

Deep Brain Stimulation: Neural Tissue Response and Analysis of Adverse Events

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Abstract - Deep brain stimulation (DBS) is a common treatment for numerous neurological disorders, especially movement disorders, including, but not limited to, Parkinson's disease, essential tremor, and dystonia. Despite growing recognition, drastic shortcomings of DBS include infection, inflammation, hardware breaks, and extreme withdrawal syndrome. Brain-machine interfaces can be implemented only if the neural tissue response to electrodes and implants is understood and optimized. In this study, we analyzed adverse events resulting from DBS implantation. Through the past decade of DBS implant malfunctions, injuries, and deaths, it is apparent that high impedance and lead problems are major blockages. High impedance blocks the transmission of signals to the brain stimulator, deeming it useless. Leads are known to cause infection, especially along the incision site of implantable pulse generators (IPG). While the surgical technique depends on the skill of the surgeon, infections occur in a significant number of patients. Infection often means complete removal of the IPG, which could cause severe withdrawal syndrome; Parkinson's patients may experience severe motor symptoms such as akinesia or rigidity, dystonia patients can develop status dystonicus, epilepsy patients may experience an increase in seizures, and obsessive-compulsive disorder (OCD) patients may have worsening neuropsychiatric symptoms and suicidal ideation. In addition, studies have shown that quality-of-life scores after DBS are usually lower than preoperative scores, indicating that the long-term efficacy of DBS for treating these disorders may not be beneficial. However, recent studies on antimicrobial catheters may present an effective and inexpensive strategy against infection. As DBS is a relatively new technique, large, randomized clinical trials are still needed to provide necessary data to draw conclusions on long-term efficacy and safety, and device modifications may be needed to optimize the tissue response.

Keywords: deep brain stimulation, neurosurgery, infection, movement disorder, brain-machine, withdrawal syndrome, antimicrobial catheter, antibiotic resistance

1. Introduction

Neuroscience is a relatively new branch of science compared to other subjects; deep brain stimulation (DBS) is one of the most recent technological advancements within it. Although the first DBS surgery did not occur until 1987, most neurosurgeons were aware of the effects of electro-stimulation since the 1930s [1]. Starting in 1966, modified cardiac pacemaker devices were used to treat chronic pain through stimulation of the spinal cord and thalamus [2]. Twenty-one years later, in 1987, French neurosurgeon Alim-Louis Benabid noted that DBS can decrease tremors in Parkinson patients [1]. This kickstarted interest in DBS; he eventually won the Lasker-DeBakey Clinical Medical Research Award in 2014 for his role in developing DBS for Parkinson patients [2].

Despite DBS usage for almost forty years, the Food and Drug Administration (FDA) did not approve use of DBS for any patients until the mid 1990s. A major setback was from 1960 to 1975 when major medical device failures skyrocketed: 10,000 injuries, 700-plus deaths, and 22,000 neurotransmitter recalls were reported [1]. With these bleak statistics, in 1976, the FDA required clinical trials to be done before neurotransmitters could be marketed. Twenty-one years later, in 1997, the FDA approved the use of unilateral DBS for essential tremor and severe Parkinson's disease. In 2002, five years later, the FDA approved the use of unilateral DBS for general Parkinson's cases and dystonia [1].

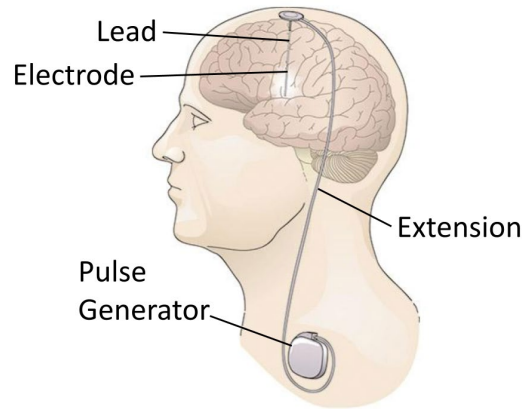


Fig. 1: Depiction of deep brain stimulation in the body [2].

Deep brain stimulation (DBS) is a surgery where a neurosurgeon places electrodes through holes in a specific area of the brain, such as the subthalamic nucleus (see Figures 1 and 2) [3]. These electrodes are connected by long wires to a neurotransmitter in the chest. The device regulates brain activity through electrical pulses, blocking faulty nerve signals that cause symptoms of Parkinson’s disease, essential tremor, and more [3]. DBS is currently used for 28 different disorders across 26 brain targets with 15,000 patients [4]. In this paper we will investigate the efficacy of DBS, adverse event reports for DBS implantation, withdrawal symptoms that may happen upon halting DBS, and potential solutions to complications.

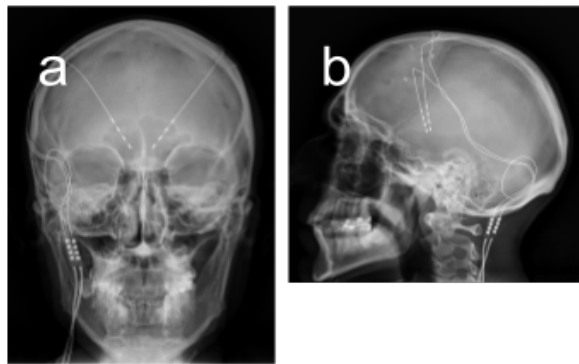


Fig. 2: X-ray showing placement of deep brain stimulation (DBS) leads in a 42-year-old male with obsessive compulsive disorder in 2013. The device is a Medtronic lead number 3391. (A) Frontal x-ray of the head. (B) Lateral x-ray of the head [19].

2. Materials and Methods

Deep brain stimulation (DBS) is an encouraging treatment method for movement disorders and psychiatric disorders. However, reports of malfunctions and injuries from the past decade inhibit further progress for widespread use of DBS. We searched the FDA Mechanical and User Facility Device Experience (MAUDE) database using the search terms “Deep Brain Stimulator for Obsessive Compulsive Disorder” and “Implanted Brain Stimulator for Epilepsy,” and recorded all adverse event reports from 2011 to 2021 in the United States. It is important to note that the FDA MAUDE database relies on voluntary reporting from patients and caregivers, as well as mandatory reporting by manufacturers and facilities. The data may not be a true reflection of the adverse event rates attributable to various classes of medical devices.

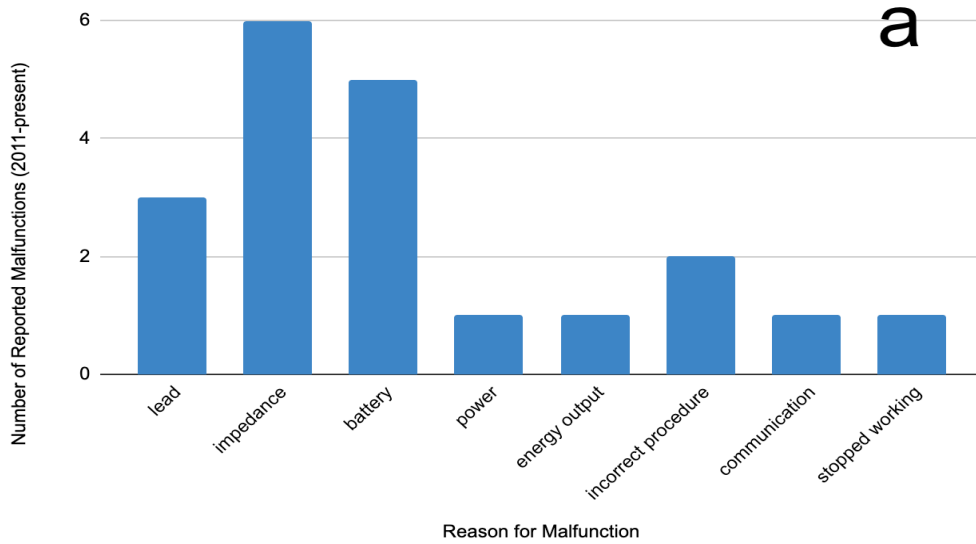
3. Results and Discussion

3.1. Clinical Safety

After sorting through malfunctions, injuries, and deaths for both search terms, we found the most common sources of DBS malfunction to be lead breaks/malfunctions, high lead impedance, and battery problems. In total, there were 20 reported malfunctions for DBS for obsessive-compulsive disorder (OCD) and 39 reported malfunctions for epilepsy from 2011 to 2021 (see Figure 3).

For reported injuries of DBS for OCD, 16 out of 30 were related to increased suicidal thoughts or depression. Impedance and battery problems remained the most common mechanical source of injury for DBS used to treat OCD (see Figure 4).

Deep Brain Stimulator for Obsessive Compulsive Disorder - Device Related Malfunctions



Implanted Brain Stimulator for Epilepsy - Device Related Malfunctions

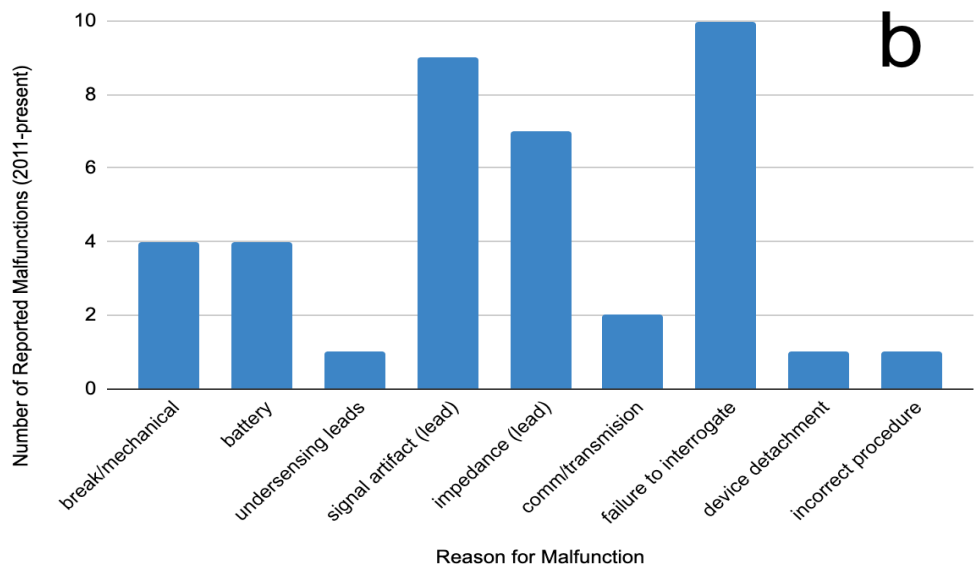


Fig. 3: Causes of reported malfunctions for DBS for the treatment of (A) OCD and (B) epilepsy from 2011 to 2021.

Deep Brain Stimulator for Obsessive Compulsive Disorder - Device Related Injuries

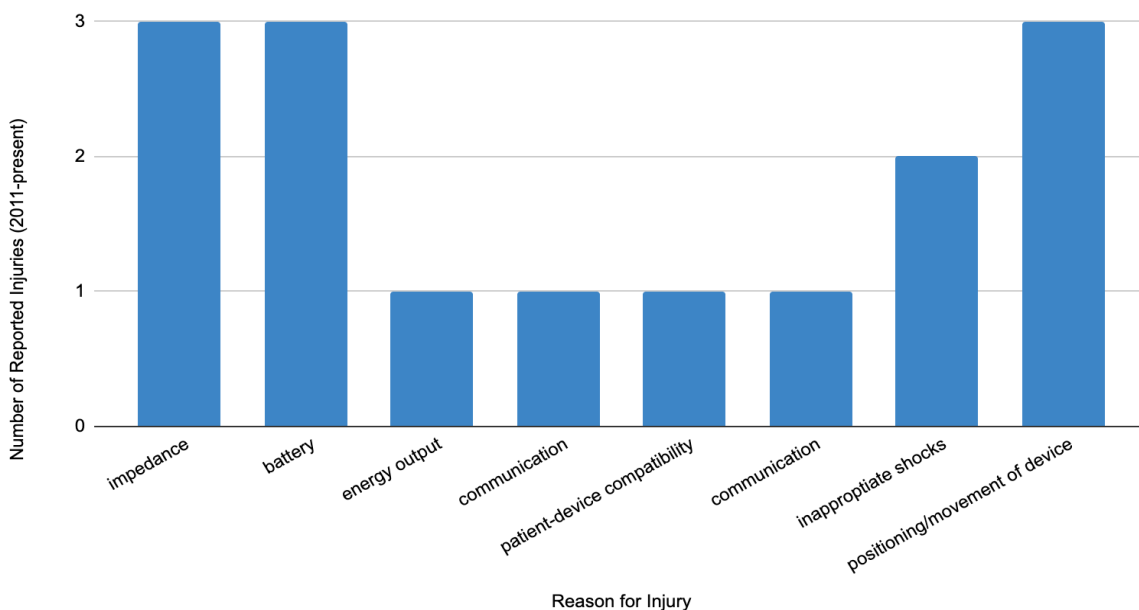


Fig. 4: Causes of reported injuries for DBS for the treatment of OCD from 2011 to 2021.

However, we found an astonishing amount of injuries of DBS for epilepsy in the past seven years (2014-2021); all 319 injuries related to bacterial infections at the wound. In 2014, there were 15 injuries related to bacterial infections. However, the average number of injuries associated with bacterial infections from 2017-2020 is 53.5, a 257% increase (see Figure 5). By August of 2021, 32 cases of bacterial infections were already reported in the year. This led us to question the clinical safety of DBS, whether these infections were simply avoidable causes of error in the implantation procedure, or whether infections are an inherent limitation of the device and technique.

Deep Brain Stimulator for Epilepsy - Device Related Injuries

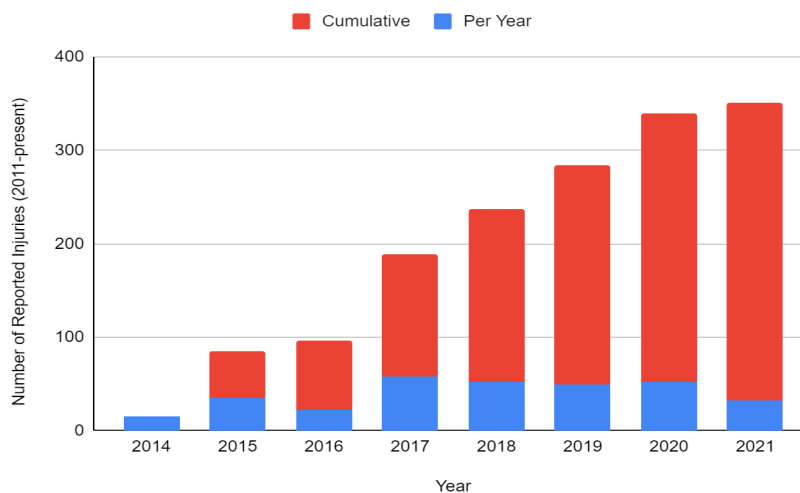


Fig. 5: Yearly and cumulative reported device-related injuries for DBS in the treatment of epilepsy, 2014 to 2021.

3.2. Clinical Efficacy

In our research, we found many successful studies of DBS for various disorders. However, many of these clinical studies were case reports with limited numbers of participants for specific disorders, rather than large randomized controlled trials. Many scientists are still unsure of the safety and tolerability of the procedure, especially for DBS in other areas of the brain and in other populations, such as children [4,5,6,7]. Most concluded that the long-term efficacy and safety of DBS is still undetermined and further well-designed randomized clinical trials are required to solve this issue [4,5,6,7].

Despite some positive results using DBS, many trials did not obtain similar results. A report on the long-term effects of DBS in Parkinson's patients made many conclusions of the decreasing effect of the stimulation by five years; for example, less improvement in motor function is reported; after five years, the remaining benefit is improvement in rigidity [5]. Additionally, decreasing functional scores were found during periods of time when the patient was on medication versus when off medications. Notably, quality-of-life scores are lower after DBS than preoperative [5]. This is because DBS does not prevent disease progression or the development of problems, such as impairments of gait, balance, and speech or cognitive disability, which are major determinants of quality of life in the long-term.

The percentage of intelligible speech after use of DBS falls from 80.8% at year one to 70.2% at five years, making the rate of decline higher than the rate of decline for a group without DBS [5]. These statistics show how previous symptoms come back after DBS even worse. Additionally, the brain becomes resistant to the procedure, causing lower levels of improvement as years pass [5]. Clinical trials of DBS for OCD have failed due to increases in depression in treated patients, and clinical trials of DBS for dementia and epilepsy have yielded average treatment outcomes, making adoption of DBS limited [8].

3.3. Complications of DBS

The most common complications of DBS include infection and lead malfunctions. The lack of standard protocols post-operation makes it difficult to determine exact data for both [9]. Patients undergoing DBS require ongoing care and outpatient clinic visits for device management [10]. These visits are similar to daily check-ups, ensuring the DBS therapy is running smoothly, and monitoring for implantable pulse generator (IPG) problems. Without these visits, problems with the IPG, especially the risk of infection, occur unnoticed and can necessitate device removal [4,10]. Frequent replacements of IPGs aggravate the surgical wound, causing further infection and lead to a cycle of replacement and infection [9]. This calls for complete removal of the IPG. While the surgical technique used depends on the skill of the surgeon, infections occur in 1.9-17.6% of patients [11]. The highest infection rates come from epilepsy (9.5%), dystonia (6.5%), Tourette syndrome (5.9%), and OCD (4.5%). Notably, Parkinson's disease has the lowest infection rate of 3.3% despite being the most common disorder used with DBS [4]. A study concluded that this may be because of the established base Parkinson's disease has in DBS, so surgeons have past experience. Another possibility is the occurrence of less follow ups with Parkinson's disease patients, leading to lower detection of rates of infection compared to newer diseases used with DBS such as epilepsy [4]. Results from the same study found that the use of different incision techniques can lead to a 11-fold higher risk of infection. The study also observed that infections are a preventable cause depending on the healthcare quality of the surgical team, implying that different surgeons have varying infection rates based on their skill level [4].

Complete removal of the IPG increases the risk for patients to experience DBS withdrawal syndrome [4,5,10,11]. Symptoms could include severe motor symptoms such as akinesia or rigidity in Parkinson's patients or status dystonicus in dystonia patients. Additionally, epilepsy patients may experience an increase in seizures, and obsessive-compulsive disorder (OCD) patients may have worsening neuropsychiatric symptoms and suicidal ideation [10]. When we looked at the FDA MAUDE database, we found a majority of reported injuries from DBS for OCD from the past decade were not directly correlated with device malfunctions; 16 out of the 30 reported injuries related to increase in suicidal thoughts and depression. While withdrawal syndrome of DBS typically relates to a backstep in physical prevention of movement disorders, these statistics show how removal of DBS can have physiological effects.

Infection not only signals something has gone wrong in the implantation process, it can also be a sign of further complications. A study of an abnormal T₂-weighted signal hyperintensity surrounding DBS leads found 15 instances of abnormality from 239 patients, a 6.3% incidence rate [12]. The researchers identified several adverse events including hemorrhage, infection, misplaced leads, and lead fracture. No significant difference between patients with the abnormality and patients without the abnormality was found in terms of patient demographics, IPG implantation side, anatomical target,

and surgical indication [12]. Researchers found the T₂ signal typically shows up three days after the surgery through postoperative MRI scans. The study concluded that the microelectrode and DBS lead insertion caused local tissue trauma, disrupting the blood-brain barrier, leading to edema and thus creating the abnormality [12].

Adverse events such as these are typically treated with antibiotics, however studies have shown that many antibiotics used to treat neural events have neurotoxic effects [13]. Vancomycin has been reported to have local neurotoxic effects, which could mean development of ventriculitis and cerebrospinal fluid (CSF) pleocytosis and eosinophilia. On the harsher side, cefazolin and cefuroxime are known to cause major neurotoxic effects in the body. This includes seizures, encephalopathy, myoclonus, truncal asterixis, non-convulsive status epilepticus (NSCE), and coma. Ciprofloxacin has also resulted in complex partial status epilepticus, generalized myoclonus with delirium, and oro-facial dyskinesias [13]. Additionally, the commonly used antibiotic rifampin, although known to have a brain protective function in stroke, has been found to have no beneficial effects on cognition or function for Alzheimers [14]. This raises questions regarding the overall use of antibiotics for DBS implant-related infections, and whether their supposed benefits outweigh the resulting detrimental effects.

3.4. Preventing Complications of DBS

Despite the many shortcomings of DBS this research has identified, antimicrobial impregnated catheters present as an inexpensive and effective strategy against infection [15,16]. Antimicrobial catheters enable targeted delivery of drugs within the implant site; the drugs used are not known to have any neurotoxic effects. This technique involves covering the end of the lead with a segment of antibiotic-impregnated ventricular catheter containing clindamycin and rifampin [15]. This prevents the need to remove DBS leads and risk further infection and inflammation [16]. A small study of eight patients reported an 87.5% success rate for antimicrobial catheters in preventing DBS implant-related infection; this success rate, paired with a lower skilled required of the surgeon and inexpensive cost to the patient, makes antimicrobial catheters an ideal solution for DBS infections [15,16].

Yet, one shortcoming of using antimicrobial impregnated catheters is the risk of antibiotic resistance [17,18]. Most infections at surgical sites are caused by the bacterial species *Staphylococcus*, which is known to cause brain diseases [4,17,18]. A study with 125 patients receiving DBS implants demonstrated a 12% complication rate with four infections (3.2%) [17]. All four infections were caused by rifampicin resistant *Staphylococcus epidermidis*. This was particularly concerning because rifampicin is used to deal with *Staphylococcus* resistance to vancomycin in methicillin-resistant *Staphylococcus aureus* (MRSA). However, *Staphylococcus* now appears to be resistant to rifampicin as well. This raises concerns as to whether the use of antibiotic impregnated catheters is adding to a pool of resistant bacteria, making diseases harder to treat [17].

Another study testing clindamycin and rifampicin susceptibility of antibiotic-impregnated external ventricular drains (AI-EVDs) found that rifampicin showed a rapid concentration drop in AI-EVDs [18]. Hypothesizing that antimicrobial protection is related to the duration of catheterization, the researchers found that clindamycin concentration is not correlated with the duration of catheterization or CSF volume drained, while rifampicin concentration had a rapid decline correlated to the duration of catheterization and CSF volume drained. Similarly, they observed that AI-EVDs loaded with rifampicin and clindamycin were bacteriostatic against methicillin sensitive *Staphylococcus* (MSSA) no matter the volume of CSF flow, while bactericidal activity only appeared against methicillin resistant *Staphylococcus aureus* (MRSA); this bactericidal activity disappeared after 10 days [18]. However, CSF flow was lower for AI-EVDs with bactericidal activity compared to AI-EVDs with bacteriostatic activity. For both methicillin resistant *Staphylococcus epidermidis* (MRSE) and MRSA, there was a quick loss of bactericidal effect and absence of antimicrobial activity from the AI-EVD catheter. Yet, there was persistent activity of at least one antibiotic against MSSA. The study concluded that AI-EVDs do not have a durable antimicrobial effect [18]. It further suggested that the lack of clinical efficacy of AI-EVDs in preventing or treating infections within the brain may be due to the rapid loss of antimicrobial activity, despite being sufficient to prevent early bacterial colonization and subsequent EVD-related infections. Overall, the study revealed that AI-EVDs could not prevent bacterial adherence and biofilm growth, eventually leading to a significant drop in AI-EVD antimicrobial activity within 10 days of catheterization and CSF flow in 9% of cases [18]. Antibiotic-impregnated catheters thus do not represent a complete solution to infections within the brain. Taken together, these findings indicate that further development of antimicrobial impregnated catheters will be necessary to solve the problem of infections associated with DBS implants.

4. Conclusion

While DBS remains a promising technique that can have further advancements, its adoption is limited by infection rates, dangerous withdrawal syndromes, and average treatment outcomes. In addition, the lack of post-operative protocols and randomized controlled studies leave researchers unable to draw conclusions on safety and efficacy. However, present data shows that malfunctions of DBS, specifically those of leads, presents a question of the safety of DBS. Additionally, infection is a general problem with device implantation, however infection in the brain seems especially problematic, increasing the chances of antibiotic resistance and life-threatening withdrawal syndromes. Further research on antimicrobial catheters and their use as prevention against infection can enable DBS to aid millions worldwide with movement disorders and other neurological signaling disorders.

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