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Neuromodulation for mood and memory: from the engineering bench to the patient bedside

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Brain stimulation, in the form of electroconvulsive therapy (ECT), has long been a gold standard treatment for depression, but today, the field of neuromodulation is rapidly changing with the advent of newer and more precise tools to alter neuroplasticity and to treat brain-based disorders. Now there are new means to induce focal seizures, as with magnetic seizure therapy (MST), or modifications to ECT. There are also surgical approaches to target brain circuits via implanted stimulators placed in the brain or on cranial nerves. Finally, there are noninvasive subconvulsive approaches for the transcranial application of either electric or magnetic fields. Collectively, these tools have transformed the face of neurotherapeutics and informed our understanding of the brain basis of complex neurobehavioral conditions.

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Introduction

Major depressive disorder is a leading public health problem that contributes to significant morbidity and mortality, affecting approximately 14 million American adults each year [1]. Epidemiological surveys estimated that depression-related absenteeism and low work performance costs US workplaces $52 billion [2]. Presently, the first line management of depression consists of antidepressant medications and/or psychotherapy. However, as found in the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, 63% of patients failed to achieve remission with their first antidepressant medication and despite subsequent antidepressant augmentations or switches, 33% failed to achieve remission [3]. For treatment-resistant depression patients, various neuromodulation approaches are currently in use or in development.

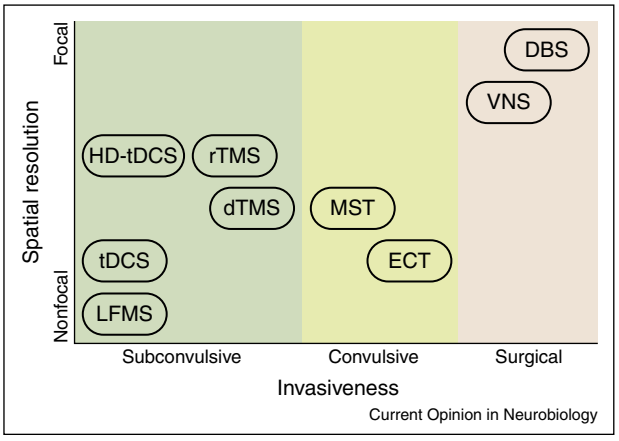
Neuromodulation approaches encompass a wide spectrum of strategies that can be categorized into convulsive, subconvulsive, and neurosurgical implantation therapies. The convulsive therapies involve the induction of a therapeutic generalized seizure in patients under anesthesia, either via the direct injection of electrical currents through scalp electrodes, as in the case of electroconvulsive therapy (ECT), or via electromagnetic induction, as in the case of magnetic seizure therapy (MST). The therapeutic mechanism is hypothesized to be related to the nature of the induced seizure, although there is evidence that stimulus parameters, and hence the induced electric field, may also effect clinical outcome. Subconvulsive therapies involve the application of electromagnetic fields at levels below seizure threshold. Such subconvulsive therapies include transcranial direct current stimulation (tDCS), high definition-transcranial direct current stimulation (HD-tDCS), transcranial magnetic stimulation (TMS), repetitive TMS (rTMS), deep TMS (dTMS), and low field magnetic stimulation (LFMS). The neurosurgical implantation therapies involve the implantation of battery-powered devices to deliver chronic or intermittent electrical stimulation, such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS). Figure 1 summaries the spatial resolution and invasiveness profile of the various neuromodulation therapies. This review describes salient features and the state of the art of each intervention.

Convulsive therapies

Electroconvulsive therapy (ECT)

ECT is administered by delivering electricity directly to the brain via scalp electrodes to induce a generalized tonic–clonic seizure. Modern ECT consists of delivering constant current (800 or 900 mA) rectangular pulses with alternating polarity. Pulse widths in the 0.5–2 ms range are referred to as 'brief', and pulse widths <0.5 ms are termed 'ultrabrief'. The practice of ECT dates back to the 1930s, and its modern version is considered the 'gold standard' brain stimulation treatment for severe major

Figure 1



Spatial resolution and invasiveness profile of various neuromodulation therapies for mood disorders. Subconvulsive therapies include transcranial direction current stimulation (tDCS), high definition-transcranial direct current stimulation (HD-tDCS), low field magnetic stimulation (LFMS), repetitive transcranial magnetic stimulation (rTMS), and deep transcranial magnetic stimulation (dTMS). Convulsive therapies include magnetic seizure therapy (MST) and electroconvulsive therapy (ECT). Neurosurgical therapies include vagus nerve stimulation (VNS) and deep brain stimulation (DBS).

depressive disorder. It is estimated that one to two million individuals receive ECT each year worldwide and its use has increased over the years [4]. The speed of response and clinical efficacy with ECT are unparalleled, with a remission rate of approximately 70% [5]. The adverse cognitive effects of ECT; however, substantially reduce its tolerability. Some of the adverse cognitive effects include post-ictal disorientation, learning and memory difficulties, and retrograde amnesia [6].

Among the approaches to mitigate side effects are alterations of the dosing of the electrical stimulus, which includes electrode placement, pulse amplitude, shape, and width, and pulse train frequency, duration, directionality and polarity. Ultrabrief pulse ECT has been shown to significantly reduce cognitive side effects while maintaining efficacy [7]. The geometry of the ECT electrodes and their placement on the patient's head, as well the head anatomy, determine the spatial distribution of the induced electric field in the brain [8•]. Electrode configuration plays a critical role in the therapeutic action and adverse effects of ECT. Sackeim *et al.* showed in a series of studies that right unilateral electrode placement, combined with proper stimulus dosing, can be as effective as bilateral ECT while having more benign cognitive side effects [9••]. In a recent feasibility study with a novel electrode configuration, focal electrically administered seizure therapy (FEAST) demonstrated tolerability and clinically meaningful antidepressant improvement [10]. Refinements of electrode configuration are key to maximizing benefits of ECT, and remains an area of active study. Work on novel electrode placements for ECT may be informed by computational modeling of the electric field distributions in the brain [11,12], such that dosing paradigms could be designed to target brain regions implicated in depression while avoiding those associated with adverse side effects. Another aspect of the ECT stimulus that could be further optimized is the pulse current amplitude [8•]. High current amplitude used in conventional ECT devices exposes the entire brain to suprathreshold stimulation that far exceeds neural activation threshold [8•]. This may contribute to the cognitive side effects of ECT. Further, the seizure threshold titration procedure for individualizing ECT dosage adjusts only the duration of the stimulus pulse train, which unlike amplitude, are unrelated to the spatial distribution of the induced electric field. Thus, conventional titration procedures do not compensate for anatomy-dependent variability in the strength and focality of stimulation [13]. Thus, individualized low current amplitude has been proposed as a means to compensate for anatomical variability and improve stimulation focality (e.g. reducing the level of direct electrical stimulation in the hippocampus) [12].

Magnetic seizure therapy (MST)

MST involves inducing a series of generalized seizures under anesthesia using high-dose repetitive transcranial magnetic stimulation (rTMS) [14]. Evidence shows that the intracerebral electric field induced by ECT is unfocal and variable due to the high electrical impedance of the skull, current shunting in the scalp, and variation of head tissue anatomy [15]. On the other hand, MST offers greater control of the induced electric field due to the lack of impedance of brain tissue to magnetic fields. *In vivo* studies in preclinical studies with nonhuman primates demonstrated the safety of MST and supported the hypothesis that the MST-induced current and resultant seizure are more focal than ECT [16]. This enhanced control represents a means to focus the treatment in targeted cortical structures thought to mediate antidepressant effects and to reduce spread to medial temporal structures implicated in the amnestic side effects of ECT. Studies support the safety of MST [17] and provide open-label evidence of antidepressant action. Clinical trials in human have suggested comparable efficacy of MST and ECT [18•], and further research is warranted. A recently completed multi-center, randomized, controlled trial that contrasted the safety and efficacy MST and ultrabrief pulse width right unilateral ECT will provide further information.

Subconvulsive therapies

Transcranial magnetic stimulation

TMS is a non-invasive technique used for numerous research and therapeutic applications, including the study of normal and pathological brain function, and the treatment of neuropsychiatric diseases [19]. The technique

involves the use of brief, intense pulses of electric current delivered to a coil placed on the subject's head to generate an electric field in the brain via electromagnetic induction. The locus of activation in the brain is approximately in the area where the induced electrical field is maximal; this location, in turn, depends on the stimulating coil geometry and placement [20••]. rTMS to left dorsolateral prefrontal cortex (DLPFC) was approved by the FDA for the treatment of major depression. However, the efficacy in the pivotal trial was modest (24% response, 14% remission at 6 weeks) [21]. Studies to date have targeted the DLPFC based on evidence of dysregulation in this region and connectivity between prefrontal cortex and the limbic system in depression [22]. However, the limited therapeutic effect size of rTMS to the DLPFC suggests that this region may not be the optimal target for depression, and has motivated the development of a TMS coil that could access deeper brain structures [23]. Work with dTMS to date has demonstrated feasibility and safety [24] and significant antidepressant benefits which are double those reported with conventional rTMS, which led to its recent FDA approval as a treatment for depression. To date, only a limited range of TMS treatment parameters has been examined in clinical trials. Since neurophysiologic understanding of TMS on the neuronal level is limited in clinical studies, ongoing preclinical studies with TMS-compatible intracerebral recordings at single-neuron resolution will help inform the interactions between the induced electric field and neuronal response, which is fundamental to understanding mechanisms of action of TMS [25].

Low field magnetic stimulation (LFMS)

There is some evidence that the subthreshold electric field induced in the brain by the gradient coils in magnetic resonance imaging scanners can have mood altering properties. Thus, LFMS employs very weak magnetic fields applied uniformly throughout the brain. Research has suggested that LFMS influences glucose metabolism in the brain [26] and exerts antidepressant effects in humans [27]. A preclinical controlled also demonstrated an antidepressant-life effect of LFMS in a rodent model of learned helplessness [28]. The gradient coils used in LFMS studies induce a more diffuse electric field compared to TMS coils with comparable depth of field penetration [20••]. Another LFMS technique called synchronized TMS (sTMS) employs rotating permanent magnets over a broad scalp area, with rotational frequency synchronized to the subject's individual alpha frequency. A randomized, sham controlled, double-blind study showed that the sTMS approach relative to sham achieved greater reduction in depression severity [29].

Transcranial direct current stimulation (tDCS)

tDCS uses constant, low-amplitude direct current (typically 1–2 mA) delivered to the brain via scalp electrodes to modulate cortical excitability that has been used to treat depression as well as enhance neurocognitive performance. Preliminary antidepressant efficacy of tDCS is supported by two randomized, sham-controlled studies [30•,31]. However, another study with similar parameters was unable to replicate the effect sizes [32]. Thus, the efficacy tDCS in treating mood disorders warrants further investigation since published data are inconsistent, and indeed there is a multi-center randomized controlled trial presently underway. There are also opportunities to refine the stimulation technique to improve its neuromodulation potency. Several computational studies have described novel tDCS electrode designs, such as high definition-tDCS [33], and electric field targeting strategy through multi-electrode optimization algorithms [34,35].

Neurosurgical implantation therapies

Deep brain stimulation (DBS)

DBS is a neurosurgical technique that involves the implantation of a pulse generator and electrodes to deliver chronic electrical stimulation to focal deep brain regions, which has provided therapeutic benefits for a variety of neurological and psychiatric conditions. As implicated in neuroimaging studies and theoretical pathways for depressive symptoms, a number of neuroanatomical targets have been proposed for the treatment of depression. Such targets include the subgenual cingulate cortex, nucleus accumbens, ventral caudate/ventral striatum, and lateral habenula [36]. For example, DBS of the white matter underlying the subgenual anterior cingulate cortex showed marked antidepressant effects in open-label studies of patients with severe treatment-resistant major depression [37]. Further, DBS was found to have no neurocognitive adverse effects in patients with depression who showed no change in general intellectual ability, processing speed, verbal and visual memory, or executive functions [38]. Technical innovations with DBS include battery power management through stimulation waveform optimization [39] and electrode design for more efficient neuromodulation [40]. To date, however, large randomized controlled trials seeking to demonstrate antidepressant efficacy did not lead to a positive result.

Vagus nerve stimulation (VNS)

VNS involves the surgical implantation of a pulse generator to deliver intermittent electrical stimulation to the left vagus nerve via helical electrodes. The use of VNS for both unipolar and bipolar depression was approved by the FDA for patients who failed to respond to at least four antidepressant trials. Although VNS showed no statistically significant acute antidepressant effect compared to sham treatment, there was a clinically meaningful antidepressant effect after 12 months of VNS [41], which suggests a potential long-term growing benefit of VNS. In terms of neurocognitive effects, patients receiving open-label VNS showed no impairment in the domains of motor speed, verbal fluency, attention, or memory, and showed improved performance on measures of psychomotor

function, language, and executive function [42]. The mechanisms by which VNS modulates mood is not fully understood, but theories include alteration of norepinephrine by projections to the locus coeruleus, elevated levels of inhibitory GABA, and enhanced cortical inhibition [43].

Understanding biological mechanisms

As clinical neuromodulation becomes more sophisticated, efforts to elucidate inherent biological mechanisms underlying both therapeutic and adverse effects become more important in order to design safer and more effective interventions. Many different theories have been formulated to explain how ECT acts to modulate brain function that spans chemical, endocrinological, immunological, and electrophysiological frameworks. Two unifying yet seemingly contradictory hypotheses emerged: the anticonvulsant hypothesis which posited that hypoperfusion, decreased seizure duration and inhibition of neural activity were associated with therapeutic effects [44], and the neurotrophic effect hypothesis that postulated increased growth factors, transcription factors and neurogenesis accounted for the clinical benefits [45]. Longitudinal neuroimaging studies over the past decade have demonstrated support for both hypotheses, leading to the intriguing proposal that an initial hypometabolic state and prolonged neurotrophic effects may both be important determinants of clinical response [46].

The single most undesirable side effect of convulsive therapeutic approaches has consistently been memory impairment [47]. To date, multiple pharmacological strategies including glutamatergic, cholinergic, and glucocorticoid manipulations have been attempted to attenuate the neurocognitive side effects of convulsive therapies. The future of the field of neuromodulation may lie in the consolidation of diverse molecular systems that parsimoniously explain a general brain-wide phenomenon, such as impaired cognitive function [48]. Perhaps the most promising development in this regard is the study of neuronal activity-dependent plasticity which has the potential to affect many of the aforementioned proposed mechanisms through control of major transcription factors and precise spatiotemporal control of gene expression [49]. By manipulating multiple genetic end-products which may have seemingly contradictory functions, a broad-ranging mechanism such as neuroepigenetics [50] can influence both the therapeutic and side effects of neuromodulatory therapy.

Conclusions and future directions

The family of neuromodulation approaches available for mood disorders is wide ranging and rapidly growing. Engineering innovations are expanding the array of stimulation modalities, and advances in neuroimaging and basic neuroscience are important for informing mechanisms of action and selection of therapeutic brain targets. To date, convulsive therapies remain the most efficacious treatment for severe major depression. Optimizing ECT electrode and MST coil configurations, as well as dosing strategies are promising ways to further maximize efficacy and enhance safety that have yet to be explored. Computational electric field modeling can help inform neurophysiological mechanisms and the development of innovative tools to refine targeting strategies. Many of these novel neuromodulation approaches have yet to be systematically evaluated in mood disorders, and may offer new hope for patients with treatment resistant depression.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Conflict of interest statement

Dr. Deng is an inventor on patents and patent applications related to TMS coil technology. Dr. Lisanby is an inventor on patents and patent applications related to TMS coil technology and ECT dosing procedure. Dr. Lisanby has served as Principal Investigator on industry-sponsored research grants to Columbia/RFMH or Duke (Neuronetics (past), Brainsway, ANS/St. Jude Medical (past), Cyberonics (past)); equipment loans to Columbia or Duke (Magstim, MagVenture); is supported by grants from NIH (R01MH091083-01, 5U01MH084241-02, 5R01MH060884-09), Stanley Medical Research Institute, National Alliance for Research on Schizophrenia and Depression, and the Wallace H. Coulter Foundation; and has no consultancies, speakers bureau memberships, board affiliations, or equity holdings in related industries. Drs. McClintock and Luber, and Mr. Oey have no conflicts of interest to declare.

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