Deep Brain Stimulation

A Technology Assessment

Aric Fitz Coy
Bamini Balaji
Deyeon Kim
Xinlin Yu

California Institute of Technology
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Introduction

The portrayal of psychosurgery and lobotomies from the 50's and earlier have sufficiently spread a public distaste to the term, “brain surgery”. Since then, the relatively benign and reversible procedure of deep brain stimulation (DBS) has revived this concept. DBS is a surgical treatment currently used for neurological symptoms and movement disorders. It also has the potential to treat for cosmetic neurology as well as psychiatric conditions.

DBS involves the implantation of a lead into the targeted region of the brain with an extension passing from the brain to behind the ear, then towards the clavicle and finally to an implantable pulse generator (IPG) positioned at the shoulder. The IPG delivers electrical stimulation, which targets specific regions of the brain through the leads. Currently, DBS is used as a treatment for the symptoms of Essential Tremor, Parkinson’s disease, dystonia and recently obsessive compulsive disorder (OCD).

Parkinson’s disease is a neurodegenerative disorder caused by death of dopamine containing cells. The primary symptom of this disorder is movement disability. Currently, there are different types of treatments. Oral medications such as levodopa/carbidopa increase the dopamine concentrations. Ablative surgeries involving lesioning of deeper brain structures such as pallidotomy and thalamotomy were used to permanently remove the abnormal stimulation activity in the central nervous system. With DBS, targeted parts of the brain include the ventral intermediate nucleus of the thalamus, subthalamic nucleus or the internal segment of the globus pallidus.

Research and clinical studies are currently focused on expanding the applicability of DBS to other disorders and conditions including obesity, depression, epilepsy, Tourette’s syndrome
and possibly even addictions. At the same time, new drugs and medical therapies that could replace DBS are also gaining momentum in research and clinical trials. While DBS is currently the best alternative for several symptoms as suggested by neurosurgeons and practitioners, its future is still subject to the development of competitive technologies and medical breakthroughs.

**History and Background of DBS Technology**

Deep Brain Stimulation was an accidental technology. Its development began in the 1960’s when Dr. Irving Cooper, a neurosurgeon at the Mayo Clinic, accidentally cut into the anterior carotid artery when performing brain surgery on a Parkinson’s patient. When he tied off the artery, it caused the patient to stroke. When the patient awoke, it was discovered that the tremors improved across half of his body where he had experienced the stroke.

Another contribution to the development of DBS occurred in 1977 when Barry Kidston, a drug addicted graduate student, was trying to synthesis Desmethylprodine, MPPP. Desmethylprodine is an opioid analgesic drug that is often created as a recreational drug. Unbeknownst to Barry Kidston, the synthesis of Desmethylprodine produced the side product 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP. When he injected the drug into his system, he developed early stage Parkinson’s disease due to MPTP.

As a result, researchers were able to develop a model to study Parkinson’s disease by injecting MPTP into monkeys. In 1983, by putting probes into the monkey’s brains, they found the direct and indirect dopamine pathway which contributes to Parkinson’s disease. From 1983 to 1990, researchers took readings in the basal ganglia of both normal and MPTP treated monkeys, hence proving the relation between the basal ganglia and movement disorders. In
France in 1987, Professor Alim-Louis Benabid and his colleagues showed that inputting 100Hz into the human thalamus could greatly reduce the effects of Parkinson’s Disease.

The technological capabilities caught the attention of Medtronic, which was the first company to invent the pacemaker device 60 years ago. Medtronic formed useful collaboration with Professor Benabid in the late 1980s. This enabled Medtronic to channel its resources and technological background from pacemakers to develop deep brain stimulators for commercial medical purposes. This partnership in industry and research in combination with suitable technological management has facilitated the development of DBS devices.

Today researchers and neurosurgeons have not completely uncovered the biochemical functions of this technology. It simply appears to block abnormal firing of neurons. Further research and clinical trials are being done to improve understanding of DBS and thereby promote the efficacy of the device.

**Stereotatic Surgical Procedure**

The surgical process of DBS is a multi-step procedure. Weeks before surgery, the patient consults with the neurosurgeon. Before considering DBS treatment, the candidate patient is screened for whether or not DBS treatment will work. If the patient passes the screening tests they are videotaped and are given a pre-operation education orientation. MRI, ECG, chest x-ray and preoperative lab tests are performed.

On the day of the surgery, the patient’s head is placed into a 3D frame. The surgeon then drills holes into the patients’ skull. Computer guidance system is used to position the stimulating electrode. The surgeon then converts the misfiring of signals into noise and interprets the static.
The electrodes are positioned where they observe the static peaks. The patient is then awakened to do test simulations and verify the efficacy of the procedure.

A week later, the patient returns to have the battery pack and the pulse generator device implanted. The device is also programmed.

Figure 1 shows a schematic of the deep brain stimulator.

![Figure 1: Schematic of Deep Brain Stimulation Technology](image)

The electrode attached to a lead is placed in the desired location of the brain. The lead is extended and connected to the pulse generator.

On meeting with neurosurgeons at Huntington hospital, we realized the importance of appropriate training and support from the device manufacturers. Representatives from device manufacturers are in constant contact with neurosurgeons and practitioners at Huntington hospital trying to ease the surgical process, device programming and to replenish stock supplies. In addition, the representatives take feedback regarding technological improvements and report to their engineers to continue developing the product. Collaboration between the device developers and medical practitioners has promoted technological improvements and it has helped establish this technology.
Research Methodology

Our focus was on current existing deep brain stimulation treatments for neurological disorders, particularly involving movement related symptoms. With our contacts at Boston Scientific and through the Caltech Alumni association, we were able to interview a diverse group of people for information on this topic. This diverse group of contacts allowed us to get many different perspectives on DBS, from those who research DBS to those who produce products for the DBS industry to those who are the end users of the technology.

We first started by researching the broad DBS field. As we dug deeper, we found that DBS as a whole was too large of a field for us to study in a 10 week period. Thus, we decided to focus on the use of DBS to counter Parkinson’s disease. We did some secondary research on the internet and in books to get some background information. We then proceeded to contact primary sources to set up interviews to gather more information.

Technology Growth and Development

Testing and Approval

In order for medical devices to be used in the United States, they are required to get approval from the Food and Drug Administration (FDA). The FDA approval process is a very lengthy and expensive one. In the approval process, companies developing DBS have to get approval for their device technology, targeted disease and also validate the site of the brain they wish to stimulate. Currently DBS has FDA approval to target the subthalamic nucleus, globius
pallidus and ventral pallidum regions of the brain. Research is underway to find more regions of the brain that can be stimulated.

The approval process is divided into three phases. Phase 1 of the trial requires a proof of concept verification to ensure that the device is capable of doing what it claims to do. In Phase 2, the safety and tolerance of the device will be tested. Phase 3 involves clinical trials on patients to show that the procedure is safe to perform on people and to show that the device has a positive effect on the problem it’s designed to solve. Following these phases, FDA decides, based on the empirical evidence, whether the device exemplifies superiority over existing technologies or if additional trials are necessary. This overall process takes 10+ years for a company to complete. Overall, we have learned that medical devices are regulated less in comparison to new drugs.

Currently, Medtronic is the only company that has FDA approval to sell its DBS devices, Activa. They have devices for essential tremor (1997), Parkinson’s disease (2002), dystonia (2003) and OCD (2009). Medtronic’s device for depression is undergoing clinical trial. St. Jude Medical is also developing its brand of DBS devices, Libra.

The overall process of FDA approval can hence be seen as a curse and a blessing for the companies seeking to launch their products. While the process is time-consuming, it allows companies to provide medical practitioners with their product as a trial-run. This also allows companies to establish partnerships with hospitals to increase awareness of their product.

Certain conditions such as OCD and dystonia that target a very small demography of less than 4000 individuals have less stringent FDA device development requirements. These devices are characterized as humanitarian use devices and are subject to humanitarian device exemptions. This encourages companies to develop these devices.
Before this process, companies do their own internal validation testing. For example, tests are performed to determine number of stress cycles leads can withstand, to study how the device responds during everyday use and also to determine how the device responds at the extrema of its design parameters. Tests are also done to determine what the expected lifetime of the device is. Physicians are then brought in to implant the device into cadavers to refine the surgical procedure and identify any problems they see with the device. Animal testing occurs next, where the device is implanted into pigs and the brain tissue is checked to ensure it’s not damaged. The results from the initial animal trials are taken into consideration as well with during the FDA approval process.

**Commercialization**

When Medtronic developed deep brain stimulation in collaboration with French scientists in the 80’s, they were looking at a completely untouched market. Once they were able to bring a FDA approved product to market, Medtronic was able to tap into this market. However, they had to get the word out about their product. There are two levels of spreading product information. Company representatives reach out to the hospitals and neurosurgeons to promote their product. Similarly, neurosurgeons recommend appropriate patients to undergo the surgery. Nowadays, DBS treats more neurological disorders. However, the general population is still relatively unaware of DBS. Through handing out pamphlets on the technology which highlights different success stories, Medtronic is attempting to gain awareness about its products. Now with the use of television specials and Youtube videos, Medtronic has also been able to increase awareness about the benefits of DBS.
DBS Market Analysis

Applicability

DBS treatment is currently applicable to patients with Parkinson’s disease, essential tremor and dystonia, which consists of over six million people globally. However, it is not recommended in certain cases. If a patient is suffering from other conditions such as Alzheimer’s disease, dementia or psychosis, there may be additional harms in the surgical procedures. In addition, DBS is not recommended for patients that are completely dependent on their medication or for elder people typically over the age of 70, or for those that are not in healthy enough to tolerate surgery. Various tests are conducted prior to the surgical procedure to ensure the patient is suitable to get DBS. Overall, this narrows the market for potential candidates for DBS treatment. There are over 300 medical centers across the United States that perform the surgery. Some centers treat up to 100 patients a year while other centers treat only a few patients.

Patient preferences of DBS are also a factor that may affect the market for this technology. <redacted for confidentiality> Because this process is invasive and there is insufficient publicity, many patients do not want to get the surgery or are not aware this procedure exists.

Over time the market for DBS has grown. Before it was considered only for patients with later stages of Parkinson’s disease, but now, it has become more widely used even for beginner stages so that early symptoms can get treated.
Customer Preferences

Preferences of neurosurgeons, patients and collaborators also have an effect on the market. One preference involves the battery lifetime. The battery lifetime is dependent on the use of the technology in stimulation and neuromodulation in the brain. If it is heavily used to generate pulses, then it may last for less time.

Recently, Medtronic has come out with rechargeable batteries called the Activa RC neurostimulator for DBS. This device allows the patient to charge the batteries thus allowing for extended battery life. The rechargeable system is very bulky and is a three part system which includes an AC power supply, recharger and a shoulder belt that is placed over the placed directly over the neurostimulator. It requires the patient to recharge the battery every three days. If they forget to recharge the battery than stimulation will cease and patients must go into back to the hospital to get the system reprogrammed. We were told that if this occurs, more than twice the patient we get a new system implanted. In addition to remembering to recharge the battery, the recharging system has many icons and buttons making the system not very user friendly. As a result, surgeons still advise patients to get the non-rechargeable battery system unless their therapy is especially battery intensive. At Huntington hospital, non-rechargeable batteries are recommended because although they must replace the battery every 5 years, the procedure is very quick and relatively painless.

Further preferences come across in device programming. Medtronic has recently released a system called Activa PC, which allows for patients to personalize their treatment and make minor adjustments in the amount of signal sent to the brain. This allows the patient to lower or increase the signal depending on the level of activity. For example, patients with essential tremor do not need to have the therapy on at night because their tremors only occur
when they are performing a task that requires intention. This is because over time with prolonged use of the stimulation, the amount of signal required must be increased. Thus by allowing the patient to decrease signal or the “on” time of their treatment, it will allow for longer time before they must increase signal to an unreasonable amount.

**DBS Device Developers and Competition**

DBS developers include Medtronic, Boston Scientific and St. Jude’s. As mentioned earlier, currently Medtronic’s *Activa* is the only FDA approved provider of this device in the United States while St. Jude’s is undergoing clinical trials for their own DBS system, *Libra*. Boston Scientific is still in the early phases of the getting FDA approval.

With the imminent entry of St. Jude’s into the market, Medtronic, which once held a monopoly, is now driven to market and improve their products. Medtronic has added released two new upgrades to their product: the rechargeable battery pack and allowing patients to make control levels of stimulation.

Huntington Memorial hospital uses products of Medtronic and also participates in St. Jude’s clinical trial. Besides the minor upgrades made by Medtronic, practitioners at Huntington hospital agree that while each system has its pros and cons, they are essentially the same. Feedback from patients shows that there is no difference in outcome between the two products. Reasons patients choose St. Jude’s *Libra* over Medtronic’s *Activa* simply because it may be cheaper and some patients like to take part in clinical trials for the “novel” product.

As a result, in the present state when St. Jude’s obtains FDA approval, hospitals may choose which product to use based on device costs, the company with whom they have a better alliance with, or the company that offers a more convincing device.
Current Competitive Technologies

DBS has taken away market from ablative surgical procedures of pallidotomy and thalamotomy. Originally these techniques were irreversible surgical procedures to destroy part of the brain and thereby treat Parkinson’s disease. With DBS, such permanent and irreversible destruction is no longer required.

In terms of oral medications such as Levodopa, Carbidopa or a combination of the two, there are other associated problems. Wearing out of the effect of these medicines and the frequency at which they must be taken is a major factor for people to choose DBS. Over time, Parkinson’s disease patients have to take more and more of the drug to relieve their symptoms. As a result, patients become heavily dependent on the drug and get many side effects like OCD, hyper sexuality, and addictive behaviors. As a result, when patients no longer benefit from the drugs or get too many side effects from the drugs, with DBS they are able to reduce the amount of medication they need to take by 50%.

Roadblocks and Risks

Roadblocks to Adoption

There are many technological challenges to the adoption of Deep Brain Stimulation treatment. In the stereotactic surgical procedures, there may be risks as it is crucial to pinpoint the exact location of the brain that requires stimulation. This requires an appropriate neurosurgeon skill set in order to undertake the surgery. Another problem is the malfunction of the implanted hardware which could cause recurrence of the illness or worsening of the symptoms.
The most significant deterrent in the establishment of DBS technology is the regulations. FDA approval for medical devices is a lengthy process designed to ensure the safety and applicability of the device which usually takes 10 years.

Another step in the regulatory procedure necessitates the hospital’s approval for surgical procedure. The internal review board of the medical institution must allow the procedure in order for its surgeon to operate.

**Treatment Risks**

DBS surgeries have many associated risks. The largest risk is the potential for hemorrhaging, seizures, infection and excessive bleeding. Excessive bleeding can sometimes lead to strokes in less than 1% of patients. Experienced surgeons from hospitals like the Huntington Memorial Hospital have found innovative ways to prevent serious risks during surgery. Surgeons have found that by carefully controlling blood pressure the likelihood of a stroke occurring greatly decreases. Additionally, infections may occur as the procedure involves drilling two holes through the patient’s skull, thereby exposing the brain to the outside environment. Statistics by Hamani and Lozano has shown that 6.1% of patients have been experience infection.

Other risks include misplacement, misalignment, lead fractures and skin erosion. Misplacement of the lead during surgery can also have serious side-effects for example speak or swallowing impediment. It was reported that 5.1% of patients suffer from misplacement and misalignment of leads. Lead fractures also occur in 5% of patients. 1.3% of patients experience skin erosion.
Other than the operative risks, there are also stimulation risks due to the fact that the electrode does not have a localized effect causing the stimulation of surrounding portions of the brain. This can lead to unwanted effects such as depression, psychosis, cognitive decline, impulsivity etc. Other risks include side effects from stimulation like facial pulling. This is can easily be alleviated by turning the program turn off or removing the device and reinstalling the device much later. Finally there is the possibility of fracturing the device or leads when the patient takes a heavy fall. Although surgeons have been able to remedy this problem by sucturing the tightly, the likelihood of fracturing the device greatly decreases.

Another cognitive drawback is memory decline in patients. Studies from Hartz shows that memory deficits and psychiatric issues were experienced by many people had underwent deep brain stimulation. Studies show that 18.8% of patients who underwent subthalamic nucleus stimulation experienced memory loss. Another study shows that 12.5% of patients who underwent globus pallidus stimulation experienced memory lose while 18.8% of patients who underwent subthalamic nucleus stimulation experienced memory loss.

Although, DBS has some drawbacks, its main benefit is that it can improve motor features of Parkinson’s disease by 40-60%. Patients fluctuate between “On phase” when their medicines are effective and an “Off phase” when their medicines do not take effect. With the progression of the disease, these fluctuations become more frequent and difficult to manage. DBS improves the “Off phase” and regulates the symptoms.
Cost Analysis

DBS is a fairly expensive procedure. However, due to the proprietary nature of this information, we were unable to obtain exact device costs. Additionally, the conflicting information we have learned makes it all the more harder to estimate product and surgery costs.

Current insurance companies such as Aetna and Empire Blue recognize treatment of the FDA approved DBS devices and have defined medical policies for their application. Additionally, Medicare reimburses DBS treatments for Parkinson’s disease and essential tremor. In comparison, Medicaid splits reimbursements 50-50 between federal and state, so some states will pay very little. As a result, doctors may not refer such patients to DBS because they are unable to pay for the procedure out of pocket.

S-Curve Analysis

Spinal cord stimulation (SCS) is an appropriate technology in which to compare and extrapolate the future of the DBS market. Both devices are classified as neuromodulation devices, and both therapies involve invasive surgery. In 1981, the first SCS device, made by the Corpis Corp., was approved by the FDA. The second device, made by Medtronic, was approved in 1985; and the last device, made by Advanced Bionics, was approved by the FDA in 2004. Currently, SCS is only approved for the use as an “aid management of chronic, intractable trunk and limb pain”. Since its first approval, the SCS market has grown to its current size of $1 billion dollars. As SCS technology improved, it has been used for broader therapy uses. The SCS
market is expected to grow to $2.6 billion globally by 2015. Even thirty years after the first FDA approval of SCS, the SCS market is expected to grow at 14% CAGR.

Currently, the DBS market is estimated to be around $360 million. According to Kim Meckwood, Medtronic representative, DBS is primarily used on Parkinson’s patients. There are 1.5 million Parkinson’s patients in the U.S., out of which only 3% have gone through the process of DBS therapy. DBS is currently approved for use in essential tremors, Parkinson’s disease, dystonia, and OCD. She claims that the biggest barrier for the growth of DBS is awareness. With more awareness, more people with Parkinson’s disease as well as other neurological disorders may decide to go through the DBS therapy. Medtronic is pushing for the approval of its DBS device for the treatment of depression, which 10 million people suffer from in the U.S. If DBS is approved for the treatment of depression, it is believed that awareness of the therapy will grow as more people can benefit from it.

If the DBS market behaves similarly to the SCS market, we can expect high growth in the DBS market until 2030. As a conservative estimate, we will consider 2030 to be the strategic inflection point for the technology. DBS has already been approved for multiple neurological disorders with more expected to be approved in the future. From analysis of this data, we created the S-curve as seen in figure 2.
Future Developments

Progress in DBS

There are ongoing studies and industrial R&D to increase the applicability of DBS to treat other diseases and disorders. Medtronic device is already in clinical trial for depression and epilepsy. Additionally, there is potential for DBS expansion to treat addicts, obesity and
Tourette’s syndrome. However, it is important to note that DBS is not a cure all treatment. There are several conditions such as Alzheimer’s disease and psychosis whose symptoms cannot be treated with DBS. The technology has a diverse range of conditions under which it can be applicable, but it also has its limitations.

DBS typically involves the insertion of two leads for bilateral stimulation. Some practitioners have implanted multiple leads in the brain to offer further relief to patients. However, the efficacy of such multiple lead systems is debatable in the medical community. Research is currently being done at places such as Huntington Medical Research Institute for multiple lead array systems to stimulate at 64 sites.

Currently, DBS is approved to be used to stimulate certain regions of the brain. There is research being done to stimulate regions of the brain that are closely connected to spinal cord.

**Photostimulation, Oral Medications and Alternative Treatments**

While DBS is gaining momentum with the new device manufacturers and increased publicity, there are also several competing technologies that are being developed. Research has revealed the importance of factors and pathways other than the dopamine pathways in the progression of Parkinson’s disease. Clinical trials are currently underway for drugs such as Droxidopa to activate the norepinephrine cascade. Similary monoamine oxidase B (MAO-B) inhibitors follow different mechanisms to boost levels of dopamine. Medication Selegeline is one such drug. Such drugs also have the potential for alleviating symptoms of Parkinson’s and these parallel developments may hinder the development and adoption of DBS technology.
Another form of treatment that is being developed involves photostimulation of the brain with the use of light as a source of energy. Stimulation with the use of electrodes has drawbacks such as scarring in the tissue known as gleocis. Photostimulation is accomplished by means of light sensitive channels and receptors. It creates photocurrents that evoke neuronal responses. This technology is currently being researched and has great potential to replace DBS.

Radiosurgical ablation is an upcoming technology that is also replacing older procedures to destroy parts of the brain. In this procedure radiation is focused onto targeted regions of the brain enabling destruction of the brains cells in that area. Unlike other surgical treatments, this is non-invasive.

Various neurosurgeons and a lead researcher at Boston Scientific believed that in the future gene therapy will surpass the potential of DBS with respect to treatment of Parkinson’s disease. Gene therapy is a technique to correct defective genes by insertion, swapping or repairing genes that affect the development of diseases. Phase 2 studies are being done on a gene therapy, NLX-P101, which dramatically decreases movement-related symptoms of Parkinson’s. Growth factors are another treatment that can ensure that dopamine cells are alive and capable of being repaired.

It is difficult to say when these alternative treatments may come to the market. However, with the development, DBS has the potential to be replaced.

How Big Will it Be?

Deep brain stimulation has shown great potential for applicability to treat a diverse range of symptoms. It can expand into various new markets for different diseases and conditions. While research is ongoing for alternative technologies and treatments, DBS is currently the best
choice on the market. While company representatives claim that current DBS technology is still at the “tip of the iceberg”, neurosurgeons and researchers are skeptical about its future market appeal. With the commercialization of gene therapy, photostimulation and superior oral medications, DBS treatment may get phased out. Nonetheless, as of now, it is the best option to alleviate symptoms of movement disorders.
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