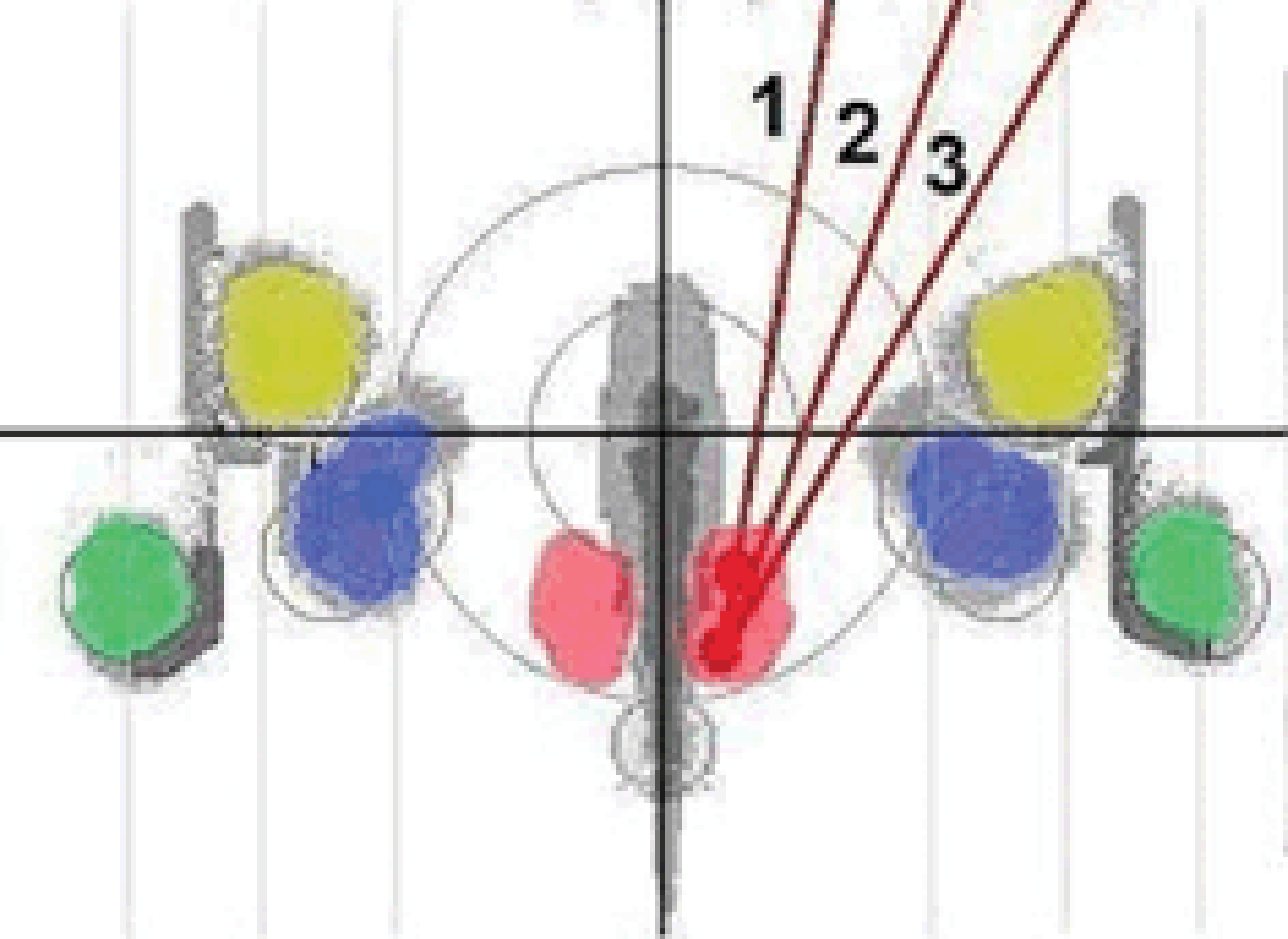
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Introduction

Deep brain stimulation: the spectrum of application

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Brain stimulation of deep, subcortical structures developed with stereotactic surgery in the mid-20th century to treat various conditions including movement disorders and chronic pain. Chronic electrical stimulation eventually largely replaced radiofrequency lesioning because of its inherent safety and treatment versatility. Regardless of the site of stimulation, parameters can be adjusted to reduce side effects and optimize clinical outcomes. Deep brain stimulation (DBS) is now widely accepted as the primary treatment for movement disorders that are refractory to medical therapies—namely Parkinson disease, tremors, and dystonia. Recent clinical studies have suggested beneficial effects of DBS applied to other conditions such as depression,[5,6] obsessive-compulsive disorder,[2–4] and epilepsy.[1]

Several key factors have led to widespread interest in investigating the use of DBS as a new treatment for additional conditions. First, the relative safety of contemporary stereotactic surgery has resulted in more acceptance of DBS as a potential modality for patients in whom other treatment options are absent. Second, DBS is recognized by referring clinicians as a therapy that, unlike the lesioning procedures, is both reversible and adjustable. Third, an improved understanding of brain targets and their role in disease has become possible because of electrophysiological studies, high-resolution MR imaging, and functional imaging techniques. Thus, numerous diseases previously thought to have limited medical therapeutic options are now being considered as conditions potentially amenable to surgery and, specifically, brain stimulation.

This current issue of *Neurosurgical Focus* examines the current state of DBS and explores the emerging applications in disorders other than Parkinson disease and tremor. The first section is devoted to setting the historical context and to the treatment of movement disorders. This includes uses of DBS in the pediatric population and the neurochemical effects of brain stimulation that can be measured with a new wireless device for near real-time detection. Professor Hariz provides a most thorough historical review of brain stimulation.

Newer indications of DBS in the treatment of psychiatric disease and epilepsy are currently under active investigation, and several articles are included that expand the basis for the use of brain stimulation. Lipsman and colleagues address the ethical issues involved in clinical trials for psychiatric patients, and they provide "criteria" for the psychiatry and neurosurgery communities to consider as surgical therapies are advanced. In addition, this section covers some potentially interesting applications of DBS being investigated for such indications as cluster headache, impaired consciousness, and morbid obesity.

This issue of *Neurosurgical Focus* serves as a modern, online chapter describing the current state of DBS and the next generation of disorders that may be successfully treated. *(DOI: 10.3171/2010.8.FOCUS.Intro)*

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Neurosurg Focus 29 (2):E1, 2010

Deep brain stimulation between 1947 and 1987: the untold story

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Deep brain stimulation (DBS) is the most rapidly expanding field in neurosurgery. Movement disorders are well-established indications for DBS, and a number of other neurological and psychiatric indications are currently being investigated.

Numerous contemporary opinions, reviews, and viewpoints on DBS fail to provide a comprehensive account of how this method came into being. Misconceptions in the narrative history of DBS conveyed by the wealth of literature published over the last 2 decades can be summarized as follows: Deep brain stimulation was invented in 1987. The utility of high-frequency stimulation was also discovered in 1987. Lesional surgery preceded DBS. Deep brain stimulation was first used in the treatment of movement disorders and was subsequently used in the treatment of psychiatric and behavioral disorders. Reports of nonmotor effects of subthalamic nucleus DBS prompted its use in psychiatric illness. Early surgical interventions for psychiatric illness failed to adopt a multidisciplinary approach; neurosurgeons often worked "in isolation" from other medical specialists. The involvement of neuro-ethicists and multidisciplinary teams are novel standards introduced in the modern practice of DBS for mental illness that are essential in avoiding the unethical behavior of bygone eras.

In this paper, the authors examined each of these messages in the light of literature published since 1947 and formed the following conclusions. Chronic stimulation of subcortical structures was first used in the early 1950s, very soon after the introduction of human stereotaxy. Studies and debate on the stimulation frequency most likely to achieve desirable results and avoid side effects date back to the early days of DBS; several authors advocated the use of "high" frequency, although the exact frequency was not always specified. Ablative surgery and electrical stimulation developed in parallel, practically since the introduction of human stereotactic surgery. The first applications of both ablative surgery and chronic subcortical stimulation were in psychiatry, not in movement disorders. The renaissance of DBS in surgical treatment of psychiatric illness in 1999 had little to do with nonmotor effects of subthalamic nucleus DBS but involved high-frequency stimulation of the very same brain targets previously used in ablative surgery. Pioneers in functional neurosurgery mostly worked in multidisciplinary groups, including when treating psychiatric illness; those "acting in isolation" were not neurosurgeons. Ethical concerns have indeed been addressed in the past, by neurosurgeons and others. Some of the questionable behavior in surgery for psychiatric illness, including the bygone era of DBS, was at the hands of nonneurosurgeons. These practices have been deemed as "dubious and precarious by yesterday's standards." *(DOI: 10.3171/2010.4.FOCUS10106)*

Key Words • deep brain stimulation • stereotactic surgery • history • psychosurgery • ethics

Treating obsessive-compulsive disorder. Options include medication, psychotherapy, surgery, and deep brain stimulation.

The Harvard Mental Health Letter, March 2009[5]

Deep brain stimulation is probably the most rapidly expanding field in neurosurgery. Parkinson disease, essential tremor, and dystonia are well-established, evidence-based indications for DBS, and a number of other neurological and psychiatric indications are currently being investigated.

Abbreviations used in this paper: DBS = deep brain stimulation; OCD = obsessive-compulsive disorder; PD = Parkinson disease; STN = subthalamic nucleus.

There is no doubt that the modern form of DBS was heralded by the neurosurgeon/neurologist team of Benabid and Pollak and their colleagues[13] in Grenoble, France, through their 1987 publication on thalamic DBS contralateral to thalamotomy in patients with tremor. Subsequently, DBS virtually replaced thalamotomy as a first-hand procedure for tremor.[12,55,62,89] The introduction of subthalamic nucleus (STN) DBS in 1993 by the same group,[77] and the documentation of the safety and efficacy of this method applied bilaterally, including its potential for reducing the dose of dopaminergic medications in patients with advanced PD,[61] eventually gave the coup de grâce to posteroventral pallidotomy,[60] which was the preferred surgical procedure for PD in the 1990s.[41] The

nondestructive, that is, the nonablative feature of DBS, its adaptability and virtual reversibility, combined with its potential for conducting in vivo research on subcortical structures and basal ganglia functions, have attracted the interest of clinicians from several other specialties as well as that of neuroscientists, historians, and ethicists.

Common beliefs conveyed by contemporary literature on DBS include the following: DBS was "invented by Benabid and coworkers;"[57,87,99] the observation that high-frequency stimulation often mimics the clinical effects of lesional surgery was first made in 1987;[10,11] DBS was initially developed for movement disorders and has only recently been applied in neuropsychiatry;[56,99] it was the observation of psychiatric side effects after STN DBS in patients with PD that prompted DBS trials for psychiatric disorders;[57,87] and early proponents of surgical intervention for psychiatric illness failed to adopt a multidisciplinary approach with neurosurgeons often working "in isolation" from other specialists.[35]

The aim of the present review was to look for the seeds of what was to become one of the most rapidly expanding and most promising techniques in the field of functional stereotactic neurosurgery, and to establish if some of the contemporary claims related to the history of DBS can be substantiated.

Methods

We examined available publications on chronic stimulation of subcortical structures published between the dawn of human stereotactic functional neurosurgery in 1947[98] and the seminal paper of Benabid et al.[13] in 1987. Relevant papers were obtained through a PubMed search as well as by retrieving pertinent references quoted in consulted papers, and references published in books and in proceedings of meetings.

Results

Origins of DBS

In 1947, at Temple University in Philadelphia, neurologist Spiegel and neurosurgeon Wycis described a stereotactic apparatus and its use in humans to perform ablative procedures.[98] This collaborative paper heralded the era of human functional stereotaxy, initially labeled "stereoencephalotomy" by its authors.[97] Their efforts were explicitly aimed at avoiding the side effects of the all-too-crude and commonly performed frontal lobotomy. In the last paragraph of their pioneering paper, the authors wrote, "This apparatus is being used for psychosurgery … Lesions have been placed in the region of the medial nucleus of the thalamus (medial thalamotomy) …."[98] According to Gildenberg,[37,38] who was a fellow of Spiegel and Wycis in the 1950s, intraoperative electrical stimulation was used from the very beginning as a mean of exploring the brain target prior to lesioning. Thus, from its very beginning, functional stereotactic neurosurgery was multidisciplinary, was directed at the treatment of psychiatric illness, and used electrical stimulation as a physiological means of assessing and corroborating the subcortical anatomical brain target. Spiegel and Wycis soon shifted their focus to the treatment of movement disorders, starting with Huntington chorea and choreoathetosis, then PD, by performing pallidoansotomies, stereotactically ablating the same areas that had been lesioned by Meyers, Fenelon, and Guiot via an open nonstereotactic approach.[96]

In 1952, neurophysiologist and neurobehaviorist Delgado and his colleagues[23] proposed a technique of electrode implantation for chronic recording and stimulation to evaluate "its possible therapeutic value in psychotic patients." The following year, the Proceedings of the Staff Meetings of the Mayo Clinic published a symposium on "intracerebral electrography" including a paper on "Neurosurgical and neurologic applications of depth electrography" containing the following statement: "An observation that may have some practical significance was that several of our psychotic patients seem to improve and become more accessible in the course of stimulation studies lasting several days."[14] The authors speculated that a likely explanation for this effect "was that the local stimulation was having a therapeutic effect comparable to that of electroshock" and concluded, "… this aspect of localized stimulation studies requires further investigation since it may lead to a most specific, less damaging, and more therapeutically effective electrostimulation technic than can be achieved by the relatively crude extracranial stimulation methods in use at present."[14]

Meanwhile, a team at Tulane University in New Orleans led by psychiatrist Heath[47] had started depth electrode studies in patients in 1950, including chronic stimulation of the septal area in psychotic patients. Also, in 1961, a book entitled "Electrical stimulation of the brain – An interdisciplinary survey of neurobehavioral integrative systems", edited by Daniel Sheer Professor of psychology at the University of Houston, was published.[94] This multiauthored book was devoted to animal and human work on subcortical recording and stimulation in epilepsy, obesity, aggressive behavior, and other neurological and behavioral conditions. Hence, from its very beginning, the technique of chronic stimulation of deep brain structures was applied in behavioral and psychiatric studies and eventually in treatment of mental disorders (see further below).

Frequency of the Electrical Current Used for Stimulation

In a review paper published in 2009, Benabid et al.[10] wrote, "In 1987, the discovery that high-frequency deep brain stimulation (DBS) was able to mimic, in a reversible and adjustable manner, the effects of ablation of functional targets has revived functional neurosurgery of movement disorders …" The Grenoble group was certainly the first to systematically study the therapeutic role of high frequency electrical current in DBS and established 130 Hz as the "ideal" frequency now commonly used worldwide in pallidal and subthalamic DBS. A review of prior stereotactic literature reveals that frequency of the applied current during intraoperative stimulation of the brain target prior to stereotactic lesioning was often a matter of debate with several authors exploring this issue. In his review on evolution of neuromodulation, Gildenberg stated,[37]

> There was considerable discussion on 'low frequency' versus 'high frequency' stimulation, but those terms were not consistently defined. Low frequency might be anywhere from 6

> to 60 Hz. High frequency might be 50-100 Hz, but rarely above …. When I first worked with Spiegel and Wycis from 1955 to 1959, routine stimulation was 6 and 60 Hz. When I returned in 1963, a more sophisticated Grass laboratory stimulator was used, and the parameters were 5, 50 and 100 Hz. There was a general feeling that low frequency stimulation might drive or increase involuntary movements, especially tremor, and high frequency stimulation might mimic the therapeutic effect, but such observations were inconsistent.[37]

In 1961, Alberts et al.[3] studied stimulation thresholds in various parts of the internal pallidum and ventrolateral thalamus in 62 patients with PD prior to lesioning. They stimulated at 60 Hz and could elicit or disrupt tremor. Walker[110] defined the optimal parameters of intraoperative stimulation as being a current of 50–100 Hz, stating that arrest of tremor had better predictive value than facilitation or initiation of tremor. Common observations reported by several authors in the process of performing thalamotomies and subthalamotomies in awake patients were that "low-frequency" stimulation could exacerbate tremor whereas "high-frequency" stimulation resulted in an improvement of that symptom.[2,46,53,73,83,95] In 1963 in France, neurophysiologist Albe-Fessard,[2] who pioneered the technique of subcortical semimicrorecording, reported that stimulation in the region of the ventrointermediate nucleus of the thalamus at frequencies of 100–200 Hz would effectively inhibit tremor in parkinsonian patients. In the same year, psychiatrist Robert Heath from Tulane University in New Orleans published a paper, "Electrical self-stimulation of the brain in Man;"[48] electrodes were implanted in the caudate, septal area, amygdala, central medial thalamus, and various areas of the hypothalamus to study "rewarding" and "aversive" reactions at various current intensities. In all these stimulations, Heath used a fixed frequency of "100 pulse/sec." In 1969, Blaine Nashold and his colleagues[73] stimulated various subcortical structures including the ventrolateral thalamus, the subthalamic nucleus, and the zona incerta and reported that tremor suppression occurred at frequencies of 120–300 Hz. In 1973, Bechtereva et al.[7] advocated the use of "electric stimulation with high-rate pulses" of subcortical structures, however, without specifying what she meant by high-rate pulses. In 1979, Laitinen[58] studied emotional responses to subcortical electrical stimulation in 135 psychiatric patients. The targets were the rostral and middle cingulum, the anterior internal capsule, and the subcaudate region of the "substantia innominata." He noted that stimulation frequency played an important role with "high frequency (60 Hz)" being by far the most effective in producing emotional responses while "low frequency stimulation (3-6 Hz) seldom caused such responses."[58] In almost all these instances, stimulation was performed intraoperatively as a means of physiological evaluation of the brain target prior to lesioning.

Deep Brain Stimulation in Psychiatry and Behavior

As stated earlier, chronic subcortical stimulation through chronically implanted electrodes was first tested in psychiatric patients. Three key individuals, a neurophysiologist, a neurophysiologist/psychiatrist, and a psychiatrist, working independently of each other, devoted much of their career exploring this method.

José Delgado, a Spanish neurophysiologist and neurobehaviorist who moved to Yale University in 1950 and worked there with Fulton, is probably best known for a motion picture showing his experiment with a bull whose charge in the arena could be stopped through remote brain stimulation.[40,105] Delgado worked extensively with chronic subcortical stimulation in rats, goats, monkeys, and humans. In a lecture delivered in 1965 titled "Evolution of physical control of the brain," he reported, "Monkeys may learn to press a lever in order to stimulate by radio the brain of another aggressive animal and in this way to avoid his attack. Heterostimulation in monkey colonies demonstrates the possibility of instrumental control of social behavior."[25] He concluded, "Autonomic and somatic functions, individual and social behavior, emotional and mental reactions may be evoked, maintained, modified, or inhibited, both in animals and in man, by electrical stimulation of specific cerebral structures. Physical control of many brain functions is a demonstrated fact … ."[25] Delgado's enthusiasm for this new technology led to a belief that there were no limits to its potentials. In 1969 he published a book titled "Physical control of the mind: towards a psychocivilized society."[26] Despite the book's provocative title, Delgado took great pains to negate the impression that mind control could be achieved by electrodes wired into people's brain and emphasized that the technique of "Electrical Stimulation of the Brain (ESB)" was meant as a research tool to study and understand the Human mind. Delgado developed a technique of subcortical stimulation using chronically implanted electrodes connected to a subcutaneous receiver implanted in the scalp, a "Stimoceiver," that could be controlled by radio waves. This technique of "radio communication with the brain" was initially developed for use in psychiatric patients.[24,27,28] Following his return to Spain, Delgado worked with Obrador and Martin Rodriguez. They implanted chronic electrodes bilaterally in the head of the caudate and septal nuclei of a patient with postplexus avulsion pain, which was probably the first implantation of a DBS device in Europe.[40]

Carl-Wilhelm Sem-Jacobsen was a Norwegian neurophysiologist and psychiatrist. He pursued a fellowship in physiology at the Mayo Clinic where his main interests were "depth electrography and depth stimulation and their application in psychiatric patients."[14] In 1963, he published an article about depth-electrographic observations in psychotic patients.[90] He stated, "electrical stimulation in some regions of the ventro-medial part of the frontal lobe resulted in a temporary improvement to complete freedom from symptoms." The specific aim of his studies was "to use chronic implanted electrodes in the target area in an attempt to improve the leucotomy operation."[93] In 1972 he reported that since 1952 in Rochester, and later in Oslo, 213 patients had been treated with his "depth-electrographic stereotactic neurosurgical technique;" of these, 123 patients were suffering from mental disorders.[93] Sem-Jacobsen's technique using chronically implanted electrodes aimed merely to study brain activity and perform intermittent chronic stimulation of various brain targets prior to subsequent lesioning. His concept of chronic stimulation was that it was not the final goal of the treatment but a means to evaluate the target area and its response to stimulation before the chronic electrodes

were used to produce incremental therapeutic permanent lesions. Sem-Jacobsen eventually shifted his interest to the surgical treatment of Parkinson disease using this same technique and concept (see further below).

Robert Heath was a psychiatrist at Tulane University, New Orleans. He implanted a multitude of electrodes in several subcortical nuclei and pathways to study the effect of stimulation on behavior and probably pioneered the concept of electrical "self-stimulation."[48] Heath started a program of DBS to treat schizophrenia as well as pain and epilepsy in the early 1950s.[6] Benefits of stimulation in schizophrenic patients turned out to be scarce, but Heath made the interesting observation that some patients described the experience of self-stimulation as "pleasant," "jovial," or "euphoric." In these patients the electrodes were located in the septal area.[6,105] This pleasurable response obtained from the "septal area" came to dominate Heath's further research on DBS applications. He reported relief from physical pain by stimulation of "this pleasure-yielding area of the brain" and extended studies of this brain area during sexual arousal and orgasm.[6,50,105] In 1972 Moan and Heath[70] described the use of septal stimulation to induce heterosexual behavior in a homosexual man. The individual was shown a pornographic video, then a female prostitute was introduced to him in the laboratory and following stimulation to his septal area, the individual and the woman had a sexual intercourse culminating in the subject's orgasm and description of the experience as "pleasurable." The authors wrote that during these sessions the individual "stimulated himself to a point that he was experiencing an almost overwhelming euphoria and elation, and had to be disconnected, despite his vigorous protests."[70] Two electrodes, each with 6 contacts, had been implanted in this individual and the paper contains 2 figures from the Atlas of Schaltenbrand and Bailey[85] depicting their location: one electrode lay in the "septal area" (close to the nucleus accumbens) and the other in the region of the centromedian nucleus of the thalamus.[70] Heath pursued similar and other experiments through the 1970s. One of his last publications from that decade was "Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness"[49] featuring an illustration showing the commonly used DBS system at the time consisting of a pulse sender with an antenna placed above the skin of the pectoral area where the receiver was implanted (the Xtrel Medtronic system). "Modulation of emotion" by DBS, an issue widely criticized in the 1970s,[105] reemerged 30 years later from the pen of another psychiatrist, Luc Mallet from Salpêtrière hospital in Paris who published a paper titled: "La stimulation cérébrale profonde: un outil pour la modulation thérapeutique du comportement et des emotions" (Deep brain stimulation: a tool for therapeutic modulation of behavior and emotions).[63]

Heath's experiments were analyzed in depth by psychologist Baumeister[6] in the paper "The Tulane Electrical Brain Stimulation Program a historical case study in medical ethics," published in Journal of the History of the Neurosciences in 2000. Baumeister reviewed 3 decades of DBS work performed at Tulane university and concluded, "… the Tulane electrical brain stimulation experiments had neither a scientific nor a clinical justification … . The conclusion is that these experiments were dubious and precarious by yesterday's standards."[6]

In 1977, Finnish neurosurgeon Laitinen[59] had already commented on the questionable ethic of one of Heath's papers,[50] concluding that: "There is no doubt that in this study all standards of ethics had been ignored. The ethical responsibility of the editors who accept reports of this kind for publication should also be discussed."[59] Laitinen was not against the use of DBS as a therapeutic tool in psychosurgery; in that same paper he wrote, "After implantation of chronic electrodes, long-term depth recordings and repeated electrical stimulations enable the psychosurgeon to accumulate knowledge about the pathophysiology of the brain and to improve the treatment of the patient in question. It may even be possible to treat the patient with repeated electrical stimulation without macroscopic destruction of brain tissue."[59] Laitinen proposed a "model of controlled trial," whereby eligible patients are randomized to either receive best available conservative therapy or stereotactic surgery and stated, "Psychosurgery will remain an experimental therapy for years. Therefore its use should be concentrated and restricted to psychosurgical research units having strong and intimate affiliation with scientists from many disciplines."[59]

Meanwhile, the 1970s saw few clinical applications of DBS in the treatment of psychiatric symptoms. In 1972, Escobedo et al.[33] implanted quadripolar electrodes bilaterally in the head of the caudate nucleus in 2 patients with epilepsy, mental retardation, and destructive aggressive behavior and described vegetative, motor, and behavioral responses to stimulation. In 1979, Dieckman[31] performed unilateral stimulation of the nondominant thalamus using a quadripolar Medtronic "deep brain stimulation electrode" to treat a woman with phobia. The electrode contacts extended over 12 mm and were located in the parafascicular and rostral intralaminar areas. Stimulation was intermittent at a low frequency (5 Hz) and resulted in disappearance of the phobias, while attempts at stimulation with 50 Hz "was experienced as being very disagreeable."[31]

Deep Brain Stimulation in Pain and Epilepsy

As stated above, early attempts were made in the 1950s to treat chronic pain with DBS. Heath, Delgado, Bechtereva, and others performed chronic stimulation of various brain targets including the septal area, the caudate, the cingulum and the sensory thalamus. Deep brain stimulation for pain was not as "sensational" as DBS for psychiatry and behavior, or indeed in later years, as DBS for movement disorders. There was a surge in the use of DBS for pain in the 1970s initiated by 2 teams independently of each other (Mazars et al. in France[66–68] and Hosobuchi et al.[52] in the US). The authors targeted the sensory thalamus to treat various conditions of deafferentation pain. Subsequently, Adams et al.[1] reported on internal capsule DBS for pain, but this target never gained popularity. Another target, the periventricular and periaqueductal gray matter was introduced in 1977 by Richardson et al.[80,81] Hosobuchi et al.[51] demonstrated that pain relief of periventricular and periaqueductal gray

matter DBS could be reversed by the opioid antagonist Naloxone. Deep brain stimulation for chronic pain, both in thalamic targets and central gray targets, became such a popular procedure that Medtronic trademarked the term "DBS" with respect to chronic subcortical stimulation for pain in the mid-1970s.[18] Despite this, DBS for pain was never approved by the US Food and Drug Administration, probably due to lack of controlled trials to prove its efficacy.[18] Deep brain stimulation for chronic pain along with occasional stereotactic ablative surgery continued to be used in Europe,[43] and interest has resurged in recent years, riding on the wave of success of DBS in movement disorders.[16]

Epilepsy was another indication that caught the early interest of the DBS pioneers listed above. The exploration and identification of epileptic foci rapidly adopted the technique of stereotactic chronic electrode implantation for recording and intermittent stimulation.[94] Indeed, one of the first human stereotactic apparatuses, designed by Jean Talairach in 1947, was fitted with a double grid system to allow precise implantation of chronic electrodes in medial temporal structures for recording and stimulation in patients with epilepsy.[69,101,102] Therapeutic chronic stimulation as treatment for epilepsy was subsequently introduced, in cerebellar as well as in thalamic and other brain structures. One of the early DBS targets was the anterior nucleus of the thalamus,[22,82,104] the very same target that has reemerged recently and shown benefit in a multicenter blinded randomized controlled trial of DBS for epilepsy.[36] According to Rosenow et al.,[82] Cooper had implanted DBS electrodes in the anterior nucleus of the thalamus in patients with refractory complex partial seizures as early as 1979. Of the 6 initial patients, 5 showed a more than 60% reduction of seizure frequency with stimulation at 3.5 V and 60–70 Hz.[82] Velasco et al.[108] published in 1987 their results of DBS for epilepsy targeting the center median thalamic nucleus. These documented historical facts challenge contemporary statements about DBS being "a new approach" to the treatment of epilepsy.[88]

Deep Brain Stimulation in Movement Disorders

Chronologically, DBS for PD and other movement disorders was the last indication of the older era of chronic subcortical stimulation. Initially, chronic stimulation of thalamic and other basal ganglia targets was used intermittently for days or weeks to ensure satisfactory results prior to lesioning via the chronically implanted electrodes. The first detailed account of this technique was provided by the aforementioned Norwegian neurophysiologist Sem-Jacobsen[91,92] in 1965 and 1966. Multiple electrodes were implanted in the thalamus around a point "midway between the foramen of Monro and the corpus pineale."[91] Chronic stimulation allowed identification of the optimal lesioning site. Sem-Jacobsen wrote, "The electrodes could be kept in for several months without any undesirable irritation around the electrode leads …. It is possible for the patient to go home for a week, on vacation, with electrodes in his head."[91] The electrode(s) yielding the best stimulation results could then be used to make incremental lesions. This recently rediscovered technique[30,79] was not uncommonly used in the past.[73,106]

The idea of using chronic subcortical stimulation as a "permanent" therapy for movement disorders was first presented in the early 1970s by Bechtereva,[7–9] who was a neurophysiologist at the Institute of Experimental Medicine in Leningrad, Union of Soviet Socialist Republics. Electrodes were implanted into the ventrolateral and the centromedian thalamus allowing intermittent sessions of "electric stimulation with high-rate pulses of suprathreshold current."[7] Bechtereva[8] coined the term "therapeutic electrostimulation" to describe this technique. Since the Union of Soviet Socialist Republics did not have access to implantable neurostimulators at that time, the last steps of the treatment were ultimately small lesions performed through the electrodes yielding the best stimulation responses[7] (Nathalia Bechtereva [July 7, 1925–June 22, 2008], personal communication to Patric Blomstedt, April 6, 2008).

In 1977, Mundinger[71] reported his experience in DBS for cervical dystonia. Electrodes were implanted unilaterally in the ventral oral anterior and ventral oral internal nuclei of the thalamus as well as the zona incerta allowing intermittent stimulation with frequencies of up to 390 Hz. In 1982 he wrote: "Stereotactic implantation of stimulation systems for autostimulation in subcortical deep brain structures (deep brain stimulation, DBS) for control of chronic pain and motor diseases is a functional and a reversible treatment which is characterized by the lack of complications involved. The advantages over dissection coagulation with irreparable destruction of nerves, nuclei or neuronal structures are obvious."[72]

Cooper[21,22] performed chronic stimulation in the thalamus and the internal capsule for various movement disorders. It is interesting that his paper from 1980 was titled "Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man."[22] "Reversibility", a hallmark of modern DBS, was an acknowledged value since the technique's inception. Cooper was probably the first to use the term "Medtronic deep brain stimulation (DBS) electrodes" in the context of surgery for movement disorders. Cooper described stimulation in the internal capsule in a patient with torticollis and illustrated the improvement of the position of the patient's head and neck after the operation.[22]

Brice and McLellan[17] from Southampton, United Kingdom, published in 1980 a paper on "deep brain stimulation" of the subthalamic area in 3 patients with intention tremor due to multiple sclerosis. In 2 of these patients stimulation continued to provide benefit at 6-month follow-up using stimulation frequencies between 75 and 150 Hz. McLellan had previously worked with Cooper with whom he published a paper in 1977 related to safety and efficacy of chronic stimulation in the brain.[20]

In 1983, Andy[4] published a paper on DBS in 9 patients with movement disorders, 5 of whom had parkinsonian tremor. Andy targeted the ventral intermediate nucleus and other areas of the thalamus and subthalamus. He reported effective stimulation frequencies ranging from 50 to 200 Hz and wrote that DBS "… in contrast to thalamic lesion … is preferred for the treatment of intractable motor disorders in high-risk elderly patients and patients with diffuse lesions secondary to trauma … the beneficial

effects are reversible even after several months of applied therapeutic stimulation …. Lesion studies indicate that optimum sites for alleviating Parkinson tremor and other movement disorders are the Vim and other thalamic and subthalamic areas. Optimum sites for stimulation electrode implants tend to parallel those findings."[4]

Deep Brain Stimulation in Minimally Conscious States

In August 2007, a paper was published in *Nature* by Schiff et al.[86] describing how bilateral central thalamic DBS improved conscience levels in a patient who had been in a minimally conscious state for 6 years following traumatic brain injury. The printed issue of this groundbreaking paper, much publicized in the lay press at the time, quoted 23 references, none of which referred to any of the several previous studies on DBS for decreased consciousness, published by various workers between 1969 and 1993 in Germany,[45,100] in France,[19,29] and in Japan.[54,103,111]

Discussion

There is no doubt that the tremendous worldwide spread of DBS in surgical treatment of movement disorders, especially DBS of the STN for PD, is the result of the pioneering work of Benabid, Pollak, and the Grenoble multidisciplinary group. While this technique is firmly established for PD, dystonia, and other movement disorders, its future potential and development seem to lie mainly in the realm of psychiatry. In the past 11 years since the publication of the first 2 papers of the modern era of DBS for psychiatric illness in 1999,[74,107] this field has known a great academic activity. Contemporary publications on DBS in psychiatry and behavior have discussed various brain targets and various applications of this technique including in OCD, Tourette syndrome, depression, aggressive behavior, obesity, and most recently addiction. However, the majority of publications dealing with psychiatric and behavioral DBS over the last decade contains no patient data and consists of reviews, editorials, opinions, viewpoints, ethical analyses, theoretical models of neuronal circuitry, and comments, none of which has really shed light on the use of DBS in psychiatry and behavior during the 1950s through the 1970s.

The Revision of History

It has been claimed, "… the observation of induced psychiatric side effects (e.g., changes in mood, hypomania, reduction of anxiety) gave the impulse to try DBS also for psychiatric disorders."[87] The fact is that the first applications of modern era DBS in psychiatric disorders had nothing to do with the observation of psychiatric and behavioral side effects of DBS of the STN. Vandewalle et al.[107] pioneered DBS for Tourette syndrome in February 1999, and Nuttin et al.[74] pioneered DBS for OCD in October 1999. Both authors targeted the very same brain structures that had been stereotactically lesioned in the past by Hassler and Dieckmann[44] in the case of Tourette syndrome, and by Leksell et al. in the case of OCD.[15]

While some contemporary publications on surgery for psychiatric illness fail to refer to, or acknowledge previous work, historical facts are sometimes misrepresented even in purportedly historical publications and reviews.[42] A review paper "Behavioral neurosurgery" published in 2006 in *Advances in Neurology* and authored by 2 psychiatrists stated, "One of the most notable surgeons was the American neurosurgeon Walter Freeman … Freeman began to apply his relatively untested procedure, the prefrontal lobotomy, in which he transorbitally inserted an ice pick into the frontal cortex."[64] It should be known by all those working in the field of psychosurgery and DBS that Freeman was a neuropsychiatrist, and James Watts was the neurosurgeon with whom he initially collaborated. The neurosurgeon actually abandoned Freeman following the latter's increasingly erratic attitude to lobotomy.[32] One may wonder whether Freeman's enthusiasm for, and prolific practice of, lobotomy had any influence on another psychiatrist, Ørnulf Ødegård, director of Norway's main psychiatrist hospital, who wrote in 1953 in the *Norwegian Medical Journal*, "Psychosurgery can be easily performed by the psychiatrist himself with the tool he might have in his pocket, and strangely enough it may be harmless and effective …"[76]

As detailed above, in the older era of DBS for psychiatry, the work of psychiatrist Heath in Tulane, had been criticized on ethical grounds by psychologist Baumeister[6] and by neurosurgeon Laitinen.[59] Therefore it came as a surprise to read the statements of neuroethicist Fins and coworkers[35] who wrote in *Neurosurgery* in 2006:

> It is ethically untenable for this work to proceed by neurosurgeons in isolation without psychiatrists determining the diagnosis and suitability of patients for treatment … Such errant behavior is especially inappropriate because it represents a recapitulation of the excesses associated with psychosurgery … If this generation of neuroscientists and practitioners hope to avoid the abuses of that earlier era, and avoid conflation of neuromodulation with psychosurgery, it is critical that neuromodulation be performed in an interdisciplinary and ethically sound fashion.[35]

Our present review of historical literature demonstrates that "errant behavior," "excesses," and "abuses of that early era" were not at the hands of "neurosurgeons in isolation." It was often nonneurosurgeons who worked in this field "in isolation," and some of the leading neurosurgeons of the old era were in fact skeptical to the use of psychosurgery altogether. In 1973, one of Sweden's most famous psychiatrists, Rylander,[84] recounted how he, as a junior psychiatrist, wanted to introduce Moniz's lobotomy procedure in Sweden. He wrote "… I approached Olivecrona, the neurosurgeon. He said definitely no, adding somewhat sarcastically that psychiatrists damaged the brain by electroshock treatment and that there was no reason to destroy part of it in such a doubtful way as Moniz had done."[84]

Multidisciplinary Approach, Ethics, and Contemporary DBS in Psychiatry

As stated above, ever since the birth of functional stereotactic surgery a multidisciplinary approach has been the rule, and it was seldom the neurosurgeons who took exceptions to that rule. In a publication from 2003, neuroethicist Fins[34] acknowledged neurosurgeon and psy-

chosurgeon Ballantine for his multidisciplinary approach whereby "Decisions to operate were to be made in conjunction with a psychiatrist, who would also make psychiatric follow up available, and patients and family were to be informed of potential risks and benefits."

One cannot but totally agree with Fins when he wrote, "… it is critical that neuromodulation be performed in an interdisciplinary and ethically sound fashion."[35] Indeed, this has been, and still is, without exception the consistent practice of the neurosurgeons involved in modern DBS (and also of old era's functional neurosurgeons as shown above). The neurosurgeon who pioneered modern DBS for movements disorders,[13] as well as neurosurgeons who pioneered modern DBS for psychiatric illness,[65,74,107] have all from the beginning been part of multidisciplinary groups involving neurologists, psychiatrists, and others. Neurosurgeons have taken the initiative on seeking ethical review on the use of DBS in psychiatry. In the June 13, 2002 issue of *Nature*, Sally Goodman wrote the following: "Last October, Alim-Louis Benabid, a neurosurgeon at the Joseph Fourier University in Grenoble, asked the French commission to consider the ethics of using neurostimulation on OCD patients."[39] Neurosurgeons collaborated with psychiatrists, neurologists, ethicists, and others to promote and establish guidelines for this kind of surgery insisting on approaches that are ethically sound and multidisciplinary, and on close interaction between the various involved specialties.[75,109] Unfortunately modern history shows that multidisciplinary teams may not always be all inclusive, as shown below.

Multidisciplinary Team for Functional Neurosurgery but Without Neurosurgeons

The September 2009 issue of the *Archives of General Psychiatry* featured a paper titled "Scientific and Ethical Issues Related to Deep Brain Stimulation for Disorders of Mood, Behavior, and Thoughts."[78] This paper summarizes a 2-day conference that was convened to examine scientific and ethical issues in the application of DBS in psychiatry, to "establish consensus among participants about the design of future clinical trials of deep brain stimulation for disorders of mood, behavior, and thought" and to "develop standards for the protection of human subjects participating in such studies."[78] Among the 30 participants at the meeting, 19 of whom are authors of the paper, there was not one single neurosurgeon.

Conclusions

Based on our review of the literature we found the following: The technique of chronic stimulation of subcortical structures through permanently implanted electrodes was proposed soon after the introduction of human stereotactic surgery in 1947. Frequency of the electrical current used for stimulation of subcortical structures has always been a consideration, with "high-frequency" stimulation being advocated early on, either to confirm electrode location and expectations prior to subsequent lesioning, or as a therapeutic mean in cases of chronic stimulation. However, what was exactly meant by "high frequency" was seldom specified in the old literature. Stereotactic ablation and electrical stimulation of subcortical structures have developed in parallel. Aside from its consistent use intraoperatively prior to lesioning, electrical stimulation has been applied through chronically implanted electrodes prior to deferred incremental lesioning, or, subsequently, as a therapy in itself. Chronic subcortical stimulation was initially used as a tool to study and eventually treat psychiatric illness. The first use of DBS mirrors that of stereotactic ablative surgery: both were initially performed to treat psychiatric disease. Chronic subcortical stimulation was not originally introduced for the treatment of movement disorders. The chronological order of applications of old time DBS was first for psychiatry and behavior, then for pain, then for epilepsy, and last for movement disorders. Modern DBS for psychiatric illness was not promoted by observations of psychiatric side effects of STN DBS. Rather, DBS was applied to the same targets that were previously lesioned for the same diseases. While "It is ethically untenable for this work to proceed by neurosurgeons in isolation without psychiatrists determining the diagnosis and suitability of patients for treatment",[35] it was indeed others than neurosurgeons who were working "in isolation" during the early era of DBS. Ethical concerns have indeed been addressed in the past, by neurosurgeons and others. Some of the erratic behavior in surgery for psychiatric illness, including the bygone era of DBS, were at the hands of nonneurosurgeons. These practices have been deemed as "dubious and precarious by yesterday's standards."[6] Neurosurgeons have been pioneers in taking the first initiatives to seek ethical opinions, and to establish multidisciplinary teams, for the application of modern era DBS into psychiatry. Multidisciplinary meetings and multidisciplinary guidelines related to functional neurosurgery without including neurosurgeons are not multidisciplinary enough.

Disclosure

Marwan Hariz and Ludvic Zrinzo are supported by the UK Parkinson Appeal. They have occasionally received travel expenses and honoraria from Medtronic for speaking at meetings.

Author contributions to the study and manuscript preparation include the following. Conception and design: Hariz, Blomstedt. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Hariz. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: all authors. Study supervision: Hariz.

Acknowledgments

We wish to dedicate this work to the memory of 2 neurosurgeons, Lauri Laitinen and Harald Fodstad, who in the past had bequeathed some of their archives of old publications and books on functional neurosurgery to us.

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Manuscript submitted April 15, 2010.
Accepted April 28, 2010.

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Neurosurg Focus 29 (2):E2, 2010

Current and future indications for deep brain stimulation in pediatric populations

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Deep brain stimulation (DBS) has proven to be an effective and safe treatment option in patients with various advanced and treatment-refractory conditions. Thus far, most of the experience with DBS has been in the movement disorder literature, and more specifically in the adult population, where its use in conditions such as Parkinson disease has revolutionized management strategies. The pediatric population, however, can also be afflicted by functionally incapacitating neurological conditions that remain refractory despite the clinicians' best efforts. In such cases, DBS offers an additional treatment alternative. In this paper, the authors review their institution's experience with DBS in the pediatric population, and provide an overview of the literature on DBS in children. The authors conclude that DBS in children can and should be considered a valid and effective treatment option, albeit in highly specific and carefully selected cases. *(DOI: 10.3171/2010.5.FOCUS1095)*

Key Words • **deep brain stimulation** • **dystonia** • **spasticity** • **epilepsy** • **children**

Over the past few decades, the introduction of DBS has revolutionized the management of several functional disorders affecting the adult population. Deep brain stimulation currently plays an established role in the management of movement disorders, providing durable symptom relief and improved quality of life with minimal morbidity and side effects. In addition, the role of DBS procedures is currently under investigation in many other neurological and psychiatric disorders previously considered to be beyond the realm of neurosurgery.[4] In spite of such exciting progress, the application of this therapeutic paradigm to functional disorders affecting the pediatric population remains limited. This review summarizes our institutional experience with DBS in children and discusses the current and potential future role of DBS procedures in the multidisciplinary management of pediatric functional disorders.

Institutional Experience

From 2001 to the present, we have treated 6 children (2 boys, 4 girls) with DBS procedures (Table 1). The mean age at the time of treatment for this cohort was 13 years (range 8–18 years). Clinical indications for DBS treatment included 3 patients with DYT1 dystonia, 1 with secondary dystonia (viral encephalitis), 1 with glutaric acidemia Type 1, and 1 patient who presented with dystonia of unknown origin. All patients had undergone unsuccessful medical management of their movement disorders prior to consultation. Prior functional procedures included bilateral pallidotomy in 1 patient. A second patient had undergone previous pallidotomy and insertion of bilateral GPi electrodes and presented with worsening dystonia and hardware failure. The 4 remaining patients had not undergone previous surgical procedures. Surgery in this series included bilateral GPi DBS insertion in 4 patients and bilateral subthalamic zona inserta DBS insertion in 1 patient. One patient underwent revision of their GPi DBS electrodes and pulse generator. There were no procedural or postoperative complications observed in this series. Following DBS insertion, patients were followed up in the neurosurgery clinic as well as at the movement disorders clinic at Toronto Western Hospital. The mean follow-up duration for available patients was 32 months (range 1–77 months), which was limited by the fact that 5 of 6 patients included in this study were referred from institutions outside Canada and did not frequently return to Canada. Follow-up was unavailable in 1 patient. No DBS-related side effects were documented in this series under normal stimulation parameters. Clinical outcomes

Abbreviations used in this paper: CP = cerebral palsy; DBS = deep brain stimulation; GPi = globus pallidus internus; OCD = obsessive-compulsive disorder.

TABLE 1: Summary of pediatric patients undergoing DBS at our institution

Age (yrs), Sex	Indication/Previous Treatment	DBS target	Outcome
8, F	primary dystonia of unknown origin	bilat GPi	no improvement
12, F	secondary dystonia	subthalamic zona inserta	no follow-up available
18, M	DTY1 dystonia w/ previous pallidotomy & GPi DBS	bilat GPi (revised GPi electrodes & pulse generator)	improvement of motor symptoms, ambulation
15, M	DYT1 dystonia w/ previous pallidotomy	bilat GPi	improvement of motor symptoms, ambulation
9, F	DYT1 dystonia	bilat GPi	improvement of motor symptoms, ambulation
16, F	dystonia, glutaric acidemia Type 1	bilat GPi	mild improvement in motor symptoms

were available for 5 patients. All patients with DTY1 dystonia who were treated with bilateral GPi DBS showed significant improvement in their motor symptoms; 2 patients who were confined to a wheelchair due to axial and limb dystonia gained the ability to walk independently after surgery. One patient with progressive dystonia due to glutaric acidemia Type 1 who was treated using bilateral GPi DBS showed mild improvement of her right upper and lower extremities 2 months postoperatively. Finally, 1 patient with progressive dystonia affecting all extremities of an unknown origin was treated with bilateral GPi DBS and showed no significant improvement in her symptoms (Table 1).

Current Indications for Pediatric DBS

Currently, most DBS procedures in the pediatric population have been performed for movement disorders, specifically dystonia. Because most centers combine their pediatric and adult patients when reporting results, it is difficult to estimate the number of pediatric patients who have undergone implantation with DBS electrodes. Furthermore, there are currently no prospective studies examining DBS for pediatric movement disorders. Nevertheless, several centers have reported their experiences with DBS in children, some with promising results, indicating a possible therapeutic benefit for DBS in this population.

Dystonia remains the most frequent current indication for surgical intervention in children. Dystonia is a disorder of dysfunctional neuronal-muscle firing, leading to involuntary and sustained muscle contractions, causing abnormal twisting and posturing. Primary dystonia is due to inborn mutations in the *DYT* gene, of which there are several kinds, and in which *DYT1* is the most common. Secondary dystonia is acquired, and most frequently is related to CP or neonatal asphyxia, or is the result of brain degeneration or accumulation of organic deposits such as iron or bilirubin. Due to the multiple different causes of secondary dystonia, this population is subsequently more diverse and heterogenous, making broad generalizations of treatment efficacy more difficult. Nevertheless, DBS has been applied in children suffering from both primary and secondary dystonia (Table 2). There is a long history of the use of thalamotomy and pallidotomy in children with dystonia;[12] more recently, pallidotomy was reintroduced with striking results.[24,33] This development led to the rapid introduction of pallidal DBS for dystonia, first in adults and then quickly in children.[27,29] Among the earliest reports of DBS for dystonia in a child came from Coubes et al. in 1999,[13] in which an 8-year-old child underwent GPi DBS for primary dystonia, with significant functional outcomes at 3 years. One study[37] reported the use of GPi DBS in 4 children with primary generalized dystonia following the failure of medical therapy, and found that dystonic movements were significantly improved at 6 months postoperatively. Importantly, targets for adult and pediatric patients with dystonia remain the same, as most centers have used the GPi as the target. A further study[34] involving GPi DBS that examined 10 patients, of which 3 were children, also found significant improvements in both dystonic movements and functional disability after 2 years. One of the largest case series to date[54] that specifically included pediatric patients involved 12 patients with childhood onset dystonia, of which 8 had primary and 4 secondary dystonia. In this study, all but 1 patient derived a significant functional benefit from GPi DBS. Such results are similar to a more recently reported series[2] in which 15 pediatric patients underwent bilateral pallidal DBS. This series reported a minimum improvement in dystonic posturing of 40% in all patients at 1 year, with substantial improvements in disability scores for all children.

The rarity of secondary dystonia in children, and the heterogeneity of the patient population, has resulted in a scarcity of reported outcomes of DBS for these diverse conditions. Cases of children undergoing DBS for Cockayne syndrome and Lesch-Nyhan syndrome have been reported, all with positive results.[11,21] Despite these seemingly positive outcomes, it appears that children with secondary dystonia respond less robustly to treatment in general, and to DBS in particular.[2] Clearly, the rarity of these disorders precludes the design of adequate trials, but it appears that the experiences of multiple institutions supports continued research into the application of DBS for secondary dystonia in medically refractory cases.

Tremor is uncommon in the pediatric literature, and when present, is typically secondary to neurodegenerative disorders or otherwise secondary causes. The experience with DBS in tremor in adults, using the ventral intermediate nucleus of the thalamus as the target, has been

TABLE 2: Summary of DBS studies for primary dystonia in children*

Authors & Year	Indication	No. of Patients	Outcome
Coubes et al., 1999	primary dystonia (dystonia musculorum)	1	dramatic improvement in symptoms at 6 wks
Zorzi et al., 2005	primary & secondary dystonia	12 (8 primary, 4 secondary)	dystonic movements significantly decreased in 11 patients
Alterman et al., 2007	primary dystonia	15	7 discontinued medications, 6 reduced medications by > 50%
Parr et al., 2007	idiopathic generalized dystonia	4	significant reductions in dystonic movements in all patients
Magariños-Ascone et al., 2008	primary dystonia	10 (3 children)	significant reductions in dystonic movements in all children w/ DBS

* The DBS target for all studies was the GPi.

reviewed elsewhere, and its application has been explored for essential tremor and tremor associated with multiple sclerosis. In children, a single case report exists of the successful treatment of a Holmes tremor secondary to a thalamic abscess with DBS of the ventral intermediate nucleus of the thalamus.[38]

Tic disorders, such as Tourette syndrome, are among the most common neurological disorders of childhood. In addition to causing significant functional and social impairment, they often coexist with other, primarily psychiatric, disorders such as OCD and/or attention deficit disorder. The management of tics is primarily pharmacological, with surgical alternatives, particularly in children, reserved for only the most refractory and challenging cases. The target and timing for DBS, the optimal surgical strategy, and patient selection are all controversial topics, generating significant research.[45] The largest reported series to date of DBS for Tourette syndrome comes from Italy,[43] in which 18 patients underwent surgery, of whom 4 were under the age of 20 at the time of operation. Patients all had tic onset during adolescence or younger and the surgical target was the centromedian thalamic nucleus. All 4 pediatric patients experienced significant reductions in tic severity.

Surgery for Tourette syndrome and other tic disorders is complicated by the unpredictable natural history of tics in general. Tics in a substantial number of pediatric patients spontaneously remit by the age of 20, leading many authors to question the role of invasive neuromodulation in children.[31] We agree with this assessment, and believe that surgical management of Tourette syndrome in the pediatric population should be reserved for exceptional circumstances, such as the development of myelopathy or spinal cord injury secondary to severe and treatment-refractory tics.

Future Indications for Pediatric DBS

Future indications for DBS in the pediatric population will focus on existing indications and expand on them. More sophisticated neuroimaging, more compact and streamlined implantable technology, as well as a more clear elucidation of the underlying mechanisms and circuitry of many of these disorders will lead to substantial improvements in the efficacy and safety of DBS. Among the areas with most promise and controversy will be in the domain of DBS for psychiatric indications, specifically with a focus on the impulse control disorders, such as OCD and anorexia nervosa.

Obsessive-Compulsive Disorder

Currently, DBS OCD programs have focused on the adult population, with some pediatric patients included only in the overlapping literature on Tourette Syndrome. The OCD experience with DBS has been thoroughly reviewed elsewhere.[16,42] Importantly, the use of DBS for refractory OCD has been subjected to a double-blind randomized study, whose positive result indicates that the technology is indeed an effective form of last-resort treatment.[35] Such studies satisfy important criteria for the application of this technology to pediatric populations, where the threshold for surgical intervention is typically higher.

Disorders of impulse control likely share common neuroanatomical and physiological roots. Accordingly, similar structures may underlie their pathophysiology, and their disruption may lead to improvements in overt pathological behavior. As a result, some researchers have sought to implant DBS electrodes in patients with comorbid conditions, and, either retrospectively or prospectively, observe the effects on both conditions. For example, 1 paper reports improvement in an intractable eating disorder with subgenual cingulate stimulation for depression.[25] The use of DBS for the treatment for eating disorders is still in the early investigational stages, but as most eating disorders, anorexia nervosa in particular, strike in adolescence, the use of surgery for debilitating and life-threatening disease in some pediatric patients remains a future possibility.

Epilepsy

Epilepsy is one of the most common neurological conditions affecting children, with approximately 20,000 to 45,000 cases diagnosed in the US annually.[9,20] While approximately two-thirds of children will attain seizure remission with antiepileptic medication, a significant proportion will go on to develop a chronic seizure disorder. Apart from the devastating burden of uncontrolled seizures and antiepileptic side effects, children with epi-

lepsy are also at increased risk for other comorbidities including developmental delay, depression, anxiety disorders, substance abuse, suicide, and sudden death.[39,44,46] The effects of childhood epilepsy on marital status, education, employment, and overall quality of life are also significant.[44] Until recently, the role of neurosurgery in pediatric epilepsy has been limited mostly to patients with structural abnormalities of the brain. In the setting of cortical dysplasia, vascular malformations, neoplasms, and mesial temporal sclerosis, resection of epileptogenic foci leads to alleviation of seizures in as many as 60–87% of cases.[6,8,18,23,51] For children with generalized, nonlocalizable refractory seizures, an additional smaller proportion may derive benefit from palliative neuromodulatory procedures such as vagus nerve stimulation of disconnective procedures such as corpus callosotomy or functional hemispherectomy.[7,17,26] Of the 30% to 40% of children whose seizures fail to be controlled despite multiple antiepileptic medications, a significant number will not be eligible for surgery due to multifocal, nonlocalizable disease or the identification of an epileptic focus arising from eloquent brain tissue.[19]

Deep brain stimulation has recently emerged as an effective alternative treatment modality for adults with medically refractory epilepsy. Although the anatomical substrates and circuits responsible for seizure initiation and propagation are largely unknown, the results of preclinical animal studies have lead to the identification of several promising anatomical targets that have recently been explored in prospective human clinical trials. Among the most common targets investigated in adult DBS studies are the hippocampus, subthalamic nucleus, and thalamus.[14,19] Among these studies, Velasco et al.[48] demonstrated that hippocampal stimulation reduced interictal spikes as well as the frequency of complex partial and tonic-clonic seizures in patients with medically refractory temporal lobe epilepsy. Benabid et al.[5] treated a child with inoperable cortical dysplasia and refractory epilepsy with subthalamic nucleus DBS and observed an 83% improvement in seizure frequency as well as improvement of motor function. A number of studies have investigated the effect of anterior nucleus of the thalamus stimulation on medically refractory seizures, including 1 at our institution.[3,22,28,32] Bilateral anterior nucleus of the thalamus DBS was associated with a reduction in seizure frequency in all 6 patients in our study, an effect that was independent of stimulator parameters.[3] Although we found little short-term improvement in patients who underwent centromedian nucleus of the thalamus stimulation for medically refractory epilepsy, results from other groups demonstrated promising results, particularly in patients with absence and generalized seizures in the setting of Lennox-Gastaut syndrome.[3,49] The long-awaited preliminary results from a large, multiinstitutional, prospective randomized double-blinded trial of anterior nucleus of the thalamus stimulation in 110 adults with medically refractory epilepsy (SANTE trial) have recently been made available. Patients treated with anterior nucleus of the thalamus DBS experienced a statistically significant reduction in seizure frequency compared with sham-treated participants, an effect that increased over time.[36]

In addition to conventional DBS systems, epilepsy patients will also soon benefit from advances made in the field of brain-machine interfaces. This paradigm involves the collection and processing of neural activity to help drive external devices.[10] In this model, implanted depth or surface electrodes can be used to detect epileptiform activity that is sent to an implantable processing unit, which subsequently delivers an electrical response to the brain, thereby abolishing seizure activity. The use of implantable closed-loop systems have shown promising results in small clinical studies[15] and have recently been investigated in a prospective clinical trial. In a randomized, double-blind, sham-controlled study of the implantable Responsive Neurostimulation System (Neuropace Inc.) in adults with medically refractory partial-onset seizures, 47% of patients experienced a 50% or greater reduction in seizure frequency.[40]

Given all these data, the future of DBS for medically refractory epilepsy is encouraging and will hopefully provide important alternative treatment options for children with debilitating seizure disorders. The ideal targets and stimulator parameters for individual seizure disorders will be better appreciated as larger collaborative studies are completed. Given the significant long-term effects of chronic childhood epilepsy on educational attainment, employment, marital status, and psychological health into adulthood, we may see the application of DBS techniques earlier in the disease process in an effort to reduce these long-term impairments. As children are increasingly incorporated into prospective trials of novel treatment paradigms, DBS will undoubtedly emerge as an important tool in the neurosurgeon's armamentarium against pediatric epilepsy.

Spasticity

Spasticity has been defined as a "motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (or tone) resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome."[30] In the pediatric population, the vast majority of spasticity is observed in the setting of CP, which occurs in approximately 3 or 4 per 1000 children.[53] Stroke, head injury, and spinal cord injury make up important alternative causes of spasticity in children. Functional disability in CP may be due to spasticity alone but may also be associated with other movement disorders such as tremor, dystonia, or choreoathetosis. The distinction between spasticity, CP, and secondary movement disorders can be challenging in the pediatric population, potentially requiring different treatment approaches. Although spasticity may arise from a number of causes, the pathophysiological mechanisms are often characterized by an increase in afferent excitatory input (or increased sensitivity) to spinal motor neurons combined with a reduction in inhibitory impulses to the same effectors. As such, current pharmacological and surgical interventions are aimed at restoring the balance between these opposing conditions.

Management of spasticity requires a multidisciplinary approach, careful patient selection, and a realistic appreciation of the objectives and limitations of each individual

therapeutic intervention. The mainstay of spasticity management for over 15 years has been medical management with baclofen, diazepam, and other agents that are used to treat diffuse, generalized spasticity. Botulinum toxin has been successfully employed to provide temporary relief of focal spasticity. Modern neurosurgical interventions currently offered to children with spasticity include selective dorsal/posterior rhizotomy and implantation of intrathecal baclofen pumps. Whereas dorsal rhizotomy and intrathecal baclofen improve functional disability related to spasticity in children with CP, a significant proportion of children will exhibit symptoms related to comorbid movement disorders. Although dorsal rhizotomy has no effect on dystonia, chorea, or athetosis, a significant proportion of children with dystonia will derive benefit from intrathecal baclofen, albeit at much higher doses than those used to treat spasticity.[1]

Although spasticity accounts for a significant proportion of movement disorders affecting children, the application of DBS strategies to this population has been limited. Promising results have been found in GPi stimulation for secondary dystonias and choreoathetosis, but few studies have included children. Among adult studies, Vidailhet et al.[50] treated 13 adults with dystonia-choreoathetosis CP with GPi DBS and observed significant improvements in functional movement scores, functional disability, pain, and mental health–related quality of life. In one of the first pediatric DBS reports, Thompson et al.[47] treated 2 patients with choreiform movement disorders using thalamic DBS, one of whom had CP. In that 15-year-old patient with bilateral choreiform movements of the upper extremities, unilateral DBS of the ventral intermediate nucleus of the thalamus lead to pronounced improvement in the contralateral chorea as well as improved ease of handwriting and eating. Both the patient's and parents' satisfaction lead to consideration of another DBS procedure to treat the other extremity. In addition to its role as a primary treatment modality, the effect of combined DBS and conventional surgical interventions for mixed movement disorder CP subtypes also remains undefined. In one study, Woon et al.[52] treated 3 children with dystonia secondary to CP and suggested that DBS may be used to treat the primary functional disease while associated spasticity may be synergistically controlled by intrathecal baclofen infusion. Overall, these studies highlight the significant heterogeneity in movement impairments among children with CP. An understanding of the cortical, subcortical, and spinal reorganization that occurs following early CNS insults will be paramount to elucidating potential DBS targets for children with spasticity.

Ethical Issues in Pediatric DBS

The threshold for surgical intervention in a child, no matter the indication, always needs to be higher than that in the adult. Children are not small adults, and their ongoing brain development, both structural and physiological, can have an influence on the mechanism of DBS, particularly given the plasticity of the developing brain and its circuits. As an example, a recent expert panel has suggested that DBS not be used in children for psychiatric indications, as the long-term effects of chronic brain stimulation are unknown.[41] Deep brain stimulation is, however, a potentially powerful tool that may significantly alter a child's quality of life, and we propose that strict ethical guidelines and criteria be employed prior to any DBS application in the pediatric age-group.

Strict attention needs to be given to the informed consent process, and to a comprehensive discussion of the risks, benefits, and treatment expectations and goals. Parents need to be made aware of the largely investigational use of DBS for refractory conditions, be they psychiatric or motor, and that the use of DBS necessitates continuous battery changes and the potential for hardware complications. Furthermore, the treating surgeon needs to be aware of all possible treatment options, medical and surgical, for their patients, to gauge whether their patient has truly reached a treatment refractory stage. The burden of acquiring sufficient evidence rests with the treating team, to prove that DBS can provide an effective and safe last resort for treatment.

Conclusions

Pediatric patients will certainly benefit from the continued development of DBS technology for the management of refractory neurological, and with time, psychiatric conditions. Currently, several studies support the use of DBS for movement disorders in highly selected patients, with ongoing research exploring additional, exciting indications. The future of pediatric functional neurosurgery will focus on the development of safer, smaller, and more flexible technology that will improve the child's quality of life, while minimizing exposure to surgical risk.

Disclosure

Dr. Lozano serves as a consultant to Medtronic and St. Jude Medical.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Drafting the article: Lipsman, Ellis. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Lozano.

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Manuscript submitted April 10, 2010.
Accepted May 20, 2010.
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Neurosurg Focus 29 (2):E3, 2010

Best surgical practices: a stepwise approach to the University of Pennsylvania deep brain stimulation protocol

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Deep brain stimulation (DBS) is the treatment of choice for otherwise healthy patients with advanced Parkinson disease who are suffering from disabling dyskinesias and motor fluctuations related to dopaminergic therapy. As DBS is an elective procedure, it is essential to minimize the risk of morbidity. Further, precision in targeting deep brain structures is critical to optimize efficacy in controlling motor features. The authors have already established an operational checklist in an effort to minimize errors made during DBS surgery. Here, they set out to standardize a strict, step-by-step approach to the DBS surgery used at their institution, including preoperative evaluation, the day of surgery, and the postoperative course. They provide careful instruction on Leksell frame assembly and placement as well as the determination of indirect coordinates derived from MR images used to target deep brain structures. Detailed descriptions of the operative procedure are provided, outlining placement of the stereotactic arc as well as determination of the appropriate bur hole location, lead placement using electrophysiology, and placement of the internal pulse generator. The authors also include their approach to preventing postoperative morbidity. They believe that a strategic, step-by-step approach to DBS surgery combined with a standardized checklist will help to minimize operating room mistakes that can compromise targeting and increase the risk of complication.
(DOI: 10.3171/2010.4.FOCUS10103)

Key Words • **deep brain stimulation** • **dystonia** • **essential tremor** • **surgical technique**

Over the past 20 years, DBS has emerged as the most promising and safest surgical option in managing advanced PD, particularly in patients suffering from medically induced dyskinesia.[2,4,8,11,15,18] Deep brain stimulation has also proven to be effective in other movement disorders, including refractory essential tremor and dystonia.[7,8,12,18] More recently, DBS has shown efficacy in various neuropsychiatric disorders.[10,13,16] It is an extremely attractive option for many patients given its reversibility and titratability. However, careful patient selection is crucial in optimizing the efficacy of this procedure. Moreover, the clinical efficacy of DBS depends largely on accurate targeting and implantation of the lead. In fact, subthalamic nucleus localization using MR imaging and a stereotactic head frame can have an accuracy of < 1 mm^2. The need for such precision demands rigid practice and surgical guidelines in lead placement. Indeed, we have incorporated the use of an intraoperative checklist to detect and remediate procedural errors.[5] Further, efforts to reduce the incidence of morbidity, such as infection, are crucial for optimizing the overall outcome of this elective surgical procedure. In the present review, we outline in a step-by-step manner the details of the standard pre-, intra-, and postoperative courses used at our institution for all patients undergoing DBS. Our institution has documented a complication rate of 12.6% and a permanent sequelae rate of 4.6%, indicating a relatively low incidence of permanent complications.[14] We believe that such a review can be helpful to all members of a functional neurosurgical team in both developing and/or self-evaluating their practice, particularly as we discover new diseases and targets requiring neuromodulation.

Abbreviations used in this paper: AC = anterior commissure; DBS = deep brain stimulation; IPG = internal pulse generator; LM = localizer marking; PC = posterior commissure; PD = Parkinson disease.

Preoperative Preparation

All candidates for DBS surgery are evaluated by a movement disorder specialist at our institution prior to being referred for surgery. In patients with PD, levodopa responsiveness; the presence of tremor, bradykinesia, and/or rigidity; frequent on-off fluctuations; and decreased functional on-times are characteristics of good candidacy. It is essential that careful selection and diagnostic criteria are met for the best surgical outcome, as patients with moderate to severe cognitive dysfunction and other parkinsonian syndromes have been shown to have unfavorable outcomes.[3,9] Patients are considered appropriate candidates if they are in relatively good general health and have exhausted medical management. We do require all patients older than 50 years with medical comorbidities to obtain medical clearance from their respective doctors (that is, medical, cardiac, and pulmonary). Patients exhibiting cognitive deficits are required to undergo neuropsychiatric evaluation before being scheduled for surgery.

Patients and their families are seen in the neurosurgery clinic to confirm candidacy and discuss the risks and benefits of surgery as well as the anticipated outcomes and recovery period. At this time, a history is taken, a physical examination is performed, the patient is educated, and the overall preparation for surgery, including self-image preservation and postdischarge plans, is undertaken. Patients undergo routine preadmission testing including an electrolyte panel, complete blood count, coagulation studies, blood type and screen, urine analysis, electrocardiography, and chest radiography. Results are reviewed and faxed to any clearing physicians. Patients are given Bactoshield CHG 4% and chlorhexidine gluconate 4% (both Steris Corp.) with instructions to wash from head to waist twice the night before surgery and not to apply any cosmetic or hygiene products following this wash. All blood-thinning agents, including aspirin, clopidogrel, warfarin, and nonsteroidal anti-inflammatory drugs, are withheld for 1 week prior to surgery. Although instructed to hold all movement disorder medications (that is, carbidopa-levodopa, propranolol, baclofen, and so forth) on the morning of surgery, patients may take pertinent medications such as antihypertensives.

Day of Surgery

Frame Assembly

At our institution, we use the Leksell MicroStereotactic System Model G Frame (Elekta), which is fixed with the angled face plate directed superiorly as depicted in Fig. 1. The short posts are fixed into the posterior corners of the frame so that 1 cm is exposed inferiorly below the frame (Fig. 2). Place the long posts into the anterior slots, positioned so that 4 cm is exposed below the frame. Insert the disposable plastic screw hole inserts in all 4 screw hole sites. Attach the ear bar adapters to the sides of the frame with the angled portion directed anteriorly. The anterior edge of the ear bar adapters should be positioned 125 mm anterior to the posterior-most aspect of the frame. Insert ear bars through the middle ear bar insertion points. Do not lock the ear bars in place. Antibiotic ointment such as that used at our institution (Bacitracin Zinc and Polymyxin B sulfate ointment, E Fougera & Co.) should be available for placement on the pins.

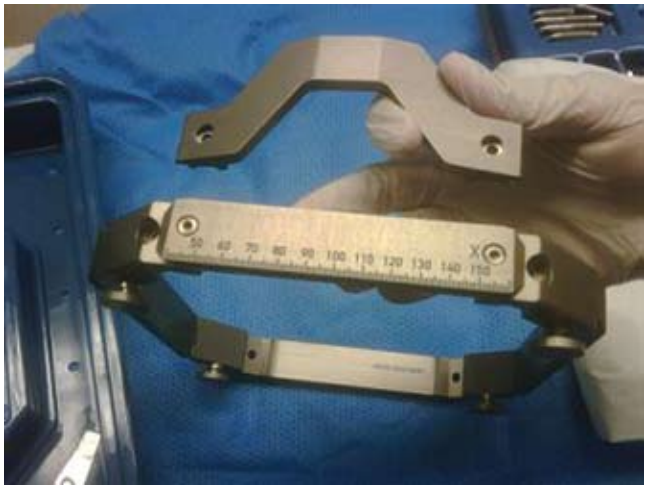

Fig. 1. Photograph of the base of the Leksell frame with the straight face plate attached and the angled face plate held in the correct position.

Frame Placement

Once the patient enters the room on a stretcher, place cotton balls soaked in lidocaine gel into his or her ears. Keep the patient on the stretcher in an upright position at nearly 90°. If the patient has long hair, apply a lubricated gel such as Medichoice Bacteriostatic lubricating gel (Owens & Minor) to the anticipated posterior screw sites to facilitate placement. Alcohol should be applied to the patient's forehead.

Remove cotton balls from the patient's ears. Place the frame around the patient's head while an assistant holds the head straight and in a firm position. Place ear bars into the external auditory canal in the unlocked position for easy adjustability. A slight turn of the pins in opposite directions will lock the frame in position. The frame should be positioned precisely midline. We refrain from using the nose as a midline surface landmark but instead use the zygomatic arches and lateral canthi. Inject 2.5 ml

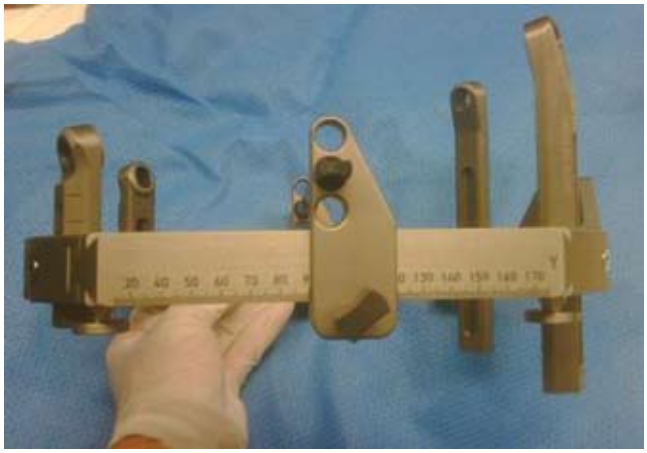

Fig. 2. Photograph of the completed Leksell frame, lateral view.

of lidocaine 1% subcutaneously into the anticipated insertion points of the 4 screws. Screw length should be determined based on the distance of the posts' screw holes from the scalp. Hand-tighten the screws in a diagonally oriented fashion (that is, tighten adjacent screws) to prevent altering the frame position. Tighten with the appropriate screwdriver until adequate bone purchase is achieved. Again, tighten the screws in a diagonal fashion to prevent frame slippage. Recheck the position of the frame and obtain confirmation of its midline position from another member of the functional team.

Place the Leksell Frame MR Imaging Localizer onto the frame itself. Ensure that the localizer's metal clip attachments are secured to the frame as seen in Fig. 3. Lay the patient supine for Foley catheter insertion, and prepare the patient for transport to MR imaging. Ensure that adequate oxygen is available during travel as well as the frame kit for any necessary adjustments and lidocaine for scalp pain related to screw placement.

Magnetic Resonance Imaging

On arriving in MR imaging, sit the patient upright and place the Leksell frame MR imaging adapter around the posterior aspect of the frame. Ensure that it is locked in place on the proper frame attachments. Lay the patient supine and flat and transfer him or her to the MR imaging table, ensuring insertion of the adapter into the appropriate slot on the table. Place a bolster under the patient's legs for comfort. It is important that such measures are taken to prevent any motion during scanning. For MR imaging at our institution we use a 1.5-T magnet (Signa, General Electric). We use 1.3-mm slices on axial T1-weighted images to localize the AC and PC to perform indirect targeting of the planned neural target. To enhance our accuracy we perform direct targeting of the planned neural target by using 2.5-mm slices of axial T2-weighted images. These slices can provide excellent definition of subcortical structures for direct visualization.

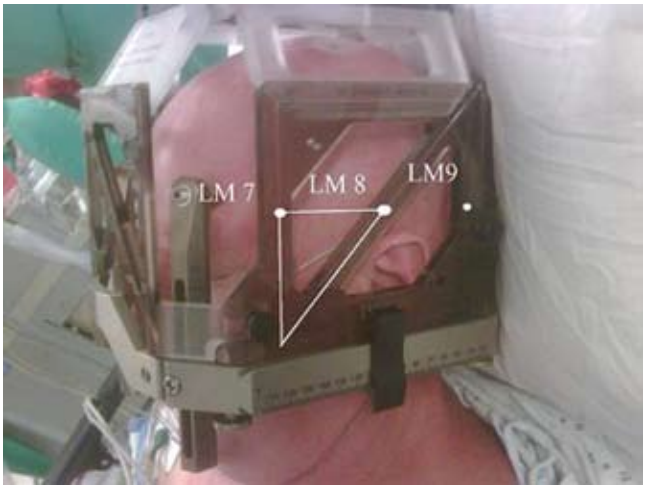

Fig. 3. The Leksell frame placed on a patient's head, with the MR imaging localizer attached. The diagonal line seen crossing just anterior to the patient's left ear is represented on axial slices by LM8. The diagonal line on the opposite side (right side) of the patient's head is represented by LM2. The lines running perpendicular to the Leksell frame here are marked by LM7 (anterior line) and LM9 (posterior line), and those on the right side of the patient's head are marked by LM1 (posterior line) and LM3 (anterior line). An isosceles triangle is superimposed on the MR imaging localizer to assist with the determination of the Z coordinate for a given axial slice.

Coordinates and Measurements

Some general concepts about the coordinate and measurement system are outlined as follows. 1) The X coordinate corresponds to the mediolateral axis, the Y coordinate to the anteroposterior axis, and the Z coordinate to the superoinferior axis. 2) The X, Y, and Z coordinates at the patient's rightward-most, posterior-most, and superior-most points are represented by 0, 0, and 0. 3) For reference in the discussion below, the LM seen on MR imaging in the axial plane will be labeled LM1–9 (Fig. 4). 4) The distance between LM1 and LM3 is 120 mm, as is the distance between LM7 and LM9. 5) The superoinferior lines LM1 and LM3, and LM7 and LM9 are connected by diagonal contrast lines. On any given MR imaging slice, the diagonal contrast lines create LM2 and LM8, which sit between LM1 and LM3 and between LM9 and LM7, respectively. Thus, on any given image slice, an isosceles triangle can be drawn connecting LM2 to LM1 (or LM3) and LM8 to LM7 (or LM9; Fig. 3). The dimensions of this triangle, which sits in the Y and Z plane, allow a calculation for the Z position of the image slice in question. 6) Indirect targeting using the coordinate system (X, Y, and Z) in relation to the midcommissural point (see below) or the PC are as follows: a) subthalamic nucleus, 11–13 mm, –2 mm, and 5 mm; b) ventrointermedial nucleus, 14 mm, quarter of the AC-PC distance measured from the PC, and 0 mm; c) globus pallidus internus, 21–23 mm, 2 mm, 5 mm. 7) The declination is determined by the slope of the arc in the anteroposterior plane, and the azimuth is the angle of approach in the mediolateral axis. 8) Register the MR imaging to a sagittal cut in which the AC and PC are both easily visible, placing the MR imaging slices in the plane of both the AC and PC. 9) Measure the AC-PC line. The midpoint of the AC-PC line is the midcommissural point. Using the measure stick function on the axial cut, insert a line connecting LM1 to LM7 and LM3 to LM9 (Fig. 4). The intersection of these lines is the precise center of the Leksell frame. Given their

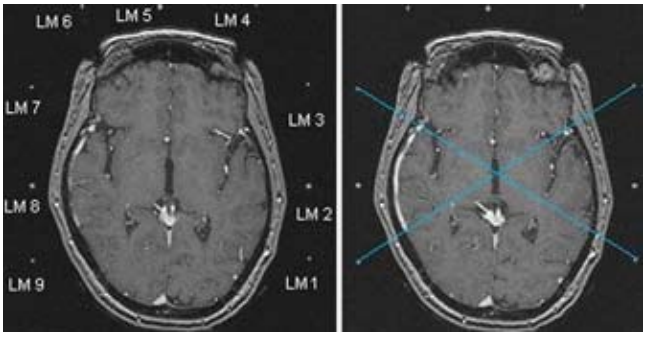

Fig. 4. Leksell frame MR imaging localizer marks as seen on an axial cut on MR imaging **(left)**. The diagonal lines are made from LM1 to LM7 and LM3 to LM9 **(right)**. The intersection of these diagonal lines is the 100, 100, and 100 point of the Leksell frame. The coordinates of the AC, PC, and target are determined by measuring the distance of this intersection from the midline and subsequently calculating the X, Y, and Z coordinates of each landmark.

distances in millimeters from the 0 coordinate on the Leksell frame, the center X, Y, and Z coordinates are 100, 100, and 100. We recommend superimposing a grid over the center of the intersecting lines to assist with measurements. 10) Determine the X, Y, and Z coordinates of the AC and PC in relation to the Leksell frame. Again, the 0, 0, and 0 coordinate is the point most rightward, posterior, and superior. 11) For the X coordinate of the AC, measure the lateral distance from the AC to the anteroposterior plane of the midpoint. If the X coordinate of the AC or PC is more than 4 mm from the plane of the midpoint, the Leksell frame should be repositioned with new screw sites and a new MR sequence. Once the lateral distance of the AC from the midpoint is determined, subtract this number from 100 if the AC is to the right of the midline or add this number to 100 if the AC is to the left of the midline; this determines the X coordinate of the AC. The same can be done for the PC. 12) For the Y coordinate, measure the distance from the AC to the mediolateral plane of the midpoint. Add this number to 100 if the AC is more anterior to the axis center or subtract from 100 if the AC is more posterior to the axis center. The same can be done for the PC. 13) Determine the Z coordinate of the AC and PC. As mentioned above, LM2 and LM8 are part of an isosceles triangle that helps derive Z coordinates. By measuring the distance between LM2 (or LM8) and LM1 (or LM9) for the particular axial slice containing the AC and PC, an indirect measure of the Z coordinate is made because of the isosceles triangle depicted in Fig. 3. A 40-mm correction is used to determine the length of Z. In the axial view the distance from the superior-most post to the inferior-most post is exactly 120 mm. So the distance from the center of the frame to each post is 60 mm. Given that we want the center coordinate to be 100 (and not 60), we add 40 mm to the distance from LM1 to LM2 and from LM8 to LM9.

Target Coordinates: Indirect and Direct

Based on the aforementioned methods, determine the indirect target coordinates. If possible, obtain direct measurements of the targets based on anatomical visualization of the target's center on T2-weighted axial images.

Transfer the patient onto the stretcher from the MR imaging table. Remove the frame adapter and return to the operating room.

Operating Room Setup

Transfer the patient to the operating table, ensuring that the most superior aspect of his or her shoulders is flush with the head of the table. Hold the frame during the transfer. Position the head of the patient at the foot of the operating table to allow for use of fluoroscopy during DBS. If the neurosurgical and anesthesia team agree on the use of general anesthesia, induction can ensue. We prefer general anesthesia in patients with severe dystonia and in any patient at high risk for obstructing an airway, as determined by the attending anesthesiologist. Of note, we have successfully performed microelectrode recordings despite general anesthesia using desflurane gas (unpublished data).

Once the patient is lying on the operating table, place the frame adapter on the Leksell frame with the turn knob directed superiorly (Fig. 5). Ask for assistance to hold the frame while placing the adapter. The frame adapter should then be attached with firm tightening of all screws. Reinject all screw sites with 2.5 ml of Marcaine.

StimPilot System

At our center, we remeasure the coordinates of the AC and PC as well as the planned target by using StimPilot (Medtronic, Inc.). The StimPilot system measures in fractions of millimeters and thus is very helpful in making precise calculations. When differences arise in the calculations of coordinates between MR imaging and the StimPilot, weighted averages are taken based on clinical judgment.

Patient Prep and Drape

The patient's head should be prepared using the normal sterile technique. At our institution, we do not shave a patient's head prior to prepping. We use Steris Bactoshield CHG 4% and chlorhexidine gluconate 4%. We wash with 2% chlorhexidine gluconate/7% isopropyl alcohol solution.[17] In fact, we have demonstrated improved rates of infection at our own center by using a chlorhexidine wash without increased rates of complication with this prep (unpublished data).

Put on lead and thyroid shield and scrub. Set up an intravenous pole on either side of the patient's head. Using long folded drapes, cover the patient's body in the caudal to cranial direction but do not cover the patient's head. Place a drape around the head. An up-going drape should be placed to exclude the anesthesia station from the surgical field. Place an Ioban drape (3M Health Care) on the patient's head, extending it from the anterior-most portion of the Leksell frame and over the patient's head. As depicted in Fig. 5, place an isolation drape (3M Health Care) along the top of the intravenous poles in front of the patient. Place a Neurodrape (3M Health Care) under the patient's head. Securely attach suction tubing to the bottom of the Neurodrape, and place a Floor Dry directly under the patient's head.

Procedural Setup

Determine the location of the coronal suture. We make the incision approximately 2 cm anterior to the coronal suture extending about 2 cm posteriorly. At our institution, we use a correction factor of 1.5 mm added to the left X and 1.0 mm added to the right X.

Set the 2 coordinates on the arc adapters to the frame and set the Y. Set the X coordinates on the stereotactic arc prior to placing it in position. On the right side, adjust the X coordinate and tighten. The stereotactic arc should be able to loosely pivot in the anteroposterior direction, allowing the surgeon to adjust the declination. Circular plate inserts with the circular (left) and square (right) targets should be placed on the arc attachments to assist in determining the target's center point by using fluoroscopy (Fig. 6).

Fluoroscopic Analysis

Position the C-arm with a sterile cover around the

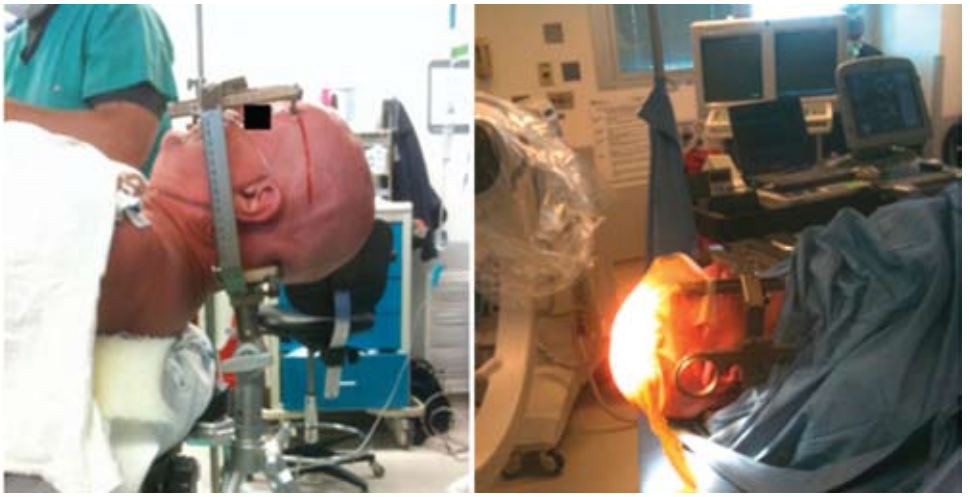

Fig. 5. Left: The Leksell frame in place on the patient's head and attached to the Mayfield adapter and Mayfield bed. **Right:** The patient prepared and partially draped, with the Ioban2 drape over the patient's head. The Leksell stereotactic arc is not in place.

patient's head as seen in Fig. 6. Continuously take fluoroscopic images until the circular and square targets are centered and the approximate trajectory estimated by a metallic instrument is in the 11 o'clock position on the fluoroscopic image.

Apply the microdrive to the arc at the proper azimuth as determined by the StimPilot (Fig. 7). Insert a probe through the microdrive's center to mark the entry site and approximate bur hole position. We routinely start on the right side when performing bilateral DBS. Mark where the tip of the probe comes in contact with the scalp and draw your planned incision. Once this step is complete, adjust the arc so that the left-sided coordinates are correct and mark the scalp appropriately. Remember to adjust the X coordinates first, as historically this step is often forgotten.

Surgical Procedure

Bur Hole Placement

Pivot the stereotactic arc with the attached microdrive inferiorly, away from the incision site, and inject lidocaine. It is preferable to be liberal with the local anesthetic agent, particularly if the patient is awake. Using a number 10 blade, make the planned incision. We regularly make the first incision on the right side. Using a narrow periosteal elevator, create a plane under the periosteum for easy passage of the DBS leads to the contralateral side for connection to the extension wiring later in the case. Of note, the IPG will be placed on the right side if you are using the Kinetra system (Soletra, however, is bilateral). Use a mastoid retractor to expose the underlying calvaria. Visualize the coronal suture and ensure that your planned bur hole is directly on the suture or slightly anterior to it. Adjust the arc again so that you can insert a metal probe through the microdrive's center track. Mark where the probe touches the calvaria and place your bur hole using the Midas drill (Medtronic, Inc.). Use a curette to remove remaining bone over the dura and quickly apply bone wax to any bleeding edges to prevent an air embolism. If the case is unilateral, continue working on the appropriate side; if bilateral, however, move to the left side before puncturing the dura to avoid any unnecessary loss of CSF. Once the dura is exposed on the left, coagulate the dura in a cruciate fashion using a bipolar cautery. With an 11 blade, incise the dura carefully avoiding any visible vasculature. Use the bipolar cautery device to cauterize the

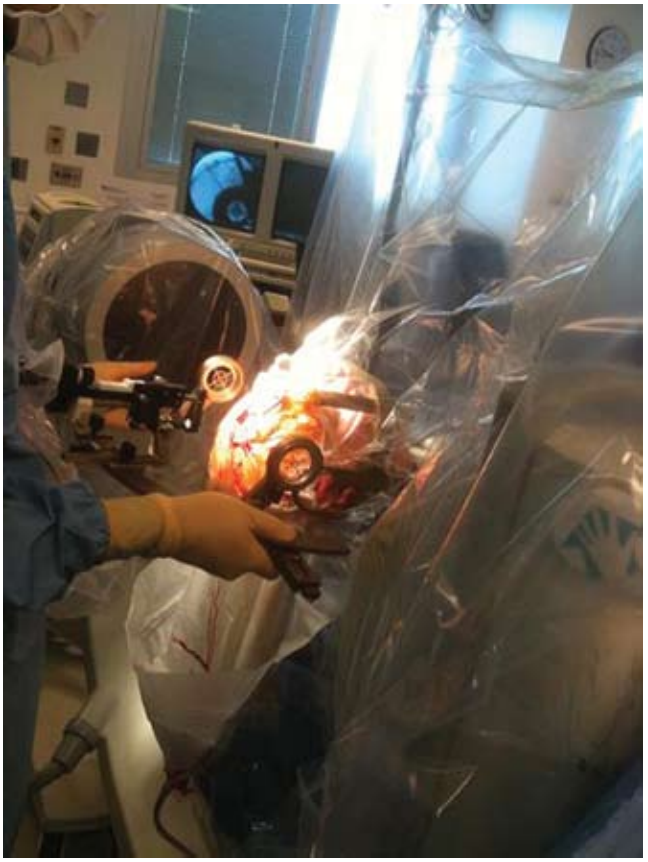

Fig. 6. The Leksell frame in place with the target inserts visualized. The circular target is visible on the left.

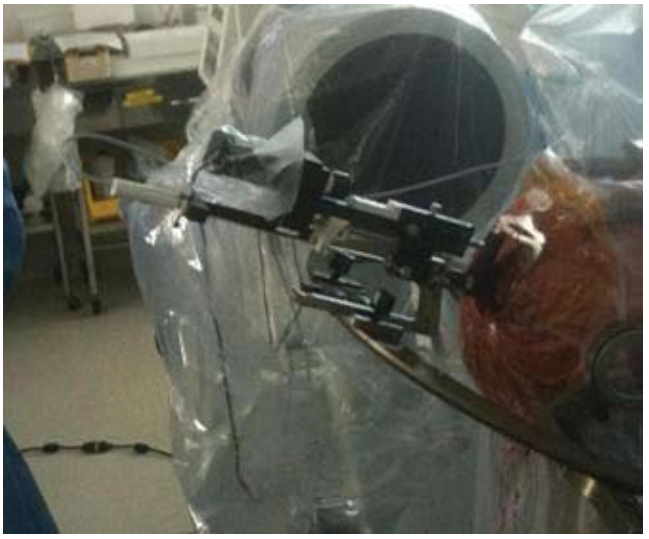

Fig. 7. The microdrive in place on the Leksell frame arc.

dural edges. Attempt to avoid CSF loss by minimizing the size of the durotomy and by applying Gelfoam and cottonoids once the microdrive is positioned in its final trajectory. At this time, the azimuth and declination can be altered to avoid traversing a sulcus or visible vasculature either superficially or on MR imaging. The electrode's trajectory using the StimPilot software will be simulated using the final coordinates.

Electrophysiological Study

Insert the guide cannula and stylet through the center trajectory of the microdrive. Once satisfied with the planned trajectory, microelectrode recordings should commence. It is important to ensure that the microelectrode lead does not abut the dural edges, as any such migrational force can compromise targeting. The ground electrode attaches to the guide cannula, while the recording electrode attaches to the distal tip of the microelectrode. Turn off all the lights, suction device, electronic operating table, Bovie, and any other unnecessary forms of electromagnetic interference. Using the microdrive, slowly guide the microelectrode to the target depth. Take intermittent fluoroscopic images at 10, 5, and 2 mm above the target to confirm proper advancement and trajectory of the microelectrode. Since the physiology team is nonsterile, they can assist the surgical team by performing sensorimotor tests when the microelectrode is approaching the target. If recordings are inadequate, a second trajectory can be attempted. The holes on the microdrive correspond to tracks 2 mm anterior, posterior, medial, or lateral to the original center hole.

Lead Implantation

Once the target is confirmed electrophysiologically and clinically, remove the guide cannula and microelectrode. Place the external guide piece onto the microdrive and insert the quadripolar macroelectrode (Medtronic, Inc.) into the microdrive (Fig. 7). Confirm placement at the target by using fluoroscopy. Begin macrostimulation of symptom release to further confirm placement and test for adverse effects. Remove the guide cannula and DBS lead stylet. Repeat fluoroscopy to ensure the lead is still in the desired position. Place the bur hole cap to lock down the DBS lead and repeat fluoroscopy to ensure the lead has not changed position. If performing bilateral DBS, reposition the arc to the proper coordinates, adjusting the X coordinates as well as the azimuth and declination, and repeat the procedure on the contralateral side.

Closing Procedure

Remove the stereotactic arc with the attached microdrive. Irrigate the surgical wounds with povidone-iodine and sterile saline. If the case is bilateral, place a Kelly underneath the scalp from the right incision to the left and pull a guide tube through to facilitate tunneling of the left DBS leads to the right side. Most of the IPGs that we place at our institution are Kinetras (that is, unilateral and on the right side). Remove the guide tube and bury both DBS wires underneath the scalp in a circular fashion around the right bur hole. Place three 2-0 Vicryl sutures in the galea on the left side and close with staples. On the right side, simply place 1 Vicryl suture and staple the wound. This side will need to be reopened when implanting the IPG.

Remove all drapes and the C-arm from the field. Proceed with washing the patient's head with warm water, 3% hydrogen peroxide (Medichoice, Owens & Minor), and baby wash (Johnson & Johnson Consumer Companies, Inc.). Disassemble the stereotactic arc. Remove the Leksell frame. Ask an assistant to hold the patient's head while the anterior screws are removed using the appropriate Leksell screwdriver. As the posterior screws are removed, the assistant will need to provide full support to the patient's head. Unlock the frame adapter, and swing the frame down and away from the patient's head. Replace the head of the bed.

Placement of the IPG

Placement of the IPG can be done with the patient under general anesthesia. The IPG should be placed approximately 4 finger-breadths inferior to the clavicle (Fig. 8) in a subcutaneous pocket. Shave the patient's chest as necessary. You will also need to shave the posterior-auricular region. Prep and drape the field in a normal sterile fashion from the right scalp incision (if bilateral or for right-sided surgery) to the posterior-auricular region as well as to the neck and right chest wall. Place an Ioban drape over the surgical field.

Open an extension kit for DBS (7482A-51, Medtronic, Inc.; Fig. 8). Using scissors, cut through the Ioban drape at the site of the right-sided scalp incision and remove the staples. Using a number 10 blade, cut along the chest incision and bluntly create a subcutaneous pocket. Place a radiopaque sponge in the pocket while the DBS extension wires are tunneled for hemostasis. Using uterine packing forceps, burrow subcutaneously from the DBS incision site to the posterior-auricular site in a manner similar to that for a standard ventriculoperitoneal shunt technique. Use a 15 blade to incise at the tips of the forceps posterior to the ear. Using the tunneling tool from the kit, tunnel subcutaneously from this skip incision down to the inci-

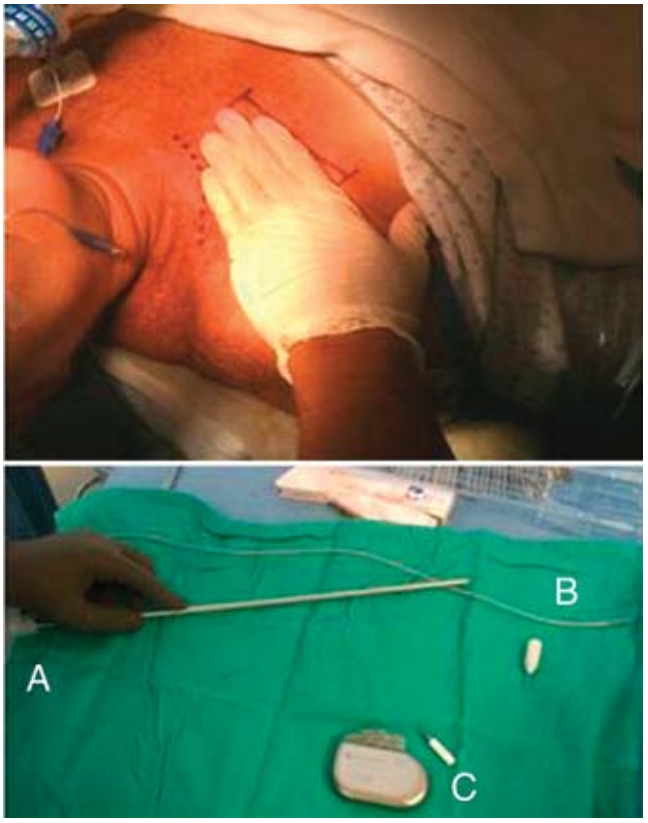

Fig. 8. Upper: Placement of the battery incision site. **Lower:** The battery and tools used for battery placement: tunneling tool (A), extension wire (B), battery and torque wrench (C).

sion in the chest wall. Remove the tunneler's stylet and insert the extension wire. Pull the tunneler with the extension through to the skip incision. Repeat with another tunneler to bring the wire from the skip incision to the scalp incision. This tunneling process must be repeated for bilateral procedures.

The white extension wire connector must be attached to the left DBS lead by using the kit's screwdriver, while the clear connector must be attached to the right lead. At our institution we use the Kinetra Dual-Program Neurostimulator for Deep Brain Stimulation for bilateral implantations for PD or the Soletra Deep Brain Neurostimulator for unilateral cases (Medtronic, Inc. for both). Use the torque wrench to tighten the extension wire connectors to the IPG and insert the left wire anterior to the right wire. Using a bayonet, coil the DBS lead and extension wires underneath the scalp. Irrigate with povidone-iodine and sterile saline and close with Vicryl sutures and staples. Insert the battery into the subcutaneous pocket after profuse irrigation. Close the battery pocket with 2-0 Vicryl and 4-0 Biosyn sutures. Close the skip incision with 3-0 Nylon sutures. Remove the drapes and wash the patient's head again before applying bandages. Extubate the patient and transfer them to the hospital bed and then to the recovery room.

Postoperative Care

All movement disorder–related drugs can be restarted in the recovery unit. Once the patient has recovered, obtain a same-day postoperative MR image to confirm lead placement and to rule out intracranial hematoma. Take the patient to the intensive care unit for 24 hours for monitoring.

Intravenous antibiotics (cefazolin or vancomycin for penicillin-allergic patients) are initiated 30 minutes prior to incision and continued every 8 hours postoperatively for 24 hours. Oral antibiotics include cephalexin or Bactrim in patients with a penicillin allergy or with a history of a methicillin-resistant *Staphylococcus aureus* infection. Deep vein thrombosis prophylaxis is initiated in the preoperative holding area before surgery with 5000 U heparin (subcutaneously) and every 8 hours after surgery until discharge. Evidence from our institution has documented no increased rate of intracranial hemorrhage with the use of perioperative subcutaneous heparin.[1] Patients also wear antithrombotic stockings as well as sequential compression devices throughout their hospitalization according to our standard protocol for prophylaxis against venous thromboembolism.[6] Patients are placed on 81 mg aspirin daily (initiated on postoperative Day 1) for 7 days.

We encourage patients to mobilize out of bed the morning after their surgery once the Foley catheter and arterial lines are discontinued. Frontal scalp dressings are removed on postoperative Day 1. Physical therapy consultation is initiated on postoperative Day 1 as well and is continued throughout a patient's hospitalization. Patients receive occupational therapy and speech therapy on an as-needed basis. On the general surgical floor, vital signs are checked every 4 hours. The neurosurgery team removes the postauricular and anterior chest wall dressings on postoperative Day 2. Patient and family education regarding disposition and recovery is provided throughout the hospitalization. Patients are discharged to home or a rehabilitation center based on recommendations by the neurosurgery team and physical therapy. The average hospital stay for our patients is 3 days. The need for in-patient rehabilitation is generally based on prior level of function. Rehabilitation services include physical, occupational, speech, and cognitive therapies. The typical rehabilitation course is 5–7 days.

Patients return to the neurosurgery office 10 days after surgery for suture and staple removal as well as initial device programming. Patients then return for their 1-month follow-up visit and further programming. They are then seen on an as-needed basis for additional programming of the device typically in collaboration with their movement disorder specialist who aims to wean dopaminergic therapy.

Conclusions

The applications of DBS surgery are rapidly expanding, making it imperative that optimal surgical techniques are used. Here, we provide our institution's standardized stepwise approach to DBS surgery. Considering the more than 600 DBS procedures completed at our center and a reported complication rate of 12.8%, the procedure outlined above is designed to maximize efficacy and minimize

complications.[14] As more data emerge to further guide the DBS surgical approach, greater accuracy in lead implantation, higher efficacy rates, and fewer complications will be achieved.

Disclosure

Drs. Jaggi and Baltuch are consultants for Medtronic, Inc.

Author contributions to the study and manuscript preparation include the following. Conception and design: Baltuch, Kramer, Halpern. Acquisition of data: Kramer. Analysis and interpretation of data: Kramer, Halpern. Drafting the article: Kramer, Buonacore, McGill. Critically revising the article: Baltuch, Kramer, Halpern, Buonacore, Hurtig, Jaggi. Reviewed final version of the manuscript and approved it for submission: Baltuch, Hurtig, Jaggi. Study supervision: Baltuch, Halpern, Hurtig, Jaggi.

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Manuscript submitted April 15, 2010.
Accepted April 30, 2010.

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Neurosurg Focus 29 (2):E4, 2010

Relationship between higher rates of adverse events in deep brain stimulation using standardized prospective recording and patient outcomes

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Object. Adverse event (AE) rates for deep brain stimulation (DBS) are variable, due to various methodologies used for identifying, collecting, and reporting AEs. This lack of a prospective, standardized AE collection method is a shortcoming in the advancement of DBS. In this paper the authors disclose the standardized and prospectively recorded AE data from their institution, correlated with clinical outcome and quality of life (QOL) measures.

Methods. All patients who underwent operations at the authors' institution for Parkinson disease (PD), essential tremor, dystonia, other tremor, and obsessive-compulsive disorder were included. Complications occurring intraoperatively or within the first 180 days following surgery were recorded, analyzed, and classified as mild, moderate, or severe, regardless of their perceived relationship to the procedure. The presence, frequency, and severity of AEs were compared with the following outcome measurements: postoperative change in the QOL scales (Medical Outcomes Study 36-Item Short-Form Survey, 39-Item PD Questionnaire); motor scales (Tremor Rating Scale, Unified Dystonia Rating Scale, Unified PD Rating Scale); and Patient Global Impression Scale (PGIS).

Results. Two hundred seventy DBS procedures were performed in 198 patients. Three hundred AEs were recorded in 146 (54.1%) of the 270 procedures, and the AEs were recorded in 119 (60.1%) of 198 patients. Of the 198 patients, the maximum severity of AEs was mild in 28 (14.1%), moderate in 35 (17.7%), and severe in 56 (28.3%). Of the 300 AEs, 102 (34.1%) of 299 were mild, 106 (35.5%) were moderate, and 91 (30.4%) were severe. The AEs were classified as probably not stimulation induced in 10 (3.4%) of 297, probably in 44 (14.9%), unclear for 89 (30%), and not applicable to stimulation in 154 (51.9%). Adverse events were also classified as probably related to surgery in 111 (37.2%) of 298, possibly related in 96 (32.2%), and probably not related to surgery in 91 (30.5%). There was no significant difference ($p = 0.22$) in QOL outcomes among patients who had no AEs compared with those who experienced mild, moderate, or severe AEs. There was no significant difference in QOL outcomes between patients who did not experience an AE compared with those who experienced any AE. There was no significant difference in the mean General PGIS score between patients without an AE versus those with any AE, as well as on the Symptom-Specific PGIS. Motor function outcomes did not vary between patients with or without AEs. For patients with PD with or without AEs, there was no significant difference in preoperative off-medicine Unified PD Rating Scale score and postoperative 6-month on-medication/on-stimulation change scores ($p = 0.59$). For patients with tremor there were no differences between those with or without AEs on the Tremor Rating Scale for motor function or activities of daily living. Patients with dystonia with and without AEs showed no differences in the Unified Dystonia Rating Scale.

Conclusions. Prospectively and systematically recording AEs may result in higher AE rates, but this does not correlate with poorer QOL, motor function, or patient-oriented outcome scores. *(DOI: 10.3171/2010.4.FOCUS10100)*

Key Words • deep brain stimulation • outcome • adverse event • hardware

Since being reintroduced for movement disorders in the late 1980s, DBS has been increasingly used to treat a variety of neurological and psychiatric diagnoses.[2,5,16] Because DBS is an elective procedure, a careful analysis of the risks and benefits is necessary for patients and clinicians to make an informed decision about pursuing therapy. However, a literature review reveals a wide range of AEs across many centers including such disparate values as 8.6%,[11] 26%,[8,15] and up to 50%.[14] Although at least 1 author has partially attributed the disparity in AEs to the surgical team's experience,[10] it is more likely that there are also other explanations. One compelling explanation is the lack of a standardized methodology for AE data collection and reporting, as well as the hesitancy to report surgical AEs unless the event was considered most likely directly related to the procedure.

Abbreviations used in this paper: AE = adverse event; DBS = deep brain stimulation; DRS = Dystonia Rating Scale; ET = essential tremor; MOS-36 = Medical Outcomes Study 36-Item Short-Form Survey; OCD = obsessive-compulsive disorder; PD = Parkinson disease; PDQ-39 = 39-Item PD Questionnaire; PGIS = Patient Global Impression Scale; QOL = quality of life; TRS = Tremor Rating Scale; UDRS = Unified Dystonia Rating Scale; UPDRS = Unified PD Rating Scale.

A recent meta-analysis designed to ascertain AE prevalence in DBS concluded that the true prevalence of AEs could not be accurately determined because there was an absence of standardized reporting.[18] In this paper, we describe our prospective and standardized method of recording AEs, that is equivalent to AE recording in pharmaceutical clinical trials. We summarized all recorded AEs intraoperatively and up to 180 days postoperatively, and we correlated these values with QOL and other clinical outcome measures.

Methods

Patient Population

All patients who underwent DBS operations at the University of Florida Movement Disorders Center between June 2002 and April 2008 for PD, ET, dystonia, other tremor (poststroke, multiple sclerosis, posttraumatic), and OCD were included in the study. Institutional review board approval and informed consent were obtained for all patients who agreed to have their data prospectively entered into the database. All diagnoses were given by fellowship-trained movement disorders neurologists using strict criteria for PD, ET, dystonia, and other tremor conditions. All patients underwent a multidisciplinary screening (neurology, neurosurgery, psychology, and psychiatry) prior to surgery. Patients who originally underwent operations at outside institutions were excluded from the study.

Surgical Method

To establish a coordinate system for DBS targeting, a Cosman-Roberts-Wells head ring (Radionics) was affixed to the awake patient and a stereotactic head CT scan was then acquired and fused to a 1.5- or 3.0-T MR image obtained on the day prior to surgery. Target coordinates were obtained after the images were fused. The Cosman-Roberts-Wells frame was set to the target coordinates and targeting accuracy was verified on a phantom ring. Multiple pass microelectrode mapping was used to verify the target position. A Medtronic DBS lead was implanted in each brain side that was operated on, and macrostimulation was performed following microelectrode recording to assess thresholds for benefits and side effects, as well as to assess programmability. Lead locations were adjusted if thresholds were discovered to be suboptimal. The lead was secured with a Navigus cap. All lead locations were assessed 1-month postoperatively by CT-MR fusion at which time pulse generators were also implanted.

Recording AEs

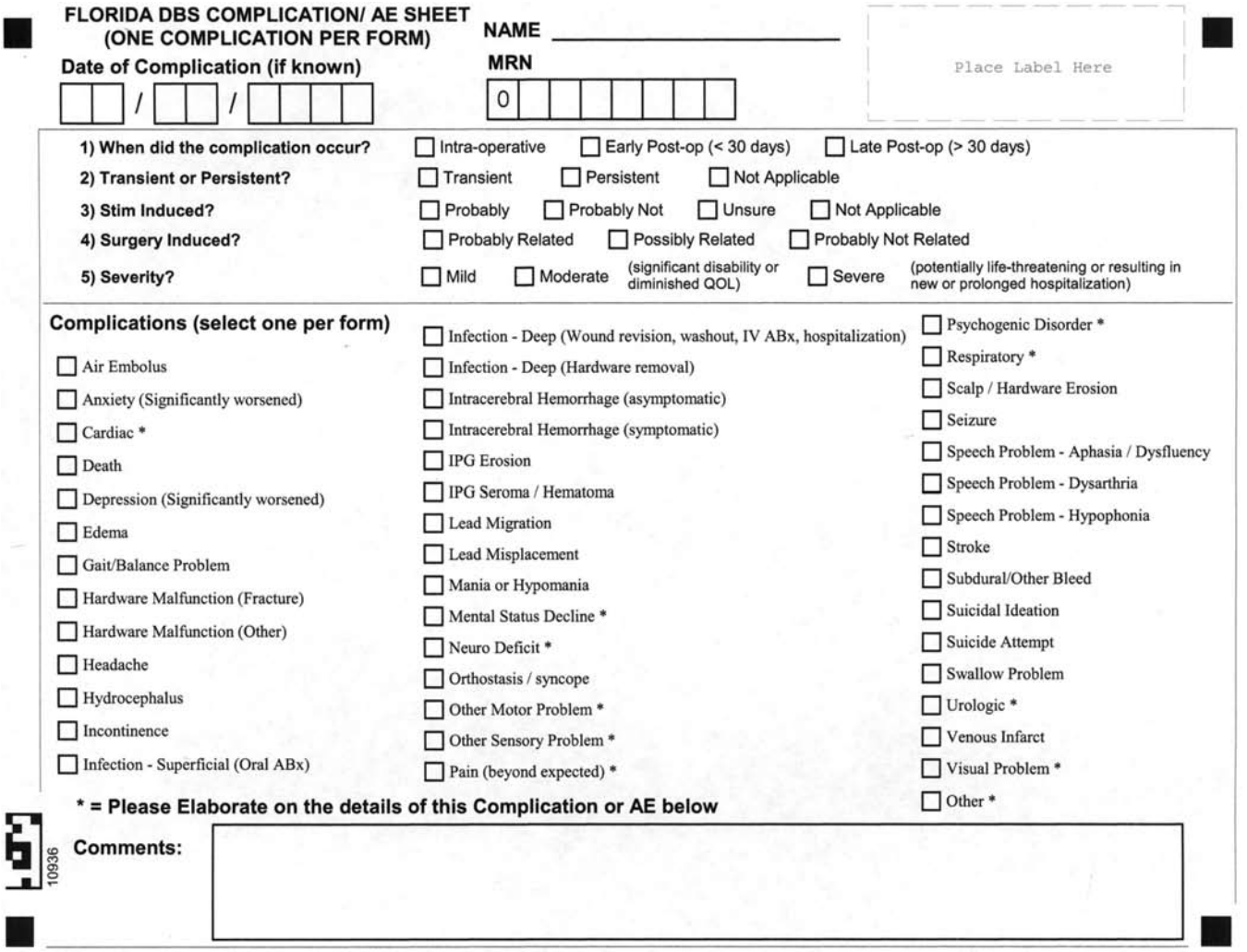
Since 2002, all AEs at the University of Florida have been prospectively recorded intraoperatively; during the patients' operative admission up to discharge; during monthly patient programming visits up to postoperative Month 6; at standard clinical assessment visits on Months 4, 6, and 12; and during unexpected visits including telephone calls regarding the patients' clinical state. All AEs are entered onto scannable forms and subsequently placed into a computerized database. Each form contains fields that describe the AE. Adverse events are categorized as transient (with resolution of symptoms) or persistent (persisting for 1 year or more); occurring in the intraoperative, early postoperative (30 days or less), or late postoperative (> 30 days) period; whether it is stimulation- or surgery-induced; and classified as mild, moderate, or severe based on the clinical team's judgment. A moderate AE is defined as resulting in significant disability or diminished quality of life. A severe AE is defined as any unexpected event that is potentially life threatening, or involving a return to surgery, or resulting in > 3 days postoperative hospitalization, or a new hospital admission.

In this study, all AEs and outcome scale scores were recorded within 180 days after DBS. These AEs were summarized and analyzed. The basic unit of analysis was each intracranial lead placement, rather than using each patient. Operations occurring > 180 days apart were analyzed separately. Lead placements within 180 days in the same patient were categorized as a bilateral procedure.

The latest version of the form used to record AEs is presented in Fig. 1. It has been revised twice over the last 6 years: once to include 2 additional descriptive categories, and once to combine AEs due to chronic stimulation, which had previously appeared on a separate programming form. This capture system combines AEs that are expected to arise from both surgery and stimulation, as both may result in DBS-related issues. The AEs are categorized so that multiple users can more easily locate the correct AE that will accurately describe their patient. The qualifiers on the forms provide valuable categorizations that can make later analysis more meaningful. For elaboration, a box for written comments at the bottom of the form is also included. A brief sentence not only validates the AE and its descriptive fields, but also allows for a description of interventions and outcomes.

Relevant Outcome Measures

Change in QOL was obtained by comparing the preoperative to the postoperative scores at 6 months on the PDQ-39 (for patients with PD) or MOS-36 (for patients with tremor and dystonia) scales. The extent of an improvement or worsening was determined by standardizing change scores as compared with the preoperative scores. The entire cohort was then categorized as having > 25% improvement, ≤ 25% improvement, ≤ 25% worsening, or > 25% worsening. Change in motor function was obtained by comparing the UPDRS score (for patients with PD), TRS score (for ET and other tremor conditions), and DRS score (for patients with dystonia) preoperatively when the patient was not taking medications, and postoperatively at 6 months off medication and on stimulation. The PGIS scores for all patients were also queried at the 6-month postoperative interval. The PGIS is a 7-point scale in which the patient determines if he or she is very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, or very much worse at the time of evaluation compared with the pre-DBS state, both in terms of the patient's general condition (General PGIS score), and separately for the main symptom that the patient wanted DBS to improve (Symptom-Specific PGIS score). These outcome measures are then compared and correlated with the presence, frequency, severity, and duration of AEs.



FLORIDA DBS COMPLICATION/ AE SHEET
(ONE COMPLICATION PER FORM)

NAME _____

Date of Complication (if known)
__ / __ / ____

MRN
0 _____

Place Label Here

1) When did the complication occur? ☐ Intra-operative ☐ Early Post-op (< 30 days) ☐ Late Post-op (> 30 days)
2) Transient or Persistent? ☐ Transient ☐ Persistent ☐ Not Applicable
3) Stim Induced? ☐ Probably ☐ Probably Not ☐ Unsure ☐ Not Applicable
4) Surgery Induced? ☐ Probably Related ☐ Possibly Related ☐ Probably Not Related
5) Severity? ☐ Mild ☐ Moderate (significant disability or diminished QOL) ☐ Severe (potentially life-threatening or resulting in new or prolonged hospitalization)

Complications (select one per form)

☐ Air Embolus
☐ Anxiety (Significantly worsened)
☐ Cardiac *
☐ Death
☐ Depression (Significantly worsened)
☐ Edema
☐ Gait/Balance Problem
☐ Hardware Malfunction (Fracture)
☐ Hardware Malfunction (Other)
☐ Headache
☐ Hydrocephalus
☐ Incontinence
☐ Infection - Superficial (Oral ABx)
☐ Infection - Deep (Wound revision, washout, IV ABx, hospitalization)
☐ Infection - Deep (Hardware removal)
☐ Intracerebral Hemorrhage (asymptomatic)
☐ Intracerebral Hemorrhage (symptomatic)
☐ IPG Erosion
☐ IPG Seroma / Hematoma
☐ Lead Migration
☐ Lead Misplacement
☐ Mania or Hypomania
☐ Mental Status Decline *
☐ Neuro Deficit *
☐ Orthostasis / syncope
☐ Other Motor Problem *
☐ Other Sensory Problem *
☐ Pain (beyond expected) *
☐ Psychogenic Disorder *
☐ Respiratory *
☐ Scalp / Hardware Erosion
☐ Seizure
☐ Speech Problem - Aphasia / Dysfluency
☐ Speech Problem - Dysarthria
☐ Speech Problem - Hypophonia
☐ Stroke
☐ Subdural/Other Bleed
☐ Suicidal Ideation
☐ Suicide Attempt
☐ Swallow Problem
☐ Urologic *
☐ Venous Infarct
☐ Visual Problem *
☐ Other *

* = Please Elaborate on the details of this Complication or AE below

10936

Comments:

FIG. 1. Latest version of the scannable data entry form used at the University of Florida Movement Disorders Center to prospectively collect and categorize AE information. This form is used by all physicians, residents, fellows, nurses, nurse practitioners, and other staff to record DBS-related AEs.

All collected data were analyzed using the SAS statistical program version 9.1. For comparisons in changes in QOL (PDQ-39 or MOS-36 score), motor function (UPDRS, TRS, and DRS scores), and PGIS scores between operations associated with and without AEs, 2-sample t-tests were employed. The association between QOL change category and AE severity was assessed using the Mantel-Haenszel test with modified ridit scores. Statistical significance of all tests was evaluated at the significance level of 0.05.

Results

Two hundred seventy DBS procedures were performed in 198 patients (Table 1). The mean age of the patients was 57.2 ± 15.8 years (range 8–89 years). One hundred thirty-three (67.2%) of the patients were male. Among that cohort of patients, 26 had dystonia, 43 had ET, 113 had PD, 6 had OCD, and 10 had other causes of tremor (multiple sclerosis, posttraumatic, poststroke). The DBS leads were implanted on the left hemisphere in 133 procedures (49.3%), on the right in 88 (32.6%), and bilaterally in 49 (18.1%).

A total of 300 AEs were recorded in 146 of the 270 procedures (54.1%; Table 2), and the AEs were recorded in 119 (60.1%) of 198 patients. Of the 198 patients, the maximum severity of AEs was mild in 28 (14.1%), moderate in 35 (17.7%), and severe in 56 (28.3%). For the 270 procedures, the AEs were mild in 42 (15.6%), moderate in 44 (16.3%), and severe in 60 (22.2%). Of the 300 AEs, 102 (34.1%) of 299 were mild, 106 (35.5%) were moderate, and 91 (30.4%) were severe. Forty-seven (15.7%) of the AEs occurred intraoperatively, 190 (63.3%) occurred within the first 30 days of the operation, and 63 (21%) occurred between Days 30 and 180. The AEs were transient in 82.6% (238 of 288) and persistent in 17%. The AEs were classified as probably not stimulation induced in 10 (3.4%) of 297 cases, probably stimulation induced in 44 (14.9%), unclear for 89 (30%), and not applicable to stimulation in 154 (51.8%). Adverse events were also classified as probably related to surgery in 111 (37.2%) of 298 AEs, possibly related to surgery in 96 (32.2%), and probably not related to surgery in 91 (30.5%). The frequency of each severe or persistent AE category is enumerated in Table 3.

TABLE 1: Patient and procedure characteristics

Variable	Value (%)
no. of patients	198
mean age in yrs (range)	57.2 (8–89)
sex	
male	133 (67.2)
female	65 (32.8)
diagnosis	
PD	113 (57.1)
dystonia	26 (13.1)
ET	43 (21.7)
other tremor	10 (5.1)
OCD	6 (3)
handedness	
rt	170 (85.9)
lt	18 (9.1)
unknown	10 (5.1)
no. of procedures	270
bilat procedures	49 (18.1)
lt hemisphere	133 (49.3)
rt hemisphere	88 (32.6)

TABLE 2: Adverse event characteristics

Variable	Value (%)
procedures w/ AEs	146 (54.1)
procedures w/o AEs	124 (45.9)
patients w/ AEs	119 (60.1)
patients w/o AEs	79 (39.9)
no. of AEs	300
intraop	47 (15.7)
early postop	190 (63.3)
late postop (>30 days)	63 (21)
transient/persistent*	
transient	238 (82.6)
persistent	49 (17)
not applicable	1 (0.3)
stimulation induced*	
probably	44 (14.8)
probably not	10 (3.4)
unsure	89 (30)
not applicable	154 (51.8)
surgery induced*	
probably related	111 (37.2)
possibly related	96 (32.2)
probably not related	91 (30.5)
severity of AEs*	
mild	102 (34.1)
moderate	106 (35.5)
severe	91 (30.4)

* Sum not equal to 300 due to some missing data.

There was no significant difference in the standardized QOL changes from before to after operations between patients who did not experience an AE versus those who experienced any AE ($p = 0.22$). Categorization on standardized QOL changes resulted in 58 operations (25.6%) with > 25% improvement in QOL, 80 operations (35.4%) with ≤ 25% improvement in QOL, 65 operations (28.8%) with ≤ 25% worsening in QOL, and 23 operations (10.2%) with > 25% worsening in QOL. The association between the QOL change category and the severity of complication was not significant. There was no significant difference in the mean General PGIS score between patients who did not experience an AE compared with those who experienced any AE (1.94 vs 2.1; $p = 0.34$) as well as the mean Symptom-Specific PGIS score (1.9 vs 2.04; $p = 0.40$).

Motor function outcomes did not vary between patients with and without AEs. For patients with PD with and without AEs, there was no significant difference in preoperative off-medicine UPDRS score and postoperative Months 4–6 on-medicine/on-stimulation changes ($p = 0.59$; Table 4). Similarly for patients with tremor there were no differences in TRS changes between those with and without AEs for motor function ($p = 0.58$) or for activities of daily living ($p = 0.15$) as measured by the TRS. Patients with dystonia with and without AEs showed no differences in the UDRS score ($p = 0.35$).

Discussion

The AE rates reported at our institution were at the high end of the spectrum. Within the first 180 days, more than 54% of the procedures involved an AE, and one-third (30.4%) of those were severe, based on a rigid definition adapted from pharmacological trials. With chronic stimulation and multiple implantable pulse generator changes, an even greater percentage of patients will likely have some type of AE during the course of treatment. These data, however, should not be discouraging, because patients with and without AEs appear to both perform well on standardized outcome measures and on the PGIS. The presence of mild, moderate, severe, or any AEs did not significantly affect patients in terms of their preoperative and 180-day postoperative motor function scale and QOL scale score changes, or of their own subjective assessment of their state after surgery (PGIS). Although this may be expected for those with mild or moderate AEs, it is somewhat surprising to find this remains true even for those who experienced severe AEs (an AE resulting in a life-threatening complication, or a new or greater than 3-day hospitalization). This finding may have been a result of the inclusive definition for a severe AE; for example, if the patient stayed in the hospital for more than 3 days due to social reasons, or was subsequently readmitted to the hospital for observation over a concern that was either unrelated to DBS or was not clinically significant, this would have been classified as a severe AE.

This study underscores some important issues facing DBS concerning AEs and AE reporting. It is clear that if prospectively acquired and recorded regardless of their

TABLE 3: Percentage and frequency of the 300 AEs*

AE	No. (%)	No. Severe	No. Persistent
mental status decline	53 (17.7)	9	5
other	43 (14.3)	5	3
gait problem	21 (7)	1	6
other motor problem	20 (6.7)	1	1
seizure	16 (5.3)	11	4
ICH (symptomatic)	16 (5.3)	10	4
lead misplacement	15 (5)	12	3
speech-aphasia	13 (4.3)	0	0
speech-dysarthria	11 (3.7)	0	3
subdural/other bleed	11 (3.7)	7	1
mania/hypomania	8 (2.7)	2	3
infection, deep (hardware removal)	7 (2.3)	7	0
air embolus	6 (2)	1	0
speech-hypophonia	6 (2)	0	2
depression	6 (2)	0	2
infection, deep (revision, IV antibiotics)	5 (1.7)	5	0
swallow problem	5 (1.7)	2	0
anxiety	5 (1.7)	2	2
incontinence	4 (1.3)	0	1
visual problem	4 (1.3)	0	1
infection, superficial (oral antibiotics)	4 (1.3)	0	0
hardware malfunction (other)	4 (1.3)	3	0
death	2 (0.7)	2	2
hardware malfunction (fracture)	2 (0.7)	2	0
hydrocephalus	2 (0.7)	2	2
neurological deficit (other)	2 (0.7)	0	0
stroke	2 (0.7)	2	0
scalp erosion	2 (0.7)	2	0
suicidal ideation	2 (0.7)	2	0
IPG seroma	1 (0.3)	0	0
other sensory problem	1 (0.3)	0	0
psychogenic disorder	1 (0.3)	0	0

* ICH = intracerebral hemorrhage; IPG = implantable pulse generator; IV = intravenous.

TABLE 4: Effect of presence or absence of AEs on outcomes measures

Outcome Measure	Mean Improvement (SD)	p Value†
QOL*		
w/ AE	14.4% (0.4)	0.22
w/o AE	10.1% (0.6)	
UPDRS		
w/ AE	–19.6 (13.3)	0.59
w/o AE	–18.3 (10.1)	
TRS (motor function/ADL)		
w/ AE	–21.9 (9.3)/–16.2 (5.2)	0.58/0.15
w/o AE	–19.9 (11.8)/–13.2 (6.5)	
UDRS		
w/ AE	–10.2 (16.7)	0.35
w/o AE	–16 (10.3)	

* Standardized change in PDQ-39 or MOS-36. Abbreviation: ADL = activities of daily living.
† After a 2-sample t-test.

perceived relationship to surgery or stimulation, the AE logs for this therapy should approximate, if not naturally exceed, the long lists of AEs reported for even the most benign pharmacological agents. The pre- and postmarketing reports of any pharmaceutical product have long adopted a standardized approach to reporting all AEs and have considered this the most important aspect of new product development, allowing the clinician a better comparison of the safety profile of each drug in its class or of each indication. Deep brain stimulation will need to move toward standardization of an approach for reporting AEs. Whereas it has already been established that DBS is an efficacious treatment for many disorders,[3,4,16,17] its risk-benefit ratio is in large part contributed to by the frequency and severity of AEs. Only standardized and prospective recording of AEs will allow the proper estimation of margins of therapeutic benefit and tolerability, the identification of the most at-risk surgical populations, and the generalizability of the benefit derived from the procedure between surgical centers.

So as not to discourage other centers from recording prospectively and classifying systematically all AEs, we looked at the QOL and other relevant outcome measures to the frequency and severity of AEs and found no difference in QOL among patients with AEs versus those without AEs. This finding is particularly important as general outcome scores from this study and from others published in the literature continue to reflect satisfaction with the results of DBS regardless of the occurrence of AEs. Since the late 1980s, DBS has evolved from an experimental procedure to an established treatment modality for many diagnoses worldwide.[1,6,7,12] Current research, especially in the field of neuropsychiatric disorders, will likely lead to a vast increase in the patient population for whom DBS will become available.[9,13,17] Because the procedure is elective, it will be important to better establish the risk-benefit ratio as well as the short- and long-term issues associated with the procedure.

Conclusions

The use of a standardized, prospective recording system for AEs reduces the bias introduced by memory, inter- and intraprovider variability, and unfocused medical record keeping. This type of system results in the reporting of higher but more accurate AE rates. If adopted by centers worldwide, such a system as reported here will allow for the more uniform comparison of AE rates between institutions. This new data set has the potential to compare AEs among differing philosophies and techniques from different institutions, uncover subtle trends that would otherwise go undetected, assess short- and

long-term risks, and most importantly provide data that are necessary for neurosurgeons and neurologists to share with their patients who will then be empowered to make more informed decisions about the use of DBS.

Disclosure

This study was funded by Grant No. K23 NS044997 from the National Institute of Neurological Disorders and Stroke, NIH, and the National Parkinson Foundation Center of Excellence. Dr. Foote and Dr. Okun have received honoraria from Medtronic and have consulted for the National Parkinson Foundation, Sabine Neurotechnology, Neuropace, and Advanced Bionics. Dr. Foote has received nonstudy support from ANS/St. Jude Medical. Dr. Okun has received clinical or research support for this study from the Michael J. Fox Foundation. Dr. Fernandez is a co-owner of DBS Solutions, Inc., which has a contractual agreement with Neurotrax to develop a software program, COMPRESS, for which he is also one of the cofounders.

Author contributions to the study and manuscript preparation include the following. Conception and design: Foote, Burdick, Fernandez, Okun. Acquisition of data: Burdick, Okun. Analysis and interpretation of data: Foote, Burdick, Fernandez, Okun. Drafting the article: Burdick, Okun. Critically revising the article: Foote, Burdick, Fernandez, Okun. Reviewed final version of the manuscript and approved it for submission: Foote, Burdick, Okun. Statistical analysis: Chi. Administrative/technical/material support: Jacobson.

Acknowledgments

The authors would like to acknowledge the National Parkinson Foundation Center of Excellence, the McKnight Brain Institute, University of Florida and Shands, and the Eric and Jennifer Scott Fund.

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Manuscript submitted April 14, 2010.
Accepted April 30, 2010.
Portions of this work have been presented in abstract and/or poster form at the 12th International Congress of Parkinson Disease and Movement Disorders, Chicago, Illinois, June 22–26, 2008; the 58th Annual Meeting of the CNS, Orlando, Florida, September 20–25, 2008; University of Florida College of Medicine Annual Research Day, April 2009; and the 13th International Congress of Parkinson Disease and Movement Disorders, Paris, France, June 7–11, 2009.

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Neurosurg Focus 29 (2):E5, 2010

Long-term follow-up of deep brain stimulation for Meige syndrome

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Object. Meige syndrome is characterized by blepharospasm, cervical dystonia, and facial oromandibular dystonia. The medical treatment of this condition is largely unsuccessful over time and is a major source of decreased quality of life in those patients suffering from this disease. Recent advances in the application of deep brain stimulation (DBS) surgery techniques for many disorders have prompted several recent reports of DBS for medically refractory cases of Meige syndrome. While the etiology for this disorder is unknown, it is considered by many investigators to be a form of idiopathic torsion dystonia. Pallidal stimulation is widely considered to be effective for dystonia.

Methods. The authors report the long-term results of bilateral globus pallidus internus (GPi) or subthalamic nucleus (STN) stimulation in 3 patients with Meige syndrome and 1 patient with Parkinson disease and associated craniofacial dystonia treated at their center.

Results. Initial 12-month and long-term follow-up Burke-Fahn-Marsden scores were substantially improved in all 4 patients compared with preoperative scores.

Conclusions. Bilateral GPi DBS may be an effective and safe treatment for medically refractory Meige syndrome. The results are comparable with those reported in the literature. Sustained and long-term improvement in symptoms does appear to be reproducible across reports. The authors' patient with Parkinson disease and associated craniofacial dystonia syndrome undergoing bilateral STN DBS noted immediate and sustained improvement in his symptoms. Further study is required, but these results, along with the other reports, suggest that bilateral GPi DBS is an effective treatment for medically refractory Meige syndrome. *(DOI: 10.3171/2010.4.FOCUS1067)*

Key Words • Meige syndrome • deep brain stimulation • globus pallidus internus • subthalamic nucleus

Idiopathic cranial cervical dystonia is an adult-onset movement disorder resulting in segmental dystonia. Several different terms have been used to label the disorder including Blake, Wood, Brueghel, and Meige syndromes.[15] Meige syndrome has become the most common eponym current used in the literature.[2,3,6,9,11,13,21,23,24,27,30] Meige syndrome is characterized by blepharospasm, cervical dystonia, and facial oromandibular dystonia. The underlying cause of Meige syndrome is unknown, but most investigators consider it a variant of idiopathic torsion dystonia.[13] Some patients can develop spasmodic dysphonia as well as dystonic involvement of the limbs.[23] The disorder is more common in females by a 3:1 ratio.[14] Medical treatment of this condition has generally been unsuccessful and often limited by partial response and adverse side effects. Stereotactic surgical ablation techniques had been used for several years with mixed results.[1,5,7,10,24,30] Both the thalamus and the GPi have been targeted. Botulinum toxin has also been shown to be effective for blepharospasm, as well as for facial, cervical, and oromandibular dystonia; however, some patients may have diminished response with time and some may develop antibodies that make them resistant to continued therapy.[2,9,16,17,25,27]

The advent of DBS for neuromodulatory treatment of a wide variety of movement and other disorders has prompted increased interest in applications to severe forms of medically refractory dystonias. Deep brain stimulation for dystonia, targeting the GPi, has been shown to be an effective treatment for primary generalized dystonia.[18,19,25,29,31] There have been several recent reports on the efficacy of GPi DBS in selected patients with Meige syndrome.[2,3,6,9,11,12,21–25,30] We report on our experience in using DBS in 3 cases of Meige syndrome and 1 case of Parkinson disease and associated craniofacial dystonia, with long-term follow-up, and we review the current literature.

Abbreviations used in this paper: BFM = Burke-Fahn-Marsden; DBS = deep brain stimulation; GPi = globus pallidus internus; IPG = implantable pulse generator; STN = subthalamic nucleus.

Methods

Patients

Three patients with medically refractory Meige syndrome underwent bilateral DBS, and 1 patient with Parkinson disease and associated craniofacial dystonia underwent STN DBS. The patient with Parkinson disease would not be considered a case of idiopathic Meige syndrome because the onset of the syndrome occurred after Parkinson disease symptoms manifested, and craniofacial dystonia can be a symptom of Parkinson disease. All patients were evaluated by a movement disorders specialist at our center. All patients suffered severe disease-related impairment and had unsatisfactory outcomes after oral pharmacotherapy, which included benzodiazepines, anticholinergic agents, muscle relaxants, antiepileptic agents, and dopaminergic agents (in the case of Parkinson disease with Meige). All patients also had poor response to botulinum toxin injections, as well as physical measures. Brain MR imaging demonstrated no structural cause for their dystonia. Preoperative and postoperative BFM Dystonia Rating Scales were performed on each patient.[4]

Surgical Procedures

Surgery was performed in all patients under the Medtronic humanitarian device exemption for dystonia. Staged bilateral GPi DBS was performed using the COMPASS stereotactic system and the Medtronic DBS model 3387S electrodes in 3 of the patients with pure Meige. The patient with Meige syndrome and Parkinson disease underwent staged bilateral STN DBS in which the Medtronic DBS model 3389 electrode was used. The surgical procedure was performed utilizing mild conscious sedation and local anesthetic. The GPi is used at our institution for DBS treatment of medically refractory primary or secondary dystonias. The initial GPi coordinates were based on the anterior and posterior commissures, 2 mm anterior and 2 mm inferior to the midcommissural point and 20 mm lateral to the third ventricle. For the Parkinson disease patient with Meige syndrome, the "midpoint" STN target was planned utilizing the coordinates 4 mm posterior, 5 mm inferior, and 12 mm lateral to the midcommissural point. Microelectrode recordings were done beginning 20 mm above the GPi or STN target using 5 concentric bipolar tungsten microelectrodes driven simultaneously by a hydraulic Alpha-Omega microdrive at incremental depths of 0.3 to 0.5 mm. Intraoperative electrophysiology with nuclear mapping was performed to locate and confirm the dorsal and ventral borders of the GPi or STN. For the GPi, the trajectory was planned to be lateral to the ventricle, traverse the posterior GPi and terminate just above the optic tract. For the STN, the trajectory was planned to terminate just above the border between the STN and substantia nigra pars reticulata. Microelectrode recordings were used to confirm GPi or STN neuronal activity and followed by microstimulation to optimize the final target. Intraoperative limb and jaw movements, speech and vision testing were used to confirm clinical responses. Medtronic quadripolar DBS electrodes were implanted bilaterally. Macrostimulation was done to further refine final electrode placement based on intraoperative effect and position confirmed with intraoperative lateral teleradiographs. At a subsequent surgery, the DBS electrodes were connected to a Medtronic IPG. Multiplanar postoperative cranial MR imaging was performed to confirm the accuracy of electrode placement in the GPi or STN (Fig. 1).

Results

Three patients underwent bilateral GPi DBS and 1 patient underwent STN DBS. In the patients who underwent GPi DBS, their primary symptoms were related to Meige syndrome. The patient who underwent STN DBS was primarily affected by his Parkinson disease symptoms. The intraoperative microelectrode recordings in the 3 GPi DBS–treated patients showed high frequency (range 60–160 Hz) and high-amplitude continuous discharges in the GPi, which were replaced by sparse low-amplitude intermittent discharges upon exiting the ventral border of the GPi. The STN DBS–treated patient exhibited medium- to high-frequency (range 40–100 Hz) and high-amplitude continuous discharges in the STN during intraoperative microelectrode recording, which were replaced by relative quiescence on going beyond the ventral border of the STN. The mean preoperative BFM score in the GPi group was 27.5 and in the STN DBS–treated patient was 12 (Table 1). The 12-month postoperative mean BFM score in the GPi group improved by a mean of 82%, and in the STN DBS–treated patient it

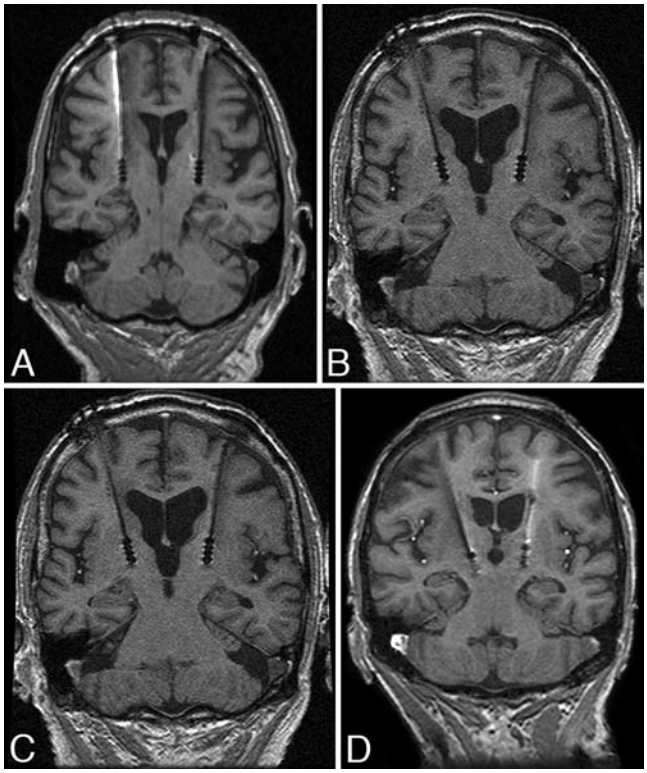

Fig. 1. Cases 1–4. Postoperative coronal T1-weighted MR images demonstrating electrode placement in 3 patients who underwent GPi DBS **(A–C)** and 1 patient with Parkinson disease who underwent STN DBS **(D)**.

TABLE 1: Clinical characteristics in patients with Meige syndrome undergoing DBS*

Case No.	Age (yrs)	Diagnosis	BFM Dystonia Rating Scale Score			Subjective Improvement (%)	Target	FU (mos)
			Preop	12 Mos Postop (% improvement)	Last FU			
1	73	Meige	28	6 (79)	5	75	GPi	54
2	63	Meige	26	4 (85)	13	80	GPi	42
3	56	Meige	28	5 (82)	6	20	GPi	48
4	71	PD & Meige	12	0 (100)	0	100	STN	66

* FU = follow-up; PD = Parkinson disease.

improved by 100%. The stimulation parameters for the 4 patients are presented in Table 2. Of the total 8 electrodes implanted in the 4 patients, 6 were on unipolar stimulation, and 2 were on bipolar stimulation at 1-year follow-up. Three of the 4 patients benefited best from stimulation frequencies from 130 to 185 Hz, whereas 1 patient benefited most from lower frequencies of stimulation (60–90 Hz). The STN DBS–treated patient had immediate and sustained relief of his dystonia symptoms until his death 5.5 years after surgery. Of the patients in the GPi group, 2 had significant improvement in symptoms, with subjective reports of 75–80%. Both of these patients noted the improvement 6 months following surgery and have only required programming adjustments once or twice a year. One of these patients has continued with sustained improvement 4.5 years and the other for 4 years following surgery. The third patient in the GPi group noted positive results at 9 months after DBS, and these results have been maintained at 3.5 years postoperatively. Of note, this patient had severe preoperative depression that has persisted. The depression has caused her to appreciate less the improvements in her craniofacial dystonia. During her 1st year, she averaged 1 programming visit every 2 months, whereas for the subsequent years, she required 2–3 programming adjustments per year.

Discussion

Renewed interest in the GPi for medically refractory forms of generalized dystonia, as reported by Tronnier and Fogel,[29] has sparked interest in using this target for patients suffering from Meige syndrome. Since Vercueil and coworkers[3] first reported their results of bilateral GPi DBS in a patient with Meige syndrome, several studies have shown that segmental dystonia responds to GPi DBS.[2,3,6,9,11,13,18–25,29–31] The reports on Meige syndrome and its response to DBS are primarily single cases, aside from the excellent report by Ostrem and colleagues[25] (Table 3). The follow-up time frame has been somewhat limited in most reports, except the cases of Loher et al.[21] at 7 years, Hebb et al.[11] at 5 years, and Capelle and associates[6] at 2 years. The response to GPi DBS for Meige syndrome has been good to excellent in the published reports. Most responses, however, do not show immediate improvement in symptoms and often take up to 6 months to achieve good results. Our results are similar to those reported in the literature in the GPi-targeted patients. One of our GPi DBS–treated patients suffered from severe pre- and postoperative depression, and although her initial BFM score at 12 months following surgery was 5, compared with 28 preoperatively, her subjective reported improvement was only 20%.

Our single case of bilateral STN DBS in a patient with Parkinson disease resulted in immediate and sustained improvement of facial dystonia until his death 66 months after surgery. This is the only case of Parkinson disease with craniofacial dystonia responding to bilateral STN DBS reported in the literature. It has been suggested that the excellent response of craniofacial muscle dystonia to GPi stimulation may reflect the somatotopic organization of the GPi, with the face being more posterior and ventral.[8] Similar somatotopic nuclear organization in the STN may, in part, explain the observed improvement in our patient undergoing bilateral STN DBS.

The long-term medical treatment of Meige syndrome is generally unsuccessful with complications from medications being the predominant limiting factor. The pathophysiology of Meige syndrome is unknown and autopsy reports have been nonspecific.[28] Single-positron emission computed tomography and functional MR im-

TABLE 2: Programming parameters at 1 year after DBS in 4 patients

Case No.	Diagnosis	Programming Parameters at 1 Yr Postop
1	Meige	lt IPG: case (+), 3(–), 2.8 V, 90 msec, 145 Hz; rt IPG: contact 3 (+), contact 2 (–), 2.4 V, 90 µsec, 145 Hz
2	Meige	lt IPG: case (+), contact 2 (–), 3 V, 60 µsec, 90 Hz; rt IPG: case (+), contacts 6 & 7(–), 3.6 V, 120 µsec, 60 Hz
3	Meige	lt IPG: case (+), contact 3 (–), 3 V, 120 µsec, 130 Hz; rt IPG: contact 3 (+), contact 0 (–), 3 V, 120 µsec, 130 Hz
4	PD & Meige	lt IPG: case (+), contacts 1 & 3 (–), 3.5 V, 90 µsec, 185 Hz; rt IPG: case (+), contact 1 (–), 3.5 V, 60 µsec, 185 Hz

TABLE 3: Published cases of Meige syndrome treated with DBS*

Authors & Year	No. of Patients	Age (yrs)	BFM Dystonia Rating/ GDR Scale Score		Improvement (%)	Target	FU (mos)
			Preop	Last FU			
Muta et al., 2001	1	61	35	7	80	GPi	NR
Vercueil et al., 2001	1	59	NR	NR	66	GPi	6
Bereznai et al., 2002	1	78	NR	NR	NR	GPi	12
Capelle et al., 2003	1	60	18	6	67	GPi	24
Foote et al., 2005	1	47	NR	NR	75	GPi	12
Houser & Waltz, 2005	1	44	44	10	75	GPi	6
Loher et al., 2008	1	60	18	7.5	NR	GPi	84
Opherk et al., 2006	1	65	NR	NR	NR	GPi	4
Hebb et al., 2007	1	49	47	10	79	GPi	60
Ostrem et al., 2007	6	54 ± 11	22 ± 8.3	6.1 ± 4.2	72	GPi	6
Blomstedt et al., 2008	1	41	25	7	72	GPi	18
Markaki et al., 2010	1	49	25	4	70	GPi	6
present study†	3; 1	64 ± 8; 71	27 ± 1; 12	8 ± 5; 12	57 ± 30; 100	GPi 3; STN 1	48 ± 6; 66

* GDR = Global Dystonia Rating Scale; NR = not reported.

† The initial value in the mean ± SD obtained in the 3 patients with Meige syndrome; the second value is that obtained in the 1 patient with Meige syndrome and Parkinson disease.

aging studies have shown thalamic and/or basal ganglia lesions in 5 of 7 cases of Meige syndrome.[26] The exact mechanism of the observed effect of pallidal stimulation on dystonia is not clear. Some authors have reported better response to monopolar stimulation, which seems to be our experience. Although most studies report favorable results with high-frequency stimulation with dystonia (≥ 130 Hz),[21] others have pointed out that low-frequency stimulation (60 Hz) may be just as effective without causing as much battery drain.[14] However, bilateral stimulation is generally considered necessary for optimal treatment of disorders manifesting with midline symptoms,[9,25] and that unilateral stimulation may fail to alleviate the axial symptoms in patients with Meige syndrome.[3]

Conclusions

Bilateral GPi DBS may be an effective and safe treatment for medically refractory Meige syndrome. The results observed in our series are comparable with those reported in the literature. Sustained and long-term improvement in symptoms does appear to be reproducible across reports. Our single case of response of Parkinson disease associated craniofacial dystonia treated with STN DBS needs confirmation in other patients undergoing STN DBS for Parkinson disease, in conjunction with craniofacial dystonia, to see if it is reproducible. While no definitive conclusions can yet be made regarding DBS for Meige syndrome, the multiple reports are encouraging. Further study is required, but these results along with those in other reports suggest that bilateral GPi DBS may be effective treatment for medically refractory Meige syndrome even in the long term.

Disclosure

Dr. Lyons has direct stock ownership in Medtronic.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lyons. Acquisition of data: Hillman, Boucher, Evidente. Analysis and interpretation of data: Lyons, Evidente. Drafting the article: Lyons, Evidente. Critically revising the article: Lyons, Birch, Evidente. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Evidente. Administrative/technical/material support: Hillman, Boucher.

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Manuscript submitted February 19, 2010.
Accepted April 19, 2010.

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Neurosurg Focus 29 (2):E6, 2010

Development of intraoperative electrochemical detection: wireless instantaneous neurochemical concentration sensor for deep brain stimulation feedback

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Deep brain stimulation (DBS) is effective when there appears to be a distortion in the complex neurochemical circuitry of the brain. Currently, the mechanism of DBS is incompletely understood; however, it has been hypothesized that DBS evokes release of neurochemicals. Well-established chemical detection systems such as microdialysis and mass spectrometry are impractical if one is assessing changes that are happening on a second-to-second time scale or for chronically used implanted recordings, as would be required for DBS feedback. Electrochemical detection techniques such as fast-scan cyclic voltammetry (FSCV) and amperometry have until recently remained in the realm of basic science; however, it is enticing to apply these powerful recording technologies to clinical and translational applications. The Wireless Instantaneous Neurochemical Concentration Sensor (WINCS) currently is a research device designed for human use capable of in vivo FSCV and amperometry, sampling at subsecond time resolution. In this paper, the authors review recent advances in this electrochemical application to DBS technologies. The WINCS can detect dopamine, adenosine, and serotonin by FSCV. For example, FSCV is capable of detecting dopamine in the caudate evoked by stimulation of the subthalamic nucleus/substantia nigra in pig and rat models of DBS. It is further capable of detecting dopamine by amperometry and, when used with enzyme linked sensors, both glutamate and adenosine. In conclusion, WINCS is a highly versatile instrument that allows near real-time (millisecond) detection of neurochemicals important to DBS research. In the future, the neurochemical changes detected using WINCS may be important as surrogate markers for proper DBS placement as well as the sensor component for a "smart" DBS system with electrochemical feedback that allows automatic modulation of stimulation parameters. Current work is under way to establish WINCS use in humans. *(DOI: 10.3171/2010.5.FOCUS10110)*

Key Words • deep brain stimulation • dopamine • adenosine • serotonin • fast-scan cyclic voltammetry • amperometry • electrochemistry

Although DBS use has increased dramatically, with clinical indications expanding to neurological and psychiatric diseases, there is a great need to improve this functional neurosurgical technique. A major challenge is incomplete understanding of the DBS mechanism, especially why stimulation of specific targets is effective. Furthermore, DBS technology and procedures have remained largely unchanged for the past 20 years.[30] Subsecond monitoring of the neurochemical efflux secondary to DBS-targeted regions has the potential to advance functional neurosurgical procedures. Surrogate neurotransmitters involved in the clinical effectiveness of DBS may directly correlate with treatment outcomes.[30] In turn, one could conceive of chemically guided placement of DBS electrodes in vivo to assist our current practice of electrophysiologically guided placement.[30] This review addresses one such step toward neurochemically guided or modulated functional neurosurgery.

Abbreviations used in this paper: DBS = deep brain stimulation; DOQ = dopamine ortho-quinone; FSCV = fast-scan cyclic voltammetry; STN = subthalamic nucleus; WINCS = Wireless Instantaneous Neurotransmitter Concentration Sensor.

Neurochemical Monitoring

Microdialysis and voltammetry are the 2 most widely used techniques for neurochemical monitoring.[7] Microdi-

alysis has excellent selectivity and sensitivity but is limited in temporal resolution and has been the workhorse technique for sampling brain neurotransmitters over the last 3 decades.[47] Unfortunately, there are limitations to microdialysis; for instance, microdialysis requires multiminute collection times and may monitor trends in neurochemicals but not second-to-second changes necessary to investigate the subsecond changes in neuronal transmission evoked by electrical stimulation.[17–20,28,43,44] Therefore, in relation to DBS, in which stimulation is applied 5 to 100s of times per second, microdialysis may not have the temporal resolution to determine neurochemical changes that are important for DBS feedback. Although predating microdialysis and offering the enticing potential of faster measurements with smaller probes and improving spatial resolution, voltammetry had initially struggled to compete with microdialysis due to poor selectivity.[5] However, the modern era of electrochemistry has seen the rise of rapid sampling voltammetry, such as amperometry and FSCV. While microdialysis has been used in humans, electrochemical techniques have not. The same analytical attributes that have made this neurochemical monitoring technique attractive for brain behavior studies in awake laboratory animals may be valuable for human research.[1,14,15,21–23,37–40]

Electrochemical Detection

In vivo electrochemistry most often uses microelectrodes of various fabrications that can be implanted into the brain and record relative changes in neurochemicals of interest. These electrodes are similar to contemporary extracellular electrodes used for electrophysiology with slight modification. The microelectrode can oxidize or reduce compounds of interest. Currents generated from these oxidation and reduction reactions may linearly be correlated to concentration of the electroactive molecule(s) in the extracellular environment. It is important to note that, while microdialysis allows for absolute determination of the concentration of a specific neurotransmitter, FSCV and amperometric techniques are limited to detect relative changes in neurotransmitters concentrations.

Amperometry

Fixed-potential amperometry, one of the simpler types of in vivo electrochemistry, involves the measurement of current at a fixed constant potential. The current is monitored continuously; therefore, measurements can occur as frequently as ≤ 1 msec. Furthermore, amperometry has superb specificity when enzymes are applied to the recording surface to produce an electrochemically active reporter molecule, such as H_2O_2, to allow measurements of molecules that are not naturally electrochemically active, such as glutamate. Currently, commercially available biosensors, not for use in humans, are sensitive to adenosine and glutamate (from both Sarissa Biomedical Ltd. and Pinnacle Technology, Inc.).[3] As seen in Fig. 1, platinum recording electrodes that are coated with glutamate oxidase, an enzyme that reacts with glutamate to ultimately produce H_2O_2, are capable of amperometrically

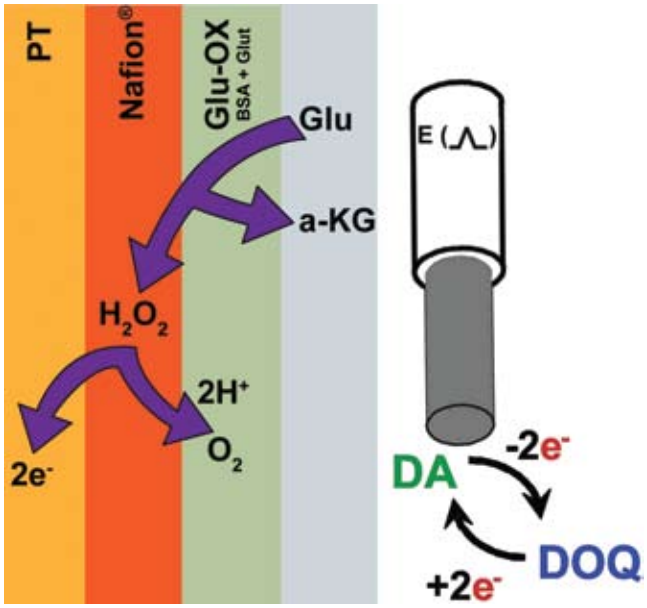

Fig. 1. Examples of electrochemical techniques. **Left:** Amperometry is performed by applying a constant potential to the biosensor, which, in this setup, is a platinum wire (PT). When used to measure glutamate as in the example, an enzymatic layer is applied to confer specificity. Here, local glutamate comes in contact with an immobilized glutamate oxidase (Glu-Ox) layer (fixed to surface with bovine serum albumin [BSA] and glutaraldehyde [glut]). Interfering molecules are blocked from the platinum wire by Nafion. Glutamate is enzymatically converted to H_2O_2, which breaks down to 2 hydrogen molecules and oxygen releasing 2 electrons (e−) that increase the current recorded in the platinum wire. **Right:** Fast-scan cyclic voltammetry is performed by applying a changing potential over a short period of time. For dopamine (DA) in this example, 10 times a second a potential is applied to a carbon fiber from –0.4 to +1.3 V and back to –0.4 V. During this cycle, dopamine is converted to DOQ releasing 2 electrons. The 2 electrons are returned (reduced) on the return to baseline potential. These electron transfers cause perturbations in the raw voltammogram. Where these perturbations occur is unique to the analyte and allows us to target specific neurotransmitters of interest. a-KG = α– ketoglutarate; E(^) = the voltage applied is varied.

measuring glutamate concentration changes. In addition, for oxidizable neurotransmitters such as dopamine, these amperometric techniques when coupled to carbon fiber microelectrodes can measure analytes of interest on rapid time scales (1–1000 msec), allowing for uptake and release kinetics of neurotransmitters to be easily studied. Thus, amperometry may be superior to microdialysis as a technique for monitoring neurochemicals in DBS.

Fast-Scan Cyclic Voltammetry

Like all voltammetry, a potential is applied to the electrode, and the current is measured. However, in contrast to amperometry where the potential is fixed, the potential is linearly changed with respect to time in FSCV. This novel detection scheme generates a voltammogram (that is, a plot of measured current versus applied potential) that serves as a chemical signature to identify an analyte. For example, dopamine oxidation occurs during a positive scan at approximately +0.6 V, and reduction of the electro-formed DOQ back to dopamine occurs during

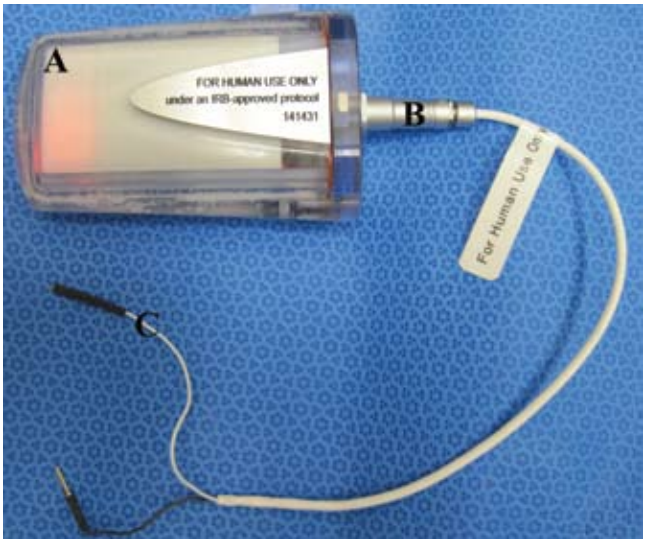

Fig. 2. Photograph of the intraoperative human use WINCS transmitter and device housing *(A)*, hermetically sealed and capable of ethylene oxide sterilization. Note that each device after rigorous internal engineer testing is approved for human use only as noted on the main housing. The cable connection to the device is a single-orientation connection *(B)*, as are the pin connections to the implantable biosensor *(C)*. This ensures that connection setup can only be done in one manner for correct use.

the negative scan at −0.2 V (Fig. 1). These electrically induced changes create 2 distinct peaks of current out of proportion to the background scan. The FSCV can detect other neurotransmitters such as serotonin, adenosine, norepinephrine, epinephrine, histamine, and nitric oxide.[8,31,45] Furthermore, nonneurotransmitter phenomena such as pH shift or oxygen concentration can be measured.[5,6,8]

Wireless Electrochemistry

Based on previous instrumentation by Garris et al., our laboratory has developed WINCS (patent pending by Mayo Clinic) designed to perform human FSCV and amperometry.[3,8,24,29] The device in its current form is pictured in Fig. 2. The WINCS is composed of front-end analog circuitry for FSCV/amperometry, a microprocessor, and a Bluetooth transmitter that is battery powered.[3,8,29] The device works either with amperometric biosensors, or may be used with a carbon fiber microelectrode to perform FSCV as detailed above. These sensors require a reference electrode, consisting of silver/silver chloride in animal experiments (in humans, the reference electrode is made of stainless steel or carbon rather than silver/silver chloride). This device is controlled by a base station computer in a Windows-XP environment and custom software controlling the operational parameters of WINCS. Wireless data acquisition may occur at a rate up to 100 kilosamples per second. This system is described in detail in previous publications and has been shown to be equivalent to wired devices that would be incapable of human use.[3,8,29] The WINCS-driven electrochemistry is summarized in Table 1.

Adenosine

Adenosine has been shown to be an important neurotransmitter in tremor, as well as epilepsy.[4,9,10] Indeed, Bekar et al.,[4] using adenosine amperometric electrodes, demonstrated that adenosine may be crucial for DBS effects for abolishing tremor in rat models. Amperometric detection of adenosine utilizes a multiple enzyme–linked biosensor consisting of adenosine deaminase, nucleoside phosphorylase, and xanthine oxidase to confer specificity to adenosine. This multienzymatic reaction results in a 2-second delay of adenosine detection.[33] On this biosensor, adenosine deaminase converts adenosine to inosine, which is subsequently converted to hypoxanthine by nucleoside phosphorylase, and ultimately, xanthine oxidase oxidizes hypoxanthine to xanthine then uric acid which results in the production of H_2O_2.[33] Again, H_2O_2 generates a signal by oxidation and release of 2 electrons detected at the platinum wire.[33] The WINCS has shown the ability to detect adenosine in in vitro experiments as well as in vivo rat experiments where adenosine is evoked by stimulation of the ventrolateral thalamus by amperometry.[2,3] Recently, Swamy and Venton[45] described FSCV as a viable technique to measure adenosine, establishing it as the fastest technique to monitor adenosine. The subtracted voltammogram and pseudocolor plot are distinguished from dopamine in Fig. 3. Our laboratory has used this technique to demonstrate the ability to detect, within the physiological range, in vitro adenosine alone, as well as in the presence of supraphysiological dopamine.[41] Moreover, it has been demonstrated that rat ventral tegmental/substantia nigra stimulation evoked release of adenosine in a time-locked manner in the caudate.[41] Finally, FSCV has been proven as an effective method of detecting adenosine release during microthalamotomy in rats.[16]

TABLE 1: Summary of WINCS FSCV and amperometry detection parameters*

Neurochemical	Mode	Wave	Parameters (V)	Scan Rate (V/sec)	Oxidation Peaks (V)	Reduction Peaks (V)
dopamine	FSCV	V shape	−0.4→+1.3→−0.4	400	+0.6	−0.2
dopamine	AMP		+0.8			
adenosine	FSCV	V shape	−0.4→+1.5→−0.4	400	+1.4, +1.0, +0.5	
adenosine	AMP		+0.5→0.6			
serotonin	FSCV	N shape	+0.2→+1.0→−0.1→+0.2	1000	+0.8	0
glutamate	AMP		+0.5→0.6			

* AMP = amperometry; sec = second.

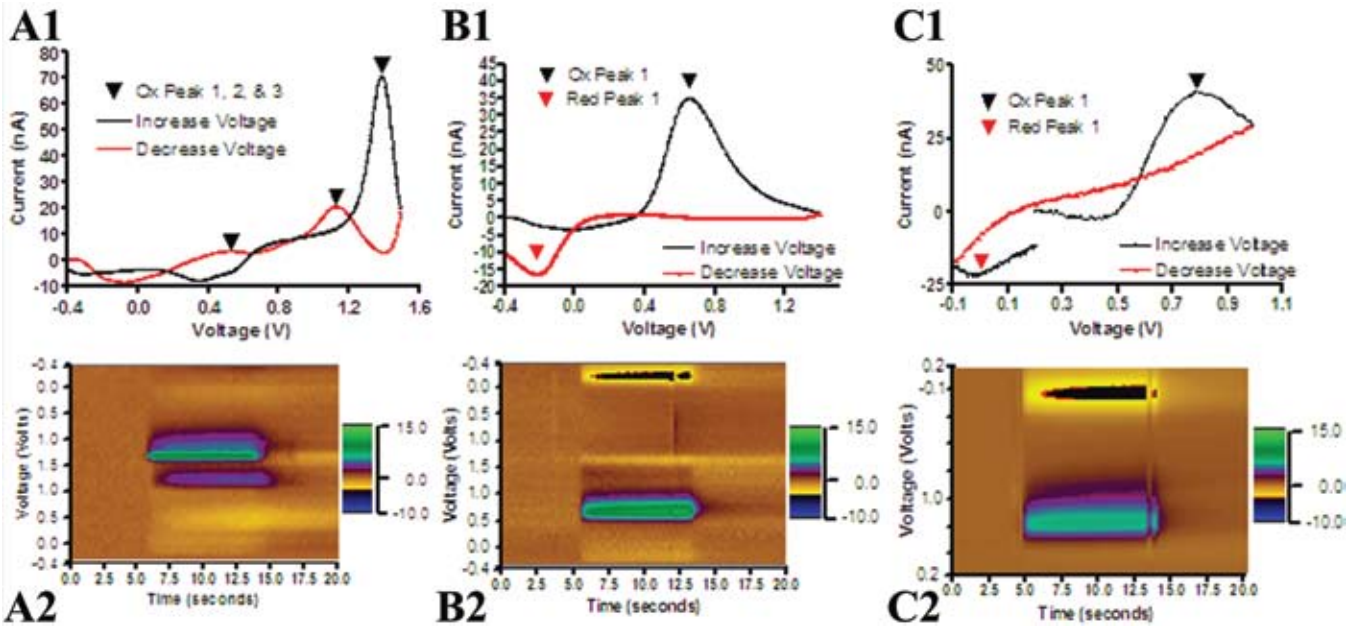

Fig. 3. Typical subtracted voltammograms **(A1, B1, and C1)** and pseudocolor plots **(A2, B2, and C2)**. Each neurotransmitter has a distinct voltammogram when the FSCV parameters are set to detect the respective analyte.

Dopamine

Dopamine is essential in the pathophysiology of Parkinson disease. Clinically, STN DBS may reduce or perhaps eliminate the need for oral dopamine and is most effective in patients with Parkinson disease who respond well to levodopa, suggesting that effective DBS requires endogenous dopamine production.[11,35] Moreover, DBS may induce dyskinesias, suggesting that there is excess dopamine present.[32] Clinical observations such as these imply that an increase in dopamine may account for the therapeutic efficacy of STN DBS in patients with Parkinson disease. Indeed, amperometric recordings in the caudate nucleus during STN stimulation has been demonstrated to release dopamine in the rat.[31] However, to date, human recordings of dopamine have not been obtained.

Due to the relative ease at which dopamine is oxidized to DOQ, dopamine is the ideal neurotransmitter to study with FSCV.[5] The typical appearance of dopamine in FSCV is seen in Fig. 3. A triangular waveform is typically applied from −0.4 V to at least +1.0 but up to +1.5 V and then back to −0.4 V (Fig. 4).[8,29,41,42] The WINCS has been shown to reliably detect dopamine in both in vitro and in vivo (rat) models in the context of interferents such as norepinephrine and serotonin.[8] Moreover, dopamine is detected in the caudate of laboratory animals such as the rat, mouse, and pig in response to stimulation of the medial forebrain bundle, ventral tegmental area, and substantia nigra.[3,8,41] Furthermore, WINCS is capable of measuring dopamine with a carbon fiber electrode by using fixed potential amperometry.[3] Although this technique is not specific, drug manipulations may be used to verify dopamine as the source of the amperometric signal.[3] Therefore, the use of WINCS to measure dopamine in humans undergoing STN DBS may prove to be valuable in proving or disproving the dopamine release hypothesis for therapeutic efficacy in patients with Parkinson disease.

Serotonin

Serotonin is thought to be an important neurotransmitter in depression due to the effectiveness of serotonin reuptake inhibitor therapy for depression.[36] Recently, DBS therapies have been approved for treatment-resistant depression.[34] Although it is uncertain if DBS contributes to local or remote serotonin release, we have demonstrated WINCS FSCV parameters that allow detection of a physiological level of serotonin in real time. Initially, FSCV parameters for serotonin were described using a V-shaped scanning protocol as is done with dopamine and adenosine; however, it was quickly realized that detection in this manner was inaccurate due to rapid and irreversible accumulation of oxidation byproducts at the carbon fiber electrode.[25–27] To counteract this, an N-shaped waveform, having a resting potential of +0.2 V, scanning to +1.0 V, then to −0.1 V and finishing at +0.2 V at a rate of 1000 V/second, was developed to measure serotonin.[12,13] We have shown, using WINCS, that bipolar electrical stimulation of the dorsal raphe nucleus in rats results in local efflux of serotonin detectable with this technique.[25] Future applications of WINCS to measure serotonin in humans undergoing neurosurgery for depression may prove to be valuable in assessing serotonin neuromodulation with DBS.

Glutamate

Glutamate is an excitatory neurotransmitter most commonly associated with epilepsy; however, its release may be important to essential tremor and other movement disorders.[2,31] Fast-scan cyclic voltammetry is not capable of detecting glutamate because glutamate is not electrochemically active; however, fixed potential amperometry is relatively straightforward for this neurochemical as

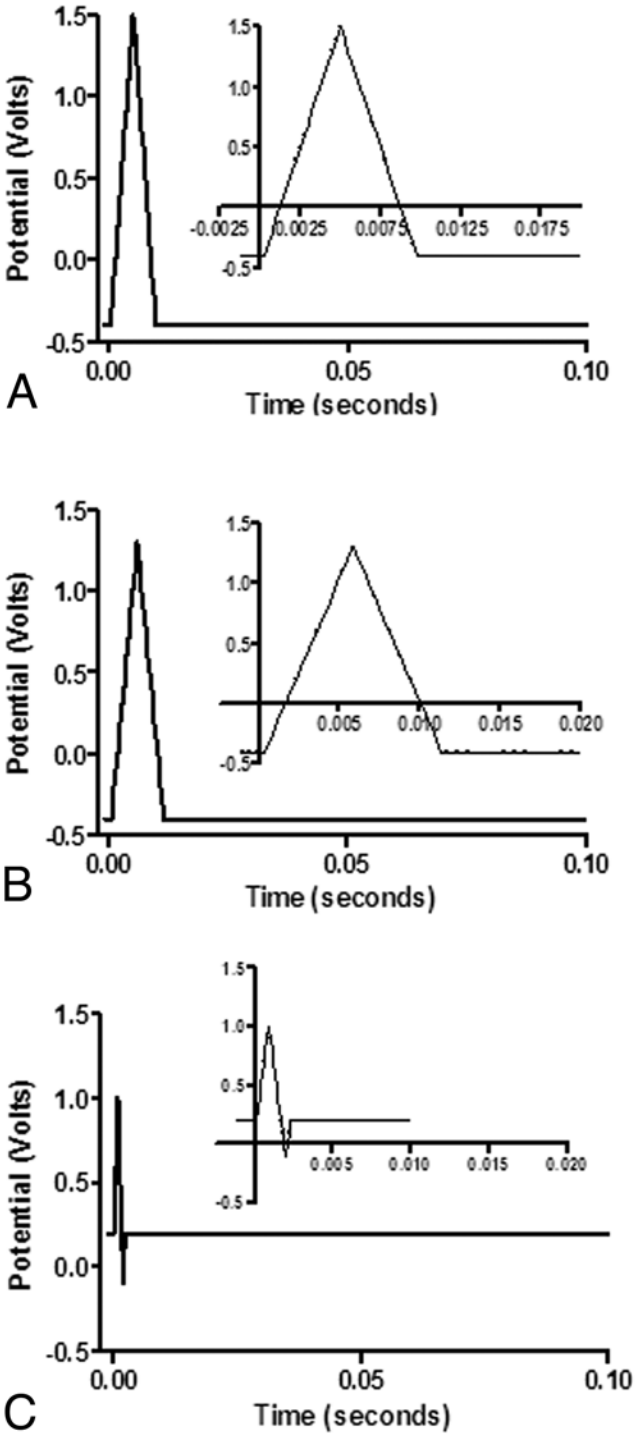

Fig. 4. Applied FSCV waveforms for adenosine (400 V/second) **(A)**, dopamine (400 V/second) **(B)**, and serotonin (1000 V/second) **(C)**. Each waveform is applied 10 times a second, which is represented in the main graphic depiction (100 msec). **Insets** are the waveform seen relative to 20 msec.

it requires only 1 enzyme to couple this for bioelectric detection. Our laboratory has shown that local thalamic stimulation results in glutamate release in rats.[2] This stimulated release is dependent on intensity, time, and frequency.[2] Furthermore, implantation of electrodes into the thalamus of the rat resulted in transient rise in adenosine and glutamate level by mechanical stimulation; this again may be involved in the microthalamotomy effect experienced by some patients after DBS surgery.[17]

Large Animal Model of DBS Surgery in Pigs

Deep brain stimulation has been demonstrated to be an effective therapy for medically intractable Parkinson disease, dystonia, and essential tremor.[46] Furthermore, there is accumulating evidence that DBS is effective for a plethora of conditions including cluster headache, epilepsy, depression, and Tourette syndrome. Using a large animal model (swine) of human DBS surgery, our laboratory is currently studying the mechanism of DBS. In this model, swine were placed in a custom-made stereotactic frame, and MR imaging was performed for targeting.[42] After imaging, STN targets were confirmed using electrophysiological mapping of the STN followed by placement of a Medtronic 3389 DBS electrode.[42] Subsequently, a carbon fiber microelectrode was placed into the caudate that was capable of detecting—by FSCV driven by WINCS—evoked dopamine in response to varying stimulation parameters.[42] In response to stimulation, there was a consistently delayed increase in dopamine relative concentration in the caudate which was dependent on stimulus intensity, duration, and frequency (see Fig. 5).[42] Interestingly, compared with similar work in rat studies, stimulation parameters were more consistent with human parameters, demonstrating the value of having a large animal model for DBS research.[42] This experimental system suggests that we may be capable of detecting dopamine changes elicited remotely by DBS and use this information for modulation and stimulation feedback. Currently, this experimental setup is being evaluated in humans by our group with the approval of the institutional review board.

Future Directions

Deep brain stimulation likely evokes changes in neural activity and neurochemical transmission in interconnected structures within the neural network, which ultimately underlie clinical benefit. Nevertheless, our understanding of these electrochemical effects remains far from complete, in large part because of the technical difficulties in measurement modalities for global assessment of neural activity and chemical-specific sensing. There is a critical need to develop and integrate novel investigative approaches with animal models and in humans to bring new insights on the mechanisms of this powerful neurosurgical treatment. The WINCS has shown promise and versatility. Furthermore, WINCS has proven to be a highly versatile instrument that allows near real-time (subsecond) detection of neurochemicals important to DBS research. In the future, the neurochemical changes detected using WINCS may be important as surrogate markers for proper DBS placement as well as the sensor component for a "smart" DBS system with electrochemical feedback that allows automatic modulation of stimulation parameters. Current work is underway to establish WINCS use in humans.

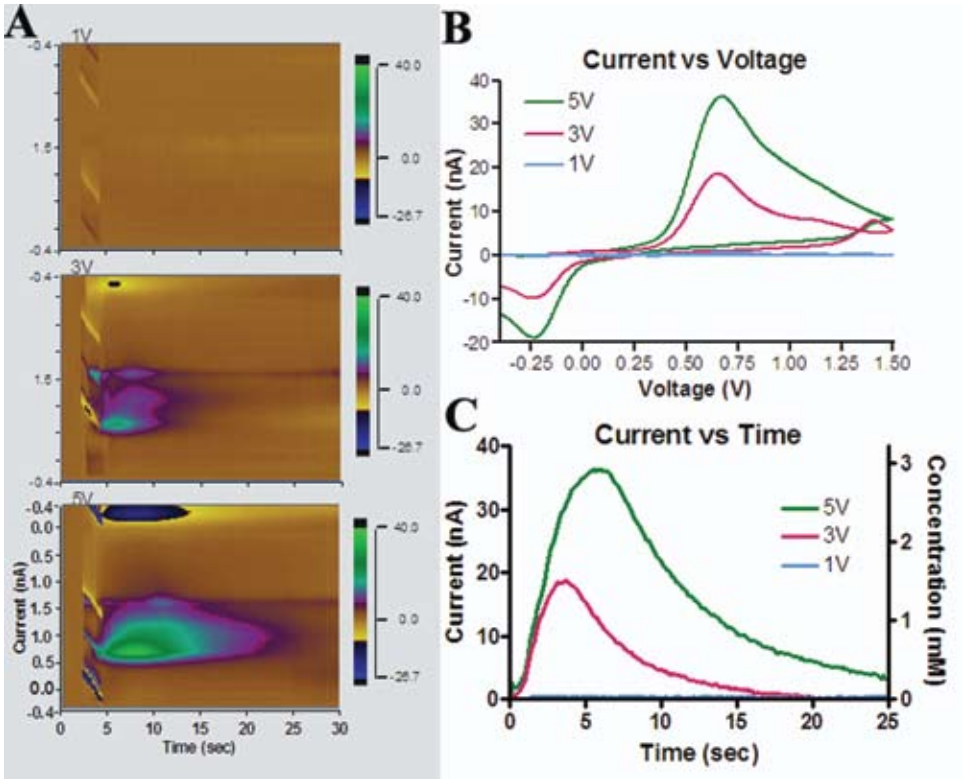

Fig. 5. **A:** Fast-scan cyclic voltammetry dopamine measurements obtained in an anesthetized pig. The dopamine signal is shown on a pseudocolor plot, recorded at a carbon fiber microelectrode implanted in the caudate. This dopamine release was seen in response to electrical stimulation of the subthalamic nucleus (at various voltage strengths (1, 3, and 5 V) from a hand-held Medtronic stimulator (held constant 120 Hz, 2-second stimulation, 0.5-msec pulse width). The varying color intensities represent the voltage. Immediately after stimulation (artifact is the *rectangular signal* at 3–5 seconds), increasing levels of evoked dopamine (*green oval* seen from 5 to 10 seconds) are seem with increasing strengths of stimulation at 1, 3, and then 5 V. There is no visible release with 1 V. **B:** This signal is identified as dopamine by the characteristic shape in the cyclic voltammogram (increasing voltage stimulations increase the relative amount of dopamine released in response to stimulation). **C:** Current versus time plot showing the increasing release of relative dopamine with increasing stimulation voltages.

Disclosure

This work was supported by NIH (Grant No. K08 NS 52232 award to K.H.L.) and the Mayo Foundation (2008–2010 Research Early Career Development Award for Clinician Scientists award to K.H.L.). This device, WINCS, has been developed and is under patent submission by K.H.L. and Mayo Clinic.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lee, Van Gompel, Chang, Goerss, Kimble, Bennet. Acquisition of data: Van Gompel, Chang, Goerss, Kim. Analysis and interpretation of data: Van Gompel, Kim. Drafting the article: Lee, Van Gompel, Chang, Goerss. Critically revising the article: Lee, Van Gompel, Chang, Goerss. Reviewed final version of the manuscript and approved it for submission: Lee, Van Gompel, Chang, Kim, Bennet. Administrative/technical/material support: Lee, Van Gompel, Chang, Kimble, Bennet. Study supervision: Lee. Other: Kimble (device development), Bennet (device development).

Acknowledgments

The authors would like to thank all the team members involved with the development of WINCS. Specifically Drs. Paul Garris, Charles Blaha, Pedram Mohseni, Susannah Tye, and John Bledsoe. Further, critical members of the engineering team: April Horne, Dave Johnson, Ken Kressin, Justin Robinson, Andrew Wenger, Bruce Winter, Sid Whitlock, and Shaun Herring.

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Manuscript submitted April 15, 2010.
Accepted May 14, 2010.
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Neurosurg Focus 29 (2):E7, 2010

Disrupting abnormal electrical activity with deep brain stimulation: is epilepsy the next frontier?

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Given the tremendous success of deep brain stimulation (DBS) for the treatment of movement and neuropsychiatric disorders, clinicians have begun to open up to the possible use of electrical stimulation for the treatment of patients with uncontrolled seizures. This process has resulted in the discovery of a wide array of DBS targets, including the cerebellum, hypothalamus, hippocampus, basal ganglia, and various thalamic nuclei. Despite the ambiguity of the mechanism of action and the unknowns surrounding potentially ideal stimulation settings, several recent trials have empirically demonstrated reasonable efficacy in selected cases of medication-refractory seizures. These exciting results have fueled a number of studies aimed at firmly establishing DBS as an effective treatment for selected cases of intractable epilepsy, and many companies are aiming at Food and Drug Administration approval. We endeavor to review the studies in the context of the various DBS targets and their relevant circuitry for epilepsy. Based on the unfolding research, DBS has the potential to play an important role in treating refractory epilepsy. The challenge, as in movement disorders, is to assemble interdisciplinary teams to screen, implant, and follow patients, and to clarify patient selection. The future will undoubtedly be filled with optimization of targets and stimulation parameters and the development of best practices. With tailored therapeutic approaches, epilepsy patients have the potential to improve with DBS. *(DOI: 10.3171/2010.4.FOCUS10104)*

Key Words • **deep brain stimulation** • **epilepsy** • **seizure**

Epilepsy affects approximately 50 million people worldwide.[85] Despite active AED development, up to 20% of patients suffer from poor seizure control even with optimal medical therapy.[64] A subset of these patients will be candidates for ATL, which in reported series has resulted in 80%–90% seizure freedom.[74] For the remaining patients, alternative therapies such as VNS,[20] lesionectomy, and multiple subpial transections have proven limited in efficacy. Given the tremendous success of DBS for the treatment of movement and neuropsychiatric disorders,[53,62] clinicians have begun to explore the potential of electrical stimulation for the treatment of a select group of patients with medication-refractory epilepsy.

Abbreviations used in this paper: AED = antiepileptic drug; AN = anterior nucleus; ATL = anterior temporal lobectomy; CMN = centromedian nucleus; CN = caudate nucleus; DBS = deep brain stimulation; MB = mamillary body; MMT = mamillothalamic tract; MTL = mesial temporal lobe; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; VNS = vagal nerve stimulation.

These investigations are especially exciting as they have the potential to further elucidate understanding of brain circuitry as well as propagation and abortion of seizures.[40] Empirical trials have resulted in the discovery of unlikely DBS targets, including the cerebellum[17] and the thalamic nuclei.[28] Additionally, DBS for epilepsy has reinvigorated interest in the possible positive neuronal changes that may occur secondary to chronic stimulation, and that may have benefits even when stimulation has ceased (for example, when batteries of devices burn out or closed-loop devices are employed).[34] This idea of neuronal-level changes is based in part on the phenomenon of secondary epileptogenesis in patients with long-term, poorly controlled seizures. Deep brain stimulation may be used to address the challenge of repeated ictal insults initiated from a single site eventually inducing remote and independent ictal activity derived from other structures.[8,34,40,47,61]

Despite recent FDA hearings for approval of DBS for epilepsy, DBS remains investigational. The mechanisms by which DBS addresses seizures—or even movement

disorders—are not completely understood. Some theorize that electrical stimulation results in the release of inhibitory neurotransmitters.[22] Others posit that stimulation inactivates neurons via depolarization blockade,[59] although most movement disorders experts agree this is probably not the mechanism of action. The benefits of DBS are likely the result of synaptic-level, neurochemical and neurophysiological changes.[42] Recently it has been discovered that DBS may actually inhibit cells close to an electrical field and excite those farther from it.[43,44,81] Stimulation of deep nuclei with broad-ranging connections to cortical structures makes DBS treatment especially attractive for epilepsy patients with multiple foci of seizure onset.

The timing and targets of electrical stimulation delivery are also an area of active research. Chronic stimulation with an "open-loop" system has been challenged by stimulation only in response to a cue (seizure) referred to as "closed-loop" treatment. Multiple targets have been evaluated for DBS in epilepsy with variable results. One of the reasons that studies have reported variable results with the same DBS target may be that certain seizure types will respond differently to stimulation of a particular target. Despite all the uncertainty, several trials have empirically demonstrated the efficacy of DBS for seizures, even in patients in whom other therapies have failed. These exciting results have fueled a number of studies designed to firmly establish DBS as an effective treatment for intractable epilepsy. In the following sections, these studies will be reviewed in the context of the various DBS targets for epilepsy and the relevant circuitry involved.

Potential DBS Targets

Most targets for electrical stimulation are deep nuclei with broad connections. These connections allow stimulation of the deep nucleus to modulate areas of cortex that produce seizure activity.[9,32] In contrast, a handful of trials have tested stimulating the seizure foci directly, such as the hippocampal and hypothalamic hamartoma trials. Both indirect and direct targets will be reviewed here.

Hypothalamus

The posterior hypothalamus, specifically the mamillary body (MB), has been implicated in seizure propagation possibly due to its connection with the anterior nucleus of the thalamus via the mamillothalamic tract (MTT) (and possibly its association with the circuit of Papez[3]). In guinea pigs, bilateral lesions of the MB and MTT resulted in a significant decrease in the presence and lethality of seizures induced by the drug pentylenetetrazol.[48,49] These studies led to a pilot study in 3 patients who had depth electrodes implanted bilaterally in the MB and MTT. One of these patients was found to have ictal activity without scalp electroencephalographic changes, giving credibility to the notion that subcortical structures can be responsible for ictal activity.[73] Subsequently, MB/MTT DBS was evaluated in patients with seizures secondary to hypothalamic hamartomas.[36] Given the risks associated with tumor resection, 2 patients underwent placement of MB/MTT DBS ipsilateral to the tumor. Both had significant reductions in seizure frequency, with 1 patient reporting seizure-freedom at the time of publication.[36] Although these results are compelling, hypothalamic stimulation will require further study to fully understand its utility for epilepsy, and selection criteria and approaches will need to be defined.

Hippocampus

The hippocampus has been a rational target for epilepsy treatment given the prevalence of mesial temporal lobe (MTL) epilepsy. Select patients with MTL epilepsy who do not respond to medical therapy are considered candidates for amygdalohippocampectomy. Multiple groups have reported excellent results (significant seizure reduction in 80%–90% of patients)[74] with this procedure. On the other hand, those with bilateral onset of seizures or with a unilateral focus that spreads to the dominant hemisphere have not traditionally been surgical candidates due to the potential risk to language and memory areas associated with bilateral resections or large dominant lobe resections.[12,67] With these patients in mind, Velasco et al.[75] studied hippocampal stimulation in 2 groups of patients. In the first group, 2 patients had placement of bilateral depth electrodes and 8 patients had unilateral surface electrode grids placed. These patients underwent hippocampal stimulation at 130 Hz for 2–3 weeks and subsequently underwent an ATL. The second group was made up of 3 patients who underwent placement of unilateral or bilateral electrodes with a pulse generator for stimulation for at least 3–4 months. The investigators found that hippocampal stimulation abolished clinical seizures and significantly decreased the number of interictal spikes in both groups studied. They did not observe any histopathological changes in the patients who underwent subsequent resection. Additionally, they found that stimulation resulted in SPECT hypoperfusion of the hippocampal region, leading to the hypothesis that stimulation resulted in neuronal inhibition.[75]

In 2007, after reporting good results in a pilot study involving 3 patients,[82] Boon et al.[10] reported on 10 patients with either unilateral or bilateral seizure onset of MTL epilepsy treated with DBS. The DBS leads were placed bilaterally with electrodes in the amygdala and hippocampus. Seven of the patients (70%) had at least a 50% reduction in seizures (one patient was seizure free).[10] Two patients had seizure frequency reduction of 30%–49% and one patient was a nonresponder. Only one patient experienced an adverse event; asymptomatic intracerebral hemorrhage was discovered on imaging to be tracking along the DBS lead trajectory. These patients were compared with 2 patients who underwent amygdalohippocampectomy who were seizure free for more than 1 year.

Patient outcomes, however, were not as robust in the only double-blind trial.[70] In this study, 4 patients with MTL epilepsy underwent placement of unilateral DBS electrodes in the hippocampus. Patients had continuous stimulation at 190 Hz and were randomized to 3 treatment pairs each with an "on" and an "off" period under double-blinded conditions. During the "on" period, patients experienced a median reduction in seizure frequency of 15%, but this failed to reach statistical significance. The patients did have continuous adjustment of AEDs during the study, and given the seizure-frequency improvement during the "off" periods, the patients may have benefited from lead

placement alone (lesional effect). A subsequent trial of bilateral hippocampal stimulation (in 2 patients) revealed no decrease in seizure load after implantation and prior to initiation of stimulation, making lesioning a less likely explanation in this cohort.[45] Importantly, none of the patients had changes in memory, cognition, or emotion.

The hippocampus continues to be evaluated as a direct target for treatment of MTL epilepsy. With subdural or DBS electrodes, the hippocampus is a viable target structure, especially for patients who are otherwise not surgical candidates for epilepsy treatment such as those with bilateral temporal lobe foci or large dominant lobe foci.

Cerebellum

After the discovery of the importance of cerebellar Purkinje cells in the generation of widespread inhibitory discharges, Cooper et al.[16] described cerebellar stimulation as a potential treatment for epilepsy. Building on older animal studies showing that the inhibitory influence of the cerebellum may be important in terminating seizures,[15,23,63] Cooper et al.[16] published the first description of noncortical stimulation for seizures, describing 7 patients who underwent placement of cerebellar electrodes for intractable epilepsy. Six patients had significant clinical improvement, and the authors reported only one complication (posterior fossa hematoma requiring evacuation). This same group subsequently described cerebellar stimulation in 15 epilepsy patients (with psychomotor, generalized tonic-clonic, or myoclonic seizures) in 1976.[17] Ten of the 15 patients had clinical benefit (some with complete cessation of seizures), although both studies used suboptimal outcome measures.[17] One patient who did not have seizure control died at home from a nocturnal seizure. The details of stimulation were variable, but based on their experience, the authors recommended anterior cerebellum stimulation with a frequency of 10 Hz. Other retrospective studies have also demonstrated improvement of epilepsy with high-frequency stimulation.[14] Stimulation of the cerebellum is hypothesized to have its effect by action on the output to the ventrolateral nucleus of the thalamus and subsequently the exertion of decreased excitatory output to the cortex.[5]

These promising results were tempered by subsequent reports that failed to reveal similar efficacy. In a follow-up analysis of 5 cases involving patients who underwent cerebellar stimulation using 10 Hz for 10-minute periods, no difference in seizure frequency was found.[72] Patients continued their AED treatment during the study and were monitored in the hospital for 4- to 6-week periods over 15–21 months.[72] Similarly, another double-blind analysis of results in 12 epilepsy patients used 10 Hz of cerebellar continuous stimulation for 2 months, then 2 months of contingent stimulation followed by 2 months of no stimulation.[86] Eight of the patients experienced some sort of morbidity (infection or CSF leak), and no difference in seizure frequency was observed.[86] Despite these findings, 11 patients felt the trial had helped them, emphasizing the problems with using patient reports as an outcome variable instead of a validated, sensitive instrument.

In the largest uncontrolled study, 27 of 32 patients, described as having spastic or epileptic seizures, were treated with cerebellar stimulation and were evaluated for long-term follow-up.[18,19] Overall, 85% (23 of 27) had some benefit from stimulation (12 had benefit despite nonfunctioning stimulators due to battery life termination, suggesting a potential lesional or long-term effect).[18] In a small double-blind pilot study, significant reductions in seizure frequency were described in 3 patients with active cerebellar stimulators compared with 2 patients with cerebellar stimulators that were placed in the off position.[76] Given the mixed results from a few existing trials and the inclusion of patients with multiple types of epilepsy in these trials, a well-powered randomized controlled trial with careful patient selection will be necessary to establish a consensus about the utility of cerebellar stimulation for seizure control.

Subthalamic Nucleus

The STN is one of the most common Parkinson disease DBS targets.[5,83] This nucleus, which is located atop the substantia nigra pars reticulata (SNr), lateral to the red nucleus and just below the zona incerta, plays a major role in the direct and indirect motor pathways implicated in the pathogenesis of Parkinson disease.[6,29] The STN possesses sensorimotor, limbic and associative areas and connections. While the sensorimotor areas are located primarily in the dorsolateral region, the limbic region is more medial and the associative area more dorsomedial.[11,68] These areas may provide reasonable individual targets for various symptoms and diseases.

The first evidence that the STN plays a role in epilepsy came from animal studies. Injection of an N-methyl-D-aspartic acid (NMDA) antagonist into the SNr suppressed seizures in a model of genetic absence epilepsy in rats.[21] Subsequently, based on anatomical and clinical evidence of the intimate relationship between the SNr and STN, it was shown that high-frequency stimulation of the STN was able to suppress seizures in the rat model.[80] In the earliest report of using STN DBS for human epilepsy, Benabid et al.[7] described 3 cases of bilateral STN DBS in which there was a decrease in seizure frequency of 50%–80%. One patient had an infection, and removal of the infected electrode resulted in an increased seizure frequency. Interestingly, the frequency did not revert to preimplantation levels.

Another study by Lee et al.[39] compared 3 patients who were implanted with STN DBS to 3 patients receiving implants in the anterior nucleus (AN) of the thalamus. The AN stimulation group had greater suppression of seizure activity (75% compared with 50%). In the STN DBS group, there was a substantial increase in regional cerebral blood flow in the frontal zones presumed to be related to epileptogenesis, and the authors suggested this as a mechanism of seizure reduction.[65] These findings suggest that select patients with frontal foci and/or spread of epileptic activity may be best treated with STN DBS, though more controlled studies must be done.

Centromedian Thalamic Nucleus

The CMN is an important structure in the reticulocortical system, and it plays a vital role in wakefulness and consciousness.[50] It also has potentially important roles as a motor and limbic relay station. Early animal

studies implicated the CMN in cortical excitability in generalized seizures.[33,46] Anatomical as well as neurophysiological data have established the CMN as a "gatekeeper" in rhythm-generating activities,[40] and therefore as a potential target for the treatment of seizures. Empirically, chronic electrical stimulation of the CMN was first explored by Velasco and colleagues in 1987.[78] Five patients with refractory, primary generalized, or multifocal seizures underwent placement of electrodes in the CMN bilaterally. They were treated with pulses in trains of 1 minute every 5 minutes alternating right and left for 2 hours per day. After 3 months of treatment, the patients reported an 80%–100% decrease in generalized tonic-clonic seizures and a 60%–100% decrease in partial complex seizures. Interestingly, in this report the authors also mention 2 patients who were treated with red nuclei stimulation with no clinical benefit.[78] Building on these impressive results, the same group later published the largest series of CMN stimulation, reporting efficacy for generalized tonic-clonic seizures and atypical absences, but not for partial seizures.[77,79] However, these data were not quantified or evaluated statistically, and the outcome measures and methodology have come under scrutiny.

The only controlled trial (double-blind, crossover) of CMN stimulation was published by Fisher et al.[25] Seven patients had surgery for placement of bilateral CMN stimulators and underwent 3-month periods of "on" or "off" stimulation. Stimulation was delivered as 90-μsec pulses at a rate of 65 Hz, 1 minute of each 5 minutes for 2 hours/day. Generalized tonic-clonic seizures were reduced by 30% when the stimulators were on as compared with 8% when the stimulators were off. Nevertheless, given the limited power of the study, this difference did not reach statistical significance. The authors did show, however, that seizure reduction was more marked when stimulators were on all day versus only 2 hours per day.[25]

Electrical stimulation of the CMN has produced some exciting results in the treatment of seizures, especially those of a generalized tonic-clonic type.[14] Nonetheless, anecdotal experience has shown variable results with some adverse events reported (nystagmus, hallucinations, and anorexia),[2] and the future of thalamic CMN stimulation for epilepsy remains unclear.

Anterior Nucleus of the Thalamus

Similar to the CMN, the AN is a viable target for DBS due to its gate-keeping activity in seizure propagation.[4] It has wide-ranging projections to multiple structures, including the cingulate cortex, amygdala, hippocampus, orbitofrontal cortex, and CN, and receives input from the mamillary bodies. Uniquely, the AN of the thalamus is not under the control of the reticular thalamic nuclei.[51] Stimulation of the AN has had mixed results in animal models of epilepsy, with some investigators reporting benefit[30] and others reporting increased seizure frequency.[38] Targeting of the AN is more practical compared with targeting of other subcortical sites owing to the fact that the AN is large and well defined for surgical approaches by stereotaxy.[40]

Preliminary data suggest that AN DBS has more potential than some of the other targets for the treatment of epilepsy. Upton et al.[71] first reported a decrease in seizure frequency in 4 of 6 patients treated with chronic bilateral AN stimulation at 60–70 Hz. Subsequently, a study of 3 patients who were treated with bilateral AN stimulation found a 75.4% decrease in seizure frequency.[39] Lozano's group in Toronto published another study of 5 patients with a wide range of epilepsy types (generalized tonic-clonic, atonic, complex partial, and partial motor), and demonstrated a mean seizure frequency reduction of 53.8% ($p < 0.05$ compared with preoperative seizure frequency) with bilateral intermittent AN stimulation.[31] The improvement in seizure frequency was seen after implantation and before stimulation—meaning no additional benefit was achieved with stimulation, suggesting a strong possibility of a lesional effect. Similar seizure reduction results were reported in other small studies with minor or acceptable complication rates.[35,41,57]

These results finally culminated in a multicenter, randomized trial (SANTE) of 110 patients to attempt to demonstrate the effectiveness of bilateral stimulation of the AN.[24] This trial was double-blinded, and the patients in both study arms received electrode implantation. In those in the control arm the electrode was not activated for 3 months while in those in the experimental arm it was activated immediately. During stimulation, patients received 5-V, 90-μsec pulses for 1 minute alternating with no stimulation for 5 minutes. The patients in the experimental arm had a 29% greater reduction in seizures than the control group ($p = 0.002$).[24] The median seizure frequency decrease was 14.5% in the control group and 40.5% in the experimental group. No significant complications resulted from the procedure. Furthermore, the benefits from stimulation lasted for the duration of the study with a 56% median percentage reduction in seizure frequency at 2 years. Six patients were seizure free for at least 6 months at 2-year follow-up. However, the authors noted that patients with seizure foci in the frontal, parietal, or occipital lobes did not have any significant improvement with AN stimulation. Only the patients with seizures of temporal lobe origin had a significant decrease in seizure frequency with AN stimulation. Nonetheless, these results make AN the most well-established target for DBS in the treatment of epilepsy to date, and these data will help the field to establish patient selection criteria (for example, seizures of hippocampal origin may be more amenable to neuromodulation).

Caudate Nucleus

Although the CN is not as well studied as the thalamic nuclei, it may be the only deep target site where low-frequency electrical stimulation is efficacious in the treatment of epilepsy. However, there remains a paucity of information from which to draw this conclusion. Chkhenkeli et al.[13] achieved improvement in bilateral epileptic discharges with low-frequency (4–8 Hz) unilateral CN stimulation in 57 patients. In contrast, high-frequency stimulation resulted in increased epileptic activity in the ispilateral hemisphere.[14] This phenomenon has been hypothesized to be a result of low-frequency stimulation causing cortical hyperpolarization and resultant clinical benefit. Nevertheless, these studies did not quantify the

results or include statistical analysis. The study populations included patients who had partial-onset seizures as well as temporal lobe foci. Furthermore, a significant proportion had previously undergone ablations or lobectomies, and the methodology for seizure evaluation was not standardized.[40] Further trials will need to be conducted to evaluate the usefulness of the CN as a target site for epilepsy treatment.

Closed-Loop Systems

Most of the studies evaluating electrical stimulation for the treatment of epilepsy involve open-loop systems due to the technical complexity of delivering an impulse in response to seizure activity. Yet, in vitro and in vivo animal studies demonstrate increased efficacy of suppressing spikes when stimulation is instituted in response to seizure activity, in contrast to random electrical stimulation.[52,60] The first attempts at seizure-responsive electrical stimulation involved large nonimplantable bedside systems.[37,58] One of these systems was evaluated in 8 patients, 4 with responsive stimulation directly in the epileptogenic focus and 4 with remote stimulation in the AN.[56] Three of 4 patients who had direct treatment had a decrease in seizure frequency (mean decrease 86%), and 2 of 4 patients who had remote treatment had a decrease in seizure frequency (mean decrease 74.3%).[56]

These earlier systems usually consisted of recordings from chronically placed subdural electrodes and an external recorder and stimulator. However, rapid advances in computer and electronic technology have allowed the design of an implantable device capable of both recording and stimulation.[1] The NeuroPace RNS system (NeuroPace, Inc.) is the first implantable closed-loop stimulator for epilepsy treatment. It is currently being evaluated for safety and efficacy in clinical trials. The RNS system monitors the patient's electroencephalographic activity and automatically delivers electrical stimulation to the seizure focus (where the depth or strip electrodes are surgically placed) when the patient's characteristic epileptiform activity is detected.[26,66] The detection and stimulation parameters are set by a programmer. Preliminary results in 24 patients demonstrated at least a 50% decrease in seizure frequency in 43% of patients with complex partial seizures and 35% of patients with total disabling seizures (simple partial motor, complex partial, and secondarily generalized tonic-clonic seizures).[27,69] Although these studies are promising, the question of whether closed-loop systems are superior to open-loop systems remains to be answered.

Patient Selection, Interdisciplinary Screening Teams, and Avoiding DBS Failures

Perhaps the greatest lessons we have learned in DBS are that patient selection is critical to success[54] and that DBS must be tailored utilizing interdisciplinary screening teams to avoid treatment failures.[55] The most exciting pearls from the epilepsy trials presented may be the observed failures. It is from the failures that we will learn the subsets of patients who may respond, the potential targets of therapy, and the approaches that will have the best chances at long-term success. The use of DBS in epilepsy, as in movement disorders, will need to move toward organization of interdisciplinary teams to screen, implant, and follow medication- and stimulation- or device-related issues. These teams will likely need representation from the fields of neurology, psychiatry, neurosurgery, neuropsychology, and in select cases from other members of the allied healthcare team. In addition, DBS boards for epilepsy will need to be convened to determine risk-benefit ratios for individual patients and to tailor therapy. We await the results of ongoing studies that will guide this process.

A criticism of most trials of DBS for epilepsy is that there is usually one arbitrary target chosen despite multiple seizure types (no tailoring). It is clear that such an approach is overly simplified, and it is from the lessons learned from DBS for movement and neuropsychiatric disorders that more tailored approaches should be implemented. In the largest controlled study of DBS for epilepsy, even though patients with a temporal lobe focus or foci had a significant reduction in seizure frequency, those with diffuse, frontal, occipital or parietal seizure foci did not have such benefit from such stimulation.[24] In contrast, to date STN DBS seems to be more effective with seizures having a frontal focus or spread.[65] Thus, it will be a tailored therapeutic approach that will likely win the day in epilepsy when the results of more clinical trials and basic science research are published.

A confounding factor in analyzing the efficacy of DBS for epilepsy is the fact that in most, if not all, patients enrolled in such studies numerous interventions (including resection of presumed seizure foci) have failed. Thus, these patients suffer from chronic epilepsy, which has been shown in both animal and human studies to result in rogue areas of secondary epileptogenesis.[28,34] It is unclear how the stimulation areas and/or parameters would have to be changed if such treatments are used for more epileptically naïve patients. Also many trials have revealed the potential of a strong placebo effect or lesional effect with DBS.

Conclusions

Despite the weaknesses of existing studies, several trials of DBS for epilepsy have demonstrated improvement in seizure activity in patients with intractable epilepsy. These results are exciting and will drive further research into the ideal targets for certain types of epilepsy and patients. Particularly exciting have been the advances in scheduled and responsive stimulation. Elucidating the advantages of closed-loop versus open-loop systems (as being studied in the NeuroPace trial) as well as certain targets will provide tremendous potential options for patients with intractable epilepsy. The future of DBS as a curative versus palliative treatment will depend on how its outcomes compare with ATL and VNS. Anterior temporal lobectomy provides a cure for almost 60% of patients, who are seizure free at 1 year followup.[84] In contrast, VNS is mostly palliative; it provides a reduction in seizure frequency of at least 50% in more than 50% of patients,[20] but most patients do not become seizure free. Further studies will be necessary to determine which pa-

tients will derive a cure and which patients will have palliative reductions in seizure frequency.

The momentum for DBS in the treatment of epilepsy is quickly building with the recent SANTE trial and the FDA's review for potential approval. The questions about the role of DBS in certain types of epilepsy and its potential side effects can only be answered by well-designed prospective studies.

Disclosure

Dr. Okun reports that he serves as a consultant to the National Parkinson Foundation; that he received support for his research from the National Institutes of Health, the Michael J. Fox Foundation, the Parkinson Alliance, and the National Parkinson Foundation; and that he has received fellowship support from Medtronic, has taught DBS courses for Medtronic prior to 2010, and has received book royalties from Manson, DEMOS, and Humana Press.

Author contributions to the study and manuscript preparation include the following. Conception and design: Rahman, Vedam-Mai, Okun, Roper. Acquisition of data: Rahman, Abd-El-Barr, Vedam-Mai. Analysis and interpretation of data: Rahman, Roper. Drafting the article: Rahman, Abd-El-Barr, Vedam-Mai, Okun. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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Manuscript submitted April 15, 2010.
Accepted April 28, 2010.
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Neurosurg Focus 29 (2):E8, 2010

Cerebellar stimulation in the management of medically intractable epilepsy: a systematic and critical review

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Object. The wide application of deep brain stimulation in the management of movement as well as other degenerative neurological and psychiatric disorders has renewed the interest in using deep brain stimulation in the management of medically intractable epilepsy. Various stimulation targets have been used with significantly varying results in aborting seizure activity. Electrical cerebellar stimulation (CS) has been used for more than 50 years in the management of epilepsy, with conflicting results. In the current study, the authors review the pertinent literature to outline the role of CS in the management of medically refractory epilepsy.

Methods. The PubMed medical database was systematically searched for the following terms: "cerebellar," "epilepsy," "stimulation," and "treatment," and all their combinations. Case reports were excluded from this study.

Results. The pertinent articles were categorized into 2 large groups: animal experimental and human clinical studies. Particular emphasis on the following aspects was given when reviewing the human clinical studies: their methodological characteristics, the number of participants, their seizure types, the implantation technique and its associated complications, the exact stimulation target, the stimulation technique, the seizure outcome, and the patients' psychological and social poststimulation status. Three clinical double-blind studies were found, with similar implantation surgical technique, stimulation target, and stimulation parameters, but quite contradictory results. Two of these studies failed to demonstrate any significant seizure reduction, whereas the third one showed a significant poststimulation decrease in seizure frequency. All possible factors responsible for these differences in the findings are analyzed in the present study.

Conclusions. Cerebellar stimulation seems to remain a stimulation target worth exploring for defining its potential in the treatment of medically intractable epilepsy, although the data from the double-blind clinical studies that were performed failed to establish a clear benefit in regard to seizure frequency. A large-scale, double-blind clinical study is required for accurately defining the efficacy of CS in epilepsy treatment.
(DOI: 10.3171/2010.5.FOCUS10111)

Key Words • cerebellum • complication • epilepsy • outcome • medically refractory seizure • cerebellar stimulation

It is well known that epilepsy represents the most prevalent serious neurological disorder across all age groups.[45] It has been reported that approximately 1% of the US population suffer from epilepsy, and this percentage increases to 5% among children and adolescents in the US or Western Europe.[24] Approximately one-third of these patients will eventually develop epilepsy that is refractory to any kind of pharmacological treatment.[25] The actual incidence of medically intractable epilepsy has been reported to be approximately 6 of 100,000 people per year, which translates to 17,000 new cases annually in the US alone.[26] Even though surgical treatment is a valuable alternative to medical treatment in very carefully selected cases, unfortunately a large percentage of these patients are not good surgical candidates.[45] It is apparent that the development of a novel treatment modality is of paramount importance for these patients.

The recently exponentially increasing clinical applications of deep brain stimulation—mainly in movement disorders, but also in a large spectrum of degenerative neurological disorders—have reignited the interest in using electrical stimulation to abort or prevent seizure activity.

The concept of brain stimulation in the management of seizure activity is not new. Pelops from Alexandria, approximately 20 centuries ago, was able to abort something that could represent a simple partial seizure, by tying

Abbreviations used in this paper: CS = cerebellar stimulation; pps = pulses per second.

a ligature around the affected limb.[17,46] Later on, Brown-Séquard, Jackson, and Gowers independently suggested that counterirritation could be a potential mechanism for abating seizure activity.[6,20,31,46] Use of deep brain stimulation has been performed in several animal experimental studies and human trials for managing epilepsy. Various stimulation targets, such as the cerebral cortex,[33,36] the anterior thalamic nucleus,[12,27,32] the centromedian thalamic nucleus,[7,51,56,57,59] the head of the caudate nucleus,[7,50,51] the hippocampus,[50,51,58] and the subthalamic nucleus[3,44] have been used, with significantly varying clinical results.

In this study we performed a systematic review of the existing animal and human studies in which CS was used in the treatment of medically refractory epilepsy. Meticulous review of the pertinent literature was done to summate the existing experience with CS, identify any controversies, and outline the potential role of this treatment modality in the management of medically refractory epilepsy.

Methods

An extensive literature search through the PubMed medical database was performed using the terms "cerebellar," "stimulation," "epilepsy," "treatment," and all possible combinations. The retrieved articles were meticulously reviewed and were categorized into 2 large groups: animal experimental studies and human clinical studies.

Articles referring to case reports were excluded from our study. Every effort was made to identify any repetition of cases among the published clinical series and/or repetition of reports in different journals. In these cases, only the original clinical series were included in our study. It has to be mentioned, however, that this task was not easy, and the reader must be aware of potential redundancies in the reported data.

In reviewing the human studies, particular attention was paid to the design of the study, its methodological characteristics, the number of participants, the type of seizures, the duration of epilepsy, the surgical technique and its associated complications, as well as the type of electrodes implanted, the stimulation parameters, and the outcome regarding seizure frequency. Data regarding psychological or social performance were also reviewed, whenever available.

Results

Animal Experimental Studies

Numerous studies exploring the role of CS in aborting seizures have been published in the literature. All of these studies were based on the widely accepted functional anatomical and electrophysiological concepts that the cerebellum exerts an inhibitory effect on the thalamus and the cerebral cortex through the synaptic action of Purkinje cells and its efferent fibers traveling via the superior cerebellar peduncle.[9,29,40,61] The output of the cerebellum to the ascending reticular formation may be implicated in the inhibitory effect of the cerebellum to the basal ganglia neuronal network, which results in decreased activity of the excitatory thalamocortical projections.[9,16] This process ultimately results in inhibition of cortical excitability. There is a wide variation in the animal models used, the seizure induction methodology, the exact stimulation target, the stimulation methodology, and the stimulation parameters. Therefore, the observed results demonstrated a significant variation and contradictory conclusions were occasionally extracted.

Cooke and Snider[8] reported on the results from their cat model, in which cerebellar surface electrical stimulation could arrest seizures induced by direct electrical stimulation of the cerebral cortex. Similarly, Hutton et al.,[28] working with cats in a penicillin-induced seizure model, found that stimulation of the cerebellar vermis, the paramedian lobulus, and the dentate nucleus resulted in seizure inhibition. Dow et al.[14] published similar findings after working with rats in a cobalt powder–induced seizure model. They stimulated the anterior cerebellar lobe and observed inhibition of the induced epileptiform activity. Mutani and Fariello[42] found that stimulation of the anterior surface of the cerebellar cortex resulted in inhibition of cobalt-induced seizures. Bantli et al.[2] also observed significant seizure reduction after applying cortical CS in their penicillin-induced seizure model.

However, a series of later animal studies in cats and monkeys could not reproduce similar results; neither lateral nor midline cortical CS had an effect on seizure activity or even provoked electrographically confirmed seizures.[15,22,38,48,52,53] Reimer et al.[48] found that stimulation of the vermis produced prolongation of the seizures induced by cortical application of cobalt powder in their cats. Likewise, Hablitz[21] and Myers et al.[43] found that CS had no effect on seizure activity in their penicillin-induced seizure models. Godlevskii et al.,[19] using a penicillin-induced seizure model, found that cortical stimulation of the paleocerebellum resulted in a decreased amount of interictal spikes, but had no effect on actual seizure activity. In addition, Brown et al.,[5,13] working on a monkey seizure model in which electrical cortical stimulation was used to abort seizures, performed light and electron microscopic examinations of cerebellum specimens obtained in the experimental animals. Specimen examination revealed attenuation of the molecular layer of the cerebellum cortex and loss of Purkinje cells in the surface areas of electrode contact. The authors found that electrical charge densities of up to 5 times the necessary threshold for cerebellar efferent activation resulted in no additional cortical damage beyond that produced by the presence of the implanted electrode. They postulated that charge densities ≤ 7.4 μC/cm^2/phase should be considered safe for stimulation of the human cerebellum, whereas a further electrical current increase may lead to cortical tissue damage, and thus, it may make the stimulation ineffective.

Electrical stimulation of the vermis appeared to arrest seizure activity caused by hippocampal stimulation in animal studies.[30,39] Similarly, stimulation of the nucleus fastigius of the cerebellum stopped seizures induced by the application of cobalt powder to the hippocampus in the animal study performed by Babb et al.[1] Interestingly, they observed that stimulation of the dentate nucleus in their study resulted in prolongation of the induced seizures. In

contrast, Hemmy et al.,[26] working with an animal model of direct stimulation-induced seizure, found that either cortical or deep nuclei CS had no effect on seizure activity. Rubio et al.[49] recently reported on their experience working with an amygdala-kindling animal model, and found that CS resulted in an initial facilitation of the induced limbic seizures. However, CS resulted in slower propagation and arrest of the secondary generalized seizures.

A review of the cerebellar animal studies shows that surface stimulation has been used significantly more frequently than deep nuclei stimulation. Laxer et al.[35] reviewed the results of 22 previously published animal experimental studies in which CS was used. They drew the conclusions that vermian and superomedial cortical stimulation appeared to be more efficient than lateral cortical stimulation, and that CS seemed more effective in models of generalized or focal epilepsy of the limbic system than those of focal epilepsy of the sensorimotor cerebral cortex. In our current review, it appears that CS of deep structures has been used in only 3 animal experimental studies, and in 2 of these there was inhibition of seizure activity,[1,28] whereas in the other study there was no effect.[26] Interestingly, stimulation of the dentate nucleus showed seizure inhibition in one study,[28] no effect on seizure activity in another,[26] and prolongation of seizure duration in the third.[1] It has to be mentioned, however, that the stimulation parameters showed a significant variation in these 3 studies, as in the majority of animal studies of CS.

Human Clinical Studies

The promising results of the early animal experimental studies and the lack of adverse events led to the design and execution of the first clinical study. Cooper and his coworkers[9–12] reported on their findings from applying cortical CS to parts of both paleo- and neocerebellum for treatment of patients with medically refractory epilepsy. Their surgical technique consisted of the implantation of 4 or 8 pairs of bipolar platinum electrodes embedded in a silicon mesh, via an occipital approach.[10] The electrodes were stimulated through an antenna fixed subcutaneously on the chest by transepidermal inductive coupling. The authors reported on 32 patients suffering medically intractable epilepsy with a mean duration of 17.6 years.[9] The included patients suffered from partial or focal seizures, generalized seizures, or partial and generalized seizures. A 4-tier outcome scale was used in their study, with 1 indicating mild improvement and 4 representing great improvement. The psychological status of their patients was evaluated pre- and poststimulation by using the Wechsler Memory Scale, the Wechsler Adult Intelligence Scale, and the Bender-Gestalt test. The stimulation parameters they used were empirically developed and were ultimately set at a rectangular pulse of 1-msec duration.[10] In the initial phase of their study there was patient-controlled periodic stimulation, whereas during the last phase of their study automatic stimulation was delivered. In the aforementioned study[9] they found that 18 (56.2%) of 32 of their patients demonstrated a 50% or more reduction in seizures, whereas 9 (28.1%) of 32 showed no response at all. The beneficial effect of CS was maintained for at least 3–42 months postoperatively (mean follow-up time 18 months), showing no seizure rebound effect. Furthermore, they documented that all their responders showed some psychological improvement, with increased alertness and improved postoperative concentration and ability to perform routine daily activities. The authors also reported that there was significant postoperative improvement of the verbal, performance, and memory IQ in their patients poststimulation, although without providing any statistical data in their study. In regard to the safety of their procedure, they reported a 1% mortality rate due to postoperative hemorrhage, and a 9% cumulative procedure-related morbidity rate (Table 1). Among the 200 patients included in a subsequent study, Cooper et al.[10] observed postoperative CSF leakage in 7 (3.5%), development of transient cerebellar edema in 3 (1.5%), infection in 4 (2%), and hydrocephalus in 1 (0.5%). The authors reported no adverse neurological or psychological events in their series. In a subgroup of 5 of their patients, cerebellar biopsy samples were obtained from the site of the electrode implantation.[11] Histological analysis of the specimens demonstrated reduction in the thickness of the molecular layer, significant decrease or depletion of the Purkinje cells, and decreased populations of stellate cells.

Sramka et al.[51] published their results from a series of 10 patients suffering various forms of medically intractable epilepsy. However, CS was used in only 3 patients, whereas in the remaining 7 patients stimulation of either the caudate nucleus or caudate and dentate nuclei was applied. The anatomical target was the dentate cerebellar nucleus, and bilateral stimulation was delivered through occipital stereotactically implanted electrodes. The stimulation parameters consisted of 10- and 100-Hz frequency, 1-msec duration, and voltage of 10 V. Stimulation was delivered once a day for a total of 3 minutes, during a 1–8-day period. They observed improvement in all their cases; however, that improvement was temporary. The authors raised concerns in their study regarding the development of a kindling phenomenon secondary to the stimulation being used.

At approximately the same time, Gilman et al.[18] reported their results from applying cortical CS in 6 patients suffering medically refractory epilepsy of various origins and with different types of seizures. In 4 of their patients, an 8-contact electrode was placed over the surface of the anterior cerebellar lobe, and a second 16-contact electrode (both from Avery Labs, Inc.) was placed over the cerebellar hemisphere, through a small suboccipital craniectomy. In the other 2 patients, an 8-contact electrode was bilaterally placed over the cerebellar hemispheres. The implanted electrodes were connected to 2 receivers (Avery Labs, Inc.) subcutaneously implanted in the anterior chest wall. The stimulation parameters used were as follows: square waves, 1-msec duration, and 10-Hz frequency. A single-blind trial was performed. The authors found that 5 (83.3%) of their 6 patients demonstrated reduced seizure frequency in the poststimulation period compared with the preimplantation baseline. They also noted that grand mal and psychomotor seizures seemed to respond better than focal motor seizures. Cerebellar tissue biopsy was possible in 4 of their 6 cases during the electrode implantation procedure. Histopathological examination of their specimens revealed severe loss of the Purkinje cells, degenerative changes

TABLE 1: Literature review of the most important clinical series in which CS was used in the treatment of medically refractory epilepsy

Authors & Year	No. of Patients	Stimulation Target	Stimulation Parameters	Sz Outcome	Poststimulation Psychological Outcome	Complications
Cooper et al., 1973	32	cerebellar cortex (paleo- & neocerebellum)	1-msec rectangular pulses	56.2% w/ >50% decrease in sz frequency	improved; increased alertness, increased verbal & memory IQ	1% mortality, 9% morbidity
Sramka et al., 1976	3	bilat dentate nucleus	10–100 Hz, 1 msec, 10 V	100% w/ temporary improvement	NA	development of kindling phenomenon
Gilman et al., 1977	6	anterior lobe & cerebellar hemispheres	square waves, 1 msec, 10 Hz	83.3% had decreased sz frequency	NA	NA
Levy & Auchterlonie, 1979	6	cerebellar cortex	3 V, 10 pps	33.3% w/ significant improvement & 33.3% w/ minor improvement	33.3% developed depression	all patients had poststimulation headache, & 16.6% developed wound infection
Davis & Emmonds, 1992	30 w/ spasticity & epilepsy; 6 w/ epilepsy only	superomedial surface of cerebellar cortex	1–1.4 mA, 0.5 msec, 150 pps, 4-min ON/OFF sequencing	71% sz free; 42% sz free	mild improvement	2 cases of wound infection
various clinical series accumulated by Krauss & Koubeissi	36	cerebellar cortex	various	33.3% sz free; 91.6% w/ significantly decreased sz frequency	NA	NA
Van Buren et al., 1978	5	superior cerebellar cortical surface	10–14 V, 10 & 200 Hz	no decrease in sz frequency	no change in IQ & memory quotient	60% w/ CSF leakage
Wright et al., 1984	12	superior cerebellar cortical surface	7 mA, 10 pps	no decrease in sz frequency	no change in psychometric test results	25% w/ electrode migration, 16.6% w/ wound infection, & 8.3% w/ mechanical failure
Velasco et al., 2005	5	superomedial surface of cerebellar cortex	2 $\mu C/cm^2$/phase, 0.45 msec, 3.8 mA, 10 pps	41% w/ decreased sz frequency	NA	60% w/ electrode migration, 20% w/ wound infection

* NA = not applicable; sz = seizure.

of the remaining Purkinje cells, and concomitant proliferation of Bergmann astrocytes. These authors postulated that patients with marked loss of Purkinje cells responded poorly to CS in their study, whereas those with less marked changes had a better response.

Likewise, Levy and Auchterlonie[37] reported their results from a series of 6 patients suffering from medically intractable epilepsy (generalized motor seizure pattern). All their participants underwent electrode implantation for cortical CS. The stimulation parameters used were 3 V and 10 pps in the vast majority of their patients. Their pre- and poststimulation evaluation included a detailed neuroradiological, electroencephalographic, and psychological examination. The authors reported that 2 (33.3%) of their 6 patients demonstrated significant seizure frequency improvement poststimulation, another 33.3% showed some minor improvement, whereas 1 (16.6%) of 6 showed some increased seizure frequency poststimulation. They reported that all of their patients complained of headache postoperatively, which could not be proven to be associated with the stimulation process, and that there was a postoperative wound infection in 1 (16.6%) of 6 patients. Two of their participants developed depression postoperatively, but no other neurological or psychological side effects occurred in their study.

Davis and Emmonds[13] published their results from a series of 30 patients with spasticity and epilepsy and 6 patients suffering medically refractory epilepsy only. Their anatomical target was the superomedial surface of the cerebellum, and twin pad electrodes were bilaterally implanted. The Avery radiofrequency system was used, and during the last phase of their study a totally implantable pulse generator was coupled to the radiofrequency system (Neurolith 601, Pacesetter Systems). The applied stimulation parameters were as follows: current intensity 1–1.4 mA, duration 0.5 msec, 150 pps, monodirectional pulses, and 4-minute ON/OFF sequencing. In one group of 7 of their patients with an average stimulation duration of 13.6 years (range 10–15 years) they found that 71% were seizure free, whereas the remaining 29% had reduction of their seizures. In another group of 12 patients with an average stimulation duration of 8 years (range 2–13 years), 42% were seizure free, 33% had reduced seizures, and 25% had no improvement. In addition, they found that the necessary amount of anticonvulsant medications was decreased in 65% of their patients. The authors reported no complications except for 2 cases of postoperative infection, for which the implanted systems had to be removed.

A number of small clinical series in which cortical CS was used in patients suffering from various forms of medically intractable epilepsy of various origins, with insufficient or no data regarding the exact stimulation target, the stimulation parameters used, and the type of the implanted electrodes, has been reported in the literature. In an attempt to summarize the results of these series, Krauss and Koubeissi[34] found that a total of 36 patients had been reported to have undergone cortical CS for their epilepsy.[4,14] The seizure frequency was found to be reduced in 33 (91.6%) of the 36 patients, whereas 12 (33.3%) had become seizure free.

Van Buren et al.[54] published their results from a series of 5 patients undergoing cortical CS for medically intractable epilepsy. Their cohort included patients with generalized, myoclonic, and/or partial seizures of various origins. Two 4-contact electrodes (Avery Labs, Inc.) were bilaterally implanted on the superior cerebellar cortex, 1 cm lateral to the midline, and were connected to 2 receivers (Avery Labs, Inc.) that were subcutaneously implanted in the anterior chest wall. All patients had pre- and poststimulation evaluation of their seizure frequency, intelligence and memory quotients, surface electroencephalograms, CSF neurotransmitters (norepinephrine, γ-aminobutyric acid, cyclic adenosine monophosphate, and cyclic guanosine monophosphate), measurements, and their family's subjective evaluations (including seizure frequency, duration and type of seizures, administered therapy, and psychological and social performance). The stimulation parameters used were as follows: 10–14 V, and 10-Hz frequency for all types of seizures but myoclonic ones, in which they applied 200 Hz. Their stimulation trial consisted of 4 phases, each of which lasted 4–6 weeks. The first evaluated early responses of patients in whom stimulation was turned ON and OFF in a nonblinded fashion, the second evaluated their responses in a double-blind fashion, and the other 2 phases evaluated the respective responses after a 10-month period of stimulation. Their statistical analysis showed no significant differences between observed seizure frequency pre- and poststimulation. The only statistically significant difference was between the observed seizure frequency in the early and late ON stage phases. In addition, no meaningful differences were noted on the electroencephalograms obtained pre- and poststimulation in their study. Similarly, the full-scale intelligence and memory quotients demonstrated no essential changes between the pre- and poststimulation evaluations. The CSF levels of norepinephrine showed some increase after stimulation, whereas the CSF levels of γ-aminobutyric acid were decreased and the cyclic adenosine monophosphate and cyclic guanosine monophosphate levels had remained essentially unchanged. Interestingly, the patients' families thought that the stimulation made the patients more alert, more sociable, less depressed, and more independent. The authors reported no major neurological or psychiatric complications in their series. Leakage of CSF occurred in 3 (60%) of 5 patients, despite the meticulous efforts to achieve watertight dural closure. They also had the opportunity to obtain cerebellar tissue biopsy samples in 3 of their patients, which showed a significant decrease of the Purkinje cell populations (in 2 cases there was a > 75% decrease compared with normal controls).[47]

Similarly, Wright et al.[60] presented their results from a double-blind prospective clinical trial, in which they used cortical CS to treat 12 patients with medically refractory epilepsy of various origins. The participants suffered epilepsy of various clinical patterns (grand mal, petit mal, atonic, absence, and myoclonic seizures) and of long duration (average 20.6 years). Their surgical technique included the implantation of bilateral 8-contact electrodes (Avery Labs, Inc.) on the superior cerebellar cortical surface, through occipital bur holes. The electrode arrays were positioned parasagittally, approximately 2 cm from the midline. The electrode leads were tunneled

subcutaneously to 2 receivers, which were implanted into subcutaneous pockets in the anterior chest wall or the axilla. The implanted receivers were activated by specially modified external transmitters (Avery Labs, Inc.). The applied stimulation parameters were as follows: intensity of 7 mA and frequency of 10 pps. The stimulation trial was divided into 3 phases, each lasting 2 consecutive months for all participants. Patients received 2 months of continuous stimulation, 2 months of contingent stimulation, and 2 months of no stimulation. The sequence of the phases was randomly selected for each participant. All patients were evaluated pre- and poststimulation by a psychiatrist, and they were clinically assessed pre- and poststimulation by 2 independent neurologists. There were data for 11 of 12 patients. The investigators found no decrease in the frequency or the severity of the patients' seizures during the stimulation periods. However, the vast majority of patients reported that the implanted stimulators helped them significantly. There were no adverse psychiatric events during the stimulation period, and the psychometric tests revealed no difference pre- and poststimulation. The authors reported no procedure-related death, but they observed electrode migration in 25% of cases, wound infections in 16.6%, and mechanical failure in 8.3%. They concluded that CS may not be a suitable treatment for patients with medically intractable epilepsy.

Recently, Velasco et al.[55] reported on their experience applying cortical CS in patients suffering medically intractable motor seizure epilepsy. In their double-blind, prospective clinical study, they included 5 patients with generalized tonic-clonic seizures (all 5 patients), tonic seizures (4 of 5 patients), drop attacks (2 of 5 patients), and myoclonic and atypical absence seizures (1 of 5 patients). All of their patients had between 8 and 22 seizures per month. Their implantation technique consisted of 4-contact electrodes (Medtronic, Inc.), which were inserted through bilateral suboccipital bur holes. The electrodes were placed 1.5 cm from the midline, on the superomedial cerebellar cortex, and their final position was verified by intraoperative fluoroscopic imaging. The electrode leads were connected through a Y-shaped connector cable to the implanted battery-operated pulse generator, which was positioned in a subcutaneous pocket in the anterior abdominal wall. The stimulation parameters were as follows: charge density 2 $\mu C/cm^2$/phase, pulse width 0.45 msec, current intensity 3.8 mA, and frequency 10 pps. The implanted pulse generator was the cathode and the case was the anode. The stimulation was turned ON for 4 minutes and then OFF for another 4 minutes throughout the day. No stimulation was delivered for 1 month after the implantation (sham period), whereas for the next 3 months a double-blind trial was done, in which 3 patients received stimulation and 2 did not. During this period, both the patients and the evaluators were blinded in regard to whether the stimulator was ON or OFF. After this double-blind stimulation period, all the implanted stimulators remained ON until the end of the study. The authors found that there was no significant seizure frequency difference in the sham period. However, during the 3-month double-blind period, there was no decrease in seizure frequency among the patients who had their stimulator OFF, whereas in the 3 patients with their stimulators ON, there was a 33% decrease in seizure frequency. This difference was found to be statistically significant. Similarly, during the 6-month period when all patients had their stimulators ON, there was a mean 41% decrease in the seizure rate. The authors reported electrode migration in 3 (60%) and wound infection in 1 (20%) of the 5 patients.

Discussion

Although it has been more than 3 decades since the publication of the first clinical series of patients undergoing CS for the treatment of medically intractable epilepsy,[8–10] this treatment methodology remains experimental. Numerous animal studies have demonstrated that electrical stimulation of the cerebellum may abort electrically or chemically induced seizures and drastically alter the electrophysiological profile of the neuronal tissue in vitro and in vivo.[1,2,5,8,13–15,19,21,22,26,28,30,35,38,39,41,42,48,49,52,53] However, there are several issues that remain to be resolved and important questions that need to be answered.

The mechanism of action of CS in aborting seizures is still unclear.[34] The previously proposed theory that stimulation of the Purkinje cells may intensify the inhibitory cerebellar output to the thalamic neuronal network, and subsequently weaken its excitatory output to the cerebral cortex, cannot be supported by the histopathological findings of several animal and human reports. These reports described significantly decreased populations of Purkinje cells in epileptic patients.[9,18,54] It has been proven that stimulation of the cerebellar cortex resulted in further degeneration and population decrease of Purkinje cells.[34] In addition, Dow et al.[14] had demonstrated in their animal experimental study that electrode stimulation resulted in a decrease in the firing rate of the Purkinje cells located adjacent to the implanted electrode. Moreover, Mutani et al.[41] have demonstrated that repetitive electrical CS completely suppressed spontaneous Purkinje cell activity.

The exact stimulation target in the cerebellum remains to be defined. The vast majority of the animal experimental studies but also the clinical trials have used the cerebellum cortical surface as stimulation target, with frequently contradictory results.[8,5,14–16,22,23,38,48,52,53] However, the stimulation of the deep cerebellar nuclei appears to provide more solid data and better seizure control.[1,35] There are several mechanisms that may explain this discrepancy in the results of the cortical CS in animal and human studies. Different areas of the cerebellum's cortical surface have been used in the published studies. Stimulation of the superior and medial surface of the cerebellum appears to provide more consistent results than stimulation of the posterior lobe. It has to be emphasized at this point that the implantation of an electrode in a certain cortical area in an animal experimental study or even in a human study does not necessarily mean that the stimulation site remains the same during the trial and is the one that was selected preoperatively, because in a large number of studies there no reports regarding verification of the final position of the implanted electrodes. Moreover, electrode migration was a commonly occurring complication, even in recent human studies.[55,60]

The interface between the implanted electrode and

the cerebellar surface has remained another puzzling issue, which may interfere in the propagation of the delivered electrical stimulus. Previous studies have demonstrated that dense arachnoidal reactive tissue usually develops at the implantation site.[18] The formation of this reactive tissue may well alter the impedance of the implanted electrode, and it may modify in an unpredictable way the characteristics of the ultimately delivered electrical stimulus.

The stimulation parameters per se represent another variable that may well be responsible for the significant variation observed in the published animal and human CS studies. There is a significant variation in the charge densities used in the previously published animal experimental studies, depending on the animal species and the seizure models. In contrast, the charge density of 2 μC/cm^2/phase was used in the vast majority of the human studies. However, the stimulation frequency varied significantly from low (10 Hz) to high (200 Hz) frequencies.[18,54,55,60] It seems that there is a consensus regarding the charge density and the low-frequency stimulation used in human studies.[19,55,56,61]

A significant confounding factor in the evaluation of the CS studies in humans is the inclusion of patients with epilepsy of various origins and different seizure patterns.[8–11,18,34,54,55,60] It is very unlikely that medically intractable epilepsy secondary to dysplastic changes and epilepsy due to the presence of vascular pathological features would respond to CS of standard parameters. Similarly, it is very unlikely that generalized motor seizures would respond to the same stimulation patterns that atonic or absence seizures would. It seems reasonable that certain seizure patterns may require specific stimulation characteristics or even different stimulation targets.[55] Because in the vast majority of epilepsy cases there are periods of bursts of pathological electrical cortical activity, the development of systems that would detect abnormal electrographic patterns and that would automatically activate the delivery of an electrical stimulus through an implanted stimulator could be more efficient in aborting or preventing seizures.

The placebo effect of the stimulation constitutes another confounding factor in the accurate evaluation of CS in the treatment of medically intractable epilepsy. In several human studies the investigators found that although the actual number of poststimulation seizures remained essentially unchanged compared with the preimplantation baseline, the patients and their relatives reported decreased seizure frequency and improved psychological and social functioning.[54,60] The execution of double-blind clinical trials significantly contributed in minimizing the placebo effect and any potential investigators' or participants' biases.[54,55,60] Interestingly, 2 of the 3 double-blind studies failed to prove any statistically significant differences in seizure frequency before and after stimulation.[54,60] There was a lot of criticism, however, by other clinical investigators[55] regarding the seizure outcome interpretation performed and the statistical analysis of the results. For example, in a study published in 2005, Velasco et al.[55] commented on the analysis of the results of the other 2 double-blind studies, and postulated that there are reports in the literature that support the idea that analysis outcome was inconsistent in Van Buren and coworkers' study. After making the appropriate corrections, it can be shown that the vast majority of their patients had decreased seizure frequency in the ON phase when compared with the OFF phase.[55] Likewise, the majority of the patients included in Wright and associates' study actually demonstrated decreased seizure frequency after the application of CS.[55] In their recent study, Velasco et al. attempted to explain the differences between their results and those of Van Buren et al.[54] and Wright et al.[60] They postulated that the criteria for patient selection, the variance in seizure types, the stimulation parameters used, the implantation technique and any procedure-related pitfalls, the design and the applied methodology of the double-blind trial, and the length of the follow-up period may be responsible for the observed differences.[55]

A critical review of the existing animal and human studies shows that stimulation of the cerebellum may be a treatment option worth exploring for carefully selected patients suffering certain types of medically intractable epilepsy who are not suitable candidates for other types of resective epilepsy surgery. The recent experience from double-blind studies indicated that generalized tonic-clonic seizures or other seizure types that are associated with supradiencephalic structures may respond better to CS than tonic seizures.[55] It seems that the most commonly used charge density of 2 μC/cm^2/phase, the frequency of 10 pps, and a pulse width of 0.45 msec may be a good set of initial stimulation parameters for superomedial cortical CS.[55] Designing a double-blind study with long-term follow-up, examining not only the seizure frequency but also other characteristics such as seizure type, seizure severity, presence of auras, duration of postictal confusion, and cognitive and psychosocial functioning, is necessary for the accurate evaluation of this emerging neuromodulative treatment option. The development of high-accuracy imaging techniques, the availability of small implantable electrodes, and the continuously improving software technology that can detect and analyze epileptiform activity, may lead in the near future to the development of a novel responsive stimulation system for cerebellar cortex. Furthermore, the continuous development and improvement of high-accuracy frameless stereotactic systems may resurrect interest in evaluating the role that stimulation of deep cerebellar nuclei plays in aborting seizures.

Conclusions

The superomedial surface of the cerebellar cortex remains a target of interest for stimulation in the management of disease in patients with certain types of medically refractory epilepsy who are not candidates for resective surgery. The existing clinical data suggest that CS may be of potential benefit. Further double-blind, large-scale clinical studies and long follow-up periods are necessary for better definition of the stimulation parameters and more accurate evaluation of the efficacy of CS in seizure management. Evaluation of seizure outcome along with detailed cognitive, psychological, and social examinations pre- and poststimulation are of paramount importance for outlining the role of CS in the management of medically intractable epilepsy.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fountas. Analysis and interpretation of data: all authors. Drafting the article: Fountas, Kapsalaki. Critically revising the article: Fountas. Reviewed final version of the manuscript and approved it for submission: Fountas.

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Manuscript submitted April 15, 2010.
Accepted May 13, 2010.

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Neurosurg Focus 29 (2):E9, 2010

Criteria for the ethical conduct of psychiatric neurosurgery clinical trials

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There is an urgent need for an effective therapy for treatment-refractory mental illness. Trials ongoing globally that explore surgical treatment, such as deep brain stimulation, for refractory psychiatric disease have produced some promising early results. However, diverse inclusion criteria and variable methodological and ethical standards, combined with the sordid past of neuromodulation, confound trial interpretation and threaten the integrity of a new and emerging science. What is required is a standard of ethical practice, globally applied, for neurosurgical trials in psychiatry that protects patients and maintains a high ethical benchmark for clinicians and researchers to meet. With mental illness, as well as treatment resistance, reaching epidemic proportions, ethically and scientifically sound clinical trials will lead to effective and safe surgical treatments that will become vital components of the clinicians' armamentarium. Ethical criteria, such as the ones proposed here, need to be established now and applied in earnest if the field is to move forward and if patients with no other therapeutic options are to receive much-needed treatment.
(DOI: 10.3171/2010.4.FOCUS09327)

Key Words • deep brain stimulation • ethics • psychiatry • psychiatric neurosurgery

Despite some success, there remains considerable controversy surrounding neurosurgery for psychiatric indications. Specifically, the application of DBS, currently used largely to manage movement disorders, to refractory psychiatric disease has met with equal parts enthusiasm and trepidation among people in the scientific community and public alike. Having undergone several transformations in the 20th century, aided by the development of novel imaging and surgical tools, the neurosurgeons are now poised to intervene in diseases of brain function, rather than diseases exclusively of structural pathology. It has not escaped the notice of ethicists and surgeons that the modulation of mood and affect with deep brain electrodes offers neuroscientists the opportunities to probe functions and characteristics of the brain and mind that previously were out of reach to empirical study. Although interest in the interface between brain structure and brain function is certainly not new, never before have practitioners and scientists been able to actively intervene in, modulate, correct, and investigate dysfunctional neuroanatomical circuits believed to underlie much of human thought and behavior. For many, we stand on the brink of a brave new world of scientific discovery.

Such enthusiasm needs to be tempered with pragmatism, grounded in scientific data, and anchored by the lessons of history. The controversy surrounding so-called "psychosurgery"—but more appropriately termed "neurosurgery for psychiatric disease"—stems not necessarily from an inherent reluctance to treat diseases of the mind, but rather from a reflexive repulsion at the history of behavior and mood modification in the 20th century. The scientific method and the institution of research ethics review boards have moved the field of ethical scientific inquiry forward, but there remains a general discomfort in both academic and general circles concerning surgical mood and behavior modification. We believe that this is multifactorial, but it is primarily due to misinformation and the overwhelming shadow of history.

Several ongoing trials are now exploring DBS for various psychiatric indications. A randomized, double-blind trial of DBS of the subthalamic nucleus in patients with refractory OCD published in 2008 demonstrated significant clinical efficacy.[3] A pilot trial, and subsequent follow-up, of 20 patients receiving DBS for refractory major depression demonstrated significant rates of remission in a majority of patients.[2,4] These trials, and others, represent the culmination of an established and exponentially growing literature surrounding dysfunctional neuroanatomical and physiological circuits behind psychiatric symptoms.[1,5] They represent the most recent in a wave of novel functional neurosurgical attempts at

Abbreviations used in this paper: DBS = deep brain stimulation; OCD = obsessive-compulsive disorder.

* All of the authors contributed equally to this work.

modulating those circuits in patients with no other treatment alternatives. Such work reflects the changing face of psychiatry, where rapid advances in the neurosciences are leading many to equate diseases of the mind with brain dysfunction, on a micro- and macroscopic level. The recognized association of Parkinson disease and Tourette syndrome with myriad psychiatric illnesses complements an exponentially growing literature that ties neurology and psychiatry together on a pathophysiological level.[1,5] Indeed, with the continued elucidation of the genetic, anatomical, and physiological correlates of diseases such as depression, OCD, and even schizophrenia, the essentially arbitrary divisions between the "neurological" and "psychiatric" will ultimately disappear.

In addition to helping address a burgeoning mental health epidemic, psychiatric neurosurgery serves to destigmatize psychiatric disease by offering patients an organic therapy for what is increasingly recognized as an organic disease. Neurosurgeons and psychiatrists are combating the image of preying on the psychologically vulnerable, and instead are validating biological models of psychiatric pathology. After centuries, and longer, of marginalization and persecution, patients with refractory psychiatric disease and their physicians are recognizing the biological roots of their disorders, roots that continue to be demonstrated on neuroimaging, in the laboratory, and in the operating room.

There is an urgent need for treatment alternatives for patients with psychiatric disorders. Psychiatric disease is common and can incapacitate a substantial proportion of patients, sometimes leading even to suicide. Surgical alternatives are beginning to become available for carefully selected patients, but care must be taken to not allow safety and ethical conduct to suffer under the weight of the enthusiasm and promise of scientific advancement.

Clinical trial methodology in psychiatric neurosurgery differs significantly between centers; however, it is crucial that ethical principles remain universal. We believe that the details of ethics approval, informed consent, patient recruitment methodology, and details of pre- and postoperative psychiatric follow-up should be as vital components of any surgical trial in psychiatry as discussions of target selection and rationale. Although recent efforts have been made, there are currently no established ethical guidelines, universally applied, that govern the development and monitoring of psychiatric neurosurgery trials.[6] Indeed, such surgeries and trials are ongoing globally and in some academic centers, with very little information provided of the details of ethical approval and oversight.

Ethical Criteria

We have identified several criteria that we believe should serve as a foundation for ethical guidelines governing clinical trials in psychiatry neurosurgery (Table 1). Diligent attention to these criteria will help ensure patient safety, as well as standardize and strengthen the integrity of research methodology.

First, there needs to be an adequate discussion of patient selection. Specifically, this discussion should be divided into psychiatric and surgical aspects, and attention should be paid to how clinical severity was gauged. Details of pre- and postoperative psychiatric assessments should be discussed together with those surrounding caregiver and family expectations of surgical results. Second, a data-driven, evidence-based rationale should be provided as part of a formal trial protocol that meets and exceeds what we refer to as a "threshold of information" that then justifies an organic, surgical intervention. To meet ethical standards, the selected disease requires a general acknowledgment of its severity, morbidity, public health impact, and demonstrated treatment resistance. Furthermore, support from the anatomical, physiological, genetic, and, if applicable, animal model literature must contribute to a body of knowledge that supports a pathophysiological model of disease that is amenable to surgical treatment. In this way, given sufficient support, an evidence-driven hypothesis for a specific target can be formulated that, although it may differ among centers, may nevertheless represent a unique node along a recognized pathological circuit. Crucially, attention must be given to the informed consent process, which acquires additional complexity in psychiatric patient populations. The onus is on researchers to demonstrate that the process was transparent, independent of the research team, and free of coercion. In patients referred for surgical treatment, there are typically years of failed pharmacological and somatic therapies, and care must be taken that the patients do not view a surgical alternative with false hope or desperation. To this end, a realistic discussion of patient and caregiver expectations needs to be undertaken at every clinical encounter, and both patient and family need to be made adequately aware of the risks and potential harms of surgery. Necessarily, informed consent is incomplete if disease and patient selection have been inadequate.

Surgical trials, and psychiatric trials in particular,

TABLE 1: Ethical criteria for clinical trials in psychiatric neurosurgery

1. transparent & independent discussion of patient selection from psychiatric & neurosurgical perspectives
2. data-driven, evidence-based rationale for disease & target selection that surpasses a consensus-derived threshold of information for surgical intervention
3. demonstration of disease burden, including qualification of its severity & refractoriness to known therapy
4. transparent discussion of the informed consent process, including the involvement of caregivers, & a qualitative demonstration of its adequacy
5. involvement of multiple disciplines, providing independent assessments & evaluations, & participating in patient selection & follow-up
6. regulated, dispassionate oversight governing the ethical conduct of clinicians & researchers, that is divorced from the informed consent & patient-selection processes
7. routine, scheduled evaluations that identify obstacles & potential challenges for the ethical conduct of the trial & the dissemination of its results

should not exist in a vacuum, and a free and open exchange regarding all facets of the trial, including patient and disease selection, should involve a multidisciplinary health care team. The involvement of psychiatry, neuropsychology, and often social work and community care and access teams should become an integral part of the trial design. More than one experienced and qualified psychiatrist should provide independent assessment and ensure redundancy in clinical conclusions and diagnosis. Safeguards should exist whereby trials cannot proceed unless a multidisciplinary team reaches a consensus on vital elements of trial design and structure. Similarly, independent and objective regulatory oversight, with a built-in systematic means of routine evaluation, should ensure that these criteria are being enforced and that additional, sometimes unexpected, ethical challenges are adequately addressed.

Currently, few psychiatric diseases meet the aforementioned stringent criteria for surgical intervention. Those that do, such as OCD and major depression, have undergone multiple pilot studies that have demonstrated safety and clinical efficacy and are now being explored in randomized, double-blind trials in centers globally. As clinicians, researchers, and consumers of the medical literature, we must ensure that a precedent is set in which only studies that meet stringent criteria of ethical conduct, as demonstrated by open and free discussion of methodology and ethical review, should be welcomed into the academic and scientific arena for discussion and dissemination.

Conclusions

Clinical trials in psychosurgery offer particularly potent ethical challenges. These challenges stem from the undertaking of a novel therapy in a population that is vulnerable and that, by definition, has reached the limits of traditional treatment. For these reasons, the ethical thresholds for patient recruitment, disease selection, and informed consent arguably all need to be higher. Anything less than diligent and careful attention to the ethical conduct of a scientifically sound clinical trial in psychiatric neurosurgery threatens the safety of patients, as well as the advancement of the field, as a whole.

Disclosure

Dr. Bernstein is a member of a Canadian Institutes of Health Research (CIHR) "States of Mind: Emerging Issues in Neuroethics" (NNF 80045). Dr. Lozano is a Canada Research Chair and has received funding from CIHR.

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Drafting the article: Lipsman. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Bernstein, Lozano.

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Manuscript submitted February 22, 2010.
Accepted April 21, 2010.

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Deep brain stimulation for obsessive-compulsive disorder: past, present, and future

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Obsessive-compulsive disorder (OCD) is a psychiatric illness that can lead to chronic functional impairment. Some patients with severe, chronic OCD have been treated with ablative neurosurgical techniques over the past 4 decades. More recently, deep brain stimulation (DBS) has been investigated as a therapy for refractory OCD, and the procedure was granted a limited humanitarian device exemption by the FDA in 2009. In this article, the authors review the development of DBS for OCD, describe the current understanding of the pathophysiological mechanisms of the disorder and how the underlying neural circuits might be modulated by DBS, and discuss the clinical studies that provide evidence for the use of this evolving therapy. The authors conclude with suggestions for how a combined basic science and translational research approach could drive the understanding of the neural mechanisms underlying OCD as well as the clinical effectiveness of DBS in the setting of recalcitrant disease.
(DOI: 10.3171/2010.4.FOCUS10107)

Key Words • **deep brain stimulation** • **obsessive-compulsive disorder** • **psychiatric neurosurgery** • **ventral striatum** • **subthalamic nucleus**

Obsessive-compulsive disorder is a psychiatric illness in which intrusive thoughts or impulses (obsessions) generate anxiety that is relieved through the engagement in ritualistic or repetitive behaviors (compulsions). Obsessive-compulsive disorder is relatively common, with a lifetime prevalence of 2%–3% in the US.[63] Standard therapeutic options consist of selective serotonin reuptake inhibitors and cognitive behavioral therapy;[32] despite these interventions, however, 20%–40% of patients with OCD have persistent symptoms leading to chronic functional impairment.[58,64]

Over the past 4 decades, some patients with severe, refractory OCD have been treated with ablative neurosurgical techniques, including anterior capsulotomy[26] and cingulotomy.[15] Although the outcomes of these lesioning procedures have been variable,[42] most reports reflect a meaningful improvement in 30%–70% of patients,[26,51] thereby offering a valuable option to debilitated patients with OCD who have exhausted less invasive therapeutic measures.

For the past 2 decades, DBS has been validated as an alternative to lesional neurosurgery for movement disorders such as PD, dystonia, and essential tremor. Since the first report in 1999 by Nuttin and colleagues,[56] DBS has also been investigated in the treatment of refractory OCD. Deep brain stimulation has certain advantages over lesional surgery, offering an adjustable, nondestructive (and reversible) means for neuromodulation. In addition, clinical studies in which DBS is used can include "on" and "off" phases, facilitating blinding and crossover designs.

Clinical studies targeting a variety of neural structures in patients with OCD have suggested that DBS may yield a therapeutic benefit comparable to that derived from ablative techniques.[43,56] In 2009, the FDA granted a limited humanitarian device exemption for using DBS in the setting of intractable OCD. This was the first such approval for a psychiatric disorder. Although the precise role that DBS will play in treating OCD has yet to be established, 4 centers—including our own—are now collaborating in a National Institute of Mental Health–supported trial to explore this issue (see www.ClinicalTrials.gov: NCT00640133). The following review offers a brief summary of the current state of DBS for OCD as well as perspective on the scientific and clinical frontiers of this evolving therapy.

Abbreviations used in this paper: ACC = anterior cingulate cortex; ALIC = anterior limb of the internal capsule; CSTC = cortical-striato-thalamo-cortical; DBS = deep brain stimulation; ITP = inferior thalamic peduncle; NAc = nucleus accumbens; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; PD = Parkinson disease; PFC = prefrontal cortex; STN = subthalamic nucleus; VC = ventral capsule; VS = ventral striatum; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

Historical Perspective

The use of chronic electrical stimulation as a treatment for psychiatric disorders mainly developed as an extension of ablative procedures, although brain stimulation has been used in neurosurgery for some time. In the 1930s and 1940s, Wilder Penfield and Herbert Jasper developed the Montreal procedure, a technique in which they applied acute electrical stimulation to the brains of patients with epilepsy to map the functions of regions in the neighborhood of planned resections.[59] Pool[62] may have been the first to use chronic stimulation for the treatment of a psychiatric condition when he stimulated the caudate nucleus in an attempt to cure depression and anorexia. Modern DBS, however, is rooted in ablative procedures. The transition from ablative procedures to DBS has been possible because the effects of chronic stimulation can be similar to those of ablation in certain cases.[48]

Egas Moniz was an early pioneer of ablative psychiatric neurosurgery, earning the 1949 Nobel Prize in Physiology or Medicine for the development of the prefrontal leukotomy. Walter Freeman, who was not a neurosurgeon, popularized a crude version of the technique, performing more than 3000 lobotomies during the 1940s and early 1950s. Lobotomies severed the connections of the frontal cortex, rendering many patients apathetic and abulic. The typical outcome was that the illness became easier to manage in patients with problematic mental health issues, but concerns grew over the ethical implications of indiscriminate application of a crude surgical procedure to the mentally ill. Lobotomies ultimately fell into disfavor after the introduction of effective oral medications such as chlorprozamine. The creation of an unfortunate group of lobotomy patients with severe and irreversible lesions led to a backlash against surgical interventions for psychiatric disorders.

Subsequent development of ablative neurosurgical procedures attempted to limit side effects by reducing lesion size. The anterior capsulotomy was introduced by Talairach and Leksell in 1949 to disrupt fibers linking the PFC and ACC to the thalamus.[40] Disruption of these cortical-thalamic connections at a different location was the goal of the subcaudate tractotomy, first performed by Knight[38] in the mid-1960s. Around the same time, the cingulotomy procedure was developed to target the ACC and underlying cingulum bundle.[8] The limbic leukotomy, a combination of both the cingulotomy and subcaudate tractotomy, was introduced in the early 1970s for patients who failed to respond to cingulotomy alone.[37] These lesioning procedures have provided significant benefit to thousands of treatment-resistant OCD patients over 4 decades, and are still in use today.[15,27]

The success of modern DBS for movement disorders and the demonstrated efficacy of lesional surgery for OCD paved the way for the extension of DBS to psychiatric disorders. The current era of using DBS in the setting of psychiatric illness began in 1999 when Nuttin and colleagues[56] used DBS to treat intractable OCD, with targeting informed by experience with the anterior capsulotomy. By that time, however, there were already indications that DBS could have psychiatric effects, including numerous reports of psychiatric effects among DBS-treated patients with PD. Deep brain stimulation held appeal for several reasons, one of which was that its theoretical reversibility offered to mitigate the risks associated with permanent lesions. Despite such advantages and an apparent efficacy comparable to ablative techniques, DBS for OCD has yet to be adopted widely, and there remain relatively few published cases in the literature more than a decade after its first introduction.

Ongoing studies of DBS for OCD focus on both patient selection and the refinement of stimulation sites to target specific dimensions of this complex disorder. Focal stimulation is expected to modulate some, but not all, disease elements. Current research is guided by the premise that the coupling of a thorough understanding of the brain circuitry underlying a psychiatric disease such as OCD with a deconstruction of the illness into clusters of pathological components will yield more effective and targeted interventions.[12,13] If patients are selected according to their unique clusters of symptoms (which presumably correspond to homogeneous pathophysiological patterns), then stimulation perhaps could be tailored for specific disease manifestations, thereby improving the probability of achieving meaningful clinical benefit.

Mechanisms of OCD

The pathophysiological basis of OCD appears to involve abnormal functioning in CSTC brain circuits that involve ventral-mesial PFC, dorsal ACC, OFC, and their associated basal ganglia and thalamic connections.[12] Looped CSTC circuits subserve a diversity of physiological functions,[3] and pathological activity in these loops might form the basis for OCD.[53] Frontal lobe and basal ganglia abnormalities have been observed among OCD patients,[25,66] and the fibers linking these regions traverse the ALIC, which is the site of anterior capsulotomy lesions. Dysregulation of neurotransmitters, including dopamine[76] and serotonin,[30,57,79] may also play an important role.

Neuroimaging has provided a revealing window into the neural circuitry underlying OCD. Hyperactivity is frequently observed in CSTC circuits (especially in the OFC and caudate nucleus) in OCD patients, and this hyperactivity can be magnified by provocation of OCD symptoms.[49,66,71] Some studies point to differences in the volumes of CSTC structures between patients with OCD and control volunteers.[33,68] Additionally, the white matter tracts linking putative CSTC nodes may be abnormal; a diffusion tensor imaging study found differences in the cingulum bundles and ALICs of patients with OCD compared with non-OCD controls.[11]

Nonhuman primate studies can tell us a great deal about fine-grained mechanisms of decision-making and reward processing, which could in turn help us understand the pathophysiological origins of OCD. Animal research suggests, for example, that the OFC manages satiety mechanisms.[69] These mechanisms dictate that rewarding actions are performed until a feeling of "fullness" is achieved. This basic process appears to be disrupted in some OCD subtypes,[60] possibly explaining why such patients develop compulsions.

The mechanisms by which DBS relieves OCD symptoms are largely unknown. Complicating the issue, distinct DBS-mediated effects evolve on different time scales, and patients have dynamic clinical trajectories. Comorbid depressive symptoms, for instance, appear to improve relatively quickly,[73] whereas the OCD symptoms themselves tend to lessen over weeks or months.[23] Everitt and Robbins[17] recently proposed a neural mechanism for drug addiction in which the transition from voluntary to habitual and compulsive drug use involves a transfer of control from PFC to striatal regions as well as a progression from ventral to more dorsal domains of the striatum. One possible mechanism of action of DBS may be to perturb the balance between cortical and subcortical influences on behavior.[28] In this scenario, exogenous stimulation may reverse the established pathological balance, ultimately leading to a transfer of behavioral control from the striatum back to PFC regions. This putative mechanism generates hypotheses that can be tested with functional neuroimaging or animal studies. Such a mechanism would agree with the known time course of the effects of DBS on OCD symptoms. It would also support the observation that patients who are treated with DBS become more receptive to standard behavioral therapies, having a heightened ability to choose new courses of action in familiar situations.[50]

Patient Considerations

Ethical objections have been raised regarding the application of neurosurgery to psychiatric illnesses, with critics often citing the notorious legacy of indiscriminate psychosurgery prior to the stereotactic era, as well as the concern over inappropriate behavioral modification or control. Although modern psychiatric neurosurgery in no way resembles the transorbital lobotomies of yesteryear, these concerns nonetheless merit cautious consideration.

Currently adopted standards for patient selection for psychiatric surgery originate from interactions between physicians and the US Congress in the late 1970s. To allay fears about the inappropriate use of psychiatric surgery, a congressional commission was formed to evaluate the indications for surgery and the criteria for patient selection. Their report[54] was the basis for guidelines surrounding the practice of psychiatric surgery that were adopted by centers performing such procedures, including ours.[16] These guidelines are summarized in Table 1, and are reflected in the inclusion and exclusion criteria of recent clinical trials. Paramount among these is involvement of a multidisciplinary team consisting of psychiatrists, neurologists, psychologists, and neurosurgeons.[14] Participation of such a team increases the likelihood that the often complicated psychiatric and medical histories of candidate patients are properly considered. The expertise of these specialists is also essential in the postoperative period as the patient is adjusting to unaccustomed changes in mood and behavior.

With respect to outcome measures, the most commonly invoked metric of efficacy is a reduction in the Y-BOCS[21] score. The Y-BOCS is a 10-item scale in which higher scores reflect more intense symptoms, and a score

TABLE 1: Guidelines for psychiatric neurosurgery based on the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Patient Selection	Evidence for OCD Intractability	Exclusion Criteria
patient should be referred to the psychiatric neurosurgery team by his/her primary psychiatrist, who should also be willing to resume psychiatric care of the patient postop	pharmacotherapy evidence for reasonable exhaustion of drugs & drug combinations acceptable doses checked by plasma levels where indicated	personality disorder, especially antisocial or borderline behavior primary substance abuse evidence of lack of reliability or compliance
decision for candidacy should be made by a multidisciplinary team composed of: qualified psychiatrist, neurologist, & neurosurgeon for patient evaluation qualified psychologist for psychometric testing	reasons for failure include lack of response, intolerance, or severe side effects individual psychotherapy group, couples, & family psychotherapy cognitive & behavioral therapy electroconvulsive therapy	unwillingness to continue medications or psychiatric evaluation postop lack of personal support systems, including family or friends
the psychiatrist & neurologist should not be primarily involved in the care of patient being evaluated	chronicity & disability illness should be of sufficient duration to permit spontaneous remission & completion of the above treatment protocols	
unanimous approval should be obtained before proceeding w/ op		

of 24 or more (of a possible 40) is considered "severe" illness. Most studies designate a therapeutic response as a Y-BOCS reduction of 35% or more from the pretreatment baseline. Some studies also report reductions of 25% or more (partial responses), which indeed can represent meaningful improvements in certain patients.

Current Targets

After a decade of small studies and case series, the application of DBS to treatment-resistant OCD remains investigational. Clinicians have used a wide variety of paradigms for selecting DBS in the treatment of OCD, giving rise to heterogeneities in patient selection, neural targeting, and stimulation protocols that preclude a rigorous meta-analysis. The following material outlines the theoretical basis and clinical outcomes for 3 DBS target regions. Table 2 offers a summary of the outcome studies published to date.

Target 1: the ALIC and VC/VS

In the first cases of DBS for OCD,[56] the site of lead implantation was based on experience with the anterior capsulotomy, a lesioning technique shown to be successful in reducing symptom severity in roughly one-half of cases.[52] In subsequent years, DBS has been applied at several loci along the rostral-caudal dimension of the ALIC. Studies have been performed to interrogate the effects of stimulating not only this VC territory but also the adjacent VS, which in turn contains the NAc. This region is often referred to as the VC/VS.

Greenberg and colleagues[23] recently reviewed outcomes from 4 centers in which the VC/VS target is used. As had been previously suggested with thermocapsulotomies and Gamma Knife capsulotomies, response rates improved as the target was shifted posteriorly, to within a millimeter of the posterior border of the anterior commissure.[41] This migration of the target site reduced the stimulation energies required for eliciting a clinical response, possibly because the fiber bundle being targeted grows more compact as it courses posteriorly.[65] The refinement in target selection was attended by an increase in the percentage of patients manifesting ≥ 35% reductions in Y-BOCS scores (from 33% to 75%). In the dorsal-ventral dimension, the most distal of the 4 contacts (contact 0) was in the VS, 3–4 mm ventral to the anterior commissure-posterior commissure line, and the next most distal contact (Contact 1) was in the VC, just dorsal to the anterior commissure–posterior commissure line. Contacts 2 and 3 were in the middle and dorsal aspect of the capsule, respectively. The observation that the 2 ventral-most contacts were chosen most often for chronic stimulation[20] further suggests that the optimal location spans the most ventral region of the capsule and the VS itself, which animal model data[77] and neuroimaging studies[74] have also suggested might hold therapeutic potential. We and others are currently involved in a clinical trial in which we are using an electrode with more compactly spaced contacts, all within this more ventral region (Fig. 1).

Citing the role of the NAc in modulating the neural circuit presumed to be dysfunctional in OCD (as reviewed by Nicola[55]), Sturm and colleagues[74] advocated stimulation of the NAc shell in OCD. They conducted a small pilot study showing that DBS of the right NAc yielded

TABLE 2: Literature review of outcomes studies after DBS for OCD*

Authors & Year	No. of Patients	Target	% Responders (ΔY-BOCS Score) ≥35%	% Responders (ΔY-BOCS Score) ≥25%	FU (mos)
Mallet et al., 2002	2	STN	100	100	6
Anderson & Ahmed, 2003	1	ALIC	+	+	3
Sturm et al., 2003	4	rt NAc	75	NA	30–34
Aouizerate et al., 2004	1	ventral Cd	+	+	15
Fontaine et al., 2004	1	STN	+	+	6
Abelson et al., 2005†	4	ALIC	50	50	10
Jiménez et al., 2007†	1	ITP	+	+	18
Mallet et al., 2008†	16	STN	NA	75	3
Plewnia et al., 2008	1	rt ALIC/NAc	–	+	24
Aouizerate et al., 2009	2	VS	100	100	15
Jiménez-Ponce et al., 2009	5	ITP	100	100	12
Huff et al., 2010†	10	rt NAc	10	50	12
Goodman et al., 2010†	6	VC/VS	67	67	12
Greenberg et al., 2010‡	26	VC/VS	62	73	3–36

* The outcomes of single case reports are indicated with either a "+" for positive response or "–" for lack thereof. A therapeutic response is represented by a score of ≥ 35%; partial response by a score of ≥ 25%. Abbreviations: Cd = caudate; FU = follow-up; NA = not applicable; Δ = change.

† Study invoked a double-blind sham-stimulation crossover design.

‡ See reference 23. Reflects results compiled for patients from other studies (Nuttin et al., 1999; Goodman et al., 2010; Cosyns et al., 2003; Nuttin et al., 2003; and Gabriels et al., 2003).

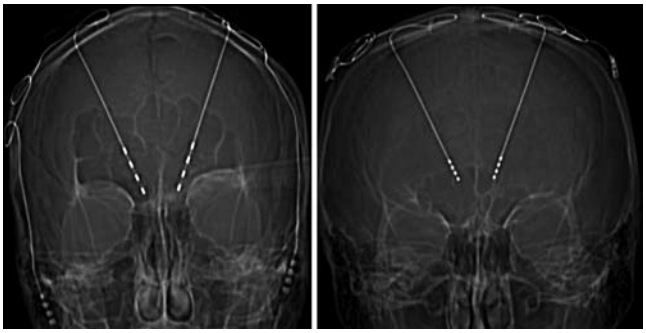

Fig. 1. Neuroimages demonstrating evolution in targeting of the VC/VS target. **Left:** In recent studies an electrode design with 3-mm leads spaced 4 mm apart (Medtronic model 3391; previously referred to as model 3387IES in 2010 articles by Goodman et al. and Greenberg et al.) was used to span the entirety of the ALIC and VS, paralleling the targeted region in the capsulotomy experience. **Right:** In the current study of the VC/VS target, an electrode with 1.5-mm contacts spaced 1.5 mm apart (Medtronic model 3387) was used. This more compact design places all the contacts within the VS and ventral-most region of the capsule.

clinical improvement and that bilateral stimulation offered no additional benefit. One precedent for this laterality of responsiveness was a previous report that right-sided lesions in the midsection of the ALIC were critical to therapeutic outcome in patients who underwent thermocapsulotomy.[41] Of 4 patients who received DBS of the shell of the right NAc, 3 achieved near complete recoveries over 2 years. However, this efficacy was not borne out subsequently in a larger series of patients;[31] in this recent study, only 1 of 10 patients manifested a Y-BOCS score reduction of 35% or more. Thus, the evidence at present favors a bilateral VC/VS implantation.

The most worrisome stimulation-associated adverse events in the preceding studies were hypomania and suicidal ideation. Hypomania has generally been transient and reversible; it also appears to be dependent on stimulation intensity.[22] Suicidal ideation has also been observed among patients with OCD who are receiving DBS, and 1 patient in a series reported by Abelson et al.[1] committed suicide during the open stimulation period (although she left a note absolving her study participation and response to DBS as motivating factors). It is important to note that the suicide rate among patients with severe depression, which frequently accompanies intractable OCD, is as high as 15%. These sobering findings underscore the importance of careful screening of DBS candidates by a multidisciplinary team.

Target 2: the STN

The STN has emerged as a possible node for modulating OCD circuitry following observations that DBS of the STN in patients with PD ameliorates obsessive-compulsive traits[2] and also reduces Y-BOCS scores in those with OCD.[18,43] Additional studies have demonstrated the capacity of STN stimulation to attenuate repetitive behaviors[7] and anxiety[29] as well as to interfere with decision-deferring processes.[19] Anatomically, the ventral anteromedial STN receives limbic and associative cortical input via CSTC circuits originating in the OFC.[36] These lines of evidence point to a role for the STN in behavioral integration.[45] Given the neurosurgical community's extensive experience with DBS of the STN for PD, this structure would thus seem to be an appealing target for OCD neuromodulation.

In 2008, Mallet et al.[44] reported the results of a crossover, double-blinded trial of STN DBS in 18 patients with OCD. These investigators targeted the anteromedial STN at the boundary of the limbic and associative territories; the center of this region lies approximately 2 mm anterior and 1 mm medial to the target used for patients with PD.[10] Stimulation resulted in Y-BOCS score reductions of 25% or more in 75% of study subjects, but there were several serious adverse events, including 1 intracerebral hemorrhage, 2 infections requiring electrode removal, and 3 cases of transient, stimulation-induced hypomania. The authors point out, however, that the number of surgery-related complications was similar to rates previously reported,[39,67] and that the stimulation-associated adverse events largely consisted of motor or psychiatric symptoms that resolved either spontaneously or promptly with adjustment of stimulator settings.

Target 3: the ITP

The ITP is a white matter bundle that has been evaluated for DBS implantation in OCD. This structure links the OFC and thalamus, and it also corresponds to part of the territory targeted by the subcaudate tractotomy.[72] Electrical stimulation of the ITP could mitigate OCD symptoms via effects propagated along the swath of OFC and ventromedial striatum projections entering the thalamus. In addition, the relative compactness of the ITP offers the theoretical advantage of reducing the charge density needed to mediate a clinical response, which could lengthen battery life.

Clinical investigation of DBS of the ITP has been reported by only one group. Jiménez-Ponce and colleagues[35] stimulated the ITP bilaterally, noting Y-BOCS score reductions of at least 35% as well as dramatic global assessment of function increases in 5 of 5 patients with OCD. This was an open series, however, and the inclusion criteria were not as stringent as in other studies (1 patient had a schizoid personality disorder and 3 were illicit drug abusers). The effects of these factors on the reported outcomes are unclear.

The potential utility of stimulating the ITP remains unsettled. The trajectories of all DBS leads in the Jiménez-Ponce[35] study traversed the anterior horn of the lateral ventricle. Recent reports have suggested that a transventricular trajectory incurs increased risk of hemorrhage[9] and reduces targeting accuracy.[81] The ITP trajectories avoiding the ventricles, if feasible, would be preferred. Also, although the authors describe and reference a method for identifying the ITP by using electrocortical recruiting responses,[78] the ITP is a small target not commonly localized by using standard microelectrode recordings. Larger series and additional experience will perhaps shed light on these issues.

Future Directions

Deep brain stimulation for psychiatric disorders is

in its infancy, especially when compared with its use for movement disorders. The nearly routine use of DBS for PD ensures that the coming generation of neurosurgeons will be well versed in the technique, most metropolitan areas will have the capability, and a rapidly growing proportion of the American public will be intimately familiar with the ameliorative effects of well-placed high-frequency stimulators within the brain for certain disorders.

As with PD, we predict that the use of DBS for OCD will contribute greatly to the scientific understanding of complex brain disorders. Our understanding of OCD is likely to benefit even more from experience with patients receiving DBS than has our understanding of PD, because there is currently no standard animal model of OCD, making the observational data obtained in patients with this disease especially valuable. Obsessive-compulsive disorder might prove to be a uniquely human condition, involving an imbalance in an elaborate human ability to assess uncertainty and to predict negative outcomes that is beyond the capacity of our nearest evolutionary relatives. It is our belief, however, that animal studies—particularly studies of awake, behaving nonhuman primates engaged in cognitively demanding tasks—will figure prominently in the near-term growth of understanding of psychiatric disorders and will set the stage for optimally targeted, effective, and individualized treatment of human patients with specific subtypes of OCD.

One experimental approach would be to begin by identifying differences between patients with OCD and healthy volunteers in their performance of various decision-making tasks. Primates could then be trained to perform similar tasks, while physiological recordings interrogate the role of various regions in the circuit implicated in OCD.[12] In our current research, we are exploring the abnormally high sensitivity to potentially aversive outcomes in OCD by training animals to perform a task in which they must weigh combined aversive and rewarding stimuli. Knowledge of the neural circuitry of OCD suggests that the OFC, basal ganglia, and thalamic targets might mediate this decision-conflict paradigm, because patients with OCD perform this task abnormally.

Once the relevant dimensions of OCD's pathological features can be identified and instantiated into a task suitable to nonhuman primates, one could then systematically explore both the parameter space and the effects of stimulation in ways that are impractical with human subjects. For example, in recent DBS studies investigators have observed improvements in patient outcomes with posterior migration of the stimulation site.[20,23] Nonhuman primate research could more quickly ascertain the effects of small, systematic refinements in the location of DBS leads.

We predict that the next major advancement in the field will result from research on how target selection could differentially mitigate symptoms of different OCD subtypes. Evidence suggests that such subtypes have origins in distinct neural circuits.[47,70] Furthermore, stimulation of individual circuits yields distinct patterns of clinical effects. For example, Aouizerate and colleagues[5] reported that caudate nucleus stimulation preferentially alleviates OCD manifestations, whereas NAc stimulation tends to improve depressive symptoms. It has also been suggested that VC/VS DBS preferentially benefits patients in whom OCD symptoms are motivated principally by a feared consequence rather than a feeling of incompleteness.[24] If the effects of stimulating different targets can be well characterized, DBS lead placement might someday be personalized based on an individual's disease manifestations.

An interesting possibility is that DBS may indirectly benefit patients with OCD by reducing symptom severity sufficiently to allow engagement in other forms of therapy. This phenomenon has been described after capsulotomy.[50] For clinical research purposes, we must first clarify the impact of DBS on OCD in isolation, but in the near future it will be important to integrate DBS treatments successfully with both cognitive behavioral therapy and modifications in pharmacotherapy.

Conclusions

Deep brain stimulation is a promising therapy for intractable OCD. Future refinements may include the development of a demand-controlled rather than an open loop stimulator.[75] This type of device could responsively apply stimulation when necessary, potentially providing greater behavioral control, reducing side effects, and extending battery life. Indeed, our understanding of the underlying mechanisms obtained through experience with DBS may even lead to completely novel and individualized approaches. Light-activated manipulation of neural circuits may allow specific activation or suppression of certain cell types.[80] Genetic material introduced into specific dysfunctional targets may permit beneficial modification of their function.[46] Harnessing emerging technologies such as optogenetics, gene therapy, and others will probably revolutionize the treatment of neurological and psychiatric disease, so that DBS might prove to be a stepping-stone to even more precise treatments in the future. Regardless of the device or technology used to treat patients with intractable OCD, however, it is important to note that these are highly complex and fragile patients. To ensure that past mistakes are not repeated, the care of these patients should be managed by a multidisciplinary team, adhering to accepted guidelines.

Disclosure

The following funding was received: National Eye Institute (Grant No. 1R01EY017658-01) to Dr. Eskandar as principal investigator; National Institute on Drug Abuse (Grant No. 1R01NS063249) to Dr. Eskandar as principal investigator; National Institute of Mental Health (Grant No. P50 MH086400-03) to Dr. Eskandar as co-investigator; National Science Foundation (Grant No. IOB 0645886) to Dr. Eskandar as principal investigator; Howard Hughes Medical Institute (Physician Scientist Early Career Award) to Dr. Eskandar as principal investigator; and National Institute for Neurological Disorders and Stroke (Grant No. R25 NS065743) to Dr. Sheth as fellow. None of the contents of this manuscript have been previously submitted for publication or presentation. The authors report no conflict of interest.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Drafting the article: Mian, Campos, Sheth. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it

for submission: all authors. Administrative/technical/material support: Eskandar.

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Manuscript submitted April 16, 2010.
Accepted April 30, 2010.

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Neurosurg Focus 29 (2):E11, 2010

Deep brain stimulation of the orbitofrontal projections for the treatment of intermittent explosive disorder

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Intermittent explosive disorder (IED) is characterized by a dysfunction in the greater limbic system leading an individual to experience sudden aggressive behavior with little or no environmental perturbation. This report describes a procedure for the treatment of IED in a 19-year-old woman with a history of IED, having had episodes of severe violent attacks against family, dating to early childhood. Due to the severity and intractability of the illness, deep brain stimulation was performed, targeting the orbitofrontal projections to the hypothalamus. The patient's history and the procedure, management, and rationale are described in detail. *(DOI: 10.3171/2010.5.FOCUS10102)*

Key Words • deep brain stimulation • orbitofrontal cortex • intermittent explosive disorder

Intermittent explosive disorder is a psychological illness characterized by episodes of impulsive aggression that are disproportionate to the provocation.[5] The root of such behavior involves a disturbance to the emotional circuitry of the brain. This includes the anterior cingulate cortex, orbitofrontal cortex, amygdala, insular cortex, ventral striatum, and other interconnected circuitry throughout the limbic system that combine to form the emotional brain.[7] The orbitofrontal cortex, the amygdala, and anterior cingulate cortex have been implicated as key regions in impulsive behavioral control, while the anterior cingulate cortex has also been shown to recruit regions of the prefrontal cortex during periods of threat and aggression.[2] The right frontobasal cortex has recently been understood to be an integral part of the limbic system involved in modulating an individual's level of anger.[4,7,15] Almost all patients with IED have brain damage, which is usually traumatic in nature and occurs in the right frontobasal cortex. This damage is associated with a reduction in serotonin binding in the region.[9] In this report, we describe DBS targeted to the projections between the hypothalamus and orbitofrontal cortex as a useful means of treating intractable IED and providing the patient with the ability to control her aggressive behavior and suppress violent outbursts.

Abbreviations used in this paper: DBS = deep brain stimulation; IED = intermittent explosive disorder.

Case Report

History and Examination. This 19-year-old woman was born of a traumatic birth and has moderate mental retardation. She was referred to our clinic for the possible treatment of her IED with stereotactic surgery. Intermittent explosive disorder had been diagnosed when the patient was a child. Throughout her life, the patient had experienced episodes in which she lost control of her emotions and engaged in violent attacks against individuals including her mother and grandmother. As she aged, she became increasingly difficult to control during these attacks and required heavy sedation to live at home and avoid institutional commitment. She also experienced depression, was diagnosed with bipolar disorder at one time, and MR imaging demonstrated bilateral atrophy of the hippocampus and hippocampal gyri. As part of her current treatment, the patient was taking Zyprexa (20 mg) at bedtime, Tegretol (200 mg) twice a day, Klonopin (1 mg) every morning, and Lunesta at bedtime. Aside from the previously stated issues, her examination and studies, including the results of her 24-hour electroencephalography, were normal. Therefore, the decision was made to proceed with a DBS procedure targeting the projections between the orbitofrontal cortex and the hypothalamus.

Operation. Under stereotactic guidance, with merged MR and CT images, a paramedian incision was made,

and the entry point extended along the coronal suture. The stereotactic electrode was directed just lateral to the lateral ventricle. Proceeding primarily through white matter tract, the electrode was guided into the region below the stria terminalis in the most inferior corona radiata projections from the frontobasal cortex to the hypothalamus. Both our preoperative planning and intraoperative guidance target selection confirmed that the electrode was correctly located at final coordinates of 15 mm anterior to the midcommissural plane, 5 mm lateral to the midsagittal plane, and with contacts level to the plane connecting the anterior and posterior commissures and traversing up to 3 mm ventral to anterior and posterior commissures (Schaltenbrand-Wahren Atlas). When satisfied with the accuracy of the placement, a Lucite lockdown device secured the device, and the electrode extension was brought down to the pulse generator in the subclavicular area. The Soletra neurostimulation system (Medtronic) was used for this patient. The location of the electrode was later confirmed on MR imaging (Fig. 1).

Postoperative Course. The patient recovered postoperatively without complications and was discharged home. She was then seen 1 month later, after her wounds had healed well, so that we could activate the stimulator. The visit took place with family, who stated that the patient was continuing with violent episodes and was completely uncooperative at times. The stimulation setting plan was to consist of high- and low-frequency stimulation trial periods with adjustments made during each period as needed. The DBS system was activated with contact settings of 0–2 negative and 3 positive. Stimulation was set to a high frequency of 130 Hz, amplitude of 4 V, with a 120-μsec peak width to block the pathway. This resulted in immediate elimination of agitation and aggression. The patient was instantly cooperative, and at this point she turned to her family and described a sudden change in her emotions, stating that she "felt much better." Her facial expression was calmed. Her motor skills were examined and her handwriting had markedly improved, likely because she previously had difficulty forming letters in an agitated state. Several hours after stimulation began, her family reported that her memory had improved and she was fully compliant with instructions. The patient's Zyprexa was therefore ceased, but the other medications were continued. The family returned 1 week later, stating that her agitation and "acting out" had markedly increased, and they asked that the stimulation be turned off. She was described as being quite irritable at times and had run away from home. Her family did, however, report a more outgoing, talkative demeanor, and they believed for the first time that the patient was vocalizing her feelings. She had taken on some independence at home, albeit little. She was described as much less lethargic, was not sleeping throughout the day, and her memory and handwriting had improved. Despite these changes, during this period she had experienced outbursts of anger that prompted psychiatric hospitalization. Klonopin was discontinued, and the Tegretol dose was reduced. We discontinued blocking stimulation and went to activation levels of stimulation. Low-frequency stimulation was then tested with initial settings at 2.8-V amplitude, 55 Hz, 270-μsec peak width, and with a cycle in which stimulation was on for 3 minutes and off for 5 minutes.

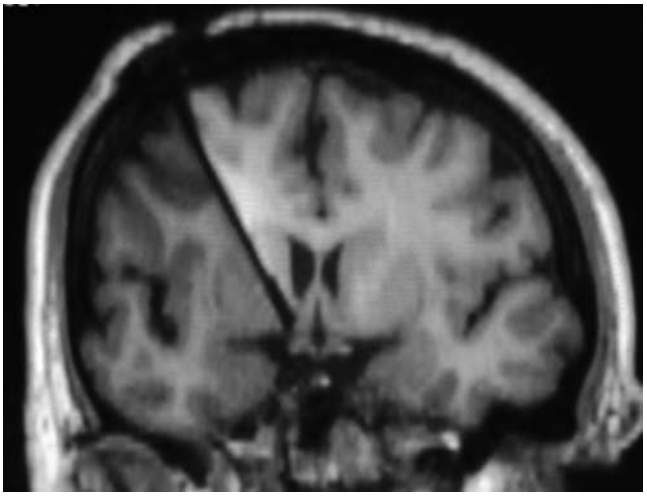

Fig. 1. Postoperative T1-weighted MR image demonstrating electrode placement in the basal projections from the orbitofrontal cortex.

Follow-Up and DBS Adjustments. After 6 weeks with the aforementioned stimulation settings, the patient's performance in school had improved significantly, and there had been no violent outbursts. She had been able to attend church and was socializing better, but she remained argumentative at times, though this was always provoked. She returned to clinic and her stimulation settings were adjusted to a cycle of 3 minutes on and 3 minutes off.

At the 5-month evaluation, the family reported a violent verbal outburst directed toward a teacher. The patient was also admitted to the hospital with pneumonia during this period. When her stimulation was turned off during testing in the hospital, she attacked the technician and was immediately calmed with restoration of stimulation. At this visit, her peak width was increased to 360 μsec and frequency reduced to 40 Hz.

At the 7-month follow-up, the patient was becoming increasingly argumentative, displayed some obsessive-compulsive behavior, and had experienced panic attacks. Once again, a reduction in her IED drugs was attempted. Six weeks following this adjustment, however, the patient became severely depressed. She overdosed on her mediation and spent the next 3 months in a psychiatric ward.

Following this episode, the patient reported for her 12-month follow-up visit. Her DBS settings were adjusted to a 2.5-V amplitude, 40 Hz, and 360-μsec peak width. These settings produced agitation and were therefore adjusted to 20 Hz, 2-V amplitude, with cycling of 1 minute on and 1 minute off stimulation. The patient was immediately calmed following this adjustment. The family reported that in the weeks following this visit the patient socialized well, and marked improvements were seen in her memory, concentration, and performance in school.

Currently, 2 years out from the operation, the patient has had no other violent outbursts or physical altercations, and she continues to control any agitation through verbal interaction. The improvements in her performance in

school have been maintained, and she no longer requires heavy sedation or antipsychotic drugs. Her socialization continues to be markedly improved. The stimulator settings have remained unchanged since the 12-month follow-up visit. We have observed, through various adjustments to the neurostimulator, that a fine line exists between control of symptoms and depression in this individual. The effects of the adjustment are quickly evident, however, thus facilitating our finding of the optimal settings.

Discussion

Prevalence of IED

Recent estimates have found shown IED may have a prevalence of 2–5% in the general population, a value that could exceed bipolar disorder or schizophrenia.[6] Furthermore, IED is associated with a high rate of lifetime bipolar disorder comorbidity.[22] The consequences for an individual with this disorder can be as severe as committing a violent crime, but it may involve more minor episodes, which remain highly detrimental to the quality of their professional and personal lives. A recent epidemiological survey found lifetime and 12-month prevalence estimates of DSM-IV IED to be 7.3% and 3.9%, with a mean of 43 lifetime attacks resulting in an average of $1359 in property damage.[17]

Surgical Approaches to Aggressive Disorders

Current and historical approaches to the surgical treatment of aggressive disorders have included both lesioning and stimulation of structures involved in modulating aggression within the limbic system. Goltz,[11] in 1892, and Klüver and Bucy,[19] in the 1930s, demonstrated that bilateral temporal lobectomy in animals attenuated aggressiveness and fear responses, rendering the animals, as Klüver and Bucy stated, psychically blind.[8] This early exploration into the neuroanatomy of the limbic system, along with Papez's 1937 description[27] of the neural circuit involved in emotion, helped to shape modern surgical approaches to treat aggressive disorders. Due to its well-defined involvement in emotion and aggression, the amygdala became the first major surgical target for aggressive disorder treatment. In 1963, Narabayashi et al.[24] published the first large series of patients treated with amydalotomy for severe aggressive disorders, reporting that surgery reduced aggression and improved social behavior in 85% of the cases. More recently, Mpakopoulou et al.[23] described historical and current perspectives on amygdalotomy. They concluded that although the procedure was used frequently since its initial description for the treatment of aggressive disorders, advances in pharmacotherapies and a growing stigma associated with psychosurgery have led to a decrease in its use. They felt, however, that with modern stereotactic surgical techniques, the procedure should still be considered for patients with severe aggressive disorders refractory to current therapies. In 2002, Kim et al.[18] reported long-term follow-up of 2 patients with aggressive disorders in whom they performed bilateral amygdalotomy and subcaudate tractotomy. A stereotactic approach and a radiofrequency lesion generator were used to target these regions. Aggression was measured pre- and postoperatively with the Overt Aggression Scale, which assigns points based on various physical and verbal behaviors.[13] The authors found a decline in aggression at 2-weeks and at 7-year follow-up visits with improvement in social behavior.[18]

Deep brain stimulation of the hypothalamus has also been described as a means of controlling intractable aggressive disorders.[10,14,20] Hernando and colleagues[14] described one such case of a young man with mental retardation and intractable aggressive disorder in whom bilateral electrodes were implanted in the medial posterior hypothalamus. The authors employed low-frequency stimulation and stated that a positive behavioral response was sustained at the time of reporting, 18 months postoperatively. Similarly, Kuhn et al.[20] reported a case involving bilateral stimulation of the posterior hypothalamus for the treatment of severe self-mutilation in a mentally retarded young woman. The authors used high-frequency (130-Hz) stimulation and achieved sustained elimination of self-mutilating behavior.

Nonsurgical Therapies for IED

Serotonin (5-hydroxytryptamine) is believed to be the critical neurotransmitter in modulating violent impulsive behavior.[9] Studies examining inhibition of serotonin biosynthesis, either in individuals with tryptophan hydroxylase enzyme polymorphism[26] or in those in whom tryptophan is removed from the diet,[3] have found significant increases in aggressive behavior associated with low levels of serotonin. Traditional treatment for IED may include behavioral therapy, pharmacotherapy, or a combination. Pharmacotherapy includes selective serotonin reuptake inhibitors, mood stabilizers, and beta-blockers, all meant to modulate the level of emotional arousal or inhibition within the limbic system. However, because controlled trials for IED pharmacotherapies are absent, the efficacy of these treatments is largely anecdotal.[1] Although these treatments are part of the standard of care, in our case the patient's condition remained refractory to such pharmacological therapies and her behavior had progressed to a point where more aggressive treatment was necessary.

Target and Procedure

As discussed earlier, the inferior tracts from the orbitofrontal cortex were chosen as a target because of their role in the conduction of signals related to emotion and particularly aggression within the greater limbic system. Recently, PET and functional MR imaging studies have shown that individuals with loss of impulse control and explosive disorders have abnormal activity localized specifically to the right orbitofrontal cortex.[4,7,28] This interesting asymmetrical involvement of the regions related to aggressive behavior prompted our use of unilateral right-side stimulation. In our case, the location of the electrode within the stria terminalis and orbitofrontal cortical projections was confirmed intraoperatively with stereotactic instrumentation in concert with MR imaging and CT overlays. In our region of stimulation, the combination of

multiple small nuclei and tracts such as the stria terminalis, nucleus accumbens, and others, in proximity, makes defining a specific target difficult. Our definition of the right orbitofrontal cortical projections through the most inferior internal capsule as our primary target is based on imaging studies and symptom reduction. The predicted reduction in symptoms related to the orbitofrontal cortex, including proper modulation of defensive rage and aggression, was seen following stimulation.[12,16,25] Figure 2 is a diagrammatic coronal slice that demonstrates the proximity of the stria terminalis to the nucleus accumbens and anterior limb of the internal capsule at approximately 16 mm anterior to the midcommissural plane. The region traversed by our electrode leads involves each of these 3 structures, and it is therefore possible that each is affected by stimulation. It is difficult, however, to compare our results with studies examining DBS of the nucleus accumbens and internal capsule, as these studies have used different stimulator settings and were for the treatment different disorders, most notably obsessive-compulsive disorder.[16,25] Due to these differences, we cannot definitively state that any single nuclear region is the sole target of stimulation. However, through careful examination of postoperative MR imaging and analysis of our coordinates with multiple stereotactic atlases, we conclude that the orbitofrontal cortical tracts remain the primary target.

Conclusions

In the case presented in this report, the goals of attenuating aggressive impulses and providing the patient with control over her emotions and violent outbursts were achieved. A significant improvement in the quality of life of both the patient and her family was seen almost immediately upon determining the proper settings of her stimulator. As mentioned previously, we found that there was a fine line between achieving control of symptoms and producing some depression as well as obsessive-compulsive disorder symptoms. The change in behavior was seen nearly instantly after adjusting stimulator settings, however, thus facilitating our determination of optimal settings at each clinic visit. While high-frequency settings appeared to stimulate defensive rage in this individual, our final low-frequency settings were successful in attenuating this pathway. This case demonstrates the vast potential that DBS holds for psychological disorders if the appropriate targets are chosen and the correct stimulation settings are achieved.

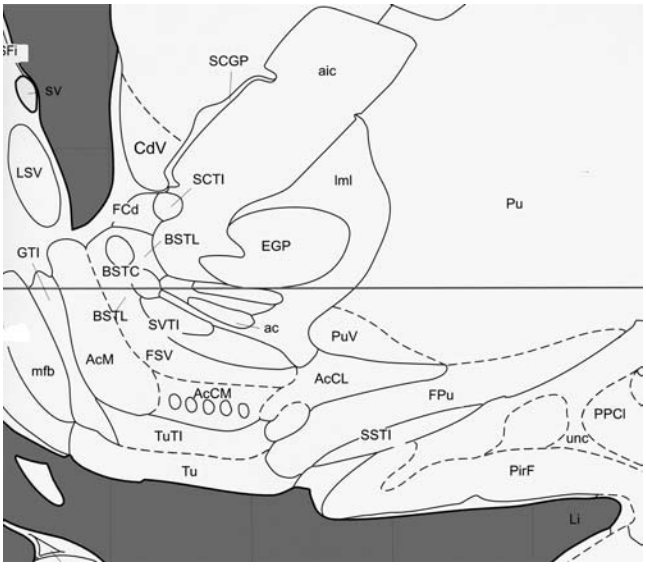

Fig. 2. Diagrammatic coronal slice at approximately 16 mm rostral to the midcommissural plane, demonstrating the region traversed by the electrode array. The *straight line* denotes the plane connecting the anterior and posterior commissures. Ac = regions of nucleus accumbens; Aic = anterior internal capsule; BSLT = bed nucleus of stria terminalis; Pu = putamen. The image is reprinted from Mai JK, Assheuer J, Paxinos G: *Atlas of the Human Brain, ed 2.* San Diego: Elsevier Academic Press, 2004.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Alvernia, Maley, Richardson. Drafting the article: Maley. Critically revising the article: Alvernia, Maley, Valle.

Acknowledgments

The authors thank Myriam Gallager, N.M.S., Lesette Constintine, Ph.D., Kevin Jackson, M.D., Mel Gitlan, M.D., and Jerry White for their critical assistance with this report. We would also like to thank Dr. David Blask for his neuroanatomical guidance with this report.

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Manuscript submitted April 14, 2010.
Accepted May 27, 2010.

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Neurosurg Focus 29 (2):E12, 2010

Deep brain stimulation of the nucleus accumbens reduces alcohol intake in alcohol-preferring rats

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Object. The authors tested the hypothesis that deep brain stimulation (DBS) in the nucleus accumbens (NAcc) decreases alcohol intake in alcohol-preferring (P) rats after each animal has established a stable, large alcohol intake and after P rats with an established intake have been deprived of alcohol for 4–6 weeks.

Methods. Bipolar stimulating electrodes were bilaterally placed in the NAcc using stereotactic coordinates. In the first study, P rats (9 animals) were allowed to establish a stable pattern of alcohol intake (about 5–7 g/day) over approximately 2 weeks, and the acute effects of DBS in the NAcc (140–150 Hz, 60-μsec pulse width, and 200-μA current intensity) on alcohol intake and alcohol preference were studied. Each animal acted as its own control and received 1 hour of DBS followed by 1 hour of sham-DBS or vice versa on each of 2 sequential days. The order of testing (sham-DBS vs DBS) was randomized. In the second study, each animal was allowed to establish a stable alcohol intake and then the animal was deprived of alcohol for 4–6 weeks. Animals received DBS (6 rats) or sham-DBS (5 rats) in the NAcc for 24 hours starting when alcohol was reintroduced to each animal.

Results. Deep brain stimulation in the NAcc, as compared with a period of sham-DBS treatment in the same animals, acutely decreased alcohol preference. Furthermore, alcohol consumption and preference were significantly reduced in the DBS group compared with the sham treatment group during the first 24 hours that alcohol was made available after a period of forced abstinence.

Conclusions. The NAcc plays a key role in the rewarding and subsequent addictive properties of drugs of abuse in general and of alcohol in particular. Deep brain stimulation in the NAcc reduced alcohol consumption in P rats both acutely and after a period of alcohol deprivation. Therefore, DBS in the NAcc coupled with other neurophysiological measurements may be a useful tool in determining the role of the NAcc in the mesocorticolimbic reward circuit. Deep brain stimulation in the NAcc may also be an effective treatment for reducing alcohol consumption in patients who abuse alcohol and have not responded to other forms of therapy. *(DOI: 10.3171/2010.4.FOCUS10105)*

Key Words • deep brain stimulation • nucleus accumbens • reward • alcohol abuse

Deep brain stimulation is a surgical procedure in which an electrode is implanted in 1 or more specific areas of the brain and high-frequency electrical stimulation (130–180 Hz) is delivered to target sites. This procedure ameliorates symptoms associated with some movement disorders[2,6] and has been a moderately effective treatment for intractable pain.[27] The use of DBS is being extended to include a variety of psychiatric disorders such as obsessive-compulsive disorder[19] and depression.[22] The NAcc has a central role in the pathogenesis of drug dependence and is an important element in the mesocorticolimbic reward circuit. It is involved in establishing the salience and reward of drugs of abuse.[36] Many investigators believe that dysregulation of the neurophysiological processes involved in establishing the quality or intensity of rewarding experiences contributes to addiction.[12]

For these reasons, the NAcc is an attractive target for DBS, and early studies are promising. Deep brain stimulation in the NAcc has selectively blocked the reinstatement of psychostimulant use[37] and attenuated morphine-induced place preference.[20] In a patient who received DBS for the primary purpose of alleviating severe anxiety and depression, stimulation in the NAcc had the unintended consequence of improving the patient's comorbid alcohol dependence.[14] Data from a subsequent animal study showed that brief periods of DBS in either the core or the shell of the NAcc reduced alcohol consumption in rats trained to drink alcohol.[10]

Abbreviations used in this paper: ADE = alcohol deprivation effect; DBS = deep brain stimulation; HFS = high-frequency stimulation; NAcc = nucleus accumbens; PD = Parkinson disease; STN = subthalamic nucleus; 6-OHDA = 6-hydroxydopamine.

There are many rat models of alcohol-seeking behavior.[11] Rats that would not "naturally" imbibe alcohol are often trained through variations in the Samson sucrose-fading procedure to consume high quantities of alcohol.[31] Alcohol-preferring rats, on the other hand, are selectively bred. These animals spontaneously consume alcohol in large quantities and do not require reinforcement schedules with sucrose to entice them to drink alcohol.[1] The P rats fulfill all the criteria of a valid model of alcohol-seeking behavior proposed by Cicero:[5] P rats drink sufficient amounts of ethanol to develop metabolic tolerance; they consume large quantities of ethanol and achieve pharmacologically relevant blood alcohol levels;[1] and they increase ethanol consumption after a period of abstinence, which is called the "alcohol deprivation effect" (ADE).[23,35] The ADE is robust and observed in myriad models of alcohol abuse including rats,[33] mice,[32] monkeys,[13] and humans.[26] Its underlying basis is unknown, but ADE may approximate relapse drinking in otherwise abstinent alcoholics.[34]

To our knowledge, DBS has not been used in P rats to suppress or prevent alcohol intake. The NAcc plays a crucial role in alcohol dependence, and lesioning the NAcc shell reduces alcohol preference in P rats already drinking alcohol.[9] Since DBS in PD is thought to mimic the effects of lesioning,[4,7] we sought to determine whether DBS in the NAcc in P rats would have an effect similar to lesioning and suppress alcohol intake. We studied the effect of DBS on alcohol intake in P rats in 2 experiments. In the first study, we tested the hypothesis that DBS would decrease alcohol intake in P rats after each animal had established a stable and large alcohol intake. In the second study, we allowed P rats to establish stable ethanol intake. We then deprived each animal of alcohol for 4–6 weeks and tested the hypothesis that DBS would prevent or reduce the burst of excess alcohol consumption usually seen in P rats when alcohol is made available after a period of abstinence. Thus, the purpose of our study was to show that DBS is effective in reducing both alcohol preference and ADE in rats known to prefer alcohol with no sucrose fading or any other behavioral modification to induce alcohol consumption.

Methods

The experiments were approved by the Institutional Animal Care and Use Committee of Dartmouth College in accordance with National Institutes of Health guidelines for the use of animals in research. We conducted 2 studies. In the first, 9 male P rats weighing between 172 and 365 g (mean ± SEM, 310 ± 10 g) were used; 11 male P rats weighing between 440 and 580 g (528 ± 12 g) were included in the second study. All rats were housed in a temperature-controlled room (21°C) under a 12/12 light/dark cycle (light on at 6:00 a.m.). The rats had ad libitum access to food pellets, water, and 10% ethanol except for 24 hours before and 24 hours after surgery to prevent interactions with the anesthetics used.

Acquisition of Alcohol Preference

Rats were given free access to alcohol for 3–7 weeks to establish a baseline level of alcohol consumption (approximately 5–7 g/kg/day). Access was discontinued in the perioperative period, when stimulating electrodes were placed in the NAcc as described below. Animals were subsequently allowed free access to alcohol for 4–7 days to reestablish baseline levels of alcohol consumption before beginning the DBS treatment.

Surgical Procedures

Each animal was anesthetized with inhaled isoflurane (2–5%, Webster Veterinary). We maintained body temperature at 37°C by using a rectal thermometer and a servo-controlled heating pad placed under the animal. Each rat's head was fixed in a stereotactic frame (Model 1430, David Kopf Instruments), and a midline incision was made starting just caudal to the eyes and ending just rostral to the ears. We placed concentric bipolar stainless steel electrodes (outer diameter 0.005 in, Plastics One, Inc.) bilaterally in the outer shell of the NAcc. The locations of the stimulating electrodes were calculated from the bregma and the brain surface using stereotactic coordinates: anteroposterior +1 mm, mediolateral ±3 mm, and dorsoventral –8 mm.[30] Electrodes were positioned in a custom-made holder before implantation to guarantee a consistent separation between the electrode tips. We secured electrodes to the skull using dental cement (Dentsply International Inc.). After surgery animals were given buprenorphine for 48 hours to alleviate pain.

Study I: Assessment of the Effect of DBS on Established Alcohol Intake

Prior to DBS treatment, animals were moved to operant chambers (Med-Associates, Inc.) and were kept on the same light/dark cycle and access regimen for alcohol and water as previously described. Animals were tethered for 1 hour on the day before DBS-treatment days to acclimate them to the tether before DBS treatment. Animals were treated with DBS for 2 days using a 2-hour treatment cycle (1 hour on/1 hour off DBS). Whether an animal received stimulation in the 1st hour or the 2nd hour on Day 1 of treatment was randomly determined, and the treatment order was reversed on the next day. Thus, each animal acted as its own control every day, and each animal experienced both DBS treatment orders. Prior to the stimulation/no stimulation treatment, animals were tethered to a cable used to deliver DBS to the electrodes implanted in each animal. Animals were given time to acclimate to the tether for at least 1 hour before treatment. Rats underwent a conditioning period of DBS 1 hour before the beginning of the dark cycle consistently at 6:00 p.m., that is, the time of day that the rats were seen to be the most active. For this DBS conditioning period, alcohol—not water and food—was withheld from the rats. At the start of the dark cycle, 10% alcohol was reintroduced to the rats, and DBS was either continued during the stimulation treatment or the pulse was discontinued during the no stimulation treatment. Both drinking bottles containing either water or 10% ethanol were weighed prior to and just after each 1-hour stimulation/no stimulation period.

Stimulation was delivered using a pulse code generator (Master-8-vp, A.M.P.I., Ltd.) and an Isoflex stimulus

isolation device (A.M.P.I., Ltd.). The stimulation current during the DBS conditioning period and treatment period consisted of monophasic square wave pulses. Stimulation was delivered at a frequency of 140–150 Hz with a pulse width of 60 μsec and a current intensity of 200 μA.

Study II: DBS Treatment of ADE

The second study was designed to show the effect of DBS on alcohol consumption in P rats after a period of abstinence from alcohol. Rats were given free access to alcohol for 4–6 weeks to establish a baseline level of consumption. Access to alcohol was then discontinued for 4–6 weeks. During the abstinence period, bipolar stimulating electrodes were bilaterally placed in the NAcc, as described above. After surgery, each animal was given a week to recover and acclimate to the testing chamber and tethering. Animals were randomly assigned to a control group (sham stimulation) or a DBS treatment group. Animals in the control group did not receive DBS during the conditioning period or when they had free access to 10% ethanol, water, and food for 24 hours. Animals in the DBS treatment group received DBS at a frequency of 140–150 Hz, a pulse width of 60 μsec, and a current intensity of 200 μA for 1 hour before they were allowed free access to 10% ethanol, water, and food and received continuous DBS stimulation for the ensuing 24 hours after the reintroduction of alcohol. In both treated and control animals, the ethanol and water volumes were recorded at the beginning and the end of the 24-hour treatment period.

Brain Histology and Electrode Placement Confirmation

At the conclusion of each experiment, each animal was given an overdose of phenobarbital and was perfused through the apex of the heart with 250 ml of saline followed by 250–300 ml of 4% paraformaldehyde in phosphate-buffered saline to fix the brain in situ. After perfusion, the brain was removed, fixed overnight in 4% paraformaldehyde, cryoprotected in 30% sucrose for 36–72 hours, and frozen at –70°C in Tissue-Tek (Sakura Finetek U.S.A., Inc.). Subsequently, 50-μm coronal sections were cut through the basal ganglia using a cryostat (Leica CM3050, Leica Microsystems, Inc.). Tissue sections were mounted on glass slides and counterstained with cresyl violet. Locations of the electrodes were identified under light microscopy based on the insertion track and tissue damage caused by the tips of the electrodes.

Statistical Analysis

In the first study, we determined the alcohol preference for each rat by calculating the grams of alcohol consumed during the stimulation-on or stimulation-off phases of the experiment. The mean and standard error of the mean quantity of alcohol and water consumed (g/hour) and the alcohol preference (the ratio of alcohol consumed/total fluid consumed) were calculated from each treatment condition over the 2-day study period. Values for the stimulation-on period were compared with values representing the stimulation-off periods by using a paired t-test.

The values for the study of alcohol deprivation reflect the mean quantity of alcohol and water consumed in a 24-hour testing period (g/kg/24 hrs) and the alcohol preference while each animal received DBS or no DBS. Because treated and control rats were 2 separate groups, the results of the alcohol deprivation experiment were analyzed using an unpaired t-test. A $p < 0.05$ was considered statistically significant.

Results

Effect of DBS on Established Alcohol Consumption

At the beginning of the studies, rats were given free access to alcohol for 3–7 weeks to establish a sufficient baseline level of alcohol consumption. The mean quantity of alcohol consumed at the end of the alcohol acquisition period in animals in the first study was 5.5 ± 1.6 g. The values were similar to those observed for male P rats in previous studies.[18] The rats behaved normally and continued to eat and gain weight before and after surgery.

The sites of the stimulating electrode tips were easily identified from the insertion tracks. Electrodes were successfully placed in the region of or adjacent to the NAcc and ranged from 0.6 to 2.7 mm anterior to the bregma, from 1.9 to 3.7 mm dorsal to the interaural line, and from 0.9 to 2.5 mm laterally on either side of the midline.

Average individual values of alcohol preference with or without DBS are shown in Fig. 1 for each of the 9 P rats studied. Over the 2 periods of DBS treatment on 2 separate days, 7 of 9 animals exhibited decreased alcohol consumption, 1 showed no effects from DBS, and 1 increased its alcohol consumption during DBS. No unusual behaviors were noted during the DBS period; that is, animals explored the cage and moved about with no outward manifestation indicating that DBS was or was not being given.

The average alcohol and water consumption levels and the alcohol preference of the rats are summarized in Fig. 2. Water consumption increased by approximately 50% during periods of DBS compared with that during sham treatments, but this change was not statistically significant ($p = 0.090$). Alcohol consumption decreased approximately 30% during periods of DBS in the NAcc as compared with the unstimulated study periods in the

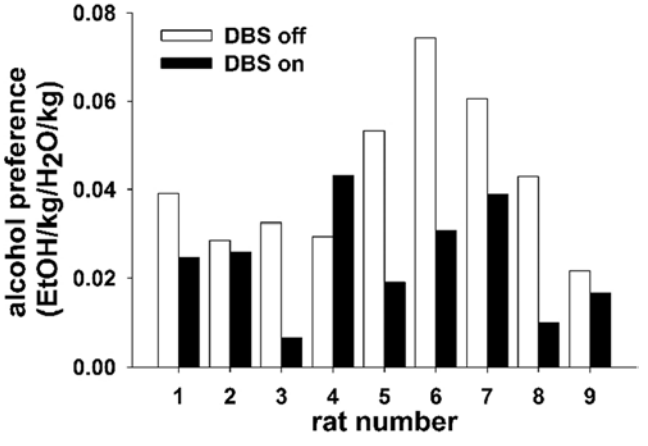

Fig. 1. Bar graph depicting the effects of DBS in the NAcc on alcohol preference in 9 individual rats. EtOH = ethanol.

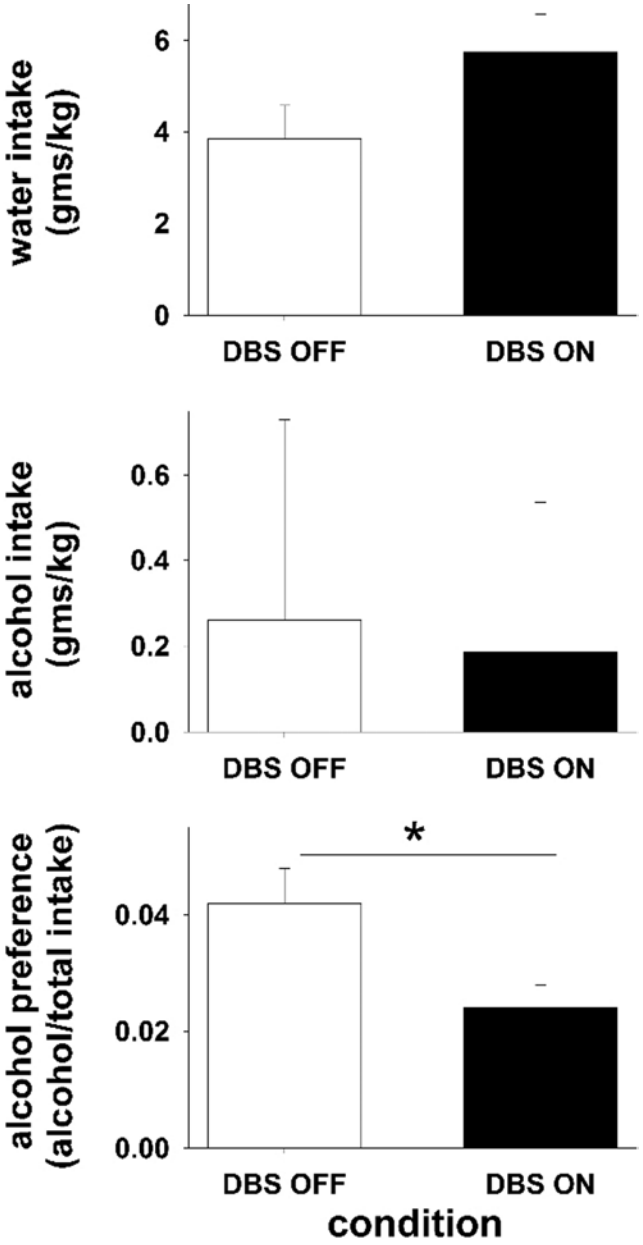

Fig. 2. Bar graphs showing average alcohol and water consumption levels and alcohol preference (± SEM) during 1 hour of acute DBS or sham-DBS in rats that established and maintained a steady, elevated alcohol intake. *Asterisk* indicates a significant difference between DBS stimulation and sham-DBS stimulation.

same animals, although the decrease was not statistically significant ($p = 0.071$). On the other hand, the increase in water intake and the decrease in alcohol intake during DBS treatment periods generated alcohol preference values (alcohol consumed/total fluid consumed) that decreased significantly during DBS compared with the sham-DBS period ($p = 0.016$). The combined amounts of alcohol and water consumed during both the DBS stimulation period and the sham-DBS period on each day were similar; there was no evidence that the order of testing affected the response to either the DBS stimulation or the sham-DBS testing.

Effect of DBS on Alcohol Consumption After Alcohol Deprivation

The average amount of alcohol and water consumed and the alcohol preference of 2 groups of animals receiving DBS or sham-DBS for 24 hours after alcohol had been reintroduced following a 4- to 6-week period of abstinence are shown in Fig. 3. Water consumption was greater in the DBS treatment group (6 rats) than in the sham-DBS group (5 rats), but this difference was not statistically significant ($p = 0.088$). Alcohol consumption over 24 hours was significantly reduced in the DBS treatment group compared with the sham treatment group ($p = 0.016$). Alcohol preference was also significantly reduced during DBS compared with during the sham treatment ($p = 0.021$).

Discussion

Deep Brain Stimulation Attenuates Alcohol Preference in P Rats

The purpose of these experiments was to show that DBS in the NAcc in P rats was capable of acutely attenuating each animal's preference for alcohol as well as the increase in alcohol consumption following a period of abstinence. Deep brain stimulation in the NAcc acutely decreased alcohol preference compared with a period of sham-DBS treatment in the same animals, and alcohol consumption and alcohol preference were significantly reduced in a DBS treatment group compared with a sham treatment group during the first 24 hours that alcohol was made available after a period of forced abstinence.

Technical Limitations of the Study

The stimulating electrodes were large relative to the size of the NAcc in rats. We selected stereotactic coordinates aimed at the shell of the NAcc, but it is unlikely that stimulation was restricted to the shell. Not all the electrodes were in or directly adjacent to the NAcc shell, and the current spread was relatively large during DBS so that stimulation of even those electrodes in the shell of the NAcc probably affected closely adjacent tissue outside the shell. Therefore, the most conservative conclusion from these data is that bilateral HFS in the region of the NAcc blunts alcohol consumption acutely, even after a period of alcohol deprivation, in P rats.

A related limitation is that our neuroanatomical localization of the electrodes was imperfect. There was a surprising amount of tissue damage at the tip of the stimulating electrodes, which tended to leave a hole or tear during tissue slicing. Thus, we know the general location within particular nuclei based on our neuroanatomical analysis, but the tissue damage precludes a more detailed description of exactly where within particular nuclei the major focus of stimulation was located. One might be concerned that electrode placement actually lesioned the NAcc, but the relative lack of effect of sham-DBS in the control animals argues in favor of the conclusion that the suppression of alcohol consumption was a response to the HFS of the nucleus and not simply to electrode placement.

Finally, the alcohol preference values are much lower in the first study than in the second. The duration of these

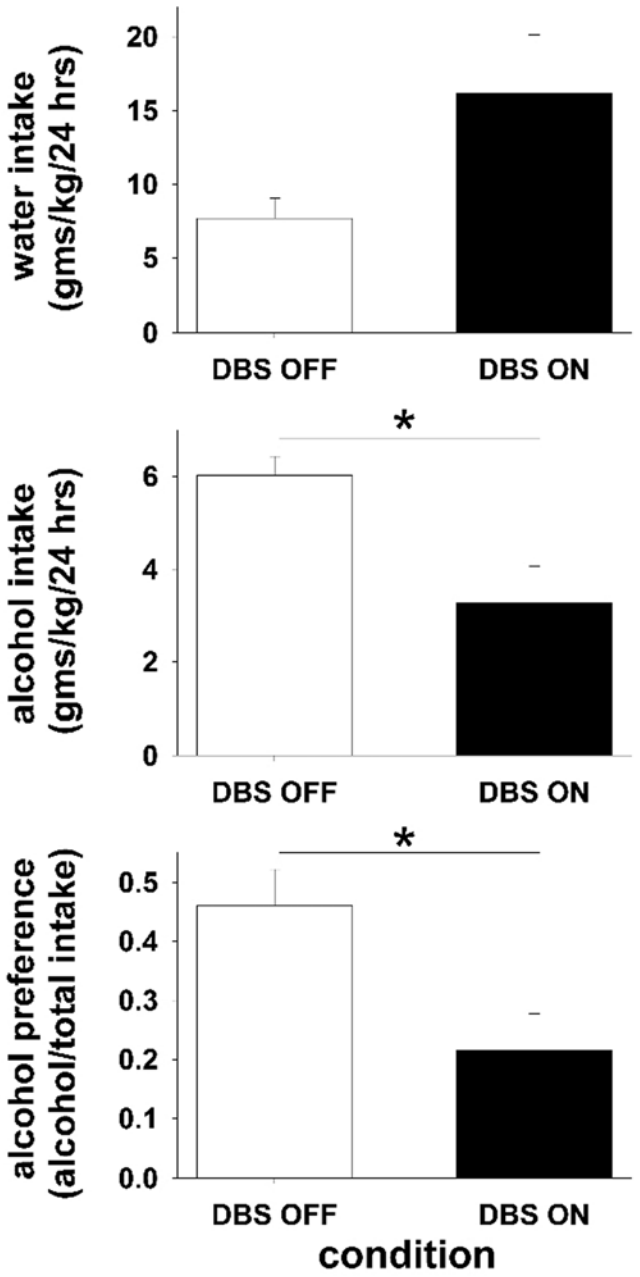

Fig. 3. Bar graphs demonstrating average alcohol and water consumption levels and alcohol preference (± SEM) in 2 separate groups during 24 hours of DBS or sham-DBS in rats that had established and maintained a steady, elevated alcohol intake but then abstained from alcohol for 4–6 weeks. *Asterisk* indicates a significant difference between DBS stimulation and sham-DBS.

studies was different, but the ratio of alcohol intake/total fluid consumed should be relatively constant regardless of the duration of the study. The low values of alcohol and water consumed in the first study may reflect the relative novelty of the cages in which tests were conducted, despite the 1-day acclimation period preceding testing. Moreover, there was no evidence of acclimation to the test environment; the preference ratios were just as low on the 2nd day of the testing. Hence, we do not have an explanation for these differences. It is reassuring, however, that the ratios were consistent from day to day in this study, and the effect of DBS on alcohol preference was still apparent despite the relatively low alcohol preference ratios.

Suppression of Alcohol Intake by DBS in P Rats

Ikemoto et al.[9] demonstrated that 6-OHDA lesions in the shell of the NAcc in P rats attenuated alcohol-seeking behavior; therefore, one might hypothesize that DBS in the NAcc is mimicking the effect of these lesions. Deep brain stimulation was originally thought to work like a lesion in movement disorders.[3] Previous work by others in which DBS delivered to the NAcc (core and shell) in rats trained to imbibe alcohol had the effect of significantly decreasing alcohol consumption,[10] and the results of our study are consistent with the hypothesis that DBS mimics the effect of a 6-OHDA lesion in the NAcc. However, the mechanism of action of DBS is hotly debated, and it is not clear that DBS achieves its lesionlike effects by actually creating functional lesions in the target sites of stimulation.

Most of the work elucidating the mechanism of action of DBS has been done in the basal ganglia in an effort to understand the beneficial effects of HFS in the STN of patients with PD. Just as is true for attenuated alcohol consumption during DBS in P rats, the therapeutic effects of DBS in PD resemble those of lesions,[29] and DBS may silence neurons in the STN as well as other nuclei within the basal ganglia.[21] The neuronal soma may be inhibited by HFS, but axons within the region of stimulation may be activated even at high frequencies.[24] Perhaps reflecting this stimulatory effect, the activity of dopaminergic neurons increases in the substantia nigra compacta during HFS of the STN.[16] Moreover, neurotransmitter levels rise within the basal ganglia during HFS of the STN: dopamine levels rise in the striatum,[15] γ-aminobutyric acid increases in the globus pallidus interna,[38] and glutamate levels increase within the STN[17] and globus pallidus interna.[38,39] The similarities between the effects of surgical lesions, which ought to eliminate neuronal activity, and the effects of DBS on the symptoms of PD are hard to reconcile with evidence of persistent neuronal activity and increased neurotransmitter levels in the basal ganglia during DBS. Thus, neurotransmitter levels are modified throughout the basal ganglia as a result of DBS in the STN, but the relationship of any one of these individual changes to the therapeutic benefit of DBS has not been established unequivocally. This same mechanistic dilemma—DBS elicits neurotransmitter release, but also seems to silence some neurons while activating others—confronts us as we try to understand how HFS in the NAcc reduces alcohol consumption in P rats. Notwithstanding the current difficulties understanding the mechanism of action of DBS, HFS of the NAcc and other nuclei in the mesolimbic reward circuit may be used as a powerful probe to understand the basic biology of the reward circuit and to elucidate the mechanism of action of DBS, especially when DBS is combined with measurements of electrical activity and neurotransmitter release in other nuclei in the reward circuit.

We believe that alcohol-seeking behavior originates

from a deficiency in the dopamine-mediated mesocorticolimbic reward circuit.[8] Thus, DBS in the NAcc may be supplanting ethanol and its effects on reward circuitry or may be affecting the "wiring" of the mesocorticolimbic circuitry so that ethanol no longer has a heightened salience or an abnormal reward value. Such a process might be mediated by an increase in dopamine release during HFS of the NAcc—just the opposite of the predicted effect of 6-OHDA lesions in the NAcc.[9] The DBS-mediated increase in dopamine in the NAcc may eliminate the need to consume ethanol, which also causes increased dopamine release in the NAcc. Alternatively, abnormalities in the reward circuit may be functionally silenced or "rebalanced" by DBS such that ethanol is not capable of producing as robust a reward signal in the presence of DBS.

Regardless of the mechanism of action, P rats are thought to approximate many features of alcoholism found in patients with a genetic predisposition toward alcoholism.[25] For this reason, DBS, which is already effective and approved for use in humans in other settings, may be a beneficial therapy in patients with severe alcoholism resistant to other forms of therapy. If DBS proves to be effective at reducing the salient effect of alcohol in abstinent drinkers, it may also decrease the risk of relapse.[28] Thus, DBS may serve as a solitary or an adjunctive therapy in patients resistant to current treatments for alcoholism.

Conclusions

The main finding in the current study was that DBS reduced alcohol intake in 2 models of alcohol consumption in P rats: alcohol preference was acutely reduced for a short duration of DBS in animals with established patterns of alcohol consumption, and alcohol consumption and alcohol preference were reduced over 24 hours of DBS when alcohol was made available after a period of abstinence. The P rats exhibit many characteristics of a valid model of alcohol-seeking behavior as proposed by Cicero,[5] and they fulfill a seventh criterion: relapse-related ADE. As far as we know, this study is the first in which DBS was used to attenuate the ADE in P rats and is the only experimental intervention to have such a robust effect. The results indicated that ADE may be mechanistically related to the NAcc. And DBS in the NAcc, however it works, seems to blunt alcohol consumption both acutely and in previously abstinent animals. We concluded, as have many others, that the NAcc plays a key role in the rewarding and subsequent addictive properties of drugs of abuse in general and of alcohol in particular. Moreover, DBS coupled with other neurophysiological measurements may be a useful tool in determining the role of the NAcc in the mesocorticolimbic reward circuit.

Disclosure

This work was supported by a COSAT grant from Johnson & Johnson (J.C.L.). Dr. Roberts holds a patent with Advanced Neuromodulation Systems, Inc., and is a consultant for Medtronic. Dr. Leiter holds a patent with Advanced Neuromodulation Systems, Inc. Dr. Green owns stock in Johnson & Johnson, Pfizer, and Mylan; has received support from Janssen and Eli Lilly; and is a member of Data Safety Monitoring Board at Eli Lilly.

Author contributions to the study and manuscript preparation include the following. Conception and design: Leiter, Henderson, Chau, Roberts, Green. Acquisition of data: Henderson, Bradford. Analysis and interpretation of data: Leiter, Henderson, Bradford, Roberts, Green. Drafting the article: Leiter, Henderson, Green. Critically revising the article: Leiter, Green. Reviewed final version of the manuscript and approved it for submission: Leiter, Henderson, Green. Statistical analysis: Leiter, Henderson. Administrative/technical/material support: Leiter, Green. Study supervision: Leiter, Roberts, Green.

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Manuscript submitted April 16, 2010.
Accepted April 21, 2010.

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Neurosurg Focus 29 (2):E13, 2010

Deep brain stimulation of the posteromedial hypothalamus: indications, long-term results, and neurophysiological considerations

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Object. The aim of this study was to review the indications for and results of deep brain stimulation (DBS) of the posterior hypothalamus (pHyp) in the treatment of drug-refractory and severe painful syndromes of the face, disruptive and aggressive behavior associated with epilepsy, and below-average intelligence. The preoperative clinical picture, functional imaging studies, and overall clinical results in the literature are discussed.

Methods. All patients underwent stereotactic implantation of deep-brain electrodes within the pHyp. Data from several authors have been collected and reported for each clinical entity, as have clinical results, adverse events, and neurophysiological characteristics of the pHyp.

Results. The percentage of patients with chronic cluster headache who responded to DBS was 50% in the overall reported series. The response rate was 100% for short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and for chronic paroxysmal hemicrania, although only 2 patients and 1 patient, respectively, have been described as having these conditions.

None of the 4 patients suffering from refractory neuropathic trigeminal pain benefited from the procedure (0% response rate), whereas all 5 patients (100%) affected with refractory trigeminal neuralgia (TN) due to multiple sclerosis (MS) and undergoing pHyp DBS experienced a significant decrease in pain attacks within the first branch of cranial nerve V. Six (75%) of 8 patients presenting with aggressive behavior and mental retardation benefited from pHyp stimulation; 6 patients were part of the authors' series and 2 were reported in the literature.

Conclusions. In carefully selected patients, DBS of the pHyp can be considered an effective procedure for the treatment of refractory trigeminal autonomic cephalalgias, aggressive behavior, and MS-related TN in the first trigeminal branch. Only larger and prospective studies along with multidisciplinary approaches (including, by necessity, neuroimaging studies) can lead us to better patient selection that would reduce the rate of nonresponders.
(DOI: 10.3171/2010.5.FOCUS1094)

Key Words • **posterior hypothalamus** • **deep brain stimulation** • **cluster headache** • **aggressive behavior** • **trigeminal autonomic cephalalgia**

Deep brain stimulation of the pHyp was the first application in which the choice of target was motivated by neuroimaging functional data.[28] Activation of the pHyp during cluster headache pain attacks was observed during PET,[38] the original observation that led to the placement of deep brain electrodes within the pHyp to inhibit the pathologically activated neuronal pool in patients with CCH.

The targeted brain volume for chronic high frequency stimulation within the pHyp was really the same target that Sano and colleagues[44] used in 1966 in using radiofrequency lesions to treat pathologically aggressive and disruptive behavior.

These 2 observations supported the rationale for the choice of pHyp DBS in patients affected with severe pain syndrome of the face and in patients presenting with disruptive behavior.

Since the first reported series in 2003,[16] several authors have used chronic stimulation of the pHyp to treat rare and severe syndromes refractory to conservative therapies. More specifically, the series reported in the literature include 51 patients affected with CCH,[3,6,11,14,31,45,47]

Abbreviations used in this paper: AC = anterior commissure; CCH = chronic cluster headache; CPH = chronic paroxysmal hemicrania; DBS = deep brain stimulation; IPG = internal pulse generator; IPP = interpeduncular point; LFP = local field potential; MCP = midcommissural point; MS = multiple sclerosis; PC = posterior commissure; pHyp = posterior hypothalamus; SUNCT = short, unilateral neuralgiform headache attacks with conjunctival injection and tearing; TAC = trigeminal autonomic cephalalgia; TN = trigeminal neuralgia.

8 patients with aggressive and disruptive behavior,[20,23,26] 5 patients with TN due to demyelinating disease,[18] 2 patients affected by SUNCT,[29,32] 1 patient with CPH,[53] and 4 patients with neuropathic pain of the face (Table 1).[18]

Although the overall number of patients surgically treated since the first pHyp implant is not very large, we can analyze a consistent amount of data from either published studies or our own experience. The topics addressed and discussed here are focused on the main aspects of pHyp DBS, including indications, percentage of responders, long-term results, side effects, and hypotheses about the mechanisms of its action.

Posterior Hypothalamus DBS for CCH

General Considerations

Cluster headache is characterized by disabling, strictly unilateral painful attacks mostly perceived in the retroorbital area. These headaches are accompanied by autonomic signs such as miosis, lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. The prevalence of the disorder is estimated to be < 1%, and it mostly affects males (M/F ratio between 2.5 and 7.1).[34,50] Fischera et al.[13] reported a lifetime prevalence of 124 cases per 100,000 persons and a 1-year prevalence of 53 cases per 100,000 persons.

Pain attacks typically last 15–180 minutes, occur daily, and are continuous or spaced out by remission periods of < 1 month.[22] In contrast, in the episodic form, attacks occur during a period ("cluster period") of 6–12 weeks interrupted by remission periods lasting up to 12 months.

Conventional conservative treatment of CCH consists of prophylactic therapy (verapamil, methysergide, lithium carbonate, melatonin, gabapentin, sodium valproate, and corticosteroids) and abortive therapy (triptans, inhaled 100% oxygen, indomethacin, and opiates). In 10–20% of patients with CCH, conservative therapy does not satisfactorily control the symptoms, and so pain attacks become severely debilitating.[25]

Inclusion Criteria for DBS in the Literature

The reports published in the literature include 46 patients with drug-resistant CCH who underwent surgical intervention with DBS of the posterior hypothalamic area and whose follow-up examination data are available.[3,6,11,14,31,45,47] The report of 1 of these studies[11] is an abstract, and so the study is not considered in this review. Thus, the number of patients in our review is 44.

Initial guidelines for inclusion criteria for DBS of the pHyp in CCH were proposed by Leone et al.:[30] 1) the presence of diagnostic criteria for CCH according to the International Headache Society;[22] 2) inadequate relief from prophylactic therapy, including verapamil, lithium, sodium valproate, methysergide, topiramate, gabapentin, nonsteroidal antiinflammatory drugs such as indomethacin, and corticosteroids; and 3) CCH lasting at least 2 years, with strictly lateralized pain attacks. Sillay and coworkers[47] expanded this criteria by also including: 1) at least 6 debilitating headache episodes per week rated by patients as at least 6 on a visual analog scale of 1–10; 2) unsatisfactory relief from abortive therapy, including oxygen, sumatriptan, and opioids; 3) failure of occipital nerve stimulation therapy for at least 1 year; and 4) completion of daily headache diaries over a period of 1 month prior to surgery. The latter criterion should be considered as strictly dependent on the design of the study that these authors performed in 2009.[47]

Exclusion criteria included the following: 1) general

TABLE 1: Summary of literature on studies published to date on pHyp DBS*

Authors & Year	No. of Patients	Pathology	pHyp Stereotactic Coordinates			Mean FU (mos)	No. of Responders
			X	Y	Z		
Leone et al., 2008	16	CCH	±2	−3	−5	48	10
Fontaine et al., 2010	11	CCH	±2	−3	−5	10	6
Bartsch et al., 2008	6	CCH	±2	−3	−5	17	3
Sillay et al., 2010	5	CCH	±2	−3	−5†	11	3
Schoenen et al., 2005	4	CCH	±2	−6	−8	14.5	2
D'Andrea et al., 2006	3	CCH	±2	−3	−5	30	2
Brittain et al., 2009	2	CCH	±2	−6	−8	11	2
Leone et al., 2005	1	SUNCT	±2	−3	−5	60	1
Lyons et al., 2009	1	SUNCT	±2	−3	−5	12	1
Walcott et al., 2009	1	CPH	±2	−3	−5	18	1
Franzini et al., 2009	6	AB	±2	−3	−5	36	4
Hernando et al., 2008	1	AB	±2	0	−2	18	1
Kuhn et al., 2008	1	self-mutilation	±2.5	−2	−2.5	4	1
Franzini et al., 2007	5	TN in MS	±2	−3	−5	41	5
Franzini et al., 2008	3	neuropathic TP	±2	−3	−5	4	0

* AB = aggressive behavior; FU = follow-up; TP = trigeminal pain.

† Authors refined the site of the intended target by locating it 4–5 mm posterior to the mammillothalamic tract and medial to the anterior border of the red nucleus.

or neurological pathological conditions increasing the risk of positioning of deep brain electrodes, such as intraparenchymal lesions, coagulopathy, severe cardiological or pulmonary diseases, or the need for anticoagulant drugs; 2) inability to perform brain MR imaging; 3) pregnancy; and 4) severe or inadequately treated psychiatric comorbidity.

Among the studies published, the main criterion for defining a patient as "a responder" to DBS was a 50% reduction in the frequency or intensity of pain attacks.

Case Studies

Belgian Study. Schoenen and coworkers[45] enrolled 6 patients for DBS treatment who had fulfilled the following criteria: 1) age of 25–55 years; 2) CCH persisting for 2 or more years; 3) 4 or more attacks per week; 4) resistance or intolerance to adequate trials with verapamil, steroids, methysergide, lithium, and/or ergotamine; and 5) no disabling medical or psychiatric disorders.

French Multicenter Study. Fontaine et al.[14] conducted a systematic study aimed at assessing the efficacy of DBS of the pHyp for the treatment of severe and drug-refractory CCH. The study was a prospective, double-blind crossover trial including 11 patients selected on the following criteria: 1) disease duration > 3 years; 2) resistance to drug treatment with up to 960 mg/day of verapamil, plasma levels of lithium ranging from 0.6 to 1 mEq/L; 3) daily pain attacks; 4) absence of substance abuse or dependence; 5) age of 18–65 years; 6) normal brain MR imaging studies; and 7) no contraindications to surgery or anesthesia.

German Study. Bartsch et al.[3] described 6 patients who were considered eligible for DBS according to the above-mentioned criteria established by Leone et al.[30]

British Study. Brittain and coworkers[6] reported on 2 patients fulfilling the diagnostic criteria for CCH who underwent the implantation of deep brain electrodes in the pHyp.

American Study. Sillay and coworkers[47] reported on 8 patients who submitted to DBS for CCH, although follow-up data were available for only 5 of them. The inclusion criteria consisted of an extended version of those suggested by Leone in 2004[30] and have been mentioned before.

Italian Study. Our center detailed the first series in 2003,[16] and since then 16 patients with CCH have undergone DBS. Our inclusion criteria to date have been as follows: 1) diagnosis of CCH made by 2 independent neurologists specializing in headaches; 2) conservative prophylactic and abortive treatments already tried in adequate dosages both alone or in combination therapy (verapamil, lithium carbonate, methysergide, valproate, topiramate, gabapentin, melatonin, pizotifen, indomethacin, and steroids); and 3) normal neuroradiological examination, including brain CT, MR imaging studies of the craniocervical junction, and venous angiographic sequences. It is important to note that since 2005, we have also included chronic stimulation of the greater occipital nerve for the therapeutic algorithm; the dual-channel IPG that is implanted can be later connected to the DBS electrodes in case of inefficacy of peripheral nerve stimulation.

Among the 16 patients who were surgically treated, 14 were men and 2 were women; the mean duration of the chronic phase of CCH was 2 years. All of our patients suffered from multiple daily pain attacks and had tried all of the aforementioned drugs, alone or in combination, without benefit. The prolonged use of steroids in some patients had produced some severe drug-related complications such as chronic intestinal bleeding, bone demineralization with aseptic necrosis of the femoral head, fluid retention with heart failure, arterial hypertension, weight increase, psychosis, and glaucoma.

Surgery and Target Choice

The surgical planning described here is used at our institute.

The planning procedure is performed with the aid of a Leksell head frame (Eleckta) with the patient under local anesthesia. A preoperative set of MR images (generally axial, volumetric, fast spin echo inversion-recovery T1-weighted with Gd and T2-weighted sets) is obtained to acquire high-definition images for precisely defining the location of anterior and posterior commissures and midbrain structures below the commissural plane (mammillary bodies and red nucleus). Magnetic resonance images are then merged with CT scans obtained under stereotactic conditions after positioning the head frame. The fusion of the 2 imaging sets is performed using an automated technique based on a mutual-information algorithm (Frame-link 4.0, Sofamor Danek Stealthstation, Medtronic). The merged images as well as every single slice of the imaging set were coregistered with the Schaltenbrand stereotactic atlas to obtain AC-, PC-, and MCP-related coordinates in millimeters.

After the stereotactic procedure, bilateral (Soletra, Medtronic, Inc.) or dual-channel monolateral (Kinetra, Medtronic, Inc.) IPGs are positioned into subclavicular subcutaneous pockets and connected to brain electrodes for chronic electrical stimulation.

Postoperative brain CT or MR imaging constitutes a useful tool both for assessing the accuracy of electrode placement and correlating the extent of the clinical benefit or adverse effects. The two sets of images can be merged, taking advantage of the lower degree of image distortion with CT and the more precise defined gray-white matter boundaries provided by MR imaging.[12]

Belgian and British Studies. Coordinates for the pHyp were 2 mm lateral to midline, 6 mm behind the MCP, and 8 mm below the intercommissural plane, according to indications by Leone et al. as reported in 2001.[28]

French Multicenter Study, German Study, and Italian Study. Coordinates were 2 mm lateral to the midline, 3 mm posterior to the MCP, and 5 mm inferior to the midcommissural plane.

American Study. The initial stereotactic coordinates were 2 mm lateral to the midline, 3 mm posterior to the MCP, and 5 mm inferior to the midcommissural plane,

but the authors refined the site of the intended target by locating it 4–5 mm posterior to the mammillothalamic tract and medial to the anterior border of the red nucleus by visualizing the region of interest using 1.5-T brain MR imaging.

The posterior hypothalamic target addressed by these coordinates was the same volume that was lesioned by Sano and coworkers in 1970.[43] Anyway, it is important to consider that in 1 previously described patient,[17] the targeting procedure based exclusively on the MCP or AC-PC plane was the basic cause of electrode misplacement, and such misplacement was due to the anatomical variability of the angle between the brainstem's major axis and the intercommissural plane. To correct this problem we took into account a new anatomical landmark that was incorporated into the final targeting procedure; we named this landmark the "IPP."[20] It is localized in the apex of the interpeduncular cistern 8 mm below the AC-PC plane at the level of the maximum diameter of the mammillary bodies. The definitive coordinates of the target, taking into account this correction point, were 2 mm lateral to the midline, 2 mm posterior to the IPP (instead of 3 mm posterior to the MCP), and 5 mm below the AC-PC plane (Fig. 1). A dedicated program and atlas have been developed and are freely available on the Internet to help in choosing the proper coordinates of this target (http://www.angelofranzini.com/BRAIN.HTM).

Intraoperative Microrecordings in the pHyp

Single-unit recordings are performed through a high impedance microelectrode to corroborate the neuroanatomical maps planned to target the nucleus of interest. This method is currently used to map the subthalamic nucleus (that is, in Parkinson disease), thalamic nuclei (that is, in pain), and the globus pallidus (that is, in dystonia). To date, such is not the case for the pHyp. In fact, just a few papers have dealt with the electrophysiological properties of pHyp neurons in pain[3,7,19,40,41,45] and behavior disorders.[8,23] Moreover, just a few have attempted to quantify the firing discharge properties;[3,8,9,40] the remaining illustrated only the raw electrophysiological traces.[20,23,41,45]

Microrecordings within the pHyp were performed in proximity to the stereotactic coordinates as suggested by us in 2003—specifically, 2 mm lateral to the commissural line, 3 mm posterior to the MCP, and 5 mm below the commissural line. All authors recorded single-unit activity with the patients fully awake and in a pain-free state. Cordella et al.[8] have described data sampled within the pHyp of 2 patients with behavioral disorders, both under general anesthesia due to the difficulty in controlling their behavior.

All data sampled in patients with TACs describe a low-frequency, tonic, and nonoscillatory discharge pattern (Fig. 2A). Differences occurred in the mean firing rate: Cordella et al.[9] described a mean discharge rate of 24 Hz in 3 patients; Bartsch et al.,[3] a mean firing rate of 17 Hz (range 13–35 Hz) in 6 patients; and Sani et al.,[40] a mean firing rate of 13 Hz in 6 patients. The firing discharge did not show variations as to tactile, motor, autonomic, and emotional stimulations in all of the tested neurons.

Recently, Brittain et al.[6] recorded LFPs within the pHyp of 2 patients with CCHs. The LFPs represent aggregate synaptic activity within the vicinity of the DBS macroelectrode, whereas microelectrodes typically represent the action potential firing of isolated neurons. In 1 of these 2 patients, it has been possible to record data during a cluster attack. The pain attack was associated with an increase in the relative LFP power and specifically a distinct 16- to 22-Hz peak in neural activity. The presence of a specific neural rhythm was the first direct evidence of pHyp involvement during the cluster pain as indirectly described in neuroimaging studies.[40] It is relevant that the stereotactic coordinates used to target the pHyp in this latter report were distinct from those previously mentioned and were 6 mm posterior, 2 mm lateral, and 8 mm inferior to the MCP. This difference, along with the intrinsic differences between the single-unit recordings and the LFPs, might be a reason for the dissimilarities between the various reports.

Cordella et al.[8] described single-unit activity in 2 patients affected by behavioral disorders. In 1 patient who also had traumatic brain injury, the discharge pattern had

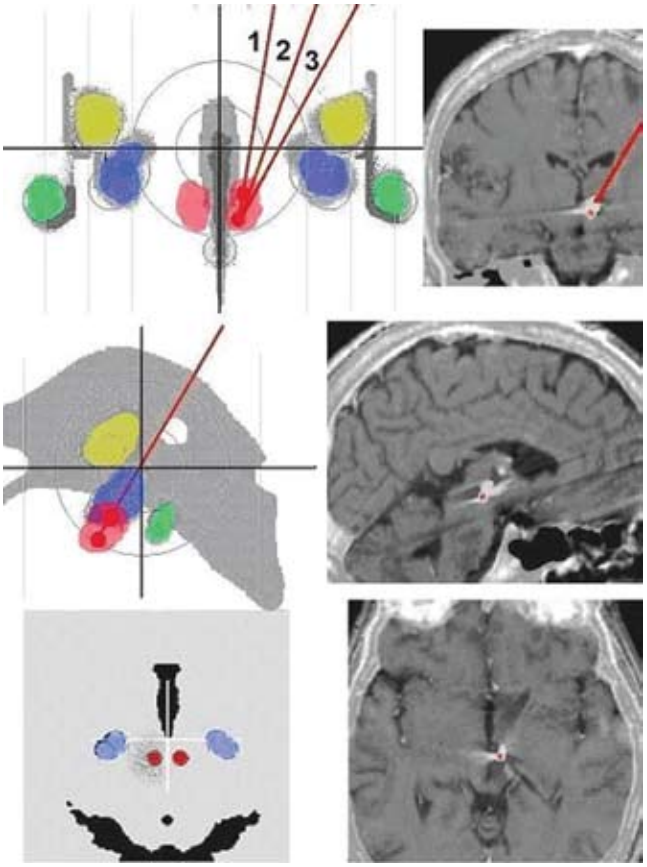

Fig. 1. Left: Virtual ventriculography plates showing the target (pHyp: *pink* and *red*) in coronal *(upper)*, sagittal *(center)*, and axial *(lower)* sections as part of surgical planning. Trajectories are numbered 1, 2, and 3 in the anteroposterior ventricular representation showing the different angles used to reach the target. Trajectories can change according to the ventricular shape and dimensions and the presence of vessels within the precoronal frontal cortex at the entry point. **Right:** Postoperative CT images merged with preoperative MR images showing the definitive location of an electrode in coronal *(upper)*, sagittal *(center)*, and axial *(lower)* planes.

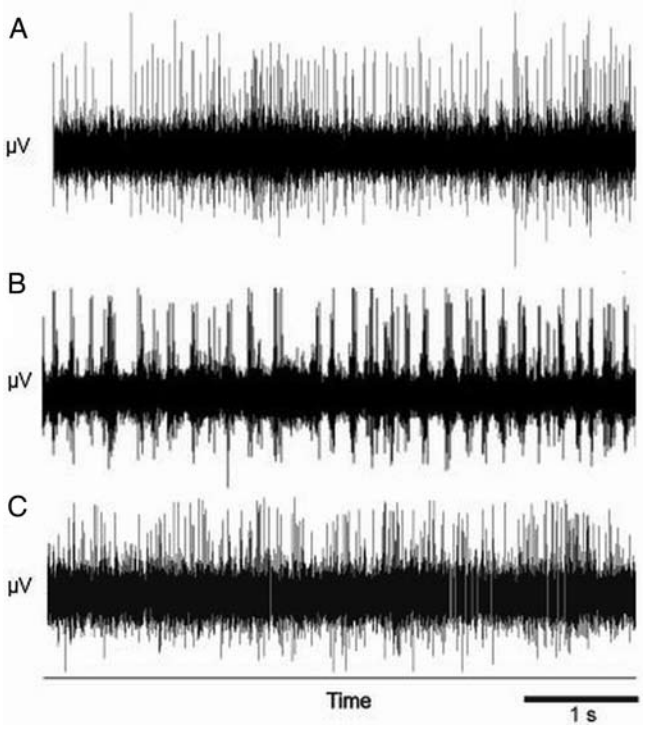

Fig. 2. Oscilloscope snapshots from intraoperative pHyp microrecording. **A:** Trace showing a low-frequency, tonic, nonoscillatory discharge pattern in a patient affected by CCHs. **B:** Trace showing a low frequency rate (19 Hz) discharge pattern with phasic oscillations at around 7–8 Hz in a patient with aggressive behavior associated with multifocal refractory epilepsy. **C:** Trace showing a low-frequency (10 Hz) discharge pattern in a patient with aggressive behaviors and traumatic brain injury. Tonic activity without significant oscillations is evident.

a low-frequency rate (10 Hz) and was tonic with no oscillations. In the other patient, who presented with gelastic epilepsy associated with behavioral disorder, there was a low-frequency rate (19 Hz) with phasic oscillations at around 7–8 Hz (Fig. 2B and C).[8] These findings might suggest how the discharge pattern of neurons in the pHyp should be evaluated with reference to the presence of concurrent pathology or behavioral states. Nevertheless, the number of analyzed units remains small. Indeed, the statement of any pathophysiological hypothesis is still hazardous and likely to sound like mere speculation; however, it is possible to safely make some observations. 1) Posterior hypothalamus neurons are spontaneously active. Indeed, the recording of single-unit activity within this nucleus is feasible. 2) It is possible to attempt to characterize the firing rate and pattern. 3) In awake patients with TACs the firing rate ranges between 13 and 24 spikes/second, with a tonic and not an oscillatory firing pattern. 4) In patients under general anesthesia and with aggressive behavior, the firing rate ranges between 10 and 19 spikes/second. 5) The patient with aggressive behavior and associated epilepsy showed phasic oscillations at around 8 Hz. 6) There is no clear evidence of the neurophysiological characteristics of either the superior or inferior borders of the nucleus. 7) However, the presence of higher firing rates above 5 mm from the target may suggest that the microelectrode is passing through the thalamus, while the lack of neuronal activity at the target site and beyond may indicate that the microelectrode is not in the pHyp but in adjacent structures (that is, the interpeduncular cistern at the inferior border). 8) To record beyond the target might be dangerous due to the proximity of the basilar artery bifurcation.

Summary of Results

Belgian Study. Unfortunately, 1 patient who underwent implantation died of an intraparenchymal and intraventricular hemorrhage 3 days after the intervention. Implantation was not undertaken in another patient because of the occurrence of a panic attack, so that the total number of patients available for follow-up is 4 in this series.

Stimulation parameters were as follows: median voltage 3.28 V, pulse width 60 μsec in 2 patients and 90 μsec in 2 patients, and stimulation frequency 185 Hz. The median follow-up was 14.5 months.

At the last clinical examination, 2 of 4 patients were pain free, another patient had a dramatic reduction in pain attacks to fewer than 3 per month, and another patient had only transient clinical benefits.

French Multicenter Study. After surgery, the patients were randomly assigned to either an active stimulation period followed by a sham stimulation period (on-off group) or vice versa (off-on group). Both random phases lasted 1 month after a wash-out period of 1 week.

An open phase of 10 months, during which all patients were set to the on-stimulation state, followed the randomization period.

Stimulation parameters were set as follows: 3 V, pulse width 60 μsec, and 185 Hz or 80% of the threshold producing eventual side effects in the randomized period. The parameters could be changed in the open phase. During the randomized phase, no significant change in the frequency or intensity of attacks in the "on" group occurred. In addition, there were no differences in the number of attacks during the last week of each period or the number of times that sumatriptan was administered. On the contrary, in the open-phase period, the mean frequency of weekly attacks decreased by 48.4%, and 6 of 11 patients were considered responders (that is, a decrease of at least 50% in the frequency of weekly attacks). No predictive factor for the efficacy of DBS was found.

German Study. Patients were stimulated with a current amplitude ranging from 1.5 to 5.5 V, a pulse width of 60 μsec, and a frequency ranging from 130 to 180 Hz. Three of the 6 patients were almost completely attack free (mean number of pain attacks per month 1) after a follow-up period ranging from 9 to 17 months. One patient benefited from the procedure for only 6 months after intervention, whereas 2 patients reported only a transient and mild benefit after the first weeks following the operation, followed by a return to the baseline frequency of pain attacks.

British Series. Both patients were stimulated with a frequency of 180 Hz. One patient was stimulated with 4.5

V at a pulse width of 60 μsec; the other with 4.0 V and a pulse width of 90 μsec. Both patients benefited from the procedure: the first patient reported only infrequent pain attacks (7 injections of sumatriptan) at the 11-month follow-up, and the second patient reported a decrease in attack frequency, from daily to weekly with "massive reduced severity."

American Study. Stimulation parameters were as follows: 1–3 V, pulse width 60 μsec, and stimulation frequency 185 Hz. The duration of the follow-up was 12 months for the first 4 patients and 6 months for a fifth patient. Three of these 5 patients could be considered responders because of a "> 50% reduction in headache frequency, intensity, or both."[47]

Italian Study. The parameters used for chronic electrical stimulation were as follows: frequency 185 Hz, pulse width 60–90 μsec, amplitude 1–3 V in unipolar configuration (case as anode). The IPG was turned on a few days after the intervention in all of the patients, and the current amplitude was progressively increased but remained below the threshold for adverse effects.

In the entire series, 71% of the postoperative days were pain free, and the intensity and duration of pain bouts was significantly reduced. The overall drug dosage was reduced to < 20% of the preoperative levels. The mean time to pain freedom or reduction was 42 days (1–86 days); the mean amplitude of stimulation used was 2.4 V (0.6–3.3 V).

The mean follow-up was 4 years; after the first 2 years of clinical follow-up, major improvements in pain or pain disappearance was observed in 15 (94%) of 16 patients. After a mean of 4 years of follow-up, a state of persistent freedom from painful attacks was still present in 10 patients (62%). Four patients (25%) still required prophylactic drugs to prevent pain attacks. In the last 2 years of follow-up 3 patients no longer benefited from stimulation despite several changes in the parameters. In these 3 patients, the disease turned from the chronic form to the episodic form (that is, periods of complete remission lasting several months alternating with periods of attacks).

With the above-reported series taken as a whole, the percentage of patients considered to be responders to DBS surgery is 63%.

Adverse Events and Side Effects

Among our surgically treated patients, a small and asymptomatic intraventricular (third ventricle) hemorrhage was disclosed on postoperative CT.[27]

The main limiting postoperative and stimulation-related side effect was visual disturbance. We have noticed that it occurs only when the amplitude is increased too much or too rapidly after implantation, subsiding after a few minutes or a few days after increasing the voltage of the electric field. Such observations have been reported by other authors as well.[3,36,45,47]

Weight loss occurred after 6 postoperative months (mean 3.0 kg), but it can be attributed to steroid withdrawal. One patient had ceased menstruating 4 months before the intervention as a result of excessive drug intake, but her cycles returned to normal after 1 month.[27]

Posterior Hypothalamus DBS for SUNCT

General Considerations

Short, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) are a rare and highly disabling form of TAC characterized by very frequent episodes (3–200 per day) of short-lasting (5–240 seconds) pain unilaterally localized in the orbital, supraorbital, or supratemporal region, which can be of pulsatile or stabbing type. The pain bouts are usually accompanied by reddening of the ipsilateral conjunctiva, tearing, and a runny nostril. The course and severity of this pathological condition are quite variable, ranging from long periods of pain relief to a severe chronic modality of presentation devoid of pain-free periods. Unfortunately, the condition in a majority of patients is resistant to conventional pharmacological treatment.[22,48]

The scientific literature addressing the potential role of DBS of the posterior hypothalamic region in the treatment of drug-refractory SUNCT is, to date, limited to 2 patients treated in such a manner.

Case Reports

Case 1. We first reported on this patient in 2005.[19] This 66-year-old woman suffering from a 14-year history of SUNCT localized in the left orbital region and upper corner of the mouth (episodically radiating to the ear, jaw, and suboccipital region) was referred to our institute. The pain bouts, which were evoked by talking, chewing, tactile facial stimuli, and tooth brushing, were accompanied by homolateral eyelid edema, eye reddening, obstruction of the ipsilateral nostril, and tearing. The frequency of pain bouts ranged from 70 to 300 per day. Neuroradiological studies were all negative for intracranial intraaxial signal alterations, and a neurological examination was nondiagnostic. The patient's condition was resistant to multiple drug treatments, including carbamazepine, gabapentin, sodium valproate, lamotrigine, indomethacin, topiramate, steroids, and tramadol.

After obtaining written informed consent from the patient and ethics committee approval, we performed ipsilateral positioning of a DBS electrode (3389, Medtronic, Inc.) into the posterior hypothalamic region in this patient in July 2003. The surgical technique and planning are the same as those described above. Coordinates of the planned target were as follows: 2 mm lateral to the midline, 3 mm posterior to the MCP, and 5 mm below the AC-PC plane.

The postoperative course was uneventful, and control CT scans revealed correct positioning of the electrode. Initial stimulation parameters were set at the bipolar mode with a frequency of 30 Hz and a pulse width of 60 μsec. These settings did not lead to any clinical improvement, so we tried unipolar stimulation with 180 Hz from the 1st postoperative day. The main limiting side effect was the ipsilateral third nerve's related disturbances as manifested by increasing the voltage.

After several clinical follow-up examinations and after taking into account the balance between clinical benefits and adverse effects, the final stimulation param-

eters were set to 1.8 V, 60-μsec pulse width, and 180-Hz frequency in the unipolar mode. The adjunct treatment of lamotrigine (100 mg/day) led to the complete and definitive remission of symptoms, which was confirmed at the last clinical examination at the 5-year follow-up.

Case 2. The second patient with drug-refractory SUNCT treated with hypothalamic DBS was described in 2009 by Lyons and coworkers.[32] This 44-year-old woman initially presented with left-sided painful attacks at the age of 8 years. Symptoms gradually worsened over time until her current presentation, when she had 120 attacks per day lasting 60–120 seconds. The attacks also included lacrimation, conjunctival injection, rhinorrhea and episodic vomiting, blurred vision, and photophobia, all resistant to multiple pharmacological treatments with antiepilepsy drugs, beta-blockers, GABAergics, tricyclic and serotoninergic antidepressants, dihydroergotamine, steroids, and botulinum toxin Type A injections. Neurological examination disclosed only left trigeminal hypesthesia, and neuroradiological examinations were nondiagnostic. The surgical procedure was similar to that described for the patient in Case 1. Definitive stimulation parameters were as follows: monopolar configuration with Contact 0 as cathode, 1.4 V, 90 μsec, and 160 Hz. The immediate improvement of symptoms consisted of a 63% reduction in the mean number of daily attacks (133 attacks/day preoperatively vs 45/day during the 1st postoperative month). At the 12-month follow-up further improvement was observed, with an 80% reduction in the frequency of pain attacks (25 attacks/day).

Posterior Hypothalamus DBS for CPH

Chronic paroxysmal hemicrania is a pathological condition consisting of pain attacks with characteristics and associated symptoms and signs similar to those for CCH, but with shorter, more frequent bouts occurring more commonly in females and responding absolutely to indomethacin.[22] The duration of pain attacks lasts from 2 to 30 minutes; localization is at the level of the unilateral orbital, supraorbital, or temporal regions; and attacks are usually accompanied by ipsilateral conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, and miosis and/or ptosis.

Attacks are described with a frequency of at least 5 per day for more than half of the time, although periods with lower frequency can occur. Probable pathophysiological analogies exist between CPH and CCH given that a recent study by Matharu and coworkers[37] showed activation of the posterior hypothalamic region during acute CPH attacks, whereas the administration of indomethacin resulted in deactivation of the same area.

Walcott and coworkers[53] reported on the clinical case of a patient affected by CPH who was treated with ipsilateral pHyp stimulation in 2009. This 43-year-old woman had a 19-month history of unilateral lancinating right headache attacks at the level of the eye and retroorbital space accompanied by nasal congestion, conjunctival injection, tearing, and ptosis. The attacks occurred 10–20 times per day. During the neurological examination period at their institute, she experienced 4 headache episodes in 50 minutes.

Pharmacological therapy undertaken without benefit consisted of ergotamine, antiepileptics, triptans, GABA agonists, melatonin, verapamil, amitriptyline, zonisamide, lithium, and tramadol; however, the administration of indomethacin was effective in alleviating symptoms. Unfortunately, this drug was later discontinued because of a diagnosis of iatrogenic gastritis superimposed on a preexisting Barrett's esophagus. The patient was then referred for implantation of a DBS system at the level of the ipsilateral pHyp. The surgical technique was similar to the one described above. Final coordinates of the target were 2 mm lateral, 3 mm posterior, and 5 mm inferior to the MCP. Initial stimulation parameters were 1.5 V, 80 μsec, and 140 Hz, which were changed to 1.5 V, 60 μsec, and 185 Hz during the 27-month follow-up period. She underwent several deactivations of the IPG, with subsequent recurrence of pain attacks. Turning on the device resulted in major improvement of symptoms in all cases. At the last clinical examination, the patient was reported to be free from "signs and symptoms of CPH."

Posterior Hypothalamus DBS for Secondary Neuropathic Trigeminal Pain

Four patients with neuropathic trigeminal pain at our institute underwent implantation procedures for pHyp DBS. One patient was a 47-year-old man with an expanding right posterior mandibular carcinoma who had undergone radical transmandibular tumor resection in 2002. After surgery he started to experience hypesthesia and burning pain in the second and third right trigeminal branches, which progressively worsened with time. A second patient was a 52-year-old woman with a 3-year history of facial pain. Symptoms appeared after a minor dental procedure and were described as continuous and disabling burning pain to the area innervated by the second and third right trigeminal branches. The third patient was a 55-year-old man with a nasopharyngeal carcinoma who had undergone radiotherapy. A few months after radiotherapy, continuous and severe burning right facial pain developed more intensely in the area innervated by the first and second divisions of the trigeminal nerve. For all of these patients, pharmacological therapy with any kind of analgesic drug (including opioids) was ineffective.

All of the patients underwent brain CT and MR imaging studies that did not disclose any intracerebral pathology.

Unfortunately, none of the 3 patients had a reduction in painful symptoms. The stimulation target's coordinates as well as the stimulation parameters were the same as for TACs (180 Hz, 60 μsec, and 1.3 V mean voltage). After 4 months of continuous stimulation, the continuous pain was the same as preoperatively, and repeated changes in the stimulation parameters did not modify the picture. Amplitudes beyond 3 V induced dizziness and oculomotor symptoms in all cases. When the IPG was switched off in 2 of the 3 patients without their awareness of it, the episodes of paroxysmal pain were described as being even slightly more intense than with active stimulation.

The fourth patient is not described because of the short follow-up.

Posterior Hypothalamus DBS for MS-Related TN

From 20 to 80% of patients affected by MS suffer from neuropathic pain, with appendicular central pain and TN being the most common forms.

Trigeminal neuralgia is a pathological condition characterized by short, shock-like pain episodes, referred to as "electric bouts" by patients, that are limited to one or more of the territories innervated by the divisions of cranial nerve V. It usually begins in the second or third division of the trigeminal nerve and involves about 5% of patients with MS, usually beginning many years after the occurrence of nontrigeminal pain. The clinical characteristics of TN in patients with MS are similar to those in patients without MS, although they tend to appear at a younger age and more commonly involve the first branch of the trigeminal nerve. Signal alterations on brain MR imaging in these patients can disclose vascular compression by an artery at the level of the root entry zone, demyelinating lesions affecting trigeminal pathways across the pons, or enlargement of the trigeminal nerve at the root entry zone. Conventional antiepileptic treatment in patients with MS could cause an elevated incidence of adverse effects at low dosages, resembling clinical worsening of MS relapse. Microvascular decompression results in these patients are usually poor with a high probability of late recurrence of paroxysmal pain, whereas ablative procedures (such as radiofrequency lesioning) harbor a high risk of nerve damage with subsequent hypesthesia/hyperesthesia, secondary deafferentation and corneal reflex impairment, corneal anesthesia, neuropathic keratitis, hearing loss, and transitory masticatory weakness.

Evidence that drug-refractory TN in some patients involves the first trigeminal division and that TACs share the same painful territories (that is, orbital region, eye, and forehead), along with the reversible nature of the DBS procedure, led us to postulate that stimulation could represent an effective treatment in appropriately selected MS patients with refractory TN involving the first trigeminal branch, without the previously noticed side effects. At our institution, 5 MS patients affected by refractory TN submitted to pHyp DBS intervention after providing written informed consent. These patients were 3 males and 2 females with a mean age of 56, a mean primary disease duration of 23 years, and a mean TN duration of 12 years. Two patients reported pain in all 3 trigeminal branches, and the remaining 3 described pain in the first and second branch. In all of these patients preoperative brain MR imaging used for target planning showed multiple demyelinating lesions at the level of the cerebral white matter, the internal capsule, and the pontomesencephalic region.

Trigeminal neuralgia in all of the patients was refractory to high-level dosages of carbamazepine, phenytoin, gabapentin, and lamotrigine. All of the patients had undergone several surgical procedures—microvascular decompressions, radiofrequency lesioning, and percutaneous balloon compressions—without benefit or with only temporary relief of pain.

After pHyp electrodes were positioned ipsilateral to the pain, 3 patients had beneficial effects within 24 hours of the procedure. All patients reported a reduction in paroxysmal pain attacks within the ophthalmic branch after surgery. Three patients reported recurrent pain in the second and third branches—although not in the first—and underwent further radiofrequency thermorhizotomies. The relapse occurred at varying time intervals (mean 23 months). Note that this time interval is longer than the interval observed after neurosurgical procedures used before DBS (mean 6 months).

The other 2 patients reported pain relief in all 3 trigeminal branches through a combination of stimulation with analgesics without the need for further surgical procedures.

The data point to procedural efficacy in controlling TN's paroxysmal pain when it is localized in the first branch.

Posterior Hypothalamus DBS for Aggressive Behavior

Several data led our group to pioneer pHyp DBS for aggressive and impulsive behavior refractory to any conservative treatment: 1) Previous experiences reported by Sano and Mayanagi,[42] Arjona,[2] Schvarcz et al.,[46] and Ramamurthi[39] in the "lesional era"; 2) the report regarding disruptive behavior induced by electrical stimulation in the so-called triangle of Sano in a Parkinsonian patient;[4] 3) the well-known occasional onset of self-aggressive and violent behavior in patients with CH during pain bouts, suggesting a common anatomofunctional involvement of the pHyp in the etiopathogenesis of both symptomatologies;[42,46,51] 4) experimental evidence about functional connections between the pHyp, amygdala, and the Papez circuit.[49]

Taking into account these data, we decided to consider for aggressive and impulsively behaved patients the option of a more conservative, reversible, and nondestructive procedure that could replace the lesional procedures previously performed, as an extreme alternative to major restraining measures (forced hospitalization or use of straightjacket) and complete social isolation. Even though our clinical experience is only based on a small series of patients, it is the only neuromodulatory procedure available to treat these patients.

Since 2002 we have treated 6 patients, including 1 female, with ages ranging from 21 to 68 years. All of them had below-average IQ scores. Two patients also had comorbid refractory and generalized multifocal epilepsy. Disease etiology was posttraumatic in 1 case with subsequent permanent damage of the temporomesial structures; congenital or unknown origin in 3 cases with normal brain MR imaging; and heart arrest in 1 case with diffuse damage of the bilateral frontal cortex. All of the patients needed major restraint measures, and 2 were chronically hospitalized.

After informed consent was obtained from relatives, the patients underwent stereotactic placement of DBS electrodes in the pHyp region and subsequent subcutaneous positioning of IPGs (Kinetra or Soletra, Medtronic, Inc.).

Summary of Results

Stimulation parameters were as follows: frequency 185 Hz, pulse width 60–90 μsec, and stimulation amplitude in monopolar mode with case positive 1–3 V.

The patient in Case 1 showed quick improvement, with prompt disappearance of self-aggression. Bursts of uncontrolled violence gradually became less frequent and completely disappeared within 3 weeks. The patient returned to live with his family and started to attend a therapeutic community facility specializing in the care of mentally impaired patients. Generalized epileptic seizures disappeared, and partial seizures and absences were reduced by 50%. The antiepileptic drug therapy was consistently reconsidered and reduced to 30% of the original dosage.

Violent outbursts immediately disappeared in the patient in Case 2, and bed restraints were withdrawn. He was discharged from the hospital within 3 months of surgery and was admitted to a therapeutic community facility for mentally disabled patients. Three years later, after the IPG was temporarily turned off for knee surgery, the violent behavior–related symptoms returned, and when chronic stimulation was restored the therapeutic effect was considerably reduced despite an increase in the current amplitude, which could not be set higher than 2 V due to the appearance of side effects. Psychiatrists who had been following the patient suggested a possible evolution of the original disease to explain the loss of the therapeutic effect. Note, however, that with the IPG turned on the outbursts of violence were still less frequent and less intense than in the absence of stimulation.

The patient in Case 3 revealed a marked reduction in the frequency and duration of violent attacks only when the amplitude of stimulation was set to 1.8 V a few months after surgery. This patient is still calm, and her social activities have steadily improved. She is now able to participate in a specialized community facility, and her family integration is good. Violent outbursts appear occasionally, but only if the patient is provoked by adverse events.

The patient in Case 4 demonstrated an improvement only in his sleep pattern: before surgery he slept only 2 hours per night, and after surgery he sleeps more than 6 hours per night. Unfortunately, his behavior was not affected by the stimulation despite an increase in the electrical current to 2 V in amplitude. Two years after surgery the stimulator was turned off, but his sleep pattern did not return to the preoperative condition; by the 3-year follow-up he continued to sleep more than 6 hours per night. The same patient had a stable decrease in arterial pressure, and all antihypertensive drugs could be withdrawn. This effect is still present despite the fact that the IPG was turned off.

The patient in Case 5 had a prompt and marked improvement in behavior, and the family care became consistently easier. The therapeutic effect was stable at the 1-year follow-up, but when both IPGs were turned off the violent behavior reappeared within a few hours. The left IPG has recently been removed due to skin erosion, and the therapeutic effects seem to be sustained by right pHyp stimulation alone.

The patient in Case 6 demonstrated an impressive decrease in the frequency of epileptic seizures to 50% of the preoperative condition just a few weeks after surgery. The insertion of a second electrode at the target was immediately followed by the disappearance of interictal epileptic activity from scalp electroencephalography. This patient has undergone frequent follow-up examinations due to the onset of frequent states of somnolence after the surgical intervention. The aggressive behavior showed a progressive but significant decrease over time. Disruptive bouts have been abolished by stimulation, and the actual current amplitude is 2 V.

Hernando et al.[23] reported on the clinical case of a 22-year-old man with drug-resistant aggressiveness and mental retardation. Stereotactic bilateral electrodes were implanted in the medial portion of the pHyp; the authors used intraoperative microrecording and electroencephalographic responses for target localization. Interestingly, at the 18-month follow-up sustained clinical improvement was demonstrated using low-frequency stimulation.

Kuhn et al.[26] reported on the case of a 22-year-old woman with repetitive self-mutilating behavior in the mouth area following severe traumatic brain injury. After bilateral pHyp deep brain stimulation, complete resolution of the self-mutilation behavior was noticed at the 4-month follow-up.

Studies on Surgically Treated Patients

Schoenen and coworkers[45] studied 2 kinds of nociceptive reflexes in their surgically treated patients: the nociceptive blink reflex and the biceps femoris flexion reflex. The former was obtained with supraorbital stimulation and the latter with stimulation of the sural nerve at the ankle. Perception and pain threshold were determined bilaterally and at each site by using ascending and descending sequences of 0.2-mA intensity steps, with stimulus intensity set at 1.5 times the individual pain threshold. Responses were measured by quantifying the area of electromyography responses, assessed preoperatively and at 1 week and 1 month after surgery. The thresholds for pressure pain were determined using an algometer bilaterally positioned over the temple, the extensor muscles of the upper forearm, and the lateral aspect of the heel.

After surgery the supraorbital electrical pain threshold decreased after 1 week but not after 1 month on the side of the CCH bouts. Pain thresholds at the level of the sural nerve were higher after 1 month of DBS as compared with baseline, but only contralateral to the side of the CCH attacks.

Preoperative pressure pain thresholds were lower over the temple than over the extracephalic sites. During neurostimulation, thresholds at such sites increased, whereas at cephalic levels the thresholds did not significantly change. The level of significance was reached only after 1 month of stimulation: at the forearm ipsilateral to the CCH attacks and at the heel contralateral to the attacks. No significant change in response areas of nociceptive blink and biceps femoris flexion reflexes were noted, except for a significant increase in the ipsilateral nociceptive blink reflex response area following supraorbital stimulation ipsilateral to CCH bouts after 1 month compared with the preoperative assessment.

Endocrine tests were also performed.[45] Urinary excretion of melatonin was measured at different time epochs preoperatively. Twenty-four hour urinary excretion of cortisol was also determined, as were plasma levels of oxytocin and vasopressin. No significant hormonal changes were found postoperatively with respect to baseline.

The same group of authors also evaluated the response to sublingual nitroglycerin administration (1.2 mg) in 4 of 6 surgically treated patients. Nitroglycerin provoked CCH attacks in 3 patients preoperatively, in 2 after 1 week, and in none of 3 patients after 1 month of stimulation.

Cardiovascular effects of pHyp stimulation were studied by Cortelli et al.[10] in 8 patients who were surgically treated at our institute. Given that the pHyp, defined as the region above the mammillary bodies beside the third ventricle, is known to be involved in cardiovascular regulation[35] (and was defined as the "ergotropic area" in older literature), the authors decided to evaluate the role of the pHyp as an important component of the central autonomic nervous system. They monitored systolic and diastolic blood pressure, cardiac output, total peripheral resistance, heart rate, and breathing. Such parameters were measured during supine rest and during the head-up tilt test, Valsalva maneuver, deep breathing, cold face test, and isometric handgrip, both before and after surgery. They found that diastolic blood pressure, total peripheral resistance, and heart rate variability significantly increased during the head-up tilt test in the postoperative period with respect to baseline, and thus they concluded that DBS of the pHyp in patients with CCH could be associated with an enhancement of excitatory sympathetic drive on the cardiovascular system, resulting in mild orthostatic arterial hypotension at subclinical values.

Effects on sleep were evaluated by Vetrugno et al.[52] in 3 patients affected by refractory CCH who were surgically treated at our institute. Vetrugno and colleagues took into account the occurrence of several sleep disorders in patients with CCH (increased incidence of obstructive sleep apnea as compared with that in healthy volunteers) and the role of the pHyp region in the control of behavioral states of the sleep-wake cycle and arousal.[1] The 3 patients underwent 48-hour (consecutive) polysomnographic study and body core temperature monitoring before and after 4 months of DBS. Before implantation, all patients experienced at least 2 daytime and 1–2 nighttime CCH attacks. The baseline polysomnography showed a sleep structure characterized by prevalent light non-REM sleep Stages 1–2, normal REM sleep, and reduced sleep efficiency (ratio between total sleep time and time in bed). The total sleep time was 394.8 minutes, and wakefulness after sleep onset was 70.5 minutes. The mean arousal index and periodic limb movements (while asleep) index were increased.

Body core temperature rhythm was normal before and during stimulation of the pHyp, whereas DBS improved sleep architecture and sleep quality as compared with baseline: postoperative polysomnography showed a more continuous sleep pattern, with increased sleep time, sleep efficiency, and amount of slow-wave sleep stages. Polysomnographic indices of fragmented sleep (arousal and periodic limb movements while asleep) also decreased. All 3 patients presented with the disappearance of CCH nocturnal attacks at the 4-month follow-up.

The effects of hypothalamic stimulation on thermal sensitivity were assessed by Jürgens et al.[24] in 2009. These authors examined thermal thresholds for warm and cold sensations and for heat and cold pain in 3 groups: the DBS group (11 CCH patients with pHyp stimulation who were surgically treated at our institute), the medically treated CCH group (15 patients with unilateral CCH), and a control group (29 healthy controls with no history of primary or secondary headaches). These physiological responses were evaluated bilaterally at the forehead (first trigeminal branch), at the ventral forearm, and at the lateral lower leg and were then compared in the 3 groups. In the DBS group, the tests were performed with the stimulator switched on and again after 30 minutes off stimulation.

In the control group, thermal detection and pain thresholds did not differ significantly between the right and left side, so median values for thresholds of the right side were used for comparison with those of the stimulated side in the DBS group and with those of the painful side in the medically treated CCH group; the left side thresholds in healthy controls were compared with thresholds of the nonstimulated side in the DBS group and with thresholds of the healthy side in the medically treated CCH group.

No significant individual difference between the conditions of "on" versus "off" stimulation was found for any variable in the DBS group. Thresholds of simple detection of cold stimuli were significantly increased at all the tested locations bilaterally in the DBS group as compared with the control group; warm stimulus detection thresholds were higher bilaterally at V1 in the DBS group compared with the control group. At any rate, the thresholds for cold pain detection were only increased at the ipsilateral V1 in the DBS group.

The DBS group also showed higher thresholds for simple cold detection compared with nonimplanted patients with CCHs.

Note that in this study the difference in thresholds of cold pain detection was found after long-term stimulation, but evaluation in the "off" period was performed only after short-term cessation of the stimulus; it was not possible to examine the patients after a longer interruption of the stimulation because a recurrence in pain attacks would have been likely. For this reason, a carryover effect accounting for this lack of difference between the 2 states in the DBS group cannot be excluded.

In this study it is noted how direct reciprocal connections between the pHyp and trigeminal nuclei could justify these results.[5,33] To explain the differences found between simple and pain cold thresholds the authors suggested that the thermal perception and thermal pain perception are conveyed through different pathways and receptors, but they also stated that because of crossing fibers a central integration of the 2 systems cannot be ruled out.

Discussion

Chronic electrical stimulation of the posteromedial hypothalamus, originally introduced to treat patients with

CCHs refractory to conservative treatments, demonstrates positive results in neurological diseases other than CCH. They include facial pain involving the orbital region such as SUNCT, CPH, and first-branch TN in patients with MS. Moreover, pHyp DBS also improves other severe neurological conditions such as multifocal epilepsy[21] and disruptive behavior.[19]

Other functions modified during neurostimulation include thermal sensitivity,[24] sleep regulation,[52] and blood pressure regulation.[10] Susceptibility to nitroglycerin in patients with CCHs was also modified by chronic hypothalamic stimulation.[45]

Data suggest that the pHyp interacts with different neural networks that have a link or a common path in this small volume of brain. In particular, to understand the possibly involved neurophysiological circuits we must note the following phenomena involved in pHyp DBS: the neurovegetative responses linked to the pain threshold of the ipsilateral orbital region (CCH, SUNCT, and blood pressure regulation); the effect on cortical excitability and reticular system (multifocal epilepsy, psychomotor agitation, and sleep); the behavior responses (rage, aggressiveness, and disruptive behavior).

From these data we can argue that the pHyp modulates different neurological functions, and its dysregulation can result in a consistent variety of neurological symptoms. Unfortunately, our data are still not sufficient to build up a specific theory that could define the precise role of the pHyp, although we can hypothesize that it controls relationships between the neurophysiological circuits involved in pain behavior and the neurovegetative system. Note also that during pHyp DBS no endocrine changes have been demonstrated,[45] and so we must consider that the functions of this area are independent from the classic hormonal mechanisms controlled by the more anterior hypothalamic nuclei. Another relevant point is related to the latency periods that elapse between the beginning of stimulation and the appearance of therapeutic effects. This phenomenon has been highlighted by the French multicenter study. In fact, in the French study, turning the stimulator on and off at 1-month intervals resulted in an ineffectiveness in the control of pain in patients with CCHs; after 1 year of continuous stimulation in the same group of patients the therapeutic effect developed as in other reported series in the literature.[14]

The latency between the start of stimulation and the beginning of therapeutic effects is still much more variable and unpredictable in SUNCT,[32] although the long-term results in this syndrome appear to be good. Moreover, patients subjected to pHyp DBS for refractory aggressive behavior showed a certain delay between implantation and the full therapeutic effect. We hypothesize that pHyp DBS acts through the remodeling of neural circuits and so it requires a certain amount of time conditioned by individual neural plasticity. Similar mechanisms may be called upon to explain the time-related effects of pallidal DBS in dystonia or the latency between the start of stimulation and the therapeutic effects in depressed patients treated with CG25 area chronic stimulation or even in patients treated with vagal nerve stimulation for depression or epilepsy.

From a practical view the most relevant point in the discussion of pHyp DBS is the incidence of nonresponders, which may realistically be estimated at about 50% of all reported cases.

This percentage is not very low if we consider that, worldwide, surgically treated patients were refractory to any other treatment. Nevertheless, it is true that we cannot predict the outcome of DBS in new patients. In the future, the selection criteria will include the loss of response to greater occipital nerve stimulation, contributing to narrowing down the pool of patients selected for DBS.[47] In the future, functional neuroimaging, including PET and MR imaging, may help to disclose individual hypothalamic involvement in patients affected by CCHs. Furthermore, MR imaging spectrography in steady-state conditions has been used to search for a hypothalamic notch in patients with CCHs. In other words, patient selection based on imaging modality will improve the clinical selection based on the International Headache Society criteria.

Another ongoing problem is the place that pHyp DBS has held in the hierarchy of available surgical treatments for CCH. In our opinion, lesioning procedures such as trigeminal thermorhizotomy or surgical removal of the trigeminal nerve should be abandoned given the irreversibility of the facial sensory deficits, which may worsen patients' conditions when dysesthesias or painful anesthesias develop. The only promising lesioning technique is radiosurgical lesioning of the sphenopalatine ganglion, which should be attempted in patients who obtain significant benefits from a sphenopalatine ganglion lidocaine injection test.

Microvascular decompression of cranial nerve V has been attempted in selected cases, but the results of such a procedure are still unpredictable. Greater occipital nerve stimulation is the most promising neuromodulation procedure and will, like vagal nerve stimulation or sphenopalatine ganglion stimulation, act through peripheral electrical stimulation to modulate the CNS structures alleged to be primarily involved in the origin of pain bouts. In our opinion, DBS should be considered in highly selected cases after all of these less invasive procedures have been tried. Of the 75 pHyp DBS cases reported in the literature, a severe complication occurred in only 1 case. The safety of pHyp DBS has been confirmed by different authors.

Conclusions

In summary, we think that pHyp DBS is a powerful tool in the hands of functional neurosurgeons in treating extremely severe and rare conditions such as CCH, SUNCT, and disruptive behavior in patients with below average IQs. While the mechanisms of action are still unknown, they do seem to be mediated by a remodeling of network circuits through neural plasticity. New applications of pHyp DBS may be expected in the field of sleep disorders, epilepsy, and perhaps some other diseases involving the autonomic nervous system.

Disclosure

The authors report no conflict of interest concerning the mate-

rials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Franzini, Messina. Analysis and interpretation of data: Cordella. Critically revising the article: Marras, Broggi.

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Manuscript submitted April 6, 2010.
Accepted May 18, 2010.
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Neurosurg Focus 29 (2):E14, 2010

Deep brain stimulation in the management of disorders of consciousness: a review of physiology, previous reports, and ethical considerations

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Patients suffering from disorders of consciousness constitute a population that exists largely outside of the daily practice patterns of neurosurgeons. Historically, treatment has focused on nursing and custodial issues with limited neurosurgical intervention. Recently, however, deep brain stimulation has been explored to restore cognitive and physical function to patients in minimally conscious states. In this article, the authors characterize the physiological mechanisms for the use of deep brain stimulation in persistently vegetative and minimally conscious patients, review published cases and associated ethical concerns, and discuss future directions of this technology.
(DOI: 10.3171/2010.4.FOCUS1096)

Key Words • **deep brain stimulation** • **minimally conscious state** • **persistent vegetative state** • **thalamus** • **disorder of consciousness** • **ethics**

The application of deep brain stimulation (DBS) has grown to include a wide variety of clinical situations. A fairly novel and sparsely studied application involves the use of DBS in improving the clinical condition of patients in a persistent vegetative state (PVS) or minimally conscious state (MCS) following traumatic brain injury. Beginning in the 1950s, infrequent reports of the use of DBS for disorders of consciousness had been described. More recently, a widely publicized case of dramatic improvement in a patient in an MCS who was treated with DBS rejuvenated interest in this therapeutic intervention.[33] Still, many factors may ultimately contribute to or confound the possible success of this treatment, including spontaneous recovery, incorrect diagnosis, and the fluctuating baseline consciousness of the patient.

While it is known that a spectrum of consciousness exists from comatose to fully conscious, not until recently has a distinction between a PVS and an MCS been established.[16] A PVS is defined as a degree of consciousness after severe brain injury whereby a patient has developed wakefulness with some degree of sleep-wake cycling but without any demonstration of environmental awareness.[3,27] The patients who fall into this category of consciousness have a functional brainstem and various dispersed "islands" of dysfunctional cortex.[22] In contrast, an MCS represents a more advanced stage of consciousness in which a patient demonstrates an increased awareness of his or her environment via observed, cognitively mediated behaviors but remains inconsistent in his or her communication abilities.[3,16,27] On functional brain imaging tests, these patients may have organized cortical functioning despite appearing grossly unconscious.[26,28] While either state may result from a traumatic brain injury and both have profound functional consequences, differentiating between the two states may be important in determining the possible benefit of DBS therapy.

This review characterizes the physiological mechanisms for the use of DBS in disorders of consciousness, reviews published cases of its use in the literature, the associated ethical concerns, and provides a discussion of the possible future for this application of DBS.

Physiological Basis for DBS in PVS or MCS

Initial theories regarding stimulation of the reticular formation and thalamus as a means of stimulating wakefulness date to early basic science studies conducted in the 1960s elucidating these activating centers.[6,29] Further

Abbreviations used in this paper: DBS = deep brain stimulation; MCS = minimally conscious state; PVS = persistent vegetative state.

work revealed the role of the intralaminar nuclei in maintaining attention and memory based upon their anatomical neural connections and physiological characteristics.[23] The subsequent discovery of widespread thalamocortical projections then contributed to the understanding of the importance of the central lateral nuclei of the intralaminar nuclei of the thalamus in promoting arousal.[30,39]

Many thalamic nuclei share important roles in the relay of sensory and motor functions. Biochemical advances have revealed a specific type of thalamic neuron thought to be involved in the more basic function of activating cortical networks.[20,21] These calbindin-positive staining neurons differ from the standard thalamic relay neurons in that they maintain axonal projections to more diffuse areas of cortex, including portions of the frontal lobe and other areas not traditionally involved in sensory or motor function. Moreover, these neurons synapse in layers of the cortex where relay neurons are typically absent.[20,21] These special characteristics, combined with the finding that a significant portion of the intralaminar nuclei (nuclei previously believed to be important in the activating system) were composed of such calbindin-positive neurons, helped establish the importance of specific thalamic nuclei in arousal. More recent research has demonstrated that such neural connections between the central lateral nuclei and the cortex are reciprocal and that these nuclei are densely innervated by brainstem arousal systems as well.[31]

Multiple cases have been reported whereby a lesion restricted to these nuclei resulted primarily in disturbances of consciousness and behavior, further confirming the importance of intralaminar nuclei in cognitive arousal and particularly attention and concentration.[4,38] Patients with specific ischemic infarctions of these nuclei primarily demonstrated disturbances in attention. Subsequent SPECT imaging performed in these patients revealed decreased blood flow to the frontal cortices.[38]

As basic neuroscience research demonstrated the importance of these thalamic nuclei for wakefulness, theories regarding the possibility of stimulating such nuclei to possibly induce an awake state in unconscious patients became increasingly popular. The initial trials involving artificial stimulation of these areas were correspondingly designed and performed in patients with disorders of consciousness. However, a major distinction in the conscious state of the patient was not discovered until much later in the process—namely, the difference between PVS and MCS patients. Schiff et al.[33] suggested that patients most likely to show improvement with DBS therapy are those with relatively preserved areas of essential cortical functioning with damage primarily involving the arousal centers (that is MCS patients rather than PVS patients). These authors reported on a carefully selected study subject in an MCS who showed dramatic improvement with DBS. The positive outcome in this case was hypothesized to relate to the patient's having had an underlying primary defect in the arousal system while overall cortical function had been preserved.[33] The authors suggested that the central lateral thalamic nuclei of the intralaminar nucleus would be the highest yield targets for stimulation based upon neurophysiological calculation and that MCS patients would be the most likely to benefit. Unfortunately, this conclusion may be confounded by growing evidence of a bias to classify patients as in a PVS, when they may truly be in an MCS.[2]

Review of Reported Cases

The earliest published cases of electrical stimulation as a therapy for patients with decreased arousal were conducted in the late 1960s and 1970s. Hassler et al.[19] were the first to report nonspecific behavioral and electroencephalographic arousal after stimulating an unspecified projection system (possibly the rostral ventral thalamic nucleus or intralaminar thalamic nucleus) in a posttraumatic persistently vegetative patient. Although Hassler was unaware of the exact neurophysiological underpinnings of the projection system at the time, it has since been suggested that they likely involved the recently discovered calbindin-positive thalamocortical pathway from the intralaminar nucleus.[35] In 1979, Sturm et al.[36] reported that bipolar stimulation of the nucleus reticulatus polaris thalami in a patient with a medial midbrain infarct resulted in improvement in following commands, wakefulness, verbal communication, and an increased oral intake. The patient initially was described as having "some kind of unconsciousness which was neither manifest coma nor a typical apallic [PVS] syndrome." The patient died 2 months after the implantation of electrodes. Unfortunately, these early cases were confounded by a limited understanding of the differences in the states of impaired consciousness, which have since been shown to alter the prognosis for recovery and outcome. The fact that stimulation was performed within the spontaneous recovery period further limits the conclusions that can be drawn from these early studies. A more recent study suggests that spontaneous recovery in MCS patients can occur up to 1 year following the initial insult.[25]

More recent reported cases of the use of DBS in PVS or MCS patients include reports by Tsubokawa et al.[37] These authors performed therapeutic DBS targeting the mesencephalic reticular formation and nonspecific thalamic nuclei and followed 8 patients in a PVS as a result of severe brain injury (closed head injury, cerebrovascular accident, or anoxia) over 6 months. Improvement in vocal communication and arousal was noted in 4 of the 8 patients. Over the following decade, the same group increased their cohort to a total of 21 patients (including the heavily publicized case of Terri Schiavo), 8 of whom showed improvement in ability to obey verbal commands.[42] Despite the large number of patients in the more recent trials, this study was limited by the timing of DBS therapy within the accepted 1-year time frame of spontaneous recovery. The decision to attempt DBS in patients whose condition was initially diagnosed as a PVS, a cohort that is less likely to benefit from such stimulation than patients in an MCS, may have also limited their findings.[32]

The most recent and widely publicized published case of DBS-based improvement in PVS or MCS patients was reported by Schiff et al. in 2007.[33] In this case, DBS therapy was attempted in a 38-year-old man whose condition was diagnosed as an MCS 6 years after a traumatic

brain injury. Prior to DBS stimulation, the patient demonstrated visual pursuit and intermittently followed simple commands.[32] Following implantation and therapy, the researchers reported improvements in level of arousal (sustained eye opening, head turning to voices), functional limb movements, ability to feed orally, and improvement in the JFK Coma Recovery Scale-Revised score despite a 6-year history of minimal consciousness. The patient was soon able to name objects, move objects with his hands, and feed himself.

A major difference between this case and previous attempts to evaluate DBS in PVS or MCS patients was the patient selection criteria. This patient was in a clearly defined MCS and demonstrated preservation of cortical structure and language function but suffered primarily from inconsistency and loss of arousal. Additionally, he demonstrated improvement outside of the 1-year window whereby the likelihood of spontaneous improvement is low, unlike patients in previous studies.[33] This is an important consideration given that the window of spontaneous recovery, which strongly confounded prior studies, has only recently been described.[25] Moreover, this study was the first to use a widely accepted outcome measure, the JFK Coma Recovery Scale-Revised, to determine the clinical benefit of periods when DBS was turned on.[17] While most previous studies reported subjective outcome improvements such as verbalization, behavioral changes, or limb motion improvements, this was the first to document objective clinical improvement. This report also demonstrated that the bulk of improvement occurred when stimulation was turned on outside of a 50-day postoperative window to minimize any possible residual surgical source of improvement. Additionally, Schiff et al.[33] demonstrated carry-over improvement from prior DBS stimulation periods even after DBS stimulation was turned off.

Despite being based upon only one case, the Schiff et al.[33] report provided much less biased information in the study of DBS for MCS patients. The applicability of this single case however remains difficult to determine. Moreover, the patient chosen for this study was among the higher functioning patients in the MCS state prior to DBS therapy. While the rationale for this decision was that a patient with largely preserved cortical function would be the most likely to recover meaningful function, the gains demonstrated in the case may not be as significant as initially believed given the patient's high baseline level of functioning.

Ethical Considerations in the Treatment of Disorders of Consciousness

Since being first described approximately 4500 years ago in the Edwin Smith Papyrus, damage to the adult CNS in humans has been regarded as an "ailment which cannot be treated."[7] This view still seems to be the prevailing one with respect to disorders of consciousness. Despite recent developments in neuroimaging, pharmacology, and neuromodulation, the functional utility of these improvements in the setting of disorders of consciousness remains largely untapped.[11] In a recent editorial, Wijdicks and Rabinstein[40] presented guidelines for meeting with families whose loved ones are comatose, stating, "the attending physician of a patient with a devastating neurologic illness will have to come to terms with the futility of care." Often, clinicians evaluate brain-injured patients relatively early in the course of injury and are unaware of any longitudinal recovery.[11] Clinicians are trained to respect patient preferences at the end of life and often believe they are advocating on behalf of the patient by steering families toward less-aggressive treatment. Palliative measures are often advocated based on an ethical sense that nothing can or should be done for patients with catastrophic brain dysfunction.[9] While this approach is generally appropriate in the neurointensive care unit, it is essential that acute-care clinicians avoid prognostic errors about outcome based solely on decreased consciousness in the setting of brain injury. This reduced level of consciousness may be a precursor to brain death or the beginning of a variable recovery process depending upon the underlying anatomical severity.[11]

Over the past several years, counseling families with regard to the decision to withdraw life-sustaining therapy from patients with severe brain injuries has become more complex. Since the 1968 creation of brain death criteria, the description of brain states has been refined.[10] Patients who are brain-dead and those in a PVS are often believed to be hopelessly damaged and permanently unconscious. A vegetative state is generally considered permanent 3 months after anoxic injury and 12 months after trauma.[13] However, shortly after injury, PVS patients may progress to an MCS, of which the natural history is not yet known. Unlike patients in a vegetative state, the minimally conscious may demonstrate inconsistent evidence of self- and environmental awareness.[15] Patients in an MCS may show a spectrum of behavior ranging from responding to environmental stimuli to following simple commands or possibly the production of incongruous verbal communication.[15] Unfortunately, the diagnostic timeline introduces a piquant paradox. To fully determine whether recovery from the vegetative state is possible, a patient with a traumatic brain injury might have to be observed for as many as 12 months. Currently, decisions about withholding life-sustaining therapy are typically made within days to weeks of presentation for patients with disorders of consciousness because options for withdrawal diminish as the patient moves from the acute to the chronic stage of illness.[9]

Arriving at an accurate diagnosis in a patient with a decreased level of consciousness is challenging. Diagnostic error rates of roughly 40% have been reported in nursing home patients in an MCS who were labeled as vegetative.[1,5,41] The most famous example of such cases is that of Terry Wallis, a minimally conscious Arkansas man who was erroneously diagnosed as vegetative 19 years previously; he began to speak fluently in 2003 and it was subsequently learned that he likely experienced episodic consciousness.[8] Two goals should be achieved in the evaluation of patients in PVS and MCS.[28] First, it should be ascertained whether the patient retains the capacity for a purposeful response to stimulation, even if it is inconsistently manifested. Such an aptitude implies at least partial awareness (MCS), which has ramifications

for subsequent care, level of rehabilitation, and ethical decision making. Second, clinical assessment should also focus upon reproducible communication, as consistent communication is the upper boundary of MCS.[15] Monti et al.[28] used functional MR imaging to evaluate preserved awareness in a series of 54 patients in PVS and MCS. In this series, 3 MCS and 2 PVS patients were determined to able to modulate their brain activity by generating voluntary, reliable, and repeatable neuroimaging responses in predefined neuroanatomical regions when prompted to perform imagery tasks.[28]

Neurostimulation for MCS is still an area of investigation and not yet a widely accepted therapy.[18] While advances in neuromodulation have the ability to offer new therapeutic interventions for patients with disorders of consciousness, these interventions have not been tested in large clinical trials and have been performed in only a small number of patients. Moreover, conducting clinical research trials in patients with PVS and MCS is difficult as a result of regulatory complexity. These patients are deemed a vulnerable population and thus are subject to special protections with regard to enrollment in clinical trials.[9] Although the patient's surrogate may consent to therapeutic procedures with demonstrated benefit, the surrogate's ability to authorize enrollment in a research trial is curtailed when the medical benefit of the treatment is yet to be demonstrated.[10] Ultimately, these restrictions may result in counteracting advances in neuromodulation that could aid the population that the United States National Bioethics Advisory Commission has sought to protect from exploitation.[10] These issues severely limit the potential for Phase I surgical trials in individuals who are unable provide consent for the very procedure that may restore some of their decision making capacity. Accordingly, some bioethicists have argued that clinical trials to reestablish consciousness would be ethically appropriate, even with the challenges posed by surrogate consent, when these distinctions and the burdens imposed on these patients and families are taken into consideration.[12] Overcoming these barriers is essential if translational research is to be accomplished in this population, which has historically been sequestered from clinical research and would otherwise remain in a hopeless clinical situation.[14]

With improvements in consciousness also comes the possibility of unexpected burdens.[12] In some cases, after stimulation, an individual may become more aware of cognitive and physical disabilities that he or she was previously unable to perceive. Cognitive improvements resulting from stimulation would need to be evaluated to determine if the increased awareness of self, others, and the environment is, in fact, a "patient-centered benefit."[32] In this sense, the harm associated with conscious awareness of one's cognitive and physical impairments might be enough to abolish any benefits.[18] An appraisal should not only be restricted to third-person interpretation, but also a first-person affirmation by the individual who will be summarily required to function with these deficits.[18] Furthermore, several studies have determined the prevalence of suicidal ideation in people with traumatic brain injuries as varying between 3% and 33%.[34] In light of the increased prevalence of suicidality among people with severe brain injury, what would be the appropriate ethical response to a patient who received DBS only to awaken from a minimally conscious state to express the consistent desire for termination of care? These issues are not isolated to this debate; this "self-awareness paradox" of recovery is frequently encountered after initial injury by severely brain-injured patients who must come to terms with the comprehension of a "new self."[9,32]

In cases of disorders of consciousness, evaluating a patient with residual cortical activity and the potential to recover neurological functions for stimulation therapy raises the ethical questions of beneficence and nonmaleficence. Ostensibly, any procedure resulting in an improvement in cognition could be considered a benefit to the patient. However, the crux of this ethical argument hinges upon the degree to which cognitive and physical functions are restored in patients with severe brain injury.[18] If a procedure were to completely restore consciousness as well as cognitive and physical functioning, the procedure would be considered of unequivocal benefit. However, it is conceivable that some patients may experience adverse psychological effects of DBS that would outweigh the benefits of the restorative effects.[18] Furthermore, the difficulty in risk-benefit analysis is complicated by the assertion that restoration of consciousness following brain injury will likely vary along a spectrum.[18] To create a responsible research ethic, current clinical investigators must attempt to balance the principles of respect, beneficence, nonmaleficence, and surrogate consent within an ethical framework.

Conclusions

While the application of DBS for patients in vegetative and minimally conscious states is relatively novel, great promise exists for this neurosurgical intervention in cases in which limited therapeutic options currently exist. Current strategies for the medical management of patients in PVS or MCS are largely guided by principles of sustaining life rather than improving a patient's clinical situation, primarily because of the very limited interventional options for such patients. The emerging prospect that DBS may be able to restore function to patients in an otherwise hopeless situation may bolster the future use of this technology as both clinicians and patients may begin to view DBS as a practicable treatment.[11]

However, before DBS can be viewed as a clinically sound therapeutic intervention for patients in MCS or even PVS, significant additional research is necessary. Given the absence of a good translational animal model, short and long-term results and complications remain predominately unknown and untested. Over the past 5 decades, only a handful of studies have been conducted on a wide variety of patients, with only one most recent study of a single patient without confounding factors like spontaneous recovery. By report, the US Food and Drug Administration approved use of this therapy in 11 additional patients to provide more clinical results.[24] Current research is extremely limited both in the number of patients studied, as well as the clinical situations in which to best consider the application of DBS therapy. Hence,

no definitive conclusions can be made based on current data regarding whether to attempt DBS therapy, or even in which patients it would be most beneficial.

While a better understanding of these clinical issues will invariably emerge following additional trials, the resultant ethical complexity that will almost certainly ensue will likely need to be thoughtfully deliberated on an individual basis. Given the abuses of psychosurgery in the previous century, the use of DBS in the minimally conscious should be supported by strong scientific evidence, stringent oversight, and the full interdisciplinary support of neurosurgeons, neuroscientists, psychiatrists, and physiatrists who can help assess a patient's suitability for DBS and provide continuous follow-up over time. Nevertheless, a significant hope for the future of this technology exists. We are only beginning to discover the full implications of this application of DBS, and an exciting future may await both patients and providers in a once hopeless clinical situation.

Disclosure

Dr. Sharan is a consultant for St. Jude, Covidian, and Medtronic; and received study support from St. Jude, honoraria from St. Jude and Integra, and other financial support from Zimmer Spine. The other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Campbell, Yadla, Sharan. Acquisition of data: Campbell, Sen. Analysis and interpretation of data: Campbell, Sen, Yadla, Sharan. Drafting the article: Campbell, Sen. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Campbell, Sharan. Study supervision: Campbell.

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Manuscript submitted April 14, 2010.
Accepted April 21, 2010.

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Neurosurg Focus 29 (2):E15, 2010

Deep brain stimulation compared with bariatric surgery for the treatment of morbid obesity: a decision analysis study

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Object. Roux-en-Y gastric bypass is the gold standard treatment for morbid obesity, although failure rates may be high, particularly in patients with a BMI > 50 kg/m^2. With improved understanding of the neuropsychiatric basis of obesity, deep brain stimulation (DBS) offers a less invasive and reversible alternative to available surgical treatments. In this decision analysis, the authors determined the success rate at which DBS would be equivalent to the two most common bariatric surgeries.

Methods. Medline searches were performed for studies of laparoscopic adjustable gastric banding (LAGB), laparoscopic Roux-en-Y gastric bypass (LRYGB), and DBS for movement disorders. Bariatric surgery was considered successful if postoperative excess weight loss exceeded 45% at 1-year follow-up. Using complication and success rates from the literature, the authors constructed a decision analysis model for treatment by LAGB, LRYGB, DBS, or no surgical treatment. A sensitivity analysis in which major parameters were systematically varied within their 95% CIs was used.

Results. Fifteen studies involving 3489 and 3306 cases of LAGB and LRYGB, respectively, and 45 studies involving 2937 cases treated with DBS were included. The operative successes were 0.30 (95% CI 0.247–0.358) for LAGB and 0.968 (95% CI 0.967–0.969) for LRYGB. Sensitivity analysis revealed utility of surgical complications in LRYGB, probability of surgical complications in DBS, and success rate of DBS as having the greatest influence on outcomes. At no values did LAGB result in superior outcomes compared with other treatments.

Conclusions. Deep brain stimulation must achieve a success rate of 83% to be equivalent to bariatric surgery. This high-threshold success rate is probably due to the reported success rate of LRYGB, despite its higher complication rate (33.4%) compared with DBS (19.4%). The results support further research into the role of DBS for the treatment of obesity. *(DOI: 10.3171/2010.5.FOCUS10109)*

Key Words • **deep brain stimulation** • **bariatric surgery** • **obesity**

The high prevalence of obesity in the US has motivated investigation of novel therapeutic approaches. Morbid obesity, defined as a BMI > 40 kg/m^2, affects more than 8 million adult Americans and reaches a prevalence of 14% in select populations.[11,24] Morbid obesity is associated with premature death,[11,25] impaired QOL,[22] and multiple morbidities, which include Type 2 diabetes, cardiovascular disease, musculoskeletal disorders, and certain cancers.[76,85] Significant weight loss, however, may lead to a 25% to 60% reduction in all-cause, cardiovascular, and cancer mortality.[1,100,111]

Bariatric surgery has emerged as a primary weight loss strategy, given the high relapse rates associated with nonsurgical approaches. Bariatric surgery is reserved for patients with a BMI > 40 kg/m^2 or a BMI > 35 kg/m^2 in the presence of significant comorbidities,[15] and most commonly involves LAGB or LRYGB.

Laparoscopic adjustable gastric banding is a purely restrictive procedure in which an adjustable device is placed circumferentially around the upper portion of the stomach, thereby creating a small pouch with a restricted outlet, whereas LRYGB involves construction of a gastric pouch in which the outlet is a Y-shaped limb of small bowel of varying length. The multiple mechanisms of weight loss following LRYGB, including restriction, malabsorption, and hormonal alterations may contribute to a higher reported postoperative excess weight loss compared with LABG.[11] Despite reductions in mortality rates[1,89] and improvements in obesity-related morbidi-

Abbreviations used in this paper: BMI = body mass index; DBS = deep brain stimulation; DVT = deep venous thrombosis; LAGB = laparoscopic adjustable gastric banding; LH = lateral hypothalamus; LRYGB = laparoscopic Roux-en-Y gastric bypass; NAc = nucleus accumbens; PE = pulmonary embolism; QOL = quality of life; VMH = ventromedial hypothalamus; VTE = venous thromboembolism.

ties,[11] weight gain may occur following bariatric surgery due to dietary relapse, particularly in patients with a BMI > 50 kg/m^2.[14]

An increased understanding of the neuropsychiatric basis of obesity has provided both insight into limitations of available obesity therapies and motivation for new treatment approaches. Deep brain stimulation is currently being investigated as a weight loss strategy for obesity.[35,36,70,94] The VMH and LH are known satiety and appetite centers, respectively,[90] in the brain, and represent potential targets for modifying appetite and enhancing the metabolic rate. In early lesioning studies in animals, researchers observed overeating after destruction of the VMH[40,108] and early satiation after selective destruction of neurons in the LH.[2,21,104,105] In more recent DBS studies, high-frequency DBS of the VMH was associated with a moderate increase in food consumption in nonhuman primates.[62] Of note, VMH stimulation at low frequencies (for example, 60–100 Hz) inhibited feeding in hungry rats,[42,59] and more recently was shown to improve the metabolic rate.[92] Sani et al.[94] showed that stimulation of bilateral LH was associated with a small amount of weight loss that was believed to be largely due to enhanced metabolism. The concept of a dual-center theory of appetite regulation involving the VMH and LH has given way to a more integrated model, with a focus on energy expenditure and endocrine signaling in association with adipose tissue.[53,94] Last, Hamani et al.[36] performed DBS in the LH of an obese patient, with unexpected improvements in memory, although the effect on weight and food consumption was unclear.

A more potent determinant of feeding behavior may be related to the palatability or reinforcing value of food,[35,107] which is modulated by the NAc.[41,121] Animal and neuroimaging studies support the NAc as an additional target for obesity. Weight loss and decreased hoarding behavior was observed in rats after ablation of dopaminergic input to the NAc. Subsequently, levodopa administration resulted in restoration of hoarding behavior.[51] Furthermore, functional MR imaging studies have demonstrated activation of striatal reward areas during exposure to a high-fat stimulus.[5] Studies of DBS for obesity are currently investigatory and preclinical. Despite reports of the safety and efficacy of DBS for movement disorders,[33,113] this surgery is not without adverse events, which may relate to the surgical procedure, implanted hardware, or the stimulation itself.[7] More recently, pilot studies and small clinical trials have demonstrated the efficacy and safety of DBS of the NAc in neuropsychiatric diseases such as obsessive-compulsive disorder[32] and major depression that are refractory to treatment.[95] To date, however, no clinical trials have been performed for morbid obesity.

At this early stage, it is critical to determine whether DBS may have a role in the treatment of obesity based on the so-called utility associated with the proposed treatment modality. "Utility" refers to a measure of QOL. We developed a decision analysis model, taking into account the complication rates of the two most common bariatric procedures, LAGB and LRYGB, as well as the complication rates of DBS for movement disorders as a proxy of DBS for obesity. Using the success rates of bariatric surgery, we performed a threshold analysis to determine the level of success required for DBS to be at least as effective as bariatric surgery for the treatment of morbid obesity.

Methods

We performed Medline and PubMed searches of studies published in the English language literature. For bariatric surgery outcomes, we searched for articles containing the term "obesity, morbid" in the medical subject heading and "surgery" in the subheading. We limited our review to trials published between January 2000 and March 2010, comparing cases with LAGB to LRYGB, and reporting at least 25 cases in one or both arms. Only studies with a minimum 1-year follow-up were included. For DBS data, our search encompassed trials published between January 1997 and March 2010, containing the term "deep brain stimulation" in the medical subject heading and "complications" in the subheading, and reporting at least 15 cases. For utility values associated with the outcome of various complications, we searched for articles containing "quality of life" in the medical subject heading and the specific complication in the title.

We abstracted estimates of the outcomes of each of these three surgical strategies based on the reported outcomes in the papers selected from our literature search. We considered surgical treatment to be successful if the percentage of postoperative excess weight loss exceeded 45%. If only mean percentages of excess weight loss were reported, we calculated the percent of cases meeting the 45% threshold from the series' mean and SD values.

A single patient may experience more than one complication. The total number of occurrences per complication was recorded. The mean incidence of complications was derived from the total number of complication occurrences divided by the number of patients at risk. For DBS implant–specific complications, both neurological and mechanical, the frequency of complications was divided by the number of implant sites. Patients who underwent DBS had either unilateral or bilateral implants. A complication not mentioned in a report was not included in the calculations. For each study, patients were considered at risk for a certain complication only if the complication was recorded by study investigators.

We constructed a decision analysis model for treatment by using the pathways and outcomes outlined in the decision tree (Fig. 1). The three surgical approaches were compared. A fourth arm, untreated obesity, was included for reference. Because the frequencies of various complications were different for each of the treatment arms, separate subtrees were constructed for each to calculate the incidence and impact of complications on utility. The utility values were assigned for each outcome outlined in the decision tree and the complications subtrees. These represented the overall effect of the outcome for a patient's health and well-being and, by consensus, measured between 0 and 1.[102] Because there has been no clinical trial on DBS for morbid obesity and, thus, no information on its success rate, we chose an arbitrary rate of 50% as a placeholder.

We multiplied the probability of each treatment

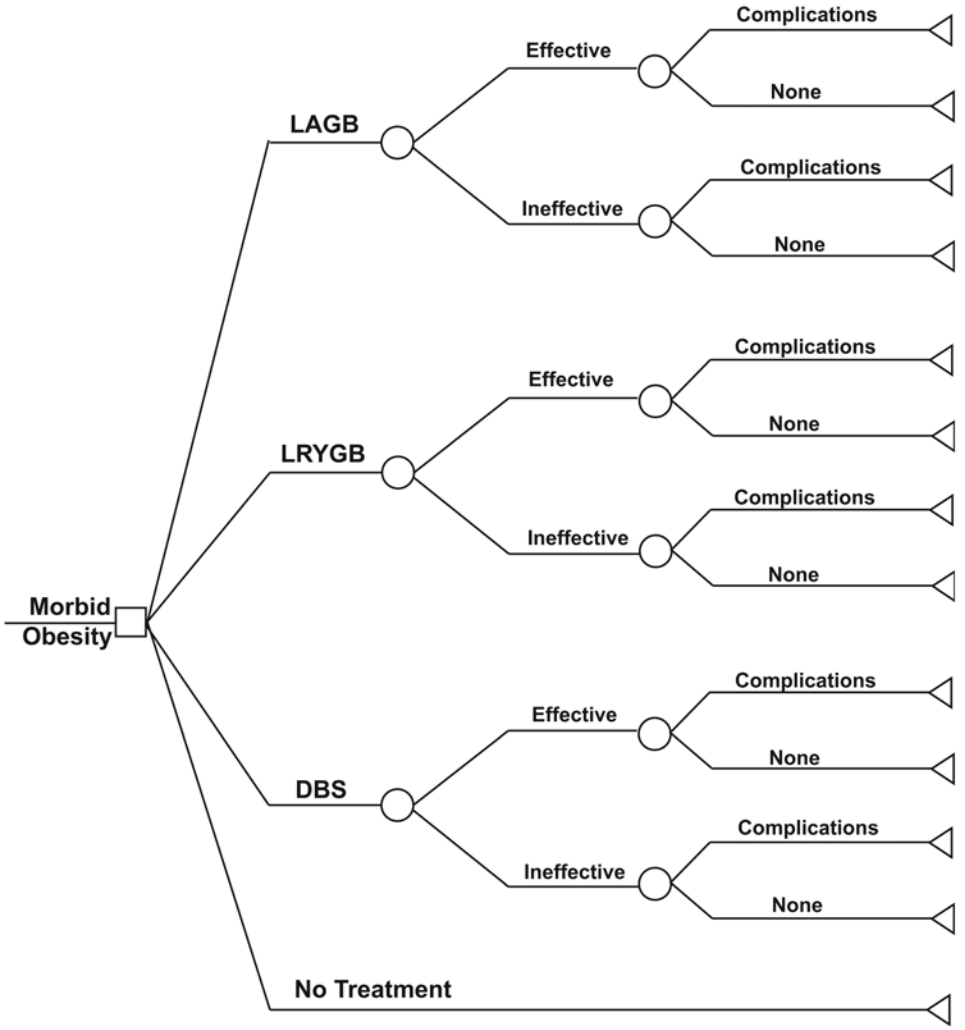

Fig. 1. Decision analysis tree with separate subtrees for the varying frequencies of complications associated with each surgical treatment. Chance nodes *(circles)* illustrate all possible responses to treatment, and *triangular nodes* represent scored outcomes.

branch by the utility of the outcome of that branch. The number obtained by adding the products is a "point estimate" of the utility of that treatment; the treatment with the highest utility is most favored. The reported point estimates of outcomes and complications from the pooled data represent variance-weighted means,[23] and these were tested for heterogeneity.[54] This step was essential given the disparity among the patients from various studies that made up the pooled data set. The conditional probability of each possible outcome for the three treatment methods (and its SD) was calculated. We used a 1-year timeline for outcome comparisons. A small dysutility, or decrease in QOL, was assigned to each surgical procedure, based on its estimated effect on health-related QOL and the expected duration of effect, consistent with previous cost-effectiveness studies of bariatric surgery.[18,46] For complications that had only temporary effects, these utilities, or QOL values, only applied to the 1st year. Multiple complications or dysutilities occurring at the same time are multiplied, as is routine in analyses of this sort.[102]

To allow for uncertainty in our data, we used a sensitivity analysis. Sensitivity analysis provides a means of determining how sensitive the conclusions of the decision analysis model are to changes in its parameters; it quantifies the influence of important parameters on utility. One-way sensitivity analyses for each model parameter included all values for that parameter within its 95% CI. Three-way sensitivity analyses, in which the parameters are varied simultaneously when recalculating outcomes, allowed more detailed assessment for parameters having the greatest impact on outcome.

For meta-analyses we used Stata 9 software (StataCorp LP). Sensitivity analyses were done using Tree Age Pro 2009 (TreeAge Software, Inc.). We considered differences for which the probability value was < 0.05 to be statistically significant.

Results

The literature search yielded 268 articles on bariatric surgery, of which 15 met the restrictions outlined above. These 15 publications included a total of 3489

TABLE 1: Incidence of complications in bariatric surgery*

Complication	Incidence w/ LAGB		Incidence w/ LRYGB	
	No. at Risk	Mean ± SD	No. at Risk	Mean ± SD
perforation	1464	0.008 ± 0.002	1738	0.005 ± 0.002
conversion to open procedure	2161	0.003 ± 0.001	2407	0.009 ± 0.002
DVT	353	0.003 ± 0.003	984	0.007 ± 0.003
PE	1209	0.007 ± 0.002	1022	0.005 ± 0.002
pneumonia	399	0.005 ± 0.004	1001	0.010 ± 0.003
hemorrhage	1151	0.005 ± 0.002	2075	0.022 ± 0.002
superficial infection	1420	0.020 ± 0.004	2404	0.039 ± 0.003
anastomotic leak	738	0.001 ± 0.001	2458	0.012 ± 0.004
bowel obstruction	1909	0.015 ± 0.003	2585	0.038 ± 0.002
ulcer	NA	NA	2210	0.018 ± 0.004
hernia (incisional, internal)	741	0.009 ± 0.004	2173	0.051 ± 0.003
cholelithiasis	586	0.017 ± 0.005	855	0.020 ± 0.005
band prolapse, slippage/dilation	1817	0.074 ± 0.006	NA	NA
erosion of band or port	1457	0.006 ± 0.002	NA	NA
port/tubing events	1739	0.043 ± 0.005	NA	NA
treatment-related death	2684	0.001 ± 0.001	2850	0.002 ± 0.0014

* NA = not applicable.

TABLE 2: Incidence of complications in DBS*

Complication	No. at Risk	Incidence (mean ± SD)
DVT	12	0.083 ± 0.079786
PE	573	0.0140 ± 0.014496
pneumonia	42	0.048 ± 0.032985
chronic SDH	3579	0.014 ± 0.001964
transient hemiparesis	3579	0.003 ± 0.000966
seizures	2223	0.014 ± 0.002492
hardware malfunction	3870	0.068 ± 0.004046
subcutaneous hemorrhage/seroma	1252	0.018371 ± 0.003795
CSF leak	1131	0.004 ± 0.001877
superficial infection	4568	0.024518 ± 21391099
treatment-related death	4568	NA

* SDH = subdural hematoma.

LAGB and 3306 LRYGB cases. The DBS search located 261 articles; 45 series, involving 2937 cases and 4938 implantations, met the criteria for inclusion. We omitted complications whose incidence was < 0.1%. The calculated incidence of complications associated with laparoscopic bariatric surgery, obtained from the case series,[4,8,10,17,28,38,44,45,52,74,77,82,83,91,120] is summarized in Table 1; complications associated with DBS studies are shown in Table 2.[6,7,9,12,16,20,26,27,31,37,39,47,55–61,64,67–69,71,78,80,81,84,86–89,96–99,103,106,109,110,112,113,115–119] Utility values associated with various outcomes are shown in Table 3. The relative success rate for each treatment is shown in Table 4.

We used sensitivity analysis, both to address the uncertainty in our data and to explore the impact that different DBS success rates might have. We systematically varied all the major parameters used in the analysis within their 95% CIs. At no values did LAGB or untreated obesity result in superior outcomes compared with the two other surgical treatments. The three parameters with the greatest influence on outcomes are as follows: 1) utility of surgical complications in patients who underwent LRYGB; 2) the probability of surgical complications in patients receiving DBS; and 3) the success rate of DBS in controlling morbid obesity.

Figure 2 represents the interactions of these three parameters. The first two listed parameters represent the x and y axes of the graph. The *black circle* represents the pooled values of utility of surgical complications in patients who underwent LRYGB, together with the probability of surgical complications in patients receiving DBS, as obtained from the literature. Each *oblique line* represents a particular value for the success rate of DBS in controlling morbid obesity. If the pooled values of the first two listed parameters fall to the left of that line *(white area)*, DBS results in better outcomes than does LRYGB. In contrast, for values falling to the right of this threshold *(gray area)*, the better outcomes follow LRYGB. Our decision analysis model demonstrated that the threshold success rate of DBS must be approximately 83% to equal the success rate of LRYGB. As expected, lower success rates for DBS move the threshold to the left.

Discussion

No clinical trial of DBS for morbid obesity has yet been conducted; thus, as derived from our literature search, our results offer the best estimate for the threshold success rate of DBS to meet the well-established efficacy of bariatric surgery. The efficacy and safety of DBS have been studied in depth with regard to the treatment of movement disorders.[33] Such investigations demonstrate a motor score improvement as high as 66% in one study.[75] Thus, the success rates required for DBS to be comparable to LRYGB may be attainable, based on the favorable results of DBS in other disease processes.

The high threshold success rate for DBS to be equivalent to LRYGB is primarily due to the high success rate (97%) for LRYGB. Buchwald et al.[11] established accepted rates of percentage excess weight loss of 47.5% for LAGB and 61.6% for LRYGB, based on the mean percentage excess weight loss in more than 7000 patients. To maintain the same success rate for each bariatric procedure, we chose to define success as > 45% excess weight loss at 1 year postoperatively. In doing so, we took on a more conservative estimate for the success rate required for DBS to be superior to LRYGB. In reality, the true efficacy requirements of DBS may be < 83% to achieve equivalence. Furthermore, the well-established tendency of the medical literature to favor the report of positive studies, known as publication bias,[101] may be considered an alternative explanation.

TABLE 3: Utility values of various treatment outcomes for morbid obesity*

Condition	Mean ± SD	No. of Patients	Authors & Year
unsuccessful treatment for morbid obesity	0.67 ± 0.102	51	Andersen et al., 2009
perforation†	0.704 ± 0.188	51	Joneja et al., 2004
conversion to open procedure†	0.9	NA	Craig & Tseng, 2002; Jensen et al., 2005
DVT	0.95	NA	Danish et al., 2005
PE	0.926 ± 0.156	44	Lega et al., 2009
pneumonia	0.948 ± 0.165	44	Lega et al., 2009
hemorrhage†	0.944 ± 0.163	44	Lega et al., 2009
superficial infection‡	0.928 ± 0.179	44	Lega et al., 2009
anastomotic leak‡	0.9	NA	Craig & Tseng, 2002; Jensen et al., 2005
bowel obstruction†	0.946 ± 0.159	44	Lega et al., 2009
ulcer	0.785 ± 0.231	771	Lane et al., 2006
hernia (incisional, internal)†	0.810 ± 0.177	56	Hope et al., 2008
cholelithiasis‡	0.801 ± 0.198	187	Sandblom et al., 2009
band/port/tubing events‡,§	0.95	NA	Craig & Tseng, 2002; Jensen et al., 2005
transient hemiparesis	0.868 ± 0.169	44	Lega et al., 2009
chronic SDH‡	0.996 ± 0.204	44	Lega et al., 2009
seizures	0.927 ± 0.168	44	Lega et al., 2009
hardware malfunction‡	0.996	NA	Craig & Tseng, 2002; Jensen et al., 2005
subcutaneous hemorrhage/seroma	0.975	NA	expert opinion
CSF leak‡	0.95	NA	Craig & Tseng, 2002; Jensen et al., 2005
superficial infection	0.971 ± 0.174	44	Lega et al., 2009
normal health	1	NA	Gold et al., 1996
death	0	NA	Gold et al., 1996

* The lack of SD signifies that the means are point estimates rather than measurements. In Craig and Tseng, Jensen et al., and Danish et al., the means represent expert opinion. Gold et al.'s values of 0 and 1 represent consensus values, used universally.
† Complications requiring major surgery (laparotomy, craniotomy); utility values reduced by 10%, as specified in Craig and Tseng, and in Jensen et al.
‡ Complications requiring minor surgery (laparoscopy, DBS revision); utility values reduced by 5%, as specified in Craig and Tseng, and in Jensen et al.
§ Band prolapse, slippage, dilation, erosion of band or port, or other band/port/tubing events.

Based on sensitivity analysis, LAGB did not result in a superior outcome at any value when compared with the other 2 procedures. The complication rate was 0.217 for LABG and 0.334 for LRYGB. Although we combined short- and long-term complication rates, other studies have demonstrated that complications occurring within 30 days of surgery are more common after LRYGB,[17,120] whereas bariatric complications after 30 days are more common after LAGB;[10,45,91] port problems and band slippage, rather than the surgical placement of the band, are the most likely reasons for delayed reoperation.[17,120] Nevertheless, the superiority of LRYGB in terms of weight loss overshadows differences in complication rates when considering the overall success of LAGB versus LRYGB, as supported by the decision analysis model and several systematic reviews.[11,29,111] Decision analysis is necessarily limited by the assumptions on which the final model is based. For example, we have simplified the spectrum of surgical results into success or failure categories. This limits the variety of health outcomes to be expected in an actual clinical trial. Additionally, we used complication rates associated with DBS for movement disorders to approximate those for obesity. The DBS procedure for movement disorders and that for obesity share similar targets or targets in close proximity. The surgical approach to the hypothalamus or NAc may be associated with injury to nearby structures such as the optic nerve, fornix, and mammillary bodies.[35] However, stereotaxy of the hypothalamus[66] and NAc[32] has been shown to be feasible, safe, and even efficacious.

Composite DBS complication rates obtained from the literature search yielded rates similar to those in individual reviews; however, we detected a hardware-related complication rate of 6.8% (Table 2), whereas another group of investigators found the rate of hardware-related complications to be 25.3% among 81 consecutive patients undergoing 160 DBS procedures in the subthalamic nucleus.[69] One potential reason for the discrepancy is the use of varying definitions of hardware malfunction. We considered the following complications requiring repeat operation to be hardware related: malposition, fracture, migration, erosion, extension wire failure, and internal pulse generator malfunction. Additionally, we determined the hardware-related complication rate by dividing

TABLE 4: Relative outcomes of treatments for morbid obesity*

Treatment	Success Rate	Incidence of Treatment- Related Complications	QALYs Overall
LAGB	0.30	0.217	1.4826
LRYGB	0.97	0.334	1.8486
DBS	0.50†	0.194	1.6320
no treatment	0	NA	1.3200

* QALY = quality-adjusted life year.
† Placeholder, not a true measure of success.

the number of observed complications by the number of implant sides. Other investigators, however, have used the number of patients rather than number of implants as the denominator, which may result in differing complication rates. Conservative estimates used in the decision analysis model may have underestimated complication rates related to LRYGB. Long-term complications associated with bariatric surgery, such as micronutrient deficiencies, were not included in the model. On the other hand, using the movement disorder population as a stand-in for the population with morbid obesity may have overestimated the expected complication rate of DBS for obesity.

In bariatric surgery, patients older than 60 years of age are approached with caution, because age is a significant predictor of complications after gastric bypass[79] and may be a factor in predicting mortality.[63] Inclusion of elderly patients with movement disorders may contribute to the complication rate associated with DBS.[13,34,81] Thus, DBS complications among younger patients who are eligible for bariatric surgery would be expected to occur less frequently. If DBS for obesity is offered to elderly patients with morbid obesity, the complication rates observed in this study would no longer be an overestimate. Although DBS has been performed in the elderly, it has not been studied thoroughly in the obese population. Obese patients are likely to have comorbidities, such as Type 2 diabetes,[76] which may result in increased complications related to wound healing, extension wire erosion, and superficial infection. They are also more likely to develop postoperative complications, such as PE, compared with those with a normal BMI.[73] Because our complication rates were based on nonobese patients with a movement disorder, DBS may have a higher complication rate among its intended population. Occurrences of VTE are relatively common among patients undergoing DBS,[4] and may be even higher among obese patients undergoing DBS. On the other hand, DBS is less invasive and more easily reversible than bariatric surgery, and does not require general anesthesia, thus making it favorable for obese patients with poor health or advanced age. Assuming equal efficacy and safety, certain patients, alternatively, may prefer bariatric surgery to DBS for reasons including

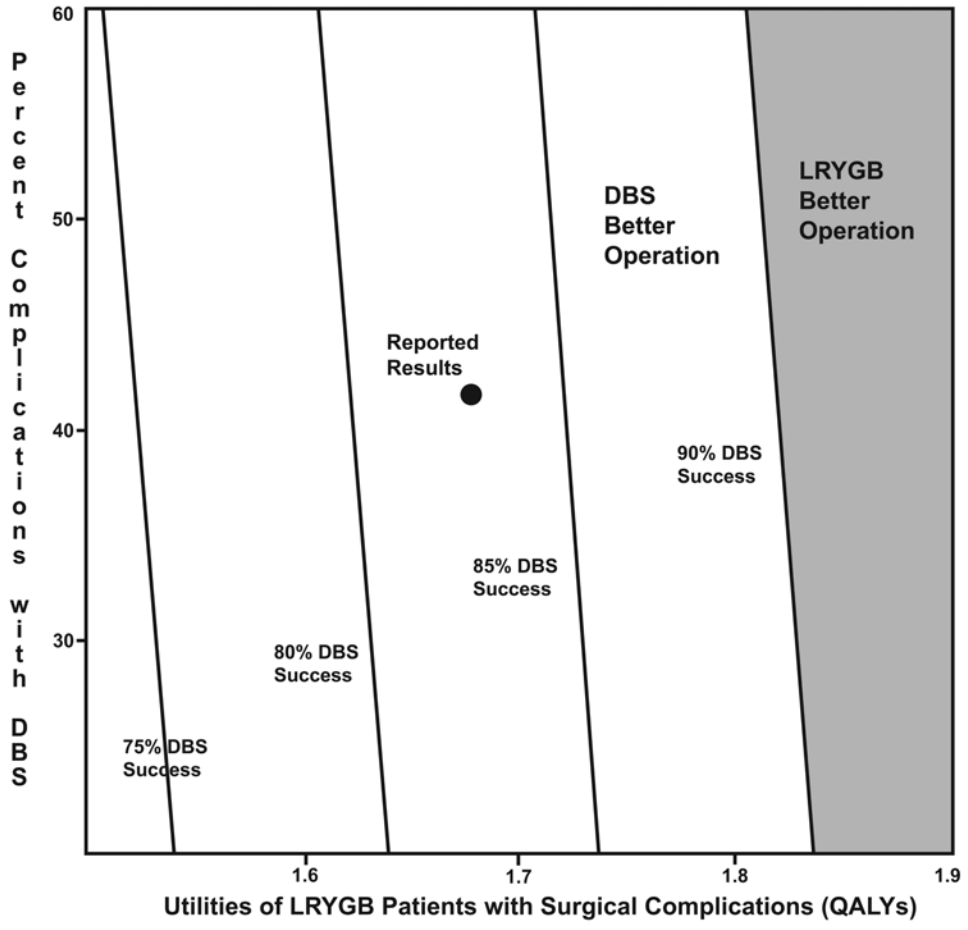

Fig. 2. Three-way sensitivity analysis (see *Results*). QALYs = quality-adjusted life years.

the need for repeated full-body MR imaging studies or an unsuccessful DBS trial. Thus, a multidisciplinary approach must be taken for patient selection and management.

Complications common to surgical procedures, such as superficial infection and postoperative pneumonia, were collected for both bariatric surgery and DBS groups. The rate of VTE, in particular, was found to be higher among patients receiving DBS. A recent decision analysis from our group supports the safety and efficacy of subcutaneous heparin in addition to mechanical compression for the prophylaxis of VTE.[4] Perhaps with the adoption of our protocol endorsing pharmacological prophylaxis, a lower rate of VTE may be seen in patients who undergo DBS.

Our estimates of complications and follow-up duration tend to favor bariatric surgery. Success and complication rates were obtained from the literature at 1 year postoperatively. Christou et al.[14] found that significant weight gain occurs 2 years postoperatively in patients with morbid obesity undergoing LRYGB. Because our success values for bariatric surgery were obtained at 1 year, future decreases in weight loss or weight gain, which would have lowered the success rate of LRYGB, were not captured in the current analysis.

Binge eating disorder may contribute to relapse following bariatric surgery in a subset of patients, but few studies commented on inclusion or exclusion of this subgroup. Self-reported binge eating once per week was found in at least 39% of patients prior to gastric bypass,[50] and up to 46% of patients reported recurrent loss of control over eating and weight gain at least 2 years following gastric bypass.[49] Because we documented weight loss at 1 year only, future relapse secondary to binge eating was not included, which may have contributed to an elevated threshold success rate for LRYGB. Despite multiple conservative estimates relating to the complication rates of bariatric surgery and DBS, the threshold efficacy of DBS nonetheless supports further research.

In addition to the success rate and QOL, monetary cost is an important societal consideration when judging alternative treatment modalities. Deep brain stimulation of the subthalamic region for Parkinson disease is associated with an acceptable incremental cost-effectiveness ratio.[114] Although DBS for Parkinson disease is associated with increased costs during the 1st year after surgery, it does become cost effective within the following year as motor symptoms are significantly improved.[72] Similar studies will be crucial for assessing the financial impact of DBS for obesity.

Conclusions

This exercise is, at best, an approximation of a well-controlled, randomized clinical trial, comparing the three surgical approaches to morbid obesity. Nevertheless, it does establish that DBS, should it prove promising in preliminary clinical use, might present a feasible adjunct or even alternative to LRYGB. Thus, it supports the need for further translational and clinical research into the potential role of DBS for the treatment of obesity.

Disclosure

The authors report no conflict of interest concerning the material or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Pisapia, Halpern, Williams, Wadden. Acquisition of data: Pisapia. Analysis and interpretation of data: Stein, Halpern. Drafting the article: Pisapia. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Stein, Pisapia, Halpern, Baltuch. Statistical analysis: Stein, Pisapia, Halpern. Administrative/technical/material support: Pisapia. Study supervision: Stein, Baltuch.

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Manuscript submitted April 15, 2010.
Accepted May 13, 2010.
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Neurosurg Focus 29 (2):E16, 2010

Stimulation of the globus pallidus internus in a patient with DYT1-positive primary generalized dystonia: a 10-year follow-up

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The authors report the case of DYT1-positive primary generalized dystonia refractory to medical management that was successfully treated with continuous deep brain stimulation of the internal segment of the globus pallidus. Prior studies have shown that neuromusculoskeletal deficits can remain permanent if early surgical intervention is not undertaken. The authors report prolonged efficacy and safety over a 10-year period in a 28-year-old man.
(DOI: 10.3171/2010.6.FOCUS10112)

Key Words • **deep brain stimulation** • **dystonia** • **DYT1** • **globus pallidus**

Dystonia is a syndrome characterized by involuntary sustained muscle contractions that result in twisting, repetitive movements, and abnormal posture.[6,7] Dystonia is typically classified by age of onset, origin, and affected body region. When the cause of dystonia is unknown, it is referred to as idiopathic or primary dystonia. Primary dystonia can be familial or sporadic in nature. Several gene mutations have been identified including the *DYT1* gene, which codes for an abnormal torsinA protein on chromosome 9q34.[2,7,19,20] This mutation is autosomal dominant and usually affects individuals early in life.[4,20]

Primary generalized dystonia[5] is a disabling condition with symptoms presenting in young adults. Pharmacotherapy is usually ineffective and the disease tends to progress.[1,8,18] Targeting of the GPi[3] for medication-induced dyskinesias in individuals with Parkinson disease renewed interest in the GPi as a target for dystonia.[18] Deep brain stimulation of the GPi has become the site of choice particularly in patients with DYT1-positive primary generalized dystonia.[12] Based on numerous case reports and case series, early surgical intervention has been recommended before permanent neuromusculoskeletal deficits develop.[1,23–25] In this case report, we describe a 28-year-old man with DYT1-positive dystonia who underwent bilateral GPi DBS, and we report the 10-year safety and efficacy data.

Abbreviations used in this paper: DBS = deep brain stimulation; GPi = globus pallidus internus; IPG = implantable pulse generator; UDRS = Unified Dystonia Rating Scale.

Case Report

History. This patient was a healthy, right-handed male who at 15 years of age noticed involuntary contractions of his right hand after fracturing his right arm. "Winged scapula" was noted on his right side at age 16 years. Involuntary movements in the right leg appeared at age 17 years, which spread into the trunk and right arm. Over the next 6 months the patient's movements became more bilateral and proximal. Violent extension and torsion of the trunk backward forced the patient into becoming bedridden.

His family history was not significant for any movement disorder or neurological disease. The patient was an only child of unrelated healthy parents of non-Ashkenazi background.

Examination and Treatments. Routine laboratory workup including complete blood count, erythrocyte sedimentation rate, electrolytes, liver function, uric acid, and thyroid function tests were all within normal limits. Copper, ceruloplasmin, serum, and urine amino acids were also within normal limits. Brain and cervical spine MR imaging showed normal results. A dystonia gene panel

(Athena Diagnostics) was positive for the GAG946 deletion mutation in the *DYT1* allele 1.

The patient had trials of numerous medications, including carbidopa/levodopa, baclofen, trihexyphenidyl, benztropine, valproic acid, risperidone, and tetrabenazine, but none provided significant relief. Haloperidol did offer modest relief but caused mild drug-induced parkinsonism, which later resolved when the drug was discontinued.

After consultation with neurosurgery, and after extensive discussion with the family, the patient elected to proceed with GPi DBS. The basis for this treatment was humanitarian because the procedure was not FDA approved in the US for the treatment of dystonia at that time.

Operation. This study was approved by the institutional review board at Allegheny General Hospital and was accepted as a humanitarian exemption trial. Prior to surgery, a head CT scan with 2-mm slices in a Cosman-Roberts-Wells frame were fused with the MR images, using software provided by the StimPilot system (Medtronic, Inc.). Targeting and stereotactic coordinates determined by fused CT and MR images were compared with the Schaltenbrand-Wahren atlas. The GPi target was 3 mm anterior to the midcommissural line, 20 mm lateral to that point, and 4 mm below the midcommissural point. The patient was positioned supine, the frames were secured, and surgery proceeded after injection of a local anesthetic with no sedation.

Microelectrode recordings were started 15 mm above the target, and the most posteroventral part of the GPi was found 2 mm deeper than the intended target. The DBS electrodes (model 3387, Medtronic, Inc.) spanned the entire GPi. Macrostimulation was performed using 0 and 3 electrode combination with a pulse width of 90 μsec, frequency of 185 Hz, and voltages of up to 6 V. There were no visual, sensory, or other symptoms during this intraoperative trial stimulation. The electrode was secured with a bur hole cap and coiled in the subgaleal space with intraoperative fluoroscopy to ensure that the electrodes had not moved from their original target. On Day 3 after placement of the left GPi electrode, an IPG (Soletra, Medtronic) was placed in the left subclavicular pocket. The patient was given perioperative antibiotics and was discharged to home on postoperative Day 1. The contralateral GPi electrode was placed 5 months later in the same manner.

Programming of the DBS Device. Initial programming was started within 12 hours of IPG placement. A movement disorder nurse and physician team used standard protocols to program the IPG. Initially, the patient underwent 3-month follow-up visits for approximately 1 year and is now being seen every 6 months. At these visits, he is assessed by a multidisciplinary team that includes a movement disorders neurologist, neurosurgeon, and nurse. The UDRS, Burke-Fahn-Marsden Dystonia Rating Scales, and standardized videotaping were used prior to surgery and during the 10 years of follow-up.

Follow-Up Course. The greatest adjustment in stimulation parameters was seen in the first 3 years (Table 1). Three years after electrode implantation, stimulation parameters have not required significant adjustments (Table 1). The time to stabilization of dystonic symptoms was approximately 12 months after the right GPi electrodes were implanted.

The patient has had 10 left IPG changes on the more symptomatic side and 5 IPG changes on the right over 10 years (Fig. 1). After 3 IPG changes in 13 months, a Kinetra IPG (Medtronic) was inserted (Fig. 1). The patient has required on average 1 IPG change annually on the left side.

There have been minimal changes in stimulation parameters in the right hemisphere with low-voltage requirements resulting in fewer IPG changes (Fig. 1). The more symptomatic side, the left, has required higher voltages. After implantation of the Kinetra IPG, the frequency of IPG changes has decreased. Kinetra batteries are double the power of the comparative Soletra batteries (Medtronic).

There have been no significant complications, neurological deficits, infection/erosion, or system malfunctions. However, 4 years after initial IPG placement, we noticed increased rigidity and more cramping on the right side with the development of diaphoresis. In the left subclavicular IPG, we observed extremely high impedances, and chest radiography revealed disconnection of that generator. After revision surgery, these worsening symptoms resolved and the patient has had no further episodes of symptom recurrence.

TABLE 1: Stimulation parameters during the 10-year period after implantation of the DBS device

Lt Hemisphere					Rt Hemisphere				
Date	Contact	Amp (V)	Frequency (Hz)	Pulse Width (μsec)	Date	Contact	Amp (V)	Frequency (Hz)	Pulse Width (μsec)
4/4/00	3+0–	4.9	185	270	8/8/00	3+0–	2.8	185	120
1/23/01	2+0–	4.0	185	330	1/23/01	3+0–	3.2	185	120
4/3/01	2+1–	4.5	185	330	4/3/01	3+0–	3.7	185	120
8/28/01	3+1–	5.5	185	330	8/28/01	3+0–	4.1	185	120
3/24/03	3+2+1–	6.0	130	330	1/8/02	3+0–	4.1	185	150
5/4/04	3+2+1–	5.8	130	330	5/4/04	3+0–	4.1	185	180
1/5/05	3+2+1–	5.8	130	330	1/5/05	3+0–	4.1	185	180
2/19/10	3+2+1–	5.8	130	330	2/19/10	3+0–	4.1	185	180

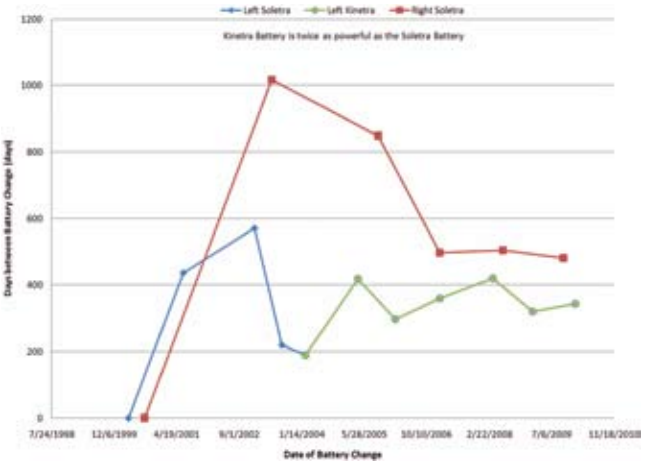

Fig. 1. Line graph of battery changes depicting the initial battery placement and changes from 2000 to 2010 in the left and right hemispheres.

There was a dramatic decrease in his UDRS score within 4 months after placing the left GPi electrode, in contrast to the rapid progression of his dystonia during the previous year. This was seen clearly clinically and supported on his UDRS scores (Fig. 2 and Video 1).

Video 1. The video is composed of 5 sections: 1) 1 week prior to left pallidal stimulation; 2) 5 months after left pallidal stimulation; 3) almost 6 months after left pallidal and 1 week after right pallidal stimulation; 4) 5 years after bilateral hemisphere stimulation; and 5) 10 years after bilateral stimulation. Click here to view with Windows Media Player. Click here to view with Quicktime.

Within 3 months of Stage 1 surgery, the patient experienced a dramatic improvement, was able to return to school, and could function independently. After contralateral GPi electrode placement, additional improvement occurred in all postoperative dystonia rating scores, and this improvement has persisted over a 10-year period. The frequency with which the batteries required changing has stabilized (accounting for change in battery type) in the last 5 years.

The patient continues to be fully independent; he is currently employed full time and has a very active lifestyle. His only minor symptoms include a mild dysarthria and a subtle rigidity while walking, none of which impedes his daily activities (Video 1). His current medication regimen includes Klonopin (3 mg daily) and Artane (1 mg daily), unchanged for the past 7 years.

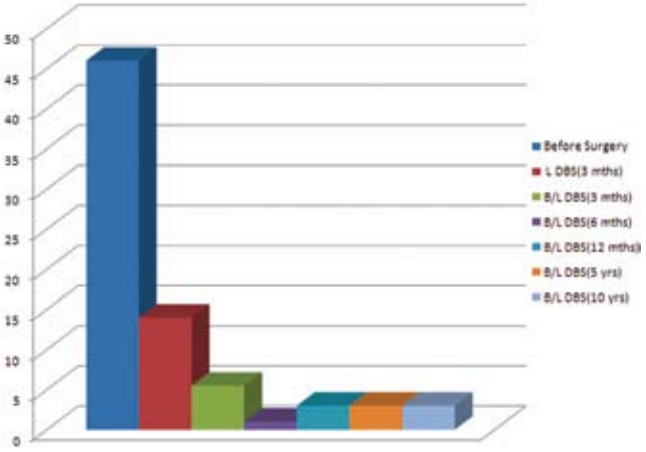

Fig. 2. Bar graph demonstrating UDRS scores (y axis). B/L = bilateral pallidal stimulation; L = left pallidal stimulation.

Discussion

Deep brain stimulation of bilateral GPi has shown promising results.[2–5,9,13,14,16,17,21,22,26] Younger individuals who are DYT1 positive have exhibited greater improvements in Burke-Fahn-Marsden Dystonia Rating Scale scores from 50% to greater than 80% compared with individuals with DYT1-negative primary generalized dystonia (40% to 70%). These gains improve maximally within 1–2 years after pallidal stimulation.[5,8,10] In these studies and others, children appear to benefit more after early intervention, before permanent dystonic posturing ensues, and surgical intervention is strongly advocated.[4,5,23] Deep brain stimulation has proven to be efficacious and is reversible and adaptable, allowing for maintenance of symptoms over time as well as the ability to capture new symptoms that may develop.[9,11–13,15–17,21] There are no comparison studies between pallidotomy and DBS of the bilateral GPi for dystonia. Such studies, we believe, may provide further evidence that DBS of GPi may be the preferred treatment for DYT1-positive individuals with dystonia.

Conclusions

In this case report, symptom control has been maintained for more than 10 years. Based on the stabilization of energy requirements, it appears that the previously noted rapid progression of dystonia in this patient has been arrested.

Disclosure

Dr. Oh is a consultant for Boston Scientific and received research support from Medronic for the current study. Dr. Whiting is a consultant for Medtronic.

Author contributions to the study and manuscript preparation include the following. Conception and design: Whiting. Acquisition of data: Baser, Angle. Analysis and interpretation of data: Oh, Cheng. Drafting the article: Alcindor.

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Manuscript submitted April 16, 2010.
Accepted June 10, 2010.

Supplemental online information:

Video: http://mfile.akamai.com/21490/wmv/digitalwbc.download.akamai.com/21492/wm.digitalsource-na-regional/FOCUS10-112_video.asx (Media Player).

http://mfile.akamai.com/21488/mov/digitalwbc.download.akamai.com/21492/qt.digitalsource-global/FOCUS10-112_video.mov (Quicktime).

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See the corresponding article, **DOI:** 10.3171/FOC-07/11/E11.

Erratum

Orbital tumors treated using transcranial approaches: surgical technique and neuroophthalmogical results in 41 patients

To The Editor: Thank you for publishing our paper, "Orbital tumors treated using transcranial approaches: surgical technique and neuroophthalmogical results in 41 patients" (*Neurosurg Focus 23 (3):*E11, 2007; *DOI: 10.3171/FOC-07/11/E11*).

After publication I realized that my surname had been incorrectly spelled "Nosek." My name should have been listed as "Erez Nossek, M.D."

I am pleased to have the opportunity to correct this error. It was corrected online as of August 1, 2010.

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Please include this information when citing this paper: published online Month Day, Year; *DOI: 10.3171/2010.6.FOCUS101254a*.