**Section B1**
**Paper #8010**



# FEASIBILITY OF TARGETING THE LATERAL HABENULA DURING DEEP BRAIN STIMULATION AS A TREATMENT FOR MAJOR DEPRESSIVE DISORDER

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***Abstract*—***Deep brain stimulation (DBS) is a procedure utilized as a treatment method for a number of cognitive disorders, and involves the implantation of electrodes into particular regions of the brain. This paper will examine the usage of DBS as a means of treating major depressive disorder (MDD), specifically within the target area of the lateral habenula. During such a treatment, a pulse generator is implanted within the patient, providing electricity to the electrodes within the lateral habenula. The region is then stimulated, normalizing its activity and function. While the lateral habenula is one of several possible target areas for DBS treatment, it is unique among these areas in its processing of "negative value" reward signals.*

*This treatment is of importance to the audience of this conference for a variety of reasons. Primarily, it is a factor in the development of neuroimaging and biomedical technologies. The successful implementation of this treatment would improve understanding of both human cognitive function and psychiatric disorders. Also, the development of this technology represents a drastic improvement over similar treatments that are already available. The usage of DBS as a depression treatment not only improves upon previous treatments for depression, but also improves understanding of cognitive behavior as a whole.*

*Key Words—Behavior, Deep Brain Stimulation, Depression Treatment, In Vivo, Lateral Habenula, Major Depressive Disorder, Neuromodulation, Neuroscience*

## INTRODUCTION AND BACKGROUND OF MDD AND DBS

Major depressive disorder (MDD) is a well known and fairly common psychiatric illness in the world today. What makes MDD unique to other psychiatric illnesses is that, depending on the patient, common treatments can have wildly different effects [1]. While antidepressants are a sufficient treatment method for many patients, approximately one-third of those suffering from MDD require additional treatment [1]. These individuals suffer from what is known as treatment-resistant depression (TRD). As such, further treatment is necessary for this group of patients. Deep brain stimulation (DBS) is one such treatment. In the DBS procedure, an electrode is implanted within a patient's brain at one of several possible target areas [1]. An electrical pulse is then passed into the electrode, stimulating that region of the brain. This stimulation allows for the increase or reduction of neural output in the targeted area, which in turn acts as a means of manipulating, or modulating, the processing of signals in a particular region of the brain. As a result of MDD being a mental disorder, the exact science behind how this modulation works is still largely unclear to researchers. As such, this paper will examine the effects of DBS through the known results of therapies and clinical trials. DBS presents a viable treatment possibility for depression, with the output of different areas of the brain being modified to suppress the symptoms of MDD. This technological application is of great benefit to society, as MDD affects nearly 350 million people - approximately one-third of them treatment resistant - and would have profound implications for the well-being and mental health of these individuals and, in turn, for that of society. Furthermore, DBS has the potential for sustainability in regard to patients' quality of life. Within the bounds of this paper, sustainability will be examined as the ability of DBS to maintain a higher post-surgery quality of life for a patient. Treatment resistant patients especially benefit from DBS in this sense, as it is one of very few treatments shown to be able to alleviate TRD symptoms.

## DBS: PROCEDURE AND EFFECTS

During DBS treatment, a lead (or leads) with an electrode at its tip is implanted in a patient and provided a continuous electrical pulse. This pulse is the source of the stimulation, and is provided by a pulse generator, a device also implanted within the patient during surgery [2]. The pulse generator can be programmed to modify the level of stimulation as needed, and the patient can take their power source with them, providing DBS stimulation at all times. Connecting the lead and the pulse generator is a thin,

implanted wire known as the extension wire, which allows the electric current to reach from the pulse generator to the lead. The implantation of all of these devices is guided by a frame attached to the patient's head during surgery, allowing for accurate incisions and implantation of the components. Implanting the lead is a delicate operation and as a result, magnetic resonance imaging (MRI) scanning is also used during surgery in order to improve accuracy. Specifically, MRI scanning can improve lead implantation procedures through allowing the spatial identification of the target site before surgery, and through allowing placement and incision accuracy to be monitored during surgery [3]. The MRI scans are used to calibrate the frame, ensuring that the correct areas are targeted, lowering the risk of mistakes. Additionally, intraoperative MRI scanning (scanning done throughout the surgery) is a useful means of identifying potential complications. For example, as the lead must be implanted into the brain, hemorrhaging and intracranial air are two common complications, but both can be monitored through intraoperative MRI scans, allowing surgeons identify potential issues and react as needed [3].

The pulse generation from the lead and electrode allows for the activity of the neurons in the DBS target area to be modulated, which has a normalizing effect for the region. This normalizing effect refers to the ability of DBS to inhibit overactive neurons, and excite underactive neurons, thus regulating both to their baseline functions. This effect is of considerable relevance to MDD, as according to recent human and animal models of depression, specific areas of the brain can become either hyperactive or inactive within those suffering from MDD [4]. Due to their known contribution to symptoms of depression, these areas have been hypothesized as ideal DBS target areas for implantation [2][4]. The activity within these areas can be modulated - in the case of hyperactivity, suppressed, and in the case of inactivity, excited - through the stimulation provided by the implanted electrode. This has the effect of essentially regulating target areas so as to normalize function within them. In this manner, hyperactive or inhibited regions of the brain which contribute to MDD can be returned to their normal function, and the corresponding symptoms of MDD can be reduced.

## DBS ADVANTAGES & DISADVANTAGES

DBS holds many advantages over similar treatments such as common antidepressants, lesioning, and electroconvulsive therapy (ECT). As noted, around one-third of patients suffering from MDD are resistant to common antidepressant related treatment. However, such patients will oftentimes respond to treatments such as ECT or DBS. For example, in a 2008 case study of a patient who suffered from MDD for four years, antidepressants and other antipsychotic treatments were incapable of relieving MDD symptoms [1]. After the failure of antidepressants, DBS surgery was provided to the patient, who was then able to achieve full remission in under 60 weeks. The patient was provided 10.5 volts to the target area of the lateral habenula (LHb). These results are illustrated in figure 1, which documents three bouts of relapse that occured during patient monitoring. Notably, one instance of relapse occurred before DBS was administered, another occurred during the initial stages, and the final relapse was after the DBS was interrupted as a result of an outside factor (DBS was subsequently resumed in this case) [1]. As the case study notes, it is unlikely that the placebo was the cause of the improvement in depression rating scores. This is because the patient had been treatment resistant in the past, and due to the major relapse occurring after DBS was interrupted.

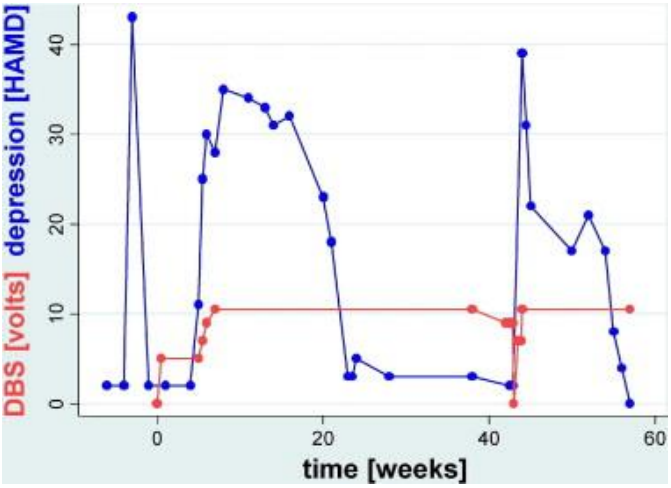


**Figure 1 [1]**
**Plot of Depression Rating and DBS voltage over time**

Thus, when applied to patients who are treatment resistant, DBS appears to hold a clear advantage over common treatments such as general antidepressants. However, DBS must also be compared to a similar procedure, ECT, which is also used for treatment resistant patients. Regarding the case study, multiple sessions of ECT were provided to the patient before DBS was administered, and remission was unable to be achieved through ECT treatments. After the ECT treatment was unsuccessful, DBS was applied, and the patient was able to achieve remission after being severely resistant to other forms of treatment. This specific case demonstrates the advantage DBS holds when treating patients with TRD, although it is important to note that patient resistance is an individual matter - what might be effective for one patient might not work on another.

## BIOCOMPATIBILITY OF DBS

Overall, DBS has a capacity for sustainability in terms of a patient's quality of life.Through the act of inhibiting symptoms, MDD or TRD patients will be able to live their lives free of a major psychological weight. Oftentimes, patients with TRD have gone without successful treatment for years, leading some to become suicidal. Alleviation of

these tendencies further shows the potential of DBS to improve sustainability of lives. However, despite the clear benefits regarding DBS and sustainability, there are downsides to the surgery. For example, while the surgery does reduce symptoms of MDD, patients have to live with the burden of having a physical implant within them. Depending on the location of the implant on the patient, they may be asked to not bend or stretch a certain section of their body, for fear of disrupting the electronics. Similarly, while the implanted lead and wire are not noticeable, the pulse generator in a patient's chest leaves a noticeable bump if loose clothes are not worn. While such issues are relatively small, they can still be important to a patient living their post surgery life to the fullest, and therefore place some limitations on the sustainability of DBS. However, one point of note is that the entire system is implanted, thus patients have no issue showering or performing similar daily activities. Overall, while the biocompatibility of DBS limits its sustainability in some ways, the effect it has towards improving TRD has a much greater positive impact on the lives of patients.

### Assessment of DBS Against Alternatives

There are, of course, other areas of similarity through which DBS and ECT may be compared. For example, DBS tends to be a much more convenient and well-tolerated treatment once the surgery is complete. In DBS, the patient carries their treatment with them in the form of implants, allowing for a consistent and sustained treatment. In ECT, however, the patient must receive a procedure every few weeks, and the effect can wear off between sessions [5]. Thus, in comparison to DBS treatment, ECT can be less consistent in its effect and requires a patient to constantly be treated; contrarily, a patient undergoing DBS treatment must only go back every few years to recharge their battery [5]. Another area of note is the difference of availability between the two. ECT, while not in widespread use, is available to a much greater degree than DBS treatments [5]. The reasoning for this is that while ECT is a tried and true treatment, DBS (as a depression treatment) is still in the clinical stage and is generally reserved for high risk patients [5]. One last point to consider is that, while DBS is incapable of completely curing depression, it is able to suppress symptoms to a point where remission can occur, so long as the stimulation continues. Thus, while ECT is of higher accessibility, DBS appears to be the superior technology in terms of treating MDD, as it has both a higher success rate on treatment resistant patients and more consistency in terms of treatment. In regard to DBS as an alternative to lesioning, or removing sections of the brain, DBS is clearly the superior option. Compared to performing surgery to remove a specific target area, DBS allows for a specific area to be inhibited in a reversible, controllable, and far less invasive method [6]. Thus, there is much less risk for a patient undergoing DBS; furthermore, should the need arise, DBS can always be turned off, but removing parts of the brain cannot be undone. Another alternative to DBS is the general group of common pharmaceutical antidepressants. In this comparison, each treatment has benefits for specific groups of people. Notably, common antidepressants can be a relatively cost effective way of managing depression, but patients with treatment resistant depression (TRD) would not find them to be a sufficiently effective treatment method. As such, treatment resistant patients may prefer a method with a greater chance of success - such as DBS - making the two useful for different reasons.

### Cost Sustainability of DBS

An additional factor in the sustainability of DBS treatment for depression is that of cost. This aspect of DBS treatment is intertwined with sustainability in terms of quality of life. Simply put, patients may be financially hindered by the procedure, or may even be prevented from receiving treatment due to inhibitory costs. As DBS is a technology in its early stages, concerns related to cost will likely be reduced as the technology progresses. With the development of DBS technology will come further optimization, resulting in reduced overall costs. Thus, as DBS expands outside of clinical trials and into the market, the price of the procedure will likely be significantly more affordable than it currently is, improving the cost sustainability of DBS.

## COMPARISON AND CONTRAST OF VARIOUS TARGET AREAS

### Introduction

Deep brain stimulation has been proposed as a treatment for depression through many hypotheses, with several different propositions as to which area of the brain would be most effective as a target for stimulation. Some of these target areas are focused and specific in their function and purpose, while others are thought to have more potential due to their nature as a "hub" or central region for processing signals from multiple other areas. Because major depressive disorder shows evidence of dysfunction in the brain's reward processing system, regions of the brain involved in such reward processing have been thought to be promising candidates for DBS as a treatment for MDD. Among these regions are the subcallosal cingulate gyrus (SCG), the nucleus accumbens (NAcc), the ventral capsule/ventral striatum (VC/VS), the medial forebrain bundle (MFB), and the lateral habenula (LHb).

For this overview of possible target areas, we will examine the results of studies investigating each area and discuss limitations of the studies, viability of the target areas, and similarities and differences in the effects of DBS in each patient sample.

### Subcallosal Cingulate Gyrus

One of the first areas of the brain to undergo studies involving DBS was the subcallosal cingulate gyrus (SCG), a region of the brain which is thought to govern or oversee many behavior and mood-related regulatory functions. A number of studies have shown that depression is associated with increased activity in this area of the brain [7]. It has thus been postulated that modulation/stimulation of the SCG could affect the activity in its "downstream targets in TRD" [8]. In one study, 20 patients with TRD underwent SCG DBS. As with similar studies, all patients had failed multiple trials of pharmacotherapy and psychotherapy, and thus were considered unresponsive to general treatment. In this group, the mean major depressive episode was 6.9 (±5.6) years. Following surgery, 40% of patients were respondent (with one in remission) at the one-week mark; at the two-week mark, response rates had dropped to 30% (with one in remission) [8]. Further on, with chronic DBS, the study found a progressive improvement in terms of response rates and remission rates. In particular, at the six-month mark, 60% of patients were respondent and 35% were in remission.

The authors of this study also forward an argument against a placebo effect being involved in this study to a significant level. The article's primary point is that, due to the progressive nature of the patient responses to the treatment, the presence of a placebo effect is unlikely. Specifically, "an initial large effect followed by a decay would be more in keeping with a placebo response" [8].

Additionally, analysis of the metabolic effects of SCG DBS on the limbic and cortical regions were indeed consistent with the system-based connectivity associated with the SCG. Several areas in this system experienced significant positive change as a result of the modulation of the SCG; thus, the article concludes that this data "provide[s] a biological basis for the observed improvements in depression in these patients" [8].

As a hub for reward processing, and with the promising results of this study, the subcallosal cingulate gyrus certainly has potential as a DBS target in MDD treatment.

### Nucleus Accumbens and VC/VS

Another area of the brain seen as a possibility for MDD DBS treatment is the nucleus accumbens (NAcc). The nucleus accumbens is a primary region involved in the processing of reward and satisfaction. In one study on the viability of the NAcc as a DBS target area, ten patients with TRD had DBS electrodes implanted into the NAcc. Summarizing the patient group, the article states, "The mean (±SD) length of the current episode was 10.8 (±7.5) years; the number of past treatment courses was 20.8 (±8.4); and the mean Hamilton Depression Rating Scale (HDRS) was 32.5 (±5.3)" [9]. The study found that after twelve months of DBS treatment, half of the patients had a 50% reduction in their HDRS score [9]. The study also states that "for a one month period, three patients were classified as in remission" [9]. Also observed was an increase in hedonic activities - that is, pleasant activities - in the entire sample group. Specifically, the sample's activity levels, for which the study used the Hautzinger list as a measure, were significantly higher than baseline following the one-month and 12-month marks [9]. This study also observed an antianxiety effect in certain cases, which was not observed in other regions of the brain.

Additionally, although this study was not sham-controlled, there were several factors which make this permissible. First, during initial attempts at "off phases", patients' symptoms significantly worsened and stimulation had to be resumed; thus, sham-controlling this study is generally impractical. Second, like the authors of the SCG DBS study, this study's authors reason that a possible placebo effect is improbable for two reasons: one, in the event of accidental discontinuation of stimulation (without prior knowledge from either the patient or clinician), "depression worsened rapidly"; and two, "the likelihood to have a placebo response decreases with treatment resistance" [9]. From this data and evidence, the NAcc is certainly a viable option for DBS treatment of MDD.

One more area of the brain postulated as a treatment option due to its involvement in reward processing is the ventral capsule/ventral striatum. The ventral striatum contains the nucleus accumbens and olfactory tubercle. One study, similar in target to the previously mentioned study on the nucleus accumbens, investigated the VC/VS as a DBS target area. It involved 15 patients, all of which had chronic treatment resistant depression. The patients received stimulation for between 6 months and 4 years. Previous studies on DBS of the VC/VS reported notable effects on both OCD and MDD symptoms. The aim of this study in particular was to further explore the effects on depressive symptoms, in contrast with the more OCD-focused studies before it. The sample of patients had a mean duration of illness of 21.0 (± 10.9) years and mean number of lifetime ECT treatments of 30.5 (± 26.3). Adverse events or effects in this study were mainly similar to those mentioned in the NAcc study; most notably, some patients experienced adverse effects upon accidental discontinuation of stimulation (again noting battery depletion as a concern) [9]. Remission rates found in this study are quite similar to those of the NAcc study - at the 6-month mark, 20% of patients were in remission, and 40% at the last follow up. Interestingly, at the one month mark, 2 of 15 patients were in remission, compared to the NAcc sample with 3 of 10 in remission.

### Medial Forebrain Bundle

Yet another possible target area is the medial forebrain bundle (MFB), a neural pathway and hub which contains fibers from several other parts of the brain, including the

ventral tegmental area (VTA). Many parts of the brain's reward pathways, including the VTA, NAcc, and amygdala, are interconnected through the MFB. It has thus been noted and hypothesized that, being in close connection with several parts of the reward processing system and serving as a hub for processing signals from multiple areas, the MFB could very well be a valid, possibly superior, target for DBS-based treatment of depression.

One particular study, more recent than those involving the subcallosal cingulate gyrus, nucleus accumbens, or VC/VS, has assessed this hypothesis [10]. In this study, seven patients were observed for 12 weeks, with four of the patients observed for longer [10]. The sample had a mean length of current major depressive episode of 7.6 (± 5) years, and a mean number of medical treatment courses of 14 (± 3.5). The mean score at baseline on the Hamilton Depression Rating Scale was 23 (±1.5). After 1 week of stimulation, four of seven patients had reached sufficient reduction on the MADRS (50%) to be considered respondent. After 6 weeks, five of seven patients were respondent. At 12 or 33 weeks, six of seven patients were respondent, with four patients in remission [10]. This can be seen in Figure 2, which shows the percent reduction in patients' MADRS score as they undergo the continued treatment process.

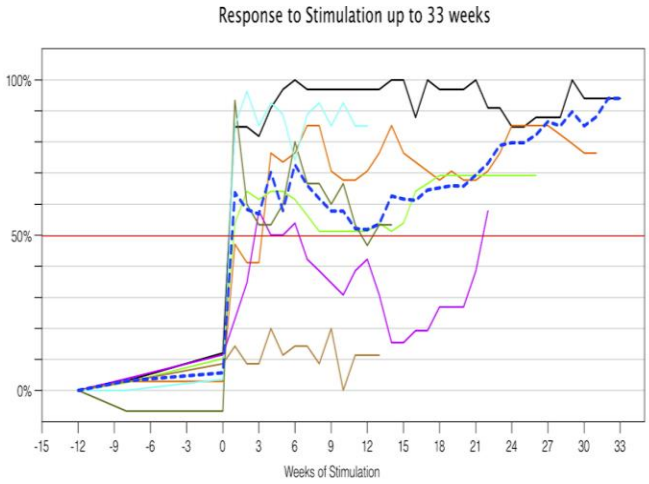


**Figure 2 [10]**
**Weeks of Stimulation vs. % Reduction in MADRS**

One interesting adverse effect involved in the stimulation of the MFB is the treatment's effect on the oculomotor system (that is, some sort of disorder in the patient's vision or eye movement - seen in all seven patients). This resulted in a limitation on the study which prevented higher intensity (i.e. higher current) stimulation from being tested on the patients [10]. As with the other studies, two primary limitations of this study are a small sample size and lack of sham-controlled testing.

**Conclusion**

Many of these proposed target areas certainly have potential as future methods for DBS treatment of depression; however, further investigation must take place for each options viability to be more thoroughly supported by evidence. Many of the studies discussed had issues with non-sham-controlled designs, and although there were arguments made that this was acceptable, standards such as this must be followed regardless. Additionally, certain areas had more limiting side effects - namely, the medial forebrain bundle with its adverse oculomotor effect and the limitations on stimulation intensity that come with it.

These studies had a great amount in common, generally - sample make-up, sample size, remission rates, response rates - although in some of these areas the investigations were lacking or had some limitation. For one, many of the sample sizes were less than ideal - one study only observed seven individuals, and even the largest was only 20. Larger sample sizes would certainly assist in gathering more reliable and definitive data. Additionally, many of the studies' results regarding remission rates and response rates leave something to be desired - typically no higher than 60% was seen. Although, it is worthwhile to consider that the patients taking part in these studies all typically displayed relatively extreme cases of MDD - every individual was considered treatment-resistant, and the mean episode for each study's patient sample was many years.

Among these studies, a strong foundation has been laid with which future studies can further investigate these treatment options. One more recently proposed target area that has only just started to see testing in human subjects is the lateral habenula (LHb). The unique features of this region of the brain make it of exceptional interest as a DBS treatment option for MDD; therefore, it will be discussed in further detail in this paper, more comprehensively than the aforementioned target areas.

## LATERAL HABENULA: DETAILED ANALYSIS

Among others, the lateral habenula (LHb) has been noted as a viable candidate for DBS treatment of MDD. One unique aspect of the LHb lies in its involvement in reward processing through "negative value" signals sent to the reward-processing-related systems [4]. It has been found that the LHb encodes negative reward prediction error; that is, unexpectedly rewarding events will suppress LHb neurons, while unexpectedly negative or non-rewarding events will excite LHb neurons [4]. Generally, these findings translate to the suggestion that the LHb plays a role in an individual's behavioural response to stress as well as in processing aversive stimuli. The role of the LHb in reward processing has thus been connected with goal-related and depressive behaviours; specifically, the deregulation of the LHb is thought to be a contributing factor to multiple psychiatric disorders, including schizophrenia and depression. Thus, the

regulation of the LHb can indeed suppress symptoms of depression and similar disorders. This fact makes the LHb a strong candidate for DBS treatment, as DBS can bring about the regulation of a hyperactive LHb. Much of the research done regarding the LHb's role in reward processing and its connection with depression related behaviours has been completed using rodents or macaque monkeys. These studies have allowed further insight into the neural processes underlying depression, specifically with regard to the lateral habenula.

Specifically, it has been found that high-frequency electrical stimulation through DBS devices has an inhibiting effect on the neural structures (such as the LHb) in rodents. For example, in a rat model study, experimenters trained rodents to consume ethanol as a means of studying changes in the brain caused by ethanol consumption. In the study, it was found that rats which underwent ethanol withdrawal had increased neuron activation within the LHb [11]. These findings are in line with what is known about the LHb; that is, withdrawal from addictions such as ethanol consumption would be considered a negative event that would excite the LHb. In turn, the hyperactive LHb creates the negative symptoms associated with such experiences, which mirrors the hyperactivity of the LHb within depressed patients. Furthermore, the study found that performing high frequency DBS on the LHb successfully decreased neural activity in the region, and in fact lowered the ethanol consumption of the rats once they were reintroduced to the substance [11]. The study validated its findings through the use of various control groups. For example, the LHb activity of the ethanol addicted rats was compared to ethanol naive rats (those not exposed to ethanol), and within the ethanol addicted group, some rats were given sham DBS treatment [11]. This study corroborates that LHb activation occurs during negative events, such as withdrawal or depression, and that symptoms felt during such events are as a result of the hyperactivity in the LHb. One specific factor of importance in this study is its usage of high frequency stimulation (HFS) as opposed to low frequency stimulation (LFS). Specifically, the study found that using high frequency stimulation during DBS had an inhibitory effect on the LHb, reducing withdrawal symptoms in the ethanol addicted rats.

The previous rat model trial is not alone in its findings regarding the LHb. In another study using the rat model of depression, LHb hyperactivity was caused by exposing rats to chronic stressors. The depression ratings of the rats were monitored through both the open-field test and the sucrose consumption test. In the open-field test, rats are placed within a walled, but relatively open, maze. The depressed rats tend to stick to the darker edges of the field, rather than the bright central area, and show body language that expresses discomfort moreso than healthy rats [12]. In the sucrose consumption test, rats are exposed to two bottles - one containing a sucrose solution and one containing water. The rats are accustomed to both bottles, but are eventually given the choice of picking one over the other. The accepted interpretation of the choice is that failure to choose the sucrose solution is indicative of depression, as a result of the rat's natural tendency towards sucrose [13]. Through such tests, the study identified rats with depression and gave them DBS treatment targeting the LHb over 4 weeks [14]. After the DBS treatment was over, the experimenters performed the open-field test again, finding that the rats treated with DBS showed far fewer signs of depression symptoms compared to prior.

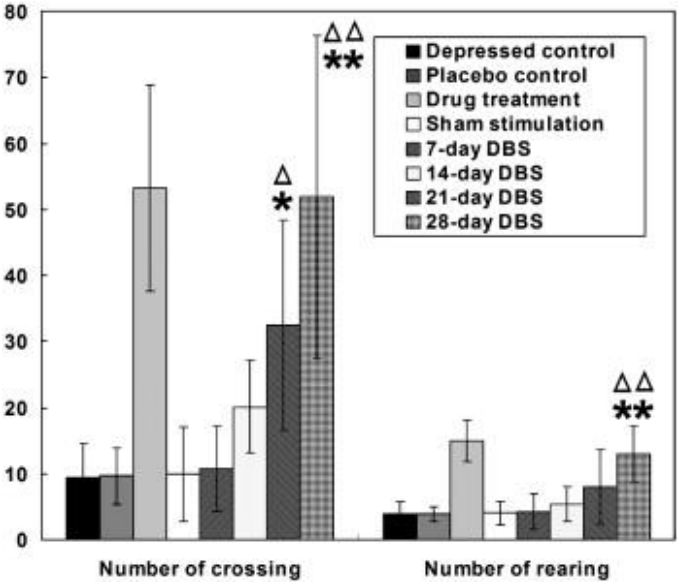


**Figure 3 [14]**
**Crossings and rearings performed by rats as DBS progressed**

The improvement is represented in the figure 3 above, in which the DBS-treated rats reached the same level as drug treated rats as the 4 week period of DBS treatment proceeded. This was measured as the number of crossings and rearings performed during the open-field test, which are behaviors indicative of a healthy state of mind in rats. This test further identifies the LHb as a specific cause of depressive symptoms, as inhibiting it lowered the depression rating of the rats. Thus, the inhibition of the LHb is of great importance; because the hyperactivity of the LHb contributes to depression, its normalization is a key role in treating depression.

## ETHICAL CONSIDERATIONS

There are many ethical concerns which must be taken into account when evaluating the potential of DBS treatment. The main ethical considerations in terms of DBS treatment are the patient's own ability to provide consent, given that psychiatric conditions such as MDD can impair decision making, and patient's understanding of MDD itself. Additionally, there is concern that potential DBS patients may not fully understand the risks of potential treatments nor

clinical trials. However, there have been many recent studies regarding the decision making capacity of patients suffering from MDD that refute this point.

For example, in a recent study regarding the ability of depressed and schizophrenic patients to consent to research, 22 patients with MDD, 21 with schizophrenia, and 21 control patients were asked if they would consider joining specific medical studies [15]. In particular, each participant was offered a low risk study with medical benefit, and a high risk study with no medical benefit, and the ability to give informed consent was measured using the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR). The study found that the MDD sample group had a "relatively high decision making capacity" and were able to identify the difference of risk between the two studies offered [15]. In fact, the study found that the MDD sample group was more likely to decline participation in both the low risk and high risk medical studies.

In a similar study, 26 female patients with MDD who were already participating in a maintenance psychotherapy study were monitored to assess their ability to provide informed consent [16]. This study also used the MacCAT-CR in order to assess to measure the ability to give consent, and the Hamilton Depression Rating Scale was used to determine the extent of depression symptoms held by each patient. The results were as follows: most participants performed well in terms of consent capacity, and no correlation was found between the degree of symptoms and a patient's consent capacity [16]. However, the study did conclude that further investigation would be required to determine if patients with psychotic depression would have the same level of performance [16]. Based on the results of these studies, it is clear that the issue of patient consent is not as severe as many think. As noted, the results do not necessarily apply to patients with severe psychotic depression, which is a population that may be in greater need of DBS; therefore, further testing on that group is required for a full understanding on this issue.

## RISK ASSESSMENT

Another topic of concern is the risks that the DBS procedure itself has on the patients using it. Specifically, due to the relatively invasive nature of the lead placement during DBS surgery, there is notable potential for complications to arise during the implantation. An example of this can be seen in a recent trial in which MRI was used during DBS in order to examine its risks. The MRI found that, throughout 289 lead placements for 143 patients, nine patients suffered from hemorrhages or hematomas of some kind, and there were 144 instances of intracranial air causing brain shift [3]. The study also found that most of these cases were easily resolvable and not of concern, apart from one case of subarachnoid hemorrhaging, which caused headaches and confusion within the patient [3]. However, even in the one case in which clear symptoms developed, there was no major risk to the patient, as they were monitored post-surgery. Another aspect of risk associated with DBS treatment comes after the surgery itself, in the form of addiction to the electrical stimulation. This can be seen in a recent study regarding the effect of DBS on TRD, which noted that its patients developed behavior similar to appetitive motivation, or behavior associated with seeking positive experiences or rewards [10]. The study also hypothesized that, at higher frequencies of stimulation, DBS could potentially elicit hedonic behavior from patients [10]. Although untested, there could very well be the potential for patients to become addicted to, and dependent on, DBS when used at high frequencies. In this sense, a major concern is that, since patients can control their frequency levels, one could become addicted to DBS without knowing it. Ultimately, the risks of both complications during surgery and unwanted behavioral change after surgery appear to be worth taking. As noted, only one of the 289 monitored placements was cause for concern during surgery, and even then it was not a major issue. Such risks are often warranted, as DBS is used for patients with severe and treatment resistant depression who oftentimes have psychotic issues such as suicidal tendencies. Additionally, postoperative behavioral change can be monitored through follow-ups as well as by informing patients about the risks of setting the pulse generator to high frequencies.

Therefore, to treatment-resistant patients who continually struggle to find an effective treatment, the potential risks of DBS may be worth taking, especially within the context of long term sustainability of quality of life. Specifically, while the operation carries the chance of issues such as hemorrhaging or intracranial air, the chances of such complications are slim, while the benefits are extensive. Primarily, the patient gets the opportunity to live their life with suppressed symptoms of MDD, oftentimes after being afflicted by the condition for years. This is especially important for TRD patients, who do not respond to any common treatments. Allowing a reprieve for such patients, and with a relatively minimal risk, is ultimately justified towards the goal of sustainability of quality of life. However, there is certainly room for improvement in this regard. For example, while all of the MRI monitored lead placements were successful in the above trial, there were 144 of intracranial air being introduced [10]. While not especially threatening, improvement upon such issues would only help to further establish the ability of DBS to promote sustainability with regard to quality of life.

## SUMMARY, EVALUATION, AND ASSESSMENT OF IMPACTS

Depression is one of the most common serious brain disorders in the world today, affecting many millions of individuals worldwide. Although there exist a number of

viable treatment options, and a large number of patients see significant improvement using these options, a significant subgroup of patients continue to suffer from the disorder even after trials of multiple treatment methods. The disorder then continues to affect the quality of life of these treatment-resistant individuals, and can result in the development of a number of life-threatening and debilitating symptoms. For these individuals suffering from TRD, further options must be considered. One such option is a treatment procedure known as deep brain stimulation, which has shown great promise not only for motor diseases like Parkinson's, but also as a truly promising treatment for depression. A number of options have been proposed as target areas for DBS to treat depression; namely, this paper discusses the lateral habenula as a unique candidate. As the LHb encodes reward-negative neurons, it is intrinsically related to the development, and symptoms of MDD. As such, moreso than other target areas, the application of DBS within the LHb has a much more focused application towards MDD. Further investigation must be made into all options to truly determine the method's viability as a clinical treatment, but early progress and results in the discipline give more than sufficient reason to explore the treatment in greater detail.

Like any treatment, there are associated risks and side effects, but one promising aspect of DBS is how well-tolerated the treatment itself is. In most cases, the majority of health risks originate from the surgery required to implant the electrodes; thus, once advances can be made in this regard, the risks associated with the treatment process of DBS can be minimized. As research and implementation of the treatment proceeds, both these health and safety risks as well as ethical dilemmas must be thoughtfully and carefully considered by a number of specialized individuals. Preventing any and all misuse or abuse of this newly emerging technology must be a top priority.

The development and refinement of a technology like DBS, particularly as applied to the treatment of depression, will not only have numerous implications for society and engineering worldwide, but life-changing significance to those individuals suffering from the disorder. When refined to minimize risks and limitations and to be applicable to a larger number of patients, DBS as a treatment for depression - a disorder affecting a substantial portion of the world's population - would be truly extraordinary in combating mental health issues in society, and a profound accomplishment in the world of science, technology, and engineering.

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## ACKNOWLEDGEMENTS

We would like to acknowledge our writing instructor, Joshua Zelesnick, for providing us with the feedback necessary to improve upon our first draft. We would also like to acknowledge our co-chair, Lauren Williams, for working with us to refine our organization and flow. Finally, we acknowledge our chair, Katrina Zougari for working with us to improve upon the technical aspects of our paper.