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Review

Deep brain stimulation in the treatment of depression

Blomstedt P, Sjöberg RL, Hansson M, Bodlund O, Hariz MI. Deep brain stimulation in the treatment of depression.

Objective: To present the technique of deep brain stimulation (DBS) and to evaluate the studies conducted on DBS in the treatment of therapy-refractory major depressive disorder (MDD).
Method: A review of the literature on DBS in the treatment of MDD was conducted.
Results: The results of DBS in MDD have been presented in 2 case reports and 3 studies of 47 patients operated upon in 5 different target areas. Positive effects have been presented in all studies and side effects have been minor. DBS in the nucleus accumbens resulted in a mean reduction of Hamilton depression rating scale (HDRS) of 36% after 1 year and 30% of the 10 patients achieved remission. DBS in the internal capsule/ventral striatum resulted in a reduction of 44% after 1 year, and at the last evaluation after in mean 2 years, 40% of the 15 patients were in remission. The 20 patients with subcallosal cingulated gyrus DBS had a reduction of HDRS of 52% after 1 year, and 35% were within 1 point from remission or in remission.
Conclusion: DBS is a promising treatment for therapy-refractory MDD. The published experience is, however, limited, and the method is at present an experimental therapy.

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Summations

- Deep brain stimulation (DBS) is an established treatment for movement disorders.
- DBS has been demonstrated to be a safe method and only minor complications have been reported in patients with MDD.
- The results of DBS for therapy-refractory major depressive disorder (MDD) have been promising.

Considerations

- The experience of DBS in MDD is limited.
- Several different potential targets have been presented, but it remains to be decided which is the optimal target for MDD.
- DBS for MDD is an experimental therapy that should only be performed by multidisciplinary teams with substantial experience of DBS in the treatment of other conditions.

Introduction

Depression constitutes one of the most severe challenges for modern medicine. According to WHO, it is the most common cause of disability in our society, with a prevalence in the general population of about 5% (1–3). This condition is associated with an often severe social handicap and a reduced quality of life, as well as with a significant mortality. It is estimated that 90% of suicides are related to psychiatric disease, the most common being depression, in which the mortality owing to suicide is estimated to be 10–15% (4–6).

Even though many patients with depression will respond well to non-surgical therapies, such as

pharmacological treatment, psychotherapy and electroconvulsive therapy (ECT), there remains a significant proportion of patients in whom these methods will give little or no relief. The STAR*D studies have recently demonstrated the limitations of pharmacotherapy, with only about 60% of the patients achieving remission after 12 months, and the fourth therapeutic step resulted in remission in no more than 6% of the patients. Furthermore, half of those who did not achieve remission until the fourth step had relapsed 4 months after the study (7–14). Cognitive behavioural therapy could not be demonstrated to be a more efficient alternative than pharmacological therapy (13).

The effectiveness of ECT in major depressive disorder (MDD) is well known, but the effect is often of limited duration, and there is a concern regarding cognitive side effects and other complications (15–17). Other options include vagal nerve stimulation (VNS) and transcranial magnetic stimulation, which, however, have met with limited clinical success (18, 19). Recently, stereotactic deep brain stimulation (DBS) has emerged as a possible treatment for therapy-refractory MDD.

Stereotactic functional neurosurgery involving chronic electrical stimulation of central nuclei and pathways of the brain for movement disorders, pain and psychiatric conditions has a long history going back to the 1950s (20, 21). The modern era of deep brain stimulation started in the late 1980s and early 1990s for surgical treatment of medication-refractory movement disorders, especially Parkinson's disease (PD), and the field has expanded rapidly, especially after the turn of the millennium (22). Today, more than 60 000 patients worldwide have been operated on for PD, non-PD tremor and dystonia (23). New indications for DBS are being evaluated, for example severe epilepsy and cluster headache (24–28). In DBS for psychiatric disorders, several trials have been initiated for Tourette's syndrome (29–35), obsessive-compulsive disorder (OCD) (36–41) and MDD (42–46).

Aims of the study

To briefly describe the technique of deep brain stimulation (DBS) and to report on the literature published so far concerning DBS in the treatment of depression.

Material and methods

The literature was searched for publications regarding DBS in the treatment of depression. Relevant papers were obtained using the PubMed database, and references quoted in the consulted papers. Care was taken to avoid duplicate inclusion of patients concerning multiple publications from the same institution. Reports regarding DBS for OCD with concomitant depression were not included.

Deep brain stimulation

The procedure is usually performed under local anaesthesia with the patient awake to evaluate the effect of stimulation during surgery. An MRI study is carried out with a stereotactic frame mounted to the patient's head. After calculating the brain target's coordinates and adjusting the probe carrier of the stereotactic frame accordingly, a small burr-hole is made a few centimetres from the midline close to the coronal suture, and an opening of approximately 4 mm is made in the dura. The DBS electrode, with a diameter of 1.27 mm, is then guided to the target with a precision of approximately 1–2 mm. The DBS electrode has four contacts of 1.5 or 3 mm in length each, with a space of 0.5, 1.5 or 4 mm between contacts, depending on the model. Each contact is stimulated and evaluated regarding effects and side effects. Acute effects can be very dramatic in movement disorders, such as immediate cessation of tremor in PD, while they may be more discreet or non-existent in psychiatric diseases (42–44). When the position of the electrode is deemed to be optimal, the electrode is secured to the skull, and immediate stereotactic CT/MR imaging is performed. In the second stage of the procedure, the patient receives general anaesthesia, and a pulse generator (IPG) is implanted under the subcutaneous fat below the clavicle and connected to the electrodes with extension cables tunulated below the skin (Fig. 1).

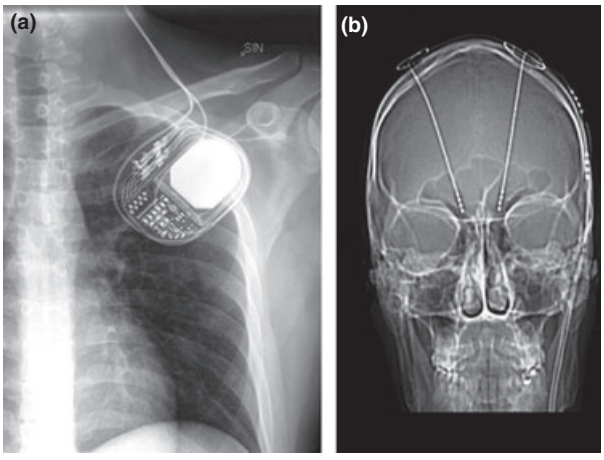

Fig. 1. Postoperative X-ray demonstrating the implantable pulse generator (a), extension cables and DBS electrodes (b).

The patient is mobilised the day after the surgery and can normally return home within 3–5 days of the procedure, unless additional time is warranted for the programming of the device (47).

The programming is carried out using an external transmitter. Different combinations of electrode contacts, voltage, pulse-width and frequency are evaluated to find the optimal stimulation parameters in the individual patient. Concerning movement disorders, a few programming sessions are normally necessary during the first 3–6 months. Regarding psychiatric conditions, the acute effects of stimulation are less noticeable and the experience more limited, making the process more challenging. The strategy for optimisation of the stimulation parameters does further vary between different studies. While some perform frequent alterations/evaluations, others choose contacts mainly based on the anatomical location and other parameters based on their experience.

Side effects and complications of DBS

Side effects and complications following DBS can be divided into stimulation-induced side effects, hardware-related complications and direct surgical complications. In patients with movement disorders, operated on in basal ganglia and thalamic targets, the most frequently encountered stimulation-induced side effect is voltage-dependent dysarthria. Rare, and often transient, side effects of DBS in the subthalamic nucleus in parkinsonian patients, as reported in the literature, include inter alia, acute depression, hypomania and hilarious laughter (20, 48, 49). The major advantage of DBS, compared with lesional procedures, is the possibility of performing bilateral simultaneous surgery and the reversibility of most side effects. Eventual side effects can be addressed by altering the stimulation parameters or by simply turning off the stimulation (47, 50).

Hardware-related complications may include malfunction of the implants, electrode breakage, external electromagnetic influence and infections. Their occurrence is rare. As for surgical complications, the major risk with DBS is intracerebral haemorrhage (ICH). In larger series, this has been estimated to be some 1–2% (48). Haemorrhages can be small and asymptomatic or can result in a severe neurological deficit, including, very rarely, death. The risk seems to be related to the use of multitrajectory microelectrode recording (51, 52). This technique is not used at our centre.

In general, DBS is a safe technique associated with few side effects of a more serious nature (20). In our experience in Umeå, with some 350 DBS operations performed since May 1993, we encountered only one minor ICH, resulting in a transient weakness for 3 weeks.

DBS in the treatment of depression

The brain targets used today for DBS in the treatment of some psychiatric illnesses are generally the same that were stereotactically ablated during the lesional era. This is also partly true

Table 1. Reports concerning deep brain stimulation for major depressive disorder

Author	No. of patients/Target/Procedures	Complications (related to surgery/stimulation)	Results
Bewernick et al. (44)	10 Nucleus accumbens	3 dysphagia, 6 swollen eye, 3 pain, 4 erythema, 3 anxiety increase, 3 sweating, 2 disequilibrium, 2 hypomania, 2 paresthesia, 2 agitation, 1 headache, 1 lead dislodgement, 1 psychotic symptoms, 1 muscle cramps, 1 affection of vision	A mean of 36% reduction of HDRS-28 after 1 year. 50% of the patients had a reduction of 50% or more, and 30% achieved remission
Jiménez et al. (46)	1 (Bipolar?) Inferior thalamic peduncle	None	Approximately 93% reduction of HDRS at evaluation at 24 months. Cessation of antidepressive medication
Lozano et al. (42)	20 (1 bipolar) Subcallosal cingulate gyrus	1 seizure, 4 infections, 5 perioperative pain, 2 worsening of mood	A mean of 52% reduction of HDRS-17 after 12 months. 55% had a reduction of at least 50% and 35% were within 1 point or less from remission
Malone et al. (43)	15 (1 bipolar) Ventral capsule/Ventral striatum	2 Hardware complications, 1 hypomanic episode, possible inducement of changes between the states in the bipolar patient	A mean of 47% reduction of HDRS-24 after 6 months. 44% reduction in the 11 patients evaluated after 1 year. At the last evaluation after a mean of 23.5 months (range 6–51), the mean reduction was 57%, and 40% had achieved remission at this point
Sartorius et al. (45)	1 Lateral habenula	None	Full remission. The patient was followed for approximately 1 year, and the HDRS-21 decreased from 45 to 0

HDRS, Hamilton depression rating scale.

regarding the current targets for DBS in major depressive disorder, which are the subcallosal cingulate gyrus (SCG) (53), the nucleus accumbens (Nacc) (54), the internal capsule (55) or the inferior thalamic peduncle (ITP) (56). So far, a total of 47 patients treated with DBS for depression in five different studies and targets have been published. The targeted structures are the SCG (42, 57–61), Nacc (44, 62), the ventral internal capsule/ventral striatum (VC/VS) (43, 63), the ITP (46, 56, 64, 65) and the lateral habenula (LH) (45) (Table 1).

The exploration of several different targets is not surprising. It is well known that in DBS in the treatment of movement disorders, different symptoms can be treated by stimulation of various nodes of the cortico-striato-pallido-thalamo-cortical circuit, and further that the same symptoms can sometimes be treated by interventions at different nodes in this circuit. This seems also to be the case in such psychiatric disorders as MDD and OCD, where the same targets have been successfully stimulated to treat different conditions (43). It also seems more likely that dysfunction in multiple limbic-cortical systems is involved in MDD and other psychiatric disorders, rather than dysfunction in specific 'mood centres' in the brain (59, 66). It might here be mentioned that ITP fibres form a part of an afferent bundle of the lateral habenula, why the mechanism of ITP and LH DBS might be identical (67).

DBS in these targets and their connections with cerebral structures implicated in MDD has gained support from PET studies. VC/VS DBS for OCD has been shown to result in changes in the metabolism of the orbitofrontal cortex (OFC) and the SCG (43, 68, 69). The Nacc, which forms a part of the striatum, constitutes a key structure in the reward circuitry and has been shown to be dysfunctional in MDD (44, 62). DBS in this nucleus results in decreased metabolism in the OFC and SCG (44). PET studies have revealed an increased activity in the SCG in depression and reduction of this activity when symptoms are successfully treated by non-surgical therapies. Based on these findings, the rationale in one of the studies was to implant electrodes directly in the SCG to reduce this increased activity (42, 70–72).

Patients

The inclusion criteria were quite uniform in the three studies including more than one patient (42–44). DBS was offered to patients suffering from chronic therapy-resistant MDD. The mean duration of disease was 17–21 years, and the mean current major depressive episode prior to surgery was 7 and 11 years respectively in the studies where this was specified. All patients had undergone extensive pharmacological trials and psychotherapy, and all but three had received ECT (42–46). Patient characteristics are presented in Table 2.

Table 2. Patient characteristics in reports of deep brain stimulation and major depressive disorder

	Lozano et al. (42)	Malone et al. (43)	Bewernick et al. (44)
No. of patients	20	15	10
Male/Female	9/11	4/11	6/4
Age at onset (years)	27.1	25.3	31.7
Age at surgery (years)	47.4	46.3	48.6
Length of current depressive episode (years)	6.9	≥2	10.8
No. of episodes	3.9		1.6
Unemployed (%) preop/1 year	90/55		
No. of drugs at surgery	4.2		4.3
Undergone ECT (%)	85	100	100
Undergone psychotherapy (%)	100	100	100
HDRS-17 preop/1 year	24.4/12.6		
HDRS-24 preop/1 year		33.1/18.5	
HDRS-28 preop/1 year			32.5/20.8
MADRS preop/1 year		34.8/18.5	30.6/20.3
BDI preop/1 year	27.5/22.6		
BAI preop/1 year	14.1/12.9		
HAMA preop/1 year			23.3/14.9
CGI severity/1 year	5.1/3.2	5.3/3.9 (6 months)	
GAF preop/1 year		43.4/58.4	
IDSSR preop/6 months		47.5/33.3	

BAI, Beck anxiety inventory; BDI, Beck depression inventory; ECT, electroconvulsive therapy; GAF, Clinical global impression of severity scale, Global assessment of function scale; HAMA, Hamilton anxiety scale; HDRS, Hamilton depression rating scale; IDSSR, Inventory for depressive symptom-SR; MADRS, Montgomery Åsberg depression rating scale.

Results

Some difficulties are encountered when comparing the results of the different studies. The follow-up period varies between different groups, and the patients have been evaluated in different ways using a variety of scales. All groups have used the Hamilton depression rating scale (HDRS); however, one group has not specified which version they used, while the others used the versions with 17, 21, 24 and 28 questions. The results are summarised in Table 1 and presented in further detail regarding the larger studies in Table 2.

Two of the studies were single case reports in which full remission was reported after LH DBS in one patient and a 93% reduction of HDRS after ITP DBS in another (45, 46). Bewernick et al. (44) have reported 10 patients treated in the Nacc. At the evaluation after 1 year, HDRS was reduced by a mean of 36%, with half of the patient having a reduction of at least 50% and 30% achieving remission.

Malone et al. (43) included 15 patients in whom the target was the internal capsule/ventral striatum. HDRS was reduced by 44% in the 11 patients evaluated after 1 year. At the last evaluation after a mean of 23.5 months (range 6–51), the reduction was 57%, and 40% had achieved remission.

With 20 patients reported with DBS in the SCG, Lozano et al. (42) have the largest series in this field, and various aspects of these patients have been presented in a number of publications (42, 57–61). The 20 patients, who underwent implantation in the SCG, had a mean reduction of HDRS of 52% after 12 months, with 55% having a reduction of at least 50% and 35% were within 1 point from remission or were in remission.

Complications and stimulation parameters

Complications related to surgery or stimulation are presented in Table 1. Complications related to the method itself were relatively few in number and not of a severe nature. As for other side effects, the largest group of patients, i.e., those who underwent implantation in the SCG, appear to have suffered the mildest/fewest adverse events, with two patients experiencing episodes of worsening of mood/irritability (42). A high frequency of side effects was reported from the group with Nacc DBS, including hypomania, agitation and psychotic symptoms. The advantage of DBS was demonstrated, however, by the fact that all side effects were transient and could be abolished by altering the stimulation. Furthermore, even though the authors did not consider these events to be related to the treatment, it should be noted that one of the 10 patients with Nacc DBS committed suicide and a second attempted suicide (44).

Stimulation parameters are also of interest because the higher the stimulation amplitude used, the faster the battery will be depleted, thus necessitating frequent replacements of the expensive neurostimulator with an inherent risk for infection. Owing to missing information in some of the studies, the stimulation parameters cannot be directly compared between the different studies. The experience of DBS for OCD has shown that high stimulation parameters are needed in the IC and Nacc (38–41, 73), and the same seems to be the case in DBS for depression in these same targets (43, 44). Stimulation levels in the SCG were, however, more moderate (42).

Discussion

Judging from this survey of the literature on DBS for MDD, this emerging therapy seems promising and is based on a scientific rationale – at least in theory. A limitation of the reports is the lack of a control group with sham stimulation. Even though it is difficult, for ethical reasons, to conduct a placebo (i.e. sham surgery) controlled study, it would be of interest to compare DBS with a control group receiving the best medical therapy. It is, however, a well-known fact that the placebo effect is limited in MDD, and it has been reported to amount to no more than 10% in the acute phase in patients treated with VNS (74, 75). Several other factors contradict the likelihood of the placebo effect being the main component of DBS in MDD patients: the effect of stimulation on symptoms was progressive over time; the effect varied with the stimulation parameters used in the individual patient; and blinded intended, as well as accidental, shutdown of stimulation, unbeknown to the patient, resulted in increasing depressive symptoms in all studies where this happened (42–46).

Some difficulties arise when comparing the effect of the treatment in the three largest studies owing to the different versions of HDRS used as well as to the uncertainties concerning the number of patients. However, when evaluated after 1 year, the largest percentage reduction of HDRS was seen in the SCG-DBS group with 52%, followed by the IC/VC DBS group with 44% and the Nacc DBS group with 36%.

DBS in other targets and diseases is known to be a safe method with relatively few side effects of a more serious nature. This was confirmed by the present studies and the neuropsychological evaluations performed. The lowest number of side effects that may be considered to be specific for the target/diagnosis was reported in the SCG, even though this was the largest study, while the high frequency of adverse events reported in the Nacc raises some concern.

The question of battery longevity is of major practical and economic importance, and it is doubtful whether it is acceptable to replace the battery more than once a year, as in the IC/VS or in the habenula, where stimulation parameters were particularly high, making this therapy very expensive, not to mention the risk for infection each time the battery has to be changed. This problem might be diminished by the recently introduced IPG:s with rechargeable batteries, with an expected duration of up to 9 years, or more. These IPG:s have, however, not been evaluated in clinical practice with the high energy consumption used in some patients with psychiatric disorders.

Sufficient data were not presented concerning stimulation parameters in the Nacc and the SCG,

but it seems likely that the battery consumption rate was the lowest in the SCG.

Of the five targets/structures hitherto presented in the treatment of MDD, we have ourselves chosen the SCG as target in a study of DBS in the treatment of depression in Umeå. We must however emphasise that at this point, it is not possible to decide which, if any, of these targets is the optimal one. Additionally, the optimal position of the electrodes within each of these targets is yet to be decided. It is also possible that there is no optimal target for MDD but that different targets are preferable for different subtypes of MDD, thereby necessitating tailoring of the therapy for each individual patient. Thus, owing to the limited amount of material in the literature, it is too early to decide on the relative merits of the different targets.

A therapy leading to remission in about one-third of the patients with chronic major depressive disorder refractory to multiple pharmacological trials, psychotherapy and ECT must be regarded as a welcome contribution to the therapeutical arsenal. If the promising results presented in these studies can be reproduced, or improved, in larger series, it seems likely that MDD may develop into one of the major indications for DBS.

Even though DBS might offer hope to many patients suffering from therapy-resistant MDD, it is important to point out that DBS for MDD remains an experimental therapy which should only be administered in clinical studies driven by multidisciplinary teams including surgeons with substantial experience of DBS in the treatment of other conditions.

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Declaration of interest

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