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REVIEW

Therapeutic Efficacy of Neurostimulation for Depression: Techniques, Current Modalities, and Future Challenges

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Abstract Depression is the most prevalent debilitating mental illness; it is characterized as a disorder of mood, cognitive function, and neurovegetative function. About one in ten individuals experience depression at some stage of their lives. Antidepressant drugs are used to reduce the symptoms but relapse occurs in ~20% of patients. However, alternate therapies like brain stimulation techniques have shown promising results in this regard. This review covers the brain stimulation techniques electroconvulsive therapy, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, vagus nerve stimulation, and deep brain stimulation, which are used as alternatives to antidepressant drugs, and elucidates their research and clinical outcomes.

Keywords Depression · Electroconvulsive therapy · Transcranial direct current stimulation · Repetitive transcranial magnetic stimulation · Magnetic seizure therapy · Vagus nerve stimulation · Deep brain stimulation · Treatment-resistant depression

Introduction

Depression is a clinical condition known to result from the disruption of brain neurochemistry [1, 2]. It is a complex neuronal abnormality characterized by disorders of mood, cognitive function, and neurovegetative functions [3] and has a wide range of causes including genetic, developmental, and environmental [4, 5]. Previous neurophysiological imaging studies have revealed structural and functional abnormalities in widely distributed brain regions, including the anterior cingulate cortex [6, 7], orbitofrontal cortex [8], dorsolateral prefrontal cortex [9], amygdala, and hippocampus [10]. Overall, these findings suggest that depression is associated with the activation of regions that putatively mediate emotional and stress responses, while areas that inhibit emotional expression have functional abnormalities that might interfere with modulation of the stress response. This functional imbalance between cortical and limbic structures may be corrected by antidepressant drugs.

Need for a Neurostimulatory Approach

Depression has no proven established therapy. One third of depressed patients are treatment-resistant, a condition in which they fail to respond to standard treatment therapies i.e. antidepressants, psychotherapy, and cognitive therapies [11]. About 40% of patients responding to antidepressant drug therapy suffer from residual symptoms later in life, whereas 30% do not respond to treatment at all [12]. Therefore, psychiatric researchers are searching for alternate ways that may involve electrical or magnetic stimulation [13] such as non-pharmacological modalities [electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS)] [14–16] as a remedy for depression [17]. This review covers the non-pharmacological treatment modalities for depression, their modes of action (Table 1), target regions (Table 1), and clinical

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Table 1 Target regions and modes of action

Modality	Pre-treatment	Target region	Mode of action	References
ECT	Anesthesia or muscle relaxant	Cerebral cortex	Small electrical current to induce seizure	[19]
tDCS	–	Cerebral cortex	Low-intensity direct current (1–2 mA) modulates neuronal excitability	[27–29]
rTMS	–	Cerebral cortex	Magnetic pulse induces electrical current which depolarizes target neurons	[40, 41]
VNS	Implantation of pulse generator in left chest wall and electrodes by minor surgery	Electrode wrapped around left vagus nerve	Modulates levels of neurotransmitters or their metabolites along with functional activity of CNS regions	[56–58]
DBS	Frame-based stereotaxis; approaching deep brain targets through a small skull opening	Nucleus accumbens, ventral striatum, inferior thalamic nucleus, peduncle, lateral habenula, subgenual cingulate	High-frequency stimulation (130–185 Hz); reduces neuronal transmission in targeted brain region by inactivating voltage-dependent ion channels, which modulates and restores neuronal circuits involved in depression	[15, 77, 78]

perspectives, as well comparing their safety and efficacy based on reported research (Table 2). The physiological impact of neurostimulatory techniques is also discussed.

Neurostimulation Techniques

Electroconvulsive Therapy

Mode of Action

ECT is the oldest therapy for treating the symptoms of depression. This procedure is used as the second therapeutic option for severe depression when medication and psychotherapy have already been tried [18]. The patients are given general anesthesia and a muscle relaxant before ECT to prevent movement during the procedure. The patient's blood pressure, breathing, and heart rate are monitored throughout the procedure [19]. A small electric current is used to stimulate a cerebral brain region and induce a seizure. The current is delivered through electrodes placed over different brain areas. The electrode placement is critical and must not interfere with cognitive behavior [19].

Electrode Placement and Target Regions

There are four methods of electrode placement, the traditional bilateral and right unilateral electrode placements, and the bifrontal and left anterior right temporal (LART) placements [20]. While performing ECT, brain areas involved in self-care and orientation are not stimulated; neither is the distance between electrodes increased, as this would affect a large region of the brain, and likewise for higher stimulation currents [21, 22].

The symmetric bitemporal electrode placement with one electrode on each temple, which covers a large brain volume and induces a high level of seizure generalization, has high efficacy but more side-effects than the other three placements. Unilateral ECT, in which the electrodes are placed on the right temple and to the right of the vertex, has lower seizure generalization, efficacy and side-effects [23]. The bifrontal placement is also symmetrical and the electrodes are placed 2.5 cm anterior to the bitemporal sites. The region covered is 50% the same as that covered by the bitemporal placement. In the LART placement, the lateral electrode positions are the same as for bitemporal placement except that the left electrode is 5 cm anterior to the left temporal site. LART is asymmetric and interferes less with cognitive behavior. The electrodes are placed in an anterior position and hence are separated from the temporal lobe and the dorsolateral prefrontal cortex (DLPFC) [20]. With respect to safety and efficacy, the UK-ECT Review Group concluded that bilateral ECT is more effective than unipolar ECT [24]. In addition, meta-analysis of six trials including 256 patients concluded that real ECT is significantly more effective than simulated (sham) ECT (standardized effect size 0.91, 95% CI −1.27 to −0.54) [24].

Clinical Perspective

Lately, ECT has been used in large-scale clinical studies of depression and has been found to be more effective than antidepressant drugs. A few studies have concluded that ECT is a valid therapy for the treatment of depression, including its severe and resistant forms [25, 26]. A 6-month randomized trial was performed to evaluate the comparative efficacy of continuation ECT (C-ECT) to prevent the relapse of depression. The results demonstrated the relapse

Table 2 Major outcomes of clinical studies

Modality	Trial title	No. of participants	Year	Location	Trial outcome	Limitation/side effects	Reference
ECT and rTMS	A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression	46	2007	USA	ECT is more effective than rTMS for short-term treatment of depression	33% of patients reported substantial memory loss after ECT	[96]
tDCS	A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression	40	2007	Israel	Significant reduction in depression scores after DLPFC tDCS	–	[33]
tDCS	A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression	40	2009	Australia	Significant improvement in depression scores after 10 tDCS sessions	Minor side-effects	[39]
tDCS	Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study	11	2011	Spain, Australia	F-EX tDCS is safe and effective for depression treatment and may lead to more rapid improvement than bifrontal montage tDCS	Open label pilot study	[37]
rTMS	A controlled trial of daily left prefrontal cortex TMS for treating depression	30	2000	South Carolina, China	Significant reduction in depression symptoms at the end of two weeks	Occasional mild headache and discomfort at site of stimulation	[46]
rTMS	Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial	301	2007	USA, Australia	rTMS is effective in treating major depression with minimal side-effects	Eye disorder, gastrointestinal disorder, application site pain, muscle twitching, skin and subcutaneous tissue disorders	[49]
rTMS	Prefrontal rTMS for treating depression: Location and intensity results from the OPT-TMS multi-site clinical trial	185	2013	USA	Stimulation at 120% of motor threshold, unadjusted for scalp-cortex distances are safe for a broad range of patients.	–	[43]
VNS	Vagus nerve stimulation (VNS) for major depressive episodes: One year outcomes	30	2001	USA	Longer-term vagus nerve stimulation is effective in follow-up treatment of depression	Mild voice alteration (21%), dyspnea (7%), and neck pain (7%)	[60]
VNS	Vagus nerve stimulation for treatment-resistant depression: A randomized, controlled acute phase trial	235	2005	USA	No definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression	Voice alteration, increased cough, dysphagia, neck pain, palpitations, wound infection	[54]
VNS	P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder	13	2006	Germany	Auditory ERP is a useful tool for investigating VNS-induced changes of information processing in major depressive disorder	Significant gender difference between groups; small sample size	[107]

Table 2 continued

Modality	Trial title	No. of participants	Year	Location	Trial outcome	Limitation/side effects	Reference
VNS	Vagus nerve stimulation for treatment-resistant depression: behavioral and neural effects on encoding negative material	1	2007	England	VNS interferes with memory for negative information, an effect that may contribute to its antidepressant role	Throat tickling, decreased heart rate during VNS	[64]
DBS	A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle	1	2005	–	DBS of inferior thalamic relieves depressive symptoms in patient with TRD	Requires invasive electrode implantation. Long term safety and efficacy needs to be evaluated	[79]
DBS	Deep brain stimulation for treatment-resistant depression	6	2005	Canada	Positive behavioral changes time-locked to stimulation	No sustained antidepressant response in two of six patients after six months of treatment	[15]
DBS	Mood improvement after deep brain stimulation of the internal globus pallidus for tardive dyskinesia in a patient suffering from major depression	1	2007	Germany	Dyskinesia and symptoms of depression improve after 18 months of treatment. Depression declines significantly over the period of treatment and shows a sustained improvement in the last 3 months of treatment	Invasive, requires electrode implantation in brain	[71]
DBS	Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression	3	2008	USA, Germany	Immediate improvement in mood when DBS is on	No side-effects in any patients, but is invasive, requiring electrode implantation in brain	[73]
DBS	Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression	15	2009	USA	Significant improvement in depression symptoms; DBS of VC/VS is a promising strategy for treating refractory depression or TRD	DBS for long periods is more effective. Remission of symptoms and response rate to treatment increase with treatment duration	[82]
DBS	Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression	10	2010	Germany, USA	Nucleus accumbens region is a potential target for treating TRD with DBS	Invasive; requires electrode implantation in brain	[81]
DBS	Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years	20	2011	–	Progressive improvement of functional impairment related to social functioning and physical health. Supports long-term safety and efficacy of DBS	Requires electrode implantation in brain; however no significant adverse effects	[70]
DBS	A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression	21	2012	Canada	Reduction in depression along with significant enhancement in mood and improvement in severity of depression; suggests Cg 25 as an attractive target for implantation of DBS electrodes to treat depression and TRD	Invasive, requiring electrode implantation in brain; however no significant adverse effects	[80]

of depression in 37.1% of the patients. Further studies are needed to investigate individual patients' tolerance and the efficacy of treatment [18].

In summary, in terms of the efficacy of ECT, clinical findings suggest that depression relapse is <40%. The target area is the cerebral cortex but the exact neuronal mechanisms that are altered in response to seizure generation are unknown. In addition, ECT is limited by the use of anesthesia and seizure induction.

Transcranial Direct Current Stimulation

Mode of Action

tDCS has been explored in humans since the 1960s for its effects on mood and on the treatment of depression. tDCS delivers a low-intensity direct current to cortical areas [27]. The stimulations last for several minutes and modulate the neuronal excitability in target cerebral regions [28].

Electrode Placement and Target Regions

The current strength reported in recent clinical trials is 1–2 mA, administered for 10–20 min per session *via* sponge-based rectangular pads (nominally 25–35 cm^2) [29, 30]. The procedure is classified as anodal or cathodal based on the electrode placement over the targeted cortical region to induce effects of interest. For example, anodal prefrontal tDCS involves placement of the anode over the DLPFC and cathode over the contralateral orbit (montage commonly used in depression trials) [31].

The stimulation is focused on the left DLPFC by precisely identifying the pF3 site using the 10/20 system. This minimizes the hypo-activity of the left DLPFC, which is prevalent in depression [31, 32].

Clinical Perspective

The tDCS procedure has been used to explore the functions of cortical regions as well as being applied to the treatment of depression [31]. In a double-blind parallel clinical trial, 40 patients suffering from major depression were divided into three treatment groups, anodal tDCS of the left DLPFC (the active group), anodal tDCS of the occipital cortex (the active control group) and sham tDCS (the placebo control group). The therapy was done in 10 sessions during 2 weeks. Later, the mood of the patients was evaluated using Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory. The results showed that the treatment had almost no side-effects and was well tolerated among all treatment groups. At the end of the treatment a significant reduction in depression was observed [33]. In another study, 1 or 2 mA of tDCS was administered for 20 min/day for 2 weeks and similar results were obtained [34]. The mechanisms might be related to modulation of activity in the DLPFC by changing the membrane resting potential during stimulation and modifying synaptic transmission [35, 36].

An additional tDCS trial was carried out on 11 depressed patients. The study involved 2 mA tDCS for 20 min every weekday for four weeks, and depression was evaluated before and after the therapy. The treatment was well tolerated and a huge decrease in depression was recorded using the Montgomery Åsberg depression rating scale (pb0.001) [37]. Further, augmented tDCS was used for depressed patients resistant to pharmacological treatments. The study included 23 patients who were treated for 5 days, with two sessions per day. The follow-up suggested good tolerability and efficacy [38].

In another double-blind randomized trial on 40 depressed patients, anodal stimulation was given over the left DLPFC and the cathode was placed on the lateral aspect of the contralateral orbit. tDCS was given for 10 successive sessions per patient and mood outcomes were evaluated using the Montgomery–Åsberg scale. The results revealed no adverse effects on neuropsychological function [39]. In summary, clinical studies have demonstrated the safety, efficacy, and good tolerability of tDCS. The stimulation of cortical regions by a low-intensity direct current may result in changes in membrane resting potentials and modify synaptic transmission in the DLPFC, ultimately resulting in significant reduction of depression.

Repetitive Transcranial Magnetic Stimulation

Mode of Action

TMS was introduced in 1985. It is a non-invasive neurophysiological stimulation technique for the cerebral cortex [40]. The procedure involves the delivery of magnetic pulses to the cortex. The magnetic pulses induce an electrical current in the brain tissue which depolarizes the target neurons [41]. rTMS can be of high frequency (>1 Hz) or low frequency (<1 Hz). Low-frequency rTMS inhibits certain cortical regions whereas high-frequency rTMS activates the stimulated regions [42].

Target Regions

To perform effective rTMS, the electrode placement and stimulation intensity are critical and need attention as they determine whether the patient will respond to therapy or not. Johnson *et al.* used MRI for precise electrode positioning and performed a multi-site rTMS trial for depression treatment. The study validated that the prefrontal cortex and the motor cortex locations are potential target sites for depression treatment, motor localization and motor thresholding

respectively [43]. Excitatory rTMS over the left prefrontal cortex has been well studied and is effective for depression therapy. Inhibitory rTMS, however, is under investigation and a functional correlation has been found for inhibition of the right prefrontal cortex with depression [44].

Clinical Perspective

The excitation/inhibition of cortical areas by high-frequency rTMS has been found effective for the treatment of depression [45]. In an early rTMS trial, 30 medication-free depressed patients were randomly given either active or sham stimulation. The patients who received active stimulation were further divided into two groups: one receiving 5 Hz and the other 20 Hz. The rTMS was applied over the left prefrontal cortex for 2 weeks and at the end of therapy a marked decrease in depression was recorded with active stimulation, which is promising for further antidepressant trials using rTMS [46, 47]. rTMS has been used to reduce depression even in patients with medication-resistant major depression. In one study, the patients were given 15 sessions of either active or sham rTMS delivered to the left DLPFC. Each session was composed of 32 pulses of 10-Hz rTMS in 5 s. The results demonstrated significant reduction in depression after active rTMS, and that more intense treatment may result in greater response rates [48]. Similarly, an rTMS trial on 301 medication-free depressed patients was well tolerated with very few side-effects [49]. The durability of rTMS was found promising when rTMS-based antidepressant therapy was assessed over 6 weeks in a randomized trial [50]. Recently, a trial with 27 patients was performed, in which the patients were given high-frequency rTMS (10 Hz) over the left DLPFC for 2 weeks. The results showed excellent acceptability (55.6% responders), however further research is required to optimize the protocol and determine the efficacy of stimulation [51].

In summary, rTMS is a non-invasive, painless stimulation technique for the cerebral cortex using magnetic fields. It induces changes in the central nervous system at the cellular level, which ultimately are responsible for the reduction of depression. The exact changes at the molecular level are still unknown but current research and clinical implications support the use of high-frequency (excitatory) rTMS for depression therapy. However, little research is available to support the use of inhibitory rTMS [52, 53].

Vagus Nerve Stimulation

Mode of Action

VNS modulates the concentrations of neurotransmitters or their metabolites along with the functional activity of CNS regions in depression and other mood-related disorders as demonstrated by open trials [54]. This therapy has been used in Europe and Canada to reduce the symptoms of treatment-resistant depression (TRD) since 2001 and July 2005. The therapy has been approved by the FDA for chronic depression or TRD patients aged 18 or above who do not respond to other antidepressant treatments [55].

VNS therapy basically modifies the concentrations of monoamines within the CNS. Particularly, it alters the levels of the transmitters serotonin, norepinephrine, GABA, and glutamate which are associated with depression [54, 56, 57]. VNS therapy involves implantation of a pulse generator by minor surgery under local anesthesia. The device, about the size of a pocket watch, is implanted in the left chest wall. The implanted device is connected to electrodes which are capable of delivering low-frequency pulses to the left vagus nerve (VN). The electrode is wrapped around the VN and connected to the pulse generator controlled by a physician. The patient is provided with a magnet to switch off the pulse generator [58].

Target Regions

Neuroimaging studies have shown evidence that activity in the thalamus and cortex in epileptic and depressed patients is altered by VNS therapy. Changed activity in the ventromedial prefrontal and orbital cortices was also recorded [47]. These brain compartments are involved in mood regulation and are malfunctional in patients with severe depression [59].

Clinical Perspective

In a study in which 30 adult treatment-resistant, nonpsychotic patients with major depression received 9 months of VNS therapy, the therapy was associated with sustained relief of depression and enhanced functional status [60]. In a patient-level meta-analysis, adjunct VNS therapy with treatment as usual had greater response and remission rates than treatment as usual alone in chronic TRD patients [61]. Moreover, in an open trial with 235 patients suffering from non-psychotic major depressive disorder or bipolar disorder, VNS was well tolerated and most adverse events were reduced over time [62].

Further, in 11 patients with chronic TRD, VNS therapy resulted in a significant decrease in depression at the end of the study based on the HDRS, but some severe side-effects also occurred. For instance, one patient developed pulmonary emboli and two patients suffered from vocal cord palsies [63]. Another trial evaluated the antidepressant mechanism of VNS therapy and concluded that it interferes with the memory for negative information, and this may contribute to the antidepressant effect. This effect was determined using functional magnetic resonance imaging [64].

The long-term effects of VNS therapy on TRD were promising and associated with greater antidepressant activity in a 12-month trial [65, 66]. Likewise, in a multicenter, double-blind trial with 331 TRD patients, adjunct VNS at low (0.25 mA, 130 μs pulse width), medium (0.5–1.0 mA, 250 μs), and high (1.25–1.5 mA, 250 μs) currents were effective over 1 year [67].

In summary, VNS is the only FDA-approved therapy for chronic depression or for TRD patients who are resistant to pharmacological treatment. It interferes with the memory for negative information by modifying the concentrations of monoamines within the CNS. The therapy requires minor surgery which affects the patients' quality of life and makes the procedure a bit complicated and less favorable than the non-invasive therapies (tDCS, rTMS).

Deep Brain Stimulation

Mode of Action

DBS has been used to treat behavioral and psychiatric disorders [68]. It is a targeted approach involving stereotaxic placement of unilateral or bilateral electrodes in targeted brain regions. The electrodes are connected to a permanently implanted neurostimulator that electrically stimulates the targeted region. Although the mode of action is unclear, hypothetically, chronic high-frequency stimulation of 130–185 Hz reduces neuronal transmission in targeted regions by inactivating voltage-dependent ion channels [69, 70]. DBS can precisely target the brain regions involved in depression. It can modulate and restore the activity and function of those specific neuronal circuits [71–73].

Electrode Placement and Target Regions

Several studies targeting different areas for treating TRD have been reported: these include the nucleus accumbens (NAcc), ventral striatum (VS) [74, 75], inferior thalamic peduncle (ITP) [76], lateral habenula [77], and subgenual cingulate cortex (Cg25) [15, 78]. A single case study by Jimenez and colleagues reported the ITP as a competent target area. In this study, DBS of the ITP relieved the depressive symptoms in a patient suffering from TRD. Electrodes were implanted for stimulation of the ITP and its surrounding area, and continuous bipolar stimulation at 130 Hz, 0.45 ms, 2.5 V was delivered. This study reported significant potential of ITP DBS in treating recurrent unipolar depression [79].

In another study, Mayberg and colleagues targeted the Cg25 area as they previously found that it is metabolically overactive in patients with TRD. The results showed that chronic DBS in the subgenual cingulate white matter reversed the depression in four of six patients suffering from refractory depression. This study showed preliminary but promising results for the treatment of depression in patients otherwise resistant to pharmacotherapy and psychotherapy [15]. Lozano *et al.* in 2012 also reported a study targeting the Cg25 region. They showed that implantation of bilateral electrodes in the subcallosal cingulate gyrus in TRD patients led to a significant reduction in depression. DBS was delivered for 12 months to 21 patients implanted with bilateral Cg25 electrodes. Using HDRS-17, an average 50% reduction in depression score was recorded during the year. This reduction was coupled to significant enhancement in mood and improvement in the severity of depression. This study suggests Cg25 as an attractive target for implantation of DBS electrodes to treat depression [80]. Similarly, DBS of the NAcc region has antidepressant, antianhedonic, and antianxiety effects in TRD patients. Twelve months of treatment with bilateral DBS in the NAcc resulted in a 50% reduction of HDRS in five of 10 patients. Further, NAcc DBS reduced metabolism in the subgenual cingulate cortex, amygdala, and prefrontal regions, which might be the reason behind its antidepressant, antianhedonic, and antianxiety effects. This study highlights the NAcc as a potential target for the treatment of TRD through DBS [81].

Clinical Perspective

Kosel and colleagues have demonstrated the potential of DBS as a treatment option for TRD and movement disorders [71]. In a female suffering from recurrent depression and dyskinesia for 15 years, the DBS system was implanted bilaterally into the globus pallidus internus and stimulated for 18 months. The results showed that both the dyskinesia and the symptoms of depression improved. More specifically, the dyskinesia improved significantly in her limbs, but only slightly in the oromandibular area. Depression declined significantly over the period of treatment and showed a sustained improvement in the last 3 months of treatment.

Schalfer and colleagues in 2008 studied the effects of DBS on anhedonia, that is the inability to experience pleasure, a prominent symptom among depressed patients. In this study, DBS electrodes were implanted bilaterally in the NAcc in three patients suffering from extremely resistant depression. The NAcc was selected because it is a key structure in the reward system, and depression is responsible for impaired reward processing as seen in anhedonia. Immediate improvement in mood occurred when DBS was on, and no side-effects were observed in any of the patients [73]. Malone *et al.* investigated the effects of DBS of the ventral capsule/ventral striatum (VC/VS) on TRD. In 15 TRD patients, electrodes were

implanted bilaterally in the VC/VS region for continuous stimulation. Significant improvements in depressive symptoms occurred during stimulation. Response rates with the HDRS were 40% at 6 months of DBS and 53.3% at last follow-up. Also, remission rates were 20% at 6 months and 40% at last follow-up. This study suggests that DBS of the VC/VS is a promising strategy for treating refractory depression or TRD [82].

Kennedy and colleagues evaluated the long-term safety and efficacy of DBS for TRD by the extended follow-up of 20 TRD patients receiving DBS of Cg25. After an initial 12 months of DBS, the patients were tested annually for 3–6 years. An average response rate of 62.5%, 46.2%, and 75% using HDRS-17 was seen 1, 2, and 3 years after DBS implantation. Functional impairment related to social functioning and physical health improved progressively while no significant adverse effects of the DBS were recorded [70]. In a study by Moreines *et al.* the safety and efficacy of DBS of the subcallosal cingulate white matter were evaluated. Neuropsychological functions in TRD patients either remained stable or improved with acute and chronic DBS [16].

In summary, DBS involves surgical placement of electrodes unilaterally or bilaterally in targeted brain regions. Its exact mode of action is unclear but clinical studies have reported reduction in depression. However, few clinical data are available because the procedure is critical and requires brain surgery.

Physiological Impact of Neurostimulatory Techniques

Stress-related disorders result in a reduction of brain-derived neurotrophic factor (BDNF) in the hippocampus and cortex [83]. Under normal circumstances, BDNF is involved in the metabolism of noradrenaline and serotonin, neurotransmitters that play significant roles in synaptic connectivity [84]. Prolonged stress leads to depression and it has been reported that the prefrontal cortex is abnormal in depressed patients [85, 86]. These regions are involved in emotional development and cognitive abilities. Any incongruity may lead to mood disorders [87]. It has been shown that increasing the excitability of the left DLPFC or decreasing the excitability of the right DLFPC causes a significant reduction in depression [88].

Neurostimulation has physiological impact on these regions. Although little is known about the mechanism of action of these treatment modalities, it has been suggested that such stimulation is associated with changes in cortical regions. This is supported by the increased neurogenesis after ECT. The response is dose-dependent and can be recorded up to 40 days after ECT application [89, 90]. ECT, VNS, rTMS, and tDCS increase cortical inhibition in a similar manner. VNS, DBS, and ECT require surgery or anesthesia which makes them undesirable. tDCS has side-effects such as nausea, headache, and fatigue [91] but is non-invasive, and a number of studies have reported its safety and stability in depressed patients. A study on rTMS involving PET has shown the desired significant effects on prefrontal cortex with minimal or no adverse effects, and the stimulation protocol is entirely non-invasive. These make rTMS convincingly the future research topic for depression treatment [92, 93, 94, 95, 88].

Comparative Analysis of Safety–Efficacy of Neurostimulatory Techniques and Future Challenges

Initial studies have shown that ECT is even more effective than rTMS [96]. However, despite the greater efficacy of ECT, its use is limited due to the adverse cognitive effects as well as the use of anesthesia. To minimize these limitations, a few changes were made to achieve greater control over seizure induction. Magnetic seizure therapy (MST) has been developed as an alternative [97]. Both ECT and MST induce seizures but MST is more focused, and has greater antidepressant efficacy and better tolerability [4, 97]. Seizure therapy is very effective in TRD but side-effects such as frequent memory loss and cognitive effects have limited the use of ECT/MST as long-term treatment for most patients [98]. For long-term treatment, FDA-approved VNS can be used [99]. It is promising and superior to other antidepressant and has no adverse cognitive effects [100]. The therapy is advanced and popular, but its invasiveness is a limitation for most patients and clinicians [58].

More recently, neuroscientists have focused on non-invasive stimulation techniques. tDCS is effective in reducing the symptoms with minimal side-effects such as redness, itchiness, and headache [33, 34, 39]. However, a lot more research is required to make it a standard treatment. rTMS, another non-invasive procedure has recently attracted attention from clinicians and patients [101]. Unlike other procedures, it does not involve anesthesia, seizures, or invasive electrode placement to stimulate focal areas of cortex. When comparing rTMS with already existing depression treatments, some studies have demonstrated significant antidepressant effects of rTMS [46, 50, 102–104]. Unlike ECT, which is associated with irreversible cognitive effects [4, 100], the side-effects of rTMS are mild and last for a short period of time. Hence, rTMS is a potential therapy and can be used for effective depression treatment in the same way as psychotherapy or pharmacotherapy. However, the neuronal mechanisms involved need to be investigated [105, 106]. Moreover, despite the

promising results, larger scale trials must be carried out before commercialization of this treatment.

In conclusion, in this review we address the main aspects of clinical research on neuromodulatory techniques for treating depression. To date, no such therapy has been used for long-term treatment because of the lack of information regarding the neuronal processes that are altered as well as the adverse effects that might be a risk in response to brain stimulation therapies. Bringing such procedures to clinics would increase the risk of mortality and raise ethical and legal issues. However, the techniques requiring minimal invasive procedures and having mild side-effects such as rTMS must be subjected to long-term trials with detailed follow-ups to explore the response to therapy.

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