# Deep brain stimulation in the treatment of depression

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*Major depressive disorder is a worldwide disease with debilitating effects on a patient's life. Common treatments include pharmacotherapy, psychotherapy, and electroconvulsive therapy. Many patients do not respond to these treatments; this has led to the investigation of alternative therapeutic modalities. Deep brain stimulation (DBS) is one of these modalities. It was first used with success for treating movement disorders and has since been extended to the treatment of psychiatric disorders. Although DBS is still an emerging treatment, promising efficacy and safety have been demonstrated in preliminary trials in patients with treatment-resistant depression (TRD). Further, neuroimaging has played a pivotal role in identifying some DBS targets and remains an important tool for evaluating the mechanism of action of this novel intervention. Preclinical animal studies have broadened knowledge about the possible mechanisms of action of DBS for TRD. Given that DBS involves neurosurgery in patients with severe psychiatric impairment, ethical questions concerning capacity to consent arise; these issues must continue to be carefully considered.*

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Major depressive disorder (MDD) is a common disorder with a prevalence of 4.7% (4.4% to 5.0%) worldwide,[1] and a 7% prevalence in the United States.[2] It is a disorder that affects a patient's ability to work and function in society; it leads to increased morbidity and consequently increased use of health resources. In a World Health Organization study from 2004, it ranked third in worldwide contribution to disease burden and first in high-income countries for individuals under 60 years of age.[3] From 1990 to 2010, MDD has advanced worldwide from 15th to 11th place in contributing to years lost due to disability, indicating a 37% increase during these 20 years.[4]

The most common current treatments available for MDD are antidepressant medications and evidence-based psychotherapy. Although many patients respond to these treatments, only a third enter complete and sustained remission.[5] Patients with treatment-resistant depression (TRD) have increased disability and a higher risk of relapse. Electroconvulsive therapy (ECT) can be efficacious in patients with TRD,[6-8] but has several drawbacks. First, it must be done in a center that can provide anesthesia and associated monitoring, thus limiting access. Second, ECT is associated with cognitive side effects that can be significant in a minority of patients.[9-12] Third, 10% to 50% of TRD patients do not achieve and/or maintain remission with ECT.[13,14] Ablative neurosurgical procedures have been used to treat the most

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## Selected abbreviations and acronyms

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| ***DBS*** | *Deep brain stimulation* |
| ***ECT*** | *Electroconvulsive therapy* |
| ***NAc*** | *Nucleus accumbens* |
| ***SCC*** | *Subcallosal cingulate* |
| ***TRD*** | *Treatment-resistant depression* |
| ***VC/VS*** | *Ventral capsule/ventral striatum* |

severely ill TRD patients for whom all other treatment approaches have failed.[15] These irreversible surgical interventions have shown efficacy in some patients, but have also been associated with infection, permanent cognitive side effects, and seizures.[15-17]

Over the past two decades, novel treatment approaches for TRD have emerged. Two devices for performing repetitive transcranial magnetic stimulation are now Food and Drug Administration (FDA)-approved for the treatment of MDD with a modest degree of treatment resistance.[18,19] However, repetitive transcranial magnetic stimulation is likely not as efficacious as ECT[20] and requires daily treatments over several weeks—this may present a significant logistical barrier to some patients. Another minimally invasive treatment being investigated for treating modestly resistant depression is transcranial direct current stimulation (tDCS). Although preliminary studies have shown some evidence of antidepressant efficacy, these data are mixed, and results from larger, placebo-controlled trials are lacking.[21-24] A vagus nerve stimulation (VNS) device has been approved by the FDA for TRD. VNS is more invasive than ECT, TMS, and tDCS, requiring minor surgery to implant the stimulation electrode and the battery pack/controller.[25] Efficacy of VNS is somewhat controversial.[26,27] The only randomized and sham-controlled trial of VNS for TRD showed no difference between active and sham stimulation after 10 weeks.[28] The remaining efficacy data are limited to open-label long-term results in comparison with a nonrandomized treatment-as-usual control group. These data suggest some benefit for long-term VNS in TRD, though absolute response and remission rates are relatively low.[29]

Deep brain stimulation (DBS) involves a neurosurgical procedure to stereotactically implant electrodes into a specific brain region; these electrodes are connected to a subcutaneous implantable pulse generator that controls stimulation and provides the power source for the DBS system. Typically, continuous electrical stimulation is provided. DBS is a relatively well-tolerated therapy, the most common adverse events being associated with the neurosurgical procedure: infection, hemorrhage, perioperative headache, seizure, and lead fracture.[30,31] Specific side effects can be associated with acute and chronic stimulation.

The target for DBS electrode placement can vary significantly based on the disorder being treated and the neuroanatomical models of the disorder. DBS devices have been approved by the FDA for the treatment of movement disorders and have shown good efficacy in treatment of Parkinson's disease, essential tremor, and dystonia.[32] Additionally, DBS has been explored in several neuropsychiatric disorders. The first neuropsychiatric application of DBS was for obsessive-compulsive disorder (OCD),[33] with electrodes placed in the anterior limb of the internal capsule—a previous ablative target for treating severe, treatment-refractory OCD. Subsequent studies have suggested a modest, but clinically significant benefit for DBS in patients with severe, treatment-refractory OCD.[34] A DBS system has received a Humanitarian Device Exemption from the FDA for the treatment of OCD. The first cases of using DBS for Gilles de la Tourette syndrome occurred around the same time as for OCD,[35] and in larger studies efficacy has been demonstrated for various targets.[36] DBS has also been proposed for the treatment of severe, treatment-resistant addiction, where a small dataset supported efficacy in treating this disorder.[37] The unexpected observation of cognitive improvement in dementia in a study of DBS for obesity[38] has led to its evaluation as a treatment for Alzheimer's disease and Parkinson's dementia.[39]

Significant interest has been generated by the potential for DBS to treat severe TRD. In this review, the clinical data on safety and efficacy of DBS in TRD will be presented. The role of neuroimaging in the development and optimization of DBS will be discussed, as well as its role in studying mechanisms of action. Further, preclinical animal data on potential mechanisms of DBS for TRD will be reviewed. Finally, critical ethical issues related to decision-making capacity and informed consent for TRD patients considering DBS will be examined.

## Clinical data on deep brain stimulation for treatment-resistant depression

### Subcallosal cingulate

The first target investigated for DBS for TRD was the subcallosal cingulate (SCC) white matter, occasionally

referred to as Cg25 or Brodmann area 25.[40] This target was chosen based on a neuroimaging database which suggested that this region was critical for depression and the antidepressant response—especially in TRD.[41] In an initial proof-of-concept study, four of six patients with extreme TRD were in or near remission following 6 months of open-label chronic SCC DBS. An expanded study of 20 patients showed a 60% response rate at 1 year and a remission rate around 50%—results that were generally maintained over several years.[31,40,42] Of note, most symptoms of depression improved, with insomnia, decreased energy, interest and psychomotor speed, disturbed social contact, apathy, anhedonia, poor concentration, and planning all showing improvement after 3, 6, and 12 months of follow-up.

Subsequent open-label studies of SCC DBS in TRD have demonstrated remission rates ranging from 33% to 58% with chronic stimulation (12 to 36 months).[43-47] A case report showed efficacy for SCC DBS in a patient who previously had a dorsal anterior cingulotomy (which was initially beneficial, but followed by a depressive relapse).[48] In one study, blinded discontinuation was associated with a significant increase in depression that improved when stimulation was reinstated.[44] Across these various studies, no adverse effects were seen with acute or chronic SCC DBS. No cognitive impairments were found with long-term stimulation, and improvements were noted[49] (Moreines et al, unpublished data). In one study including seven patients with bipolar II disorder, none showed hypomania or mania with acute or chronic stimulation.[44]

**Ventral capsule/ventral striatum and nucleus accumbens**

The ventral internal capsule/ventral striatum (VC/VS) was the first target for the treatment of OCD, based on previous lesional therapies. Interestingly, depression also improved in OCD patients treated with DBS in this region.[34,50] This observation led to an open-label pilot study of VC/VS DBS in TRD, which demonstrated a 53% response rate and 40% remission rate at last follow-up (between 6 and 51 months of stimulation).[51] These encouraging preliminary data led to a pivotal, double-blind, randomized, sham-controlled trial of VC/VS DBS in 30 patients with TRD. Unfortunately, no statistically significant efficacy was seen for active vs sham (off) DBS after 4 months of chronic treatment. Response rates were 20% and 14.3% in the active and sham groups, respectively.[52] In studies of VC/VS DBS for OCD and depression, a number of mood, anxiety, and other changes have been associated with acute stimulation (eg, panic attacks, euphoria, facial muscle activity). However, these changes could be eliminated with adjustment of stimulation parameters and did not appear to relate to long-term efficacy.

The nucleus accumbens (NAc) comprises the majority of the ventral striatal aspect of the VC/VS DBS target. More focal DBS of the NAc for TRD was hypothesized to have potential efficacy based on its importance in reward-seeking behavior (recognizing the prominent role of anhedonia in the syndrome of depression).[53,54] Indeed, in initial testing, anhedonia was one of the first symptoms to improve during NAc stimulation in TRD.[54,55] In 11 patients with TRD, 12 months of chronic, open-label NAc DBS resulted in a 45% response rate and 9% remission rate.[54-56] Acute return of depressive symptoms was seen with discontinuation of stimulation in three patients; reinitiation of stimulation resulted in the return of the antidepressant effects.[54] This study of NAc DBS reported similar acute effects of stimulation as with VC/VS DBS; as with VC/VS DBS, these effects could be ameliorated with stimulation parameter adjustment. No negative neuropsychological effects were identified with either acute or chronic VC/VS or NAc DBS.

**Medial forebrain bundle**

A more recent DBS target for TRD is the medial forebrain bundle (MFB), which includes ascending and descending white matter fibers connecting the ventral tegmental area with the nucleus accumbens. As with the NAc, a role for the MFB in TRD was hypothesized based on its role in reward processing.[57,58] In an open-label, proof-of-concept study, rapid antidepressant effects were seen in six of seven TRD patients with MFB DBS, with benefits maintained for at least 12 to 33 weeks.[58] Vision/eye movement changes were seen in all patients, related to specific stimulation parameters. No cognitive impairments were noted following months of stimulation.

**Other targets**

Other targets considered for DBS for TRD include: (i) the inferior thalamic peduncle[59]—this target may also

have benefits for OCD[60,61]; (ii) the lateral habenular complex[62]; and (iii) the rostral cingulate gyrus.[63]

**Summary**

Preliminary studies of DBS in the treatment of TRD have suggested safety and efficacy for several targets. The most experience to date is with the SCC target. Unique among these studies are data on the MFB target which suggest more rapid antidepressant efficacy than with the other targets. However, in interpreting these data, caution is warranted. The majority of the studies are small and open-label. The one sham-controlled study of a DBS target (VC/VS) showed no separation between active and sham stimulation for antidepressant efficacy. This highlights the importance of sham-controlled trials before embracing treatment modalities with encouraging preliminary data.

## Application of neuroimaging to studies of deep brain stimulation for treatment-resistant depression

As above, functional neuroimaging played a pivotal role in the development of the SCC DBS target for TRD,[41] and also helped validate the lateral habenula as a potential DBS target for TRD treatment.[64] Intraoperative magnetic resonance imaging (MRI) may help improve accuracy of lead placement for DBS and assist in evaluating acute changes associated with neurosurgery, such as hemorrhage, intracranial air, or brain shift.[65] Diffusion tensor imaging (DTI) an MRI technique especially useful for imaging white matter and providing a white matter tractography, was used to locate the MFB target in a patient-specific manner.[58] DTI may eventually be helpful in optimizing electrode placement for other DBS targets for TRD.[66-70] Much of this work suggests that using patient-specific tractography activation models would improve targeting: these models calculate the volume of stimulation/activation from the electrode and perform patient-specific tractography from these volumes.[67,68,71,72]

Additionally, neuroimaging has been used to assess the mechanism of action of DBS. One DTI study showed high interconnectivity between multiple targets used in DBS for patients with TRD,[73] and other identified key areas of overlap in projections from these targets suggesting common downstream regions that may need to be impacted for antidepressant efficacy.[70] Similarly, functional neuroimaging (primarily using positron emission tomography) has shown changes in brain activity associated with successful DBS for TRD with the SCC,[40] and the NAc targets.[54,55] A resting-state electroencephalography study assessed brain activity before and after SCC DBS for TRD and found that baseline prefrontal/anterior cingulate theta activity predicted which patients would have a greater antidepressant effect with chronic stimulation.[74] Additionally, this theta activity showed differential changes over time in responders vs nonresponders.[74] This is consistent with prior studies showing that prefrontal/anterior cingulate theta activity is related to symptoms of depression, such as attention, emotional regulation, and memory,[75] as well as studies associating prefrontal theta activity with antidepressant response to medication.[76,77] Functional MRI studies have been utilized less in the postoperative study of DBS, due to concerns about patient safety. Generally, the brain regions implicated by the diffusion tensor imaging and functional neuroimaging studies overlap, helping to confirm that the structural and functional connectivity of these regions with the DBS target are critical to the success of the intervention.

## Preclinical studies of deep brain stimulation for treatment-resistant depression

In contrast to the typical way of evaluating new treatment modalities for depression, DBS in TRD was first investigated in patients rather than animal models. This was largely based on the safety/efficacy of DBS in patients with movement disorders, a history of relatively safe/efficacious ablative surgery in humans with severe psychiatric illness, strength of neuroimaging data delineating the presumed neural circuitry of depression, and the absence of adequate animal models for TRD. However, once preliminary safety and efficacy of DBS for TRD was demonstrated in humans, many investigators have turned to animal studies to help investigate potential mechanisms of action for this intervention.
In rats, high-frequency stimulation of the ventromedial prefrontal cortex (vmPFC, a homologue of the SCC) has been associated with antidepressant-like effects using the forced swim test.[78,79] Both vmPFC and NAc stimulation have been shown to reverse anhedonic-like states in rats exposed to chronic stress.[80,81] In a mouse model of enhanced depression- and anxiety-like behavior, NAc DBS induced antidepressant and anxiolytic responses in

affected animals, but no behavioral changes in normal depression/anxiety animals.[82]

Animal studies have additionally helped clarify effective parameter sets. For the vmPFC/SCC target, a series of studies showed that: (i) high-frequency stimulation (130 Hz) was more effective than low-frequency stimulation (20 Hz); (ii) prelimbic (PL) cortical stimulation was more effective than infralimbic (IL) stimulation[78]; (iii) a current intensity between 100 to 300 microA was more effective than 400 microA; and (iv) unilateral left-sided stimulation was as effective as bilateral stimulation.[78] Simple ablation of the PL/IL region was not associated with significant antidepressant-like effects,[79] though other studies have shown antidepressant-like effects with ablation or inactivation of the IL target.[83,84] Interestingly, lesions of the local gray matter, while preserving white matter fibers of passage, was associated with antidepressant-like effects.[79] This suggests the mechanism of DBS for TRD may not be simply due to local inhibitory effects, but may involve stimulation of white matter tracts—similar to findings seen in Parkinson's disease.[85]

For the NAc target, it has been shown that continuous stimulation was more effective than intermittent stimulation.[86] Consistent with imaging studies in humans, DBS of the NAc has been associated with remote brain activity changes in the prefrontal cortex, insula, cingulate, and parahippocampus in a pig model.[87]

Depletion of serotonin blocks the antidepressant-like effects of medial frontal stimulation in rats, while depletion of norepinephrine does not[79]; this suggests a critical role for serotonin (among other monoamines) in the mechanism of action of DBS for TRD. Stimulation of the NAc has been associated with increased monoamine levels in rats corresponding to improvement in depressive- and/or anxiety-like behaviors,[86,88,89] though another study showed that internal capsule stimulation resulted in greater anxiolytic effects.[90] Beyond the monoamines, stimulation of the vmPFC, NAc, or ventral tegmental area has been associated with increased brain-derived neurotrophic factor (BDNF) levels in rats using a chronic mild stress paradigm[80,81,90]; prior to stimulation the rats prone to depressive-like behavior showed lower BDNF levels than control rats.[91] Therefore, as with other antidepressant treatments (including medication and ECT), the mechanism of DBS for TRD may involve upregulation of neurotrophic systems.[92,93]

## Ethical concerns associated with deep brain stimulation for treatment-resistant depression

Ethical considerations in medicine include beneficence, non-malfeasance, and autonomy.[94,95] Consequently, regulations and supervision need to be implemented for clinical trials, especially considering the potential impairment in decision-making inherent to neuropsychiatric illnesses and the invasiveness of DBS.[96,97] In depression, one must consider the goal of treatment: happiness versus euthymia. If a treatment induces "joy" or "feeling good," then how much is too much? Rather than simply treating depression, the effects of treatment might be seen as an end itself, similar to studies of intracranial self-stimulation in animals.[98] This is a potential concern with some DBS targets for neurologic and neuropsychiatric disorders where euphoria, and even frank mania, can be induced with stimulation.[34,51,55,99-101] However, in these studies, primary efficacy could be obtained without these side effects via careful selection of stimulation parameters for chronic stimulation. For depression studies, the goal should be euthymia and normal mood regulation, not heightened hedonic response above a patient's nondepressed baseline.

Another important ethical concern is decision-making capacity. Can patients with severe TRD (often with some degree of suicidal ideation) truly give free, informed consent to participate in a study with potentially serious/life-threatening risks? Additionally, patients may have unrealistic expectations related to the intervention.[102,103] Recognizing these concerns, groups are beginning to assess this in conjunction with clinical trials. Some groups have advocated for extensive external review boards to monitor and approve patients for study inclusion; this is largely based on a concern that DBS not be viewed in the same vein as prefrontal leucotomy[104,105] and protect patients whose decision-making capacity and judgment might be impaired by their severe psychiatric illness.[105] Therefore, these recommendations were largely theoretical and not evidence-based, encouraging investigators in this field to "be on the safe side." However, based on a careful review of the literature, Dunn et al have argued that no *additional* specific safeguards are needed in obtaining informed consent from patients with severe TRD compared with other patients with severe, life-threatening, disabling medical conditions—depression, in and of itself, does not uniquely impair decision-making

capacity or judgment.[106] However, decision-making capacity, as well as understanding of the study must be carefully assessed. To this end, a study-specific MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) was used in a trial of SCC DBS for TRD patients and found that patients with TRD showed no significant deficits in study understanding, though there was a trend for patients with more severe depression to have greater "therapeutic misconception": ie, on average, subjects gave answers that appeared to show that they misunderstood the purpose of the study, likelihood of personal benefit, or individualization of treatment (eg, overestimating likelihood of benefit, underestimating risk).[107] However, a more detailed analysis of these data and patient's specific comments validated that patients demonstrated intact decision-making capacity and informed consent procedures were appropriate.[108]

As the indications for DBS expand, concerns related to specific populations will arise: eg, how should the informed consent process be conducted in "vulnerable" populations such as children, patients with dementia, and patients with severe cognitive disorders?[97] On the one hand, these patients should not be denied enrollment in trials of a potentially efficacious treatment simply because of limited decision-making capacity.[109] On the other, very careful attention must be paid to voluntariness, consent/assent, and appropriateness for inclusion. To this end, eligibility criteria should be carefully considered (to insure scientific validity for studies likely to have a small sample size), and the informed consent process should include mechanisms to evaluate decision-making capacity as well as patients' understanding and appreciation of the risks/potential benefits of the study. Ideally, a comprehensive registry of efficacy and safety should be created. In developing guidelines for such studies, input from all stakeholders should be considered.[97]

## Conclusion

DBS is emerging as a potential intervention for patients with severe depression for whom no reasonable treatment options are available. Data remain quite preliminary for the various targets that have been investigated. Beyond simple demonstration of safety and efficacy, a growing number of human and animal studies are beginning to delineate potential mechanisms of action for DBS for TRD. As the field expands (to larger studies and new indications), a number of ethical concerns should be considered, especially related to voluntariness, informed consent, and the possibility of therapeutic misconception. With careful and considered study, the hope is that DBS might become an important treatment option for some of the most severely affected patients with neuropsychiatric diseases, as it has in the field of neurology. ❑

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## *La estimulación cerebral profunda en el tratamiento de la depresión*

*El trastorno depresivo mayor es una enfermedad a nivel mundial que deteriora la vida del paciente. Los tratamientos habituales incluyen farmacoterapia, psicoterapia y terapia electroconvulsiva. Ya que muchos pacientes no responden a estos tratamientos se ha generado la investigación de otras alternativas de intervención terapéutica. La estimulación cerebral profunda (ECP) es una de estas modalidades. Esta terapia se empleó inicialmente con éxito para el tratamiento de trastornos motores y luego se ha extendido al tratamiento de trastornos psiquiátricos. Aunque la ECP todavía es un tratamiento naciente, en los ensayos preliminares en pacientes con depresión resistente al tratamiento (DRT) se ha demostrado su prometedora eficacia y seguridad. Además, las neuroimágenes han jugado un papel central en la identificación de algunos blancos para la ECP y se mantienen como una importante herramienta para la evaluación del mecanismo de acción de esta nueva intervención. Los estudios animales preclínicos han ampliado el conocimiento sobre los posibles mecanismos de acción de la ECP para las DRT. Dado que la ECP involucra neurocirugía en pacientes con deterioro psiquiátrico grave, surgen aspectos éticos respecto a la capacidad de consentir y estos temas deben ser tomados en cuenta con mucho cuidado.*

## *Stimulation cérébrale profonde dans le traitement de la dépression*

*L'épisode dépressif caractérisé est une pathologie mondiale aux effets débilitants sur la vie des patients. La pharmacothérapie, la psychothérapie et l'électroconvulsivothérapie sont des traitements courants. De nombreux patients ne répondent pas à ces traitements, ce qui a conduit à la recherche de traitements alternatifs. La stimulation cérébrale profonde (SCP) en est un. Elle a d'abord été utilisée avec succès pour le traitement des dyskinésies et a depuis été élargie au traitement des troubles psychiatriques. Bien que la SCP soit encore un traitement récent, des études préliminaires chez des patients déprimés résistants au traitement (DRT) ont montré une efficacité et une sécurité prometteuses. De plus, la neuro-imagerie a joué un rôle pivot dans l'identification des cibles pour la SCP et reste un outil important pour évaluer le mécanisme d'action de cette nouvelle technique. Des études précliniques chez l'animal ont élargi la connaissance sur les mécanismes d'action possibles de la SCP pour les DRT. La SCP impliquant un geste de neurochirurgie chez des patients ayant un trouble psychiatrique sévère, des questions éthiques se posent quant à la capacité de consentement des patients. Ces questions doivent continuer à être soigneusement prises en considération.*



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