19 Deep Brain Stimulation: A Promising Therapeutic Approach to the Treatment of Severe Depressed Patients — Current Evidence and Intrinsic Mechanisms

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Abstract

Major depressive disorder represents one of the most severe disabling disorders, affecting around 4.7% of the worldwide population. Many patients suffering this neuropsychiatric illness are treated successfully with various treatments, including antidepressant drugs and psychotherapy but also physical measures (electroconvulsive therapy, repetitive transcranial magnetic stimulation, vagal nerve stimulation). Despite the different treatment approaches available, unfortunately 30–40% of the patients fail to respond to most first-line treatments, and between 5 and 10% do not respond to conventional therapy at all. Thus, a considerable number of patients have a poor outcome and unfortunately fail to reach sustained remission. These data highlight the need to find new therapeutic approaches that especially focus on refractory patients. In this context, deep brain stimulation (DBS) emerges as an innovative physical treatment for refractory depressed patients. DBS has been successfully used for years in some neurological disorders such as Parkinson's disease. Currently, in addition to its use in treating depression, DBS is also being tested in other psychiatric illness such as obsessive–compulsive disorder. Most studies on DBS have focused on efficiency and efficacy, or improvement in the technique, and a few

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were devoted to understanding the intrinsic mechanisms responsible. Understanding the molecular mechanisms of action of DBS is currently considered as crucial, not only in order to understand its efficacy but also to propose new antidepressant approaches. The aim of this chapter is to review the foundations, the efficacy, and the efficiency of DBS in depression, and to provide insight into the intrinsic mechanisms of action described until now. In addition, future developments will be discussed.

Keywords
Deep brain stimulation • Major depressive disorder • Ventral capsule/ventral striatum • Nucleus accumbens • Subgenual cingulate cortex • Lateral habenula • Medial forebrain bundle • Inferior thalamic peduncle

Introduction

Major depressive disorder (MDD) is a psychiatric illness with a prevalence around 4.7% among the worldwide population [1]. According to the World Health Organization this disorder ranks among the leading causes of disability [2], and it is expected to be the second most common cause of disability by 2020 [3]. Nowadays, clinical, neurochemical, neuroimaging, and postmortem evidence suggests that MDD is not a disease that affects a particular anatomical region or a single system of neurotransmission. It is postulated that MDD is a dysfunction of cortical, subcortical, and limbic system areas and their connections, and hence neurotransmitter systems and molecular mediators.

Multiple pharmacological and psychotherapeutic treatments are currently available for MDD. The first-line therapy for depression involves the use of antidepressant drugs that mainly act by inhibiting monoamine reuptake, thereby increasing monoamine levels in the synaptic cleft. But unfortunately, it has been estimated that 30–40% of MDD patients do not improve in response to this pharmacological treatment [4]. As such, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a randomized and multi-center clinical trial conducted in 2004 in the USA, patients diagnosed with non-psychotic MDD received sequenced treatment at four levels, and the overall cumulative remission rate was 67% after the four levels of treatment [5]. Other non-pharmacological approaches are effective for MDD, such as psychotherapy or physical approaches including electroconvulsive therapy, repetitive transcranial magnetic stimulation, or vagal nerve stimulation [6–9]. Although the majority of patients with MDD respond to the broad range of current treatments, between 5% and 10% fail to respond, having a poor outcome and failing to achieve sustained remission [4, 5, 10]. This critical issue results in an enormous economic burden, poor quality of life, personal suffering, and a high risk of suicide [3, 11, 12]. Thus, the lack of a satisfactory response in treatment-resistant depressive patients highlights the need to progress toward the discovery of effective alternative therapies.

In this context, deep brain stimulation (DBS) therapy arose as an experimental alternative for patients suffering from resistant MDD. DBS is an invasive approach involving stereotaxic surgery. Stimulation electrodes are permanently connected to a neurostimulator with the capacity to deliver electrical chronic stimulation of a targeted brain region. Several data indicate that DBS produces similar benefits to the ablation of the target area [13, 14] but with fewer side effects, because DBS is a reversible approach and the stimulation device is adjustable to attain the desired therapeutic effect. Indeed, electric current intensity, pulse width, and frequency of the stimulation applied can be appropriately modified. Thus, the parameters of stimulation are adapted for each disease, each target of stimulation, or even depending on the individual needs of each patient. The extensive experience using this technique reveals that it is a safe and well-tolerated therapy, and most of the side effects

reported are related to the surgical procedure. Originally, DBS was developed as a technique for movement disorders. The effectiveness demonstrated in several neurological disorders such as Parkinson's disease, dystonia, and essential tremor [15] led to the exploration of this approach to manage psychiatric diseases. As a result, the US Food and Drug Administration approved DBS for treatment-resistant obsessive-compulsive disorder (OCD) in 2009. DBS is currently used in research studies to treat other neuropsychiatric disorders such as MDD.

Although multiple trials have been performed using this technique, the mechanisms underlying the therapeutic effects of DBS have not yet been elucidated. However, authors have proposed several hypotheses. Indeed, some studies have suggested that DBS induces a simple local neuronal activation of the targeted area [16], while other results indicate that DBS preferentially inhibits cell bodies and only stimulates axon terminals [17]. Nevertheless, DBS seems to present a much more complex mechanism of action than a simple activation or inhibition of the target area, even being able to widely modulate brain network activity [18, 19]. In this way, understanding the inherent mechanisms of DBS could give us crucial information to discern the distinctive biological features related to treatment-resistant disorders.

With regard to DBS for treating refractory MDD, only a few clinical trials have been reported. Even so, DBS was effective in patients suffering resistant MDD, showing a promising improvement of depressive symptomatology. In this way, several brain areas have been tested as targets for DBS: subgenual cingulate cortex (SCC), nucleus accumbens (NAc), ventral capsule/ventral striatum (VC/VS), inferior thalamic peduncle (ITP), medial forebrain bundle (MFB) and lateral habenula (LHb). Despite the fact that DBS causes a significant reduction in depression rating scales when applied to most of them, there is still considerable debate about which is the best stimulation target to treat refractory depressed patients.

The aim of the present chapter is to collect evidence of clinical and preclinical data and attempt to discern potential intrinsic mechanisms of DBS in the different brain sites of stimulation tested for resistant MDD.

Ventral Capsule/Ventral Striatum and Nucleus Accumbens

Based on the efficacy of capsulotomy, a lesional therapy widely used for more than 50 years in OCD patients, the VC/VS was proposed as a brain area to be stimulated by DBS for this psychiatric disorder. The VC/VS target corresponds anatomically with the ventral limb of the internal capsule and the adjoining ventral striatum (Fig. 19.1), and DBS applied to this region has been found to be effective for intractable OCD [20, 21]. Given that an unexpected improvement in depressive symptoms was observed in patients primarily diagnosed with OCD [20, 22, 23], this area was proposed as a putative DBS target for refractory MDD patients. The first clinical intervention targeting VC/VS showed encouraging results for MDD patients, who achieved close to a 60% response rate at the last follow-up visit [24]. However, the randomized sham-controlled clinical trial using VC/VS DBS did not report significant differences between DBS and sham control patients, and the response rate obtained was only 20% in both cohorts [25].

The ventral striatum complex includes the NAc, another region that was proposed as a DBS target area for refractory depressed patients (Fig. 19.1). The NAc plays a crucial role in the reward circuitry and motivation processes [26]. Given that impairment in reward processing is related to the anhedonic symptoms of depression

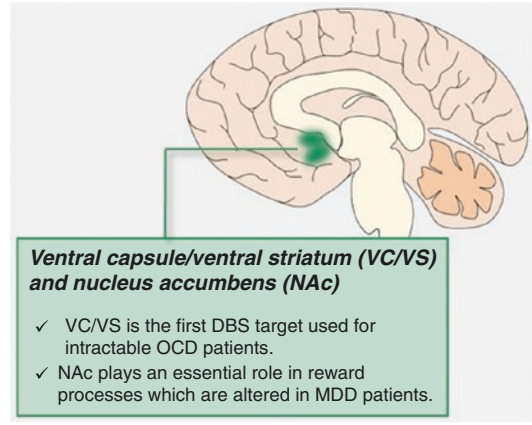

Fig. 19.1 General schematic representation of the VC/VS and NAc as targets for refractory MDD

[27, 28], the effectiveness of DBS on the NAc was evaluated in clinical studies. They reported a sustained alleviation of depressive symptomatology, reaching approximately 50% in the rate of response, accompanied by an antianhedonic and anxiolytic effect [29–31]. Additionally, functional neuroimaging in patients revealed changes in metabolic activity induced by NAc DBS. Among the changes found, the hypofunction observed in prefrontal subregions such as the SCC should be highlighted [29].

Neuropsychological assessments are routinely performed in these patients since as an invasive technique, DBS could impair attention, memory, or other cognitive processes. Interestingly, a significant improvement in cognitive performance tasks was reported after NAc DBS [32], and VC/VS DBS [33] did not produce neuropsychological decline. The safety and the encouraging response obtained in these clinical trials could promote additional controlled studies to verify the efficacy of DBS of both targets for resistant MDD.

To extend our knowledge and understanding of the mechanism of action of DBS, preclinical studies applying DBS in the core or shell portion of NAc have been performed in naïve and animal models of depression. In this way, NAc DBS in naïve animals induced an antidepressant-like effect measured in the forced swimming test (FST) [34, 35]. The FST is the most often used behavioral test to predict antidepressant-like activity in rodents. This is a classical paradigm to screen the response when the subject is faced with a problem without an obvious solution ("waiting/searching strategy") [36, 37]. Additionally, considering that one of the essential symptoms of depression is anhedonia, the antidepressant-like effect is also assessed by the portion of sucrose intake in the sucrose consumption test (SCT) [38]. Surprisingly, NAc DBS fails to produce a clear and remarkable hedonic effect [35, 39].

Furthermore, the antidepressant effect of NAc DBS has been reported in several animal models of depression. Chronic DBS to the NAc core induced an antidepressant-like effect in the Flinders sensitive line (FSL) [40], a validated genetic animal model of depression [41]. This effect was also observed in the high anxiety-related behavior (HAB) mouse model [42] and the model of depression induced by chronic adrenocorticotropic hormone (ACTH) administration [43]; both models resistant to standard antidepressant therapies [44, 45]. Additionally, chronic NAc DBS increased sucrose intake preference in animals submitted to mild randomized stressors for several weeks [46], in a rodent depression model called the chronic unpredictable mild stress (CUMS) model [47], yet the antianhedonic effect was not observed in the FSL model [40]. However, a single session of DBS applied to the NAc core or shell was not enough to attain an antidepressant response in animal models of depression including HAB mice and the CUMS [39, 42].

The anxiolytic effect observed in patients treated with NAc DBS was also evaluated in naïve animals. Unfortunately, the data available do not confirm the anxiolytic properties of DBS NAc. This therapeutic approach reduced the escape latency in the home-cage emergence test [39] but it did not increase the time spent in the open arms of the elevated plus maze (EPM) [48], which is the most widely used paradigm to detect anxiety-related behavior in rodents [49]. It should be noted that changes in locomotor activity were not reported following acute or chronic DBS of the NAc, indicating that the behavioral effects described were not due to an alteration in the spontaneous locomotor activity [34, 39, 42, 46, 50].

The possible cognitive alterations induced by DBS were also assessed using animal paradigms such as the Morris water maze (MWM). This test evaluates the spatial memory, and it is often used as a general assay of cognitive function [51, 52]. Interestingly, NAc DBS did not induce learning impairments in CUMS animals [46]. This is according to the neuropsychological data reported in the clinical studies.

To discern the molecular mechanisms underpinning the antidepressant effect of NAc DBS, several preclinical studies have been performed to ascertain potential substrates involved. As such, the modulation of neurotransmitters release, neurotrophic factors, adult neurogenesis, or the activation of intracellular signaling pathways have

been evaluated, given that they could be the main factors to achieve the satisfactory response.

The monoaminergic theory postulates a deficiency in brain serotonergic, noradrenergic, and dopaminergic neurotransmission in depression [53]. Thus, a solid basis was established to conceptualize this neurobiological disease, which was a breakthrough for the development of current pharmacological antidepressants [54, 55]. However, the involvement of monoamines in the pathophysiology of this disease appears to be insufficient to fully understand this illness. Although monoamine regulation itself does not explain the processes that cause or maintain the depressed mood, the effect of DBS on monoamine release has been evaluated. Local monoamine levels remained unaltered after acute NAc core DBS [56], but it did induce a general cortical increase of serotonin (5-HT) and dopamine (DA) levels in the prefrontal cortex and of DA and noradrenaline (NA) in the orbitofrontal cortex [57]. However, the effect of chronic DBS on monoamine levels depends on the site within the NAc that is stimulated. DBS of the NAc core did not produce either local or cortical modifications, and NAc shell stimulation enhanced local but not cortical monoamine levels [58]. Only one study evaluated the monoamine release in an animal model of depression describing a decrease in cortical monoamine levels after NAc shell DBS in Wistar–Kyoto animals [50], a rat strain with a defined depressive phenotype [59, 60].

On the other hand, MDD is associated with a dysfunction in neuronal network plasticity. A large body of evidence has demonstrated the reduction in brain-derived neurotrophic factor (BDNF) expression and adult hippocampal neurogenesis in depressed patients [61–63]. Indeed, it has been reported that antidepressant drugs can improve both processes [64, 65]. Bearing in mind the relevance of these processes, it has been evaluated how NAc DBS affects them. Stimulation of the NAc in naïve animals was not sufficient to increase hippocampal neurogenesis [66]. However, in animal models of chronic depression, DBS was able to enhance this [42], and to promote the expression of BDNF [46].

Additionally, NAc DBS potentiated cortical dendritic plasticity [50] and it modified neuronal activity in the piriform cortex and subcortical regions, such as the VTA and lateral hypothalamus [34]. Moreover, DBS in HAB animals activated the LHb, the dentate gyrus of the hippocampus, and the orbitofrontal cortex, and it decreased the activity in the prelimbic cortex [42]. Thus, DBS is able to modulate the activation pattern of several brain areas located both close to and distant from the stimulation site.

Subgenual Cingulate Cortex

The SCC is a part of the limbic cortex, located ventral to the genu of the corpus callosum (Fig. 19.2). The SCC region has been chosen as a target for DBS on the basis of previous findings, showing that this area is generally hyperactive in depressed patients, and that antidepressants and electroconvulsive therapy decreased the metabolism in this region [67–69]. Furthermore, the functional activity of the SCC region has been proposed as a predictor of the response to antidepressant treatments [70, 71]. So, the safety and efficacy of DBS in the SCC for treating resistant MDD is currently under investigation. Previous data from three independent clinical trials have demonstrated that DBS was effective in refractory MDD patients, showing an approximately

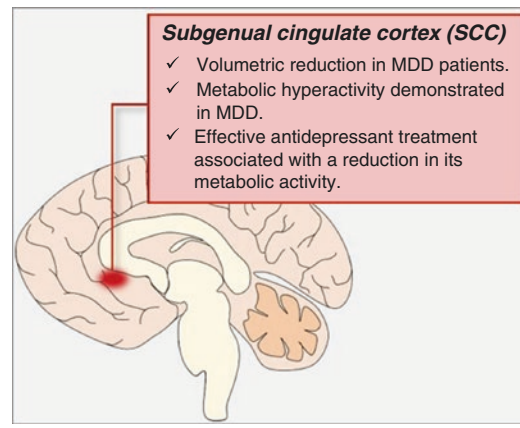

Fig. 19.2 General schematic representation of the SCC as a target for refractory MDD

60% response rate [72–74]. During the follow-up period (3–6 years) a progressive reduction in the severity of depression symptoms was reported, with only 10% of patients failing to show a decrease in symptom scores [75]. Indeed, at final follow-up, 42.9% of patients were in remission [72]. Moreover, cognition function after SCC DBS was preserved in patients, indicating the safety of this stimulation target for MDD [76, 77]. However, despite the promising results reported in these open-label trials, the last multicenter prospective randomized trial failed to demonstrate the effectiveness of SCC DBS (letter from St. Jude Medical Clinical Study Management). Thus, further clinical trials must be carried out to elucidate the efficacy of this therapy for treating refractory MDD patients.

Many studies focused on the intrinsic mechanisms of SCC DBS have been performed in animal models of depression. The ventromedial prefrontal cortex (vmPFC) is the rodent cortical region homologous to the human SCC [78]. This region compromises the infralimbic and prelimbic cortices, and there is still considerable debate as to which part of the vmPFC is the best target to apply DBS [79, 80].

Preclinical behavioral studies indicated that short- and long-term DBS applied in the vmPFC induced an antidepressant-like effect in the FST [34, 35, 79–84] and a hedonic response in the SCT in naïve animals [35, 84]. In addition, an anxiolytic effect was described after acute vmPFC DBS in the home-cage emergence test and the novelty suppressed feeding (NSF) [39, 80, 82]. The NSF measures a rodent's aversion to eating in a novel environment, and it is sensitive to chronic but not acute antidepressant treatment [85]. Therefore, the onset of action of DBS appears to be shorter than common antidepressant drugs.

Chronic DBS was able to reverse the depressive phenotype induced by the following animal models of depression: FSL, CUMS, olfactory bulbectomy (OBX), and chronic social defeat stress (CSDS) model [39, 84, 86–88]. The OBX produces a depressive behavior by disrupting the normal functioning of the limbic system [89], whereas the CSDS is based on the confrontation among conspecific animals to induce a psychosocial stress [90]. Furthermore, the anxiolytic effect of vmPFC was also demonstrated in the CUMS model of depression, increasing the time spent in the open arms in the EPM [86]. On the other hand, learning performance was not affected by vmPFC DBS in the MWM [46]. Overall, this indicates that DBS exerts an antidepressant response accompanied by an anxiolytic effect that is not associated to a cognitive impairment.

As occurred using NAc DBS, the spontaneous locomotor activity after acute or chronic DBS in the vmPFC remained unaltered [34, 39, 46, 80, 82, 86]. On the other hand, using the intracranial self-stimulation (ICSS) paradigm in FSL rats, it has been reported that the hedonic effect of DBS in the vmPFC does not depend on a direct modification of the mesolimbic dopaminergic reward system [84, 91].

The monoaminergic implication in the antidepressant-like effect induced by vmPFC DBS has been studied as a possible mechanism of action. Thus, vmPFC DBS was able to locally enhance 5-HT, NA, and DA at the site of stimulation [80, 87]. Nevertheless, the large majority of the studies available were carried out to discern the role of the serotonergic system. Despite 5-HT levels remaining unaltered in the dorsal raphe (DR) nucleus after vmPFC DBS, it has been shown to modulate the electrical activity of 5-HT neurons and enhance the glutamate concentration in this brain area [39, 80, 81, 88, 92]. This increase in the main excitatory neurotransmitter might trigger the drastic 5-HT release reported in DR projection areas, specifically in the vmPFC and hippocampus [80, 82].

But the relevance of the serotonergic system in the antidepressant-like effect of vmPFC DBS is still unclear, given that the two studies available showed opposite effects. In one of them, the antidepressant-like effect of vmPFC DBS persisted when the serononinergic neurotransmission was compromised, but in the other study this effect seemed to depend on the integrity of the 5-HT system [80, 82].

Additionally, DBS was able to potentiate neural plasticity in the DR neurons of naïve animals. Thus, an increase in excitatory presynaptic and

postsynaptic densities was found, and in CSDS animals, DBS normalized dendritic arborization [81, 88]. vmPFC DBS also promoted synaptic plasticity locally, in the hippocampus and in the basolateral amygdala, even restoring the reduction induced by the CSDS model [88, 93].

The activation of specific intracellular cascades, such as the mammalian target of rapamycin (mTOR) pathway, has a rapid impact on synaptic plasticity. This pathway promotes the synthesis of several proteins involved in the function, formation, and maturation of new spine synapses [94], and it has been closely related to the antidepressant effect of drugs with a short onset of action [95]. DBS of the vmPFC increased cortical phosphorylation of Akt and cAMP-response element binding (CREB) [87], both components linked to the activation of mTOR signaling cascade. Moreover, an inhibitor of mTOR, temsirolimus, was able to block the antidepressant-like effect induced by vmPFC DBS, indicating that the mTOR pathway is a limiting factor [87].

As mentioned above, neurotrophic factors and neurogenesis play an important role in the antidepressant response. The effect of DBS on neurogenesis is still not clear in naïve animals and opposite results have been reported using different protocols to address this issue [66, 81]. Nonetheless, chronic vmPFC DBS restored the reduction in adult hippocampal neurogenesis induced by stress in the CUMS model [86]. On the other hand, the most relevant neurotrophic factor related to affective disorders and the unique analyzed in clinical and preclinical DBS studies is BDNF. vmPFC DBS normalized the deficient BDNF levels in CUMS animals in the striatal, cortical, and hippocampal regions [46, 86, 96]. However, peripheral BDNF concentration has been evaluated in only four patients who received DBS of the SCC, and they showed a reduction in serum BDNF levels [97].

Many original studies have evaluated the activity of several brain areas after DBS through the molecular expression of neuronal activation markers. Thus, vmPFC DBS induced the activation of the neurons around the site of stimulation, as well as in other cortical regions such as piriform, entorhinal, and orbitofrontal cortices [34, 39, 80, 88]. Additionally, the activity of several distant regions directly connected to the vmPFC was increased by DBS, for instance the hippocampus, basolateral amygdala, insula, or LHb [34, 39, 80, 88]. Thus, DBS applied to this target is able to regulate the activity of several limbic areas included in the neuronal circuitry that regulates emotions.

Lateral Habenula

The LHb is located dorsally to dorsal thalamus (Fig. 19.3). The LHb receives information from cortical and limbic structures and it is directly connected to dopaminergic-, noradrenergic-, and serotonergic-releasing midbrain areas [98]. This area constitutes a target for DBS as its volume tends to be reduced in depressed patients, and some authors have hypothesized that an overactivity in this region is related to MDD [99, 100]. In this context, a patient diagnosed with resistant MDD was treated with LHb DBS. The results showed the antidepressant response of this therapy; the patient achieved sustained remission from 4 to 12 months after the beginning of the treatment. Indeed, the patient suffered decay by the accidental cessation of stimulation, corroborating the effectiveness of this DBS target [101]. Thus, these promising results have led to the

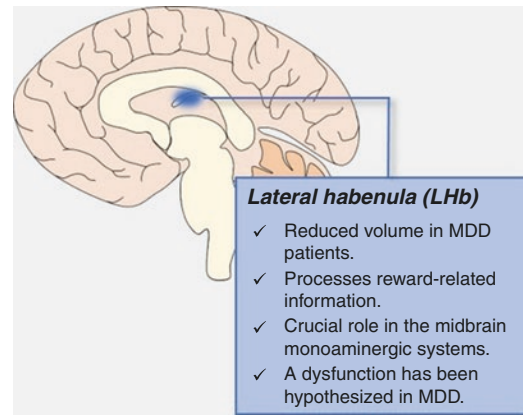

Fig. 19.3 General schematic representation of the LHb as a target for refractory MDD

intention to carry out additional clinical trials using LHb DBS for resistant MDD. In fact, a single-center study enrolling six patients is currently being conducted (ClinicalTrials.gov; identifier: NCT0198407).

The antidepressant-like effect of LHb DBS has been demonstrated in several animal models of depression. As such, DBS restored the depressive phenotype induced by CUMS, chronic ACTH administration, and in the learned helplessness (LH) model [39, 102–104]. This LH model is an experimental depression model based on exposure to repeated uncontrolled and inescapable stress, leading to helplessness [105].

Monoamine release was measured in CUMS animals after LHb DBS. Chronic exposure to unpredictable stressors provoked a reduction of 5-HT, NA and DA levels in the hippocampus and blood serum which is restored by LHb DBS [104].

An increase of BDNF was found in the blood serum of the patient treated with LHb DBS. Indeed, the BDNF levels were correlated with the improvement of depressive symptoms in this patient [106]. Furthermore, the antidepressant-like effect of LHb DBS has been preclinically linked with some molecular and cellular changes which could be crucial in the mechanism of action of DBS. In this way, LHb DBS regulates the local and cortical activation of the Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) intracellular pathway which modulates downstream signaling cascades involved, among others, in synaptic plasticity and neuronal survival [102]. New insights about cellular and molecular changes induced by LHb DBS could help in understanding the intrinsic mechanisms underpinning the antidepressant effect of DBS.

Medial Forebrain Bundle

The MFB is a fiber tract connecting the midbrain tegmentum and elements of the limbic system (Fig. 19.4) which plays an important role in the reward system [107, 108]. Clinical studies have reported the efficacy of MFB DBS as a therapeutic approach for intractable MDD patients. The pilot trial included seven patients, and DBS in the MFB induced a rapid and chronic antidepressant response, with an 86% response rate at the last follow-up [109]. Additionally, a second study demonstrated a significant alleviation of depressive symptoms in two of three patients enrolled 6 months after the beginning of DBS [110]. Finally, a third trial was approved to study the effectiveness of the MFB DBS in 12 patients diagnosed with refractory MDD (ClinicalTrials.gov; identifier: NCT01778790).

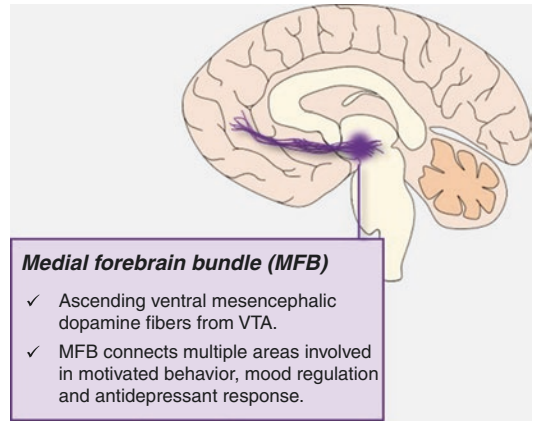

Fig. 19.4 General schematic representation of the MFB as a target for refractory MDD.

Preclinical data indicated that DBS in the MFB had an antidepressant-like effect in the FST [111] and that it reversed the anhedonic and depressive phenotype of FSL rats [91]. Surprisingly, MFB DBS induced an anxiety-like behavior assessed as an increase in the time spent in the closed arms in the EPM paradigm [91] without altering locomotor activity [111]. Only some molecular changes were evaluated after DBS is applied to the MFB. In this way, the effect of acute MFB DBS on monoamine release was assessed in the NAc and interestingly, no changes in DA or 5-HT release were reported [111]. Bearing in mind that the MFB is the fiber tract which connects the VTA with the NAc, and considering the antianhedonic effect of MFB DBS, this result was unexpected. Maybe instead of acute stimulation, chronic stimulation of the MFB

could lead to a modification of monoaminergic neurotransmission.

In addition, stimulation of the MFB altered the activity pattern of a few brain areas, such as the piriform and prelimbic cortices, the shell portion of NAc, the anterior regions of the caudate/putamen, dorsomedial thalamic nuclei, LHb, and the VTA [111, 112]. This suggests that DBS of the MFB induces changes in areas widely linked to the pathophysiology of MDD.

Inferior Thalamic Peduncle

The ITP is a bundle of fibers that connects the nonspecific thalamic system to the orbitofrontal cortex (Fig. 19.5), and DBS delivered in this region seems to be beneficial in refractory OCD patients [113]. However, only one case has been reported with regard to the efficacy of ITP stimulation in a refractory MDD patient, who achieved remission state from the first month of DBS [113–115]. Although the depressive symptomatology of this patient improved, she also suffered from bulimia and borderline personality disorder, making it difficult to extract conclusive data supporting the suitability of this target. Furthermore, up to now there are no preclinical data available that may help clarify the possible effectiveness of this therapy in this target brain area.

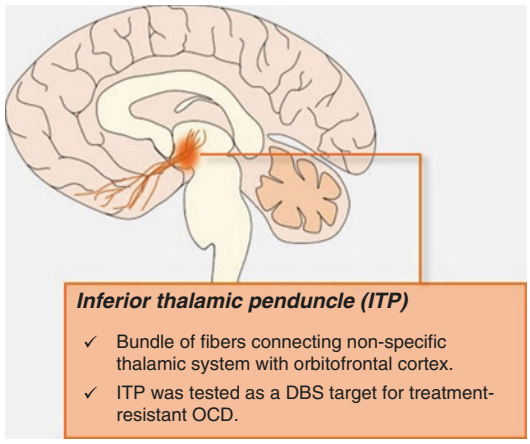

Fig. 19.5 General schematic representation of the ITP as a target for refractory MDD

Conclusions

In the last decade, the efficacy of DBS for treating refractory MDD has been evaluated, targeting several brain areas. Clinical studies that have enrolled most resistant MDD patients have been performed on the SCC and NAc regions. Indeed, they showed the most promising outcomes. Despite the data available from clinical trials, the mechanism of action underlying the antidepressant effect of DBS is still unclear. To clarify this issue, preclinical studies have evaluated the cellular and molecular changes modulated by DBS using animal models of depression. They have demonstrated that DBS regulates the release of several neurotransmitters in brain areas closely related to MDD. Moreover, DBS can enhance BDNF expression, and promote neurogenesis and neuronal plasticity. Overall, this suggests that DBS presents a complex mechanism of action involving many components, which could contribute to the initiation of remarkable neuronal network reorganization.

The evidence obtained through the studies performed to date indicates that DBS could be a safe alternative for the treatment of refractory MDD. But unfortunately, the multicenter trials fail to demonstrate a substantial improvement of the depressive symptomatology in all patients. For this reason, the search for indicators that will help to identify patients who can satisfactorily respond to DBS is mandatory. The detection of alterations in activity patterns through neuroimaging, or changes in peripheral proteins expression, could be used as clinical biomarkers to predict DBS response. Moreover, further studies will be necessary to identify the best target of stimulation in order to attain the maximum therapeutic response in each patient.

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References

1. Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med. 2013;43(3):471–81.
2. World Health Organization. World report on disability. Geneva: WHO; 2011.
3. Murray CJ, Lopez AD. Evidence-based health policy – lessons from the Global Burden of Disease Study. Science. 1996;274(5288):740–3.
4. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991;48(9):851–5.
5. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905–17.
6. Cuijpers P, Clignet F, van Meijel B, van Straten A, Li J, Andersson G. Psychological treatment of depression in inpatients: a systematic review and meta-analysis. Clin Psychol Rev. 2011;31(3):353–60.
7. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007;62(11):1208–16.
8. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry. 2005;58(5):347–54.
9. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet. 2003;361(9360):799–808.
10. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003;53(8):649–59.
11. Hawton K, Casanas ICC, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. J Affect Disord. 2013;147(1–3):17–28.
12. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007;370(9590):851–8.
13. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet. 1991;337(8738):403–6.
14. Hardesty DE, Sackeim HA. Deep brain stimulation in movement and psychiatric disorders. Biol Psychiatry. 2007;61(7):831–5.
15. Kalia SK, Sankar T, Lozano AM. Deep brain stimulation for Parkinson's disease and other movement disorders. Curr Opin Neurol. 2013;26(4):374–80.
16. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol. 2004;115(6):1239–48.
17. Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. II. Evidence from selective inactivation of cell bodies and axon initial segments. Exp Brain Res. 1998;118(4):489–500.
18. Kringelbach ML, Green AL, Aziz TZ. Balancing the brain: resting state networks and deep brain stimulation. Front Integr Neurosci. 2011;5:8.
19. McIntyre CC, Hahn PJ. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol Dis. 2010;38(3):329–37.
20. Greenberg BD, Gabriels LA, Malone DA, Jr Rezai AR, Friehs GM, Okun MS, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010;15(1):64–79.
21. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet. 1999;354(9189):1526.
22. Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A, et al. Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. J Neurosurg. 2004;101(4):682–6.
23. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology. 2006;31(11):2384–93.
24. Malone DA, Jr Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry. 2009;65(4):267–75.
25. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry. 2015;78(4):240–8.
26. Sesack SR, Grace AA. Cortico-basal ganglia reward network: microcircuitry. Neuropsychopharmacology. 2010;35(1):27–47.

27. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 2008;10(3):291–9.
28. Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, Hevenor S, et al. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. Arch Gen Psychiatry. 2005;62(11):1228–36.
29. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010;67(2):110–6.
30. Bewernick BH, Kayser S, Sturm V, Schlaepfer TE. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. Neuropsychopharmacology. 2012;37(9):1975–85.
31. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology. 2008;33(2):368–77.
32. Grubert C, Hurlemann R, Bewernick BH, Kayser S, Hadrysiewicz B, Axmacher N, et al. Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. World J Biol Psychiatry. 2011;12(7):516–27.
33. Kubu CS, Malone DA, Chelune G, Malloy P, Rezai AR, Frazier T, et al. Neuropsychological outcome after deep brain stimulation in the ventral capsule/ventral striatum for highly refractory obsessive-compulsive disorder or major depression. Stereotact Funct Neurosurg. 2013;91(6):374–8.
34. Hamani C, Amorim BO, Wheeler AL, Diwan M, Driesslein K, Covolan L, et al. Deep brain stimulation in rats: different targets induce similar antidepressant-like effects but influence different circuits. Neurobiol Dis. 2014;71:205–14.
35. Lim LW, Janssen ML, Kocabicak E, Temel Y. The antidepressant effects of ventromedial prefrontal cortex stimulation is associated with neural activation in the medial part of the subthalamic nucleus. Behav Brain Res. 2015;279:17–21.
36. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci. 2002;23(5):238–45.
37. Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology (Berl). 1995;121(1):66–72.
38. Papp M, Willner P, Muscat R. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. Psychopharmacology (Berl). 1991;104(2):255–9.
39. Lim LW, Prickaerts J, Huguet G, Kadar E, Hartung H, Sharp T, et al. Electrical stimulation alleviates depressive-like behaviors of rats: investigation of brain targets and potential mechanisms. Transl Psychiatry. 2015;5:e535.
40. Rummel J, Voget M, Hadar R, Ewing S, Sohr R, Klein J, et al. Testing different paradigms to optimize antidepressant deep brain stimulation in different rat models of depression. J Psychiatr Res. 2016;81:36–45.
41. Overstreet DH, Wegener G. The Flinders sensitive line rat model of depression – 25 years and still producing. Pharmacol Rev. 2013;65(1):143–55.
42. Schmuckermair C, Gaburro S, Sah A, Landgraf R, Sartori SB, Singewald N. Behavioral and neurobiological effects of deep brain stimulation in a mouse model of high anxiety- and depression-like behavior. Neuropsychopharmacology. 2013;38(7):1234–44.
43. Kim Y, McGee S, Czeczor JK, Walker AJ, Kale RP, Kouzani AZ, et al. Nucleus accumbens deep-brain stimulation efficacy in ACTH-pretreated rats: alterations in mitochondrial function relate to antidepressant-like effects. Transl Psychiatry. 2016;6(6):e842.
44. Iijima M, Ito A, Kurosu S, Chaki S. Pharmacological characterization of repeated corticosterone injection-induced depression model in rats. Brain Res. 2010;1359:75–80.
45. Landgraf R, Kessler MS, Bunck M, Murgatroyd C, Spengler D, Zimbelmann M, et al. Candidate genes of anxiety-related behavior in HAB/LAB rats and mice: focus on vasopressin and glyoxalase-I. Neurosci Biobehav Rev. 2007;31(1):89–102.
46. Gersner R, Toth E, Isserles M, Zangen A. Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: potential role of brain-derived neurotrophic factor. Biol Psychiatry. 2010;67(2):125–32.
47. Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. Neurosci Biobehav Rev. 1992;16(4):525–34.
48. van Dijk A, Klanker M, van Oorschot N, Post R, Hamelink R, Feenstra MG, et al. Deep brain stimulation affects conditioned and unconditioned anxiety in different brain areas. Transl Psychiatry. 2013;3:e289.
49. Handley SL, Mithani S. Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behaviour. Naunyn Schmiedebergs Arch Pharmacol. 1984;327(1):1–5.
50. Falowski SM, Sharan A, Reyes BA, Sikkema C, Szot P, Van Bockstaele EJ. An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. Neurosurgery. 2011;69(6):1281–90.

51. Brandeis R, Brandys Y, Yehuda S. The use of the Morris water maze in the study of memory and learning. Int J Neurosci. 1989;48(1–2):29–69.
52. Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods. 1984;11(1):47–60.
53. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry. 1965;122(5):509–22.
54. Heninger GR, Delgado PL, Charney DS. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry. 1996;29(1):2–11.
55. Ruhe HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry. 2007;12(4):331–59.
56. van Dijk A, Mason O, Klompmakers AA, Feenstra MG, Denys D. Unilateral deep brain stimulation in the nucleus accumbens core does not affect local monoamine release. J Neurosci Methods. 2011;202(2):113–8.
57. van Dijk A, Klompmakers AA, Feenstra MG, Denys D. Deep brain stimulation of the accumbens increases dopamine, serotonin, and noradrenaline in the prefrontal cortex. J Neurochem. 2012;123(6):897–903.
58. Sesia T, Bulthuis V, Tan S, Lim LW, Vlamings R, Blokland A, et al. Deep brain stimulation of the nucleus accumbens shell increases impulsive behavior and tissue levels of dopamine and serotonin. Exp Neurol. 2010;225(2):302–9.
59. Lahmame A, Armario A. Differential responsiveness of inbred strains of rats to antidepressants in the forced swimming test: are Wistar Kyoto rats an animal model of subsensitivity to antidepressants? Psychopharmacology (Berl). 1996;123(2):191–8.
60. Will CC, Aird F, Redei EE. Selectively bred Wistar–Kyoto rats: an animal model of depression and hyper-responsiveness to antidepressants. Mol Psychiatry. 2003;8(11):925–32.
61. Kempermann G, Kronenberg G. Depressed new neurons – adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. Biol Psychiatry. 2003;54(5):499–503.
62. Neto FL, Borges G, Torres-Sanchez S, Mico JA, Berrocoso E. Neurotrophins role in depression neurobiology: a review of basic and clinical evidence. Curr Neuropharmacol. 2011;9(4):530–52.
63. Samuels BA, Hen R. Neurogenesis and affective disorders. Eur J Neurosci. 2011;33(6):1152–9.
64. D'Sa C, Duman RS. Antidepressants and neuroplasticity. Bipolar Disord. 2002;4(3):183–94.
65. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry. 2003;54(1):70–5.
66. Winter C, Bregman T, Voget M, Raymond R, Hadar R, Nobrega JN, et al. Acute high frequency stimulation of the prefrontal cortex or nucleus accumbens does not increase hippocampal neurogenesis in rats. J Psychiatr Res. 2015;68:27–9.
67. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of cortical–limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004;61(1):34–41.
68. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic–cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry. 1999;156(5):675–82.
69. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, et al. Limbic–frontal circuitry in major depression: a path modeling metanalysis. Neuroimage. 2004;22(1):409–18.
70. Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007;164(5):778–88.
71. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry. 2000;48(8):830–43.
72. Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, et al. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. Am J Psychiatry. 2011;168(5):502–10.
73. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651–60.
74. Puigdemont D, Perez-Egea R, Portella MJ, Molet J, de Diego-Adelino J, Gironell A, et al. Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. Int J Neuropsychopharmacol. 2012;15(1):121–33.
75. Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry. 2012;69(2):150–8.
76. McNeely HE, Mayberg HS, Lozano AM, Kennedy SH. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. J Nerv Ment Dis. 2008;196(5):405–10.
77. Serra-Blasco M, de Vita S, Rodriguez MR, de Diego-Adelino J, Puigdemont D, Martin-Blanco A, et al. Cognitive functioning after deep brain stimulation in subcallosal cingulate gyrus for treatment-resistant depression: an exploratory study. Psychiatry Res. 2015;225(3):341–6.

78. Vertes RP. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse. 2004;51(1):32–58.
79. Hamani C, Diwan M, Isabella S, Lozano AM, Nobrega JN. Effects of different stimulation parameters on the antidepressant-like response of medial prefrontal cortex deep brain stimulation in rats. J Psychiatr Res. 2010;44(11):683–7.
80. Jimenez-Sanchez L, Castane A, Perez-Caballero L, Grifoll-Escoda M, Lopez-Gil X, Campa L, et al. Activation of AMPA receptors mediates the antidepressant action of deep brain stimulation of the infralimbic prefrontal cortex. Cereb Cortex. 2016;26(6):2778–89.
81. Etievant A, Oosterhof C, Betry C, Abrial E, Novo-Perez M, Rovera R, et al. Astroglial control of the antidepressant-like effects of prefrontal cortex deep brain stimulation. EBioMedicine. 2015;2(8):898–908.
82. Hamani C, Diwan M, Macedo CE, Brandao ML, Shumake J, Gonzalez-Lima F, et al. Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. Biol Psychiatry. 2010;67(2):117–24.
83. Perez-Caballero L, Perez-Egea R, Romero-Grimaldi C, Puigdemont D, Molet J, Caso JR, et al. Early responses to deep brain stimulation in depression are modulated by anti-inflammatory drugs. Mol Psychiatry. 2014;19(5):607–14.
84. Rea E, Rummel J, Schmidt TT, Hadar R, Heinz A, Mathe AA, et al. Anti-anhedonic effect of deep brain stimulation of the prefrontal cortex and the dopaminergic reward system in a genetic rat model of depression: an intracranial self-stimulation paradigm study. Brain Stimul. 2014;7(1):21–8.
85. Bodnoff SR, Suranyi-Cadotte B, Aitken DH, Quirion R, Meaney MJ. The effects of chronic antidepressant treatment in an animal model of anxiety. Psychopharmacology (Berl). 1988;95(3):298–302.
86. Bambico FR, Bregman T, Diwan M, Li J, Darvish-Ghane S, Li Z, et al. Neuroplasticity-dependent and -independent mechanisms of chronic deep brain stimulation in stressed rats. Transl Psychiatry. 2015;5:e674.
87. Jimenez-Sanchez L, Linge R, Campa L, Valdizan EM, Pazos A, Diaz A, et al. Behavioral, neurochemical and molecular changes after acute deep brain stimulation of the infralimbic prefrontal cortex. Neuropharmacology. 2016;108:91–102.
88. Veerakumar A, Challis C, Gupta P, Da J, Upadhyay A, Beck SG, et al. Antidepressant-like effects of cortical deep brain stimulation coincide with pro-neuroplastic adaptations of serotonin systems. Biol Psychiatry. 2014;76(3):203–12.
89. Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. Neurosci Biobehav Rev. 2005;29(4–5):627–47.
90. Golden SA, Covington 3rd HE, Berton O, Russo SJ. A standardized protocol for repeated social defeat stress in mice. Nat Protoc. 2011;6(8):1183–91.
91. Edemann-Callesen H, Voget M, Empl L, Vogel M, Wieske F, Rummel J, et al. Medial forebrain bundle deep brain stimulation has symptom-specific antidepressant effects in rats and as opposed to ventromedial prefrontal cortex stimulation interacts with the reward system. Brain Stimul. 2015;8(4):714–23.
92. Srejic LR, Hamani C, Hutchison WD. High-frequency stimulation of the medial prefrontal cortex decreases cellular firing in the dorsal raphe. Eur J Neurosci. 2015;41(9):1219–26.
93. Chakravarty MM, Hamani C, Martinez-Canabal A, Ellegood J, Laliberte C, Nobrega JN, et al. Deep brain stimulation of the ventromedial prefrontal cortex causes reorganization of neuronal processes and vasculature. Neuroimage. 2016;125:422–7.
94. Hoeffer CA, Klann E. mTOR signaling: at the crossroads of plasticity, memory and disease. Trends Neurosci. 2010;33(2):67–75.
95. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010;329(5994):959–64.
96. Hamani C, Machado DC, Hipolide DC, Dubiela FP, Suchecki D, Macedo CE, et al. Deep brain stimulation reverses anhedonic-like behavior in a chronic model of depression: role of serotonin and brain derived neurotrophic factor. Biol Psychiatry. 2012;71(1):30–5.
97. Ramasubbu R, Vecchiarelli HA, Hill MN, Kiss ZH. Brain-derived neurotrophic factor and subcallosal deep brain stimulation for refractory depression. World J Biol Psychiatry. 2015;16(2):135–8.
98. Geisler S, Trimble M. The lateral habenula: no longer neglected. CNS Spectr. 2008;13(6):484–9.
99. Ranft K, Dobrowolny H, Krell D, Bielau H, Bogerts B, Bernstein HG. Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia. Psychol Med. 2010;40(4):557–67.
100. Sartorius A, Henn FA. Deep brain stimulation of the lateral habenula in treatment resistant major depression. Med Hypotheses. 2007;69(6):1305–8.
101. Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW, et al. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biol Psychiatry. 2010;67(2):e9–e11.
102. Kim Y, Morath B, Hu C, Byrne LK, Sutor SL, Frye MA, et al. Antidepressant actions of lateral habenula deep brain stimulation differentially correlate with CaMKII/GSK3/AMPK signaling locally and in the infralimbic cortex. Behav Brain Res. 2016;306:170–7.
103. Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, et al. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature. 2011;470(7335):535–9.
104. Meng H, Wang Y, Huang M, Lin W, Wang S, Zhang B. Chronic deep brain stimulation of the lateral

habenula nucleus in a rat model of depression. Brain Res. 2011;1422:32–8.
105. Seligman ME, Rosellini RA, Kozak MJ. Learned helplessness in the rat: time course, immunization, and reversibility. J Comp Physiol Psychol. 1975;88(2):542–7.
106. Hoyer C, Kranaster L, Sartorius A, Hellweg R, Gass P. Long-term course of brain-derived neurotrophic factor serum levels in a patient treated with deep brain stimulation of the lateral habenula. Neuropsychobiology. 2012;65(3):147–52.
107. Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. J Neuropsychiatry Clin Neurosci. 2012;24(2):223–36.
108. Coenen VA, Schlaepfer TE, Maedler B, Panksepp J. Cross-species affective functions of the medial forebrain bundle-implications for the treatment of affective pain and depression in humans. Neurosci Biobehav Rev. 2011;35(9):1971–81.
109. Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013;73(12):1204–12.
110. Fenoy AJ, Schulz P, Selvaraj S, Burrows C, Spiker D, Cao B, et al. Deep brain stimulation of the medial forebrain bundle: distinctive responses in resistant depression. J Affect Disord. 2016;203:143–51.
111. Bregman T, Reznikov R, Diwan M, Raymond R, Butson CR, Nobrega JN, et al. Antidepressant-like effects of medial forebrain bundle deep brain stimulation in rats are not associated with accumbens dopamine release. Brain Stimul. 2015;8(44):708–13.
112. Furlanetti LL, Dobrossy MD, Aranda IA, Coenen VA. Feasibility and safety of continuous and chronic bilateral deep brain stimulation of the medial forebrain bundle in the naive Sprague-Dawley rat. Behav Neurol. 2015;2015:256196.
113. Jimenez F, Velasco F, Salin-Pascual R, Hernandez JA, Velasco M, Criales JL, et al. A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. Neurosurgery. 2005;57(3):585–93.
114. Jimenez F, Nicolini H, Lozano AM, Piedimonte F, Salin R, Velasco F. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. World Neurosurg. 2013;80(3–4):S30. e17-25
115. Jimenez F, Velasco F, Salin-Pascual R, Velasco M, Nicolini H, Velasco AL, et al. Neuromodulation of the inferior thalamic peduncle for major depression and obsessive compulsive disorder. Acta Neurochir Suppl. 2007;97(2):393–8.