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REVIEW

Somatic Treatments for Mood Disorders

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Somatic treatments for mood disorders represent a class of interventions available either as a stand-alone option, or in combination with psychopharmacology and/or psychotherapy. Here, we review the currently available techniques, including those already in clinical use and those still under research. Techniques are grouped into the following categories: (1) seizure therapies, including electroconvulsive therapy and magnetic seizure therapy, (2) noninvasive techniques, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and cranial electric stimulation, (3) surgical approaches, including vagus nerve stimulation, epidural electrical stimulation, and deep brain stimulation, and (4) technologies on the horizon. Additionally, we discuss novel approaches to the optimization of each treatment, and new techniques that are under active investigation.

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INTRODUCTION

Often in the history of medicine, we find treatments that emerge as promising but that disappear as time and experience prove them not efficacious or with side effects and risks that no longer justify their use. Before the advent of pharmacotherapy, in the 1930s and 1940s, there was a time of great enthusiasm surrounding the new somatic treatments that were being developed for psychiatric disorders (Shorter and Healy, 2007). Insulin coma and malarial fever therapy, for example, were intensely studied and clinically used. Convulsive therapies (chemical and electrical) also initially appeared in that era. After the advent of antidepressant medications and other pharmacologic treatments, only electroconvulsive therapy (ECT) remained as a nonsurgical and nonpharmacological tool originating in those early years still in routine clinical use over seven decades later. Today we are experiencing a re-emergence of nonpharmacological somatic treatments, possibly because of the limitations of medications for a significant percentage of the patients (Rush *et al*, 2006), and because engineering advances have enabled previously unprecedented tools for noninvasive neuromodulation. Controlled trials and clinical experience will show which of these will survive and develop in a way that can help our patients in their struggle with severe mood disorders. Here, we review recent developments across multiple categories of somatic treatments in depression: (1) seizure therapies, (2) noninvasive techniques, (3) surgical approaches, and (4) technologies on the horizon.

The seizure therapies involve the induction of a seizure, under anesthesia, either through the direct application of electricity to the scalp (ECT), or via the indirect induction of electricity in the brain through the application of rapidly alternating magnetic fields to the scalp (magnetic seizure therapy (MST)). In these cases, the therapeutic mechanism is hypothesized to be related to the nature of the seizure induced, however, the electric field itself, and its parameters, are thought to contribute to clinical outcomes.

The noninvasive techniques involve the transcranial application of electrical (direct or alternating) or magnetic fields to the scalp at subconvulsive levels. These interventions include repetitive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and cranial electric stimulation (CES). Given the absence of an induced seizure, these interventions are hypothesized to act through plastic effects exerted by the repeated electrical stimulation of cortical circuits (in the case of alternating currents), or via potentiation of endogenous firing (in the case of direct currents).

The surgical approaches involve the implantation of devices to chronically stimulate brain structures directly

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TABLE 1 Comparison of Somatic Therapies for Mood Disorders

Somatic therapy	Surgical?	Anesthesia?	Convulsive?	Deep brain?	Contactless?	Focal?	Form of stimulation
CES—cranial electrical stimulation	N	N	N	N	N	N[a]	Electrical—AC
DBS—deep brain stimulation	Y	Y	N	Y	N	Y	Electrical—AC
ECS—epidural cortical stimulation	Y	Y	N	N	N	Y	Electrical—AC
ECT—electroconvulsive therapy	N	Y	Y	Y	N	N	Electrical—AC
FUS—focused ultrasound	N	N	N	Y	Y	Y	Ultrasound
LFMS—low field magnetic stimulation	N	N	N	Y	Y	N	Magnetic
MST—magnetic seizure therapy	N	Y	Y	N	Y	Y	Magnetic
NIR—near infrared light therapy	Y	Y	N	N	Y	Y	Optical
Optogenetic	Y	Y	N	Y	Y	Y	Optical
rTMS—repetitive transcranial magnetic stimulation	N	N	N	N[a]	Y	Y	Magnetic
tDCS—transcranial direct current stimulation	N	N	N	N[a]	N	N[a]	Electrical—DC
VNS—vagus nerve stimulation	Y	Y	N	Y[b]	N	N[b]	Electrical—AC

[a]Function of coil type or electrode array.
[b]Limited to vagal afferents.

(as in epidural electrical stimulation of lateral cortical regions, and deep brain stimulation (DBS) of deep targets) or indirectly (as in vagus nerve stimulation (VNS)). As with the transcranial application of alternating fields, surgical approaches are hypothesized to act through altering firing patterns (via inhibitory, facilitatory, or modulatory actions). Unlike the transcranial approaches, implanted approaches typically involve chronic, continuous stimulation while the transcranial approaches rely on the cumulative effects of intermittent application.

Table 1 summarizes the main aspects of the treatments/techniques discussed in this article.

SEIZURE THERAPIES

Electroconvulsive Therapy

ECT remains the most efficacious and rapidly acting antidepressant treatment available today for acute severe major depression (Husain *et al*, 2004) and is recommended by the APA for depression, bipolar disorder, and other conditions (Weiner *et al*, 2001). Its drawbacks include cognitive side effects (Prudic *et al*, 2000) and the significant risk of relapse after remission (Kellner *et al*, 2006). While ECT is our oldest somatic treatment for mood disorders, the procedure has evolved substantially over the years, with progressive improvements in its safety. The currently used technique consists of delivering biphasic electrical stimulation through electrodes placed on the scalp. Bilateral (fronto-temporal) positioning is the more common electrode positioning used in the United States and probably around the world (Chanpattana *et al*, 2010; Gangadhar and Thirthalli, 2010; Rosa *et al*, 2006), although it is usually related with more cognitive side effects than other electrode placements (Sackeim *et al*, 2007b).

The longstanding controversy about the adoption of unilateral electrode positioning received new light with a series of studies by the Columbia University group (Sackeim *et al*, 1987; Sackeim, 1991) showing right unilateral ECT to be dose-dependent (one has to go well above the minimum charge needed to induce a seizure, the seizure threshold, to have clinical benefits). This electrode placement has a more benign profile of cognitive side effects and is considered part of standard practice by the APA guidelines (Weiner *et al*, 2001). The equivalent efficacy of RUL compared with BL and bifrontal approaches was confirmed in the recently published multi-center trial by the Consortium for Research on ECT (Kellner *et al*, 2010). Alternative approaches to further improve the focality of ECT, and thereby reduce its cognitive side effects, include novel electrode configurations, like in focal electrically administered seizure therapy (FEAST) (Spellman *et al*, 2009), in which a large electrode is placed over the parietal region and a small one on the forehead and unidirectional stimulus is delivered. Antidepressant effects of FEAST are yet to be reported. Work on novel electrode placements for ECT may be informed by realistic head modeling of the field distributions in the brain, such that dosing paradigms could be designed to target brain regions implicated in depression while avoiding those associated with adverse side effects (Lee *et al*, 2010).

Recent approaches to further improve the risk–benefit ratio of ECT include the use of ultrabrief pulse width, which substantially reduces the cognitive side effects without loss of efficacy (Sackeim *et al*, 2008), although response may take longer and mid-course dose adjustments may be necessary to ensure efficacy (Loo *et al*, 2010a). The advantage of ultrabrief pulse ECT is thought to stem from its relatively more efficient pulse width, being closer to the chronaxis for neural depolarization of mammalian neurons (Nowak and Bullier, 1998; Sekirnjak *et al*, 2006).

New work on modeling of the electric field induced in the brain by various ECT configurations suggests that another parameter of the ECT stimulus that could be further optimized is the pulse amplitude (Deng *et al*, 2011). Conventional pulse amplitudes (0.8–0.9 A) are far in excess of the minimum needed for neuronal depolarization, and may expose the brain to unnecessarily highly field strengths (Peterchev *et al*, 2010b). Lowering pulse amplitude, and individualizing it, may be useful strategies for further optimization of an already highly effective treatment. The ability to induce seizures with substantially lower fields strengths has already been demonstrated (Rosa *et al*, 2010), and is not surprising given that seizure induction had already been shown to be feasible via magnetic stimulation, using induced electric fields far weaker than those seen with conventional ECT (see below for more on MST).

The recognition that individual parameters of the electrical stimulus pulse influences clinical outcomes in distinct ways calls for a re-examination of the methods we use to describe ECT dosage. The commonly used approach is to employ a summary metric, such as charge (expressed in millicoulombs), which collapses across all of the parameters. While convenient and in routine clinical use now, summary metrics like charge fail to reveal the individual contributions of specific parameters, such as pulse width and amplitude (Peterchev *et al*, 2010b). Innovative ways of more accurately defining the dosage of ECT, and of individualizing and determining in a safer way the seizure threshold (other than seizure titration), are being developed by our group.

Magnetic Seizure Therapy

The idea of inducing a therapeutic seizure using magnetic pulses was developed to try a more focal induction paradigm, avoiding medial temporal lobe regions, possibly related to adverse cognitive side effects (Lisanby *et al*, 2001). With repetitive TMS it is possible to target the cortical region to be stimulated in a way that is not possible with electrical stimulation, because of the lack of impedance of the scalp and skull to the passage of magnetic fields (Deng *et al*, 2011). The enhanced precision in targeting afforded by magnetic seizure induction offers the ability of focusing the electric field and also the site of seizure initiation in a more targeted fashion. In addition to its therapeutic potential, the ability to induce focal seizures from targeted brain regions opens the possibility of studying the mechanisms of action of seizure therapy in a way not previously possible (Rowny *et al*, 2009a). Specifically, in the case of conventional ECT both the volume of brain exposed to the electric field and involved in seizure expression are quite broad. In the case of MST, only superficial cortex is exposed to the induced fields, while the seizure may secondarily generalize to broader brain regions (Rowny *et al*, 2009b). Decoupling field exposure from seizure involvement opens the possibility to examine independently the contributions of these two aspects of seizure therapy (the seizure inducing field and the seizure itself).

As in ECT, MST requires muscle relaxation and general anesthesia, although the anesthetic dosage requirements for MST were lower in one study comparing it with ECT (White *et al*, 2006). The translational work was developed by our group using non-human primates as a model. This work with animals started in 1998 and showed it to be safe (Dwork *et al*, 2004, 2009) and with a more benign cognitive side effect profile (Lisanby *et al*, 2003b). The first human received MST treatment in 2000 (Lisanby *et al*, 2003a) and soon comparisons with ECT in within-subject (Lisanby *et al*, 2003a) and between-subject (White *et al*, 2006) trials followed. Trials from Germany (Kayser *et al*, 2009, 2010) and a case report from Australia (Hoy and Fitzgerald, 2010) have reported comparable efficacy of MST and ECT. A two-site controlled double-blind trial from our group is underway.

Currently, MST requires modified devices that limit its use in clinical practice, but novel parameter combinations and coils are being evaluated to optimize this technique and make it simpler and more accessible to the practitioner. These approaches are being explored to maintain efficacy while having a much better cognitive side effect profile than the gold standard ECT.

NONINVASIVE TECHNIQUES

Repetitive TMS

Repetitive TMS is now a very well-known brain stimulation technique that modulates cortical activity with several different uses ranging from neurophysiologic studies to the treatment of depression (George and Aston-Jones, 2010). Its basic principles are reviewed elsewhere (Wagner *et al*, 2007) but consist basically in a device that generates a pulsating electric current that passes through a coil creating an alternating magnetic field that depolarizes the underlying brain tissue. It is being tested for the treatment of a range of neurological and psychiatric disorders, but at present is only approved in the United States for the treatment of unipolar depression in adults that has failed to respond to a single medication trial (O'Reardon *et al*, 2007). Evidence supports that the likelihood of responding to TMS is better in those individuals who have failed to respond to a single medication trial in the current episode (Lisanby *et al*, 2009).

While other mood disorders have been investigated, unipolar depression is the most studied condition with TMS at present. According to the World Federation of Societies of Biological Psychiatry's guidelines (Schlaepfer *et al*, 2010) 'there is sufficient class I evidence of acute efficacy for TMS in depression in medication-free unipolar depressed patients. The large body of evidence from single site small sample trials suggests that it may also be useful clinically in moderately treatment-resistant patients, either alone or used adjunctively with medications. We thus recommend

that psychiatrists consider using TMS in non-psychotic adults with major depression. Typically patients will have tried and failed at least one attempt at medication therapy, although this is not required. There are only limited data about using it in a maintenance fashion after acute response. As TMS efficacy data are continuing to emerge, the choice of stimulation parameters including frequency, laterality, intensity, and duration of treatment will need to be determined by a psychiatrist familiar with the relevant and recent TMS literature'.

A recent meta-analysis showed an overall weighted mean effect size for treatment of 0.39 (95% confidence interval 0.25–0.54, $z = 6.52$, $p < 0.0001$) (Schutter, 2009).

The effect size for the FDA-approved protocol with TMS as monotherapy for one failed trial is significant (0.9). For more resistant patients it is still modest and there remains great potential for identifying response predictors and modifying the treatment to enhance potency. Evidence for this can already be seen in recent studies that explore: (i) optimizing TMS pulse and train parameters, (ii) deeper coils, and (iii) combination therapy paradigms, coupling TMS with psychotherapy and/or pharmacotherapy.

Low-frequency stimulation and laterality. Low-frequency stimulation (1 Hz) of the right DLPFC has also been extensively studied (Stern *et al*, 2007). Lower frequencies tend to have a better safety profile for accidental seizure induction (Rossi *et al*, 2009). Its use for the treatment of mood disorders is based on the interhemispheric disequilibrium theory in depression (Herrington *et al*, 2010).

Results so far suggest an antidepressant effect as compared with medication (Bares *et al*, 2009), although, as with high frequency, it seems inferior to ECT (Hansen *et al*, 2011). There are data suggesting a similar efficacy of high frequency applied to the left side or low frequency applied to the right side (Fitzgerald *et al*, 2009a).

A study of patients that did not improve with low frequency to the right DLPFC TMS and subsequently received high frequency (5 or 10 Hz) to the left DLPFC showed a significant improvement of both high frequencies (Fitzgerald *et al*, 2009b).

Another relatively unexplored approach it the bilateral stimulation that can be done sequentially (Conca *et al*, 2002; Fitzgerald *et al*, 2006) or simultaneously (Loo *et al*, 2003).

Optimizing TMS pulse and train parameters. Optimization of TMS parameters, for example, including theta burst paradigms (Chistyakov *et al*, 2010) and bilateral stimulation (Pallanti *et al*, 2010) are under intense investigation and hold some promise in enhancing the potency of the treatment. Some evidence suggests that increasing the number of pulses, and accelerating their application, may speed response (Hadley *et al*, 2011; Holtzheimer *et al*, 2010).

Another approach is to optimize the characteristics of the TMS pulse itself. Although ECT today uses brief rectangular pulses, conventional TMS stimulators employ dampened cosine waveforms. As seen in the case of ECT, the shape of the pulse affects physiological and clinical outcomes. This observation motivated the move from sine wave ECT to brief pulse ECT, and along with that transition came a dramatic lowering of side effects and increased efficiency in seizure induction. Conventional TMS devices, however, only allow very limited control over pulse shape. Recent engineering advances in controllable pulse TMS devices (cTMS), however, have now enabled the production of TMS pulses with user controlled characteristics such as pulse width, pulse shape, and directionality (Peterchev *et al*, 2010a). This device also offers the possibility of possibility of repetitive high-frequency unidirectional stimuli, which studies suggest may be more efficient in inducing plasticity (Sommer *et al*, 2006).

Deeper coils. New coils are being developed, like the H-coils (Harel *et al*, 2011) and other designs (Deng *et al*, 2011), which have a deeper penetration of the magnetic fields. Given the focality/depth trade off, these coils also stimulated a larger volume of brain. Although it is possible (Levkovitz *et al*, 2009), there are no data yet to suggest that by virtue of the increased volume or increased depth these coils will have more potent effects risk of accidental seizures also seems to be increased.

Combination therapy—pharmacological enhancement. While most of the trials on TMS in the treatment of depression and other conditions used TMS as an add-on to stable pharmacotherapeutic treatments, the potential interaction and synergy between TMS and pharmacotherapy has rarely been the topic of direct study. Clinical trials typically describe the ancillary medication treatments, and ensure that the dosage have been stable before the TMS application, so that observed clinical effects could be safety attributable to the TMS and not delayed onset of action of the concomitant medication. Although this is reasonable, it fails to address the possibility that the action of TMS could be altered in the presence of receptor agonism or antagonism. Should such interactions exist, they may not only be a source of noise to avoid and control for, but may be a target and potential avenue for optimization.

Effects of pharmacological agents on responses to TMS have been documented using a variety of measures including electromyography (for a review, see Paulus *et al*, 2008) and TMS/fMRI interleaving (Li *et al*, 2010). This should not be surprising because TMS induces release of endogenous neurotransmitters, which in turn act at pre and post-synaptic receptors, and should receptor function be subjected to agonism or antagonism at the time of TMS, altered effects of the TMS would be expected. Furthermore, neuronal depolarization induced by TMS is itself an event mediated by ion channel function, thus ion channel agents would be expected to affect this action.

Although the action of a single TMS pulse can be altered by pharmacology, the action of a train of pulses may likewise be impacted. On the basis of the hypothesis that lasting effects of trains of TMS may come about through mechanisms of plasticity, then pharmacological agents affecting plasticity may be useful targets to enhance the action of TMS. Effects of D-cycloserine on plasticity induced

by theta burst stimulation have already been reported (Teo *et al*, 2007).

Combination therapy—cognitive/behavioral enhancement. As with the relative inattention to concomitant medication, concomitant psychotherapy has rarely been the focus of study in TMS trials and there is no certainty on how many patients in these trials were actually in ongoing psychotherapy. Is this merely a time-saver, or could simultaneous TMS and psychotherapy have a synergistic effect? Evidence in the neurorehabilitation literature already suggests that TMS can prime response to motor training and possibly aide in motor recovery post stroke when coupling cortical TMS with motor training. It has been proposed that the same could be true of cognitive rehabilitation (Miniussi and Rossini, 2011). Rather than physical therapy, the conjoint administration of a cognitive/behavioral therapy during targeted induction of plasticity via TMS could theoretically enhance action, as has been recently reported in a proof of concept study in post-traumatic stress disorder (Osuch *et al*, 2009). The extension of this concept to depression and cognitive/behavioral approaches to mood disorders is at the early stages of exploration (Vedeniapin *et al*, 2010).

Transcranial Direct Current Stimulation

tDCS (also called 'polarization') has some important advantages over its counterparts: it is inexpensive, it is relatively safe (although case reports of skin lesions or burns were reported—(Palm *et al*, 2008)), it is easy to use, and has few side effects (slight tingling under the electrodes, headache, fatigue, and nausea are the most common). It consists of using two sponge electrodes soaked with saline solution that are placed on the head (Figure 1). It uses extremely low currents (1–2 mA) that are in the range of those used in portable flashlights. The procedure entails a unidirectional constant (as opposed to pulses of stimulation used in all other forms of brain stimulation) flux of low-intensity current from one electrode to the other (the first one is the anode and the second is the cathode). Early animal work showed that cortex activity could be changed according to the region being stimulated and if it was under the cathode (where there would be reduced activity because of hyperpolarization) or the anode (where there would be increased activity because of sub threshold membrane depolarization) (Scholfield, 1990).

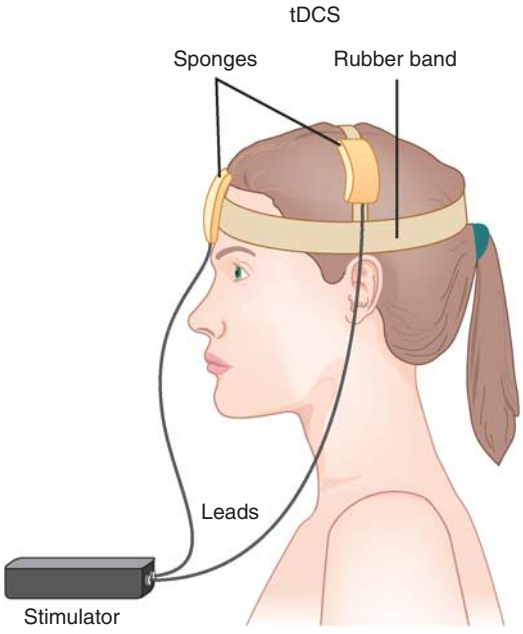

Figure 1. Transcranial direct current stimulation (tDCS).

It was demonstrated in humans that the after-effects of tDCS depend on modifications of NMDA receptor-efficacy. The after-effects of tDCS are blocked by the NMDA receptor antagonist dextrometorphan, and prolonged by the partial NMDA receptor-agonist D-cycloserine (Liebetanz *et al*, 2002; Nitsche *et al*, 2003, 2004). This tDCS polarity-dependent alteration of NMDA receptor function seems to be initiated by the respective membrane potential shift and probably by the accompanying cortical activity modification, because it is prevented by the sodium channel blocker carbamazepine. Intraneuronal calcium concentration also contributes, because calcium channel antagonists eliminate the excitability-enhancing after-effects of anodal tDCS (Nitsche *et al*, 2003).

There were early reports of neuromodulation by tDCS (Bindman *et al*, 1964; Creutzfeldt *et al*, 1962; Purpura and McMurtry, 1965) that suggested a possible role as a therapeutic tool. There were some open pilot studies and clinical observations showing some effects (eg, Baker, 1970; Nias and Shapiro, 1974; Ramsay and Schlagenhauf, 1966) but those were not confirmed in a controlled trial (Arfai *et al*, 1970) and no further studies were pursued at that time.

Recently, tDCS was rediscovered as a possible tool for the treatment of depression, possibly based on the success obtained by TMS in modulating prefrontal cortex excitability and showing clinical efficacy.

The first randomized, double-blinded, sham-controlled study, the effect of tDCS on depression was published as a letter and evaluated a small sample of 10 patients with first episode major depression without antidepressant medication treatment (Fregni *et al*, 2006). After five sessions with 1 mA for 20 min/day, an impressive result was seen with four out of five patients benefiting from active treatment and none in the sham group and the mean reduction in the depression scores were between 60 and 70%, relative to baseline values.

The same group tried the technique with a higher intensity (2 mA) in a larger sample ($n = 40$) randomized to three different groups: anodal stimulation of the left dorsolateral prefrontal cortex ($n = 21$), anodal stimulation of the occipital cortex ($n = 9$), or sham stimulation ($n = 10$). The number of responders was significantly larger in the prefrontal stimulation group (8 *vs* 2 *vs* 0, respectively). Benefits were reported to have lasted at least 1 month after the end of the trial (Boggio *et al*, 2008). However, an

independent group (Loo *et al*, 2010b) did not replicate these findings studying 40 depressed patients for 5 days with 1 mA current strength. tDCS was also tried in bipolar depressed patients in an open study with good effects (Brunoni *et al*, 2011).

tDCS clearly has effects on cortical excitability but with relation to treating mood disorders, although promising, published data are still not consistent or conclusive and there is a need of more sustainable data from well-controlled studies. There are also opportunities to refine the technique to improve its focality through novel electrode designs (Bikson *et al*, 2008; Minhas *et al*, 2010).

Cranial Electrical Stimulation

CES also called transcranial electrostimulation (Boutros and Krupitsky, 1998) is perhaps the oldest way of stimulating the brain noninvasively (Figure 2). It includes a variety of different techniques that have in common the use of low-level alternating electrical (low current amplitude) signals applied to the scalp or earlobes (Klawansky *et al*, 1995). Although tDCS can be considered a form of CES, it was treated separately because there are data suggesting that its effects are quite different in the brain physiological effects (Stagg and Nitsche, 2011). There is also a 'mixed' form of CES in which constant electric current (similar to tDCS) is combined with pulses of alternating current. This form of stimulation was used in Russia especially for narcoanalgesia (Boutros and Krupitsky, 1998).

It has been in wide clinical use in Europe since 1950 and in the United States since the 1960s, and became FDA sanctioned for the treatment of depression, anxiety, and insomnia in 1978. CES was never subjected to the level of regulatory review now required for new technologies because it was 'grandfather-ed' based on a device that predated the current FDA regulations. The device is being marketed and sold for these conditions; however, there is a relative lack of controlled clinical trials supporting its efficacy. Despite the wide use of, no well-controlled trials of its efficacy have been done, in part because of improper blinding of the operator. It has also been proposed for the treatment of pain, headaches, fibromyalgia, smoke cessation, and opiate withdrawal (Boutros and Krupitsky, 1998; Bystritsky *et al*, 2008).

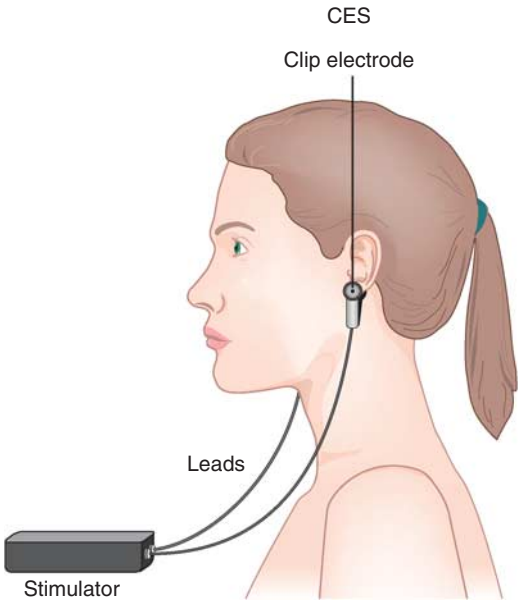

Figure 2. Cranial electric stimulation (CES).

The output parameters of the commercially available CES devices vary widely. The Fisher–Wallace Cranial Stimulator (model SBL500-B), which became FDA sanctioned for the treatment of anxiety, insomnia, and depression in 1990 (510 K approval), uses 0.5–2 mA alternating currents administered as rectangular pulses modulated in three frequencies (15, 500, and 15 000 Hz) with alternating polarity at 7.5 Hz. This is the same device as the Liss Cranial Stimulator (model SBL201-M), a class III device, which has been marketed since the 1970s for treatment of depression, anxiety and insomnia. The Alpha–Stim Stress Control System generates bipolar, asymmetric, rectangular pulses with a frequency of 0.5, 1.5, or 100 Hz and a current amplitude that can be adjusted continuously to provide between 10 and 600 μA. In addition to these, there are several other available manufacturers with a range of electrode placements (eg, cathodes over the orbits and anodes over the mastoids; cathodes over frontal areas and anodes over occipital regions, and so on). The waveform parameters of the devices are wide ranging with currents from 0.1 to 4 mA, frequencies from 0.5 to 167 000 Hz, pulse width from 0.00003 to 1 s, and duration of application from 5 min to 3 consecutive months. The lack of standardization in practice makes drawing conclusions regarding its clinical potential in mood disorders fraught.

Headache and nausea are the most common side effects described, followed by skin irritation (Kirsch and Smith, 2000).

The mechanism of action of CES is unclear. There is evidence that weak cranial currents (0.26 mA, 0.75 Hz) applied during sleep can affect memory and brain oscillations (Kirov *et al*, 2009; Marshall *et al*, 2006). Furthermore, weak electric fields ($\sim$ 0.5 V/m = $\sim$ 2 mA) can affect neural function (Deans *et al*, 2007; Radman *et al*, 2007). Alterations in neurotransmitters and hormones have been described (Ferdjallah *et al*, 1996), including increased thyroxine production (Jarzembski, 1985). Also, increase in platelet MAO-B activity and plasma GABA concentrations were reported (Klawansky *et al*, 1995). Finally, changes in EEG readings during and after stimulation have been described, especially slowing of alpha waves (Jarzembski, 1985). However, there is a lack of significant work in animal models, and there remains the possibility that the effects may be at least in part mediated via cranial nerve stimulation rather than direct brain stimulation.

CES has been used in a variety of disorders, but especially anxiety, headaches, and insomnia (Klawansky *et al*, 1995). There is no controlled trial on its use for major depression or other affective disorders, although some benefit was

reported in patients with comorbid alcoholism and depression (Krupitsky *et al*, 1991), and it has been reported to have anxiolytic effects in an open-label trial of 12 patients (Bystritsky *et al*, 2008). Little consistency exists in the literature surrounding the specific parameters and electrode placements used, and there are no controlled trials on its use, making it difficult to draw conclusions about its potential value. In their meta-analysis, Klawansky *et al* (1995) concluded insufficient controlled evidence existed and that available evidence was probably not adequately blinded.

SURGICAL APPROACHES

Vagus Nerve Stimulation

The use of VNS for chronic or recurrent depression (uni or bipolar) was approved in 2005 by the FDA, for patients that have failed to respond to at least four antidepressant trials (Figure 3).

Stimulating the vagus nerve to treat mood disorders was supported by several lines of evidence. Beneficial effects on mood were seen in epileptic patients that used VNS (Elger *et al*, 2000; Harden *et al*, 2000). Also, VNS is successfully used for epilepsy and there is evidence of beneficial effects of anticonvulsants as mood stabilizers and antidepressants (Goodwin and Jamison, 2007). In addition, ECT is also hypothesized to act, in part, through its anticonvulsant properties (Sackeim, 1999). Effects on different neurotransmitters (Ben-Menachem *et al*, 1995) and imaging findings (Henry *et al*, 1998) also favor this indication of VNS.

The mechanism of action is not fully understood, but stimulation is intended to enter the brain through the primary afferent pathways of the nerve that connect to the nucleus tractus solitarius and from it to many brain areas, including the forebrain, largely through the parabrachial nucleus and the locus ceruleus (Crawley, 1985; Frisina *et al*, 2009; Momose-Sato and Sato, 2011). VNS does, for instance, enhance cortical inhibition and affect hippocampal plasticity (Zuo *et al*, 2007). Interestingly, ECT has also been demonstrated to increase cortical inhibition (Bajbouj *et al*, 2006).

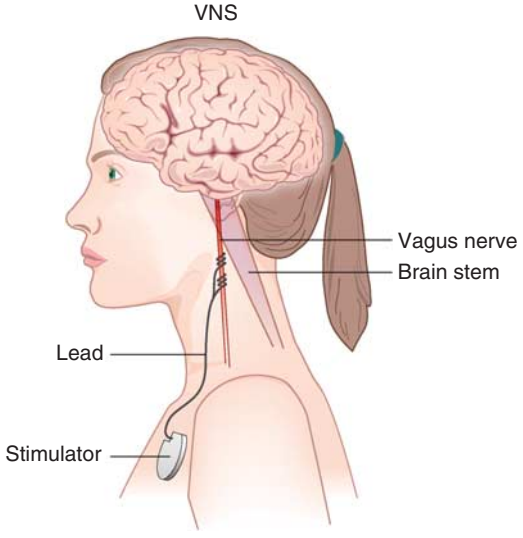

Figure 3. Vagus nerve stimulation (VNS).

Side effects include hoarseness, cough, and neck or jaw pain.

The first VNS implant for depression was performed in July 1998 at the Medical University of South Carolina in Charleston (Rush *et al*, 2000), a decade after the first human epilepsy implant (Penry and Dean, 1990). The left vagus is used based on the knowledge that right vagus is closely associated with the cardiac atria and the left vagus with cardiac ventricular function. This is supported by the lack of cardiac effects of left VNS although stimulation parameters could also be a possible explanation. The first pilot study included 30 patients with resistant major depression (uni and bipolar) and VNS showed response in 40% after 10 weeks, an encouraging result given the degree of resistance of the sample.

The only published double-blind, randomized, controlled study (Rush *et al*, 2005a) studied 235 outpatients with depression (unipolar, $n = 210$ and bipolar, $n = 25$) and the effects of acute (10 weeks) treatment with VNS. The groups did not significantly differ in response rates (active = 15.2% and sham = 10.0%). This well-controlled study found no supporting evidence for acute antidepressant benefits of VNS. A parallel but not randomized group receiving 'treatment as usual' was followed for 12 months and compared in an open-label fashion with the VNS group (George *et al*, 2005). After 1 year, response rate for the VNS group was 27 and 13% for the treatment as usual group (statistically significant). The latter study was the basis for FDA approval of VNS for resistant depression (Rush *et al*, 2005b).

There are some published studies dealing with long-term follow-up on the benefits of VNS. Schlaepfer *et al* (2008b), in an open study, report that after a remission and response rate of 37 and 17% in the first 3 months, a sustained response (no relapse in 1 year) of 44% was observed. Nahas *et al* (2005) report a response rate of 42% (25/59) after 2 years. Also, Sackeim *et al* (2007a) analyzed the durability of response to VNS. In a pilot and a pivotal study, they classified the outcomes as early responders (50% reduction in symptom scores within 3 months), later responders (same reduction within 12 months) and non-responders. In the pilot study, 72.2% and 61.1% of early responders ($n = 18$) were responders at 12 and 24 months, respectively; 78.8% of late responders ($n = 14$) were responders at 24 months. In the pivotal trial, of early responders ($n = 30$), 63.3% and 76.7% maintained response at 12 and 24 months, respectively; of late responders ($n = 40$), 65.0% maintained response at 24 months.

A recent naturalistic study (Bajbouj *et al*, 2010) assessed the efficacy and the safety of VNS in 74 European patients with therapy-resistant major depressive disorder. After 2 years, response rate was 53.1% (26/49) and remission was 38.9% (19/49). Important to note is that two patients

committed suicide during the study; no other deaths were reported. The results of this 2-year open-label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with treatment-resistant depression.

All these results should be contrasted with naturalistic outcomes reported in the literature for patients with treatment-resistant depression receiving treatment as usual which. In a naturalistic outcome, Dunner *et al* (2006) found a response rate of 11% (13/112) in 12 months and 18% (19/103) in 24 months. Only 5 out of the 13 responders at 12 months were still responders at 24 months. A similar thing was observed with remission, being 3.6% (4/112) at 12 months and 7.8% (8/103) at 24 months. Similarly, only one of the four remitters remained a remitter at 24 months.

For bipolar disorder, a pilot prospective, open-label, study of nine rapid-cycling bipolar patients (excluded from larger trials) found evidence of benefit over 12 months (Marangell *et al*, 2008).

Deep Brain Stimulation

Direct electrical stimulation of the brain was tried in the 1960s (Heath, 1963), but modern DBS started in the 1980s with works on movement disorders (Leiphart and Valone, 2010) (Figure 4).

DBS, although more invasive than the other techniques, is arguably the most focal way of treating mood disorders available (Butson and McIntyre, 2006). An area in the millimeter range is usually used for stimulation. Different brain regions have been tried, some based on beneficial effects on depression while treating other primary disorder (eg, Parkinson or obsessive–compulsive disorder), and some based on hypothetical pathways related to mood symptoms. Animal work on DBS is largely focused on exploring the mechanisms of action (Hamani *et al*, 2010). A number of regions have been proposed with DBS to treat depression, with some degree of overlap in the circuits that they modulate (for a review, see Hauptman *et al*, 2008).

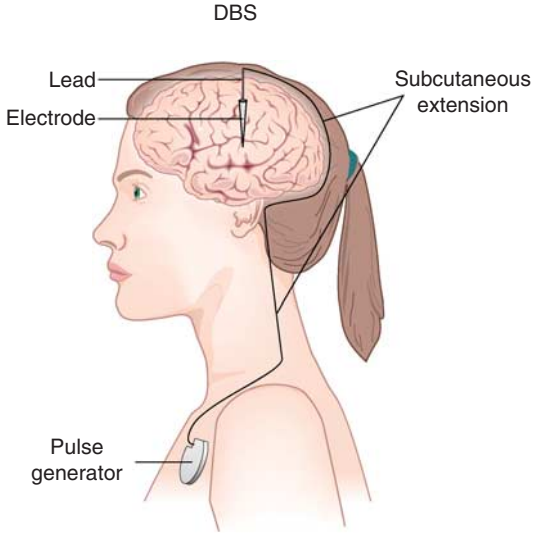

Figure 4. Deep brain stimulation (DBS).

Most of the studies used stimulation of the subgenual cingulate, the ventral anterior internal capsule (ventral capsule/ventral striatum (VC/VS)) and the nucleus accumbens. There are also case reports of stimulation of the inferior thalamic peduncle and lateral habenula (Figure 5). These will be briefly discussed.

The subgenual cingulate cortex. The subgenual cingulate cortex (more specifically, the white matter of Brodmann's area 25). Is a region connected to the nucleus accumbens and limbic cortical loop. It is also connected to orbitofrontal, dorsomedial prefrontal, dorsolateral prefrontal, and dorsal cingulate cortices. Increases in blood flow are seen in this area during induced sadness (Vago *et al*, 2011). Early studies have implicated the subgenual cingulate cortex (Cg25) in acute sadness and antidepressant effects (Mayberg *et al*, 1999; Seminowicz *et al*, 2004) and a decrease in Cg25 activity has been associated with immediate clinical response to a number of antidepressant treatments including serotonin reuptake inhibitors (Mayberg *et al*, 2000), ECT (Nobler *et al*, 2001), TMS (Mottaghy *et al*, 2002), and ablative surgery (Dougherty *et al*, 2003). DBS has been thought as an instrument to functionally inhibit the activity in this region. Mayberg *et al* (2005), implanted DBS electrodes in the bilateral subgenual cingulate cortex in six patients with treatment-resistant depression. Chronic stimulation at 130 Hz resulted in a significant response and remission of depression in four of the six patients at 6 months; in the two remaining patients, one experienced a significant reduction in depression over the first 4 months that fluctuated over time and remained submaximal, and the other patient had no response. A subsequent extension report came from this group with 20 implanted patients. In all, 12/20 patients had a reduction of at least 50% in the 17-item Hamilton Rating Scale for Depression (HRSD-17) score and 7 patients met criteria for remission (HRSD-17$\leqslant$7). PET studies of some responders showed widespread changes in cortical and limbic metabolic activity, including increased activity in lateral prefrontal cortex and Cg25WM, but a reduction in Cg25 grey matter (Lozano *et al*, 2008).

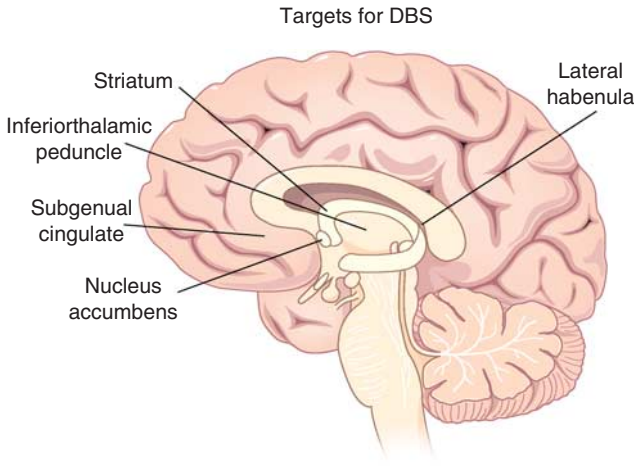

Figure 5. Targets for deep brain stimulation (DBS).

This group recently published an extended follow-up of these patients. After an initial 12-month study of DBS, patients were seen annually and at a last follow-up visit. The average response rates 1, 2, and 3 years after DBS implantation were 62.5%, 46.2%, and 75%, respectively. At the last follow-up visit (range = 3–6 years), the average response rate was 64.3%, two patients died by suicide during depressive relapses (Kennedy *et al*, 2011).

Ventral anterior internal capsule. A region that has been a DBS target for treating depression is the same used for the treatment of OCD patients (Nuttin *et al*, 1999) that got better from depressive symptoms, the ventral anterior internal capsule (VC/VS). In this case, the nucleus accumbens is not the target. Malone *et al* (2009) attempted bilateral VC/VS DBS in 15 patients with treatment-resistant depression. They found that the proportion of patients with at least 50% reduction in HRSD-24 was 47% at 3 months, 40% at 6 months, and 53% at last follow-up, while remission rates with HRSD-24 were 20% at 6 months and 40% at last follow-up.

Nucleus accumbens. The nucleus accumbens/VS are regions that have long been regarded as part of the circuitry associated with depression and drug addiction (Monk *et al*, 2008; Thomas *et al*, 2000). The first case report of DBS implant in this region was for a patient with OCD and major depression. Stimulation of the bilateral NAC and ventral caudate at 130 Hz resulted in significant relief from depression and anxiety, with a remission at 6 months (Aouizerate *et al*, 2004). Subsequently, three patients had bilateral implantation (Schlaepfer *et al*, 2008a) with improvement in anhedonia and depression. In addition to other effects, there was an increases in the metabolism of dorsolateral and dorsomedial prefrontal cortices. Metabolism of the ventral and ventrolateral medial prefrontal cortex, shown in previous studies to be hyperactive in depression, was decreased. In an extension of this study (Bewernick *et al*, 2010), 10 patients with refractory depression received bilateral stimulation to the nucleus accumbens, 5 (50%) of which had a response associated also with a reduction in anxiety after 12 months.

Inferior thalamic peduncle. The inferior thalamic peduncle, is a bundle of fibers connecting the thalamus to the orbitofrontal cortex and aids the inhibition of input of irrelevant stimuli, providing selective attention. Velasco *et al* (2005) identified this region as a potential target to treat depression. This region, along with the orbitofrontal cortex is hyperactive in depression and reverts with pharmacological treatment. The first case treated with DBS implanted in this site was a 49-year-old woman with severe TRD and multiple hospitalizations (Jimenez *et al*, 2005) that improved with the treatment. Patient maintained remission scores during 8 months of active stimulation without antidepressant medication. When stimulation was turned off, fluctuations on depression scores were observed and disappeared when the device was again turned on by month 20. Borderline personality disorder and bulimia were also present and may complicate generalization of conclusions.

Lateral habenula. Finally, the last region tested so far as a DBS target for depression is the lateral habenula (Sartorius and Henn, 2007), a region implicated in reward processing and emotional decision making. This region is located in the diencephalon, behind the thalamus and consists of a group of nerve cells neighboring the pineal gland. It is traditionally divided in a lateral part (limbic) and a medial part (motor). The putative use of this region is based on animal work showing that when the lateral habenula is inhibited by electrical stimulation in rats, norepinephrine in the hippocampus/prefrontal cortex increases, as does serotonin in the striatal circuits. Reduced depressive behaviors were observed in an animal model following lesions of the lateral habenula, and this effect was thought to be mediated through increased dorsal raphe serotonin (Yang *et al*, 2008). On the other hand, DBS of the lateral habenula has been reported to attenuate positive reward-associated reinforcement. The first case report reached remission after about 20 weeks of stimulation and had a relapse a couple of days after the DBS unit was switched to off because of an incidental bicycle accident. The patient achieved remission again after 12 weeks of high voltage (10.5 V) stimulation (Sartorius *et al*, 2010). Intracranial hemorrhage is the most common surgical complication (Binder *et al*, 2003). It has been reported to be around 1–2% in large series of patients with implants for the treatment of Parkinson. Hemorrhage can be small and asymptomatic or can result in severe neurological deficit. No severe hemorrhagic complications were published so far for patients treated DBS for depression (Blomstedt *et al*, 2011). Side effects such as depression and suicide ideation have been reported, but usually associated with misplacement of electrodes (Berney *et al*, 2002; Bezerra *et al*, 1999).

Side effects/complications in depressive implanted patients included: dysphagia, swollen eye, pain, erythema, anxiety increase, sweating, disequilibrium, hypomania, paresthesia, agitation, headache, lead dislodgement, psychotic symptoms, muscle cramps, affection of vision (with nucleus accumbens stimulation); seizure (one case in 20 implanted), infections, perioperative pain, worsening of mood (with subgenual cingulate cortex stimulation); on hypomanic episode (out of 15 implanted with VC/VS stimulation). No complications were reported in the cases with DBS in the inferior thalamic peduncle or lateral habenula (Blomstedt *et al*, 2011).

The most appropriate target, optimal stimulation parameters, and long-term effects and efficacy remain uncertain. What is clear is that large-scale trials must be conducted to adequately assess the safety and efficacy of stimulation for depression. Data from such studies will provide information regarding optimal target localization, stimulation parameters, and adverse effects. Also important will be the illumination of the mechanism of action. Although DBS is often thought of as a 'virtual lesion', recent evidence demonstrates that the effects of DBS can be subtler and may modulate information flow rather than halt it. For example, studies in Parkinson's disease indicate that DBS of the

subthalamic nucleus appears to exert its therapeutic action by suppressing pathological oscillations in a specific frequency range (Eusebio *et al*, 2011). According to McIntyre *et al* (2004), the general hypothesis to explain the mechanism of high-frequency DBS stimulation are depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathological network activity. Using the results from functional imaging, neurochemistry, neural recording, and neural modeling experiments, these investigators suggest that stimulation-induced modulation of pathological network activity represents the most likely mechanism of DBS. In addition, computational modeling of frequency-specific action of DBS suggests it may act by regularizing pathological patterns of activity within thalamic/basal ganglia circuits (Dorval *et al*, 2009). While oscillatory abnormalities in depression are incompletely understood, such modeling work may ultimately inform the appropriate targets and dosing paradigms for application in mood disorders.

Epidural Cortical Stimulation

Although DBS has the drawback of requiring invasive electrode implantation, chronic electrical stimulation of superficial targets can be achieved less invasively via implanted epidural stimulators, a technology that has been used in pain treatment, stroke recovery, and movement disorders. A multi-center industry sponsored trial attempted left sided prefrontal cortical stimulation and reported modest success (Dougherty *et al*, 2008). One group did an open-label case series of five patients implanted with bilateral epidural prefrontal cortical stimulation (targeting the anterior frontal poles and midlateral prefrontal cortex) and found on average 55% improvement in depression scores (Nahas *et al*, 2010). While work with this technology is at an early stage, its lower invasiveness relative to DBS merits further study.

Ablative Techniques

Surgical ablative approaches were tried in the past to treat neurological and psychiatric disorders and have undergone a renaissance in recent years. Ablations guided some of the DBS electrode positioning for movement disorders (Benabid *et al*, 1991) and provided the rationale for some DBS approaches for psychiatric disorders (Leiphart and Valone, 2010).

The advances that were made in neurosurgical techniques, in particular the development of stereotactic operation, have dramatically improved the accuracy, making it possible to place tiny lesions with high precision. These lesions have minimal side effects in individual brain regions, their substructures or fiber tracts of the projection pathways (Juckel *et al*, 2009). Techniques relevant to the treatment of depression are cingulotomy and limbic leucotomy.

Cingulotomy uses thermocoagulation to perform a bilateral lesion (about 1 cm wide and extend dorsally 2 cm into the callosum) of the cingulum. The aim is to interrupt the thalamo–fronto–cortical pathways and thus relieve anxiety (Cosgrove and Rauch, 2003). Limbic leucotomy combines the cingulotomy with subcaudate tractotomy (lesion of the white substance) anterior to the head of the caudate nucleus. It destroys fiber strands between the prefrontal cortex and the limbic system (connections between the prefrontal cortex and the hippocampus, amygdala, thalamus, and hypothalamus) and leads to a secondary degeneration of the dorsomedial thalamic nucleus.

Therapeutic effects usually take long (about 1 year) to manifest after the surgery. The most common side effect is spontaneous seizures (1–2% of patients). It should be kept in mind that these techniques have the characteristic of being irreversible and more studies are needed define its place in the clinical setting.

TECHNOLOGIES ON THE HORIZON

An ever-broadening array of approaches are beginning to be explored, as novel technologies become available and older technologies are rediscovered or repurposed. Examples on the horizon include focused ultrasound (FUS), near infrared light therapy (NIR), low field magnetic stimulation (LFMS), and optogenetic stimulation.

Focused Ultrasound

In addition to being an imaging modality, ultrasound can be used, contingent upon the parameters and apparatus employed, in a focused fashion to achieve several types of effects of potential relevance to mood disorders such as nonsurgical ablative approach, or to focally impact blood/brain barrier for targeted drug delivery. For the purpose of this review, it could be thought of as a putative means of neurostimulation.

The potential for low-intensity, low-frequency ultrasound to stimulate neuronal circuits has been reported to induce neuronal activation in *ex vivo* preparations, presumably via activating voltage-gated sodium and calcium channels (Tyler *et al*, 2008). The ability to achieve similar effects noninvasively through the intact skull remains to be demonstrated.

Near Infrared Light Therapy

NIR is an emerging neurostimulation technology that is able to depolarize neurons *in vitro* (Katz *et al*, 2010), but its cellular mechanism of action remains unresolved. Recent work has shown that a pulsed laser light placed at a distance is able to modulate the growth of axons of primary neuronal cell cultures (Mathew *et al*, 2010). Its place as a neuromodulation tool is still uncertain.

Low Field Magnetic Stimulation

The serendipitous observation that bipolar patients receiving echo planar magnetic resonance spectroscopic imaging (EP-MRSI) reported mood improvement (Rohan *et al*, 2004) led to the hypothesis that the oscillating magnetic fields (LFMS) applied during the EP-MRSI imaging sequence may represent a novel form of neurostimulation possessing mood altering properties. In contrast to the high-intensity magnetic fields used with TMS, LFMS employs relatively weak magnetic fields (<10 G) and electric fields (~ 1 V/m) applied uniformly at 1 kHz and a pulse width of 0.25 ms, resulting in a bidirectional pulse training of alternating polarity.

Supplementing the initial anecdotal observation initially reported in 23/30 bipolar patients receiving real EP-MRSI compared with 3/10 receiving sham, a controlled study in rats demonstrated activity of LFMS in a rodent model of learned helplessness (Carlezon *et al*, 2005). That these fields could plausibly change brain function was supported by a recent FDG-PET study finding the degree of metabolic decrease was correlated with applied field strength, although no changes in mood ratings were observed in the 15 healthy volunteers tested (Volkow *et al*, 2010). The potential value of this approach in the treatment of depression is yet to be examined systematically.

Optogenetic Stimulation

Microbial proteins called opsins are light sensitive molecules that can be introduced into neurons and function as ion channels that open or close according to light exposure. One of these is called channelrhodopsin-2 (ShR2) and allows Na + ions to enter the cell following exposure to ~ 470 nm blue light (Zhang *et al*, 2007). The advent of this technique has raised the possibility of enhancing the selectivity of neurostimulation via implanted DBS by targeting specific fiber tracts that overlap in space. The ability to selectively activate or inactivate specific projection neurons to the same target has great intrinsic appeal as a more sophisticated tool than conventional DBS. This technology also has the advantage of being a contactless form of stimulation relying on photo-activation. Although this technology still requires surgical implantation of the light emitting electrode, its potential uses in studying and 1 day potentially treating mood disorders are worth tracking. Indeed, antidepressant effects of optogenetic stimulation of medial prefrontal cortex have already been reported in a chronic social defeat stress model in rodents (Covington *et al*, 2010).

FUTURE RESEARCH DIRECTIONS

The family of somatic therapies available for mood disorders is broad, varied, and rapidly growing. Engineering advances are expanding the available toolbox, and neuroscience advances are informing the selection of targets and stimulation paradigms.

ECT remains a major treatment for severe depression, especially when psychosis is present or when it is refractory to medications. Developments in its technique (such as the use of ultra-brief pulses) are already being widely used.

TMS has a place in clinical practice, for less severe and less refractory cases. VNS seems to have a long-term benefit for some patients.

Major developments have been seen across the categories of seizure therapies, noninvasive brain stimulation, and surgical approaches. The risks of seizure therapy have been lessened through refinements in treatment technique and the advent of magnetic induction. At the same time, new approaches to dosing and targeting hold out promise for enhancing the efficacy of the noninvasive approach of TMS. The surgical approaches are quickly evolving, informed by new anatomical targets, novel clues to neurophysiological mechanisms, and innovative tools to refine selectivity of targeting. Adding to this, on the horizon stand an array of approaches yet to be systematically evaluated in mood disorders, each offering the hope of deeper, more focal, more selective, and ever less invasive strategies to combat these debilitating illnesses.

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