation (mean 3.5 years), the average response rate was 64.3% and the average remission rate was 42.9%. Patients showed considerable improvement in social functioning and in the degree of involvement in work-related activity at last follow-up.[61] While no unexpected neurocognitive or device-related complications were reported, two patients committed suicide, although these deaths could not be attributed expressly to either stimulation or device failure. In short, all data to date suggest that SCG DBS is safe, effective, and durable in treating patients suffering from TRD.

Several other targets for DBS in depression other than the SCG have now emerged. Preliminary data from pilot studies of bilateral DBS of the ventral caudate/ventral

striatum (VC/VS),[75] nucleus accumbens (NAcc),[12,101] inferior thalamic peduncle (ITP),[57] and lateral habenula[99] show similar efficacy to SCG stimulation. As with the SCG, these alternate targets may effectively be thought of as critical nodes within the neurocircuitry of depression. Currently, there are no head-to-head data establishing the superiority of one target over any other; it remains to be seen if there is in fact a single optimal target in TRD or whether different symptoms lend themselves to different targets.[40] Proving long-term efficacy will ultimately require rigorous placebo-controlled trials in which antidepressant response is assessed by observers blinded to stimulation status.

OTHER PSYCHIATRIC DISORDERS: TOURETTE'S SYNDROME, OBSESSIVE–COMPULSIVE DISORDER, ADDICTION

Gilles de la Tourette syndrome (TS) is characterized by the childhood onset of intrusive and chronic motor or vocal tics.[66,72] Though self-limited in most patients, with a significant decline in tic frequency after the age of 20,[36] DBS has been applied to treatment-resistant cases persisting into adulthood. The first case report of DBS for TS was published in 1999;[122] the patient was treated with electrodes placed bilaterally in the thalamus, aiming to target intralaminar and the ventral oralis internus nuclei. Since this initial report, several studies have reported efficacy with thalamic,[2,4,9,54,73,97,104] pallidal,[4,22,26,77] NAcc,[65] and anterior limb of the internal capsule (ALIC) stimulation.[33,65] To date, there have been four small randomized, blind trials of DBS in adult TS which have all reported significant symptom improvement in the on state but no consensus regarding the optimal target.[3,54,73,132]

Obsessive-compulsive disorder (OCD) is an anxiety disorder in which unwanted and repeated thoughts, feelings, ideas, or sensations (obsessions) result in patients feeling compelled to perform certain repetitive behaviors (compulsions). Functionally disabling in 40% and medically intractable in 10% of sufferers, OCD has long been treated with ablative neurosurgical procedures including cingulotomy and anterior capsulotomy, with some success.[27,82] Several small series of DBS for OCD have been published in the last decade. Targets have included the ALIC,[16,87-90] STN,[34] VC/VS,[7,43] ITP,[58] and NAcc.[90] More recently, randomized, double-blind trials have assessed DBS in the NAcc (bilaterally[23] and unilaterally[55]) ALIC,[42] and STN.[74] As with DBS in other psychiatric disorders, the optimal target has yet to be defined, and the response to stimulation has been variable, though promising: as reported in recent reviews, approximately one-third to half of all patients treated to date would be classified as responders, demonstrating at least a 35% reduction in Yale–Brown Obsessive Compulsive Scale (Y-BOCS) scores.[21,43] Overall, DBS in the setting of OCD has been safe, although unanticipated adverse neuropsychiatric effects due to stimulation, such as mania, have been reported.[48]

The well-established importance of dopamine release in the NAcc to the reward system of the brain[56] has stimulated interest in applying DBS at this target to control addiction. Preliminary reports on the experience with this application are now emerging. Kuhn *et al.*[64] treated a 54-year-old patient with agoraphobia, panic attacks, depression, and comorbid alcohol dependency with bilateral NAcc DBS. Although the patient exhibited only a slight improvement in anxiety and depression at 1 year, there was a dramatic and sustained reduction in alcohol consumption. Since this initial report, Muller *et al.*[85] have published their clinical experience with NAcc DBS in three patients with chronic resistant alcoholism, reporting a sustained reduction in alcohol cravings, as well as complete alcohol abstinence in two patients and a marked reduction in intake in the third, following one full year of chronic DBS. Zhou *et al.*[138] recently published a case report of a 24 year-old man suffering from heroin dependence in whom bilateral, high-frequency stimulation of the NAcc was employed, producing an immediate and complete abstinence from drug use and opioid-seeking behavior. The patient remained relapse-free at 6 years of follow-up, despite stimulation having been permanently discontinued 2½ years after DBS implantation. He also experienced a dramatic decrease in smoking behavior. Similarly, Mantione *et al.*[76] described a patient treated with NAcc DBS for OCD in whom postoperative unintended and effortless smoking cessation was observed. The patient also experienced weight loss; indeed NAcc stimulation has also been suggested as a potential target for the treatment of morbid obesity, given that modulation of reward sensations may affect dietary preferences.[45,72] However, preliminary attempts to use DBS in obesity have mainly targeted the lateral and ventromedial hypothalamic regions corresponding to the appetite and satiety centers of the brain, with some evidence of effect on food intake but unconvincing results with respect to actual weight loss.[45,95,117] No doubt DBS will have to prove its worth compared to standard therapies for addiction and obesity.

EPILEPSY

It is estimated that 1% of all adults suffer from epilepsy, with close to 30% of cases being refractory to conventional antiepileptic therapy.[50,51] While carefully selected patients may benefit from resective surgical procedures, a large number are not candidates for surgery and there is a definite need for effective treatment alternatives. Neuromodulatory procedures for epilepsy have long

attempted to fill that void and predate the modern era of DBS by several decades.[5,35] Chronic electrical stimulation of the superomedial cerebellar cortex was initially employed over 40 years ago.[17,18] Overall, cerebellar stimulation has been applied at both the cortical surface[20,63,68,120,125,135] and deep cerebellar nuclei,[108] with widely varying degrees of efficacy against seizure activity. Three trials have employed a controlled, double-blind methodology,[120,125,135] representing a combined experience of 22 patients. Evidence of stimulation efficacy was only found in the study by Velasco and colleagues.[125] Large-scale blinded clinical trials using current DBS hardware in well-defined patient cohorts remain to be undertaken, mainly due to the ongoing debate about the optimal site of cerebellar stimulation.[5,35]

Outside the cerebellum, direct stimulation of the hippocampus has also been investigated in epilepsy. Structures of the mesial temporal lobe are a natural target for neuromodulation in view of the proven effectiveness of mesiotemporal resective surgery in patients with temporal lobe epilepsy.[5] Classically, hippocampal stimulation has been applied to patients with bitemporal seizure foci or at high risk for memory impairment with open surgical resection.[5] A number of clinical reports have been published on the use of hippocampal DBS so far.[14,114,123,124,127-130] Notably, in studies by Velasco *et al*.[123] and Tellez-Zenteno *et al*.,[114] a double-blind stimulation protocol was used, with divergent results: in the former, patients with normal imaging had >95% and patients with hippocampal sclerosis had >50% seizure reduction at long-term follow-up, while in the latter seizure reduction was only 15% with no clear neuropsychological or quality-of-life benefit. Consequently, hippocampal DBS remains investigational, with more data being required to prove efficacy and confirm safety particularly with respect to memory impairment.

Thalamic DBS has increasingly gained importance in the treatment of epilepsy. Following an initial report of success with centromedian (CM) nucleus stimulation,[126] >50% seizure reduction was demonstrated in two early double-blind trials – one with placebo – employing DBS at the same target.[32,57] Subsequently, the anterior nucleus (AN) superseded the CM nucleus as the most commonly studied thalamic target for neuromodulation against epilepsy.[6,62] The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial[31] enrolled 110 adults with partial or generalized seizures unamenable to conventional resective surgery. Patients underwent bilateral implantation of standard quadripolar DBS electrodes into the AN. During an initial 3-month blinded period, half of the patients received continuous high-frequency stimulation, while the control half were implanted but not stimulated. At 3 months, the stimulated group experienced a significantly greater reduction in seizure frequency compared to unstimulated controls. All patients then went on to receive unblinded stimulation for 2 years. At trial completion, the median overall reduction in seizure frequency was 56%. Additionally, 14 patients were seizure-free and more than half reported seizure reductions of at least 50%.

Other recent novel developments include the responsive neurostimulator, which is an implanted device designed to detect early epileptiform activity and responds – much like a cardiac defibrillator – by delivering pulses of abortive electrical stimulation.[112] Preliminary studies with such systems are encouraging,[107] and a randomized, double-blind, multicenter trial evaluating its efficacy is currently underway in the United States.[72]

ALZHEIMER'S DISEASE

With 27 million people currently afflicted worldwide, and a predicted increase in accrual of cases as the world population ages, Alzheimer's Disease (AD) is the most prevalent of neurodegenerative dementias.[15] A cause of substantial disability and caregiver burden, current medical treatments are largely ineffective at halting its unrelenting course. AD is characterized by pathological changes leading to functional impairment in neural circuits subserving cognitive and memory processes, especially in the hippocampus/entorhinal cortex complex,[59] as well as cholinergic structures. Turnbull *et al*.[119] have used chronic, cyclical, unilateral, monopolar stimulation of the left nucleus basalis of Meynert in a patient with AD. Though they did not find any convincing clinical effect, they observed some evidence of preserved cortical metabolism on serial PET scans.

Based on the serendipitous observation of memory enhancement due to electrical stimulation of the hypothalamic/forniceal region in a patient being treated for obesity,[46] a phase I trial was conducted using forniceal DBS in six patients with mild-to-moderate Alzheimer's-type dementia.[67] Initial results have proved encouraging. Following 1 month of stimulation, PET showed a striking reversal of the typical AD-related glucose hypometabolism in the temporal and parietal cortex. These metabolic changes were sustained at 1 year. Scores on the Mini-Mental Status Exam (MMSE) improved in two patients, and the rate of decline for the group as a whole was slower than expected compared to typical AD patients. No adverse effects attributable to DBS were seen in any patient.

MINIMALLY CONSCIOUS STATE

Using neuromodulation to reverse disorders of consciousness caused by traumatic brain injury has been attempted since the 1950s. These early attempts were confounded by the initiation of stimulation in the period soon after brain injury, when some degree of spontaneous

recovery is expected, and further weakened by a very limited understanding of the differences in impaired states of consciousness, which may impact recovery and outcome.[103] The distinction has now been made between a persistent vegetative state (PVS), in which patients demonstrate wakefulness with some degree of sleep–wake cycling but without any environmental awareness, and a minimally conscious state (MCS), in which there is an awareness of the environment despite impaired communication and, importantly, preservation of organized cortical function.[39] This knowledge, coupled with physiological data implicating the intralaminar nuclei of the thalamus in maintaining wakefulness, arousal, concentration, and attention, paved the way for thalamic DBS as a potential treatment of MCS.[121] To date, the largest clinical experience with this technique has been from a single center in Japan, with several published reports.[118,136,137] In the largest and most recent report, the authors describe a total of 26 patients – 21 with PVS and 5 with MCS.[137] They targeted the mesencephalic reticular formation in two patients and the centromedian–parafascicular (CM–Pf) nuclei of the thalamus in the other 24. Overall, 8/21 PVS recovered the ability to follow verbal commands and 4/5 MCS patients showed sufficient recovery to be discharged from hospital. The experience of this group has been criticized, however, because of the inclusion of several PVS patients and early initiation of DBS within the year following brain injury when spontaneous recovery might still be expected. More recently, considerable interest was generated by a widely publicized case report by Schiff *et al*.,[100] who used DBS in intralaminar thalamic nuclei to treat a 38-year-old man exhibiting MCS 6 years after a traumatic brain injury. Using an on–off, double-blind, 6-month crossover design, they reported significant improvement in several objective measures of consciousness with active stimulation. Confirmation of these promising results in larger trials is awaited.

CONCLUSION

DBS has been shown to be a safe and effective surgical option for a number of movement disorders including essential tremor, PD, and the dystonias. Neural modulation of non-motor circuits is now being investigated for the treatment of several other refractory neurological and psychiatric diseases. Rigorous clinical trials providing robust outcome measures will be needed to establish the safety and efficacy of DBS for these emerging indications.

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