Transcranial Magnetic and Direct Current Stimulation in the Treatment of Depression: Basic Mechanisms and Challenges of Two Commonly Used Brain Stimulation Methods in Interventional Psychiatry

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Keywords

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Abstract

Noninvasive neuromodulation, including repetitive transcranial magnetic stimulation (rTMS) and direct current stimulation (tDCS), provides researchers and health care professionals with the ability to gain unique insights into brain functions and treat several neurological and psychiatric conditions. Undeniably, the number of published research and clinical papers on this topic is increasing exponentially. In parallel, several methodological and scientific caveats have emerged in the transcranial stimulation field; these include less robust and reliable effects as well as contradictory clinical findings. These inconsistencies are maybe due to the fact that research exploring the relationship between the methodological aspects and clinical efficacy of rTMS and tDCS is far from conclusive. Hence, additional work is needed to un-

derstand the mechanisms underlying the effects of magnetic stimulation and low-intensity transcranial electrical stimulation (TES) in order to optimize dosing, methodological designs, and safety aspects.

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Introduction

Transcranial neuromodulation driven by repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) has been found to be a promising noninvasive treatment for a variety of neuropsychiatric conditions [1–8]. Therapeutic utility of these methods has been claimed for psychiatric conditions such as depression, acute mania, bipolar disorder, panic, hallucinations, obsessions/compulsions, schizophrenia, catatonia, posttraumatic stress disorder, and drug cravings; neurologic diseases such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, epilepsy; rehabilitation of aphasia or of hand function after

stroke; and pain syndromes such as neuropathic pain, visceral pain, or migraines [7–9].

TMS offers potential for higher efficacy and a lower number of adverse effects relative to pharmacotherapy or electroconvulsive therapy. As a result, the importance of this technique and the therapeutic possibilities are exponentially increasing. The most successful example has been the treatment of major depressive disorder (MDD), which resulted in several countries approving its use in clinical settings. The most frequently applied evidence-based treatment approach for MDD is high-frequency (10 Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC). It has a level A recommendation in the guidelines for good clinical practice, especially for the acute phase of treatment-resistant depression [9].

Similarly, with regard to the application of tDCS for MDD, the current approach is to enhance neural activity in the left DLPFC with anodal stimulation and/or to reduce neural activity in the right DLPFC with cathodal stimulation [10, 11]. tDCS is recognized with a level B of evidence regarding the antidepressant efficacy of anodal tDCS of the left DLPFC in the guidelines for good clinical practice [8].

In spite of the therapeutic success in MDD, there are still several open questions with respect to the general clinical use of these methods in interventional psychiatry. Studies based on knowledge of rTMS effects, usually in the motor area, have led to further research and, consequently, guidelines for using rTMS protocols in therapeutic practice [9, 12]. However, many unanswered questions persist regarding how these differences in parameters of rTMS protocol might impact treatment efficacy and what are the possible ways forward to reduce such variations for maximal rTMS stimulation benefits. Currently, rTMS and tDCS are usually applied either as a monotherapy or as augmentation to pharmacotherapy and/or psychotherapy. Although the response to these treatment options is better than sham results in randomized controlled trials (RCTs), a large proportion of patients do not respond. It is therefore imperative to seek optimization of the treatment protocol through personalization of brain stimulation. Furthermore, relating to clinical practice, there is good evidence for beneficial antidepressant effects of transcranial stimulation, although to date the appropriate place of this technique in the therapeutic decision tree is still not clearly defined.

In this short review, we briefly outline the basic principles of rTMS and tDCS. Additionally, we describe how rTMS influences functional connectivity (FC) in response to depression treatment and discuss the sources that in-

troduce disparity in the response to stimulation. Finally, we suggest ways to overcome some of these disparities. Applying these is crucial to boost the performance of rTMS in the treatment of depression.

Transcranial Magnetic Stimulation

TMS was first proposed as a method of brain stimulation in 1985 [13]. It facilitates not only relatively focal stimulation of cortical targets, but also more diffuse stimulation of larger brain volumes, thus penetrating deeper brain regions than tDCS can [14]. The basic principle behind TMS remains the same across protocols and works on Faraday's principle, i.e., a changing electric field induces a changing magnetic field of a few tesla, which in turn induces a perpendicular electric current in conductors in the near vicinity, i.e., a population of neurons [15]. There are several adjustable parameters when designing TMS protocols, such as the number of pulses, frequency, train length, and intertrain interval (ITI) [16]. The research has explored TMS protocols with variations of these parameters mostly on motor-evoked potentials (MEPs) and resting motor threshold (RMT) [17].

While single pulses can evoke MEPs that result in muscle responses when targeted at the primary motor cortex (M1), they are usually not enough to induce longer-lasting effects. Hence, the single pulses of TMS are applied in succession, in prescribed repetitive patterns that allow sustained after effects from the stimulation [18], called rTMS. Therefore, the frequency at which the pulses are delivered and the duration for which they are applied [19] contribute to the variations seen in rTMS protocols that impact the after effects observed. Frequencies of rTMS delivery ≤ 1 Hz are called low-frequency stimulation and induce inhibitory effects; high-frequency stimulation is ≥ 5 Hz, and induces excitatory effects in brain [17, 20]. Another important factor that can impact the effects of rTMS includes the intensity relative to the RMT at which the stimulation is delivered. Previous work has shown that if high-frequency rTMS is delivered at intensities lower than the RMT it decreases cortical excitability, while if delivered above the RMT it causes an increase in cortical excitability [21]. A recent study also showed that having adequate ITI during high-frequency rTMS may be essential to its efficacy, as the appropriate ITI can prevent the conduction failure of neurons and thus allow rTMS effects to carry through [22]. It has been proposed that the length of ITI may play a role in rTMS protocol efficacy and should be optimized for the disorder or a desired outcome.

Combining rTMS with brain imaging has increased the understanding of rTMS effects and created the potential to dissect anatomical and functional cross-talk between different brain regions [16]. This ability to modulate brain activity and FC using rTMS has led to its use in clinical settings for therapeutic benefits [23], where it is employed to compensate for processes that are disturbed in psychiatric illnesses. For example, in MDD, rTMS over the DLPFC is used to compensate for deficient cortical excitability and FC [24].

Past research using positron emission tomography (PET) has shown left prefrontal glucose hypometabolism in patients with depression [25]. The use of excitatory rTMS as a treatment stemmed from the expectation of correcting for this hypoactivity in the frontal regions, as several groups had shown that the use of rTMS resulted in an increased blood flow in the prefrontal regions [26, 27] and increased activity under the TMS coil [27–29]. Studies have now gathered evidence for the clinical efficacy of high-frequency (10 Hz) rTMS [30, 31] to the left DLPFC, low-frequency (1 Hz) [32] to the right DLPFC, and bilateral rTMS treatment to both the left and the right DLPFC [33]. More recently, a large study established the noninferiority of intermittent theta-burst stimulation (iTBS) [34] over rTMS protocol. It showed that iTBS stimulation did not differ from 10-Hz rTMS treatment in terms of dropout rates, expected side effects, safety, or tolerability as well as clinical benefits [35]. Thus, it has been established that rTMS (left high-frequency, right low-frequency, and bilateral) and iTBS are effective and reliable treatment options for depression, albeit with different degrees of response.

While PET studies have made a case for rTMS in the treatment of depression, other neuroimaging studies using simple and noninvasive techniques, such as resting-state functional magnetic resonance imaging (rsfMRI), have contributed important knowledge about FC aberrations and changes in depression cohorts compared to healthy populations. Studies have reported that depression patients consistently have dysfunctions associated with the default mode network (DMN), central executive network (CEN), and salience network (SN) [36–38]. Several studies have shed light on the importance of the subgenual anterior cingulate cortex (sgACC), an important node within the DMN, and its negative correlation to the stimulation site at the DLPFC for a better therapeutic response to rTMS [39–41]. Such results from studies using rsfMRI in subjects with depression have allowed for building a FC-based model of the disease. Utilizing these FC-based models, it is possible to stimulate such net-

works to better understand the antidepressant mechanism of rTMS. For example, Liston et al. [37] reported on the effects of 10-Hz rTMS on the functional networks in depressed subjects: higher sgACC-DMN connectivity in these subjects was decreased post-rTMS treatment, suggesting that rTMS acts by influencing sgACC-to-DMN connectivity. This is in line with the general implication of sgACC in depression treatment, where normalizing sgACC hyperactivity is associated with an antidepressant response [42, 43]. Another study [44] using iTBS for antidepressant treatment showed higher sgACC connectivity to the DLPFC and precuneus in individuals with depression, which normalized in response to rTMS treatment.

Numerous FC features have been employed to predict the response to rTMS and/or iTBS in MDD. For example, Baeken et al. [44] reported that positive connectivity between the sgACC and medial orbitofrontal cortex at baseline could differentiate responders from non-responders to accelerated iTBS. Another study reported that the higher FC within DMN and SN characterized responders for both iTBS and 10 Hz rTMS patient groups [45]. In the case of 5-Hz rTMS, there are reports of more negative pretreatment FC between sgACC and DMN predicting clinical response [46]. For 10-Hz rTMS, the connectivity of DLPFC to several brain regions, namely, reduced FC to the left caudate [47], higher FC to the striatum [48], and greater negative FC to the sgACC [39], has been shown to predict treatment response, highlighting the importance of not only DLPFC but also its FC to distant brain regions in the rTMS treatment mechanisms of MDD.

As is clear from above, there seems to be a wide variety of markers predicting rTMS and iTBS responses and symptoms improvement. In future studies, it would thus be important to replicate the predictive values and investigate combinations of markers that increase specificity and sensitivity or even promote the use of either rTMS or iTBS. Such future development of predictive features, possibly with multivariate data analysis, would allow for greater efficiency of rTMS in clinical settings, thereby benefitting the health care system and providing patient satisfaction by preventing treatments being undertaken that are not expected to work.

While rTMS has been established as an effective treatment for MDD, the percentage of patients that respond to this treatment remains low, varying from 40 to 50% [49]. This likely stems from interindividual variability in the response to rTMS. Some of the factors that contribute to these differences include age, gender, variations in

Fig. 1. The standard MNI (anatomical) coordinate-based left DLPFC (denoted with a filled star) versus targets selected when employing individual rsfMRI data (denoted with filled circles).

individual cortical excitability, neurophysiological traits, white-matter connectivity, anatomical and functional variability, and genetic polymorphisms [16].

Although age has an influence on the effect of single- or paired-pulse techniques [50], evidence of rTMS being influenced by age remains inconclusive [16]. MEP variability, however, has been shown to be higher in females than in males [51]. White-matter connectivity also influences how the local effects of rTMS spread across networks, so a variation in white-matter pathways would contribute to differences in rTMS effects [52–54]. Similarly, as rTMS is known to cause its effects via tissue reorganization and plasticity (inducing a long-term potentiation/depression-like phenomenon), the genes involved in regulating such events can influence the outcome of rTMS [55, 56].

Other factors such as scalp-to-cortex distance can also influence the outcome, because the magnetic field induced by rTMS decays as a function of distance [27]. Hence, variations in scalp-to-cortex distance between subjects result in nonequivalent amounts of current being induced in the same cortical region when the same threshold, relative to RMT, is used for each individual. In this sense, simple corrective measures to calculate the re-

quired compensatory increase or decrease in rTMS intensity based on scalp-to-cortex distance have been suggested [57].

Apart from the reasons mentioned above, the target site for stimulation is also important to note. In the case of rTMS for the treatment of depression, the common practice of delivering stimulation at 5 cm anterior to the motor cortex has been shown to be ineffective at reaching the desired DLPFC target [58]. Hence, it has been suggested that EEG-based landmarks and structural or functional MRI to guide the rTMS coil to the DLPFC using online neuronavigation systems be used. Figure 1 illustrates standard versus personalized sites for stimulation. However, an anatomically based landmark for targeting rTMS often fails to account for differences in the functional architecture of the brain from individual to individual [59–61]. Thus, using anatomical landmarks can provide a general location of various brain regions, but might still grossly miss the functionally important regions in terms of either network connectivity or functional activity.

We therefore suggest directing rTMS at cortical targets using functional activity-related information. This can be task-based fMRI, which uses a task that engages the re-

gion of interest at which the stimulation is then aimed. The idea of engaging the aberrant targeted region arises from the knowledge that the effects of TMS or rTMS are very much dependent upon the activity occurring in the region being targeted [62, 63]. Previous studies [64] have shown that TMS pulses or bursts usually activate the subpopulations of neurons, which are exhibiting the lowest levels of excitability. This is the state-dependency phenomenon of neurostimulation, where the current state of a subject's brain influences the outcome of the stimulation. Therefore, by engaging particular regions of the brain, researchers can probably influence the anticipated impact of rTMS.

Similarly, it can be based on rsfMRI, where network-based FC is used to identify the important nodes of a network that are targeted using rTMS. As described in studies by Weigand et al. [39] and Fox et al. [40, 41] our research group utilized rsfMRI to identify left DLPFC targets based on the connectivity to the sgACC [65]. We selected rTMS target nodes in the left DLPFC that had a higher negative connectivity to the sgACC as it has been suggested that this has a better clinical outcome. Our study forms the basis that it is in fact practical to use individual rsfMRI to target rTMS, hence opening up new avenues for personalization of rTMS treatment.

However, fMRI sessions are currently not a standard part of MDD treatment and care, and the suggestion of personalized targeting of the site of stimulation based on FC data is a preliminary one that requires further validation. This fMRI-based decision could prove important for the 50% of patients who are refractory to therapy and so do not benefit from rTMS [49]. More RCTs exploring the benefits of FC-based versus anatomically based targeting (or 10/20 EEG-system based) are needed; this would encourage the clinical integration of fMRI data for use in rTMS therapy. If the efficacy of such an approach is established from multicenter RCTs, we believe the benefits will outweigh the costs associated with fMRI and would have a positive impact on tertiary health care of patients with MDD.

Transcranial Direct Current Stimulation

Low-intensity transcranial electrical stimulation (TES) methods encompass the external application of electrical current to the brain using at least two electrodes. The externally applied current modulates the spontaneous firing rates of neurons by de- or hyperpolarizing resting membrane potentials (as initially observed in the case of

tDCS >50 years ago [66, 67]), thereby changing cortical excitability and activity. Evaluating the functional and behavioral consequences of this method, low-intensity tDCS is particularly appropriate for gaining a further insight into the causative functional role of a given brain area and in functionally connected brain networks, e.g., how brain processes arise and could be changed. The magnitude and direction of the induced after effects are highly dependent on the duration and intensity of the stimulation as well as electrode size and montage [68]. Originally, the tDCS effect was estimated by measuring the amplitude of the MEPs induced by single-pulse TMS [69–71]. Several studies conducted on the M1 showed that the MEP size increased after approximately 10 min of anodal stimulation and decreased after cathodal stimulation [review 71] and remained in this state for up to 60 min after the end of the stimulation. Because this “long-lasting” effect of tDCS is thought to be related to neuroplastic changes in the brain, many studies have addressed the issue of its impact on visual perception and cognitive functions, including motor-learning, working memory, and semantic and episodic memory in healthy subjects as well as its therapeutic applications in neurologic and neuropsychiatric diseases [e.g., 72–79].

In the last few years, studies have been published that question the efficacy of tDCS. High between- and within-group variability and even individual variability were observed, and several of the studies could not be replicated by other investigators. The reason for the relatively high variability is far from being understood [80–85]. Many researchers and clinical practitioners concentrate on the manipulation of four adjustable tDCS parameters: current intensity, stimulation duration, electrode size, and electrode position. These technical variables are easily regulated and play a large role in tDCS effects. However, even these controllable parameters are not always discussed in any cogent manner with regard to increasing efficacy, understanding the mechanisms, or decreasing the variability.

The traditional description of tDCS effects is related to changes in “cortical excitability,” i.e., it is thought that the anode that is positively charged enhances the excitability of the underlying cortex while a negatively charged cathode suppresses the excitability of the targeted cortical area [69]. Generally, there is evidence at the neuronal level that anodal tDCS hyperpolarizes the membrane potential in the apical dendritic regions and depolarizes it in the somatic region, whereas the cathodal electrode has an opposite effect [86–90]. Furthermore, besides cell morphology, the extent to which neurons are affected by tDCS

(and how) also depends on the orientation of the cells with regard to the induced electric field.

TDCS is typically applied at 1–2 mA (maximum 4 mA), but the electric field in the brain is reduced due to shunting effects (of skin and scalp); it is therefore estimated to maximally reach 0.4–0.8 mV/mm when 1.0 mA is applied externally [91, 92]. While early studies observed that the magnitude and length of the induced after effects (at least after M1 stimulation) increased with higher current intensities and longer stimulation duration [70, 93], later studies reported that doubling the intensity of tDCS led to an opposite effect after cathodal stimulation [94] and increasing the duration of anodal tDCS to 26 min led to MEP decreases [95]. With regard to other cortical areas, the effects of different stimulation intensities and durations have not yet been systematically investigated.

The magnitude and duration of the after effects also depend on the functional state of the brain, i.e., whether the stimulation is given during rest or before/together with a motor or cognitive task [96]. When tDCS has no effect during tasks, it can be speculated that the effect is perhaps too weak to manifest when the activity is being performed [97].

The size of the electrodes and their montage are highly relevant for the efficacy of the stimulation. Conventionally, tDCS involves two electrodes placed on the scalp. Typical electrode sizes range between 4 and 35 cm². A first limitation here derives from the wide electric field induced in the cortex by such large electrodes [86, 91, 98, 99]. The consequence is poor focusing, which can make the interpretation of the results difficult because of the impossibility of precisely locating the structures affected by tDCS. It should also be considered that almost all previous studies targeted single brain regions with low-intensity TES to modulate brain function. However, brain regions interact with each other through networks; the stimulation of a single brain area may thus influence and/or be influenced by other regions and networks. Because of this complexity, the type of stimulation that was originally seen as “excitatory” (anodal tDCS) might not always increase “cortical excitability” and vice versa. A better description of the tDCS effect in the future might be that it modifies the “excitability-inhibitory balance” in the stimulated and related cortical areas. With regard to the parallel stimulation of multiple regions of a network [100], high-definition multielectrode tDCS arrays, of up to 32 electrodes (HD tDCS), have recently become available [101, 102].

Regarding the use of tDCS for the treatment of depression, the current approach is similar to that de-

scribed above for rTMS. Most of the clinical trials have concentrated on enhancing the neural activity in the left DLPFC with anodal stimulation and/or reducing the neural activity in the right DLPFC with cathodal stimulation [11, 103–108]. Computer modeling and neuroimaging (fMRI) tDCS studies suggest that, in fact, the stimulation also largely affects deeper brain structures, such as the sgACC, amygdala, and hippocampus [86, 99, 109, 110].

The antidepressant effect of anodal tDCS on the left DLPFC was investigated in at least 15 RCTs [8], as well as in several case reports and open-labeled studies. Unfortunately, most of the RCTs investigating the beneficial effects of tDCS had large patient sample variability (related to the diagnosis of drug-resistant, unipolar, or bipolar depression) and different goals (comparing different stimulation protocols, add-on treatment [pharmacotherapy], or long-term treatment), so no solid conclusions can be made based on these data. One of the critical points is that the concomitant administration of antidepressant medication, benzodiazepines, and antiepileptics can influence tDCS-mediated effects on brain excitability and may indeed have increased variability and reduced the therapeutic impact in these studies. On the other hand, in a recent clinical trial, the combination of anodal tDCS with sertraline (50 mg/day) was superior to each treatment applied alone and to placebo, suggesting an additive interaction of tDCS and antidepressant medication (the SELECT-TDCS trial [111–113]). Previous studies implied that the outcome of tDCS in healthy subjects may be mediated by pharmacological modulation of noradrenergic serotonergic pathways. Therefore, serotonergic enhancement might increase the neuroplastic effects of anodal tDCS, thus resulting in synergistic effects [114, 115].

A precise understanding of the differences between responders and nonresponders may help in the identification of patients responsive to tDCS at the beginning of the therapy. In a recent trial (Escitalopram vs. Electrical Current Therapy for Treating Depression Clinical Study [ELECT-TDCS]), it was observed that the plasma levels of nerve growth factor predicted early depression improvement due to tDCS; this should be explored in further clinical studies [106].

Recent clinical guidelines recommend the following when using tDCS for treating depression: anodal tDCS of the left DLPFC (with right orbitofrontal cathode) delivered for at least 10 days (stimulation intensity: 2 mA and duration: 20–30 min) in medicated or drug-free patients with MDD. There is also an appropriate amount of evi-

Table 1. A summary of possible approaches for reducing variability in the rTMS and tDCS response in patients with depression

First author [Ref.], year	Suggested method of reducing interindividual variability
McClintock [118], 2018	Consensus recommendation by experts in the field of rTMS on effective and safe use of rTMS for depression treatment. The expert panel suggests that MRI-guided coil positioning achieves greater precision; however, evidence of greater efficacy is still limited. In the absence of a neuronavigation system or MRI, coil positioning at F3 based on the international 10–20 system is preferred for clinical use.
Singh [65], 2019	Proof-of-concept study showing the use of rsfMRI connectivity to identify relevant networks covering the left DLPFC and sgACC and identifying functionally relevant nodes within the left DLPFC region that also have a negative correlation to the sgACC
Siddiqi [119], 2019 Siddiqi [120], 2019	Using rsfMRI connectivity-based dorsal attention network and DMN to identify left DLPFC targets based on maximal negative connectivity to the sgACC
Luber [121], 2017 Neacsiu [122], 2018	A case for linking rTMS to the underlying neurocircuitry in depression disorder and using this model to individualize the rTMS targets based on task-based fMRI
Sathappan [123], 2019	A review on how concurrent or sequential use of cognitive interventions can allow controlling the state of the neural network being targeted, facilitating a more efficient and optimized response to rTMS
Stokes [57], 2005	Using T1-weighted images to scale the motor threshold to avoid over- or understimulation
Nord [124], 2019	Anodal tDCS is significantly superior to sham in individuals with high left prefrontal cortex BOLD activation at baseline during the performance of an <i>n</i> -back task (86% accuracy in predicting clinical response using this measure)
Filmer [125], 2019	Pre-tDCS baseline measures of GABA and glutamate, acquired using MRS, correlated with the extent to which stimulation modulated behavior
Bajbouj [126], 2018	CBT combined with active bifrontal tDCS performed during psychotherapy sessions (anode over F3 and cathode over F4, current intensity 1–2 mA, applied 10 min after starting CBT and lasting 30 min) increased the efficacy of the stimulation and resulted in a stronger antidepressive effect
Lefaucheur [7], 2016	Concomitant administration of benzodiazepines or antiepileptics may influence the tDCS-mediated effect on cortical excitability and reduce its therapeutic impact in patients with depression
Brunoni [127], 2013	Concomitant administration of anodal tDCS over the left DLPFC with sertraline hydrochloride (50 mg/day) is superior to each treatment on its own or placebo, suggesting an additive interaction of tDCS and antidepressant pharmacotherapy
Lefaucheur [7], 2016	Good care must be taken to ensure that subjects cannot differentiate between stimulation and control conditions

Of note, these suggestions may have the potential to be applied to other psychiatric disorders. Based on the underlying neural circuitry implicated in the psychopathology, neuroimaging methods can be adopted to more precisely target relevant brain regions/networks.

dence to make a level B recommendation concerning the absence of efficacy using the same tDCS protocol in patients with drug-resistant depression.

Conclusion

rTMS and tDCS have been widely explored for the treatment of depression and their efficacy, safety, and tolerability have been established. By combining these data with rsfMRI information, a developed FC-based model indicates that MDD is associated with aberrant DMN,

CEN, and SN connectivity, possibly due to hyperactivity of the sgACC. rTMS is believed to normalize these functional networks, which is reportedly in line with reduced sgACC activity in response to antidepressant treatment. Despite the current understanding, the effectiveness remains low for the treatment of MDD, partly stemming from age, gender, and individual genomic, anatomical, and functional variability. Of these, age and gender vary in the real-world patient population; an effort should thus be made to increase stimulation efficiency independent of age and gender. Table 1 summarizes suggestions to reduce variability in the response to standard rTMS by

means of integrating individual neuroimaging data. As mentioned earlier, these recommendations are still in need of rigorous scientific testing. Multicenter RCTs will establish the utility of these approaches, for the treatment of depression and other psychiatric disorders.

Similar to rTMS, one of the critical points in tDCS is to increase the efficacy of stimulation. Early studies used a maximum of 20-min-long sessions of 1 mA anodal tDCS over the left DLPFC and a cathode placed over the right supraorbital region. Current trials support the use of a longer stimulation duration (30 min) and a higher intensity (2 mA), with the cathode placed over the right DLPFC. However, it must still be demonstrated whether increasing the duration and intensity of stimulation automatically leads to improved therapeutic efficacy in MDD. With regard to the long-term effects of tDCS, the number of studies is very limited. In a small study (on 11 patients) who completed a 3-month follow-up after a 10-day tDCS protocol, it was found that 45% of the patients were still responders at the latest time point [116]. Nevertheless, a higher relapse rate has been reported when the repetition of the sessions was reduced from weekly to bi-weekly [111, 117].

Thus, we believe that attempting to reduce variability in factors such as target location and stimulation protocols, which contribute to the differences in response to brain stimulation, is the way forward for increasing the clinical effectiveness of transcranial stimulation. Furthermore, continued searches for predictive markers of brain stimulation response, molecular/genetic markers, and rs-fMRI-based FC markers for both tDCS and rTMS will likely augment the effective use of brain stimulation. Adequately sensitive and specific markers will allow for more efficient use of both clinical resources, including better utilization of patients' time and the overall impact on health, thus benefiting the economy in the larger run.

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The authors declare there are no conflicts of interest.

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