

## Transcranial Brain Stimulation Techniques For Major Depression: Should We Extend TMS Lessons to tDCS?

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**Abstract:** Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are non-invasive brain stimulation techniques that, by means of magnetic fields and low intensity electrical current, respectively, aim to interfere with and modulate cortical excitability, at the level of dorsolateral prefrontal cortex, in patients with major depression and poor response to standard antidepressants. While the clinical efficacy of TMS in major depression has been extensively investigated over the last 10 years, tDCS has attracted research interest only in the last years, with fewer randomized clinical trials (RCTs) in the field. Nevertheless, in spite of the different rationale and mechanism of action of the two techniques, tDCS recent acquisitions, in relation to the treatment of major depression, seem to parallel those previously obtained with TMS, in terms of treatment duration to achieve optimal benefit and patient's history of drug-resistance. After briefly introducing the two techniques, the article examines possible common pathways of clinical use for TMS and tDCS, emerging from recent RCTs and likely orienting future investigation with non invasive brain stimulation for the treatment of major depression.

**Keywords:** Brain stimulation, major depression, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS).

Within transcranial brain stimulation techniques, both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) represent non-invasive interventions, increasingly used in psychiatric research and clinical practice, to focally and selectively stimulate the dorso-lateral prefrontal cortex (DLPFC) in patients with major depression and poor response to standard antidepressant treatments.

While TMS utilizes coil-generated magnetic fields to penetrate the brain and, then, convert in electric current modulating cortical excitability, in tDCS, weak electric currents (1-2 mA) are directly applied to the scalp with the same purpose, by means of two electrodes: the anode (where the current enters), positioned over the left DLPFC, and the cathode (generally on the right DLPFC, where the current flows out).

While magnetic impulses can directly interfere with polarization process of cortical neurons and strengthen synaptic connections through mechanisms of long-term potentiation and depression, tDCS effects are supposed to be more oriented toward modulation of neurotransmitter systems and promotion of brain derived neurotrophic factor-dependent synaptic plasticity, even though tDCS induced changes in resting membrane potential, spontaneous neuronal firing rates, cerebral blood flow and metabolism as well as increase in myo-inositol brain content have been reported [1-3].

In spite of a different rationale and peculiar mechanisms of action, both TMS and tDCS are aimed to restore the functional balance between the 2 brain hemispheres, which is supposed to be altered in major depression [4]. Current pathophysiological models, in fact, converge in suggesting that two major groups of brain regions - a "dorsal" and "ventral" network - account for the formation of the varied symptoms of depressive illness [4]. Within this theoretical framework, depression is hypothesized to involve concurrent hypoactivation of dorsal prefrontal regions and hyperactivation of ventral prefrontal regions, particularly in the left hemisphere [5]. Symptom remission is, therefore: supposed to require facilitation of hypoactive dorsal brain regions and inhibition of hyperactive ventral areas, which is actually what transcranial stimulation techniques aim to obtain [4, 5].

With respect to clinical use of transcranial stimulation techniques, compared to tDCS, repetitive TMS has been more extensively investigated in the field of major depression, over the last years, in terms of large randomized, sham controlled trials yielding meta-analyses [6], guidelines recommendations [7] as well as, in some countries, specific approval by local regulatory agencies. Taken as a whole, the aforementioned studies have allowed at least two important acquisitions, aimed to maximize treatment response and better characterize TMS candidate: 1) longer duration of treatment (*i.e.*, more tms sessions) produce higher response and remission rates and 2) higher treatment resistance level to previous treatments reduces tms response. Therefore, even though other stimulation parameters still need to be further investigated (e.g., tms as monotherapy or augmentative treatment, need for and schedule of maintenance sessions after acute treatment, efficacy in unipolar vs bipolar depres-

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sion, etc.), it is currently well established that the best candidate for TMS response should be treated for not less than 3/4 weeks and should not be a highly treatment resistant subject.

With respect to tDCS, a more limited number of sham-controlled studies has been published to date, yielding room for only two meta-analyses [8, 9], but no specific treatment guideline, in the field of major depression. In such perspective, however, the recently published, largest controlled trial (published after the aforementioned meta-analyses) showed that tDCS was superior to placebo/sham tDCS over a six-week treatment course, as well as comparable efficacy to sertraline [10]. Of note, authors found that baseline severity and treatment resistance to more than 1 failed antidepressant trial were associated with a lower response. Previously, another sham-controlled, randomized trial found an increased number of responders after 6 weeks of treatment compared to 3 weeks, suggesting that antidepressant effects might be enhanced with longer treatment [11]. Taken as a whole, tDCS recent results in terms of duration of treatment and baseline level of treatment resistance, in relation to outcome, seem to parallel previous, large multicenter TMS studies [12, 13], supporting the perspective of a similar profile for candidate choice to transcranial non-invasive stimulation techniques. While further studies are required to confirm such aspects, the debate as to which technique to offer patients [14] should also start to consider more specifically tolerability-related issues and procedure-related costs as well as other clinical features that may orient clinician's choice.

#### CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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