

DOES DEEP BRAIN STIMULATION REALLY WORK?

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

By:

Craig Barrett
IQP-43-DSA-4530

Wei Chen
IQP-43-DSA-8732

Samantha Gauthier
IQP-43-DSA-6553

Christopher Massar
IQP-43-DSA-4613

Jonathan Morse
IQP-43-DSA-8240

Kenechukwu Nduwke
IQP-43-DSA-7986

August 19, 2016

APPROVED:

Prof. David S. Adams, PhD
WPI Project Advisor

ABSTRACT

The overall goal of this project was to document and evaluate the technology of deep brain stimulation (DBS), including its non-invasive transcranial stimulation alternatives, to assess their technical, ethical, and legal problems to help determine whether they should move forward in the U.S. We performed a review of the current research literature and conducted interviews with academic researchers and bioethicists. Based on the research performed for this project, our team's overall conclusion is that DBS can be effective, but comes with serious side-effects that must be carefully weighed against the benefit to the patient. The non-invasive alternatives have less serious side-effects, but the effectiveness of the direct current type is controversial. The FDA regulates DBS procedures, and we make recommendations for resolving conflicts of interest between patients, device manufacturers, and doctors. The transcranial field has little current regulation, and we make recommendations for controlling the do-it-yourself home stimulation users.

TABLE OF CONTENTS

Title Page	01
Abstract	02
Table of Contents	03
Acknowledgements	04
Authorship	06
Project Goals	07
Executive Summary	08
Literature Review, Deep Brain Stimulation.....	18
Section-1: DBS History	18
Section-2: DBS Safety	44
Section-3: DBS Alternatives and Advances	53
Section-4: DBS Ethics and Regulations	65
Methods	72
Results/Findings	73
Conclusions/Recommendations	81
Appendix	85

ACKNOWLEDGEMENTS

This IQP would not have been possible without the support of all of the individuals listed below. We would like to thank the following individuals for allowing us to interview them for this IQP project (last names listed in alphabetical order):

Dr. György Buzsáki, MD, PhD. Biggs Professor of Neural Sciences, NYU Neuroscience Institute, New York University Langone Medical Center, East River Science Park, 450 East 29th Street, 9th floor, New York, NY 10016.

Dr. Philippe Coubes. Professor, Department of Neurosurgery, CHRU Montpellier, Montpellier, France.

Dr. Milind Deogaonkar. Department of Neurosurgery, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH 43210, USA.

Dr. Joseph J. Fins. Division of Medical Ethics, New York Presbyterian-Weill Cornell Medical Center, 435 East 70th Street, Suite 4-J, New York, NY 10021, USA.

Dr. Benjamin D. Greenberg. MS, PhD. Professor of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906.

Dr. Ihtsham Haq, MD. Associate Professor, Movement Disorders Section, Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA.

Dr. Benzi M. Kluger. Department of Neurology, University of Colorado Denver, P.O. Box 6511, Aurora, CO 80045, USA.

Dr. Jens Kuhn. Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany.

Dr. Michael S. Okun, MD. Adelaide Lackner Professor and Chairman of Neurology, University of Florida Center for Movement Disorders & Neuro-restoration, Gainesville, Florida 32607, USA.

Dr. M. Porta. Tourette Center- IRCCS Galeazzi Hospital, via R. Galeazzi 4, 20161 Milano, Italy.

Dr. Eric Racine (responding: Roxanne Caron). Neuroethics Research Unit, Institut de recherches cliniques de Montréal, Montréal, QC, Canada.

Dr. Ashwin Viswanathan, MD. Assistant Professor, Department of Neurosurgery, Baylor College of Medicine, 1709 Dryden, Suite 750, Houston, TX 77030 (USA).

Anonymous. Bioethicist. Columbia University, New York, NY 10032.

In addition to the interviewees listed above, we would also like to thank **Dr. David Adams** for serving as project advisor for this IQP. Dr. Adams was invaluable, from the very onset of the project to its final conclusion. We thank him for his enthusiasm, dedication, and continued guidance.

AUTHORSHIP

Author	Areas Covered
Kenechukwu Nduwke	DBS History Parkinson's Disease Treatment-Resistant Depression Epilepsy
Jonathan Morse	DBS History Obsessive-Compulsive Disorder Tourette's Syndrome
Craig Barrett	DBS Safety
Christopher Massar	DBS Safety
Wei Chen	DBS Alternatives and Advances Transcranial Direct Stimulation Transcranial Alternating Current Stimulation Transcranial Magnetic Stimulation Closed Loop Neuro-stimulators
Samantha Gauthier	DBS Ethics DBS Regulations

PROJECT GOALS

The overall goal of this project is to document and evaluate the technology of deep brain stimulation (DBS), including the more recent and popular modifications of transcranial stimulation, magnetic stimulation, and closed loop neuro-stimulators, to determine whether the techniques really work, and to assess their ethical and legal problems.

The specific objectives are to:

- 1 **Develop** a comprehensive assessment of the scientific experiments that led to the development of DBS, and discuss the technique's potential applications.
- 2 **Characterize** what key scientific and IVF stakeholders believe are the strengths and weaknesses of this technology, and their ethical and legal concerns.
- 3 **Evaluate** all of the obtained evidence and prioritize the remaining problems.
- 4 **Recommend** potential solutions to remaining problems.

EXECUTIVE SUMMARY

Deep brain stimulation (DBS) is the application of electrical current to various regions of the brain using surgically implanted electrodes and a stimulator to treat neurological disorders. The technique has been used for years to treat motor diseases, such as Parkinson's disease, Essential Tremor, Tourette's syndrome, and Epilepsy, but more recently has been used to treat psychiatric disorders, such as Obsessive Compulsive Disorder (OCD) and treatment-resistant depression. The technique has seen varied success, from high rates of improvement to slight benefits.

However, the studies are difficult to compare to each other, with protocols differing in the precise placement of the electrodes, stimulation Hertz, stimulation length and frequency, and type of electrode used. And some clinical trials have shown undesirable side-effects, from mild easily treatable headaches or temporary memory loss, to the far more serious problem of suicide in some cases. Scientists are not even sure of the exact mechanism(s) for how the benefits occur. More recent advances to DBS include closed-loop stimulators that respond to a patient's own brain waves to initiate a correcting signal, or non-surgical advances (the electrodes are applied directly to the scalp skin) such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS). Some of the new techniques are not currently regulated, and have created a market for do-it-yourselfers who purchase cranial caps on the web and stimulate their own brainwaves in an attempt to enhance cognition. Thus, there are ethical and legal issues surrounding this technology.

The overall goal of this project was to document and evaluate the technology of deep brain stimulation (DBS), including the more recent and popular modifications of transcranial stimulation, magnetic stimulation, and closed loop neuro-stimulators, to determine whether the techniques really work, and to assess their ethical and legal problems. The specific objectives were to: 1) Develop a comprehensive assessment of the scientific experiments that led to the development of DBS, and discuss the technique's potential applications. 2) Characterize what key scientific and IVF stakeholders believe are the strengths and weaknesses of this technology, and their ethical and legal concerns. 3) Evaluate all of the obtained evidence and prioritize the remaining problems. 4) Recommend potential solutions to remaining problems.

To accomplish objective-1, we performed a review of the current literature, including reputable academic journal articles, relevant books, scholarly websites, and other pertinent materials. To accomplish objective-2, we conducted a set of interviews with various academic researchers and bioethicists. The interviewees included individuals who have performed DBS procedures on patients, and bioethicists who have investigated the ethics and regulations of the DBS field. The purpose of the interviews was to determine the interviewees full range of opinions on DBS, and to solicit their help gauging the strengths and weaknesses of this new technology. After performing the review of the literature and interviews, the group synthesized all of the information collected to ascertain the strength of the evidence, and then created recommendations for moving the field forward.

Introduction to Deep Brain Stimulation

Deep brain stimulation (DBS) is a technique that, as its name implies, uses electrical stimulation deep in the brain to treat a variety of neurological and mental disorders. In the DBS procedure, one or more electrodes are surgically implanted deep in the brain at specific targets that are selected depending on which disorder is being treated. The electrodes are connected by a subcutaneous wire to a pulse generator that includes a battery, and then the pulse generator is used to apply either high frequency stimulation (HFS) or low frequency stimulation (LFS). The generator is usually implanted below the collarbone (as shown in the diagram), and is relatively undetectable. A minor surgical procedure is needed every 3-5 years to change the battery. DBS has been researched for over 52 years (since 1964, including animal experiments) as an alternative to lesion surgery, and is the most widely used therapeutic technology that uses a human brain-to-machine interface.

The DBS system can be programmed telemetrically to provide pulses of various hertz (frequency) and duration, which are also selected to fit the specific disorder being treated. The frequency of the stimulation dictates whether the neural circuit is disrupted or stimulated: high frequency stimulation (above 130-180 Hz) attenuates neural networks, while low frequency stimulation causes neuronal activation by classic neuro-physiology mechanisms.

Both HFS and LFS techniques lack spatial specificity. The electrical effects spread in all directions in the brain. The technique is adjusted for each patient; the optimal tuning frequency varies from person to person. The effects are usually reversible, so most patients require lifelong stimulation. And if any side-effects are observed, the current can be adjusted or terminated.

Even after decades of research the mechanism through which DBS achieves these results is still unclear. The proposed physiologic effects of DBS include: axonal excitation, depolarization blockade, synaptic release of neurotransmitters, normalizing abnormal neuronal firing, and disruption of pathological neuronal synchrony by activating inhibitory interneurons ([Lozano et al., 2002](#)).

Examples of DBS Applications

The very earliest DBS experiments were done in 1964 on rats by stimulating the cerebral cortex ([Bindman et al., 1964](#)), which means that DBS has been investigated for over 52 years now. The U.S. Food and Drug Administration (FDA) has approved DBS for treating several types of movement disorders, and it is also currently being researched to treat a variety of psychiatric mental disorders. The following are some FDA-approved DBS applications: Parkinson's disease (the first FDA-approved DBS application), essential tremor (rhythmic shaking), epilepsy, dystonia (involuntary muscle contractions), and treatment-refractory obsessive-compulsive disorder (FDA approved in 2009). Several non-FDA approved DBS applications are also being researched: depression, addiction, regular OCD, Tourette's syndrome, and post-traumatic stress disorder.

For Parkinson's disease, the DBS procedure involves placing high frequency stimulating electrodes in the ventral intermediate nucleus of the thalamus (VIM) (which can significantly reduce tremors), or in the subthalamic nucleus (STN) or internal segment of the globus pallidus

(GPi) (which reduces tremors and decreases bradykinesia, rigidity, and gait impairment) (Perlmutter and Mink, 2006). The precise surgical procedure for electrode implantation varies on a case-by-case basis. A typical procedure begins with a brain imaging study using an MRI or CT-scan. These images of the brain are used to calculate the position of the desired brain target and to guide instruments to that target with minimal trauma to the brain. The target precision can also be improved by using a brain mapping procedure, where fine microelectrodes are used to record brain cell activity in the region of the intended target to confirm that it is correct, or to make very fine adjustments of 1 or 2 millimeters, though the patient must be awake for this procedure. Once the correct target site is confirmed with imaging, the permanent DBS electrode is inserted and tested, then it is anchored to the skull and a pulse generator is placed in the chest and a connector wire is tunneled between the brain electrode and the pulse generator unit.

Evaluating both the short and long-term effects of DBS on PD patients is of paramount importance. Several studies have looked at the improvements of motor complications in patients with severe PD over several months, while other studies focused on long-term results over several years. We reviewed several individual PD DBS studies, but one in particular is worth mentioning here as it relates to project conclusions. One study (Brocker et al., 2013) showed that DBS stimulation is more effective when applied in a non-regular pattern, so the temporal pattern of DBS stimulation may be an important variable to test in the future.

For treatment-resistant depression (TRD) patients, functional neuroimaging studies have shown that depression is associated with increased neural activity in the subcallosal cingulate gyrus (SCG) area of the brain which is involved in mood regulation (Mayberg et al et al., 2005). Various interventions that suppress the activity of this area, including DBS, pharmacotherapy, transcranial magnetic stimulation, and electroconvulsive therapy, improve the clinical features of depression, so this supports the theory that over-activity of the SCG is important in the pathophysiology of depression. Several studies noted patient suicides (which naturally are increased in this population), so this should be carefully monitored with these patients.

For epilepsy patients, some newly developed antiepileptic drugs or surgery work well, but for the remainder of patients, DBS might be suitable as an alternative. Caution must be used with this disorder because it can vary by the severity and frequency of the seizures, the age of onset, whether the seizures are inherited, the portion of the brain involved, and the pattern of brain imaging. So, DBS treatment requires knowledge of the part of the brain that must be targeted for that individual patient. Of particular importance for these patients is the recent use of closed loop stimulators that are used to detect abnormal circuit firing, and once detected initiate a corrective firing pattern. So, these detectors both produce current and detect abnormal currents.

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by recurrent unwanted thoughts or ideas (obsessions) and repetitive behaviors or mental acts performed in order to relieve these obsessions (compulsions) (Bourne et al., 2012). OCD affects approximately 2% of the general population, and even when the best available treatments are used, approximately 10% of patients remain afflicted (Denys et al., 2010). OCD is one of the most disabling of the chronic psychiatric disorders, and the effects can completely take over someone's life. OCD has been traced to abnormal activity in the cortico-striato-thalamo-cortical (CSTC) circuits (Bourne et al., 2012), so these circuits have been tested during DBS stimulation. The results were generally positive, and most side-effects were transient and treatable.

Gilles de la Tourette Syndrome (GTS, or sometimes shortened to TS), is a complex inheritable childhood-onset neurological and neurobehavioral disorder characterized by multiple disabling motor and vocal tics lasting more than a year (Saleh et al., 2012). The condition often includes frequent involuntary movements, such as vocalizations or severe head and arm jerks. Approximately 0.3% - 0.8% of the population has this disorder, and of these about 50-90% also have co-symptoms such as Obsessive-Compulsive Disorder (OCD) or Attention Deficient Hyperactive Disorder (ADHD), or both. Usually most GTS patients grow out of it during the second decade of life in their teenage years. However, some patients do not progress out of the disease, and they require lifelong medical and behavioral treatments. The mechanism of GTS is poorly understood, but is thought to involve the activation of aberrant groups of striatal neurons (reward system of the brain) with inhibitory projections to the GPi and SNpr, which disinhibits thalamocortical projections leading to a tic (Vinwanathan et al., 2012). The first report using DBS to treat GTS was in 1999 (Vandewall et al., 1999), and since then only around 100 patients have used the technique. So, the DBS literature is weak in this area. Overall, the brain locations stimulated with DBS have included: the thalamic centromedian nucleus, subthalamic periventricularis, posteroventral globus pallidus internus (GPi), and ventromedial globus pallidus internus. Stimulation of the GPi has been the most effective. The most common side-effects were anxiety and hardware malfunction. One individual study worth mentioning here (Piedimonte et al., 2013) showed that involuntary tics immediately returned to a TS patient when his DBS battery ran out of power, which helps show the benefits of DBS stimulations. For TS patients, we conclude that more long-term large controlled clinical trials are needed in this area. One interviewee noted problems recruiting a sufficient number of TS patients into his clinical trial, so perhaps cooperation between medical centers would increase the number of available patients.

Overall, the DBS experiments reviewed in this section showed that for specific types of disorders, DBS stimulations can significantly improve symptoms. The technique seems to be generally effective for its purpose...as a last resort for treatment-resistant cases of movement and psychiatric disorders. But last resort treatments come with some degree of danger, and some studies showed serious side-effects, including 5 deaths for one 2010 epilepsy study and 24 suicides out of 5311 PD patients. However, most of the studies reported relatively mild, transient, and manageable side-effects. Another perk about DBS is it is completely reversible, and in the studies reported here any unwanted side-effects due to the DBS stimulation could be managed by slightly adjusting the current. And if a patient experienced negative symptoms from the stimulation, the current was simply switched off. Another advantage of DBS is that once the electrodes have been surgically implanted, it can work long-term, as long as the battery is changed every few years. The common location of the pulse generator near the collarbone makes for a relatively easy battery replacement.

DBS Safety

In spite of the success seen with some DBS treatments, the technique has some safety issues. We identified four broad categories of safety issues: 1) patient history, 2) surgical problems, 3) DBS electrical stimulation problems, and 4) brain location problems.

With respect to patient history, we found that the side-effects can vary depending on the patient's previous medical history, age, and severity of the medical condition(s) being addressed. The most serious problem in this area was suicide, more frequently seen in severely depressed patients that did not respond to DBS treatments.

With respect to surgical problems, as with any surgical technique, some DBS problems arise during the surgical implantation of the electrodes in the brain. DBS is not trivial surgery. It requires a highly skilled team of neurosurgeons and support doctors. The surgical procedure can cause swelling, infection, pain, fatigue, or bleeding. And the long-term presence of the implants can cause an immune Foreign Body Reaction (FBR) where the integrated material can retard the healing process, or the implant can become rejected.

DBS electrical stimulations can cause problems such as increased patient anxiety, depression, uncontrollable mood swings, muscles tightness, numbness and tingling, speech problems, and balance issues. With transcranial direct current stimulation (tDCS), this is not a surgical procedure so there are no surgical side-effects, but some problems have been associated with differing modes of stimulation (anodal, cathodal or sham).

The specific area of the brain chosen for DBS stimulation can increase the risks of some side-effects, while decreasing the risk of others. Risks have been identified with several locations including: the subthalamic nucleus (STN), the Globus pallidus, thalamic area, and the Pedunculopontine nucleus (a newer form of DBS). Subthalamic nucleus DBS is one of the most effective forms of DBS, and is often used to treat motor disorders; but it has been associated with changes in mood such as depression and hypomania. DBS stimulation of the Globus pallidus has been used to target the effects of Parkinson's disease, dystonia, and Tourette's syndrome; it may have fewer side-effects but it is not as effective as subthalamic DBS. Thalamic DBS is used to target patients with tremors and rigidity, however the risks associated with this area include voice, speech and swallowing complications.

The most DBS literature was found for Parkinson's patients, so this literature contained the most information on side-effects. Some of the serious side-effects were mentioned above, but of particular note was the study done at the National Institute of Neurological Disorders and Stroke, NIH (Bethesda) who investigated the rates of suicide in PD patients receiving DBS (Voon et al., 2008). Their data showed that the completed suicide percentage was 0.45% (24/5311), and the attempted suicide percentage was 0.90% (48/5311). The suicide rates in the first post-operative year (0.26%, 263/100,000/year) were higher than expected for the age, gender, and country adjusted controls ($P < 0.001$), and also remained higher in the 4th postoperative year (0.04%, 38/100,000/year) ($P < 0.05$). Another PD study (Espay et al., 2010) showed that the initial DBS surgery resulted in complications in as many as 25% of PD patients, and infections were noted in 1.8-6.3% of the patients, which can cause irreparable brain damage. A 2010 study performed in China (Hu et al., 2010) showed that of 161 PD patients receiving DBS, the complications included: confusion (the most common side-effect) (11 cases, 6.83%), asymptomatic intracranial hemorrhage (1 case, 0.62%), electrode misplacement (2 cases, 1.24%), infection of the subcutaneous pocket receiving the pulse generator (1 case, 0.62%), skin erosion (2 cases, 1.24%), pulse generator seroma (fluid build-up) formation in 6 cases (3.72%), and device malfunction (1 case, 0.62%). They concluded that hardware-related complications could be reduced by increasing the experience of the surgeons, and closely following standard operative surgical routines. The side of the brain being stimulated may also be important,

stimulating the left side of the brain (Skodda, 2012) caused an improvement in 50% of the PD patients, but 36% showed deterioration, including negative effects on speech articulation and intellect. Higher voltage DBS was also determined to have a higher risk of speech deterioration.

Transcranial direct-current stimulation (tDCS) is progressively being used as a non-surgical option for DBS to treat a variety of disorders or to alter neuronal plasticity. In 2007, a team in the Department of Clinical Neurophysiology, Georg-August University (Göttingen, Germany) summarized various adverse effects of tDCS in 567 sessions performed in their labs over a two year period (Poreisz et al., 2007). The side-effects reported were (in descending order): a mild tingling sensation (70.6%), moderate fatigue (35.3%), a light itching sensation under the stimulation electrodes (30.4%), headache (11.8%), nausea (2.9%), and insomnia (0.98%). So, the types of side-effects seen with tDCS appear to be milder than those observed with DBS.

Overall with respect to safety, although DBS stimulation has helped improve the symptoms for hundreds of patients with various motor and psychiatric disorders, the technique is associated with some side-effects. The type and severity of the side-effect varies depending on the overall health and age of the patient, when the DBS is applied relative to the onset of the disorder (earlier is better), problems with the surgical implantation of the electrodes and neuro-stimulator (swelling, infection, pain, fatigue, bleeding, foreign body reaction), problems caused by the electrical stimulation itself (increased anxiety, depression, mood swings, numbness, tingling, speech problems, balance issues), and problems associated with the specific area being stimulated (the most serious are successful suicides and suicide attempts, which are especially associated with DBS Parkinson's studies and treatment-resistant depression). But as with any medical technique, the DBS side-effects must be weighed against the severity of the disorder being treated. In the vast majority of patients, the side-effects were transient, were considered medically "mild", and could usually be managed with standard pharmacologic treatments or by adjusting the DBS current, while allowing the patient to receive the benefits of the treatment.

DBS Alternatives and Advances

Alternatives to the DBS field include the development of several types of non-surgical (non-invasive) transcranial stimulation options applied to the skin. Advances to the DBS procedure include the development of closed-loop stimulators that respond to abnormal brain currents to apply a correcting current.

Transcranial direct current stimulation (tDCS) was the first type of transcranial stimulation method developed. It is not new, Aldini first used this technique in 1804 to treat melancholic patients. tDCS uses a device placed on the head with electrodes in contact with the skin to deliver current (in this case direct current) to the brain to cause an effect. Some studies indicate the technique can improve learning, memory, alertness, pain, and depression. Because it is non-invasive, some scientists argue tDCS could easily be used to intervene earlier in disorders than DBS. The device uses only 1-2 milliamps, which can easily be delivered by a 9 volt battery. Unfortunately, its ease of use has made the technique easy to implement at home by untrained individuals (several companies sell the head devices online), and the tDCS field has relatively little safety oversight. The mechanism of how tDCS works is unknown, but some

studies indicate that neurons located near the anode are more likely to fire, while neurons near the cathode are less likely to fire. However, it is difficult to target a specific region of the brain using this technique.

Some studies argue tDCS does not work. This finding is backed up by the human cadaver study (mentioned previously) showing that at 1-2 mA no detectable current enters the brain. The studies we reviewed showed mixed results. Positive results were seen in some controlled blind trials (Costain et al., 1964; Fregni et al., 2006; and in smaller studies (Marshall et al., 2004; Kincses et al., 2004; Roizenblatt et al., 2007; Chadaide et al., 2007; Ferrucci et al., 2008; Boggio et al., 2008; Antal et al., 2008; Dockery et al., 2009; Reis et al., 2009; Cohen et al., 2010). Other studies indicated that tDCS had no effect or negative effects (Ferrucci et al., 2008; Koenigs et al., 2009; Sellers et al., 2015). Perhaps the most thorough study done showing a lack of tDCS efficacy was from the University of Melbourne, School of Psychological Sciences (Melbourne, Australia) who reviewed the tDCS literature in healthy subjects for every neurophysiological outcome measure reported in the literature by at least two different lab groups (Horvath et al., 2015). Whenever possible, the data was pooled and quantitatively analyzed to assess significance. Their review of the literature showed that of the 30 neurophysiological outcomes reported by at least two different research groups, tDCS was found to have a reliable effect on only one: motor excitability potential (MEP) amplitude. So, the authors work raises questions about whether tDCS really works to enhance cognition.

Transcranial alternating current stimulation (tACS) was developed in 2006, and uses different electrical frequencies (Hertz) within normal brain electrical ranges to affect behavior. The frequency used helps dictate the response: 0.75 Hz (low end of delta waves) has been reported to enhance memory retention; 5-8 Hz (theta rhythm) improves working memory; 7.5-12.5 Hz (alpha frequency) enhances creativity, and >30 Hz (gamma frequency) is thought to enhance memory maintenance. The mechanism of how tACS works is unknown, but it is thought that the rhythmic stimulations from the device interact with existing natural brain rhythms to facilitate the effects. The literature for tACS is generally positive, although few studies have been done. One study showed significantly improved language retrieval accuracy following tACS in the theta frequency range (Antonenko et al., 2016). Another study showed slightly improved (10%) symptoms in treatment-refractory schizophrenia patients following tACS at theta rhythm frequency (4.5 Hz, 20 min, 2 mA) (Kallel et al., 2016). tACS has also been successfully used to treat stroke patients in China (Wu et al., 2016). In this study they found in 60 patients treated at (20 Hz, < 400 μ A, 30 min) that the mean stroke score improved significantly relative to the control group ($p < 0.001$).

Transcranial magnetic stimulation (TMS) uses a focused 3 tesla magnetic field in a small area to induce a small number of neurons to fire. The electro-magnetic field generated by TMS penetrates the skin of the scalp and infiltrates brain tissues to a depth of about 2 cm, causing neuronal depolarization and generating motor, cognitive and affective effects (Pastuszak et al., 2016). Depending on the stimulation frequency, TMS or repetitive TMS (rTMS) can stimulate or inhibit the brain cortex. Studies using animals have shown that rTMS stimulation can generate brain changes similar to those seen after electric shock therapy, but without provoking seizures. The mechanism of TMS remains unknown, but it likely enhances neurotransmitters, enhances the modulation of signal transduction pathways in the central nervous system, alters gene transcription, and releases neuro-protective substances. The literature in this field is relatively recent and few studies have been done. The data are generally positive, with TMS showing

improvements in treating refractory-resistant depression ([Pastuszak et al., 2016](#); [Kang et al., 2016](#)), and strokes ([Smith and Stinear, 2016](#); [Chang et al., 2016](#)).

Closed-loop neuro-stimulators, are second-generation DBS devices that not only deliver current to specific regions of the brain, they also monitor brain electrical currents at all times for abnormal firing, and once detected it delivers a corrective current. The hope is that these second-generation devices will allow researchers to begin to correlate specific types of brain neural patterns with specific symptoms, and then respond with a tailored type of stimulation best suited for that abnormality. Two example closed-loop devices are the Medtronic device (Minneapolis, Minnesota) and NeuroPace (Mountain View, CA). The Medtronic device was the first developed, and has been available since August 2013. The device allows real-time immediate measurements of success or failure, so it is a type of personalized precision medicine ([Medtronic, 2016](#)). The NeuroPace device uses a closed-loop technology, and was FDA-approved in November of 2013 for epilepsy, and is about 5 years away for approval for Parkinson's disease. In October 2013, DARPA approved a new \$70 million program to support the development of closed-loop devices for soldiers with post-traumatic stress disorder, anxiety, and brain injury ([NeuroPace, 2016](#)).

Overall, several advances to DBS have been made over the years to attempt to make it more effective or less invasive. The closed-loop neuro-stimulator devices are relatively new, and no clinical trials have been performed. Several non-surgical electrical stimulation options to DBS have also been developed, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS). All three of these non-invasive techniques have refereed articles showing they significantly improve patient outcomes, although the literature for tDCS is conflicting. No technique is perfect. The tDCS field has been generally criticized for a lack of rigor, as many of the experiments have been performed by home users. And early studies sometimes pooled the results from multiple sets of experiments, each done with different devices and procedures. Worse, some of the very recent studies that have been carefully designed and controlled are starting to show no effects of the tDCS technique. Many of the studies did not analyze for any off-target or side-effects, so more attention should be paid to safety. A stimulation intensity of up to 2 mA and a duration of about 20 min appears to be generally safe, and the observed adverse effects are minor, consisting of light itching beneath the electrodes or mild headaches. Such effects have been observed in healthy subjects and in patients with different neurological disorders. Risks include the generation of electrochemically produced toxins, deposit of electrode dissolution products at the electrode-tissue interface, excite-toxic damage to overdriven neurons, and electrode placements that could result in brainstem or heart nerve stimulation. Moving forward, it is important to standardize the stimulation protocols to enhance the comparability of research results.

DBS Ethics and Regulations

As a medical device, DBS implants fall under the jurisdiction of the Food and Drug Administration (FDA). Since 1997, DBS has been approved by the FDA for two motor disorders: Parkinson's disease (PD) and Essential Tremor Disorder (ET); under these guidelines, over 55,000 patients have received DBS treatment ([Focquaert, 2013](#)). DBS has also been investigated as a possible treatment option for other non-motor disorders including: Tourette's

syndrome, substance abuse, refractory depression, obesity, chronic pain, and multiple sclerosis (Bell et al., 2009; Schlaepfer et al., 2010; Focquaert, 2013). DBS implants have become the most widely used therapeutic brain interface technology currently available (Erickson-Davis, 2012). However, as discussed earlier, DBS has drawbacks that need to be evaluated, with up to 10% of DBS patients experiencing serious side-effects, such as post-operative infection, intra-cerebral hemorrhage, or seizures (Appleby et al., 2007). This has given rise to ethical concerns over clinical trials, and the need for strong oversight from the FDA.

Conflicts of interest (COI) are especially problematic with DBS treatments. COI's are situations in which financial or personal gain can compromise the uses of a new treatment. DBS research and treatments rely on a complex web of relationships between academic researchers, institutions (clinics or universities), and industries that produce the implantable product. As a complex medical device, the number of companies manufacturing DBS devices is small, making monopolies possible, which would disrupt the web of relationships. The 3-way relationship between individual researchers, the special interests of the institution, and sensible profits in industry, can cause COI's making the use of DBS in a given situation unethical (Fins et al., 2011). To further complicate the issue, the FDA has no guidelines on innovative surgeries, including DBS (Erickson-Davis, 2012). One example of a COI in the DBS field is Medtronic who has become the world's largest supplier of DBS technology. This domination has created a situation where industry's role possibly overshadows the role of researchers and institutions, raising concerns for a lack of a market-driven approach. In addition, the 1980 Bayh-Dole Act, allows the transfer of intellectual property from government funded programs to institutions that conduct the research, and they can in turn transfer these rights further to a third party, such as Medtronic. This fund transference and control can lead to overly-close relations between specific clinics and companies that undermines independent research (Erickson-Davis, 2012).

The most effective way to identify and resolve these COI's is through transparency from all individuals involved with DBS research and usage. In the case of funding, researchers should reveal and justify why corporate funding is needed, make an effort to balance funding from multiple sources to avoid conflicts, and all possible conflicts-of-interest should be made public. Companies should release their "Rights of Reference", which is their approval to use existing data on the device they are using, so it does not impede new treatments that are only in the investigative phase. Cooperation should be transparent, including ensuring that researchers are not employees of the company that their institution is working with, and that researchers who are working on corporate-sponsored research must refrain from being corporate board members. All researchers must take full responsibility for their publications, and these publications should not be controlled by a financial partner. In regards to intellectual property rights and the Bayh-Dole Act, all monetary transfers should be made transparent, using institutional policies (Fins et al., 2011).

To further DBS scientific research, tight ethical guidelines should be followed, not only at the large institutional and corporate levels, but also by individual researchers, physicians, and patients (Bell et al., 2009). In a clinical trial, patients should be selected using criteria that indicates they are likely to benefit from the treatment; this will keep the cost down and prevent patients who likely will not respond from becoming further frustrated. These selections should be made by a team from multiple disciplines, including neurologists, neuropsychologists, psychiatrists, neurosurgeons, and advance care nurses. Prior to qualifying, patients should

present proof that multiple previous conventional treatments have failed. When choosing a patient, it is important to evaluate their expectations, their commitments to the long-term treatments, and their family support system (Bell et al., 2009).

Informed consent is especially important with DBS procedures. Informed consent is defined as a patient or their legal proxy knowing fully the risks involved, and the patient understands the procedure thoroughly enough to make an informed decision. For example, a PD patient should be aware that when treating PD with DBS the complication rates can exceed 25%, and permanent complications can occur in 4-6% of the cases. They should also have knowledge of the DBS device itself, and the need for future surgeries to replace the device's battery (Bell et al., 2009). From industry's perspective, the informed consent should include a complete transparency of intellectual property rights, monetary compensations, and all individuals involved in their treatment, including the DBS device (Fins et al., 2011).

DBS psychiatric treatments have additional issues to take into concern, as it is important to consider the patient's vulnerability from their specific illness, such as depression or OCD (Bell et al., 2014). With psychiatric conditions, providers should take into consideration the family's role as caregivers in possibly pressuring the patient into agreeing with the treatment. Many patients and families are at the 'end of their rope', and media may sell DBS treatments as 'miracles', or it may negatively influence them by confusing DBS with lobotomy or older forms of electroconvulsive shock (Bell et al., 2009). Enrolling psychiatric patients in invasive surgical procedures is risky, and a discussion should ensue about their ability to provide free and informed consent, including evaluating their vulnerability in a broad relational context that includes their caregivers (Bell et al., 2014).

Despite the fact that DBS is currently performed on children, there are very few guidelines that deal with the decision making of the child. Child protectionists claim that children are immature emotionally and cognitively, and cannot exercise their rights or make informed consent, while child liberationists argue that more emphasis must be placed on child autonomy, with little input from parents or guardians (Focquaert, 2013). In a video-tape analysis of 105 patient tapes, 72% of parents were non-supportive of their children, meaning they did not involve their child in treatment discussions. When dealing with a pediatric patient, a 3-way communication should be facilitated between the physician, parents, and the child whenever possible, and the issue of 'caregiver's burden' should be taken into account by the physician (Focquaert, 2013).

With respect to the three types of non-invasive electrical stimulation techniques (transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS), these were developed to avoid problems associated with surgical implantation of DBS devices, but are not conflict free. Although these transcranial techniques are relatively safe and affordable, compared to DBS, the effectiveness of tDCS is questionable, and few regulations govern their usage (Jwa, 2015). Worse, for tDCS, the affordability of the device (it is available online and is run with a 9 volt battery), has generated a do-it-yourself home crowd with little oversight. Although the device has some significant risks, it is not covered by current FDA (or other) regulations. And there have been no large-scale, well-controlled, long-term clinical trials of safety. Thus, some researchers have argued we need guidelines for the personal use of tDCS.

LITERATURE REVIEW

Section-1: History of Deep Brain Stimulation

Jonathan Morse and Kaycee Nduwke

Introduction to Deep Brain Stimulation

Deep brain stimulation (DBS) is a technique that uses electrical stimulation deep in the brain to treat a variety of neurological and mental disorders. In the DBS procedure, one or more electrodes are surgically implanted deep in the brain at specific targets that are selected depending on which disorder is being treated (**Figure-1**). The electrodes are connected by a subcutaneous wire to a pulse generator that includes a battery, and then the pulse generator is used to apply either high frequency stimulation (HFS) or low frequency stimulation (LFS). The generator is usually implanted below the collarbone (as shown in the diagram), and is relatively undetectable. A minor surgical procedure is needed every 3-5 years to change the battery. DBS has been researched for over 52 years (since 1964, including animal experiments) as an alternative to lesion surgery, and is the most widely used therapeutic technology that uses a human brain-to-machine interface.

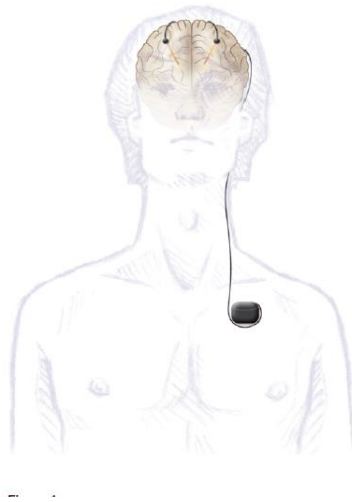


Figure-1: Diagram of Deep Brain Stimulation. Shown is a standard DBS setup, including electrodes implanted in the brain (in this case bilaterally, one on each side) connected by an extension wire (right side) to a battery-operated pulse generator implanted below the collarbone. Diagram is from: [Williams and Okun, 2013](#).

The DBS system can be programmed telemetrically to provide pulses of various hertz (frequency) and duration, which are also selected to fit the specific disorder being treated. The frequency of the stimulation dictates whether the neural circuit is disrupted or stimulated:

High Frequency Stimulation (HFS): This is typically done above 130-180 Hz. In contrast to common sense, HFS lowers or attenuates the aberrant firing of a large neural network that has become abnormally activated during a disease. HFS does not mimic any of the natural (1-100 Hz) signals in the brain. Each electrical burst is 60-90 microseconds, and several orders of magnitude greater in current than any neuron or groups of neurons normally generate in the brain. In a typical example, HFS is used to disrupt or weaken the firing of an abnormal circuit that has become elevated in Parkinson's patients which is causing their motor dysfunctions.

Low Frequency Stimulation (LFS): LFS typically causes neuronal excitation by classic neurophysiology mechanisms. The LFS technique is better researched than HFS. LFS is used to treat disorders where the firing of a particular area of the brain has become weakened.

Both HFS and LFS techniques lack spatial specificity. The electrical effects spread in all directions in the brain. The technique is adjusted for each patient; the optimal tuning frequency varies from person to person. The effects are usually reversible, so most patients require lifelong stimulation. And if any side-effects are observed, the current can be adjusted or terminated.

Examples of DBS Applications

The very earliest DBS experiments were done in 1964 on rats by stimulating the cerebral cortex ([Bindman et al., 1964](#)), which means that DBS has been investigated for over 52 years now. The U.S. Food and Drug Administration (FDA) has approved DBS for treating several types of movement disorders, and it is also currently being researched to treat a variety of psychiatric mental disorders. Below are listed some DBS example applications, a few of which are discussed in detail below.

- **FDA-Approved DBS Applications:**
 - Parkinson's disease. The first FDA-approved DBS application. Used in more than 100,000 patients.
 - Essential Tremor (rhythmic shaking).
 - Epilepsy.
 - Dystonia (involuntary muscle contractions).
 - Treatment-Refractory Obsessive-Compulsive Disorder (OCD) (FDA approved in 2009)
- **Non-FDA-Approved DBS Applications:**
 - Depression.
 - Addiction.
 - Regular OCD.
 - Tourette's syndrome.
 - Post-traumatic stress disorder.

DBS and Parkinson's Patients (Kaycee Nduwke)

Parkinson's disease (PD) is a debilitating neurodegenerative disease that affects motor function (U.S. National Library of Medicine, 2016). Patients show various motor symptoms, such as tremor, rigidity, stiffness, slowed movement, or gait impairment. PD patient brains show a loss of dopaminergic neurons (dopamine-producing) in the substantia nigra area of the brain, so treatments such as Levodopa or Sinemet attempt to increase the levels of dopamine. However, as PD progresses, the drugs become less effective. This leads to the so called "on-off phenomenon" in PD, where the patient feels better (on) as a new dose of the medication takes effect, and then off as it wears off. Eventually the "off" periods are greater than the "on" periods (What Happens...2016).

Parkinson's disease (PD) was the first FDA-approved DBS application, and it has already been used in more than 100,000 PD patients (reviewed in Okun, 2012; Williams and Okun, 2013). In 1990, DBS was first tested in PD animal models before it was applied to human patients (reviewed in Hamani and Temel, 2012). DBS at high frequency was first used in 1997 in PD patients to replace surgical thalamotomy (reviewed in Benabid, 2003), and the technique has since been applied to the pallidum and the subthalamic nucleus (basal ganglia) (Figure-2). Inhibition of electrical currents in these areas improves symptoms in PD animal models and in human PD patients, and can be applied either short-term or long-term to mimic the effects of levodopa treatment. DBS appears to work by disrupting abnormal neural circuits associated with PD, but it also improves neural plasticity and neural protection.

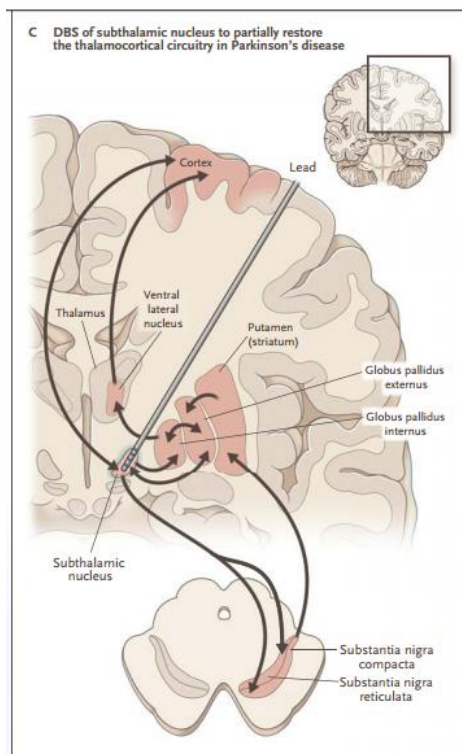


Figure-2: Diagram of the Main Brain Regions of Interest in Parkinson's disease. Shown is the subthalamic nucleus (lower left) which signals to the substantia nigra (lower center) and the globus pallidus (center right) in an interconnected network affected in PD. Scientists have tested DBS in many of the areas shown. Figure is from Okun, 2014.

The DBS procedure for treating PD involves placing high frequency stimulating electrodes in the ventral intermediate nucleus of the thalamus (VIM) (which can significantly

reduce tremors), or in the subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi) (which reduces tremors and decreases bradykinesia, rigidity, and gait impairment) (Perlmutter and Mink, 2006). Even after decades of research the mechanism through which DBS achieves these results is still unclear. The proposed physiologic effects of DBS include: axonal excitation, depolarization blockade, synaptic release of neurotransmitters, normalizing abnormal neuronal firing, and disruption of pathological neuronal synchrony by activating inhibitory interneurons (Lozano et al., 2002).

The precise surgical procedure for electrode implantation varies on a case-by-case basis. A typical procedure begins with a brain imaging study using an MRI or CT-scan. These images of the brain are used to calculate the position of the desired brain target and to guide instruments to that target with minimal trauma to the brain. The target precision can also be improved by using a brain mapping procedure, where fine microelectrodes are used to record brain cell activity in the region of the intended target to confirm that it is correct, or to make very fine adjustments of 1 or 2 millimeters, though the patient must be awake for this procedure. Once the correct target site is confirmed with imaging, the permanent DBS electrode is inserted and tested, then it is anchored to the skull and a pulse generator is placed in the chest and a connector wire is tunneled between the brain electrode and the pulse generator unit.

Evaluating the long and short term effects of DBS on PD patients is of paramount importance. Several studies have looked at the improvements of motor complications in patients with severe PD over several months, while other studies focus on long-term results over several years.

In 1990, scientists in the Department of Neurology at Johns Hopkins Hospital (Baltimore, MD) tested in monkeys the hypothesis that excessive neural activity in the subthalamic nucleus may contribute to PD (Bergman et al., 1990). They lesioned the subthalamic nuclei in monkeys previously given PD by administration of the neurotoxin MPTP. Their data showed that the lesions reduced all the major PD motor disturbances in the contralateral limbs, including akinesia, rigidity, and tremor. So, their data supports the hypothesis that excessive neural activity in the subthalamic nucleus is important in PD.

In 1991, a team of scientists led by the Department of Clinical and Biological Neurosciences, INSERM Preclinical Neurobiology, Joseph Fourier University (Grenoble, France) tested whether high frequency DBS stimulation (HFS-DBS) of the ventral intermediate nucleus (Vim) could lower tremors in PD and essential tremor patients (Benabid et al., 1991). Tremor was assessed by accelerometry. Of the 43 patient Vim's stimulated, 27 no longer showed any tremor, and 11 showed major improvements (88%). The improvement lasted up to 29 months. The adverse side-effects were mild, and could be eradicated by reduction or cessation of the stimulation. The authors concluded that DBS, due to its reversibility and adaptability to control any side-effects is preferable to surgical thalamotomy, especially when treatment of both sides of the brain is required.

In 1993, scientists at the Laboratoire de Neurophysiologie, CNRS (Bordeaux, France) analyzed the effects of high frequency DBS stimulation on the MPTP-induced PD monkey model (Benazzouz et al., 1993). Their data showed that in two PD monkeys DBS could alleviate parkinsonian rigidity and bradykinesia, without causing dyskinesia or hemiballismus. So, their

data supports the hypothesis that elevated subthalamic nucleus firing plays a strong role in PD, and that DBS can help alleviate the symptoms.

In a 2005 multicenter study, 69 patients were treated with bilateral DBS of the STN or GPi (Rodriguez-Oroz et al., 2005). Patients were assessed pre-operatively, and at 1-year and 3-4 years post-operatively. The study gauged the outcome of the treatment by looking at the motor scores and the percent of time spent in the symptomatic stage using the Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) (Rodriguez-Oroz et al., 2005). Their data showed that the DBS significantly improved the motor scores and decreased the frequency and severity of the symptomatic periods. The cardinal PD motor features (tremor, rigidity, bradykinesia, and gait) remained significantly improved in both groups at 3-4 years (except for postural stability in the GPi group and speech in both groups). This study supports the use of DBS stimulation of the STN or GPi to improve PD symptoms.

In 2008, scientists at the Neuroscience Research Institute of North Carolina (Winston-Salem, NC) summarized their investigations of the mechanism for how DBS works in PD rodent models (Chang et al., 2008). They concluded that DBS can modify ion channels, lower the firing rate, and normalize irregular bursts from the basal ganglia thalamo-cortical circuits to improve motor function.

In 2010, a team of scientists at the Human Motor Control Section, National Institute of Neurological Disorders and Stroke, NIH (Bethesda, MD) assayed the effects of transcranial magnetic stimulation (rTMS) on 11 patients with advanced PD (Kang et al., 2010). They focused especially on the so-called “sequence effect” (SE), a progressive slowing of movements in PD patients. Their data showed that Levodopa alone, or rTMS alone, could improve general slowness, but that rTMS had no additive effect on the Levodopa. Levodopa alone, rTMS alone, or their combination had no effect on the progressive slowing. They concluded that dopaminergic dysfunction and abnormal motor cortex excitability (known to be affected by Levodopa and rTMS) are not important in the sequence effect.

In 2013, a team of scientists in the Department of Biomedical Engineering at Duke University (Durham, NC) did a comparison of high frequency DBS delivered in regular versus non-regular temporal patterns in PD patients (Brocker et al., 2013). They found that three of their non-regular DBS regimes improved performance on a finger-tapping task better than regular DBS stimulations. All of the DBS patterns suppressed the abnormal beta-band oscillatory activity in the brain, and the degree of suppression strongly correlated with the patient's clinical outcome. So, the study shows that DBS stimulation can help treat PD symptoms, and is more effective when applied in a non-regular pattern. So, the temporal pattern of DBS stimulation is an important variable to test in the future.

Also in 2013, a team of scientists predominately in the Department of Neurology, University Hospital Schleswig–Holstein (Germany) reported their findings of a 2-year clinical trial (NCT00354133) of 251 patients with advanced PD that had developed severe Levodopa-induced motor complications (Schuepbach et al., 2013). They found that subthalamic DBS stimulation was able to reduce their motor disabilities and improve patient quality of life, as measured by the Parkinson's Disease Questionnaire (PDQ-39) (higher scores indicate worse function). The DBS group lowered their score on average by 7.8 points, while the traditional medical-therapy group increased (worsened) the score by 0.2 points ($p=0.002$). Unfortunately,

serious adverse events occurred in 54.8% of the DBS patients compared to 44.1% in the medical-therapy group. Side-effects in the DBS group were related to surgical implantation in 17.7% of patients.

In 2013, a group of scientists from the Department of Neurology, Academic Medical Center (Amsterdam, Netherlands) announced the results of their randomized, blind, controlled clinical trial comparing DBS of the globus pallidus pars interna (GPi) versus DBS of the subthalamic nucleus (STN) (Odekerken et al., 2013). Their 128 PD patients were recruited from five medical centers in the Netherlands, and had PD symptoms in spite of standard drug treatments. They found no statistical difference between the two DBS treatment methods, but the STN stimulated group showed better secondary improvements ($p=0.03$), so they concluded that site could be the preferred stimulation site.

In 2016, a study led by scientists at the Fondazione IRCCS Ca' Granda (Milan, Italy) assayed whether tDCS applied daily to the cerebellum (cerebellar-tDCS) or motor cortex (M1-tDCS) could improve motor and cognitive symptoms and levodopa-induced dyskinesias in PD patients (Ferrucci et al., 2016). They delivered bilateral anodal (2 mA, 20 min, five consecutive days) and sham tDCS, in random order, during three separate sessions held at least 1 month apart to 9 PD patients (aged 60-85 years). Their data showed that after 5 days of either cerebellar-tDCS or M1-tDCS treatment, the cognitive scores improved significantly ($p < 0.001$).

Bibliography for Parkinson's

Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet*, 1991 Feb 16; 337(8738): 403-406.

Benabid AL (2003) Deep brain stimulation for Parkinson's disease. *Current Opinion in Neurobiology*, 2003 Dec; 13(6): 696-706.

Benazzouz A, Gross C, Féger J, Boraud T, Bioulac B (1993) Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *European Journal of Neuroscience*, 1993 Apr 1; 5(4): 382-389.

Bergman H, Wichmann T, DeLong MR (1990) Reversal of experimental Parkinsonism by lesions of the subthalamic nucleus. *Science*, 1990 Sep 21; 249(4975): 1436-1438.

Bindman LJ, Lippold OC, Redfearn JW (1964) The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *Journal of Physiology*, 1964 Aug; 172: 369-382.

Brocker DT, Swan BD, Turner DA, Gross RE, Tatter SB, Koop MM, Bronte-Stewart H, Grill WM (2013) Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease. *Experimental Neurology*, 2013 Jan; 239: 60-67.

- Butson CR, Cooper SE, Henderson JM, Wolgamuth B, McIntyre CC (2011) Probabilistic analysis of activation volumes generated during deep brain stimulation. *Neuroimage*, 2011; 54(3): 2096–2104.
- Campbell MC, et al. (2012) Mood response to deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neuroscience*, 2012; 24(1): 28–36.
- Chang JY, Shi LH, Luo F, Zhang WM, Woodward DJ (2008) Studies of the neural mechanisms of deep brain stimulation in rodent models of Parkinson's disease. *Neuroscience and Bio-behavioral Reviews*, 2008; 32(3): 352-366.
- Chopra A, et al. (2011) Voltage-dependent mania after subthalamic nucleus deep brain stimulation in Parkinson's disease: a case report. *Biological Psychiatry*, 2011; 70(2): e5–e7.
- Deuschl G, et al. (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, 2006; 355(9): 896–908.
- Eusebio A, Cagnan H, Brown P (2012) Does suppression of oscillatory synchronisation mediate some of the therapeutic effects of DBS in patients with Parkinson's disease? *Frontiers of Integrative Neuroscience*, 2012; 6: 47.
- FAQ for PD Patients: Deep Brain Stimulation for Parkinson's disease. Retrieved 6-22-16 from: http://neurosurgery.ucsf.edu/index.php/movement_disorders_parkinsons.html#where_surgery
- Ferrucci R, Cortese F, Bianchi M, Pittera D, Turrone R, Bocci T, Borroni B, Vergari M, Cogiamanian F, Ardolino G, Di Fonzo A, Padovani A, Priori A (2016) Cerebellar and Motor Cortical Transcranial Stimulation Decrease Levodopa-Induced Dyskinesias in Parkinson's Disease. *Cerebellum*, 2016 Feb; 15(1): 43-47.
- Follett KA, et al. (2010) Pallidal versus subthalamic deepbrain stimulation for Parkinson's disease. *New England Journal of Medicine*, 2010; 362(22): 2077–2091.
- Frankemolle AM, et al. (2010) Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. *Brain*, 2010; 133(pt 3): 746–761.
- Hamani C, Temel Y (2012) Deep brain stimulation for psychiatric disease: contributions and validity of animal models. *Science Translational Medicine*, 2012 Jul 11; 4(142): 142rv8.
- Houeto JL, et al. (2003) Subthalamic stimulation in Parkinson disease: intraoperative predictive factors. *Archives of Neurology*, 2003; 60(5): 690–694.
- Kang SY, Wasaka T, Shamim EA, Auh S, Ueki Y, Lopez GJ, Kida T, Jin SH, Dang N, Hallett M (2010) Characteristics of the sequence effect in Parkinson's disease. *Movement Disorders*, 2010 Oct 15; 25(13): 2148-2155.

Kluger BM, et al. (2012) The prevalence of fatigue following deep brain stimulation surgery in Parkinson's disease and association with quality of life. *Parkinson's Disease*, 2012; 2012: 769506.

Lozano AM, et al. (2002) Deep brain stimulation for Parkinson's disease: disrupting the disruption. *The Lancet Neurology*, 1(4): 225-231.

Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC (2009) Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. *Journal of Neurology and Neurosurgical Psychiatry*, 2009; 80(6): 659–666.

McNeely ME, et al. (2011) Effects of deep brain stimulation of dorsal versus ventral subthalamic nucleus regions on gait and balance in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2011; 82(11): 1250–1255.

Moscovich M, Morishita T, Foote KD, Favilla CG, Chen ZP, Okun MS (2013) Effect of lead trajectory on the response of essential head tremor to deep brain stimulation. *Parkinsonism Relat Disord*. 2013; 19(9): 789–794.

Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, et al. (2013) Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *The Lancet, Neurology*, 2013 Jan; 12(1): 37-44.

Okun MS, et al. (2009) Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Annals of Neurology*, 2009; 65(5): 586–595.

Okun MS, Foote KD (2010) Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Reviews in Neurotherapy*, 2010; 10(12): 1847–1857.

Okun MS, et al. (2011) Do stable patients with a premorbid depression history have a worse outcome after deep brain stimulation for Parkinson disease? *Neurosurgery*, 2011; 69(2): 357–360.

Okun MS (2012) Deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, 2012 Oct 18; 367(16): 1529-1538.

Okun MS, et al. (2012) Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurology*, 2012; 11(2): 140–149.

Okun MS (2013) Deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, 2013 Jan 31; 368(5): 483-484.

Okun MS (2014) Deep-Brain Stimulation: Entering the Era of Human Neural-Network Modulation. *New England Journal of Medicine*, 371: 1369.

Oyama G, et al. (2012) GPi and STN deep brain stimulation can suppress dyskinesia in Parkinson's disease. *Parkinsonism Relat Disord.* 2012; 18(7): 814–818.

Perlmutter JS, Mink JW (2006) Deep brain stimulation. *Annual Review of Neuroscience*, 29: 229.

Rodriguez-Oroz MC, et al. (2005) Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain*, 128(10): 2240-2249.

Rubin JE, McIntyre CC, Turner RS, Wichmann T (2012) Basal ganglia activity patterns in parkinsonism and computational modeling of their downstream effects. *European Journal of Neuroscience*, 2012; 36(2): 2213–2228.

Sauleau P, et al. (2005) Motor and non-motor effects during intraoperative subthalamic stimulation for Parkinson's disease. *Journal of Neurology*, 2005; 252(4): 457–464.

Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hessekamp H, Navarro SM, et al. (2013) Neurostimulation for Parkinson's disease with early motor complications. *New England Journal of Medicine*, 2013 Feb 14; 368(7): 610-622.

Tang JK, et al. (2007) Neuronal firing rates and patterns in the globus pallidus internus of patients with cervical dystonia differ from those with Parkinson's disease. *Journal of Neurophysiology*, 2007; 98(2): 720–729.

Tykocki T, Nauman P, Koziara H, Mandat T (2013) Microlesion effect as a predictor of the effectiveness of subthalamic deep brain stimulation for Parkinson's disease. *Stereotactic and Functional Neurosurgery*, 2013; 91(1): 12–17.

U.S. National Library of Medicine (2016) Parkinson's disease.
<https://medlineplus.gov/parkinsonsdisease.html>

Voon V, et al. (2008) A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain*, 2008; 131(pt 10): 2720–2728.

Weaver FM, et al. (2012) Randomized trial of deep brain stimulation for Parkinson disease: thirty-six month outcomes. *Neurology*, 2012; 79(1): 55–65.

What Happens in Parkinson's When Your Medication Stops Working Well? (2016) Retrieved June 20, 2016, from: <https://www.verywell.com/on-off-phenomenon-2612093>

Williams A, et al. (2010) Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurology*, 2010; 9(6): 581–591.

Williams NR, Okun MS (2013) Deep brain stimulation (DBS) at the interface of neurology and psychiatry. *Journal of Clinical Investigation*, 2013 Nov; 123(11): 4546-4556.

Zahodne LB, et al. (2011) Binge eating in Parkinson's disease: prevalence, correlates and the contribution of deep brain stimulation. *J Neuropsychiatry Clin Neurosci.* 2011; 23(1): 56–62.

DBS and Treatment-Resistant Depression (TRD) (*Kaycee Nduwke*)

Major depression is the most common of all psychiatric disorders, ranking among the top causes of worldwide disease burden, and is the leading source of disability in adults in North America under the age of 50 (WHO, 2001). Depression is usually effectively treated in the majority of patients using either medications or psychotherapy, but up to 20% of patients fail to respond to these standard interventions (Wijeratne and Sachdev, 2008). For these treatment-resistant depression (TRD) patients, trial-and-error combinations of more aggressive approaches are often required, such as multiple medications or electroconvulsive therapy (Mayberg et al., 2005), and DBS stimulation may be a new course of action.

Functional neuroimaging studies have shown that depression is associated with increased neural activity in the subcallosal cingulate gyrus (SCG) area of the brain which is involved in mood regulation (Mayberg et al et al., 2005). Various interventions that suppress the activity of this area, including pharmacotherapy, transcranial magnetic stimulation, and electroconvulsive therapy, improve the clinical features of depression, so this supports the theory that over-activity of the SCG is important in the pathophysiology of depression. But even after decades of research, the mechanism through which DBS achieves these results is still unclear. And the best location for planting the electrodes varies from case-to-case.

In 2005, scientists at the Rotman Research Institute at Baycrest Centre, and the Departments of Psychiatry and Neurology, University of Toronto (Toronto, Canada) performed a study to determine whether DBS of the subgenual cingulate region (Brodmann area 25) could help alleviate symptoms in 6 patients with treatment-resistant depression (TRD) (Mayberg et al., 2005). Their previous data showed that this area of the brain is metabolically over-active in TRD patients, so they hypothesized that DBS might lower the elevated activity. Their data showed that chronic stimulation of this region of the brain was associated with a striking and sustained remission of depression in four of six patients. With respect to mechanism, the improvements were associated with a reduced blood flow to the cingulate region, and also changed in areas known to be downstream from this site.

In 2008, scientists at the Klinik für Psychiatrie (München, Germany) reported their findings of a double-blind placebo-controlled study of the effects of anodal transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) in therapy-resistant depression patients (TRD) (Palm et al., 2008). They enrolled 10 patients with moderate to severe major depression (DSM-IV criteria) in a 4 week trial. All 10 patients had undergone ineffective antidepressant therapy with no effects. Real or placebo tDCS were applied in random order at 1 mA for 20 min per day, two weeks per patient. For the placebo tDCS, the authors used a novel sham device which is indistinguishable to the person doing the treatment. Their data was somewhat disappointing, there was no significant difference between real and sham tDCS for clinical improvement, although the data trends did look promising. The tDCS appeared to be tolerated well, with only minor side-effects. So, tDCS did not appear in this study to help

treatment-resistant depression patients, although it appeared to help regular depression patients in previous studies. The authors suggested extending the treatments for a longer period of time.

In 2011, scientists in the Department of Psychiatry, Division of Neurosurgery, University Health Network (Toronto, Canada) published their findings of long term follow-up trial of 20 patients receiving DBS stimulation for treatment-resistant depression (Kennedy et al., 2011). The DBS was applied to the subcallosal cingulate gyrus. Their data showed average response rates for 1, 2, and 3 years post-DBS of about 62.5%, 46.2%, and 75%, respectively, while at the last follow-up visit (range of 3-6 years) it was 64.3%. The patient's physical health and social functioning progressively improved up to the last follow-up visit. No significant adverse events were reported, although two patients died by suicide during depressive relapses. The authors suggest that additional clinical trials with larger samples be performed to confirm the findings.

In 2012, scientists in the Department of Psychiatry, Dartmouth Medical School (Lebanon, NH) published the findings of the 2-year safety and efficacy of subcallosal cingulate bilateral DBS in patients with treatment-resistant depression (TRD) accompanied by either major depressive disorder (MDD) or bipolar II disorder (BP) (clinical trial NCT00367003) (Holtzheimer et al., 2012). The trial design was open-label with a sham lead-in phase. 323 TRD patients were screened to obtain those with additional MDD (10 patients) or BP (7 patients). Patients received single-blind sham stimulation for 4 weeks, followed by active stimulation for 24 weeks. Patients then entered a single-blind discontinuation phase, but it was stopped after the first 3 patients because of ethical concerns (the patients without DBS deteriorated, so DBS was resumed). Their data showed a significant decrease in depression and increase in function with DBS treatment. Remission was seen in 18%, 36%, and 58% after 6 months, 1 year, and 2 years, respectively. General positive responses for the same time periods were 41%, 36%, and 92%, respectively. No patient achieving remission experienced a spontaneous relapse. Efficacy was similar for patients with MDD and BP. The long term DBS stimulation appeared safe and well tolerated.

In 2012, scientists in the Division of Neurosurgery, Toronto Western Hospital (Toronto, Ontario, Canada) published their results of a 3-center clinical trial of DBS stimulation of the subcallosal cingulate gyrus (SCG) for patients with treatment-resistant depression (TRD) (Lozano et al., 2012). Previous promising results were obtained from one single center trial for patients with major depression, and the purpose of this study was to determine whether those promising results could be replicated at several different centers for patients with TRD. They conducted a 3-center prospective open-label trial of bilateral SCG DBS for 12 months in 21 patients with treatment-resistant depression. Their results indicated that the DBS patients showed positive response rates of 57% at 1 month, 48% at 6 months, and 29% at 12 months. Their findings indicate that DBS may be applicable to patients with TRD, and were successful at several different medical centers.

In 2012, scientists in the Department of Psychiatry and Psychotherapy, University Hospital, (Bonn, Germany) published the results of their 4-year follow-up of their clinical trial of 11 patients with treatment-resistant depression (TRD) and DBS delivered bilaterally to the nucleus accumbens (NAcc-DBS) (Bewernick et al., 2012). Their 1 year follow-up data indicated that DBS might improve symptoms. The outcomes were compared at baseline (time zero), 1 year, 2 years, and 4 years. Their data shows that 5 of 11 patients (45%) were classified as responders after 12 months, and they remained sustained responders at 4 years. Ratings of both

depression and anxiety were significantly reduced in the NAcc-DBS cohort. All patients improved in their quality of life measures. One non-responder committed suicide. No severe adverse events related to the DBS were reported.

Bibliography for Treatment-Resistant Depression

Bewernick BH, et al. (2010) Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol Psychiatry*, 2010; 67(2): 110–116.

Bewernick BH, Kayser S, Sturm V, Schlaepfer TE (2012) Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. *Neuropsychopharmacology*, 2012 Aug; 37(9): 1975-1985.

Drevets WC, Ongur D, Price JL (1998) Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Molecular Psychiatry*, 1998; 3(3): 220–226.

Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J (2006) A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry*, 2006; 163(1): 88-94.

Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand*, 2007; 116(3): 165-173.

Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, et al. (2005) A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*, 2005; 57(3): 585–593.

Holtzheimer PE, et al. (2012) Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry*, 2012; 69(2): 150–158.

Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, Lozano AM (2011) Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *American Journal of Psychiatry*, 2011 May; 168(5): 502-510.

Li X, Nahas Z, Anderson B, Kozel FA, George MS (2004) Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depression and Anxiety*, 2004; 20(2): 98-100.

Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, Debonnel G, Sadikot AF, Lam RW, Howard AK, Ilcewicz-Klimek M, Honey CR, Mayberg HS (2012) A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *Journal of Neurosurgery*, 2012 Feb; 116(2): 315-322.

Malone DA, et al. (2009) Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry*, 2009; 65(4): 267–275.

Malone DA (2010) Use of deep brain stimulation in treatment-resistant depression. *Cleveland Clinical Journal of Medicine*, 2010; 77(suppl 3): S77–S80.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. *Neuron*, 2005 Mar 3; 45(5): 651-660.

Mayberg HS (2012) Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Archives of General Psychiatry*, 2012 Feb; 69(2): 150-158.

Mayberg, H (2013) Optimizing subcallosal cingulate DBS for treatment resistant depression. Society of Biological Psychiatry 68th Annual Scientific Convention, May 16–18, 2013. San Francisco, CA.

O’Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC (2005) Long-term maintenance therapy for major depressive disorder with rTMS. *J Clin Psychiatry*, 2005; 66(12): 1524-1528.

Palm U, Keeser D, Schiller C, Fintescu Z, Reisinger E, Mulert C, Pogarell O, Möller H, Padberg F (2008) Transcranial direct current stimulation in therapy-resistant depression: Preliminary results from a double-blind, placebo-controlled study. *Brain Stimulation*, 1(3): July 2008, Pages 241–242.

Puigdemont D, et al. (2011) Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. *International Journal of Neuropsychopharmacology*, 2011: 1–13.

Ramasubbu RA (2013) Double-blind optimization of subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. Society of Biological Psychiatry 68th Annual Scientific Convention, May 16–18, 2013. San Francisco, CA.

Rezai A (2012) Deep brain stimulation (DBS) for treatment-resistant depression: a randomized controlled trial. 2012 ASSFN Biennial Meeting Abstracts, Oral Presentation. June 3-6, 2012. San Francisco, CA.

Riva-Posse P, Holtzheimer PE, Garlow SJ, Mayberg HS (2012) Practical considerations in the development and refinement of subcallosal cingulate white matter deep brain stimulation for the treatment resistant depression. *World Neurosurgery*, 2012; pii:S1878-8750(12)01436-2.

Rizvi SK, et al. (2013) Investigation of the targeted effects of deep brain stimulation on depressive symptom profiles: a pooled analysis. Society of Biological Psychiatry 68th Annual Scientific Convention, May 16–18, 2013. San Francisco, CA.

Sartorius A, et al. (2010) Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biological Psychiatry*, 2010; 67(2): e9–e11.

Schlaepfer TE, et al. (2008) Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*, 2008; 33(2): 368–377.

Wijeratne C, Sachdev P (2008) Treatment-resistant depression: critique of current approaches. *Australian and New Zealand Journal of Psychiatry*, 42(9): 751-762.

World Health Organization (2001) Chapter 2: Burden of Mental and Behavioral Disorders. In *The WHO Report 2001: Mental Health, New Understanding, New Hope*. <http://www.who.int/whr/2001/chapter2/en/Index3.html>.

DBS and Epilepsy (*Kaycee Nduwke*)

Epilepsy is the fourth most common chronic neurologic disease ([Epilepsy Foundation, 2016](#)). Drug treatments sometimes reduce the seizure frequency, but despite this some patients remain treatment-refractory ([Kwan and Brodie, 2000](#)). Some therapeutic options offered to epilepsy patients include trials with newly developed antiepileptic drugs or epilepsy surgery. But for the remainder of patients, DBS might be suitable as an alternative.

There are several types of epilepsy symptoms, so this disorder is often called a syndrome. Epilepsy can vary by the severity and frequency of the seizures, the age of onset, whether the seizures are inherited, the portion of the brain involved, and the pattern of brain imaging. So, diagnosing and treating the disorder can be challenging. DBS treatment requires knowledge of the part of the brain that must be targeted for that individual patient.

In 1994, scientists at the Baylor College of Medicine (Houston, Texas) reported their findings of a long-term follow-up of 67 seizure patients treated with vagus nerve stimulation (VNS) ([George et al., 1994](#)). Previous VNS studies showed positive anti-convulsive effects in preclinical studies, in human pilot studies, and in the early phase of a multi-center, double-blinded, randomized study. The high VNS-stimulated group (all 67 patients who extended the trial) showed a significant decrease in seizure frequency ($p < 0.01$) compared to baseline. For the patients who had received high VNS throughout the study, they achieved a 52.0% mean seizure frequency reduction as compared with baseline, while patients who had originally received low energy VNS (and high VNS in the final phase) achieved a 38.1% reduction. No significant safety issues were identified in the long-term follow-up, although minor side-effects were observed, including hoarseness/voice change, coughing, and paresthesia (sensations in the neck and jaw). These side effects were well tolerated. During the follow-up period, 1 patient died of thrombotic thrombocytopenia, and 5 patients discontinued treatment because of unsatisfactory efficacy.

In 2007, a DBS study analyzed 10 patients with refractory medial temporal lobe (MTL) epilepsy ([Boon et al, 2007](#)). The patients underwent long-term MTL-DBS. The protocol included invasive video-EEG monitoring for onset localization. Side-effects and changes in seizure frequency were carefully monitored. Patients were assessed pre-operatively and at a mean follow-up of 31 months post-operatively. Their data showed that 8 of the 10 patients (80%) had a 30-90% reduction in seizure frequency, while 1 patient became seizure free. One patient was

non-responsive to the DBS (Boon et al, 2007). None of the patients had adverse effects from the DBS treatment.

In 2010, scientists in the Department of Neurosurgery at the Medical College of Georgia (Augusta, GA) reported their use of cranially implanted closed-loop (responsive) DBS neuro-stimulation to reduce seizure frequencies in an epilepsy patient (Smith et al., 2010). The patient had previously undergone surgical resection of the left frontal opercular cortex, which had resulted in a sustained 50% reduction in seizure frequency. The team's addition of the closed loop DBS stimulation, caused a further 60% reduction of seizures. The authors concluded that the closed-loop DBS technique might be an effective alternative to higher risk surgery.

In 2010, scientists in the Department of Neurology, Stanford University School of Medicine (Stanford, CA) reported their results of a multicenter, double-blind, randomized trial of bilateral DBS stimulation of the anterior thalamic nuclei for localization-related epilepsy (Fisher et al., 2010). The trial enrolled 110 adults with medically refractory partial seizures. In the last month of the 3-month initial trial, the stimulated group had a 29% greater reduction in seizures compared with the control group ($p = 0.002$). The instances of complex-partial and "most severe" seizures were also significantly reduced by the DBS. By the end of 2-years, the DBS group showed a 56% median reduction in seizure frequency, 54% of the patients had a seizure reduction of at least 50%, and 14 patients were seizure-free for at least 6 months. Five deaths occurred, but none were from the implantation or the DBS stimulation. Two participants had acute, transient stimulation-associated seizures.

In 2011, scientists at NeuroPace, Inc. (Mountain View, CA) published the findings of their multicenter, double-blind, randomized controlled trial assessing the safety and effectiveness of closed loop (responsive) cortical stimulation in 191 adults with medically refractory epilepsy (Morrel et al., 2011). The neuro-stimulator was programmed to detect abnormal electrical activity, and once detected deliver a corrective stimulation. In the treatment group, seizures were significantly reduced (37.9%, $n = 97$) compared to the sham group (17.3%, $n = 94$; $p = 0.012$). There was no difference in the two groups for adverse side-effects. There was no deterioration in mood or neuropsychological function.

In 2013, scientists in the Department of Neurological Surgery, Thomas Jefferson University Hospital (Philadelphia, PA) performed a review of the literature for three neuro-stimulation techniques used to treat medically refractive epilepsy patients (Wu and Sharan, 2013). They compared: 1) vagus nerve stimulation, 2) deep brain stimulation (DBS), and 3) closed-loop responsive neuro-stimulation (RNS). Their review of 189 publications from 1938 to 2012 showed positive findings for all 3 techniques against medically-refractive epilepsy, so these electrical stimulation techniques might serve as alternatives to surgical ablations.

Bibliography for Epilepsy

Boon P, et al. (2007) Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia*, 48(8): 1551-1560.

Epilepsy Foundation (2016) What is Epilepsy?

<http://www.epilepsy.com/learn/epilepsy-101/what-epilepsy>

Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, et al. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*, 2010 May; 51(5): 899-908.

George R, Salinsky M, Kuzniecky R, Rosenfeld W, Bergen D, Tarver WB, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 3. Long-term follow-up on first 67 patients exiting a controlled study. First International Vagus Nerve Stimulation Study Group. *Epilepsia*, 1994 May-Jun; 35(3): 637-643.

Kwan P, Brodie MJ (2000) Epilepsy after the first drug fails: substitution or add-on? *Seizure*, 2000 Oct; 9(7): 464-468.

Morrel MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*, 2011 Sep 27; 77(13): 1295-1304.

Smith JR, Fountas KN, Murro AM, Park YD, Jenkins PD, Morrell M, Esteller R, Greene D (2010) Closed-loop stimulation in the control of focal epilepsy of insular origin. *Stereotactic and Functional Neurosurgery*, 2010; 88(5): 281-287.

Wu C, Sharan A (2013) Neurostimulation for the Treatment of Epilepsy: A Review of Current Surgical Interventions. *Neuromodulation*, 2013; 16: 10–24.

DBS and Obsessive-Compulsive Disorder (OCD) (*Jonathan Morse*)

OCD Introduction

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by recurrent unwanted thoughts or ideas (obsessions) and repetitive behaviors or mental acts performed in order to relieve these obsessions (compulsions) (Bourne et al., 2012). OCD affects approximately 2% of the general population, and even when the best available treatments are used approximately 10% of patients remain afflicted (Denys et al., 2010). Doubt, and its behavioral parameter, checking, is a normal phenomenon of human cognition that is dramatically exacerbated in OCD (Burbaud et al., 2013). OCD is one of the most disabling of the chronic psychiatric disorders, and the effects can completely take over someone's life. It has been known to have "repercussions on family relationships, social life, and the ability to function at work" (Malet et al., 2008; Denys et al., 2010).

OCD Pathogenesis

OCD has been traced to abnormal activity in the "cortico-striato-thalamo-cortical (CSTC) circuits, including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventral

striatum, and mediodorsal (MD) thalamus” (Bourne et al., 2012), so these circuits have been tested during DBS stimulation.

OCD Standard Treatments

The initial treatment for OCD is typically “a combination of serotone reuptake inhibitors and cognitive-behavioral therapy” (Mallet et al., 2008). But between 10% and 40% of OCD patients do not improve with traditional non-surgical methods, so for them the only option for about 40 years was ablative surgery. The surgery typically included an anterior capsulotomy and anterior cingulotomy (Greenberg et al., 2010). “An anterior capsulotomy is a cataract-type surgery used to make a small round opening in the front of the capsule that contains the eye's natural crystalline lens” (visionrx). “Anterior cingulotomy involves the placement of bilateral lesions in the anterior cingulate under stereotactic guidance” (Steele et al., 2007).

DBS and OCD

Although DBS was first applied to movement disorders such as Parkinson’s disease and essential tremor, psychiatric disorders such as OCD were a logical extension to test. DBS has been performed for OCD on the “ventral anterior limb of the internal capsule and adjacent ventral striatum, the subthalamic nucleus, and the nucleus accumbens” (Steele et al., 2007).

In 2007, scientists in the Department of Neuroscience at the University of Pittsburgh (Pittsburgh, PA) used high-frequency DBS to the nucleus accumbens (NAc) region in a rat model of treatment-resistant obsessive-compulsive disorder (OCD) (McCracken and Grace, 2007). Previous studies had shown that DBS improves OCD symptoms by lowering the activity of the orbitofrontal cortex (OFC) (which is fed by the NAc). They used 30 min NAc of DBS at 130 Hz applied to the NAc, and determined that DBS reduced the mean firing rate of OFC neurons, while other inter-neurons were excited by DBS. A single pulse of electrical current to the NAc mimicked OCD, while DBS lowered the signal. Their results suggest that NAc-DBS might alleviate OCD symptoms by reducing the activity of subsets of OFC neurons, while DBS also activates specific “inhibitory” neurons.

In 2008, scientists at the INSERM Avenir Team, Behavior, Emotion, and Basal Ganglia, Centre d’Investigation Clinique (Paris, France) studied the effects of subthalamic nucleus DBS stimulation on patients with treatment-refractory obsessive-compulsive disorder (OCD) (Mallet et al., 2008). They reported the findings of their 10-month double-blind, multicenter study (NCT00169377) on 8 DBS patients and 8 non-DBS patients. 8 patients received actual DBS for the first 3 months and 8 patients received sham treatment. Then both groups completed the wash out period, and then groups switched roles. The severity of the OCD was measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (lower scores indicate less severe symptoms). General functioning and tolerance were measured by standardized psychiatric tests, the Global Assessment of Functioning (GAF) scale, and neuropsychological tests. Their results indicated that the OCD scores were significantly lower for the DBS patients than the sham controls ($P=0.01$), and the GAF score for general function (higher scores indicate higher levels of functioning) was significantly higher (56 ± 14 vs. 43 ± 8 , $P=0.005$). Not altered by the DBS were depression or anxiety. Unlike the other studies, this study observed some serious side-effects.

“There were 15 serious adverse events, of which 4 were related to the surgical procedure, including 1 intracerebral hemorrhage, 2 infections requiring removal of the electrode, and 7 were related to the DBS stimulation but were transient” (Mallet et al., 2008).

In 2010, scientists in the Department of Psychiatry at the Academic Medical Center, University of Amsterdam (Netherlands) published their findings of a clinical trial (ISRCTN23255677) designed to test whether bilateral deep brain stimulation (DBS) of the nucleus accumbens is an effective and safe treatment for treatment-refractory obsessive-compulsive disorder OCD (Denys et al., 2010). The study consisted of 16 patients (aged 18-65) in an open 8-month treatment phase, followed by a double-blind crossover phase with randomly assigned 2-week periods of active or sham stimulation, ending with an open 12-month maintenance phase. Their data showed that in the open phase, the mean OCD behavioral score (Y-BOCS) in the DBS group decreased by 46% after 8 months ($p < 0.001$). Nine of 16 patients were classified as responders, with a mean decrease of 72%. In the double-blind, sham-controlled phase ($n = 14$), the mean behavioral score decrease was 25% ($p = 0.004$). Depression and anxiety decreased significantly. The only side-effects observed were mild forgetfulness and word-finding problems.

In 2010, scientists at the Mount Sinai School of Medicine (New York) published their findings of a 6 patient pilot study (NCT00057603) using bilateral deep brain stimulation (DBS) of the anterior limb of the internal capsule of the brain in patients with treatment-resistant severe obsessive compulsive disorder (OCD) (Goodman et al., 2010). Using a randomized, staggered-onset design, patients were stimulated for 12 months at either 30 or 60 days post-surgery under blinded conditions. Their data showed that after 12 months of DBS stimulation, 66.7% of the patients met the criterion as "responders" with $\geq 35\%$ improvement. The sham-stimulated patients showed no improvement. Global functioning improved for the responders. The team reported some side-effects associated with the DBS, but they were generally mild and could be controlled by changing the DBS settings. Stoppage of the DBS resulted in rapid (but reversible) onset of depression in two cases.

In 2010, scientists led by the Department of Psychiatry and Human Behavior, Division of Neurosurgery, Butler Hospital, Alpert Medical School of Brown University (Providence, RI) reported the findings of their long-term (8-year) clinical trial of DBS stimulation of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) for patients with severe and highly treatment-resistant OCD (Greenberg et al., 2010). Four large medical centers were involved: Leuven/Antwerp, Butler Hospital/Brown Medical School, the Cleveland Clinic, and the University of Florida. Their long-term data showed clinically significant symptom reductions and functional improvement in about two-thirds of the patients. The DBS treatment was well tolerated, and any adverse side-effects were “overwhelmingly transient”. Interestingly, the improvements were strongest for patients implanted most recently, which suggests the teams developed stronger surgical skills over time, especially the refinement of the implantation site to a slightly more posterior position.

In 2012, scientists in the Department of Neurosurgery at Massachusetts General Hospital (Boston) investigated the mechanism for how DBS helps OCD patients (Bourne et al., 2012). Although DBS was initially thought to mimic a functional lesion as with ablative surgical procedures, increasing amounts of data now indicate DBS works by either quieting large-scale networks, by activating specific inhibitory fibers, or by altering the release of critical

neurotransmitters. The authors reviewed the literature on DBS for OCD through 2012, and discussed plausible mechanisms.

In 2013, scientists at the Institut des Maladies Neurodégénératives (CNRS UMR5293), Université Victor Segalen (Bordeaux, France) investigated the mechanism of how DBS stimulation improves the symptoms of OCD patients (Burbaud et al., 2013). They used electrodes to record the activity of individual neurons in the target area (the associative-limbic area of the subthalamic nucleus, a central core of the basal ganglia) while the subjects performed a cognitive task. The task gave the patients the option of unrestricted repetitive checking (OCD) after they made a choice. The team hypothesized that the neurons in the target area would increase their activity with doubt and checking behavior. They recorded 87 task-related neurons in 10 patients. 60% of the target neurons tested responded to various combinations of instructions, delay, movement or feedback. Importantly, decision checking increased the activity of the target neurons, but not without checking. These results suggest that the associative-limbic subthalamic nucleus pathway plays a role in doubt-related repetitive thoughts, and that DBS quiets this activity.

Bibliography for OCD

Abelson JL, et al. (2005) Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry*, 2005; 57(5): 510–516.

Bourne SK, Eckhardt CA, Sheth SA, Eskandar EN (2012) Mechanisms of deep brain stimulation for obsessive compulsive disorder: Effects upon cells and circuits. *Frontiers in Integrative Neuroscience*, 2012 Jun 14; 6: 29.

Burbaud P, Clair AH, Langbour N, Fernandez-Vidal S, Goillandeau M, Michelet T, Bardinet E, Chéreau I, Durif F, Polosan M, Chabardès S, et al. (2013) Neuronal activity correlated with checking behaviour in the subthalamic nucleus of patients with obsessive-compulsive disorder. *Brain*, 2013 Jan; 136(Pt 1): 304-317.

Chabardès S, et al. (2012) Deep brain stimulation for obsessive-compulsive disorder: subthalamic nucleus target [published online ahead of print March 30, 2012]. *World Neurosurg*. doi:10.1016/j.wneu.2012.03.010.

Denys D, Mantione M, Figeet M, van den Munckhof P, Koerselman F, Westenberg H, Bosch A, Schuurman R (2010) Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Archives of General Psychiatry*, 2010 Oct; 67(10): 1061-1068.

Fins JJ, et al. (2011) Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder. *Health Aff (Millwood)*, 2011; 30(2): 302–311.

Fontaine D, et al. (2004) Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease. Case report. *Journal of Neurosurgery*, 2004; 100(6): 1084–1086.

Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, Shapira NA, Wu SS, Hill CL, Rasmussen SA, Okun MS (2010) Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biological Psychiatry*, 2010 Mar 15; 67(6): 535-542.

Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA (2006) Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology*, 2006 Nov; 31(11): 2384-2393.

Greenberg BD, Gabriels LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, et al. (2010) Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Molecular Psychiatry*, 2010 Jan; 15(1): 64-79.

Haq IU, et al. (2010) A case of mania following deep brain stimulation for obsessive compulsive disorder. *Stereotact Funct Neurosurg*. 2010; 88(5): 322–328.

Harrison BJ, et al. (2013) Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. *Biol Psychiatry*, 2013; 73(4): 321–328.

Huff W, et al. (2010) Uni-lateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. *Clin Neurol Neurosurg*. 2010; 112(2): 137–143.

Jimenez-Ponce F, et al. (2009) Preliminary study in patients with obsessive-compulsive disorder treated with electrical stimulation in the inferior thalamic peduncle. *Neurosurgery*, 2009; 65(6 suppl): 203–209.

Le Jeune F, et al. (2010) Decrease of prefrontal metabolism after subthalamic stimulation in obsessive-compulsive disorder: a positron emission tomography study. *Biol Psychiatry*, 2010; 68(11): 1016–1022.

Lipsman N, Neimat JS, Lozano AM (2007) Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery*, 2007; 61(1): 1–11.

Lujan JL, Chaturvedi A, McIntyre CC (2008) Tracking the mechanisms of deep brain stimulation for neuropsychiatric disorders. *Frontiers in Bioscience*, 2008; 13: 5892–5904.

Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, du Montcel ST, Yelnik J, Chéreau I, Arbus C, Raoul S, Aouizerate B, Damier P, Chabardès S, et al. (2008) Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *New England Journal of Medicine*, 2008 Nov 13; 359(20): 2121-2134.

McCracken CB, Grace AA (2007) High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. *Journal of Neuroscience*, 2007 Nov 14; 27(46): 12601-12610.

Mian MK, Campos M, Sheth SA, Eskandar EN (2010) Deep brain stimulation for obsessive-compulsive disorder: past, present, and future. *Neurosurg Focus*, 2010; 29(2): E10.

Saleh C, Okun MS (2008) Clinical review of deep brain stimulation and its effects on limbic basal ganglia circuitry. *Front Biosci*. 2008; 13: 5708–5731.

Steele JD, Christmas D, Eljamel MS, Matthews K (2008) Anterior cingulotomy for major depression: clinical outcome and relationship to lesion characteristics. *Biological Psychiatry*, 2008 Apr 1; 63(7): 670-677.

van den Heuvel OA, et al. (2008) The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain*, 2009; 132(pt 4): 853–868.

DBS and Gilles de la Tourette’s Syndrome (GTS) (*Jonathan Morse*)

GTS Introduction

Gilles de la Tourette Syndrome (GTS) is a complex inheritable childhood-onset neurological and neurobehavioral disorder characterized by multiple disabling motor and vocal tics lasting more than a year (Saleh et al., 2012). The condition often includes frequent involuntary movements, such as vocalizations or severe head and arm jerks. “The tics are often preceded by a premonitory sensory phenomenon or an urge, and are relieved by the execution of the movement or sound” (Viswanathan et al., 2012). In community-based studies, it is reported that 0.3% - 0.8% of the population has this disorder. Approximately 50-90% of GTS patients also have co-symptoms such as Obsessive-Compulsive Disorder (OCD) or Attention Deficient Hyperactive Disorder (ADHD), or both. Usually most GTS patients grow out of it during the second decade of life in their teenage years. However, some patients do not progress out of the disease, and they require lifelong medical and behavioral treatments.

Before 1960, it was believed that GTS was a very rare neuropsychiatric disorder. Then during the 1960s, it was discovered that neuroleptic drugs can lead to clinical improvements in GTS. After that discovery, there was a gradual shift that GTS was actually a relatively common, genetic, and neurobiological disorder (Viswanathan et al., 2012).

GTS Pathogenesis

The pathophysiology of GTS is poorly understood, but is thought to involve the “activation of aberrant groups of striatal neurons (reward system of the brain) with inhibitory projections to the GPi and SNpr, which in turn disinhibits thalamocortical projections involved in a specific unwanted motor pattern, leading to a tic” (Viswanathan et al., 2012).

Standard GTS Treatments

The standard treatments for GTS start with non-surgical and non-invasive remedies due to the risk associated with surgical and invasive procedures. The first line of non-surgical

treatments for GTS are α 2-adrenergic agonists, which attempt to stimulate the neurons that inhibit the unwanted motor patterns. The second more extreme line of non-surgical treatment includes using anti-psychotic agents, benzodiazepines, or botulinum toxin (Saleh et al., 2012). Behavioral therapies are also sometimes used (Viswanathan et al., 2012).

Surgery is considered for GTS when the tics do not respond to standard therapies, and become troublesome, disabling, or self-injurious. The 1960s saw the start of surgical treatments for GTS, but it was used sparingly. “If the symptoms markedly interfere with daily activities or are associated with a self-injurious behavior (so-called ‘malignant TS’) surgical intervention may need to be considered” (Viswanathan et al., 2012). “In the early 1960s a procedure was described in the *Canadian Medical Association Journal* that involved a bimedial frontal leucotomy” (Viswanathan et al., 2012). In the early 1970s, two more documented surgical procedures were performed on patients with GTS: one was performed by Nadvornik and co-workers in the Czech Republic (cerebellar surgery lesioning the cerebellar dentate nuclei), and the other was performed by Hassler and Dieckmann (stereotatic coagulation of the rostral intralaminar and medial thalamic nuclei).

GTS DBS Treatments

For patients suffering severe side-effects that do not respond to pharmacologic treatments, DBS might serve as an alternative. DBS is reversible and adaptive (Mallet et al., 2008). The first report using DBS to treat GTS was in 1999 (Vandewall et al., 1999), and since then around 100 patients have used the technique. The brain locations stimulated with DBS have included: the thalamic centromedian nucleus, submtia periventricularis, posteroventral globus pallidus internus, and ventromedial globus pallidus interus. Overall, bilateral stimulation of the internal globus pallidus (GPi) DBS has been the most effective.

In 2005, scientists in the Department of Neurology at Massachusetts General Hospital (Boston) published their findings of a single case of DBS treatment of a 37-year-old woman with severe Tourette syndrome who had not responded to over 40 different medications (Flaherty et al., 2005). Her symptoms included frequent vocalizations, and severe head and arm jerks that caused blindness. The team implanted bilateral electrodes in the anterior limb of the internal capsule of the brain, terminating in the vicinity of the nucleus accumbens. The data indicated that at an 18-month follow-up test, the DBS stimulation significantly lowered her tic frequency and severity, indicating that stimulation of the anterior internal capsule may be a safe and effective procedure for the treatment of Tourette syndrome.

In 2012, a team at the Neuropsychiatric Institute at Prince of Wales Hospital (Randwick, New South Wales, Australia) published their findings of DBS treatment of 11 patients with severe medically intractable Tourette’s syndrome (TS) stimulated bilaterally in the anteromedial globus pallidus interna (Cannon et al., 2012). The primary outcome measure was the Yale Global Tic Severity Scale, and the secondary outcomes measured included the Yale-Brown Obsessive Compulsive Scale, the Hamilton Depression Rating Scale, the Gilles de la Tourette Syndrome-Quality of Life Scale, and the Global Assessment of Functioning Scale. Follow-up occurred at 1 month and then at a mean of 14 months after surgery (range=4-30 months). Their data showed that of the 11 TS patients, 10 (91%) showed an improvement in tic severity soon after DBS. The patients showed a 48% reduction in motor tics, and a 56.5% reduction in phonic tics at the final

follow-up. Six patients (54.5%) had a >50% reduction, sustained for at least 3 months, and only 2 patients required ongoing drug therapy for tics post-DBS. The patients improved significantly on all secondary assays. Adverse outcomes included one patient who discontinued the DBS, two patients with increased anxiety, and 3 patients with hardware malfunction.

In 2012, a team of scientists in the Department of Neurosurgery at Baylor College of Medicine (Houston, TX) published their review of the literature through 2012 on the surgical techniques, DBS stimulation parameters, DBS outcomes, and stimulation target choices for TS patients ([Viswanathan et al., 2012](#)). Their search of the literature indicated that since the first application of DBS to TS patients in 1999, only 100 patients have been reported. The stimulated targets have varied widely, including the thalamic centromedian nucleus and substantia periventricularis, posteroventral globus pallidus internus, ventromedial globus pallidus internus, globus pallidus externus, anterior limb of the internal capsule, and the nucleus accumbens. The authors concluded that the field best needs a multi-center, randomized clinical trial plus a deeper understanding of TS neurobiology.

In 2012, scientists at the Tourette Center- IRCCS Galeazzi Hospital (Milano, Italy) published their study of 18 patients with severe and refractory Tourette Syndrome (TS) who underwent bilateral thalamic DBS ([Porta et al., 2012](#)). The initial surgical procedures and stimulation processes were published in 2008, and the 2-year follow-up was reported in 2009 ([Porta et al., 2009](#)). Here, the authors report their long-term (5-6 year) outcome assessment on the patient's tics, obsessional behaviors, anxiety, mood, and overall general health. Many of the GTS patients had secondary symptoms such as OCD, ADHD, anxiety, or depression. Only 4 patients had GTS with no other conditions, but their GTS improvement was the same as patients having additional disorders. The study used the Yale Global Tic Severity Scale (YGTSS) for measuring tics, the Yale Brown Obsessive Compulsive Scale (YBOCS) for OCD, the Strait Trait Anxiety Inventory (STAI) for anxiety, and the Beck Depression Inventory (BDI) for depression. At the 5-6 year follow-up, the DBS patients showed a significant reduction in tic severity ($p < 0.001$), and significant improvements in the secondary disorders of OCD ($p = 0.003$), anxiety ($p < 0.001$), and depression ($p < 0.001$). The DBS patients required less medication. The problems encountered in the long-term study included patient non-compliance, a few long-term complications, and differences in the opinions of the medical teams, surgical teams, and post-DBS patients as to their outcome/satisfaction with the procedures. The authors conclude that the field needs more controlled long-term clinical trials, and need to improve patient selection for DBS.

In 2012, scientists in the Department of Neurosurgery, CHRU Montpellier (Montpellier, France) published their study of a review of the literature from 1999 to 2012 on TS patients treated with DBS ([Saleh et al., 2012](#)). Their search uncovered 33 research articles treating 88 patients. The majority of the patients received thalamic DBS stimulation, while others received stimulation of the globus pallidus internus, internal capsule, or nucleus accumbens. The subthalamic nucleus was selected once. All target area caused positive results, but of different magnitudes. Only 14 patients exhibited the highest level (1) of improvement. The authors concluded that for TS patients, in view of the wide spectrum of secondary symptoms observed, that multiple networks may be involved, and multiple networks may need to be stimulated. The optimal electrode locations within the cortico-basal ganglia-thalamocortical circuits remain to be determined. Direct comparisons of the data between the various 33 studies was difficult due to the wide differences in patient numbers per target area, large protocol differences, and

differences in the quality of the reporting. The authors call for an increased number of large randomized controlled trials using standardized procedures.

In 2013, scientists at the Fundacion CENIT para la Investigación en Neurociencias (Buenos Aires, Argentina) showed that battery exhaustion in a DBS-treated Tourette's syndrome (TS) patient partially decreases the therapeutic effect (Piedimonte et al., 2013). Their 47-year-old patient was considered a candidate for DBS on the basis of prior resistance to treatments. The DBS target coordinates were determined by inversion recovery MRI. DBS electrodes were implanted bilaterally in the globus pallidus externus (GPe) and connected to the pulse generator in the same surgical procedure. No surgical complications were observed. The DBS stimulation caused a marked improvement of his symptoms. "The patient appeared to be satisfied with the surgery, perceiving a global tic reduction of approximately 80%" (Piedimonte et al., 2013). Initially before the operation the patient had an YGTSS score (tics) of 78, but 3 months after DBS initiation the patient saw a 45-point (55.7%) reduction in YGTSS score, and after 6 months of DBS saw a 55-point reduction (70.5%). The patient also saw a 75% improvement in anxiety symptoms and an 82.3% improvement in depression after 6-months. However, the patient's battery became exhausted after two years, and the patient showed a partial loss of therapeutic effect. So, the team concluded that, indirectly, their data confirms the beneficial action of the DBS treatment (the benefit went away immediately with DBS battery failure).

Bibliography for Tourette's Syndrome

Ackermans L, et al. (2011) Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain*, 2011; 134(pt 3): 832–844.

Cannon E, Silburn P, Coyne T, O'Maley K, Crawford JD, Sachdev PS (2012) Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome. *American Journal of Psychiatry*, 2012 Aug; 169(8): 860-866.

Flaherty AW, Williams ZM, Amirnovin R, Kasper E, Rauch SL, Cosgrove GR, Eskandar EN (2005) Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: technical case report. *Neurosurgery*, 2005 Oct; 57(4 Suppl): E403; discussion E403.

Kuhn J, Janouschek H, Raptis M, Rex S, Lenartz D, Neuner I, Mottaghy FM, Schneider F, Schaefer WM, Sturm V, Gründer G, Vernaleken I (2012) In vivo evidence of deep brain stimulation-induced dopaminergic modulation in Tourette's syndrome. *Biological Psychiatry*, 2012 Mar 1; 71(5): e11-13.

Maciunas RJ, et al. (2007) Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. *J Neurosurg*. 2007; 107(5): 1004–1014.

Makki MI, Govindan RM, Wilson BJ, Behen ME, Chugani HT (2009) Altered fronto-striato-thalamic connectivity in children with Tourette syndrome assessed with diffusion tensor MRI and probabilistic fiber tracking. *J Child Neurol*. 2009; 24(6): 669–678.

- Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, du Montcel ST, Yelnik J, Chéreau I, Arbus C, et al. (2008) Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *New England Journal of Medicine*, 2008 Nov 13; 359(20): 2121-2134.
- Martinez-Torres I, Hariz MI, Zrinzo L, Foltynie T, Limousin P (2009) Improvement of tics after subthalamic nucleus deep brain stimulation. *Neurology*, 2009; 72(20): 1787–1789.
- Martinez-Fernandez R, et al. (2011) Deep brain stimulation for Gilles de la Tourette syndrome: a case series targeting subregions of the globus pallidus internus. *Movement Disorders*, 2011; 26(10): 1922–1930.
- Neuner I, Podoll K, Lenartz D, Sturm V, Schneider F (2009) Deep brain stimulation in the nucleus accumbens for intractable Tourette's syndrome: follow-up report of 36 months. *Biological Psychiatry*, 2009 Feb 15; 65(4): e5-6.
- Piedimonte F, Andreani JC, Piedimonte L, Graff P, Bacaro V, Micheli F, Vilela Filho O (2013) Behavioral and motor improvement after deep brain stimulation of the globus pallidus externus in a case of Tourette's syndrome. *Neuromodulation*, 2013 Jan-Feb; 16(1): 55-58.
- Porta M, Brambilla A, Cavanna AE, Servello D, Sassi M, Rickards H, Robertson MM (2009) Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome. *Neurology*, 2009 Oct 27; 73(17): 1375-1380.
- Porta M, Servello D, Zanaboni C, Anasetti F, Menghetti C, Sassi M, Robertson MM (2012) Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. *Acta Neurochirurgica (Wien)*, 2012 Nov; 154(11): 2029-2041.
- Sachdev PS, Cannon E, Coyne TJ, Silburn P (2012) Bilateral deep brain stimulation of the nucleus accumbens for comorbid obsessive compulsive disorder and Tourette's syndrome. *BMJ Case Rep.* 2012; 2012. pii: bcr2012006579.
- Saleh C, Gonzalez V, Cif L, Coubes P (2012) Deep brain stimulation of the globus pallidus internus and Gilles de la Tourette syndrome: Toward multiple networks modulation. *Surgical Neurology International*, 2012; 3(Suppl 2): S127-S142.
- Servello D, Porta M, Sassi M, Brambilla A, Robertson MM (2008) Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. *J Neurol Neurosurg Psychiatry*, 2008; 79(2): 136–142.
- Servello D, et al. (2009) De novo and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: a multiple case report. *J Neurology*, 2009; 256(9):1533–1539.
- Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J (1999) Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet*, 1999, 353: 724.

Viswanathan A, Jimenez-Shahed J, Baizabal Carvallo JF, Jankovic J (2012) Deep brain stimulation for Tourette syndrome: target selection. *Stereotactic and Functional Neurosurgery*, 2012; 90(4): 213-224.

Welter ML, et al. (2008) Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Arch Neurol*. 2008; 65(7): 952–957.

Section Conclusion

The experiments discussed in this section of the Lit Review show that for specific types of disorders, DBS stimulations appear to significantly improve symptoms. The technique seems to be effective for its purpose, as a last resort for treatment-resistant cases of different movement and psychiatric disorders. Usually last resort treatments come with some degree of danger, and some studies reported here showed serious side-effects, including 5 deaths for one 2010 epilepsy study. However, most of the studies reported relatively mild, transient, and manageable side-effects. Another perk about DBS is it is completely reversible, and in the studies reported here any unwanted side-effects due to the DBS stimulation could be managed by slightly adjusting the current. And if a patient experienced negative symptoms from the stimulation, the current was simply switched off. Another advantage of DBS is that once the electrodes have been surgically implanted, it can work long-term, as long as the battery is changed every few years. The common location of the pulse generator near the collarbone makes for a relatively easy battery replacement.

Section-2: DBS Safety

Craig Barrett and Christopher Massar

Safety Introduction

As discussed in the previous sections of the Lit Review, deep brain stimulation (DBS) is a type of electrical stimulation delivered deep in the brain to treat a variety of motor and psychiatric disorders. In a surgical procedure, electrodes are implanted in the brain at locations depending on the disorder being treated. Wires lead to the neuro-stimulator device, which is usually implanted underneath the collarbone. High frequency stimulation can disrupt a circuit, while low frequency stimulation can stimulate a circuit. The most common use of DBS is to disrupt (attenuate) abnormally high signals present with specific disorders, especially for patients that have not responded to any standard types of therapy. However, in spite of the success seen with some DBS treatments (discussed in Section-1), DBS has safety issues that need to be addressed. The broad categories of safety issues include:

1. Patient History: DBS has a broad range of treatments, and the side-effects can vary depending on the patient's previous medical history, age, and severity of the medical condition(s) being addressed.

2. Surgical Problems: As with any surgical technique, some DBS problems arise during the surgical implantation of the electrodes in the brain. This is not trivial surgery, and requires a highly skilled team of neurosurgeons and support doctors. The surgical procedure can cause swelling, infection, pain, fatigue, or bleeding. And the long-term presence of the implants can cause an immune Foreign Body Reaction (FBR) where the integrated material can retard the healing process, or the implant can become rejected.

3. DBS Electrical Stimulation Problems: The DBS electrical stimulation itself can cause problems, such as increased patient anxiety, depression, uncontrollable mood swings, muscles tightness, numbness and tingling, speech problems, and balance issues. With transcranial direct current stimulation (tDCS), this is not a surgical procedure so there are no surgical side-effects, but some problems have been associated with differing modes of stimulation (anodal, cathodal or sham).

4. Area of Stimulation: The area in which DBS is applied can increase the risks of some side-effects, while decreasing the risk of others. Risks have been identified with several locations including: the subthalamic nucleus (STN), the Globus pallidus, thalamic area, and the Pedunculopontine nucleus (a newer form of DBS). Subthalamic nucleus DBS is one of the most effective forms of DBS, and is often used to treat motor disorders; but it has been associated with changes in mood such as depression and hypomania. DBS stimulation of the Globus pallidus has been used to target the effects of Parkinson's disease, dystonia, and Tourette's syndrome; it may have fewer side-effects but it is not as effective as subthalamic DBS. Thalamic DBS is used to target patients with tremors and rigidity, however the risks associated with this area include voice, speech and swallowing complications.

DBS Side-Effects and Parkinson's

In an early study, scientists in the Department of Clinical and Biological Neurosciences, Joseph Fourier University (Grenoble, France) investigated the effects of bilateral DBS stimulation of the subthalamic nucleus in 3 patients with advanced PD ([Limousin et al., 1995](#)). On the positive side, 3-months post-surgery the scores of daily living activities improved 58-88%, and motor scores by 42-84%. But one patient was confused for 2 weeks post-surgery, and another developed neuropsychological impairment (hallucinations) related to a thalamic infarction (although this improved over 3 months). One patient showed an increase in involuntary movements (ballism) caused by the stimulation, but the movements ceased when the stimulation was turned off ([Limousin et al., 1995](#)).

In 2008, scientists at the National Institute of Neurological Disorders and Stroke, NIH (Bethesda, MD) investigated the rates of suicide in PD patients receiving DBS ([Voon et al., 2008](#)). The authors report the data of their international multi-center survey of advanced PD patients stimulated in the subthalamic nucleus, focusing specially on identifying factors associated with suicide attempts. On the suicide questions, 55 of 75 centers participated. Their data showed that the completed suicide percentage was 0.45% (24/5311), and the attempted suicide percentage was 0.90% (48/5311). The suicide rates in the first post-operative year (0.26%, 263/100,000/year) were higher than expected for the age, gender, and country adjusted controls ($P < 0.001$), and also remained higher in the 4th postoperative year (0.04%, 38/100,000/year) ($P < 0.05$). The variables that correlated with suicide attempts were: postoperative depression ($P < 0.001$), being single ($P = 0.007$), and a previous history of impulse control or the use of medicine to combat compulsions ($P = 0.005$). Lesser correlates were for younger disease onset ($P < 0.05$), and previous suicide attempts. Completed suicides were associated with postoperative depression ($P < 0.001$). The authors concluded that postoperative depression should be carefully assessed and treated in DBS PD patients ([Voon et al., 2008](#)).

In 2010, a study was published by scientists in the Department of Neurology at the Movement Disorders Center, University of Cincinnati (Ohio) showing that Parkinson's patients receiving stimulation to the subthalamic nucleus (STN-DBS) showed a much higher quality of life when the DBS was applied earlier in the disease than later ([Espay et al., 2010](#)). The authors applied their study to a cohort of 22 STN-DBS PD patients and 21 non-STN-DBS PD patients. The data showed that early STN-DBS was superior, with a gain of 2.5 quality-adjusted life years (22.3) relative to late DBS (19.8). In Monte Carlo simulations, early STN DBS was preferred in 69% of 5,000 test runs. Their data also showed that the initial surgery can result in complications in as many as 25% of the patients, which factors into the decline of quality of life. Infections were also noted in 1.8-6.3% of the patients, which in the brain can cause irreparable damage.

In 2010, scientists in the Department of Neurosurgery, Second Military Medical University (Shanghai, China) published their findings of hardware-related complications in PD DBS patients ([Hu et al., 2010](#)). The authors performed a retrospective analysis of PD patients who received DBS in their institution over a 9-year period, from March 2000 to December 2008.

They reviewed the data from 161 patients (85 male and 76 female) for complications, and found 25 cases of surgical and hardware-related complications in 24 patients. The complications included confusion (the most common side-effect) (11 cases, 6.83%), asymptomatic intracranial hemorrhage (1 case, 0.62%), electrode misplacement (2 cases, 1.24%), infection of the subcutaneous pocket receiving the pulse generator (1 case, 0.62%), skin erosion (2 cases, 1.24%), pulse generator seroma (fluid build-up) formation in 6 cases (3.72%), and device malfunction (1 case, 0.62%). They identified no permanent neurological deficits. The authors concluded that hardware-related complications could be reduced by increasing the experience of the surgeons, and closely following standard operative surgical routines.

In another 2010 study, a team of scientists at the Université de Grenoble (Grenoble, France) studied the effects of bilateral DBS stimulation of the pedunculopontine nucleus on 6 PD patients with gait disturbances (Ferraye et al., 2010). Gait problems are frequent and disabling in advanced PD, and this type of side-effect responds poorly to standard treatments. The patients tested here not only responded poorly to the PD drug Levodopa, but also responded poorly to DBS stimulation of the subthalamic nucleus, so DBS stimulation of a different area (the pedunculopontine nucleus) was tested. Their data showed that at 1-year post-surgery, the DBS improved (decreased) the duration of freezing episodes, and decreased falls related to freezing. Of the 6 patients tested, one patient showed major improvements, 4 patients showed moderate improvements, and one patient showed a global worsening. Although no serious adverse events were reported, during surgery one patient could not withstand the stimulation so it was discontinued, and at 1-year, one patient showed akinesia and breathing difficulties. Additionally, in four of the patients the DBS dosage had to be decreased due to the presence of leg or orofacial dyskinesias, but these were manageable. Patient number four initially had two epileptic seizures following electrode implantation, but he quickly recovered when the current was lowered. Additionally in the study the authors warned of the risk of bleeding in the brain due to implantation of the stereotactic electrodes, which can be lethal, but they had no problems. The study concluded that more studies are needed to find the most precise areas to stimulate, and to lower the observed side-effects (Ferraye et al., 2010).

In 2011, a study done at the University of Florida Center for Movement Disorders and Neurorestoration (Gainesville, Florida) on 110 PD patients (Okun et al., 2011), showed that PD patients with a preoperative depression history had higher Beck Depression Inventory scores after DBS than patients without a history of depression, but because the patients began with greater levels of depression, the data by itself does not prove that DBS caused the depression. In a related study, there was no clear indication of whether DBS benefited PD patients suffering from depression (Gökbayrak et al., 2014).

Another study was done in 2011 at the Movement Disorders Center in the Department of Neurosurgery, University of Florida (Gainesville, FL) where the scientists investigated whether deep brain stimulation (DBS) of the subthalamic nucleus (STN), the globus pallidus internus (GPi), and/or the ventralis intermedius thalamic nucleus (Vim) in PD patients made the patients angrier (Burdick et al., 2011). The authors analyzed a total of 322 DBS procedures for: STN (n=195), Vim (n=71), and GPi (n=56). Their data showed that at 1-3 months post-surgery, the STN and GPi groups were significantly angrier ($p=0.004$), and the GPi patients were significantly more confused compared to STN patients ($p=0.016$). For every year added of

disease progression, the VAMS anger score increased by 0.24 ($p=0.022$). The anger score was not related to patient surgery side, handedness, gender, ethnicity, education, or age at surgery. The authors concluded that STN and GPi DBS for PD patients were associated with significantly higher anger scores, compared to Vim for essential tremor.

A 2012 study showed that the side of the brain being stimulated in PD patients had an effect (Skodda, 2012). The study showed that stimulation on the left side of the brain caused an improvement in 50% of the patients, but 36% of the PD patients showed deterioration, including negative effects on speech articulation and intellect. Higher voltage DBS was also determined to have a higher risk of speech deterioration (Skodda, 2012).

Also in 2012, scientists in the Department of Neurology, University of Colorado Denver (Aurora, CO) investigated the prevalence of fatigue following DBS in PD (Kluger et al., 2012). This study was the first to focus on some of the non-motor symptoms in PD. The team recruited 44 PD patients, and at 1-year post-surgery administered a Fatigue Severity Scale survey (FSS), the Parkinson's Disease Questionnaire (PDQ-39), the Beck Depression Inventory, the Beck Anxiety Inventory, and a neuropsychological battery. Their results found that 58% of the patients had moderate to severe fatigue, which was significantly associated with quality of life, depression, and anxiety. Depression preoperatively was a predictive factor of fatigue post-operatively.

In 2014, a study led by scientists in the Department of Psychology, University of Rhode Island (Kingston, RI) critically evaluated the data from seven recent clinical trials of Parkinson's disease (PD) patients on the ability of DBS to alleviate non-motor symptoms, such as depression (Gökbayrak et al., 2014). Their review found that DBS effectiveness as a treatment for depression in PD patients was mixed, likely due to wide variations in the anatomical placement of electrodes and differences in the methods used. The authors concluded that larger, more controlled clinical studies are needed. They also found that the patient's pre-surgery medical conditions can affect the outcomes and observed side-effects. For example, speech performance typically declines as PD advances, and the DBS generally improved that feature, but other symptoms increased including abnormalities in speed and repetition (Gökbayrak et al., 2014).

In recent 2016 studies, conducted in the Department of Neurosurgery, Städtisches Klinikum Karlsruhe (Karlsruhe, Germany) (Cyron, 2016), built upon the earlier observations of DBS side-effects, and reported alarming psychiatric disturbances, ranging from hypomania to suicidal thoughts. Some patients even attempted suicide. Hypomania can become dangerous if the patient shows an inability to generate a clear sense of judgement and are not aware of their capabilities. To outsiders, the patient's actions are viewed as reckless and potentially dangerous. Over time, hypomania can evolve into an unstable emotional state which can lead to more aggressive or depressive tendencies, making the patient more difficult to care for (Cyron, 2016).

Side-Effects and DBS Timing

In 2016, scientists in the Department of Neurosurgery at the Tazuke Kofukai Medical Research Institute (Tokyo) provided an overview of issues associated with DBS treatments of dyskinesia and dystonia (Toda et al., 2016). The authors identified several important side-effects

that have arisen in this category of patients, including: the timing of the DBS intervention relative to the onset of the disease, the exact selection of the stimulation target in the brain, and the occurrence of refractory symptoms. From their review of patients in this category, approximately 18% suffered from severe adverse events during surgery and DBS stimulation. The most serious events were suicides, while other noted concerns were decreased verbal fluency, postural instability, gait freezing, increased likelihood of falls, and problems with the initial surgical procedure. In older patients, the side-effects were generally more frequent and severe than in younger patients (Toda et al., 2016).

DBS Side-Effects for Transcranial Direct Stimulation (tDCS)

Transcranial direct-current stimulation (tDCS) is progressively being used as a non-surgical option for DBS to treat a variety of disorders or to alter neuronal plasticity. In 2007, a team in the Department of Clinical Neurophysiology, Georg-August University (Göttingen, Germany) summarized various adverse effects of tDCS in 567 sessions performed in their labs on cortical areas (occipital, temporal, parietal) over a two year period (Poreisz et al., 2007). Their questionnaire on outcomes was completed by 102 patients with the following characteristics: healthy subjects (75.5%), migraine patients (8.8%), post-stroke patients (5.9%), and tinnitus patients (9.8%). The side-effects reported were (in descending order): a mild tingling sensation (70.6%), moderate fatigue (35.3%), a light itching sensation under the stimulation electrodes (30.4%), headache (11.8%), nausea (2.9%), and insomnia (0.98%). The team concluded that the side-effects reported for tDCS were overall relatively minor in healthy humans or patients (Poreisz et al., 2007).

DBS Side-Effects for Obsessive Compulsive Disorder (OCD)

In a 2006 study, scientists in the Department of Psychiatry and Human Behavior, Brown Medical School (Providence, RI) analyzed 10 patients with highly-resistant obsessive-compulsive disorder (OCD) stimulated by DBS in the anterior commissure extending into adjacent ventral capsule/ventral striatum (VC/VS) (Greenberg et al., 2006). 8 of the 10 patients were followed for at least 36 months. The DBS treatment lowered OCD symptoms (as measured by the Group Yale-Brown Obsessive Compulsive Scale, YBOCS) from 34.6 ± 0.6 at baseline (severe) to 22.3 ± 2.1 (moderate) at 36 months ($p < 0.001$). Their Global Assessment of Functioning scores improved ($p < 0.001$), as did depression, anxiety, self-care, independent living, and work, school, and social functioning. Surgical side-effects included an asymptomatic hemorrhage, a single seizure, and a superficial infection. Psychiatric adverse effects included transient hypomanic symptoms. The OCD and depression immediately worsened when the DBS battery ran out of power, but this helps to prove that the DBS stimulation was providing the improvement.

In 2010, scientists in the Department of Neurology at Wake Forest University (Winston-Salem, NC) reported some of their unexpected psychiatric side-effects from their previous experiments with patients with obsessive-compulsive disorder (OCD) (Haq et al., 2010). The authors stated that during a multiyear DBS experiment with OCD patients, they encountered several unanticipated DBS stimulation-induced psychiatric side-effects. The authors then

describe in detail the case of a young woman treated for OCD with DBS of the anterior limb of the internal capsule and nucleus accumbens region, who subsequently showed a manic episode.

In another study done in 2010, scientists in the Department of Psychiatry, University of Florida (Gainesville, FL) reported their findings of panic and fear induced in one OCD patient by DBS ([Shapira et al., 2006](#)). DBS of the anterior limb of the internal capsule and nucleus accumbens region was undertaken to treat a 52 year old man with treatment-refractory OCD. They noticed that DBS stimulation at the distal contact elicited a panic attack, where the patient felt flushed, hot, and fearful. His heart rate increased from 53 to 111. The panic began immediately after turning the device on, and immediately ceased when turned off. The authors conclude the panic attack may have resulted from activation of the limbic (fear) and autonomic networks.

DBS Side-Effects for Treatment-Resistant Depression (TRD)

Major depression is a disorder that affects patients with their quality of life, typically treated with medication and psychotherapy, but studies show that stimulation may have considerable benefits.

In 2012, scientists at the University of British Columbia (Vancouver) and the Royal College of Surgeons Medical School (Dublin, Ireland) wrote a letter to the *Journal of Neurosurgery* describing a DBS case for treatment-resistant depression (TRD) in which the patient attempted suicide following two unknown deactivations of her DBS pulse generator ([Howard et al., 2012](#)). On the first occasion, the woman attempted suicide. And on the second occasion, the deactivation provoked a depressive relapse with active suicidal thoughts. The authors concluded that this is the first report of suicidality prompted by discontinuation of therapeutic DBS to their knowledge, and they recommend carefully monitoring this particular patient population as they are already highly susceptible to suicide.

In 2014, a team of scientists at three locations, including the Department of Psychiatry and Psychotherapy, University Hospital (Bonn, Germany), the Departments of Psychiatry and Mental Health, The Johns Hopkins University (Baltimore, MD), and the Department of Stereotactic and Functional Neurosurgery, University Hospital (Freiburg, Germany) published their review of the published research on DBS stimulation for treatment-resistant depression (TRD) ([Schlaepfer et al., 2014](#)). They report that several uncontrolled studies with a relatively small number of TRD patients have been performed for about a decade, stimulated in different areas of the brain, and have shown clinically relevant antidepressant effects in about half of the patients. But on the downside, DBS procedures are associated with surgical risks (hemorrhage) and psychiatric complications (suicidal attenuation and hypomania), and have high dollar costs. The side effects of the DBS stimulation itself (which occurred within minutes to hours following DBS stimulation) included: erythema (redness), increase in anxiety, agitation, and mood changes. Battery depletion caused unexpected aggravation. Some studies noted suicide and suicide attempts, despite close monitoring is prior to stimulation, during stimulation frequency changes, and upon follow-up changes. Unfortunately for these serious TRD patients, the quality of life remains relatively low, even with the DBS health benefits, so some scientists consider

DBS a “halfway technology”, a term coined by Lewis Thomas to depict “therapies that only ameliorate but do not eliminate a disease condition” (Schlaepfer et al., 2014, page 1311). The authors concluded that better animal models for OCD are needed for pre-clinical testing, and that for human studies larger sample sizes, longer follow-up periods, and double blinded strategies are needed to draw final conclusions (Schlaepfer et al., 2014).

DBS Side-Effects for Tourette’s

With Tourette’s syndrome (TS), few large-scale clinical studies have been performed due to the relatively low numbers of qualifying patients, a lack of standardized protocols between medical centers (not allowing data mergers), and less research money than for Parkinson’s disease (Servello, 2016). Compared to Parkinson’s patients, relatively few TS patients qualify for clinical DBS studies, because DBS is the “last therapeutic option and needs to be balanced against the severity of the disease, the natural evolution of the disease, and the disease-related morbidity risks”. So, relatively few DBS studies have been performed on TS patients compared to Parkinson’s patients. So, TS DBS clinical studies are few, and the field needs more of them. Although the author acknowledged that DBS improved tic episodes in TS patients, he stated that up to 29% of TS patients suffered from adverse effects of the DBS (Servello, 2016).

Section-2 Conclusion

While DBS stimulation has helped improve the symptoms for hundreds of patients with various motor and psychiatric disorders, the technique is associated with some side-effects. The type and severity of the side-effect varies depending on the overall health and age of the patient, when the DBS is applied relative to the onset of the disorder (earlier is better), problems with the surgical implantation of the electrodes and neuro-stimulator (swelling, infection, pain, fatigue, bleeding, foreign body reaction), problems caused by the electrical stimulation itself (increased anxiety, depression, mood swings, numbness, tingling, speech problems, balance issues), and problems associated with the specific area being stimulated (the most serious are successful suicides and suicide attempts, which are especially associated with DBS Parkinson’s studies and treatment-resistant depression). But as with any medical technique, the DBS side-effects must be weighed against the severity of the disorder being treated. In the vast majority of patients, the side-effects were transient, were considered medically “mild”, and could usually be managed with standard pharmacologic treatments or by adjusting the DBS current, while allowing the patient to receive the benefits of the treatment.

Section-2 Bibliography

Burdick AP, Foote KD, Wu S, Bowers D, Zeilman P, Jacobson CE, Ward HE, Okun MS (2011) Do patient's get angrier following STN, GPi, and thalamic deep brain stimulation. *Neuroimage*, 2011 Jan; 54 Suppl 1: S227-S232.

Cyron D (2016) Mental Side Effects of Deep Brain Stimulation (DBS) for Movement Disorders: The Futility of Denial. *Frontiers in Integrative Neuroscience*, 2016 Apr 20; 10: 17.

Espay AJ, Vaughan JE, Marras C, Fowler R, Eckman MH (2010) Early versus delayed bilateral subthalamic deep brain stimulation for Parkinson's disease: a decision analysis. *Movement Disorders*, 2010 Jul 30; 25(10): 1456-1463.

Ferraye MU, Debû B, Fraix V, Goetz L, Ardouin C, Yelnik J, Henry-Lagrange C, Seigneuret E, Piallat B, Krack P, Le Bas JF, Benabid AL, Chabardès S, Pollak P (2010) Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain*, 2010 Jan; 133(Pt 1): 205-214.

Gökbayrak NS, Piryatinsky I, Gavett RA, Ahmed OJ (2014) Mixed effects of deep brain stimulation on depressive symptomatology in Parkinson's disease: a review of randomized clinical trials. *Frontiers in Neurology*, 2014 Aug 11; 5: 154.

Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA (2006) Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology*, 2006 Nov; 31(11): 2384-2393.

Haq IU, Foote KD, Goodman WK, Ricciuti N, Ward H, Sudhyadhom A, Jacobson CE, Siddiqui MS, Okun MS (2010) A case of mania following deep brain stimulation for obsessive compulsive disorder. *Stereotactic and Functional Neurosurgery*, 2010; 88(5): 322-328.

Howard A, Honey CR, Hurwitz TA, Ilcewicz-Klimek M, Woo C, Lam RW, Berman N (2012) Deep brain stimulation interruption and suicidality. *Journal of Neurosurgery*, 2012 Feb; 116(2): 467-468.

Hu X, Jiang X, Zhou X, Liang J, Wang L, Cao Y, Liu J, Jin A, Yang P (2010) Avoidance and management of surgical and hardware-related complications of deep brain stimulation. *Stereotactic and Functional Neurosurgery*, 2010; 88(5): 296-303.

Kluger BM, Parra V, Jacobson C, Garvan CW, Rodriguez RL, Fernandez HH, Fogel A, Skoblar BM, Bowers D, Okun MS (2012) The prevalence of fatigue following deep brain stimulation surgery in Parkinson's disease and association with quality of life. *Parkinson's Disease*, 2012; 2012: 769506.

Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet*, 1995 Jan 14; 345(8942): 91-95.

Okun MS, Wu SS, Foote KD, Bowers D, Gogna S, Price C, Malaty I, Rodriguez RL, Jacobson CE, Ward H (2011) Do stable patients with a premorbid depression history have a worse outcome after deep brain stimulation for Parkinson disease? *Neurosurgery*, 2011 Aug; 69(2): 357-360.

Poreisz C, Boros K, Antal A, Paulus W (2007) Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, 2007 May 30; 72(4-6): 208-214.

Schlaepfer TE, Bewernick BH, Kayser S, Hurlemann R, Coenen VA (2014) Deep brain stimulation of the human reward system for major depression--rationale, outcomes and outlook. *Neuropsychopharmacology*, 2014 May; 39(6): 1303-1314.

Servello (2016) Evaluating Risk and Benefits of Deep Brain Stimulation for Treatment-Refractory Tourette syndrome. *Neurosurgery*, 78(5): E764-765.

Shapira NA, Okun MS, Wint D, Foote KD, Byars JA, Bowers D, Springer US, Lang PJ, Greenberg BD, Haber SN, Goodman WK (2006) Panic and fear induced by deep brain stimulation. *Journal of Neurology, Neurosurgery, and Psychiatry*, 2006 Mar; 77(3): 410-412.

Skodda (2012) Effects of Deep Brain Stimulation on Speech Performance in Parkinson's disease. *Handawi Publishing Corporation*, Vol 2012, 1-10.

Toda H, Saiki H, Nishida N, Iwasaki K (2016) Update on Deep Brain Stimulation for Dyskinesia and Dystonia: A Literature Review. *Neurologia Medico-Chirurgica (Tokyo)*, 2016 May 15; 56(5): 236-248.

Tsai (2016) Neurophysiological comparisons of subthalamic deep-brain stimulation for Parkinson's disease between patients receiving general and local anesthesia. *Tzu Chi Medical Journal*, xxx. 1-5.

Voon V, Krack P, Lang AE, Lozano AM, Dujardin K, Schüpbach M, D'Ambrosia J, Thobois S, Tamma F, Herzog J, Speelman JD, Samanta J, Kubu C, Rossignol H, Poon YY, Saint-Cyr JA, Ardouin C, Moro E (2008) A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain*, 2008 Oct; 131(Pt 10): 2720-2728.

Section-3: DBS Alternatives and Advances

Wei Chen

Previous sections of the Lit Review addressed some of the applications of deep brain stimulation (DBS) for improving the symptoms of various motor and psychiatric disorders. The DBS technique has been performed for decades now, with various levels of success, and is especially useful for treatment-refractory disorders when the patient has no other options. The previous sections also addressed some of the DBS safety issues that result from the surgical technique used to implant the electrodes and neuro-stimulator, or that result from application of the electrical current itself. The technique has shown statistically significant successes, but scientists are always seeking to improve the technique. The purpose of this section of the Lit Review is to focus on some of the recent trends in the DBS field. The advances include the development of several types of non-surgical (non-invasive) transcranial stimulation options applied to the skin, and the development of closed-loop stimulators that respond to abnormal brain currents to apply a correcting current.

Transcranial Direct Current Stimulation (tDCS)

tDCS was the first type of trans-cranial stimulation developed. It uses a device placed on the head with electrodes placed outside the brain to deliver current (in this case direct current) to the brain to cause an effect. Some studies indicate the technique can improve learning, memory, alertness, and depression. Because it is non-invasive, some scientists argue it could easily be used to intervene early in mental disorders. The device uses only 1-2 milliamps which can easily be delivered by a 9 volt battery. Vastly expanding its use, the technique is easy to implement at home by untrained individuals, and several companies sell the head devices online. This means that the tDCS field has relatively little safety oversight.

tDCS consists of applying direct current over the scalp, usually delivered by a small battery-driven constant current stimulator. The electrodes of different polarities are in contact with the skin. The electrodes are made of conductive rubber and are put in saline-soaked synthetic sponges to prevent chemical reactions at the contact point between electrode and skin. Most of the electrodes used in human studies have a size of 25–35 cm², which results in a current density of 0.03–0.08 milliAmperes (mA) when stimulated at 1–2 mA. In order to focus the effects of the electrode, some authors recommend a smaller electrode size. Making the opposite electrode larger makes it functionally less active and enhances the selectivity of its opposite electrode.

The mechanism of how tDCS works is unknown, but some studies indicate that neurons located near the anode are more likely to fire, while neurons near the cathode are less likely to fire. However, it is difficult to target a specific region of the brain using this technique.

tDCS has been shown to affect moods, pain, and cognitive functions. The idea of treating mood disorders with tDCS is not new. Aldini first used this technique in 1804 to treat

melancholic patients successfully. And when tDCS returned in the 1960s, scientists in England (Costain et al., 1964) conducted a controlled double-blind trial with 24 depressed patients. The anode was placed over each eyebrow and the cathode was placed on the leg, and a current of 0.25 mA was delivered for several days, each session lasting for 8 hours. The authors reported an antidepressant effect of the stimulation, as indicated by psychiatrists' and nurses' ratings, as well as the patient's self-ratings.

In a 2006 study (Fregni, et al., 2006a) scientists investigated the effects of repeated stimulation on major depression. tDCS stimulation with bilaterally attached electrodes at the fronto-cortical sites and on the mastoids, led to an improvement of mood after stimulation during wake intervals and during sleep. In a controlled, randomized double-blind trial, they treated 10 patients with anodal stimulation of the left DLPFC. They provided a total of 5 sessions, distributed over 9 days. The scores in the Beck Depression Inventory and the Hamilton Depression Rating Scale in the treatment group decreased significantly, compared to their baseline scores.

In another clinical population, scientists at the Harvard Center for Non-invasive Brain Stimulation (Fregni et al., 2006b) studied patients with pain after traumatic spinal cord injury. Their data showed therapeutic effects of anodal tDCS delivered over the M1 area. The treatment procedure included 20 min of 2 mA tDCS, for 5 consecutive days. For patients with symmetric pain on both body sides, the anode was placed over the dominant left M1, while for those patients with asymmetric pain it was placed over the contralateral M1. Significant reductions were obtained in pain rating intensity after 5 sessions. This beneficial effect did not vary with changes in anxiety or depression during the treatment.

The same team at Harvard also used tDCS in patients with fibromyalgia (Fregni et al., 2006c). Fibromyalgia is a chronic disease with pain in all areas of the body, generalized weakness, neurological symptoms, attention and sleep deficits, chronic fatigue, and a general reduction of physical and mental capacities. Two different tDCS conditions were compared: anodal tDCS of the primary motor cortex (same application procedure as Fregni, Boggio, Lima, et al., 2006) and anodal tDCS of the left DLPFC, as well as sham stimulation over M1. The greatest improvements were seen for anodal M1-tDCS, which agrees with the findings reviewed above. Scientists in the Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil (Roizenblatt et al., 2007) also studied fibromyalgia patients, and investigated the effects of anodal M1-tDCS (primary motor cortex) and anodal DLPFC-tDCS on sleep and pain in fibromyalgia patients. As with the other studies, the best data was obtained with M1-tDCS, where they observed an increase in sleep efficacy and an improvement in clinical parameters.

Scientists in the Department of Clinical Neurophysiology, Georg-August University, Göttingen, Germany (Chadaide et al., (2007) investigated the effects of tDCS on migraine headaches. Migraine results in some cases from an over-excitability of the visual cortex. This excitability can be assessed by measuring altering levels of phosphine thresholds. Using tDCS, the authors revealed changes in such phosphene thresholds; anodal tDCS had the highest impact in migraine patients with aura, showing a decrease in cortical excitability, while cathodal tDCS showed no effect in migraine patients with or without aura. In healthy subjects cathodal tDCS increased the phosphene threshold, which indicates a reduction in cortical excitability.

In 2008, scientists in the Department of Clinical Neurophysiology at the University of Göttingen (Germany) published their summary through 2008 of the tDCS technique (Nitsche et al., 2008). The authors noted that the effects of weak electrical currents on the brain and neuronal function were first described decades ago, so tDCS is not a recent approach, however the use of homemade tDCS devices is recent and has been reintroduced as a noninvasive technique to alter brain cortical activity. The authors summarize the findings of several experiments showing that tDCS of different cortical areas alters perceptual, cognitive, and behavioral functions, and can induce beneficial effects in some brain disorders. Direct current was first used on rats, and demonstrated that weak direct currents when delivered by intracerebral or epidural electrodes, induce cortical excitability which can be stable long after the end of the current stimulation. The article also mentions that the long-lasting cortical effects are dependent on new protein synthesis and are accompanied by modifications of intracellular levels of cAMP and Ca⁺⁺, which also function in long-term potentiation (LTP) and long-term depression (LTD).

Other scientists (Boggio et al., 2008) reported tDCS stimulation effects lasting for 4 weeks after 10 sessions of anodal stimulation over the left DLPFC in 40 medication-free patients suffering from major depression. A single session of anodal tDCS of the left DLPFC combined with cathodal stimulation of the fronto-polar cortex improved the performance in 26 patients with major depression, but only for pictures containing positive emotions. No significant correlation with mood changes occurred after 10 treatments with tDCS. The authors conclude that the left DLPFC plays a role in the processing of positive emotions, but that the effects of tDCS on cognition and mood in major depression are independent of each other.

With respect to using tDCS to help alleviate pain, scientists at the Department of Clinical Neurophysiology, Georg-August University, Göttingen, Germany (Antal et al., 2008) demonstrated beneficial effects on acute pain perception after tDCS was applied over the somatosensory cortex in 10 healthy subjects. The effects on pain perception were assessed in terms of pain intensity ratings, and with EEG components that were related to the induction of pain by laser stimulation. Only cathodal tDCS showed significant effects (behavioral and EEG), while anodal and sham tDCS were ineffective. Moreover, differential effects on pain perception in healthy subjects arising from different tDCS stimulation sites were reported by Boggio et al. (2008a). Three different application conditions with anodal and cathodal tDCS were investigated: over the primary M1, DLPFC, and the occipital cortex (V1). The perception threshold and the pain threshold evoked by peripheral electrical stimulation of the right index finger were measured as outcomes. As with Antal et al. (2008), here the greatest effects were found after anodal stimulation of M1 (the motor cortex in the hemisphere related to the stimulated finger), a marginal effect with DLPFC tDCS, and no effect of V1 stimulation.

In 2009, scientists at the Brain Stimulation Unit, National Institute of Neurological Disorders and Stroke, NIH (Koenigs et al., 2009) re-examined the technique of bilateral frontal tDCS, using an extra-cephalic electrode, in 21 healthy individuals. They concluded that it had no effect on emotional affect, arousal, emotional state, emotional decision-making, or psychomotor functions.

With respect to tDCS improving cognitive functions, several studies show improving functions, while others show inhibitory effects. [Kincses et al. \(2004\)](#) demonstrated that anodal, but not cathodal, stimulation of the left prefrontal cortex improved learning. And bilateral tDCS over the left or the right DLPFC (with the cathode over the contralateral DLPFC) reduced risk-taking behavior. In a related study, [Beeli et al. \(2016\)](#) recently found that anodal tDCS over the left and the right DLPFC (with the cathode over the ipsilateral mastoid) evoked more cautious driving in normal subjects placed in a driving simulator. [Marshall et al. \(2004\)](#) investigated the effects of tDCS, delivered during sleep on verbal memory. They showed that bilateral anodal tDCS at fronto-cortical electrode sites during sleep periods rich in slow wave sleep improved the retention of word pairs. This was not observed during wakefulness. But on the negative side, intermittent bilateral tDCS at fronto-cortical electrode sites during a modified Sternberg task impaired response selection and preparation ([Marshall et al., 2005](#)). And [Ferrucci et al. \(2008a\)](#) showed that anodal and cathodal tDCS over the cerebellum disrupted the practice-dependent improvement in reaction times in a verbal working-memory task.

In a clinical study with patients suffering from Alzheimer's disease, [Ferrucci et al. \(2008b\)](#) tested the effects of tDCS on a word recognition memory task. Current was delivered bilaterally by two direct current stimulation devices, one electrode of each device was placed over the temporo-parietal areas and the other electrodes over the right deltoid muscle. Anodal stimulation improved, whereas cathodal stimulation decreased, memory performance in the patients. [Boggio et al. \(2009\)](#) also showed positive effects of tDCS on a memory task in patients with Alzheimer's disease. Anodal stimulation over the left DLPFC, as well as over the left temporal cortex, improved the performance in a visual recognition memory task. However, since the second electrode was placed over the right supraorbital area, the improvements might also be the result of the stimulation of this area.

In 2009, scientists at the Max Planck Graduate School of Neural & Behavioral Sciences, University of Tuebingen (Germany) published their data that tDCS enhances planning ability ([Dockery et al., 2009](#)). Executive functions such as planning ability are thought to involve the brain's dorsolateral prefrontal cortex, so the authors examined the effects of tDCS (1 mA, 15 min) of the left dorsolateral prefrontal cortex on planning function in 24 healthy volunteers. The team obtained complex information depending on whether the stimulation was cathodal or anodal. Cathodal tDCS improved performance when applied during acquisition and early memory consolidation stages, but not in the later training session. In contrast, anodal tDCS enhanced performance when applied in the later sessions. Their data indicate that both anodal and cathodal tDCS can improve planning performance, in different ways depending on the time of the stimulation. The improved performance was also seen in follow-up trainings at 6-months and 1-year.

In 2009, scientists in the Human Cortical Physiology Section and Stroke Neuro-Rehabilitation Clinic, National Institute of Neurological Disorders and Stroke, National Institutes of Health (Bethesda, MD) investigated the effects of tDCS on enhancing skill acquisition for a motor skill task ([Reis et al., 2009](#)). Motor skills usually take weeks to months to acquire, and diminish over time in the absence of continued practice. Healthy subjects practiced over 5 consecutive days while receiving tDCS over the primary motor cortex (M1). The authors assessed the effects of anodal (relative to sham) tDCS both within the same day of stimulation, and between days. Anodal tDCS was found to improve the skill acquisition compared to sham,

and did not affect the rate of forgetting at a 3-month follow-up. The authors conclude that tDCS may hold promise for the rehabilitation of brain injury.

In 2010, scientists in the Department of Experimental Psychology and Oxford Centre for Functional MRI of the Brain, University of Oxford (Oxford, UK) published the results of their experiment to determine whether tDCS of the parietal lobe improves numerical abilities (Cohen et al., 2010). The authors estimate that approximately 20% of the population exhibits moderate to severe numerical disabilities, which can decrease further with stroke or degenerative diseases. tDCS can selectively inhibit or excite neuronal populations by either modulating GABAergic activity (anodal stimulation) or glutamatergic activity (cathodal stimulation). So the authors used tDCS of the parietal lobe during numerical learning tasks. They trained subjects for 6 days with artificial numerical symbols, and found that the tDCS, depending on the polarity stimulated (anodal or cathodal) either enhanced or impaired the number processing. And the improvement was still present 6-months after training.

In 2015, scientists in the Departments of Psychiatry and Biomedical Engineering at the University of North Carolina at Chapel Hill, (Chapel Hill, NC) published their experiments on tDCS, showing that the technique actually *decreased* performance on the WAIS-IV intelligence test (Sellers et al., 2015). The authors point out that due to the conflicting evidence on the efficacy of tDCS to modulate performance on cognitive tasks, they implemented the first randomized, double-blind, sham-controlled clinical study on the effects of tDCS on a variety of cognitive processes. The study used 41 healthy adult participants who completed the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) as a baseline measure, and then at least one week later received either bilateral tDCS (2 mA at each anode for 20 min) or a sham type of tDCS delivered for a much shorter time (2 mA for 40 s). Their data showed that frontal tDCS *diminished* improvement on specific metrics of the WAIS-IV, and raises questions about the effectiveness of tDCS in cognitive enhancement (Sellers et al., 2015).

Supporting this finding of lack of tDCS efficacy, in 2015, scientists at the University of Melbourne, School of Psychological Sciences (Melbourne, Australia) published their review of the tDCS literature in healthy subjects for every neuro-physiological outcome measure reported in the literature by at least two different lab groups (Horvath et al., 2015). Whenever possible, the data was pooled and quantitatively analyzed to assess significance. When pooling was not possible, the data was qualitatively compared to assess reliability. Their review of the literature showed that of the 30 neurophysiological outcomes reported by at least two different research groups, tDCS was found to have a reliable effect on only one: motor excitability potential (MEP) amplitude. So, the authors work raises questions about whether tDCS really works to enhance cognition.

Transcranial Alternating Current Stimulation (tACS)

The tACS technique was developed in 2006, and uses different electrical frequencies (Hertz) within normal brain electrical ranges to affect behavior. The exact frequency used dictates the response:

- 0.75 Hz (low end of delta waves): enhanced memory retention.
- 5-8 Hz (theta rhythm): improves working memory.

7.5-12.5 Hz (alpha frequency): enhances creativity.
>30 Hz (gamma frequency): enhances memory maintenance.

The mechanism for how tACS works is unknown, but it is thought that the rhythmic stimulations from the device interact with existing natural brain rhythms at specific frequencies to facilitate the effects.

In 2016, scientists in the Department of Neurology, NeuroCure Clinical Research Center, Charité Universitätsmedizin (Berlin, Germany) published a review the literature applying tACS to enhance cognition, and show their pilot data administering theta-frequency tACS (6 Hz) (associated with long-term potentiation) over the temporo-parietal cortex for 20 min during language learning in healthy young and older adult (Antonenko et al., 2016). Their data show a significantly increased language retrieval accuracy following tACS, and provide the first use of tACS in older adults. They conclude tACS in the theta frequency range may serve as a tool to enhance cognition, but future studies are needed to identify the best position for the electrodes, the best frequencies, the effects of age, and the effects of brain pathologies.

tACS has also been applied to treatment-refractory patients with schizophrenia (Kallel et al., 2016). Scientists at the Résidence ENNESRINE, Cab G12, 2036 (La Soukra, Tunisia) and the Centre Interdisciplinaire de Recherche en Réadaptation, Santé Mentale Medical School (Québec, Canada) assessed the efficacy and safety of theta-rhythm tACS in patients with clozapine-resistant schizophrenia. 3 patients received 20 sessions of 4.5 Hz-tACS (20 min, 2 mA) applied over the dorsolateral pre-frontal cortex. The treatment decreased specific symptoms (-10 %), decreased general symptoms (-18 %), and improved patient insight into the illness. The authors concluded that 4.5 Hz-tACS might be a suitable alternative treatment for clozapine-resistant symptoms of schizophrenia (Kallel et al., 2016).

tACS has also been used to treat stroke patients (Wu et al., 2016). Scientists in the Department of Rehabilitation Medicine, Huashan Hospital, Fudan University (Shanghai, China) tested whether tACS could improve post-stroke rehabilitation when applied bilaterally over the mastoids (tACS-bm) (back part of the temporal bone). They enrolled 60 sub-acute post-stroke patients (15 to 60 days after the stroke onset), and randomly assigned them to receiving 15 sessions of the usual rehabilitation program without (n = 30) or with (n=30) tACSbm (20 Hz and < 400 μ A for 30-min). Stroke symptoms were assayed using the NIH Stroke Scale (NIHSS). The results showed that at the 15th session, compared to baseline, the mean stroke score in the tACS-bm group improved significantly [18.3 ± 2.6 vs. 10.8 ± 2.7 ; $p < 0.001$] than the control group [19.1 ± 2.7 vs. 13.0 ± 2.4]. Mean brain blood flow velocity (MFVs) also increased significantly than the control ($p < 0.001$).

Transcranial Magnetic Stimulation (TMS)

The TMS technique uses a focused 3 tesla magnetic field in a small area to cause small numbers of neurons to fire. Its direct effect is easier to measure than tDCS. The electro-magnetic field generated by rTMS penetrates the skin of the scalp and infiltrates brain tissues to a depth of about 2 cm, causing neuronal depolarization and generating motor, cognitive and affective effects (Pastuszak et al., 2016). Depending on the stimulation frequency, rTMS can stimulate or

inhibit the brain cortex. Studies using animals have shown that rTMS stimulation can generate brain changes similar to those seen after electric shock therapy, but without provoking seizures.

The mechanism of action of rTMS remains unknown, but it likely enhances neurotransmitters, enhances the modulation of signal transduction pathways in the central nervous system, alters gene transcription, and releases neuro-protective substances. Interestingly, this technique has been used to show that key differences exist between individuals that affect transcranial signals: skin conductivity, skull thickness, and brain anatomy. Some experiments have shown that the more sensitive a person is to TMS, the more sensitive they are to tDCS, and the better they improve doing a motor learning task.

In 2016, scientists in the Department of Neurology, Central Clinical Hospital of the Ministry of National Defense, Military Institute of Medicine (Warsaw, Poland) published their review of the literature regarding the use of rTMS to treat psychiatric and neurological disorders (Pastuszak et al., 2016). Their review showed that rTMS has a proven effectiveness for treating drug-resistant depression, and is currently being evaluated for treating obsessive-compulsive disorder, schizophrenia, autism, strokes, tinnitus, Alzheimer and Parkinson diseases, cranial traumas, multiple sclerosis, migraine, and dystonia.

In 2016, scientists at the Institute of Behavioral Science in Medicine & Department of Psychiatry, Yonsei University College of Medicine (Seoul, South Korea) published the results of their randomized, sham-controlled clinical study investigating the therapeutic effects of 2-weeks of repetitive transcranial magnetic stimulation (rTMS) on patients with major depression (Kang et al., 2016). 24 patients were randomly assigned to active rTMS (n = 13) or sham (n = 11) groups. rTMS was applied for 10 minutes at 10 Hz over the left dorsolateral prefrontal cortex (DLPFC). Depression was evaluated using the Hamilton Depression Rating Scale (HDRS). Their results showed that participants in the active rTMS group had a significant clinical improvement in depression scores compared to those in the sham group ($P < .001$). They also showed a positive correlation between residual depressive symptoms and the rTMS connectivity strength after 2-weeks ($r = 0.46$, $P = 0.023$).

Also in 2016, scientists in the Department of Medicine, University of Auckland (New Zealand) reviewed the published literature using rTMS to treat strokes (Smith and Stinear, 2016). Their review indicated that the use of TMS has increased dramatically over the last decade due to the expansion of using single-pulse TMS to predict motor function recovery after stroke, and the use of repetitive TMS to modify the excitability of the motor cortex after strokes. They concluded that predicting recovery after stroke is a complex process, and TMS alone is not sufficient but is highly useful when combined with clinical assessment and MRI. With respect to therapy, rTMS temporarily modulates cortical excitability after stroke, but very few rTMS studies have been completed. They conclude that further investigation is needed before these techniques can be applied in routine clinical care.

In 2016, scientists in the Department of Physical and Rehabilitation Medicine, Center for Prevention and Rehabilitation, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine (Seoul, Korea) published their study identifying factors associated with improved motor function when using high-frequency rTMS to treat sub-acute stroke patients (Chang et al., 2016). The authors state that although high-frequency rTMS has previously been shown to aid motor recovery in patients with sub-acute stroke, the response

is highly variable between patients, so they aimed to identify which factors most directly correlate with improved function. They enrolled 62 patients with sub-acute stroke, and applied rTMS over the primary motor cortex of the affected hemisphere at 10Hz with 1,000 pulses/day for 10 days. The upper limb motor function was scored using a Fugl-Meyer Assessment tool (FMA-UL), and any change ≥ 5 points was considered clinically significant. Their results identified two factors with the greatest impact on score improvement: 1) the functional integrity of the cortical-spinal tract, and 2) the patient's genotype of brain-derived neurotrophic factor (BDNF) ($p < 0.05$). BDNF presumably helps facilitate the motor functional recovery.

Closed-Loop Neuro-Stimulators

These second-generation DBS devices not only deliver current to specific regions of the brain, they monitor brain electrical currents at all times for abnormal firing, and when detected, it delivers a corrective current. The hope is that these second-generation devices will allow researchers to begin to correlate specific types of brain neural patterns with specific symptoms, and then respond to them with a tailored type of stimulation best suited for that abnormality. Several types of closed-loop devices have already been developed:

- **Medtronic** (Minneapolis, Minnesota): This device was the first developed of the advanced generation of neuro-stimulators, and has been available since August 2013. The device not only sends out impulses, but can read the body's neural signals, so the device is either in the stimulating state or in the native state. The device allows real-time immediate measurements of success or failure, so it is a type of personalized precision medicine. Each patient is different in the precise area that needs stimulating, and is different in the timing of when that circuit needs attenuation or stimulation. The read outs from this device may help scientists identify specific brain network patterns that correlate with specific symptoms, and may also allow scientists to determine how the network signals vary when the patient undergoes specific activities. These types of studies were not previously possible ([Medtronic, 2016](#)).
- **NeuroPace** (Mountain View, CA): The device uses a closed-loop technology, and was FDA-approved in November of 2013 for epilepsy (a relatively simple disorder to treat by stimulation), and is about 5 years away for approval for Parkinson's disease. The device monitors neural networks constantly looking for abnormal activity, then when detected, it uses current to prevent the seizure. In October 2013, DARPA approved a new \$70 million program to support the development of closed-loop devices for soldiers with post-traumatic stress disorder, anxiety, and brain injury ([NeuroPace, 2016](#)).

Section-4 Conclusion

In general, several advances to the technique of deep brain stimulation (DBS) have been made over the years to attempt to make it more effective or less invasive. Closed-loop neuro-stimulators were designed to detect abnormal brain circuits in a patient, and when detected

deliver a correcting current. But these devices are relatively new, and no clinical trials have been performed. Several non-surgical electrical stimulation options to DBS have also been developed, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS). All three of these non-invasive techniques have refereed articles showing they significantly improve patient outcomes. TMS (or rTMS) has been used to improve patients with drug-resistant depression, and is currently being evaluated for treating obsessive-compulsive disorder, schizophrenia, autism, strokes, tinnitus, Alzheimer and Parkinson diseases, cranial traumas, multiple sclerosis, migraine, and dystonia. tACS has been used to improve cognition or to treat patients with schizophrenia or stroke. The most literature exists for tDCS. tDCS has been used to improve moods, pain, major depression, fibromyalgia, migraines, Alzheimer's disease, and cognition.

No technique is perfect. The tDCS field has been generally criticized for a lack of rigor, as many of the experiments have been performed by home users. And early studies sometimes pooled the results from multiple sets of experiments, each done with different devices and procedures. Worse, some of the very recent studies that have been carefully designed and controlled are starting to show no effects of the tDCS technique. Many of the studies did not analyze for any off-target or side-effects, so more attention should be paid to safety. A stimulation intensity of up to 2 mA and a duration of about 20 min appears to be generally safe, and the observed adverse effects are minor, consisting of light itching beneath the electrodes or mild headaches. Such effects have been observed in healthy subjects and in patients with different neurological disorders. Risks include the generation of electrochemically produced toxins, deposit of electrode dissolution products at the electrode-tissue interface, excitotoxic damage to overdriven neurons, and electrode placements that could result in brainstem or heart nerve stimulation. Because many laboratories have just started using this technique, it is necessary to standardize stimulation protocols to enhance the comparability of research results. It is also important to underscore that tDCS research is in its early stages and therefore future studies might change some of the current concepts.

Section-4 Bibliography

Antal A, Brepohl N, Poreisz C, Boros K, Csifcsak G, Paulus W (2008) Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clinical Journal of Pain*, 2008 Jan; 24(1): 56-63.

Antonenko D, Fixel M, Grittner U, Lavidor M, Flöel A (2016) Effects of Transcranial Alternating Current Stimulation on Cognitive Functions in Healthy Young and Older Adults. *Neural Plasticity*, 2016; 2016:4274127.

Beeli G, Koeneke S, Gasser K, Jancke L (2016) Brain stimulation modulates driving behavior. *Behavior and Brain Function*, 2008 Aug 6; 4: 34.

Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, Fregni F (2008) A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology*, 2008 Mar; 11(2): 249-254.

Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F (2009) Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. *Journal of Neurology and Neurosurgical Psychiatry*, 2009 Apr; 80(4): 444-447.

Chadaide Z, Arlt S, Antal A, Nitsche MA, Lang N, Paulus W (2007) Transcranial direct current stimulation reveals inhibitory deficiency in migraine. *Cephalalgia*, 2007 Jul; 27(7): 833-839.

Chang WH, Uhm KE, Shin YI, Pascual-Leone A, Kim YH (2016) Factors influencing the response to high-frequency repetitive transcranial magnetic stimulation in patients with subacute stroke. *Restorative Neurology and Neuroscience*, 2016 Issue Jun 25, [Epub ahead of print].

Cohen Kadosh R, Soskic S, Iuculano T, Kanai R, Walsh V (2010) Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Current Biology*, 2010 Nov 23; 20(22): 2016-2020.

Costain R, Redfean JW, Lippold OC (1964) A controlled trial of the therapeutic effect of polarization of the brain in depressive illness. *British Journal of Psychiatry*, 1964 Nov; 110: 786-799.

Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. *Journal of Neuroscience*, 2009 Jun 3; 29(22): 7271-7277.

Ferrucci R, Marceglia S, Vergari M, et al. Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory. *J Cogn Neurosci* 2008 Mar 17. epub ahead of print.

Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F, Zago S, Barbieri S, Priori A (2008a) Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory. *Journal of Cognitive Neuroscience*, 2008 Sep; 20(9): 1687-1697.

Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, Cogiamanian F, Barbieri S, Scarpini E, Priori A (2008b) Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology*, 2008 Aug 12; 71(7): 493-498.

Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, Silva MT, Barbosa ER, Nitsche MA, Pascual-Leone A (2006) Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Movement Disorders*, 2006 Oct; 21(10): 1693-1702.

Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A (2006a) Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. *Depression and Anxiety*, 2006; 23(8): 482-484.

Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, Castro AW, Souza DR, Riberto M, Freedman SD, Nitsche MA, Pascual-Leone A (2006b) A sham-controlled, phase II

trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain*, 2006 May; 122(1-2): 197-209.

Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, Bravo R, Rigonatti SP, Freedman SD, Nitsche MA, Pascual-Leone A, Boggio PS (2006c) A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis and Rheumatism*, 2006 Dec; 54(12): 3988-3998.

Horvath JC, Forte JD, Carter O (2015) Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia*, 2015 Jan; 66: 213-236.

Kallel L, Mondino M, Brunelin J (2016) Effects of theta-rhythm transcranial alternating current stimulation (4.5 Hz-tACS) in patients with clozapine-resistant negative symptoms of schizophrenia: a case series. *Journal of Neural Transmission (Vienna)*, 2016 Issue May 19. [Epub ahead of print].

Kang JI, Lee H, Jung K, Kim KR, An SK, Yoon KJ, Kim SI, Namkoong K, Lee E (2016) Fronto-striatal Connectivity Changes in Major Depressive Disorder After Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Controlled Study. *Journal of Clinical Psychiatry*, 2016, Issue July 5, [Epub ahead of print].

Kincses TZ, Antal A, Nitsche MA, Bártfai O, Paulus W (2004) Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia*, 2004; 42(1): 113-117.

Koenigs M, Ukueberuwa D, Champion P, Grafman J, Wassermann E (2009) Bilateral frontal transcranial direct current stimulation: Failure to replicate classic findings in healthy subjects. *Clinical Neurophysiology*, 2009 Jan; 120(1): 80-84.

Marshall L, Mölle M, Hallschmid M, Born J (2004) Transcranial direct current stimulation during sleep improves declarative memory. *Journal of Neuroscience*, 2004 Nov 3; 24(44): 9985-9992.

Marshall L, Mölle M, Siebner HR, Born J (2005) Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. *BMC Neuroscience*, 2005 Apr 8; 6: 23.

Medtronic (2016) <http://www.medtronic.eu/index.htm>

NeuroPace (2016) <http://www.neuropace.com/>

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A (2008) Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, 2008 Jul; 1(3): 206-223.

Pastuszek Ż, Stępień A, Piusińska-Macoch R, Brodacki B, Tomczykiewicz K (2016) [Evaluation of repetitive transcranial magnetic stimulation effectiveness in treatment of psychiatric and

neurologic diseases] [Translated from Polish] *Polish Merkur Lekarski*, 2016 Jun 29; 40(240): 388-392.

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Celnik PA, Krakauer JW (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences, USA*, 2009 Feb 3; 106(5): 1590-1595.

Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, Boggio PS, Valle AC (2007) Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. *Pain Practice*, 2007 Dec; 7(4): 297-306.

Sellers KK, Mellin JM, Lustenberger CM, Boyle MR, Lee WH, Peterchev AV, Fröhlich F (2015) Transcranial direct current stimulation (tDCS) of frontal cortex decreases performance on the WAIS-IV intelligence test. *Behavioural Brain Research*, 2015 Sep 1; 290: 32-44.

Smith MC, Stinear CM (2016) Transcranial magnetic stimulation (TMS) in stroke: Ready for clinical practice? *Journal of Clinical Neuroscience*, 2016 issue July 6, [Epub ahead of print].

Wu JF, Wang HJ, Wu Y, Li F, Bai YL, Zhang PY, Chan CC (2016) Efficacy of transcranial alternating current stimulation over bilateral mastoids (tACSbm) on enhancing recovery of subacute post-stroke patients. *Stroke and Rehabilitation*, 2016 May 4: 1-10.

Section-4: DBS Ethics and Regulations

Samantha Gauthier

As discussed in previous sections, deep brain stimulation (DBS) is a surgical technique used to modify abnormal electrical signals in the brain. Electrodes are implanted into the patient's brain, then an electrical current is generated from a neuro-generator device implanted under the patient's shoulder blade. The technique was originally investigated in animal experiments, and has been studied in several clinical trials (described earlier). As a medical device, DBS implants fall under the jurisdiction of the Food and Drug Administration.

Since 1997, DBS has been approved by the FDA for two motor disorders: Parkinson's disease (PD) and Essential Tremor Disorder (ET); under these guidelines, over 55,000 patients have received DBS treatment (Focquaert, 2013). The success of these early motor cases led to the subsequent usage of DBS for dystonia (involuntary muscle contractions) and epilepsy (Schlaepfer et al., 2010). In 2009, the FDA approved the first application of DBS in psychiatry to treat Refractory obsessive compulsive disorder (OCD), cases of OCD that have failed to be alleviated by standard psychiatric medicine.

DBS has been investigated as a possible treatment option for other non-motor disorders including: Tourette's syndrome, substance abuse, refractory depression, obesity, chronic pain, and multiple sclerosis (Bell et al., 2009; Schlaepfer et al., 2010; Focquaert, 2013). DBS implants have become the most widely used therapeutic brain interface technology currently available (Erickson-Davis, 2012).

However, as discussed in Section 3 of this Literature Review, DBS has drawbacks that need to be evaluated. Some reports indicate DBS is a complication-prone operation, with up to 10% of patients experiencing serious side-effects, such as post-operative infection, intra-cerebral hemorrhage, or seizures (Appleby et al., 2007). This has given rise to ethical concerns over clinical trials, and the need for strong oversight from the FDA.

Conflicts of Interest

Conflicts of interest are situations in which financial or personal gain can compromise the uses of a new treatment. DBS research and treatments rely on a complex web of relationships between academic researchers, institutions (such as clinics or universities), and the industries that produce the implantable product. In addition to DBS being used to treat some types of psychiatric disorders, the electrodes can also be used by a physician to gain information on the patient's disease itself. Being a complex medical device, the number of companies manufacturing DBS devices is small, making it possible that a monopoly could form, which would disrupt the web of relationships. The 3-way relationship between individual researchers, the special interests of the institution, and sensible profits in industry, can cause conflicts making the use of DBS research or treatment potentially unethical (Fins et al., 2011). To further complicate the issue, the FDA has no guidelines on innovative surgeries, including DBS (Erickson-Davis, 2012).

An example of a potential conflict of interest, Medtronic has become the world's largest supplier of DBS technology, leading to a near monopoly by this company. This domination has created a situation where industry's role in DBS possibly overshadows the role of researchers and institutions, raising concerns for a lack of a market-driven approach for DBS. In 2009, the FDA approved Medtronic's Reclaim™ device for DBS treatment of OCD under a Humanitarian Device Exception (Medtronic, 2016). To qualify for this type of exception, the device must be developed for a disease that affects fewer than 4,000 people in the U.S. Despite OCD affecting nearly 200,000 individuals, Medtronic claimed that the possible OCD patients benefitting from Reclaim™ did not exceed 4,000 (Erickson-Davis, 2012). According to the FDA, the purpose of the Humanitarian Device Exception is to benefit populations for a disease that is not currently being treated due to cost-benefit reasons; such diseases would have too few patients to make it worth a company investing in research for a treatment (FDA, 2014). This exemption is granted when a product is deemed safe without having had efficacy adequately proven under other regulations (Schlaepfer et al., 2010). Author Cordelia Ericson-Davis questions, "Whether the approval of DBS for OCD exemplifies the humanitarian ideal of HDE, or [...] better represents a least burdensome approach to industry regulation" (Erickson-Davis, 2012). With respect to the application of Medtronic's DBS device for OCD, Dr. Benjamin Greenberg's study was used to gain approval for the use of DBS for OCD (Greenberg et al., 2010). But out of 34 individuals in the main study, 31 were tied to researchers that had monetary support from Medtronic (the company often donated resources to further DBS research). And in at least 3 instances, Medtronic's personnel reported the data, not academic researchers.

Furthermore, the Bayh-Dole Act (1980), originally sponsored by two senators, Birch Bayh of Indiana and Bob Dole of Kansas (37 C.F.R. 401.) allows the transfer of intellectual property from government funded programs to institutions that conduct the research (such as clinics), and they can in turn transfer these rights further to a third party, such as Medtronic. This transferring of funds and their control can lead to very close relations between specific clinics and companies that undermines independent research. These conflicts of interest at the industry and research level could undermine value of DBS to physicians and their patients (Erickson-Davis, 2012).

Resolving Conflicts of Interest

The most effective way to identify and resolve these conflicts of interest is through transparency from all individuals involved with DBS research and usage. In the case of funding, researchers should reveal and justify why corporate funding is needed, make an effort to balance funding from multiple sources to avoid conflicts, and all possible conflicts-of-interest should be made public. Companies should release their "Rights of Reference", which is their approval to use existing data on the device they are using, so it does not impede new treatments that are only in the investigative phase. Cooperation should be transparent, including ensuring that researchers are not employees of the company that their institution is working with, and that researchers who are working on corporate-sponsored research must refrain from being corporate board members. All researchers must take full responsibility for their publications, and these publications should not be controlled by a financial partner (Fins et al., 2011).

In regards to intellectual property rights and the Bayh-Dole Act, all monetary transfers should be made transparent, using institutional policies. All corporate monetary concerns should be established in a way that continues to keep the scientific research on-going and successful. A researcher's ability to continue researching the topic outside the scope of a study should not be infringed upon by contracts within institutions or industries. It should be kept in mind at all times that the profits made through Intellectual Property Rights are gained through individuals with an illness. Researches and institutions should collectively work to assure that through the use of their patents, industry does not make treatments inaccessible to underprivileged populations (Fins et al., 2011).

Researchers, institutions, and industry need to take into consideration the ethical implications that arise when DBS is needed in underrepresented populations, and is used by an over-burdened health care system. Even in the developed world, budget allocations for mental illnesses are especially low. With restricted budgets, teams must decide who will be able to receive DBS treatments. With long wait lists, an individual who was a good candidate for the procedure may no longer be when it is their turn. Although the health care expenditures for DBS are not yet fully known, the economic burden of mental illness is. In all countries, one of the highest economic burdens result from the mortality or disability from mental illness. In the United States the cost is over \$53 billion annually, mainly due to a loss of productivity. This puts mental illness on par with diabetes, heart disease, and hypertension. Based on one study gathered from insurance providers, "it has been noted that treating depression reduces the number of days that patients are unable to work so significantly that their improvement accommodates the costs of treatment" (Bell et al., 2009). Institutions and industries must work hard to gain more resource allocations for DBS research and treatments.

Ethical Considerations for the Treatment of Patients

To further DBS scientific research, tight ethical guidelines should be followed not only at the large institutional and corporate level, but also by individual researchers, physicians, and patients (Bell et al., 2009). In a clinical trial, patients should be selected using criteria that indicates they are likely to benefit from the treatment; this will keep the cost down and prevent patients who likely will not respond from becoming further frustrated. These selections should be made by a team from multiple disciplines, including neurologists, neuropsychologists, psychiatrists, neurosurgeons, and advance care nurses. Prior to qualifying, patients should present proof that multiple previous conventional treatments have failed. The severity of the disorder, and how much it impacts the patient, should also be a consideration when deciding if the treatment will be beneficial. For example, with Parkinson's patients, the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) can be used to pick the patients that best qualify; these criteria evaluate "age, motor symptoms, response to levodopa, neuropsychological and psychiatric status of the patient, presence of other medical illnesses, quality of life, presence or history of substance abuse or dependence, and presence of drug-induced psychosis" (Bell et al., 2009). However, based on these criteria, it may be harder to select psychiatric patients, because many have co-morbid diseases, such as substance abuse or a combination of OCD and depression. Lastly, when choosing a patient, it is important to evaluate their expectations, their commitments to the long-term treatments, and their family support system. However, a patient's support system cannot be the sole deciding factor, because those

with little or no support are already at a disadvantage when it comes to receiving care for their diseases (Bell et al., 2009).

Informed consent is defined as a patient or their legal proxy knowing fully the risks involved, and the patient understands the procedure thoroughly enough to make an informed decision. A patient should be aware that when treating Parkinson's disease with DBS the complications rates can exceed 25%, and permanent complications can occur in 4-6% of the cases. They must be aware of times of medication applications and withdrawals, functions of stereographic equipment, which imaging modalities are used, and the basis for their brain target selection. Patients must also be informed of what the surgery entails and what their role will be during it, and all potential complications. They should also have knowledge of the DBS device itself, and the need for future surgeries to replace the device's battery (Bell et al., 2009). From industry's perspective, the patient informed consent should include a complete transparency of intellectual property rights, monetary compensations, and all individuals involved in their treatment, including the DBS device (Fins et al., 2011).

DBS psychiatric treatments have additional issues to take into concern. A psychiatric illness may affect a person's cognition or mood, but this may not necessarily relinquish the patient's decision-making capacity, and should not rule out their ability to state their health care preferences and make their ultimate decision. Despite this, it is important to consider the patient's vulnerability that arises due to their specific illness, such as depression or OCD (Bell et al., 2014). With psychiatric conditions, providers should take into consideration the family's role in possibly pressuring the patient into agreeing with the treatment. The role that the media plays in influencing a patients should also be evaluated. Many patients and families are at the 'end of their rope', and media may sell DBS treatments as 'miracles', or it may negatively influence them by confusing DBS with lobotomy or older forms of electroconvulsive shock (Bell et al., 2009). All companies and institutions should avoid the word 'therapy' or 'therapeutic' when any treatment is still in an investigational phase (Fins et al., 2011). Despite potential risks and the need for careful patient selection, researchers and physicians need to recommend DBS if it is indicated as a beneficial treatment, but they must be able to deal with pressure from caregivers and patients pushing for DBS when it may not be in the patient's best interests (Bell et al., 2009). Enrolling psychiatric patients in invasive surgical procedures is risky, and a discussion should ensue about their ability to provide free and informed consent, including evaluating their vulnerability in a broad relational context that includes their caregivers (Bell et al., 2014).

Ethical Considerations for the DBS Treatment of Children

Despite the fact that DBS is currently performed on children, there are very few guidelines that deal with the decision making of the child. Farah Focquaert, of the Department of Philosophy and Moral Sciences at Ghent University, describes two competing ideologies: "child protectionists" and "child liberationists" (Focquaert, 2013). Child protectionists claim that children are immature emotionally and cognitively, and thus they cannot exercise their rights or make informed consent, and it is the burden of the parents to make the right decisions in consultation with professionals. This assumption relies on the parent's having their child's best wishes at heart. Child liberationists argue that more emphasis must be placed on child autonomy,

with little input from parents or guardians (Focquaert, 2013). Many child liberationists point to the following parts of the United Nation's Conventions on the Rights of the Child:

States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child. – Article 12.1 UNCRC (1989)

States Parties recognize the right of a child who has been placed by the competent authorities for the purposes of care, protection or treatment of his or her physical or mental health, to a periodic review of the treatment provided to the child and all other circumstances relevant to his or her placement.-Article 25 UNCRC (1989)

However, it is important to note that while there are 196 State parties on the UNCRC treaty, the U.S. signed the document but has not ratified it to become a member of the treaty. In a video-tape analysis of 105 patient tapes, 72% of parents were non-supportive of their children, meaning they did not involve their child in treatment discussions. As noted before, family pressure can infringe on a patient's ability to make informed consent; parents of a child with a psychiatric disorder may decide on more drastic measures, despite their child's view that they have a fine quality of life. The decision to choose DBS may be more geared to relieving parental stress than truly helping the child, an effect known as 'caregiver burden'. However, child liberationists may be too drastic, since children are dependent on their parents and discussing their issues with their parents rather than making the decision on their own usually benefits the child. When dealing with a pediatric patient, a 3-way communication should be facilitated between the physician, the parents, and the child whenever possible, and the issue of 'caregiver's burden' should be taken into account by the physician (Focquaert, 2013).

Ethics and Regulations for the Transcranial Stimulation Techniques

As discussed previously in sections-1 and -4, three main types of non-invasive electrical stimulation techniques have been developed to avoid problems associated with surgical implantation of DBS devices: 1) transcranial direct current stimulation (tDCS), 2) transcranial alternating current stimulation (tACS), and 3) transcranial magnetic stimulation (TMS). These three techniques lack the surgical problems associated with DBS, but are not conflict free.

Transcranial direct current stimulation (tDCS) is used for both therapeutic effects and cognitive enhancement, and compared to DBS is relatively effective, safe, and affordable. However, according to an FDA Executive Summary in 2012 on the Classification of Cranial Electrotherapy Stimulators, "There is no regulation for therapeutic tDCS" (FDA, 2012). Furthermore, there are no laws in the United States that restrict the marketing of products used for cognitive enhancement. The European Union also lacks any regulation for tDCS, either for therapeutic uses or cognitive enhancement. With no regulations in place, tDCS has developed a "Do-it-Yourself" (DIY) community. Two factors make this possible, the first is the ability to create a tDCS device with easily obtainable supplies combined with guidelines for construction

on the Internet. Second, companies are beginning to sell pre-made tDCS devices, making this technology even more widely usable, with costs ranging between \$200-400 USD (Jwa, 2015).

The DIY use of tDCS devices has raised concerns for multiple reasons: 1) DIY users may not have enough knowledge of the brain to fully understand tDCS effects, 2) the users may misunderstand where to place electrodes to cause beneficial effects, 3) the users do not understand how tDCS may interact with other medications, especially those used for psychiatric treatment, and 4) manufacturers of the pre-made tDCS devices do not need to follow any regulations for the manufacturing standards of medical devices. (Jwa, 2015)

Anita Jwa of Stanford University's Law School conducted a study of the tDCS DIY community via two internet sources, an online community at Reddit.com/r/tDCS/ and a personal blog by a lay expert in tDCS at diytdcs.com. These sources gave valuable input from real DIY users to express their opinions and tDCS uses to academics and possible regulators. The most noteworthy conclusion is her stance that it may be impossible to regulate tDCS devices, compared to other forms of brain stimulation, due to the capability of building the devices at home. The sentiment is expressed that, even with regulations, users would continue to make tDCS devices, and regulations would be difficult to enforce (Jwa, 2015).

The Jwa study pointed out a theme that has already developed among DIY users where they encourage each other to take safety first. This self-safety theme has led to the idea that a regulatory agency might be able to build on the ideas already present within the DIY community in a "bottom up" approach. The majority of the DIY users rejected any idea of government regulation, but they support and encourage the use of official guidelines, specifically in the area of placing electrodes since that has the most important implications for both usefulness and side effects of tDCS (Jwa, 2015).

Section-4 Bibliography

Appleby BS, Duggan PS, Regenberg A, Rabins PV (2007) Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience. *Movement Disorders*, 2007 Sep 15; 22(12): 1722-1728.

Bayh-Dole Act (1980) <https://grants.nih.gov/grants/bayh-dole.htm>

Bell E, Mathieu G, Racine E (2009) Preparing the ethical future of deep brain stimulation. *Surgical Neurology*, 2009 Dec; 72(6): 577-586.

Bell E, Racine E, Chiasson, Dufourcq-Brana M, Dunn BL, Fins JJ, Ford JP, Glannon W, Lipsman N, Macdonald Ellen M, Mathews HJD, McAndrews Pat M (2014) Beyond Consent in Research; Revisiting Vulnerability in Deep Brain Stimulation for Psychiatric Disorders. *Cambridge Quarterly of Healthcare Ethics*, (2014), 23: 361-368.

Erickson-Davis C (2012) Ethical Concerns Regarding Commercialization of Deep Brain Stimulation for Obsessive Compulsive Disorder. *Bioethics*, 26: 440-446.

FDA (2012) FDA Executive Summary Prepared for the February 10, 2010 meeting of the Neurologic Device Panel: Petition to Request Change in Classification for Cranial electrotherapy Stimulators. Accessed on 8-18-16 at:
<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/neurologicaldevicespanel/ucm290787.pdf>

FDA (2014) US Food and Drug Administration. Humanitarian Device Exemption (HDE): Questions and Answers - Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff Accessed on 6-30-16 at:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm389154.htm>

Fins JJ, Schlaepfer TE, Nuttin B, Kubu CS, Galert T, Sturm V, Merkel R, Mayberg HS (2011) Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation. *Journal of Neural Engineering*, 2011 Jun; 8(3): 033001.

Focquaert F (2013) Deep Brain Stimulation in Children: Parental Authority versus Shared Decision-Making. *Neuroethics*, 6: 447-455. [Published online January 25, 2011]

Greenberg BD, Gabriels LA, Malone DA Jr, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, et al. (2010) Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Molecular Psychiatry*, 2010 Jan; 15(1): 64-79.

Jwa A (2015) Early adopters of the magical thinking cap: a study on do-it-yourself (DIY) transcranial direct current stimulation (tDCS) user community. *Journal of Law and the Biosciences*, 292–335.

Medtronic (2016) Deep Brain Stimulation for Psychiatric Disorders.
<https://professional.medtronic.com/pt/neuro/dbs-pd/edu/about/index.htm#.V45dxfrKUK>

Schlaepfer TE, George MS, Mayberg H, WFSBP Task Force on Brain Stimulation (2010) WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry. *World Journal of Biological Psychiatry*, 2010 Feb; 11(1): 2-18.

The United Nations (1989) “Convention on the Rights of the Child.” *Treaty Series* 1577 (November): 3. <http://www.ohchr.org/en/professionalinterest/pages/crc.aspx>

METHODS

To accomplish objective-1, we performed a review of the current literature, including reputable academic journal articles, relevant books, scholarly websites, and other pertinent materials.

To accomplish objective-2, we conducted a set of interviews with various academic and medical researchers, bio-ethicists and legal experts to determine their full range of opinions on the strengths and weaknesses of DBS technology, and to determine which obstacles remain for its further expansion in the U.S.

Who: The stakeholders included individuals working with DBS, bioethics experts, and legal experts. Some of the stakeholders initially were identified by referral from the project advisor, Dr. David Adams, but other interviewees were identified from the literature as authors on key scientific papers, or by referral from the initial interviewees.

Where and When: Whenever possible, interviews were conducted in person, but the majority were performed by email, phone, or Skype.

How: We developed our interview questions based on our background research. A preliminary set of questions is shown in the Appendix. Based on our background search of each interviewee, we designed a pertinent initial question. Any subsequent questions were based on their response to the initial question. The appendix shows the topics covered in our interviews.

With respect to the method of the interview, after establishing contact with an interviewee, we informed the interviewee about the purpose of our project, and asked for permission to quote them (see interview preamble in the Appendix). If the need arose for confidentiality, we protected it by either not quoting them directly, or by giving them the right to review any quotations used in the final published report, explaining that the interview is voluntary, and explaining that they may stop the interview at any time or refuse to answer any question. At the end of the interview, we sometimes asked the interviewee to recommend other potential stakeholders we might interview, to further increase the number of interviews with key individuals.

With respect to the total number of interviews performed for our project, we discontinued our interviews once we had obtained sufficient information to represent all sides of the DBS problem, and when the unclear points had been clarified.

To accomplish objectives-3 and 4, the IQP team synthesized all of the information collected in our literature research, interviews, and follow-up interviews to ascertain the strength of the evidence for and against DBS, and created recommendations for further research.

RESULTS / FINDINGS

Results: Early History of DBS

Jonathan Morse and Kaycee Ndukwe

The review of the literature in this area showed that DBS has been applied over many years to a variety of disorders, some more effectively than others. The studies were difficult to compare to each other because the protocols differed even when treating the same disease.

To obtain more information on this topic, we interviewed **Dr. Benjamin D. Greenberg**, a Professor of Psychiatry and Human Behavior at the Alpert Medical School of Brown University, Butler Hospital in Providence, RI. Dr. Butler was corresponding author on a 2010 paper in the journal of *Molecular Psychiatry* (2010 Jan; 15(1): 64-79), titled “Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience”. The authors summarized the combined long-term results from four neurosurgery groups in Europe and the U.S. collaborating on DBS treatments of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) for severe and highly treatment-resistant obsessive-compulsive disorder (OCD). The initial team was located in Leuven/Antwerp, followed by other teams at Butler Hospital (Brown Medical School), then the Cleveland Clinic, and most recently the University of Florida. Although the four centers used comparable patient selection criteria, the specific area targeted by the DBS changed during the 8-year period. Overall, their data showed a significant symptom reduction and functional improvement in about two-thirds of the patients. The DBS treatment appeared to be well tolerated, and the adverse effects were transient. The results improved over time, indicating a 'learning curve' both within and across centers, especially regarding the refinement of the electrode implantation site. Initially, the team tested anterior capsulotomy sites, then later used more posterior sites at the junction of the anterior capsule, anterior commissure and posterior ventral striatum. When asked whether his team has done any further electrode implantation refinements since publishing the paper, Dr. Greenberg responded: “We're still looking at this. We will have more data on this in the next year. Another team is looking even more posterior than we are. But, it might be the case that individual variability in neural pathways will trump specific group targeting sites”. So, Dr. Greenberg brought up an interesting point that for DBS, regardless of how experienced a particular team becomes over time, in the end they will still have to vary their electrode placement based on that patient's individual neural circuits.

The next interview was with **Dr. Ashwin Viswanathan**, MD. Assistant Professor, Department of Neurosurgery, Baylor College of Medicine, 1709 Dryden, Suite 750, Houston, TX 77030 (USA). Dr. Viswanathan was corresponding author on a 2012 paper in *Stereotactic and Functional Neurosurgery* (2012; 90(4): 213-224), titled “Deep brain stimulation for Tourette syndrome: target selection”. Tourette syndrome (TS) is a complex neurological disorder manifested chiefly by motor and phonic tics, but is also accompanied by a variety of behavioral co-morbidities, such as attention disorder, obsessive-compulsive disorder, and impulse control problems. Surgical treatment is increasingly considered when the patient does not respond to normal treatments, when the tics become especially troublesome or disabling, or if the patient

becomes self-injurious. The authors reviewed the literature on DBS treatments for TS, and critically reviewed the target choices. DBS was first tested on TS patients in 1999, and since that time approximately 100 TS patients have been treated. The studies varied in their target locations, which included: the thalamic centromedian nucleus and substantia periventricularis, the posteroventral globus pallidus internus, the ventromedial globus pallidus internus, the globus pallidus externus, and the anterior limb of the internal capsule and nucleus accumbens. The authors concluded that to best determine the target location for DBS will require a future multi-center, randomized trial, plus an expanded understanding of TS neurobiology. When asked whether a large multi-center trial for TS DBS has been initiated yet, Dr. Viswanathan replied: “Unfortunately, patient recruitment has been a barrier to initiating a multi-center study. However, the University of Florida has taken the lead on a registry for TS patients implanted with DBS which will hopefully help us understand how best to treat these patients”. So, Dr. Viswanathan believes that a large controlled clinical trial will be required to determine the best locations for electrode placements in TS patients, but that TS patients are hard to come by. Hopefully, the University of Florida trial will begin soon.

The next interview was with **Dr. M. Porta** of the Tourette Center, Galeazzi Hospital, Milano, Italy. Dr. Porta was corresponding author on a paper published in *Acta Neurochirurgica*, (2012 Nov; 154(11): 2029-2041), titled “Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up”. This paper described a study with 18 patients with severe and refractory Tourette Syndrome (TS) who underwent bilateral thalamic DBS. Their original surgical procedures were reported in 2008, and the 2-year follow-up was published in 2009. Here, the authors report the long-term outcome (5-6 years) on tics, obsessional behaviors, anxiety, mood, and overall patient general health. Their results show that at the 5-6 year follow-up, there was a significant reduction in tic severity ($p < 0.001$), and significant improvements in obsessive compulsive behaviors ($p = 0.003$), anxiety ($p < 0.001$) and depression ($p < 0.001$). The patients, in general, required less medication. Although this long-term follow-up appears to be successful in terms of a significant improvement in tics and a reduction in potentially disabling symptoms, compared to the author’s results at 2 years the later results showed long-term difficulties such as patient non-compliance, medical complications, and showed problems with differences in opinion between the medical and the surgical teams. The authors concluded that what is needed are controlled studies with long-term follow-ups and improved patient selection for those willing to endure a long-term clinical trial. When asked his opinion on the most serious complications observed in their long-term study, Dr. Porta replied: “The most important complication was infection. This complication was observed not only in an early phase of the first procedure period but also after several months. We started to treat the infections using antibiotics but in the majority of cases we were obliged to remove the DBS device”. So, Dr. Porta points out that a very important side-effect of the surgical procedure is infections that are serious enough to require removal of the DBS device from the patient. Other papers published on DBS occasionally mentioned infections at the site of surgery, so perhaps this is what happened here.

The next interview was with **Dr. Jens Kuhn** in the Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany. Dr. Kuhn was corresponding author on a paper published in *Biological Psychiatry* (2012 Mar 1; 71(5): e11-13), titled “In vivo evidence of deep brain stimulation-induced dopaminergic modulation in Tourette's syndrome”. Some experiments on TS patients indicate that dopamine neurotransmission is abnormally elevated in TS patients: PET scan experiments on TS brains show hyperactive dopaminergic

innervations, and patient symptoms sometimes improve when using dopamine receptor antagonists (that block dopamine receptor function). Based on this data, some scientists reasoned that DBS stimulation may help improve TS patients by suppressing dopaminergic function in the basal ganglia. To help provide data to support this hypothesis on TS mechanism, and to determine whether DBS of the basal ganglia can improve TS patient function, Dr. Kuhn's team used DBS over 6-months while monitoring with a special type of PET scan, 18-F-fallypride-positron emission tomography (FP-PET), which allows quantification of dopamine receptor availability in a single 3-hour scan. The team used their technique on 3 TS patients suffering from medication-resistant TS. Following DBS, all 3 patients showed substantial (30-80%) improvements in the Yale Global Tic Severity Scale (YGTSS). In untreated patients, their FP-PET scans showed low FP-PET signal (low FP binding, and elevated levels of occupied dopamine receptor) in the basal ganglia. In DBS-treated patients, the FP-PET scan showed higher activity (elevated levels of unoccupied dopamine receptors, low dopaminergic activity). So, the data support the hypothesis that TS patients show a hyperactive dopaminergic system, which is lowered with DBS. The patient with the best improvements in symptoms showed the highest FP-binding (lowest dopaminergic activity) in the striatum basal ganglia. When asked whether his team has been able to use this state-of-the-art FP-PET scan on more than 3 patients he replied: "Thank you for your interest. No, we were only able to include three Tourette patients". So, Dr. Kuhn's interesting FP-PET approach for monitoring dopaminergic activity in the brains of TS patients has not yet been tested beyond his published data.

The next interview was with **Dr. Philippe Coubes**, a Professor in the Department of Neurosurgery, CHRU Montpellier, Montpellier, France. Dr. Coubes was the corresponding author on a paper in *Surgical Neurology International* (2012; 3(Suppl 2): S127-S142), titled "Deep brain stimulation of the globus pallidus internus and Gilles de la Tourette syndrome: Toward multiple networks modulation". Their article discussed Gilles de la Tourette's syndrome (GTS), a complex neuropsychiatric disorder characterized by disabling motor and vocal tics. Conventional treatments usually include pharmacological and behavioral interventions. DBS is an alternative treatment for patients not responding to pharmacological treatment. Their paper summarized the finding of 33 research articles on DBS treatment of GTS, published from 1999 to 2012. The articles included the data from 88 TS patients. The majority of patients received thalamic DBS stimulation, while a fewer number of patients received stimulation of the globus pallidus internus, the anterior limb of the internal capsule, the nucleus accumbens, or the subthalamic nucleus. Although all of the brain area targets produced positive results, the results were variable. Because GTS patients show such a wide spectrum of behavioral co-morbidities (attention disorder, obsessive-compulsive disorder, or impulse control problems), the authors concluded that multiple neural networks may need to be modulated in GTS patients. They also concluded that the optimum locations within the basal ganglia thalamo-cortical circuits remain to be determined. The authors found that it was difficult to compare the currently published studies because each involved a different number of patients, used different stimulation methods, and used different assays to measure behavioral improvements. So, they concluded that larger randomized controlled trials with a standardization of procedures are urgently needed. When asked how multiple neural networks are stimulated in one patient, and whether it involves using multiple electrodes simultaneously, Dr. Coubes responded:

"Yes. Treating multiple neural pathways is needed in complex behavioral disorders where the expression of the genetically-determined biochemical dysfunction (GABAergic networks in Tourette) implicate many networks partially supported by grey nuclei. The

idea is to analyze which symptom reflects which network dysfunction. If this network can be suspected of dysregulation due to lack of inhibition, DBS electrical neuro-modulation can be proposed. This is the philosophy of our group!

So, Dr. Coubes pointed out the importance of identifying exactly which circuits show abnormally elevated firing in each TS patient, so those can be treated with DBS. And the circuit involvement will be different between patients.

Results: DBS Health Concerns

Craig Barrett and Christopher Massar

Medical procedures usually come with risks. Sometimes the side-effects are treatable, sometimes not. The risks need to be weighed against the potential benefit of the treatment for the patient. In the case of DBS, our search of the literature identified several types of side-effects associated with DBS, ranging from mere headaches to patient suicide. It is difficult to determine whether the DBS caused the suicides; most of the suicides were seen in patients treated for severe depression, a population where suicide rates are already elevated. In some experiments, the suicide rates were higher in the DBS-treated patients than the placebo patients, although it was elevated for both groups. Our search of the literature also showed that some problems resulted from the DBS hardware inserted during surgery (infection, DBS hardware malfunction, DBS hardware interactions with pacemakers), and were common to all types of procedures, while other side-effects depended on which area of the brain was being stimulated. To provide more information on this topic, we performed a series of interviews with scientists performing DBS procedures.

The first interview was with **Dr. Ihtsham Haq**, MD, an Associate Professor in the Movement Disorders Section, Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina. Dr. Haq was corresponding author on a paper published in the journal of *Stereotactic and Functional Neurosurgery* (2010; 88(5): 322-328), titled “A case of mania following deep brain stimulation for obsessive compulsive disorder”. The authors described their experience during a multiyear period using DBS to treat patients for obsessive compulsive disorder (OCD) where they encountered several unanticipated stimulation-induced psychiatric side effects. They present the case of a young woman treated for OCD with DBS of the anterior limb of the internal capsule and nucleus accumbens region, who subsequently manifested a manic episode. They described the case details and potential reason for the response. When asked how the mania might be prevented when treating OCD patients, Dr. Haq responded:

“I’m not sure that we can entirely prevent it, since the patient population is a psychiatrically vulnerable one. Full and informed consent is always crucial, as is extensive pre-operative psychiatric examination. There need to be plans for surveillance and treatment in place to catch mania early when it does happen. If stimulation-induced mania occurs, then adjusting the settings would be expected to resolve it”.

So, Dr. Haq indicates that the OCD patients might be difficult to prevent DBS-induced mania (although the published findings are limited here), so it becomes important to obtain patient informed consent in advance of DBS to make sure they are aware of possible side-effects. And if a problem results from the DBS stimulation, Dr. Haq indicates it is important to alter the DBS current.

The next interview was with **Dr. Milind Deogaonkar** in the Department of Neurosurgery, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH. Dr. Deogaonkar was corresponding author on a recent 2016 paper in *Basal Ganglia* (6: 19-22) entitled “Interaction between cardiac pacemakers and deep brain stimulation pulse generators: Technical considerations”. In this paper, the authors described their experience with 3 patients with cardiac pacemakers or implantable cardio-converter defibrillators (ICD) for treating cardiac abnormalities, and they also had deep brain stimulators for treating movement disorders. The authors found that the two types of electronic devices interfered with each other, requiring the DBS stimulator to be surgically relocated. The authors concluded that it is important to keep the two types of electrical devices at least 6 inches apart in the brain, and important to use appropriate device programming parameters to avoid interference. They argue that both devices can be used in one patient if accompanied by strict vigilance. So, this paper is a good example of unforeseen problems that can occur with DBS devices. When asked whether he believes that transcranial devices could interfere with pacemakers, Dr. Deogaonkar stated: “No, they should not interfere with pacemakers, but perhaps the other way around [the pacemakers could interfere with tDCS]. But a cardiologist may be best suited to comment on the effect of transcranial stimulation on cardiac devices”. So, from this interview we learned that Dr. Deogaonkar thinks the current from transcranial devices should not interfere with electronic cardiac devices, but that the cardiac devices could interfere with the transcranial stimulations. So, if a patient has a pacemaker, this fact should be factored into any transcranial procedure.

The next interview was with **Dr. Benzi M. Kluger** in the Department of Neurology at the University of Colorado Denver, Aurora, Colorado. Dr. Kluger was corresponding author on a paper in the journal *Parkinson's Disease* (2012: 769506) entitled “The prevalence of fatigue following deep brain stimulation surgery in Parkinson's disease and association with quality of life”. This was the first study to evaluate fatigue following deep brain stimulation surgery. The team recruited 44 PD patients, and then at least 1-year following DBS surgery administered a Fatigue Severity Scale (FSS) test, a Parkinson's disease Questionnaire (PDQ-39), the Beck Depression Inventory, the Beck Anxiety Inventory, and a neuropsychological battery. Their data showed that 58% of the patients had moderate to severe fatigue. A predictor of fatigue was pre-operative depression. The fatigue was significantly associated with quality of life, depression and anxiety. When asked whether fatigue is associated with DBS and other diseases, Dr. Kluge stated: “There are no studies on DBS and fatigue for other conditions to my knowledge”. So, Dr. Kluge is not aware of any other DBS studies showing fatigue in the patients, but the fact that he observed that a majority (50%) of their Parkinson's DBS patients suffered from fatigue implies this should be monitored in other studies.

We next interviewed **Dr. Michael S. Okun**, MD, the Adelaide Lackner Professor and Chairman of Neurology at the University of Florida Center for Movement Disorders & Neurorestoration, Gainesville, Florida. Dr. Okun was corresponding author on a 2011 paper in *Neurosurgery* (69: 357-360) entitled “Do stable patients with a premorbid depression history have a worse outcome after deep brain stimulation for Parkinson disease”? The authors

compared the mood and motor outcomes for 110 Parkinson's disease (PD) patients, with and without a pre-surgical history of depression. Their data showed that patients with a pre-operative history of depression showed significantly higher levels of post-DBS depression than DBS patients without pre-operative depression. We understood this to mean that the patient's pre-operative history of depression is important, and the depression was not induced by the DBS. When asked to verify our interpretation, Dr. Okun replied: "Correct!" So, our interpretation of his data was correct, that DBS stimulation did not cause the depression. But he points out an important point that pre-operative depression is important to monitor prior to performing DBS procedures.

The last interview in this section was with **Dr. György Buzsáki**, MD, PhD, who is the Biggs Professor of Neural Sciences, NYU Neuroscience Institute, New York University Langone Medical Center, New York. Dr. Buzsaki was cited in a recent 2016 paper in *Science* (352: 397) entitled "Cadaver Study Challenges Brain Stimulation Methods". His team presented data at the Annual Meeting of the Cognitive Neuroscience Society in New York, showing that up to 90% of a 4 milliamp (mA) current applied to the outer cranium of a cadaver is not detectable inside the brain. If this result is correct, it could produce doubts about the mechanism or effectiveness of transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS) that postulate the current is altering brain electrical activity. Most tDCS and tACS devices deliver about 1-2 mA of current, and some in the field have already accepted the idea that the transcranial methods do not use enough current to trigger direct neuronal firing. When asked whether he was willing to share his working hypothesis on how tDCS might be working, and whether increasing the current would more strongly affect neural firing, he stated: "Of course, increasing the stimulus intensity will affect neuronal firing. Any current above 4 mA with the usual electrodes will do. The problem is that 4 mA will induce strong burning feeling of the skin, phosphene formation [seeing light when no light is present], strong vestibular effects, and a metal taste in the mouth".

So, Dr. Buzsaki pointed out that elevating the current during transcranial procedures produces several undesirable effects, and is not recommended. Some scientists argue that transcranial stimulations do not really work, and Dr. Buzsaki's data would support this by determining that no detectable current enters the brain. But if future transcranial procedures prove to have a verifiable benefit, we need to come up with a new mechanism to explain the improvement.

Results: DBS Ethics and Regulations

Samantha Gauthier

Our review of the literature in this area indicated that the FDA regulates DBS surgical procedures, some argue with little oversight, and there is no regulatory oversight of the transcranial stimulation field. Both techniques come with ethical considerations and conflicts of interest. To obtain more information in this important area, we performed interviews with bioethicists and scientists using these procedures.

The first interview was with an **anonymous bioethicist** who is currently evaluating DBS technology at Columbia University, New York, NY. She was a corresponding author on a paper (again anonymous) that illustrates the current lack of regulations overseeing the deep brain stimulation market, and argues it has resulted in a violation of basic ethical norms. Their discussion focused on the lack of available evidence for procedural safety and efficacy, and the numerous conflicts of interest held by research investigators in this field. These authors outline several ethical concerns that arise with industry-driven DBS research, such as: lack of transparency, limited regulations, conflicts of interest, lack of adequate evidence, etc. When asked her opinion of which of the issues outlined in her paper is the most crucial, she replied:

“I’m happy to hear you’re doing a project on this subject -- I’d be interested to hear more on what you produce! To your question: in my opinion the biggest issue is that of limited regulations. Regulations for medical devices are becoming ever-more lax with the 21st Century Cures Act. DBS is an important therapeutic tool for a few conditions, but neuro-stimulation technology is being rushed to the market for new indications with insufficient evidence of safety and efficacy. Not just “does it work as intended,” but does it improve the patient’s condition? Furthermore, after they approve it, will the FDA follow up on adverse events, and take action if and when they arise? Right now, their event detection and response protocol is thin to nonexistent. It is up to the CDRH (FDA) [Centers for Devices and Radiological Health] to request this kind of evidence and to monitor the device after it is on the market -- thus I think a shift towards this kind of role would have trickle down effects on the other, separate but related, issues of transparency, inadequate evidence, conflicts of interest, etc.”

So this bioethicist argues that requiring the FDA to mandate follow-ups on patient side-effects, and require action when detected, would have positive effects on other aspects of DBS such as transparency, inadequate evidence, and conflicts of interest.

The next interview was with **Dr. Joseph J. Fins** of the Division of Medical Ethics, New York Presbyterian-Weill Cornell Medical Center, New York, NY. Dr. Fins was corresponding author on a 2011 paper in the *Journal of Neural Engineering* (8: 033001) entitled “Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation”. The authors stated that the field of DBS has ethical conflicts of interest because the work is heavily reliant on collaborations between academic institutions, industry, and clinics. To help foster transparency and public trust, the authors provided ethical guidelines for helping manage conflicts of interest. They outline multiple guidelines and standards to put in place as an ethical framework for the use of DBS. The framework covers many areas such as industry, research, media presentation, interactions, and rights of a patent, among others. When asked of all the recommendations they stated which, in his opinion, is the most crucial to implement as a next step for advancing the field of DBS research, Dr. Fins replied: “Hard to answer that. All of it is important”. So, Dr. Fins did not prioritize the recommendations, but they remain important to help foster transparency and public trust.

The last interview in this area was with **Dr. Eric Racine** of the Neuroethics Research Unit, Institut de recherches cliniques de Montréal, Montréal, Canada. Dr. Racine was corresponding author on a 2009 paper in *Surgical Neurology* (72: 577-586) entitled “Preparing the ethical future of deep brain stimulation”. The authors identified current and emerging issues

with the use of DBS by reviewing the literature in the fields of DBS neurosurgery, medical ethics, psychology, and sociology. They also consulted regulations and reports for the U.S. Patent and Trade Organization (USPTO), Food and Drug Administration (FDA), and business reports of various DBS device manufacturers. Their results showed that important challenges remain in the areas of DBS patient selection, patient informed consent, resource allocation, and public understanding of DBS, all of which will increase as more DBS applications are found. They recommend that a combination of approaches previously used in the field of neuro-ethics also be applied to DBS, including the use of expert consensus workshops to help establish ethical guidelines, and the use of public engagement to improve public understanding of DBS. When asked whether such expert workshops have met to date, Dr. Roxane Caron, responding for Dr. Racine, pointed us to Bell et al. 2014, *Cambridge Quarterly of Healthcare Ethics*, 23: 361-368, entitled “Beyond Consent in Research: Revisiting Vulnerability in Deep Brain Stimulation for Psychiatric Disorders”. This paper argues it is important to consider the DBS patient’s vulnerability when making a decision whether to apply DBS surgery. They point out that enrolling psychiatric patients in invasive surgical procedures (like DBS) is risky, and a discussion should ensue with the patient about their ability to provide free and informed consent. This discussion should include evaluating the patient’s vulnerability in a broad relational context that includes their caregivers.

CONCLUSIONS / RECOMMENDATIONS

Based on the research performed for this project, our team has made several conclusions and recommendations.

Conclusions: DBS History and Diseases

Our review of the literature in this area identified a variety of neurological diseases and psychiatric disorders treated by DBS. Overall, the DBS experiments reviewed in this section showed that for specific types of disorders, DBS seems to be generally effective for its purpose...as a last-resort for treatment-resistant cases of movement and psychiatric disorders. But last-resort treatments come with some degree of danger, and some studies showed serious side-effects, including 5 deaths for one 2010 epilepsy study, and in another study 24 suicides out of 5311 PD patients. However, most of the studies reported relatively mild, transient, and controllable side-effects. One advantage of DBS is it is completely reversible, and in the studies reported here any unwanted side-effects due to the DBS stimulation were managed by slightly adjusting the current, and if a patient experienced negative symptoms from the stimulation, the current was simply switched off. Another advantage of DBS is that once the electrodes have been surgically implanted, the technique works long-term, as long as the battery is changed every few years. The common location of the pulse generator near the collarbone makes for a relatively easy battery replacement.

Some DBS treatments were more effective than others, and we made several conclusions. First, we found that some diseases were researched far better than others. For example, there were dozens of DBS studies on Parkinson's disease (PD) and obsessive-compulsive disorder (OCD), but relatively few on Tourette's syndrome (TS) or epilepsy patients. Because of this, we recommend that more large-scale controlled clinical trials be done, if possible, on the weak areas. However, one of our interviewees indicated he had trouble finding a sufficient number of TS patients for his clinical trial, so perhaps medical centers could cooperate on these difficult trials.

We also found that DBS surgical teams often become better over time with the procedure, and their success rates keep improving. But regardless of how proficient a team becomes, each patient's neural circuits varies slightly, so in addition to improving their electrode implantation skills, each team must establish procedures for carefully identifying the implantation site. One state-of-the-art example is the FP-PET scan of Dr. Jens Kuhn that identifies in a 3-hour scan the areas of elevated dopaminergic activity in a patient which has applications for PD and TS patients. Thus, each team will have to vary their electrode placement based on that patient's individual neural circuits.

We also found that some diseases have multiple components. For example, TS patients in addition to their involuntary tic activities can also have various co-symptoms, such as attention disorder, obsessive-compulsive disorder, or impulse control problems. These co-symptoms have their own disrupted neural circuits that are different from the main TS circuit, so the circuit

involvement varies between TS patients depending on the co-symptom present. Each TS patient must be individually evaluated, and the DBS applied to several circuits. We agree with one of our interviewees that more research needs to be done identifying which neural circuits become abnormal with each type of co-symptom.

Conclusions: DBS Safety

Medical procedures usually come with risks. When evaluating the risks, it is important to weigh their severity against the potential benefit of the DBS treatment to the patient. We found that some problems result from the DBS hardware inserted during surgery, including: swelling, infection, pain, fatigue, or intracerebral hemorrhage, DBS hardware malfunction, and DBS hardware interactions with pacemakers. These types of problems were not restricted to one type of disorder. Other types of side-effects depended on which area of the brain was being stimulated, from mild symptoms (headaches, forgetfulness, word-finding problems) to very serious symptoms (death and suicide). The mild side-effects were usually transient and treatable.

The most serious side-effect was suicide. Our search of the literature identified two types of patients most likely to attempt or complete suicide: treatment-resistant depression (TRD) and Parkinson's disease (PD). The most thorough study of suicide was done on PD DBS patients (Voon et al., 2008) who reviewed the data from 5311 patients; it showed that 24 completed suicide, and 48 attempted suicide. We also found 4 other instances of suicide in the literature for TRD patients. Although the studies showed that suicide was elevated in the DBS patients relative to sham controls, it was not proven that the DBS stimulation caused the suicides. In some cases, the suicide occurred in a patient not responding to the DBS. In any case, it is obvious that some patient populations, especially TRD patients, should be monitored closely.

Mania was a problem in some DBS-treated patients with refractory obsessive compulsive disorder (OCD). Our interviews with a scientist working with DBS OCD patients indicates he has on several occasions observed mania in these patients, but it may be difficult to prevent this side-effect in this particular population. He recommended (and we agree with) obtaining fully informed patient consent, to make sure they are aware of these possible side-effects. And if mania occurs, the DBS current should be lowered.

Severe fatigue was a problem in some PD patients. We identified only one study (Kluger et al., 2012) that specifically monitored for patient fatigue. Of 44 PD patients, 58% showed moderate to severe fatigue. The strongest predictor of the fatigue was pre-operative depression. Our interview with the corresponding author of this study indicated that he too is unaware of any other DBS studies focusing on fatigue, so we recommend this side-effect be further studied.

Infection was a common problem observed with surgical implantation of the DBS device. One of our interviewees indicated that infection is the most serious complication observed in all of his DBS patients, observed not only early post-surgery, but after several months. In some cases the DBS device had to be removed. Perhaps better methods of equipment sterilization or developing faster methods of implantation (to limit the time the brain is exposed) would help minimize this serious complication which can permanently damage the brain.

Another problem with DBS is that cardiac devices (pacemakers and defibrillators) have been found to interfere with the DBS signal. Our interview with the scientist publishing this data indicated he thought that the DBS device did not harm the cardiac device signals, but that the cardiac device signals could lower the effectiveness of the DBS. In this patient, he simply relocated the DBS stimulator, but this might not work for some patients where the location of the DBS electrodes must be precise. So, it is important to query the patient in advance of DBS surgery to see if they have any other implantable electronic devices.

Transcranial direct-current stimulation (tDCS) is progressively being used as a non-surgical option for DBS, to treat a variety of disorders or to alter neuronal plasticity. But this non-invasive technique also has side-effects. In 2007, a team in the Department of Clinical Neurophysiology, Georg-August University (Göttingen, Germany) summarized various adverse effects in 567 tDCS sessions performed in their labs over a two year period (Poreisz et al., 2007). The side-effects reported were (in descending order): a mild tingling sensation (70.6%), moderate fatigue (35.3%), a light itching sensation under the stimulation electrodes (30.4%), headache (11.8%), nausea (2.9%), and insomnia (0.98%). So, the types of side-effects seen with tDCS appear to be milder than those observed with DBS.

Conclusions: DBS Alternatives and Advances

Several non-surgical electrical stimulation options to DBS have been developed, including: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS). All three of these non-invasive techniques have articles showing they significantly improve patient outcomes, although the literature for tDCS is conflicting, with some studies arguing it does not work. The tDCS field has been generally criticized for a lack of rigor, as many of the experiments have been performed by home users. And early studies sometimes pooled the results from multiple sets of experiments, each done with different devices and procedures. Some of the very recent studies that have been carefully designed and controlled are starting to show no effects of the tDCS technique. Many of the studies did not analyze for any off-target or side-effects, so more attention should be paid to safety. For the transcranial techniques, a stimulation intensity of up to 2 mA and a duration of about 20 min appears to be generally safe, and most frequently observed adverse effects are minor: light itching beneath the electrodes and headaches. Such effects have been observed both in healthy subjects and in patients with neurological disorders. Other lesser seen risks include the generation of electrochemically produced toxins, deposit of electrode dissolution products at the electrode-tissue interface, excitotoxic damage to overdriven neurons, and electrode placements that could result in brainstem or heart nerve stimulation. Moving forward, it is important to standardize the stimulation protocols to enhance the comparability of research results.

With respect to the controversy whether tDCS works, one of our interviewees discussed his data showing that no electrical current is detectable inside the human cadaver cranium from tDCS used at the usual 1-2 mA. So, he argues the human skull is too thick to transmit electrical currents at only 1-2 mA. Elevating the current to 4-5 mA is not feasible for safety reasons, as it produces several undesirable side-effects. So, our interviewee's data supports several of the negative studies we found arguing that tDCS does not work, because in his case no electrical

current entered the brain. But if future transcranial procedures prove to have a verifiable benefit, we will need a new mechanism to explain the improvement.

Closed-loop neuro-stimulator devices are relatively new. These innovative devices continuously monitor the patient for abnormal electrical activity, and once detected initiate a corrective DBS stimulation. These devices are especially effective with epilepsy patients where they have been found to significantly reduce seizure frequencies. Unfortunately, no clinical trials have been performed, so their efficacy cannot be evaluated yet.

Conclusions: DBS Ethics and Regulations

Our review of the literature identified several ethical problems associated with DBS, including conflicts of interest (COI) between patients, surgeons, device manufacturers, and researchers. Our interviewees pointed out that the DBS field is susceptible to COI because the work depends heavily on collaborations between academic institutions, industry, and clinics, each with their own agenda. The highest priority in this area is to improve the transparency of the entire DBS process, including: 1) patient selection (determining which patients are likely to benefit from DBS), 2) device selection (what is the rationale for a surgeon choosing a particular device, and does that device work well for this particular disorder), 3) brain target selection (how was a particular patient's site chosen, and what are the potential side-effects likely to be encountered), and 4) requiring the monitoring patient side-effects for long periods of time. This transparency should help improve public acceptance of DBS technology, and help improve any conflicts if they arise.

With respect to regulations, we recommend that the FDA mandate that surgeons performing DBS be required to do long-term follow-ups on all patients looking for potential side-effects, and once detected, corrective action be taken including removing the device. One of our interviewees who has performed a review of the DBS field complained that few regulations require long-term follow-ups.

With respect to tDCS devices, we recommend that safety studies be performed at a variety of currents, and that devices capable of stimulating more than 2 mA not be publically available unless later proven to be safe. Furthermore, effective guidelines from reliable sources should be put in place so that risks associated with tDCS do-it-yourself applications can be minimalized.

As more DBS applications are discovered each year, the above mentioned problems will become even more important. We recommend that successful approaches used by others in the field of neuro-ethics be applied to DBS, including the use of expert consensus workshops to help establish DBS ethical guidelines, and the use of public engagement meetings to help improve the public understanding of DBS.

APPENDIX

Example Questions for Deep Brain Stimulation (DBS) Experts:

1. Clinical Trial Comparisons: Our search of the literature indicates that it is very difficult to compare clinical trials to each other because they often used different DBS techniques. And most of the trials are relatively small. Do you agree with our assessment? Do you agree that larger trials are needed?
2. Mechanism: What is your lab's working hypothesis on how DBS works to alleviate your patient's symptoms?
3. Side-Effects: Have you observed any undesirable side-effects in your DBS patients? If so, which side-effects, and were they easily treatable? Do you think the medical benefits of treating the primary disorder outweigh any side effects?
4. Equipment Malfunction: It is our understanding that the hardware (electrodes, wires, stimulator) sometimes malfunction. Have you observed this? Is the technology improving? Are some devices more reliable than others?
5. Which Diseases: Which diseases seem to respond best to DBS in your opinion (which applications show the strongest data)?
6. Patient Selection: In your opinion, is there a way to determine which patients are most likely to respond to your DBS technique? To our knowledge, most DBS patients have not responded to previous conventional therapies, is this the case in your studies?
7. Cost: How expensive are most current DBS surgical implantations?
8. Alternatives: Would any of the alternatives to DBS, including transcranial stimulation, work with the diseases you study?

Example Questions for Transcranial Stimulation Experts:

1. Applications: Which types of applications do you think transcranial stimulation works best for? Improving cognition? Improving depression?
2. Efficacy: How strong is your lab's evidence that transcranial stimulation works? What applications does your lab study? What types of experiments would be necessary to prove your technique works for a given application?
3. Side-Effects: Has your lab observed any deleterious side-effects? If so, which ones, and were they easy to treat? Are you aware of any long-term studies looking for side-effects?

4. Equipment Malfunction: Have you ever observed equipment malfunction? Is the technology improving? Are some devices more reliable than others?

Example Questions for Bioethicists:

1. Safety: How safe do you think DBS is? Are you aware that some studies have reported suicide deaths following DBS, were these cases expected given the particular disease being treated, or were they a result of the DBS?
2. Cognition: What is your opinion of the ethics of transcranial stimulation for improving cognition? Is this a fair practice for improving, for example, exam scores in school? For improving sports performance?
3. Ethical Studies: Are you aware of any ethical studies done on transcranial stimulation techniques? Which types of experiments would you like to see completed to provide greater insight into DBS technology?

Example Questions for Legal Experts

1. DBS Laws: What laws currently regulate DBS technology in the U.S.? What changes do you think should be implemented?
2. Transcranial Stimulation Laws: It is our understanding that transcranial stimulation is currently not regulated in the U.S., do you think it should be? What regulations do you recommend? Should there be a maximum electrical current allowed for self-administering devices? If a person hurts themselves using transcranial stimulation, who do you think should pay for their treatments? What type of regulations do you recommend for maintaining quality control for stimulation devices to minimize their harm to the user?

Interview Preamble

We are a group of students from the Worcester Polytechnic Institute in Massachusetts, and for our research project we are conducting a series of interviews to investigate problems associated with deep brain stimulation (and its transcranial stimulation alternatives) for treating neurological disorders.

Your participation in this interview is completely voluntary, and you may withdraw at any time. During this interview, we would like to record our conversation for later analysis. We will also be taking notes during the interview on key points. Is this okay with you?

Can we also have your permission to quote any comments or perspectives expressed during the interview? This information will be used for research purposes only, and we will give

you an opportunity to review any materials we use prior to the completion of our final report, which will be published on-line in WPI's archive of projects.

If the subject does not agree to be quoted, we will respond as follows: "Since you would not like to be quoted during this interview, we will make sure your responses are anonymous. No names or identifying information will appear in any of the project reports or publications."

Your participation and assistance is greatly appreciated, and we thank you for taking the time to meet with us. If you are interested, we would be happy to provide you with a copy of our results at the conclusion of our study.