

Antidepressant Effects and Potential Targets of Deep Brain Stimulation

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Abstract. A serious health issue that affects people all over the world, severe depressive illness is linked to intricate neuronal circuits and neuromodulatory systems. Millions of people are affected by its increasing frequency, which places a heavy economic strain on society. Innovative methods are required because of the drawbacks of standard therapies, such as antidepressants and invasive operations. Deep brain stimulation has shown promise in the treatment of Major Depressive Disorder (MDD) since it is minimally invasive and has the opportunity for personalised care. Finding the best sites for deep brain stimulation is still difficult, though. Recent innovations, such brain biomarker-based Deep Brain Stimulation (DBS) device customization, offer fresh approaches to enhancing therapeutic effects. The present status of DBS for MDD is discussed in this study, with a focus on prospective target regions such the subcingulate colliculus (SCG), medial forebrain bundle (MFB), and bed nucleus of striatal terminal area (BNST). Modern methods like functional connectivity analysis and probabilistic stimulus mapping show probable brain regions linked to therapeutic improvement.

Keywords: MDD, DBS, medial forebrain bundle, neuro biomarkers, probabilistic stimulus mapping.

1. Introduction

Major depressive disorder (MDD) was classified as severe by the World Health Organization (WHO), a neurological condition, as the third most significant global source of disease burden in 2008 and predicted that it would overtake all other diseases by 2030 [1] Major depressive disorder has lifetime prevalence rates between 5% and 17%, with an average of 12% [2], and is linked to intricate neuromodulatory systems and neuronal circuits. 21 million adults in the US have at least once suffered from serious depression, according to NSDUH data. This figure corresponds to 8.3% of all American adults. Due to hormonal changes, the impacts of childbearing, distinct psychosocial pressures for men and women, and learned helplessness behavior patterns, the prevalence rate for women is approximately twice that of men, rising from 6.2% to 10.3%. Due to the usage of alcohol and other substances, the frequency is also rising in younger groups. 5 million teenagers between the ages of 12 and 17 in the US have gone through at least one significant depressive episode. The prevalence of MDD among 12 to 17-year-olds in the United States is 20.1%. MDD can cause severe psychological anguish in those who are affected and seriously impede a person's capacity to function in all facets of life. Major depressive illness is also linked to a number of different physical health issues. Chronic illnesses including heart disease, diabetes, and obesity are more likely to occur in those who are depressed. Not only does this put a tremendous strain on the sufferer's family and social network but can also lead to diminished productivity in the workplace, increased healthcare costs and absenteeism and economic repercussions including direct medical expenses and lost output.

Major depressive illness is a complex ailment that varies from person to person, making treatment challenging. Traditional antidepressants such selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which are not available to everyone and take some time to start functioning, can help some patients with symptom relief. Permanent tissue damage might result from destructive surgery. The ability of Deep Brain Stimulation (DBS) to modify neuronal circuits related to emotion regulation makes it a cutting-edge neuromodulation method. It is a method of neuromodulation that involves precisely inserting electrodes into particular brain regions or nuclei using stereotactic equipment. By delivering electrical impulses, it normalizes or modifies

the activity of neural circuits involved in mood regulation, which lessens the symptoms of depression [3]. DBS is notably advantageous for treating neuropsychiatric illnesses due to its advantages of relatively low side effects, minimally invasive surgery, fewer problems, and regulated therapeutic effects. DBS is currently being used extensively to treat a wide range of neuropsychiatric disorders. It has demonstrated particularly promising results in the treatment of epilepsy, Parkinson's disease (PD), idiopathic tremor, medication-resistant psychiatric disorders, medication-resistant pain, and disorders of the central nervous system that affect arousal and cognitive function.

The target for DBS electrode placement can vary significantly depending on the disorder being treated and the neuroanatomical model of the disorder due to the complexity and individuality of psychiatric disorders. This is especially true when deep brain stimulation is used to treat major depressive disorder. The use of conventional DBS for the treatment of depression, however, has had limited success based on recent clinical trials, in part because most devices can only give continuous electrical stimulation and typically only target one area of the brain. This makes it difficult to appropriately treat various brain regions that may be involved in various patients. 2021 The new DBS device was customized by medical professionals at the UCSF Health Center based on a neurobiomarker they identified that could indicate a particular pattern of brain activity in the presence of a symptom. When this pattern is recognized, the device responds by stimulating various parts of the brain circuitry to produce a neurological stimulus that specifically targets the patient's brain and the circuits causing their illness. 2022 The new DBS device is now usable in a variety of settings, including the brain, the brain, and the brain. brain and the neural circuits that contribute to their disease, producing immediate, on-demand treatments specific to the patient's brain and the neural circuits that cause their disease. This individualized approach represents a significant development in the use of DBS for the treatment of severe depressive illness [4]. Potential target regions for DBS for the treatment of MDD will be explored in this study along with clinical data on the safety and effectiveness of DBS for the treatment of MDD. The critical ethical problems surrounding informed consent and decision-making capacity for MDD patients choosing DBS will next be examined.

2. Deep Brain Stimulation

In a surgical method known as DBS, stereotactically implanted electrodes continuously stimulate predetermined neuroanatomical targets to treat a variety of diseases [5]. PD, essential tremor, and movement disorders are among the conditions for which DBS has been found to be effective; however, its ability to treat depression is still unknown. Disease-specific targeting and high personalization are features of DBS. The choice of brain regions for surgery in DBS is disease-specific, targeted, and highly individualized, depending on the particular ailment being treated. Different neural networks and parts of the brain are involved in various disorders. Additionally, each patient's individual anatomy, symptoms, and reaction to stimulation must be taken into account while choosing a target. During the process, electrode placement must also be modified in light of on-the-spot observations and patient feedback. And individualized treatment plans for each patient depend on actively exploring a variety of potential targets during deep brain stimulation therapy. This active study of alternative targets becomes essential to enhancing treatment results, especially in difficult situations, in cases of treatment-refractory depression (TRD) and resistance to initial target selection. Additionally, this method enables clinicians to pinpoint regions that may be able to produce desired therapeutic results while reducing the risk of adverse events and side effects. Individual differences in neuroanatomy and physiology can alter the brain's reaction to DBS. Additionally, active option exploration broadens the therapeutic possibilities by avoiding over-reliance on a small number of targets, increasing the possibility of finding the target that is most appropriate for each patient's unique condition.

3. Current Treatment

3.1. Subcallosal Cingulate Gyrus

The SCC has four distinct connective regions: the posterior-lateral SCC connects to the medial temporal lobe region via the uncinate fasciculus, the posterior-medial to the ventral striatum, the superior-medial to the anterior cingulate cortex (ACC), and the anterior-lateral to the medial prefrontal cortex (mPFC), via forceps vignettes (see Figure 1) [6, 7, 8]. The subcallosal cingulate gyrus (SCG), which is located ventral to the corpus callosum, is one of the typical therapeutic targets for DBS [7].

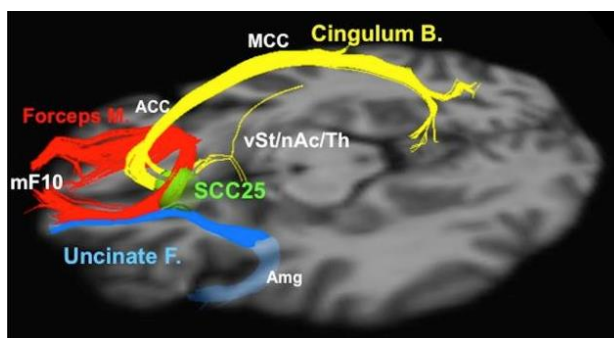


Fig. 1. Combining anatomical pictures with beam imaging [7]

Depressive symptoms and MDD have been linked in numerous studies with the changed state of Brodmann area 25. One of these, known as sACC or Brodmann area 25, is the most well-known. It has monosynaptic connections to other regions of the brain that regulate emotions and antidepressant responses [9]. Although there were many ups and downs, patients responded well to SCC DBS treatment in the most recent 14 clinical investigations, with responder rates ranging from 23% to 92% and remission rates from 27% to 66.7% [10].

All responders in a 2020 study had their medial frontal and temporal lobe projections stimulated at 6 and 12 months, indicating that DBS responsiveness may be linked to a wide variety of white matter pathways, particularly in the medial frontal lobe [11]. Recently, using bundle spectroscopy, researchers found two targets for treating depression that is resistant to medication in the SCG region [10]. In one target, the right Brodmann area 10 (BA10) and bilateral cingulate cortex had the highest stream counts, whereas in the other, the leptomeningeal tract and bilateral nucleus ambiguus had the highest stream counts. In the left and right hemispheres, a single tractography-based target and an anatomy-based target were separated by mean straight-line distances of 3.2 mm and 2.5 mm, respectively [10]. In the left hemisphere, the intra- and inter-subject goals exhibited a mean and standard deviation of 2.2 ± 1.2 and 2.9 ± 1.4 , respectively, while in the right hemisphere, these values were 2.3 ± 1.4 and 3.1 ± 1.7 , respectively [10]. Target planning for SCG-DBS in treatment-resistant depression must take individual heterogeneity and the inherent unpredictability of diffusion imaging into account, it is stressed.

3.2. Medial Forebrain Bundle

The medial forebrain bundle (MFB), which is a component of the brain's reward system, connects the nucleus ambiguus (NAc) to the ventral tegmental area (VTA). Myelinated glutamatergic fibers that originate from the medial prefrontal cortex and project to the VTA are among the potential pathways that MFB DBS has to stimulate, according to preclinical research. Dopaminergic transmission to the NAc is increased by this stimulation because it increases the expression of dopamine receptor D1 and D2 mRNA (see Figure 2) [12, 13]. Clinical outcomes showed a significant reduction in Montgomery-Sberg Depression Rating Scale scores throughout the course of the 12-month DBS treatment, and 50% of patients were classified as having remitted their depression after a year of sustained stimulation.

Comparative studies were conducted using the Sprague-Dawley control group and the FSL rodent model of depression. The mPFC of FSL rats had considerably more low gamma oscillations, according to the data [14]. Additionally, the nucleus ambiguus and ventral tegmental region had an increase in low gamma oscillations following MFB DBS, and the mPFC in FSL and SD rats as well as the NAc in FSL rats displayed an increase in Gad1 expression [14]. This reveals that the antidepressant effects of MFB DBS are caused by changes in neuronal oscillations and GABAergic interneurons. Results from a different study that tracked dopamine release from the nucleus ambiguus after mfb DBS in a rodent model using fiber photometry and the dopamine indicator GRABDA2m showed that mfb-DBS causes an increase in the dopamine response during stimulation, with a maximal peak amplitude reaching in just under a second, followed by recovery after stimulation [15]. The effects of different DBS pulse widths PW on dopamine responses indicate the prospect of varied outcomes, although further study is needed to demonstrate this.

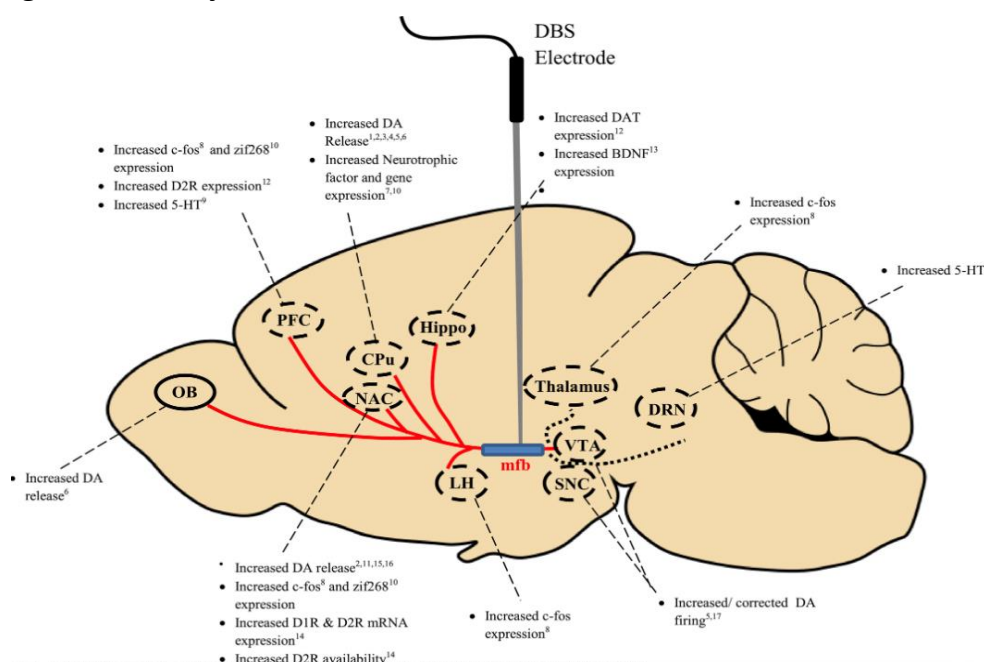


Fig. 2. Pathways of MFB - DBS [12]

4. Potential Target Areas

4.1. Potential Target Areas in SCC

Patients with a mean age of 50 years and a mean disease duration of 23 years showed widely distributed regions associated with clinical improvement in the somatocaudal and dorsoventral planes of both the left and right hemispheres when probabilistic stimulus mapping was used to identify brain regions associated with clinical improvement after SCC-DBS [16]. The right hemisphere had a larger percentage of gray matter involvement in these regions, and the left and right hemispheres had distinct optimal stimulation locations. These regions included white matter lateral to the gray-white matter border. The white matter lateral to the gray-white matter boundary contains somewhat more than half of each hemisphere's effective voxels, with a higher percentage of gray matter voxels in the right PSM [16]. Between the right and left PSM, there are significant differences in the locations of higher-value PSM voxels. High-value left PSM voxels typically concentrated in the white matter to the side of the subcallosal ACC, generally anterior and superior in location. High-value right PSM somatostatin, on the other hand, is mostly found more inferiorly and posteriorly, with the greatest clusters found in the subgenual ACC's gray matter and spreading across the surrounding white matter abutting the orbitofrontal gyrus. At the border of the gray and white matter of the subcallosal ACC, smaller clusters of high right PSM values were found.

The frontal lobe subcortical fibers were not the only white matter tracts that responded differently to the SCC-DBS. Notably, the left and right cingulate gyri were respectively implicated in 98.3% and 90% of the cases, whereas the small forceps/callosal rostral area was involved in all cases [16]. Additionally, after SCC-DBS, it was discovered that discriminating simplification was linked to bigger or lower drops in HAMD-17 scores. Additionally, common streamlines that matched the majority of the patients' tissue volume of activation (VTA) features were found. The small clamp/callosal podium, the cingulate tract, and the hook tract were the three main white matter tracts that were implicated in these streamlining groupings. Both the positive discrimination group and the common group showed substantial differences in the characteristics of the small forceps/podium of the corpus callosum, which connects the orbital region of the frontal lobe [16]. The right PSM was near to the right hook bundle and small forceps elements but had less overlap with the discriminative streamlines than the left PSM did with the left cingulate bundle. The same white matter bundles showed up when typical fiber bundle maps were seeded using the left and right PSM, strengthening their significance in the antidepressant effects of SCC-DBS.

While clinical outcomes and overlap did not significantly correlate with one another between VTA and any specific discriminative bundle in the entire primary cohort, a weakly positive correlation between left cingulate gyrus bundle involvement and clinical improvement was seen when only responders and partial responders were taken into account, according to further investigation of the correlation between differentiated streamlines and clinical outcomes using linear models. The top-performing linear model, which accounted for 21% of the variance in the declines in individual HAMD-17 scores, contained anatomical information on specific typical white matter bundles (see Figure 3). The Hamilton Depression Scale (HAMD-17) variance reduction was explained by overlap employing tissue activation volume (VTA) and certain white matter bundles, and the connection was substantial ($R = 0.46$). For TRD patients receiving SCC-DBS, this approach offers the option for personalized therapy planning.

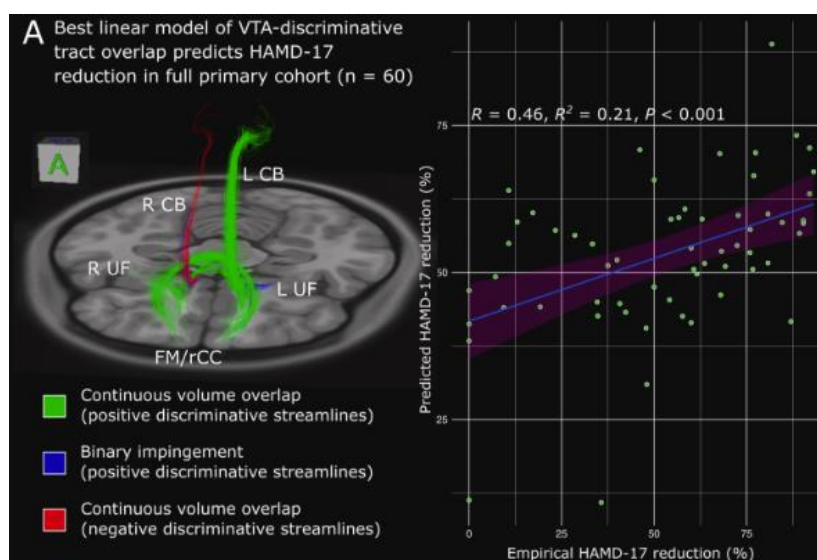


Fig. 3. SCC-DBS reaction predicted by tractography [16]

A paired t-test was conducted to compare the functional connectivity profiles of these seeded regions between the DBS-ONopt and the DBS-OFF states based on the changes in seed-based functional connectivity in cortical limbic regions during SCC-DBS, specifically the right dorsal anterior cingulate cortex [dACC], the left posterior cingulate cortex [PCC], and within the left precuneus. The results showed enhanced connectivity between the right dACC and cephalic enhanced communication between motor cortical areas, subcortical structures, the right dACC and the cephalic ACC, the medial prefrontal cortex and the frontal pole, as well as between the left PCC and the inferior frontal gyrus. The left precuneus and insula cortex, temporal regions, and subparietal lobules all showed improved connection after SCC-DBS [17]. Both the influence of SCC-DBS on functional

connectivity within cortical limbic nodes and the search for possible stimulation sites are highlighted by these findings.

4.2. Potential Target Areas in STN

Adeno-associated viral tracers were injected into the left prefrontal region of 52 marmosets to examine the 3D fiber anatomy of the prefrontal projections to the diencephalic-mesencephalic junction using tomographic beam tracing and data-driven methods. The results showed that the limbic prefrontal region projects directly to the VMT but not to the STN [18]. In mental diseases like MD, this supports the use of the superior lateral medial forebrain bundle (slMFB) as a viable target structure for DBS.

4.3. New Possible for BNST

In a patient with TRD, 12-month DBS of the bed nucleus of the striatal terminal zone (BNST) resulted in clinically substantial improvement in mood and anxiety. The patient's Beck Depression Inventory (BDI-11) score increased by 25 points, the cognitive component by 11 points, and the somato-emotional dimension by 14 points, all of which were indicative of this [19]. However, a different study concentrated on the variation in programming time and complexity required to obtain the optimum therapeutic outcomes with BNST DBS [20]. Nine white matter tracts in the MDD had microstructural anomalies, which was consistent with the brain regions controlled by the DBS targets. The group comprises white matter fibers [21]. However, further research is still needed to determine the potential of BNST combined with DBS for the treatment of depression.

5. Discussion

The antidepressant effects of SCC-DBS, the most popular treatment, include white matter bundles, suggesting a neuroanatomical basis for focusing on squamous cell carcinoma. The capacity to optimize the stimulation parameters is nonetheless constrained by the incomplete understanding of the exact mechanisms at play. Increased dopamine transmission, neuronal oscillations, and GABAergic interneuron activity have all been connected to depression and have all been associated with MFB-DBS. Additionally, a number of studies have found that mood improvement occurs. However, there aren't enough clinical studies on MFB-DBS for the treatment of depression, and since the MFB is close to other brain areas, stimulating it can have unintended negative effects.

Non-invasive deep brain stimulation methods based on the DBS principle are also being developed due to the significant risk of infection associated with the invasive nature of DBS treatment. In an effort to obtain comparable outcomes by stimulating the brain from outside the skull, numerous non-invasive neuromodulation procedures have been created. Transcranial magnetic stimulation involves creating a powerful but brief pulse of current in a stimulation coil. This pulsed magnetic field then uses the principle of induction to transmit the current to the brain through the resistive layers of the scalp, skull, and meninges, changing the electrical environment of the neurons and causing changes in cortical excitability [22]. Intensity, frequency, stimulation duration, number of stimulation pulses, etc. are only a few of the many TMS characteristics. It is required to further research the impact of its action and what adjustments should be made for various disorders because there is no universal conclusion, and the accuracy and penetration depth are not as excellent as those of DBS.

Potential applications for mood disorders include transcranial alternating current stimulation (tACS), which involves applying alternating current to the scalp to cause brain oscillations [23]. Contrarily, ultrasonic stimulation uses focused ultrasound waves to produce targeted mechanical vibrations or thermal effects that non-invasively excite a particular region of the brain. Both of these, however less well researched at the moment, offer potential in the non-invasive treatment of depression.

6. Conclusion

In summary, the prevalence of MDD as a major global health problem is steadily increasing, with far-reaching implications for physical health and wider society. The limitations of traditional treatments, including drugs and therapies, have led to increasing interest in innovative approaches such as DBS, which represents a promising frontier in neuromodulation of MDD. Although it has shown effectiveness in a variety of neuropsychiatric disorders, its application in depression remains complex due to the complexity of the disease and individual differences. Promising results have been achieved in targeted regions such as the SCC and the MFB, but the challenges of individualized treatment planning and more precise parameter settings remain.

Recent developments in DBS, such as the creation of personalized systems based on neurobiomarkers, hold promise for more precise and effective treatments. These innovations enable on-demand, patient-specific stimulation and represent significant advances in the field. In addition, ongoing research explores potential target areas and utilizes advanced techniques such as probabilistic stimulus mapping and functional connectivity analysis to further refine DBS approaches. Although noninvasive techniques such as transcranial magnetic stimulation and focused ultrasound show promise, they are not direct substitutes for invasive DBS and require further research.

Understanding the complexities of individual neuroanatomy, refining stimulation parameters, and addressing ethical issues for patients are critical in the quest for enhanced treatment of depression. DBS continues to evolve as a transformative therapy that offers a glimmer of hope for patients suffering from major depressive disorder.

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