Non-invasive electrical brain stimulation as a treatment for depression

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Title Trial of electrical direct-current therapy versus escitalopram for depression

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Summary

Major depressive disorder is a highly prevalent condition for which the treatment of first resort is often a selective serotonin reuptake inhibitor (SSRI). There is a paucity of evidence about the long-term effects of SSRI use and unpleasant side effects of SSRIs are common. As a result, interest has increased in new and nonpharmacological treatments for depression. Various forms of electrical and magnetic stimulation have been explored as possible interventions. In this study the authors compare the effects of transcranial direct current stimulation (tDCS) to those of escitalopram for the treatment of unipolar depressive disorder.

tDCS is a form of electrical stimulation that entails the application of electrodes to a participant's scalp and the passing of a direct electrical current between them. tDCS does not cause action potentials, as are typically associated with most forms of transcranial magnetic stimulation (TMS), but has been shown to temporarily alter the resting potential of the membranes of affected neurons. Physiological studies have shown that neurons in proximity to the positive electrode (anode) have a raised resting potential, and thus require a lower level of dendritic input to generate an action potential. The converse applies to neurons close to the negative electrode (cathode), which are temporarily inhibited. As the authors note, tDCS is less associated with major adverse side effects (e.g. seizures) than TMS and therefore may be more acceptable as a clinical intervention. It must be noted, however, that tDCS has been associated with minor adverse events (e.g. skin reddening, pain at the site of application, headaches) therefore its use is not wholly without issue.

In a previous study,[1] the authors compared the effects of tDCS and a SSRI (sertraline) to those of sertraline alone in the treatment of depression. They showed that the combination of stimulation and sertraline was superior to that of sertraline alone. The current study builds upon previous work by making a comparison between the effects of tDCS, a SSRI (escitalopram), and placebo. The authors investigated the hypothesis that tDCS would be non-inferior to escitalopram in the reduction of participants' scores on a standard depression index (the 17-item Hamilton Depression Rating Scale (HDRS-17)).

A total of 245 patients were assigned to one of three treatment groups. The first group received tDCS and a placebo tablet, the second received sham tDCS and escitalopram, and the third received sham tDCS and a placebo tablet. For admission to the study, participants were required to register moderate or severe depression on the HDRS-17 (indicated by a score of 17 or above out of a maximum of 52; a score of 24 or above indicating severe depression). In addition, participants were required to be naïve to tDCS and escitalopram (though not to all SSRIs). Participants taking antidepressants were required to undergo a wash-out period prior to study commencement. They were required to reduce any use of benzodiazepines to no more than the equivalent of 20 mg diazepam per day by the start of the study. Slightly over one quarter of the participants used benzodiazepines during the study.

The tDCS protocol consisted of the application of two 25 cm^2 electrodes to the participants' scalps with a current of 2 mA being applied for 30 min during each session. The anode and cathode were placed over the participants' left and right dorsolateral prefrontal cortices (DLPFC), respectively (these sites chosen as previous studies have shown that left DLPFC hypoactivity and right DLPFC hyperactivity have been associated with major depressive disorder[2]). Participants attended tDCS sessions for 15 consecutive week-days, followed by a weekly session for the next 7 weeks. In the

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case of sham tDCS, the participants underwent the same protocol with the exception that current was turned off after 30 s by the tDCS device. tDCS is most noticeable (and most unpleasant) when there is a change in the current that is applied to the skin. As such, it is invariably the case that the application of tDCS will include a fade-in period at the start of stimulation: this will entail the gradual, steady increase of current to the intended level. This fading-in minimises the sensations (generally a tingling or mild burning) associated with tDCS. A similar fade-out period is used at the end of stimulation. Given that the sensations associated with tDCS are at their strongest during fade-in and out, these periods are used to blind participants to the nature of the stimulation that they are receiving. In this study, participants receiving sham tDCS experienced fade-in, 30 s of stimulation and fade-out (followed by 30 min of no stimulation), thus giving them a comparable experience to those receiving active tDCS.

Participants received either a placebo tablet or 10 mg escitalopram daily for the first 3 weeks of the trial followed by 20 mg daily for the remaining 7 weeks.

The authors observed that the participants' level of depression (as measured by the HDRS-17) was reduced in all groups at the end of 10 weeks, with the decrease being largest in the escitalopram group (11.3 +/- 6.5), followed by the tDCS group (9.0 +/- 7.1) and then placebo (5.8 +/- 7.9). The authors specified that to claim non-inferiority of tDCS to escitalopram they would require the lower boundary of the confidence interval (on a modified t-test for non-inferiority) of the effects of tDCS to be at least 50% of the difference between the escitalopram and placebo groups. The effects of tDCS did not meet this criterion and therefore, while tDCS was superior to placebo, non-inferiority to escitalopram could not be claimed.

Participants in the active tDCS group were significantly more likely to report itching, tingling, skin redness, tinnitus and nervousness than the other groups. Two of 91 participants in the tDCS group had new-onset mania (as measured on the Young Mania Rating Scale). Participants in the escitalopram were significantly more likely to report sleepiness and constipation than those in other groups. The authors report that participants were able to guess their trial-group allocation with regard to escitalopram, but not with regard to tDCS.

Opinion

The use of SSRIs for the treatment of depression has become so commonplace that members of this family have appeared on the list of drugs most prescribed in the UK.[3] This is true in many other countries. Patients have expressed concern about the disruptive side effects that are commonly experienced, including changes to sleeping patterns, appetite and sexual function. Of additional concern to patients and physicians is a lack of a clear understanding of the effects of long-term use. These concerns have driven efforts towards 'cleaner' versions of SSRI medication (including escitalopram, a successor of citalopram) and investigations of alternative treatments. The most commonly considered alternatives have been forms of psychotherapy, which while appropriate for some cases of mild to moderate depression, have not proved effective for more serious cases. As such, there remains a strong motivation to continue the search for other treatments.

In recent years greater consideration has been given to forms of magnetic and electrical stimulation as interventions for psychological conditions. Psychological electromedicine has a long (and not always glorious) history having been used in the form of electroshock therapy and more recently deep neural stimulation for intractable depression. As the technology available for the delivery of brain stimulation has improved, the possibility of making better targeted and less dramatic interventions has increased. Investigations have been focused on the use of TMS and more recently transcranial electrical stimulation as interventions for a range of conditions. Evidence has been accumulated that suggests TMS can be effective in depression, post-traumatic stress disorder and in treating auditory verbal hallucinations. Despite the discomfort experienced by patients, recommendations have been made for the inclusion of TMS in the psychiatrist's armamentarium. There is less experience of the use of transcranial electrical stimulation and therefore the examination of its use by the present study's authors is merited.

The stimulation used in this case was transcranial direct current stimulation (tDCS), which is generally experienced by subjects as mildly unpleasant rather than painful or distressing. The adverse effects of tDCS are most commonly a burning or tingling at the scalp around the edges of the contact pads used to deliver the current. Less common effects are headaches and dizziness. The authors' note of two new-onset cases of mania is uncommon, but is seemingly becoming less so with six groups reporting cases of mania or hypomania after the application of tDCS since 2010.[4] The increased incidence of post-tDCS mania is perhaps understandable for both the increased interest in the use of tDCS as a clinical tool for the treatment of mood disorder and the challenges presented in titrating the dose of stimulation received by patients. One might also wonder whether tDCS might unmask bipolar disease in patients previously diagnosed with unipolar depression.

Examining the first point, there is a growing amount of evidence of the asymmetrical contributions of left- and right-dorsolateral prefrontal cortex to mood regulation. Given that these regions are located on 'stimulatable' surfaces of the brain and that tDCS has an opposite effect on brain tissue at its positive and negative electrodes (excitatory at the anode and inhibitory at the cathode), it is clear why the potential of tDCS to rebalance the activity of these regions would be of interest to researchers and clinicians. Repeated sessions of tDCS have been shown to promote 'conditioning' changes in brain tissue (i.e. changes that last longer than the duration of stimulation) and therefore offer the possibility of therapeutically altering and then maintaining brain activity in a manner similar to that offered by pharmacological interventions.

With regard to the delivery of a 'dose' of tDCS, we should consider the mechanism by which tDCS is delivered to brain tissue. Physiological studies have demonstrated that applying a current to neurons can alter their membrane resting potential and therefore temporarily adjust the level of dendritic input that is required to generate an action potential. It must be noted, however, that to reach brain tissue the current travelling between the stimulator pads placed in contact with the scalp must first pass through the skull, the meninges and the highly conductive cerebrospinal fluid. The conductivity of the cerebrospinal fluid and individual differences in subject anatomy mean that it is highly challenging to determine the level of stimulation delivered to a brain area of interest. In preclinical research these challenges have been approached through the use of neuroimaging to enable researchers to 'see' the structure of brain tissue beneath proposed stimulation sites,[5] and studies that have mathematically modelled likely current flows.[6] These approaches are expensive in terms of both time and resources and have not been widely applied to clinical studies.

This study gives an example of the challenges associated with blinding human subjects to their treatment group. It is interesting to note that the authors were successful in concealing the type of tDCS received (sham or verum), but were unable to prevent participants from determining they were receiving escitalopram or placebo. Creating a sham stimulation condition has been a challenge that has not always been successfully addressed: in TMS studies, the presence or absence of a 'tapping' sensation at the scalp or muscle activations have tended to inform participants of the treatment received. Progress has been made in tDCS blinding given that the sensations experienced tend to be most noticeable when the level of stimulation changes rather than when a participant receives a steady level of stimulation. This enables experimenters to blind participants by having ramp-up and ramp-down periods at either side of a period of steady or no stimulation. This has become a de facto standard and has proved effective, as was the case in this study.

Blinding a psychopharmacological intervention is challenging where participants are not naïve to the effects of this or similar medicines. The side-effects of initiating escitalopram usage are well-documented (and are essentially the same as those associated with other SSRIs: anxiety, nausea, restlessness, headaches etc.). In this study the participants were required to be naïve to escitalopram, but not other SSRIs. It is probable that this experience played a role in enabling the participants to infer their treatment group. It would be informative to determine whether blinding to psychopharmacological interventions requires treatment naïvety to be of a broader scope.

It is interesting that around one third of the participants in two groups and one fifth in the other were using benzodiazepine during the study. Anxiety disorders are commonly comorbid with depression therefore the use of benzodiazepine by this cohort is not particularly surprising, but (as noted by the author previously[7]) this family of medications can alter the effects of tDCS. Brunoni found that benzodiazepine reduced the effectiveness of tDCS, therefore removing this factor from future studies may give a clearer indication of whether tDCS is non-inferior to escitalopram in the treatment of depression.

In conclusion, the authors have presented further evidence of the potential efficacy of electrical stimulation in the treatment of depression, shown that blinding of electrical stimulation can be effective, and that the stimulation is largely well-tolerated. The authors have also highlighted that challenges still remain for the clinical application of stimulation given the uncertainties that still exist in titrating the dose of stimulation and the possibility of adverse side effects.

References

1 Brunoni AR, Valiengo L, Baccaro A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 2013; 70: 383–91.

2 Grimm S, Beck J, Schuepbach D et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol Psychiatry* 2008; 63: 369–76.

3 Mars, B, Heron J, Kessler D et al. Influences on antidepressant prescribing trends in the UK: 1995–2011. *Soc Psychiatry Psychiatr Epidemiol* 2017; 52: 193–200.

4 Brunoni AR, Moffa AH, Sampaio-Junior B et al. Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): a systematic review and meta-analysis. *Brain Stimul* 2017; 10: 260–2.

5 Bestmann S, Feredoes E. Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. *Ann N Y Acad Sci* 2013; 1296: 11–30.

6 Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. *Clin Neurophysiol* 2006; 117: 1623–9.

7 Brunoni AR, Ferrucci R, Bortolomasi M et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: findings from a naturalistic study. *Eur Psychiatry* 2013; 28: 356–61.