Deep brain stimulation targets for treating depression

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Abstract

Deep brain stimulation (DBS) is a new therapeutic approach for treatment-resistant depression (TRD). There is a preliminary evidence of the efficacy and safety of DBS for TRD in the subgenual anterior cingulate cortex, the ventral capsule/ventral striatum, the nucleus accumbens, the lateral habenula, the inferior thalamic peduncle, the medial forebrain bundle, and the bed nucleus of the stria terminals. Optimal stimulation targets, however, have not yet been determined. Here we provide updated knowledge substantiating the suitability of each of the current and potential future DBS targets for treating depression. In this review, we discuss the future outlook for DBS treatment of depression in light of the fact that antidepressant effects of DBS can be achieved using different targets.

1. Introduction

According to the World Mental Health survey \cite{1} the prevalence of unipolar depression expressed as a percentage of the whole population is 14.6% and 11.1% in the high- and low-income countries, respectively. Moreover, WHO studies continuously show a trend toward the increasing prevalence as the low-income countries continue to develop \cite{2}. Major depressive disorder (MDD) by nature has a great impact on quality of life. The total disability-adjusted life years (DALY) attributed to major depression was evaluated at 4.3%, placing depression in third position among other diseases. The WHO forecast for 2030 sets major depression as the leading contributor to the whole of the DALY global burden, with a 6.2% projection. The total mortality ratio of patients with MDD is two times higher than the rest of the population \cite{3}.

Even with the multitude of methods used to treat depression, a significant portion of patients fails to respond, resulting in an estimated 1–3% prevalence of treatment-resistant depression (TRD) \cite{4}. The most widely used therapeutic alternatives for pharmacologically refractory depression are electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) and transcranial magnetic stimulation, with ECT being the oldest technique and showing the best results \cite{5}. However, even ECT is efficacious in only about half of TRD cases \cite{5}. Despite several complications \cite{6}, deep brain stimulation (DBS) is commonly used in treating Parkinson’s disease (PD) \cite{7–9}; it is now also being applied, though off-label only, in the treatment of major depression. An optimal approach has yet to be established, as the neuropathophysiology of depression remains weakly defined, and the mechanism of DBS seems to be dependent on the stimulation site \cite{10–14}. The best targets, parameters of stimulation, and stimulation protocols have not yet been determined. DBS shows preliminary evidence for antidepressant effects largely in the open-label studies and is still considered investigational in the treatment guidelines \cite{15}. Defining the electrophysiological biomarkers indicating the suitability and efficacy of the treatment should be the next priority. In this review, we present the neuroanatomical brain structures that have been tested for treating depression with DBS. We provide an updated knowledge substantiating the suitability and efficacy of DBS treatment and personalized medicine might be the future outlook for DBS treatment of depression.

2. Current deep brain stimulation targets for treatment-resistant depression

The brain structures that have been used as DBS targets in treating severe depression, proving the safety and efficacy of the electric stimulation, are the subgenual anterior cingulate cortex (sACC), the...
ventral capsule/ventral striatum (VC/VS), the nucleus accumbens (NAcc), the lateral habenula (LHb), and the inferior thalamic peduncle (ITP) [for review see 16]. The medial forebrain bundle (MFB) [17,18] and the bed nucleus of the stria terminalis (BNST) [19,20] have also been recently used. An overview of studies that tested different targets for DBS in TRD is given in Table 1; Fig. 1 illustrates the anatomical locations of these targets. The selection of these structures has been supported mainly by neuroimaging and lesional studies. DBS studies themselves have also inspired the use of some targets through tests on animal models or use in humans for other neuropsychiatric diagnoses, in which improvement in mood was observed as a positive side effect.

Some targets have been chosen based on the knowledge of their anatomical and functional position within supposed dysfunctional neural circuits in mood disorders or of their role in neurotransmitter systems.

### 2.1. Subgenual anterior cingulate cortex

Numerous accounts have linked altered states of the sACC, also referred to as Brodmann area 25, to MDD or/and feelings of sadness. In the sACC in healthy subjects, a change of mood towards less or more happy was shown to correlate with increased or decreased regional cerebral blood flow, respectively [23,24]. An increased regional cerebral metabolic rate of glucose (CMRGlc) in the left sACC was reported
to indicate a higher chance for successful cingulotomy in treating TRD [25] and for successful treatment with accelerated high-frequency rTMS. Moreover, the CMRGlc of the responsive subgroup was shown to decrease in time during rTMS [26].

Neural connections of the sACC correspond to its involvement in the large-scale neural networks that are dysfunctional in depressed patients, either directly or through a downstream connected structure [27]. The white matter of the sACC is connected to the medial frontal cortex, the anterior and posterior cingulate cortex, the anterior medial temporal lobe, the dorsal medial thalamus, the hypothalamus, the NAcc and the brainstem nuclei [28–30]. Dysfunctions of the subcortical-cortical and limbic neural networks are proposed as a basis of the pathophysiology of depression and hence the causes of anhedonia and dysphoria [14,31–33]. Substantial findings indicate increased involvement of the sACC in the brain default mode network (DMN), and subsequently altered states of DMN are linked to major depression [34–37]. Riva-Posse and colleagues [38] distinguished three major pathways most probably contributing to the clinical effect of the sACC-DBS. The first path consists of the forceps minor and medial aspect of the uncinate fascicle connecting the sACC with the medial frontal cortex. The second pathway leads via the cingulate bundle and connects the sACC with the rostral and dorsal anterior cingulate cortex, and the midcingulate cortex. Finally, the short descending midline fibres connect the sACC with the NAcc, caudate, putamen, and anterior thalamus.

Several human trials have investigated the efficacy of the DBS of sACC in the context of alleviating TRD (Table 1). An immediate antidiaphoric effect of the stimulation of sACC has been reported [39,40] and replicated in different institutions [41]. As for the long-term effect of the stimulation, considerable responsiveness and remission rates that were observed one year after DBS implantation [40] lasted several years [42]. The efficacy of DBS in sACC was shown to increase with individualized target identification and contact selection and with the use of optimal stimulation parameters. In their recent study, Riva-Posse and colleagues [43] used a prospective connectomic approach for sACC DBS surgery. They used the group probabilistic tractography map as a ‘connectome blueprint’ to plan surgical targeting in 11 participants with TRD. At one year, 82% of the participants were responders and 55% were in remission, suggesting the utility of this approach for future sACC DBS studies. As to the stimulation parameters, the stimulation efficacy was observed to increase with the pulse duration [44].

### 2.2. Ventral capsule/ventral striatum

Increased functional connectivity of the ventral striatum (VS) with various brain areas was linked to the symptoms of depression [45]. For example, intensified connections from the left VS to the left caudate have been associated with anhedonia. Higher connections from the left VS to the right mid and superior prefrontal cortex and anterior cingulate cortex were reported to be associated with higher suicidality, while depression severity correlates with the connectivity of the left VS to the right precuneus and left caudate and mid-cingulate. Hwang and colleagues [46] found that an increase in functional connectivity between the VS and the DMN is positively associated with the Center for epidemiologic Studies Depression Scale (CES-D) score. The tractography of the anterior limb of the internal capsule revealed rich projections to the entire thalamus, hypothalamus, brainstem, frontal pole, medial temporal lobe, and the NAcc [29], which are sites associated with depressive syndrome [46].

Decreased interest in and performance of activities in depressed subjects as compared to healthy subjects was shown to be associated with lesser bilateral VS activation in response to positive stimuli [47].

Capsulotomies performed for obsessive-compulsive disorder (OCD) decreased patient scores in the Hamilton Depression Rating Scale (HDRS) and other neuropsychological scores [48]. Aouizerate and colleagues [49] performed a successful DBS trial with patients with OCD and comorbid MDD, with results showing decreases in both OCD and depression severity. In these ablative and stimulation studies, the improvement in depressive symptomatology might occur due to the amelioration or resolution of the OCD. The efficacy of DBS in VC/VS was, however, demonstrated in patients who received DBS for TRD [50–54], even though the results of the randomized controlled phase of the most recent VC/VS-DBS studies are contradictory. While Berghed et al. [54] reported significant reduction of depressive symptoms, Dougherty et al. [52] found no significant differences between the active and sham DBS. Slightly different position of the electrode, insufficient duration of the optimization phase and too short period for the evaluation of DBS settings might have led to negative results in the earlier study, as argued by the authors of the more recent study [54]. Interestingly, the two VC/VS-DBS studies differed also in the gender ratio with 57% [52] compared to 32% [54] of male participants, suggesting some influence of gender on the treatment efficacy. However, to the best of our knowledge there are no direct reports suggesting less efficacy of the VC/VS-DBS in men with TRD.

### 2.3. Nucleus accumbens

The NAcc is known for its established role in the neurocircuitry of pleasure and reward [32,55]; there are findings of increased activation of the NAcc to a presented reward and decreased activity in reaction to a punishment [56]. The trials of its stimulation in treating refractory depression have therefore a solid rationale. What further cements the link between depressive states and the NAcc are structural and functional correlates between the nucleus and the level of anhedonia, a cardinal symptom of depression. The more severe the anhedonia, the smaller the nucleus, and the lesser the activation of the NAcc to a reward [56]. Thus, a change in the activity of the nucleus could decrease the depressive symptomatology. The theoretical reasoning for stimulating the NAcc has been verified on several occasions [57–60]. Stimulation of the NAcc showed a reduced mean HDRS at every point of Bevernwick’s study [57], a year after the implantation surgery, 50% of the subjects were classified as responsive. An immediate effect of the stimulation was demonstrated in increased reward-seeking thoughts [59]. PET imaging performed by Schlaepfer and colleagues [59] after NAcc stimulation showed a bilateral increase in metabolic activity in the dorsolateral prefrontal cortex, a structure usually hypoactive in depression [61]. Additionally, decreased activity was observed throughout the study in the ventromedial prefrontal cortex, which has been reported to be hyperactive in depression [61]. Thus, a reversal of pathological activity as a result of NAcc stimulation was observed alongside with the cessation of depressive symptoms [59].

### 2.4. Lateral habenula

The LHb is known to play a key role during the acquisition of reward-related information [62]. The LHb activity corresponds negatively to the anticipation of a reward and the reception of a reward, the firing in the LHb neurons is increased in the opposite situations, namely the anticipation of a non-reward situation and the omission of a reward. The LHb causes inhibition of the ventral striatum dopamine neurons, which are active during the anticipation and reception of rewards. Shelton and colleagues [63] showed that the LHb is activated as a response to a noxious stimulus. An increase in LHb activity could therefore explain some symptoms of depression, such as increased pain sensation [64] and lowered reward-seeking behaviour [32]. In accordance with this theory, a rapid depletion of plasma tryptophan, a drug used to mitigate the exacerbation of depressive symptoms, showed increased blood flow in the habenular area [65].

In order to alleviate depression, DBS of the LHb should cause functional inhibition of the LHb. In rats, chronic DBS caused better performance in open-field tests and increased serum and brain tissue monoamines [66]. DBS of the LHb caused remission after 4 months of stimulation in a patient with MDD, supporting a critical role of this
behaviour changed dopamine levels are causal for the observed change in behaviour immediately intraoperatively [18, 82]. Significantly increased MFB was observed to increase appetitive motivation and to improve ni.

2.5. Inferior thalamic peduncle

The ITP is a bundle of fibres that reciprocally interconnect the intralaminar nucleus and the thalamic reticular nucleus with the orbitofrontal cortex (OFC) [68]. The OFC is widely accepted as playing a key role in the non-reward attractor theory of depression [69]. Lesioning of the ITP, which happens during stereotactic tractotomy of the broader area, showed the amelioration of depressive symptoms [70]. Low frequency (6 Hz) electric stimulation of the ITP and nucleus reticularis thalami caused a synchronization of the electroencephalographic (EEG) signal recorded in the frontopolar region. This suggest the existence of direct connections to the OFC. Higher frequency stimulation (60 Hz) caused desynchronization in the EEG signal of the same area [71]. Because high frequency stimulation causes EEG outputs similar to that of the simultaneous application of glutamate and N-methyl-D-aspartate into the cortex, Velasco and colleagues [71] hypothesized that this kind of stimulation can activate a glutaamatergic system related to the arousal and the cholinergic system. In a case report, DBS of the ITP was shown to have a long-lasting antidepressant effect [72, 73]. In a recent study, one patient that was stimulated in ITP continued to experience a substantial decrease in depressive symptoms 8 years after the implantation [20].

2.6. Medial forebrain bundle

The MFB consists of two distinct tracts both of which are connected to various parts of the limbic system: the inferomedial MFB (imMFB) and the superolateral MFB (slMFB). Both parts form a common trunk, which sprouts caudally to the ventral tegmental area, goes to the dentate nucleus of the cerebellum, leaves the cerebellum via the superior cerebellar peduncle, connects to the upper pons, retrobulbar area, and the periaqueductal grey, splits into the mentioned sole tracts in the ventral tegmental area, and finally the imMFB goes as far as to the lateral hypothalamus, while the slMFB passes through the thalamus into the anterior limb of the internal capsule [74]. It has been proposed that the MFB forms a part of the systems of seeking, panic, and reward [74, 75]. As those systems are dysfunctional in MDD [32, 55, 76], it seems that the MFB plays a crucial role in the pathophysiology of depression. Alterations of the MFB, such as reduced fractional anisotropy in patients with the melancholic subtype of MDD [77] were observed to correlate with depressive symptomatology. Further investigations on animal models of depression showed a significant reversal of depressive-like symptoms after DBS of MFB [78–80]. While lower levels of dopamine were observed in some rat models of depression [80], electric stimulation of the MFB in rats was suggested to increase the number of D2 receptors in the prefrontal cortex and the number of dopamine transporters in the hippocampus [78]. The overall effect on electric state, anxiety, and drive is rapid [81], as demonstrated in the increase in forced swim test scoring. It is, however, inconclusive whether the changed dopamine levels are causal for the observed change in behaviour and more importantly whether this phenomenon is of any significance in human neurocircuitry. In humans, the stimulation of the slMFB was observed to increase appetitive motivation and to improve mood immediately intraoperatively [18, 82]. Significant changes in depression scores were seen as soon as in the seventh day of the stimulation. There have been even hints of a marker for suitability of DBS in certain depressive patients, as responsive groups were reported to have stronger connectivity between the location of the stimulation and the medial prefrontal cortex [82]. Casting doubt on the similarity of the actual action of stimulation in rat models and humans, and hence of the changed dopamine levels, Bregman and colleagues [81] pointed out that dopamine axons in MFB in both rats and humans are mostly non-myelinated. Therefore, the stimulation in commonly used parameters cannot recruit dopaminergic axons. In support of this point, no increase in dopamine release during DBS of MFB in rats was observed [81]. The antidepressant effect might be delivered by other types of axons in humans.

2.7. Bed nucleus of the stria terminalis

BNST is located in the basal forebrain, serves as a major output pathway of the amygdala and has a complex role in regulating stress response. Dysfunction in this structure was suggested to play an important role in anxiety disorders, partly through serotonergic activity [83]. To date, only two studies have reported the efficacy of DBS for TRD in BNST. In a recent case study a patient, with severe MDD and comorbid anorexia nervosa, was treated with DBS in the MFB and subsequently, two years after the first DBS procedure, in the BNST [19]. While DBS MFB had to be discontinued due to blurred vision as a side effect, very profound gradual improvements were seen after DBS BNST. In a double-blind crossover study the effects of DBS in the BNST and the ITP were assessed in seven TRD patients [20]. The outcomes during the two crossover periods performed within the first 16 months after the surgery suggested better effects of BNST to ITP stimulation. Three years after the DBS implantation all patients were stimulated at BNST. Five out of seven patients were responders and two were in remission. Due to limited number of investigations efficacy of DBS in the two targets was not compared. The authors concluded that both BNST and ITP stimulation may alleviate depressive symptoms in patients with TRD. The clinical outcomes of seven MDD patients undergoing DBS BNST in another study [84] have not been presented yet. The authors rather searched for electrophysiological biomarkers of depression. Based on the finding that relative alpha-power recorded in the BNST and the MFB correlate significantly with the self-reported disease severity in MDD patients, the authors suggested that alpha activity in the limbic system might be a signature of symptom severity in MDD.

3. Candidate deep brain stimulation targets for treatment-resistant depression

Based on their anatomical proximity to the previously tested sites, we can speculate that some other brain structures might be considered as possible new targets for the DBS for treating depression. These candidate structures include anterior thalamic radiation (ATR), uncinate fasciculus (UF), subthalamic nucleus (STN), and globus pallidus pars interna (GPI). Fig. 1 illustrates the anatomical locations of these targets.

3.1. Anterior thalamic radiation

The ATR goes medially to the slMFB and ends at the anterior limb of the internal capsule, and it connects the dorsomedial thalamus, anterior thalamic nucleus, tempo-mesial region, and brain stem through the mamillo-thalamic tract. It is thought to be in a kind of antagonistic relationship with the slMFB, as its increased activation has been ascribed to an activation of the grief or/and the panic system; thus, in combination with the slMFB it forms a kind of a homeostatic system [17, 74, 85].

3.2. Uncinate fasciculus

The UF connects the prefrontal regions associated with emotions with the middle temporal lobe and hence the hippocampus and amygdala [86]. The most convincing evidence of the possible role of UF in the pathophysiology of MDD are the observed abnormalities in structural connectivity of UF in patients with MDD [87–90]. Decreased fractional anisotropy and an increased apparent diffusion coefficient between the sites connected with UF were found in depressive patients [88]. Moreover, the structural changes showed a relationship to depression severity, as reported in this diffusion tensor imaging study.
Another marker of the severity of depression linked to the UF is the decreased functional connectivity between the supragenual cingulate and extended amygdala [90].

3.3. Subthalamic nucleus and globus pallidus pars interna

Both structures form a part of the basal ganglia motor, oculomotor, associative and limbic functional loops. Their stimulation is commonly used in the treatment of PD, mostly with the intention of influencing the motor loop dysfunction that manifests in the motor symptoms of PD [7–9]. Even though the intent is to specifically target the motor subunit of the STN in DBS for PD, the adjacent limbic subunit is too close to exclude the influence of stimulation on this site [91–94]. Recent observations of a decrease in scoring in depression during stimulation of the STN for treating PD support this view [95–97]. As to the efficacy of the stimulation in terms of depression, STN and GPi seem to have nearly the same results [96].

4. The search for optimal target brain structures for DBS in depression should continue

The existing clinical trials of DBS for TRD have provided evidence of efficacy and safety for various brain targets. The fact that the trials stimulating different sites were chiefly performed by different scientific teams makes any meta-analysis difficult. They used different inclusion criteria, applied various outcome measures, and had slightly different follow-up management. Nevertheless, bearing in mind the limitations of the available data, similar efficacy and safety can be seen regardless of the choice of the target structure. Typically one third of the patients achieved complete remission, another third showed improvements and yet another third experienced no benefit in studies using sACC [39, 40, 42–98–100], VC/VS [50] or NAcc [57] as target structures. Recent studies using sACC report higher response or remission rates [43, 101–105] and thus favour the sACC over other targets.

In general, the evidence of efficacy is, however, somewhat weak for many reasons. Most of the studies involve few patients, with several even being case reports. Most studies are open-label, and thus fail to control for placebo effects, lacking control sham stimulation or control groups with the best medical therapy. Another drawback of the evidence is the very fact that complete remission rates do not exceed 30% in most studies. The reason the efficacy is not higher might be due to an undesirable study design, insufficient sample size, inappropriate patient selection, inadequate stimulation parameters, suboptimal target selection, or unfavourable electrode positions within the target structure.

To move forward in the effective DBS treatment of TRD, evidence from randomized double-blind crossover active-sham designed studies is highly appreciated. When designing such trials, optimization phase of sufficient duration, such as 6 months, with the possibility to evaluate DBS parameter setting over at least one week should precede the crossover phase [54]. That way, the highest possible efficacy in the active arm of the clinical trial is likely to be ensured, being a prerequisite for subsequent result evaluation in such study. Rapid worsening when stimulation is discontinued may preclude, however, using long time intervals due to ethical concerns [50, 105]. From this respect, the animal studies aimed at testing various DBS targets for treating depression are far more suitable with the advantage that they allow for higher control over variables that cannot be influenced in humans [106]. Antidepressant-like effect of DBS was observed in rats stimulated in ventromedial prefrontal cortex (vmPFC, rodent analogue of subgenual cingulate) [107–109], MFB [110], and NAcc [108]. Besides identifying targets for effective DBS, animal studies may also directly compare the DBS efficacy while systematically testing different brain regions. VmPFC was recently reported to outperform Nacc-DBS in the antidepressant-like effect [111]. Furthermore, animal studies might address the mechanisms underlying DBS. Functional inactivation of local neuronal populations through DBS, activation of fiber pathways near the stimulating electrodes as well as serotonergic reserve were suggested to be involved in antidepressant-like effect of vmPFC-DBS [107].

In our view, the fundamental condition for DBS treatment of depression is the proper target selection. To find an optimal node that would reduce or even completely remove the functional abnormality in TRD would be crucial. Testing new targets for DBS might help in this respect. In searching for an optimal DBS target, it is necessary, however, to consider the possibility that in general there is no one and only optimal DBS target for the treatment of depression. The fact that the antidepressant effect of stimulation can be achieved using different targets supports the view that depression is a neurocircuitry disease involving the disruption of multiple large-scale neural networks rather than an impairment of a single brain structure.

Aberrancies in the cortico-striato-thalamo-cortical loops have been suggested in the aetiology of MDD [14, 112]. This neurocircuitry of depression is considered to involve the dorsal (prefrontal, dorsal anterior cingulate and premotor cortices), ventral (sACC, orbitofrontal, and insular cortices), and modulatory (pregenual ACC, amygdala, and the hypothalamic-pituitary axis) components [112]. Each DBS-TRD target structure has its own unique anatomical and functional position within these networks, which determines its ability to improve the depressive symptomatology during stimulation. For instance, it was hypothesized that DBS applied in an area where fibres from the ventral and dorsal compartments converge, such as the NAcc, might enable simultaneous excitation and inhibition in the dorsal and ventral compartments, respectively [112] influencing the dysbalanced neural system in a complex manner. Another example of a particular role of the stimulated structure in the large-scale communication is the ACC, whose possible integrative functions in cognitive processing [113] might explain the most recently reported high efficacy of DBS to sACC in treating depression [104].

The evidence for involvement of the medial and dorsolateral prefrontal cortex, the cingulate cortex, limbic and paralimbic regions in pathogenesis of depression [114–116] allows one to speculate, whether direct stimulation of multiple brain targets within the impaired network might be beneficial. Stimulation of multiple regions is already being performed by non-invasive approaches such as ECT and rTMS, which proved their efficacy in treating depression [116–118]. The ECT directly involves robust nonfocal electric stimulation of the brain. Even the rTMS, mainly performed over the left and/or right dorsolateral prefrontal cortices, has been shown to be bioactively active not only locally but also at remote sites, presumably through transsynaptic connections [119–121, 116]. Although the mechanism of action of ECT is not yet fully understood, beneficial plasticity mechanisms (e.g. neurogenesis, dendritogenesis, synapse formation) are speculated to occur following ECT [122, 123]. For antidepressant effect, mainly the hippocampal neurogenesis seems to be necessary [124, 125]. Indeed, depression has been linked to chronic stress [126, 127] that is supposed to produce alterations in memory functions of the hippocampus [128]. It is known that low and high frequency electrical stimulation of neurons can cause long-term depression (LTD) and long-term potentiation (LTP), respectively. These physiological phenomena are considered to be involved in dynamic changes in neuronal networks underlying the learning and memory processes. If DBS of multiple brain structures involved in TRD could induce neuroplasticity analogous to the LTD or LTP this might restore these impaired networks.

It is also possible that different targets should be used in different subtypes or stages of MDD due to the existence of different underlying brain abnormalities. Despite the myriad of targets tested, neurobiological markers of these abnormalities, however, have not been identified yet. In a recent resting-state connectivity study based on EEG data, different network patterns were found in temporal lobe epilepsy patients and controls [129]. In this study, the outflow from the anterior cingulate cortex was lower in temporal lobe epilepsy patients with learning deficits or depression than in patients without impairments and then controls. These resting-state connectivity alterations were
suggested to constitute an important biomarker of temporal lobe epilepsy. We believe that identifying similar electrophysiological markers in TRD could help better identify the target structures for DBS treatment of depression.

In addition to efficacy and safety, practical aspects of stimulation such as battery longevity should influence the judgement on the suitability of a given target structure. The stimulation parameters are very high in the habenula and the IC/VC, which would lead to more frequent battery changes, an action which is not only more expensive but also riskier for the patients due to potential infection during each surgery. Rechargeable batteries have been suggested to solve this problem [130,51].

Taken together, a consensus on optimal DBS target/s for treating depression has not been reached yet, hence leaving the door for future investigations in this field still open.

5. Personalized medicine for DBS treatment in depression

In line with the concept of abnormal neurocircuitry in MDD, the observed variability in depressive symptomatology suggests the existence of variability in structural and/or functional abnormalities within the involved brain networks. Reliable biomarkers of these abnormalities are needed to determine the suitability and efficacy of DBS treatment. Personalized DBS treatment that would consider the specific needs of each patient thus could increase the overall efficacy of the DBS approach. To personalize DBS treatment, we need an individualized DBS protocol and a precise evaluation of patient impairment. First, within the efforts towards developing an individualized DBS protocol, establishing a registry for future clinical studies has recently been proposed by Morishita and colleagues [131]. They suggest that data from future clinical DBS studies for TRD be collected in an organized manner, creating a common register of variables related to the clinical status before the treatment, parameters of stimulation, precise positioning of the electrode within the brain structure, and postoperative outcomes, including side effects. Based on this accumulated data, rigorous meta-analyses would be performed and the DBS protocol could then be individualized to match the pre-surgical clinical characteristics of each patient. Recent study by Zhou and colleagues is the first step [132]. Second, to get the exact evaluation of each patient impairment an objective measure of the brain abnormality would be necessary, one that would allow for distinguishing among different subtypes of MDD and could also serve as a standard measure of treatment efficacy. Current diagnostic tools such as structured diagnostic interviews and psychometric methods seem to be insufficient in this respect, since they do not directly measure the structural or functional brain abnormalities and rather focus on the resulting symptomatology of the disease. Besides that, the use of more direct neuroimaging tools, such as standard clinical magnetic resonance imaging and electroencephalography, is mainly restricted to differential diagnostics of depression. It only serves to detect or exclude severe brain lesions and epilepsy.

In the search for an objective biomarker of brain abnormality in MDD, the EEG ‘microstate’ analysis might represent a possible solution [133]. This method is supposed to be a promising neurophysiological tool for understanding and assessing brain network dynamics on a sub-second timescale. A series of quasi-stable microstates, each characterized by a unique topography of electric potentials over the whole scalp, can be assessed to provide potential utility in detecting neurophysiological impairments. In early studies using adaptive segmentation to examine microstates in patients with depression, microstates exhibited abnormal topographies and reduced overall average microstate duration [134] but unchanged numbers of different microstates per second [135], compared to controls. These findings suggest that the resting-state EEG microstate analysis may offer a novel approach in diagnostics, making it possible to identify individually unique patterns of resting-state electrophysiological brain activity.

6. Conclusion

In conclusion, DBS in MDD should be still considered as an experimental therapy. Many questions remain. What is the neurobiology of treatment-resistant depression? What is/are the optimal target brain structure/s for deep brain stimulation in depression? What are the suitable biomarkers of brain abnormalities in depression? Will personalized medicine increase the efficacy of DBS therapies for treatment-resistant depression? Despite these still open questions, the advantages of electrical stimulation of brain structures over previously used lesioning procedures is evident right now. It is fully reversible and enables adjustments to interindividual and intraindividual variabilities of needs that rise from the existence of disease subtypes and disease progression. This method is promising and it may soon develop into a standard tool for treating depression resistant to other therapeutic approaches.

Declaration of interest

The authors have nothing to declare and have no conflict of interest.

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