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Electroceutical and Bioelectric Therapy: Its Advantages and Limitations

Bori Jung[1,2], Chaeyeon Yang[1], Seung-Hwan Lee[1,3]

[1]Clinical Emotion and Cognition Research Laboratory, Inje University, Goyang, [2]Department of Psychology, Sogang University, Seoul, [3]Department of Psychiatry, Inje University Ilsan Paik Hospital, Goyang, Korea

Given the long history, the field of electroceutical and bioelectric therapy has grown impressively, recognized as the main modality of mental health treatments along with psychotherapy and pharmacotherapy. Electroceutical and bioelectric therapy comprises electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), transcranial electrical stimulation (tES), and other brain stimulation techniques. Much empirical research has been published regarding the application guidelines, mechanism of action, and efficacy of respective brain stimulation techniques, but no comparative study that delineates the advantages and limitations of each therapy exists for a comprehensive understanding of each technique. This review provides a comparison of existing electroceutical and bioelectric techniques, primarily focusing on the therapeutic advantages and limitations of each therapy in the current electroceutical and bioelectric field.

KEY WORDS: Electroceutical and bioelectric therapy; Electroconvulsive therapy; Vagus nerve stimulation; rTMS; Deep brain stimulation; Transcranial electrical stimulation.

INTRODUCTION

Mental health treatment is provided in many forms including psychotherapy (e.g., behavioral, cognitive, and interpersonal therapy), pharmacotherapy (i.e., prescription of drugs), and other alternatives using medical devices (e.g., sonotherapy, light therapy, and brain stimulation) (Fig. 1). Among the available options, the field of brain stimulation techniques has seen rapid progress as it can provide a valuable means of modulating neuronal activity in brain regions that are underpinning major pathophysiology in various neuropsychiatric disorders [1]. Although pharmacotherapy is the primary intervention for treating common psychiatric disorders, issues associated with nonadherence, tolerability and unresponsiveness are constantly reported in patients under medications [2-4].

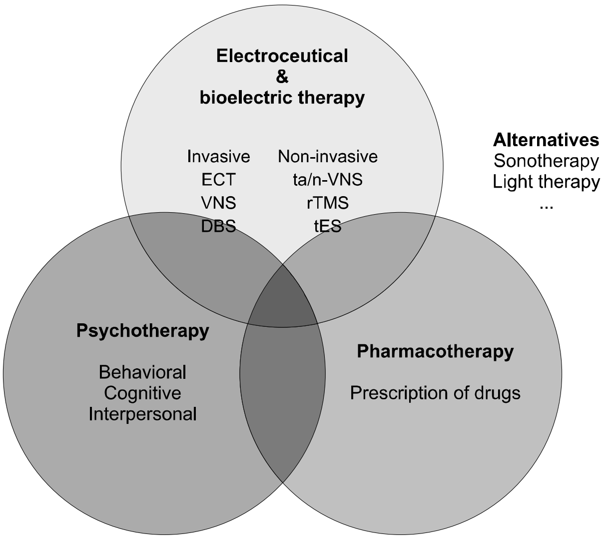

Fig. 1. Broad categories of several types of mental health treatment. ECT, electroconvulsive therapy; VNS, vagus nerve stimulation; DBS, deep brain stimulation; ta-VNS, transcutaneous auricular vagus nerve stimulation; n-VNS, non-invasive vagus nerve stimulation; rTMS, repetitive transcranial magnetic stimulation; tES, transcranial electrical stimulation.

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Address for correspondence: Seung-Hwan Lee
Department of Psychiatry, Ilsan Paik Hospital, Inje University College of Medicine, Juhwa-ro 170, Ilsanseo-gu, Goyang 10380, Korea
E-mail: lshpss@hanmail.net
ORCID: https://orcid.org/0000-0003-0305-3709

Such shortcomings of pharmacotherapy have spurred the emergence of brain stimulation techniques as adjunctive therapy for treatment-resistant patients, where magnetic fields or electrical currents are applied to affect brain function. Considering the increasing demands and effectiveness of brain stimulation to be recognized as a main therapeutic approach, we use the term "electroceutical and bioelectric therapy" to refer to the brain stimulation techniques that have been approved by US Food and Drug Administration (FDA) or actively investigated as a treatment for neuropsychiatric disorders over past few decades: electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and transcranial electrical stimulation (tES) including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). Even though these electroceutical and bioelectric therapies share some common grounds in that they mostly target patients who are resistant to conventional psychopharmacotherapy, their advantages and limitations may vary depending on the technique, underlying mechanism, and the expected therapeutic effects of each treatment. As the application of these therapies as a first line treatment has been increasing recently, this review provides a general outline of existing electroceutical and bioelectric approaches along with the therapeutic advantages and limitations of the respective treatment.

TYPES OF ELECTROCEUTICAL AND BIOELECTRIC THERAPY

ECT

ECT induces a series of electrical currents to generate a seizure through the electrodes attached at precise locations on the patient's head under anesthesia. The schedule of ECT administration is commonly twice or three times a week, encompassing about 6 to 9 treatment sessions for depression [5,6], and 10 to 20 sessions for schizophrenia [7,8]. More than 70% of patients receiving ECT treatment are diagnosed with severe depression and are usually resistant to traditional treatments of depression [9]. Other neuropsychiatric conditions that may be the target of ECT treatment include schizophrenia, malignant catatonia, and acute mania [10]. Prior studies investigating the mechanism of ECT revealed that patients during or after ECT treatment showed a) an increased seizure threshold [11], as well as b) a downregulation of hypothalamic-pituitary-adrenal (HPA) axis [12], which are neurophysiological changes associated with the effect of anticonvulsants and antidepressants, respectively. A meta-analysis that combined seven studies examining the efficacy of ECT through controlled clinical trials between 1956 and 2003, showed converging evidence that demonstrated the superiority of ECT over other comparators including placebo or antidepressant drugs [13]. Specifically, the response rate of ECT was approximately four times greater than that of antidepressant drugs (odds ratio [OR] = 3.72, 95% confidence interval [CI] 2.60−5.32), and about 11 times higher compared to the placebo (OR = 11.08, 95% CI 3.10−39.65).

Advantages of ECT

The major therapeutic benefit of ECT is that patients usually report a quick relief of symptoms. Gangadhar and colleagues (1982) [14] conducted a randomized controlled trial comparing the effect of ECT with imipramine in treating endogenous depression. Both treatments were equally effective in reducing depressive symptoms, but the effect of ECT was much quicker with fewer adverse effects. Another study investigating the efficacy of ECT in psychotic major depression reported that symptom relief was manifested within 10 to 14 days from the beginning of treatment, and the remission rate for ECT treatment reached 95% [15]. Considering that severe psychotic symptoms of depression often lead to life-threatening conditions such as food refusal or increased suicidal ideation [16], ECT treatment may be useful as a first-line treatment for severe or acute psychiatric syndromes which demand rapid intervention to relieve symptoms. In addition, ECT can be a useful option for those who suffer from the adverse effect of any pharmacotherapy or who are precluded from certain medications (e.g., women during the breastfeeding period). This may also apply to medically ill patients with depressive symptoms who are more likely to experience the worsening of their somatic symptoms as an adverse effect of antidepressant medications [17]. In such cases of intolerable adverse effects of psychopharmacological treatments, ECT is usually recommended as a monotherapy [18].

Limitations of ECT

The most commonly observed physical adverse effects of ECT are postictal headache, nausea, and muscle soreness. Up to 45% of patients with ECT have complaints of headache [19], and it usually occurs more frequently in patients at younger ages. Nausea is less often reported than headache, with rates of 1−23% and may be associated with an adverse effect of anesthesia. The process of anesthesia involves the administration of muscle relaxants (e.g., succinylcholine), and this sometimes causes intense twitching of muscles later experienced as muscle soreness. Aside from physical adverse effects, cognitive impairments are sometimes reported following ECT, which can be summarized into four categories [9]: a) transient disorientation experienced right after ECT treatment due to the effect of seizure and anesthesia; b) anterograde amnesia experienced as the inability to retain newly learned information shortly after ECT; c) short-term retrograde experienced as the inability to remember information that occurred shortly before ECT; d) retrograde memory loss characterized by a severe, persistent inability to date back past information. However, patients showing cognitive adverse effects of ECT mostly improve within a month [20], and such impairments are less prominent in the unilateral application of ECT than the bilateral [21]. Other barriers to expanding the use of ECT are high initial cost and anesthetic procedures required for the treatment.

VNS

VNS refers to a therapeutic technique that delivers intermittent electrical stimulation to the vagus nerve, which is a mixed parasympathetic nerve with 80% of afferent and 20% of motor efferent pathways that bilaterally course along the neck [22,23]. The central role of VNS is on its afferent fibers directly or indirectly transmitting the bodily inputs (i.e., visceral sensory and gustatory information) to the brain regions such as the amygdala, hypothalamus, and orbitofrontal cortex [24,25]. As changes in these brain structures are often indicated in numerous neuropsychiatric disorders, stimulating these circuits has been suggested, and was finally FDA-approved as an adjunctive treatment for patients with refractory epilepsy and treatment-resistant depression in 1997 and 2005, respectively. VNS is commonly conducted in an invasive way where a pulse generator, which is implanted on the left upper chest of the patient, sends stimulation through the wire attached to the left vagus nerve [26]. Another form of VNS is conducted in a non-invasive way where the electrical stimulation is applied to the left cymba conchae of the outer ear (i.e., transcutaneous auricular vagus nerve stimulation, ta-VNS) or on the neck (i.e., non-invasive vagus nerve stimulation, n-VNS) (Fig. 2) [27]. Because the area of cymba conchae receives the auricular branch of the vagus nerve [28], prior studies conducting ta-VNS on the area have revealed the similar effect on the brain when compared with the effect of the traditional invasive form of VNS [29,30].

Advantages of VNS

The major advantage of VNS is that it can be applied in a non-invasive form through ta-VNS by targeting an easily accessible auricular branch of the vagus nerve (ABVN) that innervates the outer ear. Unlike a pulse generator-implanted VNS, ta-VNS is a relatively less expensive, portable, and safe neurostimulation system without surgery, while still permitting a rapid application of the previously found basic mechanism of VNS [31]. In addition, the application of ta-VNS accompanies no severe side effects as mild ulceration or redness of the skin are the most commonly reported complaints [32]. Another advantage of VNS is its diverse applications across a wide range of disorders aside from depression and epilepsy. Prior studies provided evidence of an anti-inflammatory effect of VNS as it inhibits the release of proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [33-35]. Thus, VNS has the potential to be clinically used for treating a wide range of inflammatory disorders such as stroke, diabetes, sepsis, obesity, and pain management [36], although the evidence of VNS efficacy for these treatments is at a preliminary stage.

Limitations of VNS

Adverse effects of invasive VNS primarily occur during the phase of stimulation, and complications regarding implantation surgery are rare [37]. Commonly reported adverse effects during the stimulation involve voice alteration, cough, lower facial weakness, dyspnea, and headache. Most of them are predictable and dose-dependent upon stimulation parameters, with high stimulation causing more adverse effects than low stimulation conditions [38,39]. Another limitation of invasive methods of VNS is related to an expensive initial cost for device

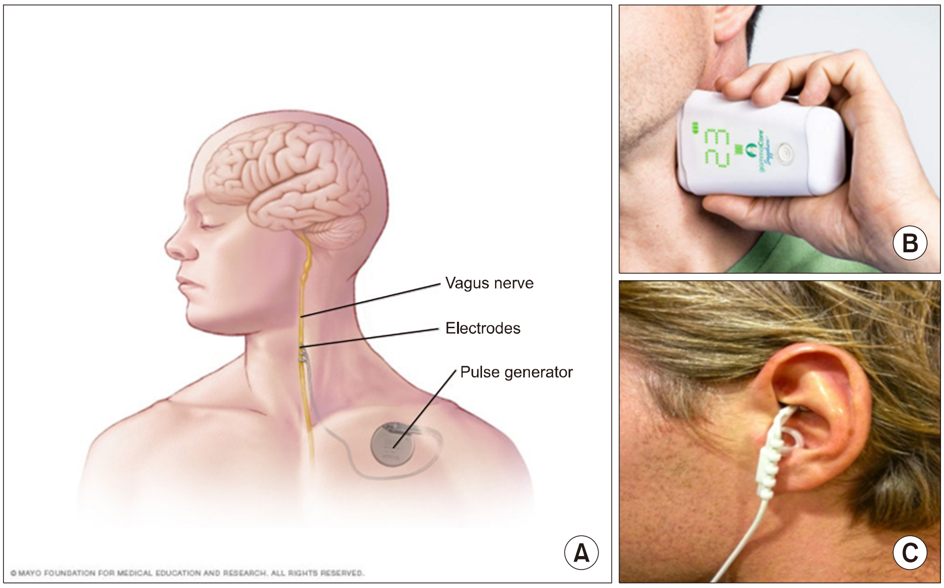

Fig. 2. Invasive and non-invasive forms of vagus nerve stimulation (VNS). (A) Invasive VNS where a pulse generator is implanted on the left chest. (B) Non-invasive vagus nerve stimulation (n-VNS). Image courtesy of electroCore Inc. (https://www.electrocore.com/). (C) Transcutaneous auricular vagus nerve stimulation (ta-VNS). Adapted from the article of Van Leusden *et al.* (Front Psychol 2015;6:102) [27].

purchase, implantation surgery, and hospitalization. Previously reported cost of the VNS pulse generator device-the NeuroCybernetic Prosthesis (NCP) System (Cyberonics [current LivaNova PLC], Houston, TX, USA)-was about USD 9,200 in the United States, and the battery of the device needs replacement after 10 years. In the case of non-invasive treatment of ta-VNS, the treatment procedure doesn't require any surgery or related adverse effects, but it has limitations in that (a) there is no established administration protocol regarding the optimal stimulation parameter [40] and (b) only a scarce number of cohort studies are available [41]. In addition, n-VNS lacks empirical evidence supporting its efficacy with only a few randomized controlled trials conducted for cluster headache [42].

rTMs

rTMS delivers magnetic pulses non-invasively through an electromagnetic coil held against the patient's intact scalp [43]. These magnetic pulses transform into electrical currents as they are near the conductor, and subsequently depolarize underlying cortical neurons of targeted brain regions [44]. Most rTMS treatments target the area of the left dorsolateral prefrontal cortex (DLPFC) [45,46], a brain region associated with top-down cognitive control [47] and is usually deactivated in patients with depression [48]. Several lines of evidence suggest that rTMS induces outlasting changes in brain activity which is similar to the synaptic plasticity [49] with a high frequency of repetitive stimulation ($>$ 1 Hz) related to a long-lasting facilitative effect, while low frequency ($\leq$ 1 Hz) related to long-lasting inhibitory effect to the brain [50,51]. Most prior studies have explored the therapeutic effects of high-frequency rTMS on the left DLPFC in treating depression [52]. A review that meta-analyzed 7 studies on the effect of brain stimulation technique in patients with depression revealed that high-frequency rTMS to the left DLPFC had shown high quality evidence regarding the rates of response (OR = 3.17, 95% CI 2.29−4.37) and remission (OR = 2.67, 95% CI 1.79−4.00) compared to that of sham group [1]. Recently, a more effective rTMS protocol known as intermittent theta-burst stimulation (iTBS) was FDA-approved as a treatment for major depressive disorder. Study investigating the feasibility of Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT)–iTBS protocol guided by functional connectivity MRI- revealed that SAINT was safe and effective in treating patients with depression [53].

Advantages of rTMS

One advantage of rTMS is that the treatment procedure doesn't need any surgery or anesthesia, reducing the risk of adverse effects that usually occur in other surgically conducted brain stimulation techniques. Commonly reported adverse effects of rTMS are minor and involve transient headache, neck pain, hearing changes, and seizure induction with a low incidence of less than 1 % [46]. A study comparing the tolerability of rTMS with other brain stimulation techniques such as ECT and DBS in patients with unipolar depression, demonstrated superior tolerability of rTMS over ECT and DBS manifested as lower rates of dropouts [54]. In addition, while prior studies have shown cognitive adverse effects of ECT, rTMS either has no negative effects or even some positive effects on cognitive functioning [55]. Another advantage of rTMS is that it can affect specifically targeted sites of the brain regions compared to more generalized stimulation of ECT. While the electrical stimulation is attenuated by the existence of the skull as it acts like a massive resistor, magnetic fields are not influenced by intervening tissue [56]. Specifically, standard rTMS uses a figure-8 magnetic coil which affects the brain regions under the skull at depth of 2−3 cm [57,58]. Thus, rTMS may induce more focal and localized neuronal depolarization to the underlying cortical tissue of the brain regions [54] with less cognitive adverse effects observed in the treatment of ECT.

Limitations of rTMS

Even though a better tolerability was obtained for rTMS, ECT outperformed the rTMS in terms of therapeutic efficacy for treating patients with depression. In a comparative study of electroceutical techniques, patients under the treatment of ECT showed 28.57% of remission rate, while patients under the treatment of rTMS achieved relatively lower remission rates of 14.21% after 4 weeks [54]. Such results indicate a limited clinical application of rTMS at present, in that it may not be suitable for patients with depression who require immediate symptom relief or show severe psychotic symptoms [59]. Because the effects of rTMS vary as a function of stimulus variables including frequency, intensity, and pulse train, further study is needed to investigate the optimal protocols of rTMS that can enhance the long-lasting therapeutic effect of rTMS in treating depression such as theta burst stimulation (TBS) [49].

tES

tES refers to the techniques that typically deliver electrical currents at low intensity (1−2 mA) between electrodes (anode and cathode) placed on a patient's scalp [43]. The anodal electrode is commonly placed over the left DLPFC and the cathodal electrode over the contralateral supraorbital area or contralateral knee as a reference electrode for treating patients with depression [60,61]. Modalities of tES vary depending on the waveforms of the currents (Fig. 3), which can be either transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS). tES shares some common features with rTMS in that it produces outlasting facilitative or inhibitory changes in brain activity (Fig. 4) which are similar to the physiological mechanisms of neuroplasticity [62, 63]. However, they are distinguished by their induction procedure and a subsequent acute effect after stimulation. While rTMS uses magnetically induced high intensity electrical current which is above the threshold of neurons to generate action potential [49,64,65], tES induces low electrical current which is below the threshold of neurons to alter the resting membrane potential and thereby modify the firing rate in the stimulated neurons [66-68]. tDCS delivers a direct current through anodal and cathodal electrodes, and polarity of electrodes determines the direction of plasticity effect: anode stimulation resulting in a

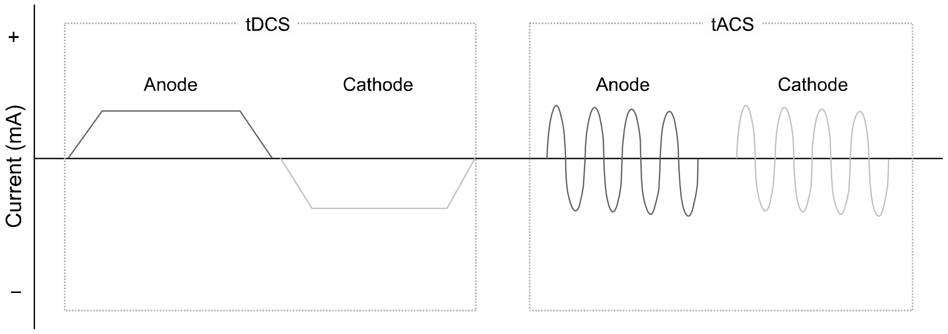

Fig. 3. Different electrical current waveforms used for types of transcranial electrical stimulation (tES). Transcranial direct current stimulation (tDCS) delivers direct and monopolar current which fades in/fades out at the beginning and end of the stimulation until the desired intensity is achieved. Transcranial alternating current stimulation (tACS) delivers biphasic sinusoidal current that alternates between positive and negative voltages and enables entrainment of brain's endogenous oscillations.

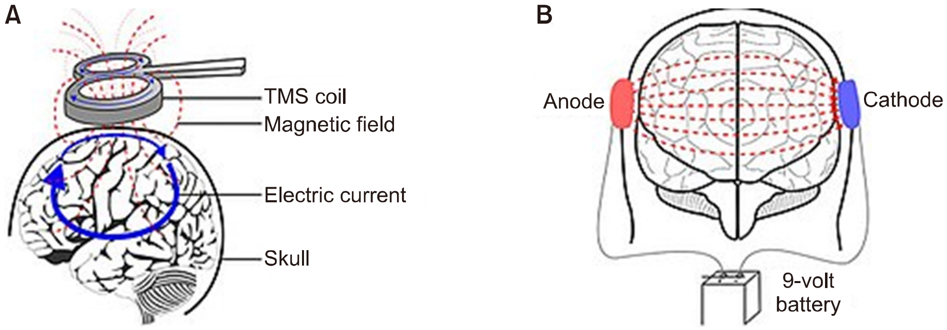

Fig. 4. Graphical illustrations of rTMS and tES application to the brain. (A) rTMS application to the brain. (B) tES application to the brain. rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; tES, transcranial electrical stimulation. Adapted from the article of Kim *et al.* (Front Neurol 2020;11:701) [43].

depolarization and cathode stimulation resulting in a hyperpolarization of the membrane potential in stimulated neurons [69-71]. Such classic neuroplasticity effect of tDCS seems to act through a glutamatergic process in that antagonizing N-methyl-D-aspartate (NMDA) receptors prevents facilitative effect of anodal tDCS and inhibitory effect of cathodal tDCS [72-74]. However, neuroplastic after-effects of tES is dependent on multiple parameters (e.g., duration, intensity, and target region) and may non-linearly alter the cortical excitability [75]. The possible efficacy of tDCS has been suggested in treating depression, fibromyalgia, and stroke [76,77]. Specifically, prior study that meta-analyzed the data from 6 randomized controlled trials in patients with depression found significantly higher rates of response (OR = 2.44, 95% CI 1.32−4.32) and remission (OR = 2.38, 95% CI 1.22−4.64) in active tDCS group compared to the sham group [78]. In addition, anodal tDCS of primary motor cortex was effective not only in motor rehabilitation for patients with chronic stroke [79] but also in motor learning of healthy subjects [80]. tDCS was also effective in reducing symptoms of schizophrenia (i.e., negative symptoms, positive symptoms and auditory hallucinations) according to a study that meta-analyzed 16 randomized controlled trials [81]. Potential therapeutic effects of tDCS have been suggested in treating patients with anxiety disorder where excitatory stimulation over the left prefrontal area and inhibitory stimulation over the right prefrontal area may be effective in reducing the severity of symptoms [82]. Anodal tDCS to the left inferior frontal cortex significantly improved the performance of word retrieval tasks and normalized abnormal network configurations in patients with mild cognitive impairment during resting-state functional magnetic resonance imaging (fMRI) as well [83].

Advantage of tES

tES is relatively cost-effective compared to other brain stimulation techniques, and easy to manipulate for double-blind randomized controlled trials [75]. The portability and simplicity of devices to modify cortical excitability is beneficial to extend its applications [84]. Another advantage of tES is associated with the use of tACS which applies a balanced sinusoidal electrical current alternating between positive and negative voltages [85]. When sinusoidal electrical current is induced through the electrodes on the scalp, the brain's endogenous oscillations are synchronized with exogenous oscillation of alternating currents [86]. Since the oscillatory state is causally related to specific cognitive phenomena of the brain [87,88], tACS probes the underlying neurophysiology of cognitive functions based on inference from oscillatory activity manipulated by the injection of sinusoidal electrical currents [89,90]. For instance, prior study that applied gamma-band tACS in primary motor cortex reported an improved acceleration and velocity in healthy subjects [91].

Limitations of tES

Adverse effects of low intensity tES involve skin burns due to suboptimal electrodes attached to the skin, headache, fatigue, prickling and burning sensation at its peak intensity, yet they are usually mild to moderate symptoms for which no medical hospitalization is necessary [92]. Treatment-emergent mania or hypomania is very rarely reported in patients with depression [93,94]. Major limitations of current tACS involve various confounding factors that make it challenging to detect the direct mechanism of tACS by affecting the entrainment of brain oscillations [95]. Another limitation is associated with a non-linear effect of tDCS, which makes it challenging to investigate the optimal protocol to enhance the effectiveness of tDCS. Whereas the application of 1mA anodal tDCS for about 13 minutes over the motor cortex resulted in the classic plasticity effects (i.e., facilitative effects of anodal), doubling the duration of stimulation reversed the direction of effects (i.e., inhibitory effects of anodal tDCS) [96]. In addition, application of 2mA cathodal tDCS over motor cortex for 20 minutes increased motor evoked potentials (MEP) amplitudes instead of inhibition [97]. Because such a reversed effect is dependent on calcium influx induced by stimulation protocols [72], simple prolongation of duration does not necessarily predict an increased efficacy of tDCS [97]. Thus, more systematic studies that explore the physiological effects of extended stimulation protocols are needed to enhance its efficacy.

DBS

DBS involves a surgical procedure of implanting electrode leads into a targeted brain region via small holes in the skull using stereotactic techniques along with neuroimaging. These electrode leads are attached to a subcutaneously implanted pulse generator (IPG) which delivers electrical stimulation to the brain. Stimulation parameters of IPG can be externally manipulated by clinicians, and are commonly set at 60−130 Hz, 2−10 volts (V), and 60−200 μs pulse width [98]. DBS has been FDA-approved as a treatment for Parkinson's disease and has largely replaced previously conducted ablative neurosurgery in patients with movement disorders such as essential tremor and dystonia [99]. Potential benefits of DBS have been also revealed in treating treatment-resistant depression [100, 101] as well as obsessive-compulsive disorder (OCD) [102, 103]. Targeted brain regions for treatment of Parkinson's disease involve the subthalamic nucleus (STN) and the internal segment of the globus pallidus (Gpi) which are structures within basal ganglia [104,105]. DBS for depression has targeted subcallosal cingulate gyrus [101,106], while OCD focused on the brain region of the anterior internal capsule [103]. The therapeutic mechanism of DBS may be associated with its complex pattern of facilitative and inhibitory effects induced by stimulation, which thereby modulates and prevents transmission of pathologic oscillations and bursting within the brain network [107]. Specifically, extracellular stimulation can inhibit the cell body while activating the axons at the same time as DBS initiates the action potential in the axon rather than the cell body. Such complex patterns of facilitative and inhibitory effects seem to interrupt the abnormal neuronal activity and replace it with a regular pattern [108].

Advantages of DBS

DBS overtook the surgical treatment of lesioning for movement disorders as it offers the advantages of reversibility and adjustability [109]. Stimulation parameters such as location, intensity, and the shape of the current field can be customized for individual needs (e.g., changes in medication) following surgical implantation [110]. Through monitoring, clinicians can easily detect any side effects that occurred via the inadvertent stimulation of brain structures adjacent to the target area. Such properties of DBS allow therapeutic effectiveness to be improved or potential side effects to be minimized over time [111].

Limitations of DBS

Despite the well-established therapeutic benefits of DBS in movement disorders, DBS usually accompanies risks in the surgical procedure as well as in managing implanted devices. Surgery- and hardwire-related complications include intracranial hemorrhages, hematomas, paralysis, infection, dislocation of electrodes, and skin erosion [112]. Stimulation-induced adverse effects such as muscle contractions, ocular deviations, headache, pain, and dysarthria are more commonly reported but less severe than those of surgery [113]. Other factors that often burden patients under the treatment of DBS involve frequent revisits, high costs of the implantation procedure, and replacement of the battery.

CONCLUSION

Different types of electroceutical and bioelectric therapy have their own strengths and shortcomings as illustrated in Table 1 depending on the technique, underlying mechanism, and the expected therapeutic effects of each treatment. They can be broadly divided into two classifications of invasive (e.g., ECT, VNS, and DBS) and non-invasive forms (e.g., ta/n-VNS, rTMS, tES). Among the invasive forms of electroceutical and bioelectric therapy, ECT shows fast symptom relief and can be a useful alternative for treating patients with intolerable adverse effects of medication considering its high efficacy. However, cognitive impairments are common during or after the use of ECT, and initial high cost along with anesthetic procedures burden the use of ECT. Conventional VNS has limi-

Table 1. Comparative table summarizing advantages and limitations of electroceutical and bioelectric therapies

Method	Indication(s)	Advantages	Limitations
ECT	Depression Catatonia Mania Schizophrenia	Rapid symptom relief Alternative for patients with intolerable adverse effect of medication	High costs Require a process of anesthesia Cognitive impairments
VNS	Depression Refractory epilepsy Inflammatory disorders	Wide range of applications Non-invasive, portable, and cost-effective method with no severe side effects for ta-VNS	Require an implantation surgery for conventional VNS Lack of established protocol for ta-VNS
rTMS	Depression Schizophrenia Motor stroke Neuropathic pain	Non-invasive treatment Superior tolerability over ECT & DBS in treating patients with depression Can induce focal and localized stimulation	Less effective than ECT in treating patients with depression
tES	Depression Schizophrenia Chronic stroke Motor deficit	Non-invasive treatment Portable, cost-effective, and simple to manipulate Can probe neurophysiology of cognitive functions based on the oscillatory activity using tACS	Difficulty finding the optimal protocol due to nonlinear effect of tDCS Various confounding factors associated with the direct mechanism of tACS
DBS	Parkinson disease Movement disorders Depression OCD	Reversible effect Adjustability following the surgical implantation	High costs Risks associated with surgical procedure and implanted device Frequent revisits and battery replacement

Indication(s) include psychiatric disorders for which the electroceutical and bioelectric therapy was FDA-approved or its efficacy has been actively investigated through randomized controlled trials as a treatment. ECT, electroconvulsive therapy; VNS, vagus nerve stimulation; ta-VNS, transcutaneous auricular vagus nerve stimulation; rTMS, repetitive transcranial magnetic stimulation; DBS, deep brain stimulation; tES, transcranial electrical stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; OCD, obsessive convulsive disorder; FDA, US Food and Drug Administration.

tations in that it is delivered in an invasive way through a surgical procedure, but is effective in treating a wide range of neuropsychiatric disorders due to its anti-inflammatory effect. High initial costs and risks associated with surgical procedures or implantation are also barriers to expanding the use of DBS. However, DBS offers the advantages of reversible and adjustable effects where stimulation parameters can be customized for individual needs. In the case of non-invasive forms of electroceutical and bioelectric therapy, rTMS allows localized and focal stimulation through magnetic fields and is superior to ECT and DBS in terms of tolerability. However, it is less effective than ECT in treating patients with depression. tES, another non-invasive therapy, applies either direct currents (i.e., tDCS) or alternating currents (i.e., tACS) by using portable and simple-to-manipulate devices. Specifically, tACS allows probing the neurophysiology of cognitive functions based on the oscillatory activity of the patient. tDCS has been cost-effective in treating patients with depression, but clinicians may have difficulty in finding the optimal protocol due to the nonlinear effect of tDCS. ta-VNS is conducted in a non-invasive way by targeting the left cymba conchae of the outer ear known to receive the auricular branch of the vagus nerve. ta-VNS is a portable and cost-effective method with no severe side effects but has limitations in that it lacks an established protocol for application. We conclude by suggesting that further advances in electroceutical and bioelectric therapy must build upon the above understanding of overall techniques to enhance the effectiveness and supplement the limitations for treating various neuropsychiatric disorders. Such direction will open a window of opportunity for wide application of electroceutical and bioelectric therapy beyond the current status.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Bori Jung, Seung-Hwan Lee. Original draft: Bori Jung. Critical revision: Chaeyeon Yang, Seung-Hwan Lee. Supervision: Seung-Hwan Lee.

■ ORCID

Bori Jung	https://orcid.org/0000-0002-7172-0473
Chaeyeon Yang	https://orcid.org/0000-0002-8355-0571
Seung-Hwan Lee	https://orcid.org/0000-0003-0305-3709

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