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Deep Brain Stimulation for Treatment-resistant Depression: Systematic Review of Clinical Outcomes

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Abstract Major depressive disorder (MDD) is a widespread, severe, debilitating disorder that markedly diminishes quality of life. Medication is commonly effective, but 20–30 % of patients are refractory to medical therapy. The surgical treatment of psychiatric disorders has a negative stigma associated with it owing to historical abuses. Various ablative surgeries for MDD have been attempted with marginal success, but these studies lacked standardized outcome measures. The recent development of neuromodulation therapy, especially deep brain stimulation (DBS), has enabled controlled studies with sham stimulation and presents a potential therapeutic option that is both reversible and adjustable. We performed a systematic review of the literature pertaining to DBS for treatment-resistant depression to evaluate the safety and efficacy of this procedure. We included only studies using validated outcome measures. Our review identified 22 clinical research papers with 5 unique DBS approaches using different targets, including nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Among the 22 published studies, only 3 were controlled trials, and 2, as yet unpublished, multicenter, randomized, controlled trials evaluating the efficacy of subgenual cingulate cortex and ventral striatum/ventral capsule DBS were recently discontinued owing to inefficacy based on futility analyses. Overall, the published response rate to DBS therapy, defined as the percentage of patients with>50 % improvement on the Hamilton Depression Rating Scale, is reported to be 40–70 %, and outcomes were comparable across studies. We conclude that DBS for MDD shows promise, but remains experimental and further accumulation of data is warranted.

Keywords Deep brain stimulation · Major depressive disorder · Ventral capsule · Ventral striatum · Brodmann area 25 · Subgenual cingulate · Nucleus accumbens

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Introduction

Major depressive disorder (MDD) is a common and potentially life-threatening disorder characterized by various symptoms, including depressed mood, hopelessness, neurovegetative symptoms, anxiety, apathy, cognitive deficits, and, in some instances, delusions and suicidal ideation. The lifetime prevalence of MDD has been reported to be 16.2 % [1]. As many as 20–30 % of patients with MDD are reported to be refractory to medical therapy [2, 3].

A variety of surgical ablative lesion therapies (anterior cingulotomy [4], anterior capsulotomy [5], subcaudate tractotomy [6], and limbic leucotomy [7, 8]) have been used to treat patients who are refractory to noninvasive treatments, including pharmacotherapy, psychotherapy, repetitive transcranial magnetic stimulation, and electroconvulsive therapy. Though these surgical treatments have been reported to be successful in select patients, early reported studies of these procedures lack modern methodological approaches

[9]. In addition to these ablative surgical procedures, neuromodulation procedures, such as vagus nerve stimulation [10], epidural cortical stimulation [11], and deep brain stimulation (DBS), have recently been employed. The theoretical advantages of these electrical stimulation therapies over lesion therapy are the reversibility and adaptability of therapy. It is noteworthy that these techniques have also enabled sham stimulation controlled studies for more accurate evaluation of efficacy [12]. Among neuromodulation therapies, DBS offers the attractive potential to modulate directly the specific malfunctioning brain circuitry responsible for the manifestation of neuropsychiatric illness, as it has done with proven success in the treatment of medication refractory movement disorders.

We review the background theory of DBS for MDD, conduct a systematic review to evaluate the efficacy and safety of DBS for MDD, and make recommendations for future clinical studies.

Depression Circuitry

Much of depression treatment has centered around the monoamine hypothesis of depression [13], although various factors, including stress exposure [14, 15], genetic [16], and neurodegeneration [17], have also been considered. In addition to these hypotheses, aberrancies in limbic cortico-striato-thalamo-cortical (CSTC) circuitry have also been postulated in the etiology of MDD.

Malfunctions of limbic CSTC circuits have been implicated in several neuropsychiatric disorders, including MDD, obsessive–compulsive disorder (OCD), and Tourette syndrome [18, 19]. In an important review paper by Alexander et al. [18], the existence of 5 segregated CSTC circuits was enumerated. Even though currently these circuits are not considered completely "segregated", this concept has contributed to the understanding of abnormal neurocircuitry in these neuropsychiatric disorders.

While variable explanations of the neurocircuitry have been reported in the literature, depressive disorders have generally been considered to involve 3 compartments of neurocircuitry: dorsal, ventral, and modulatory [20–23]. The dorsal compartment includes the thalamus, prefrontal cortices, premotor cortex, dorsal cingulate cortex, dorsal striatum, and the dorsal pallidum. This compartment is thought to mediate the cognitive and motor aspects of depressive symptoms such as apathy, attention deficits, and impaired task performance. The ventral compartment includes the thalamus, subgenual cingulate cortex (SCC), orbitofrontal cortex, insular cortex, ventral striatum, and ventral pallidum. The ventral compartment is associated with somatic and vegetative aspects of depressive symptoms. These 2 compartments interact with each other through the modulatory

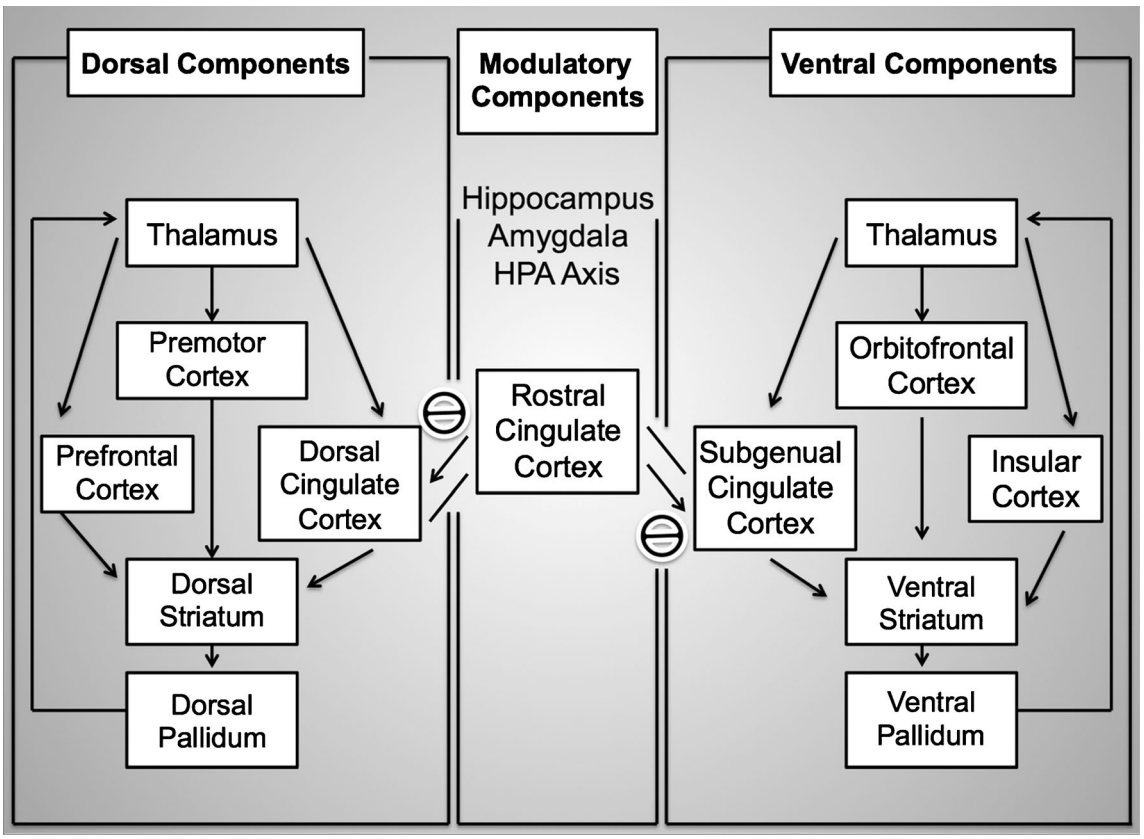

Fig. 1 A diagram of depression neurocircuitry illustrating three components. HPA axis = hypothalamic-pituitary-adrenal axis

system in an inhibitory manner (Fig. 1) [24]. The modulatory compartment includes the hippocampus, amygdala, rostral cingulate cortex, and the hypothalamic-pituitary-adrenal axis. The SCC and the dorsal cingulate cortex have an anatomical connection through the rostral cingulate cortex, which is a component of the modulatory compartment that functions to balance the dorsal and the ventral compartments.

Owing to a lack of validated animal models in psychiatric disorders, neurocircuitry models of these disorders have been primarily developed with human imaging studies. Structural imaging studies using magnetic resonance imaging (MRI) have demonstrated volume reduction in the total frontal cortex (gray matter), hippocampus, SCC, caudate nucleus, and amygdala in patients with MDD compared with healthy controls [25–27]. A meta-analysis showed a volume increase in the pituitary gland in patients with MDD [25].

Functional imaging studies such as functional MRI, positron emission tomography (PET), and single photon emission computerized tomography have shown hyperactivity of the SCC [28] and deep brain structures, including the thalamus and the caudate nucleus [29], in untreated depressed patients in the resting state. Hypoactivity has been seen in the rostral cingulate cortex, posterior cingulate, bilateral middle frontal cortices, and insular and left superior temporal cortices in patients with MDD in the resting state [29]. These abnormalities in activity have been reversed by medical [29, 30] and surgical treatment [4, 31, 32]. This observed imbalance between dorsal and ventral limbic neurocircuitry compartments, characterized by hypoactivity in the dorsal components and hyperactivity in ventral components, is widely believed to play an important role in the pathophysiology of MDD.

Despite similarities in the observed functional neurocircuitry of both unipolar and bipolar depression [21, 22], there have been reports of important structural differences. When compared with patients with bipolar disorder, patients with MDD were likely to have fewer deep white matter hyperintensities, an increased corpus callosum cross-sectional area, and a smaller hippocampus and basal ganglia [26]. Pituitary volume was also reported to be larger in patients with MDD [33]. These data, unlike functional neurocircuitry data, support differing etiologies in bipolar disorder and MDD.

Systematic Review of Clinical Outcomes

In an exhaustive literature review, we included English-language, clinical research articles pertaining to DBS for treatment-resistant depression, including both MDD and bipolar disorder. Papers that contained clear descriptions of clinical outcomes utilizing validated outcome measures, such as the Hamilton Depression Rating Scale scores (HDRS), were included [34]. For this purpose, we performed a Medline search from January 1999 to December 2013. Combinations of 3 medical subject heading terms (i.e., "depressive disorder", "depressive disorder, treatment resistant", and "depressive disorder, major") and 4 key words, including "deep brain stimulation", "psychosurgery", "neurosurgery", and "electric stimulation therapy", were used in the search criteria. After duplications were excluded, 473 reports were found. From these reports, we included only clinical studies written in English that employed validated outcome measures. To refine the literature search, we performed an additional Medline search using other key words, including "Brodmann area 25", "ventral striatum", "ventral capsule", and "medial forebrain bundle". A search of Cochrane reviews was also conducted (even though there was only a review protocol found through the Cochrane review search [35]). The search protocol is illustrated in Fig. 2. We excluded studies primarily treating other disorders (e.g., OCD, Parkinson disease, dystonia, etc.). We included all available case reports and personal communications, as the number of useful studies in the literature was limited.

In all, we identified 22 clinical research articles on DBS for MDD that met these criteria [31, 32, 36–53]. Of these, there were only 3 controlled trials with sham stimulation periods [36, 39, 49]. One article [37] was a review paper, but was included as the author described a follow-up outcome of the previous study [38]. There were 6 different anatomical sites of stimulation reported, including nucleus accumbens (NAcc), ventral capsule/ventral striatum (VC/VS), Brodmann area 25 (SCC), lateral habenula, inferior thalamic peduncle (ITP), and medial forebrain bundle (MFB).

All studies treated patients with severe, medication refractory MDD, or rarely bipolar disorder, diagnosed based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [54]. Most studies excluded patients with alcohol or substance abuse, severe psychiatric comorbidity such as bulimia, OCD, panic disorder, and/or personality disorder [31, 32, 38, 50]. All studies except for 1 [55] used HDRS as a primary outcome measure, and "responders" were defined as patients with at least a 50 % reduction in HDRS or Montgomery–Asberg Depression Rating Scale scores. However, there are variations of HDRS (i.e., number of items). Owing to the difference, HDRS scores in the inclusion criteria and definitions of "remission" were different across the studies. However, "remission" was typically defined as an improvement to a low HDRS score (<8–10). The clinical outcomes of this systematic review are summarized in Table 1.

NAcc and VC/VS

Schlaepfer et al. [36] hypothesized that the NAcc plays an important role in the abnormal reward process and motivations in MDD, and reported short-term outcomes of 3 patients with treatment-resistant MDD who underwent NAcc DBS.

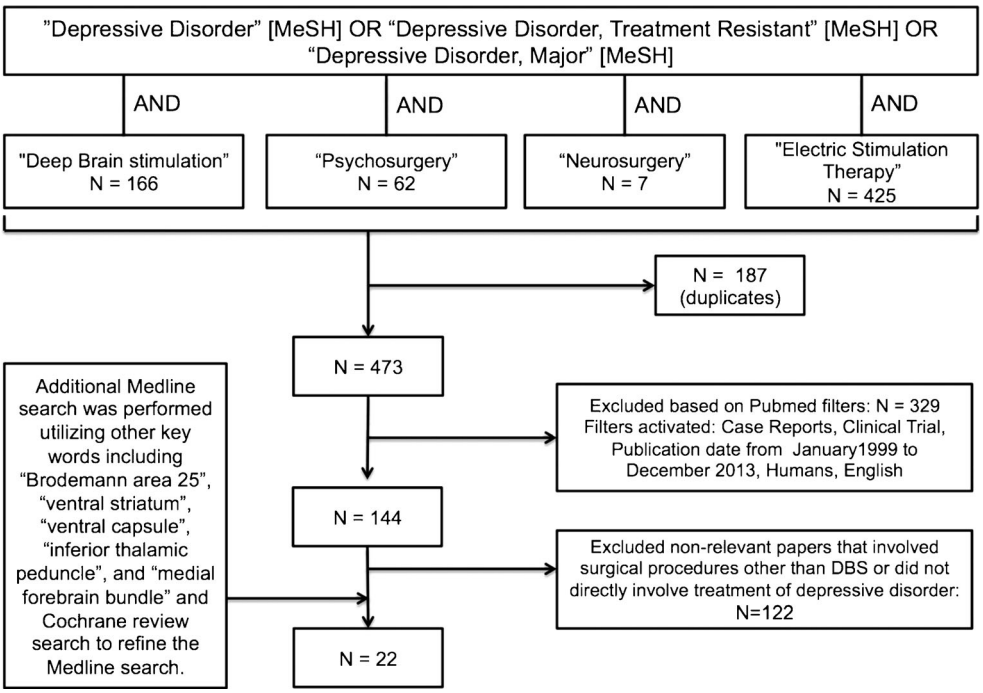

Fig. 2 Flow chart of the systematic review process. MeSH = medical subject heading; DBS = deep brain stimulation

This preliminary study showed a beneficial effect in all patients. Subsequently, the same group published long-term outcomes up to 4 years of a larger cohort, and reported that approximately 50 % of the cohort were responders [31, 32]. They performed cognitive testing and reported no cognitive decline 1 year after NAcc DBS [56]. On the contrary, cognitive performance reportedly improved postoperatively from below average to average. In this procedure, Medtronic model 3387 electrodes (each contact length was 1.5 mm and interelectrode spacing was 1.5 mm; Medtronic, Minneapolis, MN, USA) were used, and the authors described that the deepest contact was presumed to be in the "shell" of the NAcc, with middle contacts and the most dorsal contacts in the "core" of the NAcc and the ventral portion of the anterior limb of the internal capsule (ALIC), respectively [31, 32].

Several studies have demonstrated the efficacy of VC/VS DBS in reducing concomitant depressive symptoms in patients treated primarily for severely debilitating OCD [57–59]. Based on these findings, this technique was tried for treating patients with primary MDD and 1 patient with bipolar disorder. The term "VC/VS" was first introduced by Greenberg et al. [57] in their report about DBS for OCD as a target including the NAcc and the ventral aspect of the ALIC. A difference from NAcc DBS is the larger electrodes employed in the VC/VS DBS studies (Medtronic model 3387 IES; each contact length was 3 mm and the interelectrode spacing was 4 mm) [37, 38]. Malone et al. [37, 38] published outcomes of VC/VS DBS in 17 patients with treatment-resistant depression, including a patient with bipolar disorder from a multicenter trial. They reported that the response rates were 53 % at 12 months and 71 % at the last follow-up (14–67 months, with average of 37.4 months). There is also a case report describing smoking cessation in 1 MDD responder to VC/VS DBS [51].

Even though there were no reports of extreme "rewarding" effects described in classic studies [60, 61] during NAcc or VC/VS stimulation, manic episodes have been reported in patients with OCD treated with DBS utilizing the same techniques [62, 63]. It is also noteworthy that 2 patients with depression, including 1 with bipolar disorder, reported a manic episode after VC/VS DBS [38]. Given this tendency of stimulation in this region to produce manic side effects in some cases, it is conceivable that NAcc or VC/VS DBS might aggravate manic symptoms in patients with bipolar disorder. It is also unclear whether DBS in these specific targets will address the manic phase of bipolar disorder. However, the use of intermittent DBS, as illustrated in a recent study in Tourette syndrome, might potentially address this issue [64].

Despite the very encouraging outcomes reported in the open-label studies described above, a recent multicenter, prospective, randomized trial of VC/VS DBS for MDD sponsored by Medtronic failed to show significant improvement in the stimulation group compared with a sham stimulation group 16 weeks after implantation of the device [65]. This study was discontinued owing to perceived futility, and while investigators remain hopeful that modifications of inclusion criteria and technique might ultimately result in demonstrable clinical benefit in some cohort of severely debilitated,

Table 1 Stimulation parameters and outcomes of published studies

Authors [ref.]	n	Follow-up (months)	Stimulation parameters				Responder rate (%) on HDRS	% Changes in HDRS (number of HDRS items)	% Changes in MADRS	Comments
			Contact	Amplitude (V)	Frequency (Hz)	Pulse width (μs)				
NAcc										
Schlaepfer et al. [36]	3	1.5–5.8	Monopolar	4.0	145	90	NA	42.0 (24) at 1 week	31 % at 1 week	
Bewernick et al. [31]	10	12.0	Monopolar	1.5–10.0	100–150	60–210	41.7	36.0 (28)	34 %	Remission rate: 25 % (1 month)
Bewernick et al. [32]	11	12.0–48.0	Monopolar	5.0–8.0	130	90	45.5 at 24 months	31.3 (28)	33 %	6.8 V, 90 PW, 130 (responders); 7.1 V, 100 PW, 135.5 (nonresponders) Remission rate: 54.5 %
VC/VS										
Malone et al. [38]*	15	6–48	Monopolar	6.7	127	113	53.3	57.0 (24)	55	Remission rate: 40.0 % MADRS response rate: 53.3 % Remission rate: 33.3 %
Malone et al. [37]	17	14–67 (mean 37)	Monopolar	2.5–8.0	100–130	NA	71.0	NA	54	Remission rate: 35.0 %
Strong et al. [51]	1	48	Monopolar	6.0	130	120	NA	NA	79	
BA 25 (SCC)										
Mayberg et al. [39]	6	6	Monopolar	4.0	130.0	60.0	66.0	55.0 (17)	44 %	35 % improvement in CGI-S
Neimat et al. [40]	1	30	Monopolar	4.5	130.0	60.0	NA	68.0 (17)	NA	Cingulotomy prior to DBS
McNeely et al. [41]	6	12	Monopolar	3.0–4.5	130.0	60.0	66.0	65.0 (17)	NA	
Lozano et al. [42]	20	12	Monopolar	3.0–5.0	130.0	90.0	55.0	48.0 (17)	NA	60 % responder 35 % remission at 6 months
Hamani et al. [43]	20	12	Monopolar	3.0–5.0	130.0	90.0	55.0	48.2 (17)	NA	
Guinjoan et al. [44]	1	18	Monopolar	4.5	120.0	90.0	NA	89.0 (21)	NA	
Holtzheimer and Mayberg [45]	1	6	Monopolar	6.0 mA	130.0	91.0	NA	64.0 (17)	NA	
Kennedy et al. [46]	20	36-72	Monopolar	4.3	124.7	70.6	62.5 % , 46.2 %, 75 % (1, 2, 3 year), 64.3 % (average)	64.3 (17)	NA	
Puigdemont et al. [47]	8	12	Mono/bipo-lar	3.6	135.0	90.0	62.5	62.0 (17)	62	Remission rate 50 %
Hamani et al. [48]	1	6	Monopolar	2.5	130.0	90.0	NA	68.0 (17)	NA	
Holtzheimer et al. [49]†	17	24	Monopolar	6.0–10.0 mA	130.0	91.0	92	69.0 (17)		Remission rate: 58 %
Lozano et al. [50]	21	12	Monopolar	5.2 mA	128.1	93.9	29	41.4 (17)	NA	57 %, 48 %, 29 %; response rate (1, 6, 12 months)
Habenula										
Sartorius et al. [72]	1	15	NA	10.5	NA	NA	NA	100 (21)	NA	

Table 1 (continued)

Authors [ref.]	n	Follow-up (months)	Stimulation parameters				Responder rate (%) on HDRS	% Changes in HDRS (number of HDRS items)	% Changes in MADRS	Comments
			Contact	Amplitude (V)	Frequency (Hz)	Pulse width (μs)				
ITP										
Jimenez et al. [52, 53]	1	18	Bipolar	3.0–5.0	130	450	NA	83 (NA)	NA	
slMFB										
Schlaepfer et al. [55]	7	12–33 weeks	Bipolar	2.4–3.5 mA (left), 2.3–3.1 mA (right) mA	130	60	NA	NA (24 at baseline and 28 at follow-up)	63	6 patients were responders; 4 patients were remitters on MADRS

HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery–Asberg Depression Rating Scale; NAcc = nucleus accumbens; NA = not applicable; PW = pulse width; VC/VS = ventral capsule/ventral striatum; BA 25 = Brodemann area 25; SCC = subgenual cingulate cortex; CGI-S = Clinical Global Impression-Severity scale; DBS = deep brain stimulation; ITP = inferior thalamic peduncle; slMFB = superolateral branch of the medial forebrain bundle

*Included 1 bipolar patient

†Included 7 bipolar patients.

medically refractory patients with MDD, no studies investigating the efficacy of VC/VS DBS for MDD are currently open.

Brodmann Area 25 (SCC)

Mayberg et al. [66, 67] reported reduction of MDD-associated hypermetabolic activity in the SCC after treatment with antidepressants. This finding is consistent with other literature [29]. DBS in the SCC for the treatment of MDD was first reported by Mayberg et al. in 2005 [39]. In this report, stimulation in the SCC resulted in successful mitigation of depressive symptoms in 4/6 patients after 6 months ("responders" achieved>50 % reduction in HDRS score). They also reported imaging findings with normalized activity in the SCC with stimulation when assessed with PET. The efficacy of this approach has been confirmed by several subsequent open-label studies. The longest follow-up reported thus far is 3–6 years after DBS, where an average response rate of a 64.3 % reduction in HDRS score was measured at the most recent visit [46]. A recent multicenter trial (n=21) showed only a 29 % responder rate with an average 41 % HDRS score reduction at 12 months follow-up; however, 62 % of the cohort had>40 % improvement on the 17-item HDRS [50]. Cognitive function was reported improve from below average to average after 1 year of SCC DBS [41], mirroring the cognitive outcomes reported for the NAcc DBS approach. Four other case reports described positive effects of SCC DBS [40, 44, 45, 68], 1 of which reported the efficacy of SCC DBS in 2 patients who had undergone ablative cingulotomy prior to DBS [40].

One single-blind study using SCC DBS for both MDD and bipolar disorder with exceptionally good reported outcomes was published by Holtzheimer et al. [49]. In this study, which included 17 patients, an average reduction of 69 % in HDRS score was reported, with a responder rate of 92 % and with 58 % of patients reportedly achieving full remission (reduction of>90 % in HDRS). No difference in efficacy was noted between the bipolar disorder and MDD groups. It is noteworthy that the currents delivered in this study were typically higher than those in other reported studies.

A multicenter, prospective, randomized trial of SCC DBS for severe, medically refractory MDD (the BROADEN study), sponsored by St. Jude Medical, was recently discontinued after the results of a futility analysis (designed to test the probability of success of the study after 75 patients reached the 6-month postoperative follow-up) statistically predicted the probability of a successful study outcome to be no greater than 17.2 % (letter from St. Jude Medical Clinical Study Management). Similar to the discontinued Medtronic VC/VS DBS for MDD study, the researchers involved remain hopeful that modifications of inclusion criteria and technique

(e.g., higher energy delivery) might ultimately result in a demonstrable clinical benefit from SCC stimulation in some cohort of severely debilitated, medically refractory patients with MDD.

Lateral Habenula

Some authors have hypothesized that hyperactivity in the lateral habenula may be an etiologic factor in MDD based on data from imaging studies [69–71], and they have applied DBS to suppress this lateral habenular hyperactivity in 1 patient [72]. In the case report, they implanted the DBS electrodes bilaterally in the lateral habenulae, and this procedure resulted in a remission of depression symptoms after 60 weeks of stimulation. Interestingly, fluorodeoxyglucose PET showed a metabolic increase at the tip of the electrodes, and the authors interpreted this finding as a likely inhibitory effect of DBS. Currently, a single-center, double-blind pilot study enrolling 6 patients is under investigation (clinicalTrial.gov identifier: NCT0198407).

ITP

Two case reports describing the results of ITP DBS for MDD have been published with regard to the same patient [52, 53]. The same group also reported an identical approach with favorable outcomes for patients with OCD [53, 73]. This rationale of this surgical approach was to suppress pathologic orbitofrontal cortical hyperactivity using stimulation of the ITP, a fiber bundle connecting the mediodorsal nucleus of the thalamus and the orbitofrontal cortex. Interestingly, the patient with MDD that was reportedly successfully treated with ITP DBS suffered from significant psychiatric comorbidities of bulimia and borderline personality disorder. We are unaware of the current status of this provocative research.

MFB

DBS of the MFB, similar to the NAcc, has been proposed based on the idea that these are both pathologic anhedonia centers in MDD. The superolateral branch of the MFB (slMFB) is considered to be associated with reward seeking and appetitive motivation, and this fiber bundle has connections with other DBS targets, including SCC, NAcc, and ALIC [74]. As the slMFB has connections to these 3 structures, Coenen et al. [75] hypothesized that DBS in this target may have a robust antidepressant effect. slMFB DBS was performed on 7 patients, and favorable outcomes were reported [55]. It is noteworthy that this group employed diffusion tensor imaging to more clearly identify their target, as the slMFB is not readily visualized with conventional MRI. In this report, 6/7 patients (85.7 %) were reportedly responders, and 4 (57.1 %) achieved full remission during short-term follow-up based on Montgomery–Asberg Depression Rating Scale scale changes. Interestingly, signs of appetitive motivation and mood improvement were consistently observed during intraoperative macrostimulation in these patients. A single-center prospective study led by the same group is currently under way (clinicalTrial.gov identifier: NCT01778790).

Adverse Events

Most complications were minor surgery-related issues such as superficial infection. There were no serious complications reported except for 1 case of temporary hemiparesis due to intracerebral hemorrhage reported in a slMFB DBS study [55]. Stimulation-induced side effects such as mood changes were temporary and adjustable. However, it should be noted that there were patients who attempted and completed suicide after DBS [31, 32, 42, 49, 50]. Completed suicide and suicide attempts were the most significant adverse events following DBS surgery and happened both with and without stimulation. Several studies excluded patients with suicidal ideation in the hope of avoiding this adverse event [38, 42, 49, 50], but given the high incidence of suicide in patients with refractory depression, it is unlikely that this complication could be completely avoided even with such exclusion criteria. All patients included in these studies had severe, treatment refractory depression and were at higher risk of suicide owing to the nature and severity of their illness.

Conclusions

This systematic review revealed several notable issues in the design of MDD DBS studies to date. Though reported outcomes of open-label trials have been promising and fairly comparable across different research groups, inclusion criteria and outcome measures have been heterogeneous and the number of patients in most trials has been low. Ambiguous duplications of patient populations also exist among published studies, rendering a true meta-analysis difficult. It should also be noted that placebo effect may well be a confounding factor when interpreting the open-label trials owing to the nature of mood disorders and the lack of controls for comparison in the majority of these clinical series. The failure of 2 recent multicenter, prospective, randomized trials to demonstrate efficacy of either VC/VS DBS or SCC DBS for refractory MDD is disappointing and somewhat surprising given the universally positive results of reported open-label trials. This discrepancy is potentially attributable to the typical overestimation of efficacy associated with open label trials that arises from the failure to control for placebo, biases due to lack of blinding and randomization, and so on. However, it is also possible that other remediable factors such as suboptimal patient selection, inconsistent targeting, suboptimal target selection, and

insufficient current delivery might account for the failure of these 2 prospective trials. Given this possibility, the extraordinary public health burden associated with MDD, and the promising results of the open-label trials, further investigation of the potential of DBS for the treatment of MDD is warranted, but care should be taken to optimize trials and methodology as much as possible, and to maximize the consistency of outcomes measurement in order to learn as much as possible from each trial.

We propose to form a registry for future clinical studies similar to the one used in the OCD DBS literature [12, 76]. Variables should be consistently recorded, and include: 1) detailed clinical characteristics, including accurate diagnosis (e.g., MDD, bipolar disorder), various comorbidities and past response to medical and other treatments, etc.; 2) intraoperative findings; 3) meticulous measurement of DBS lead position; 4) postoperative DBS programming data; 5) preoperative baseline scores on validated and standardized outcomes scales; and 6) all adverse events.

As cumulative data are compiled, the surgical approach might be refined and the procedure tailored based on the clinical characteristics of each patient, in a similar way to that successfully employed in DBS for Parkinson disease [77, 78]. It is posited that multiple circuits may be involved in the etiology of depression in the most severe cases [65]. Certainly, as our understanding of the pathologic abnormalities in the malfunctioning limbic neuronal circuitry of MDD improves, DBS targeting might be refined, outcomes improved, and methodology tailored to the needs of patients with variable symptomatology.

It is also noteworthy that a relatively high voltage has been required to exert favorable clinical responses, and, as detailed above, one particularly successful study suggests the possibility that even higher energy input may be associated with improved clinical efficacy [49]. This issue results in frequent battery replacement and will potentially increase the physical and economic burden on patients, and increase the cumulative risk of surgical complications. As Malone suggests [37], rechargeable batteries should be considered in neuropsychiatric cases.

In total, 6 different targets have been proposed and tried for MDD DBS. Of these, only VC/VS and SCC DBS have been investigated with controlled trials with small sample sizes, and, unfortunately, recent multicenter, prospective, randomized trials have reportedly failed to confirm the efficacy of stimulation at these 2 targets (i.e., VC/VS and SCC). Despite these setbacks, the extraordinary public health burden of MDD and the promising results of various open-label trials warrant further investigation. No class I evidence exists in the literature supporting the efficacy of DBS for MDD, and the optimal DBS target for treatment-resistant depression remains unclear. DBS for MDD should therefore be considered experimental at present; further studies are indicated to clarify the malfunctioning neurocircuitry associated with MDD and to evaluate the efficacy and safety of the various MDD DBS strategies. As always, surgical therapy for the treatment of psychiatric disorders should only be performed in the setting of a multidisciplinary team, which should include, as a minimum, a dedicated psychiatrist, neurologist, neurosurgeon, and neuropsychologist.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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