White paper

Transcranial direct current stimulation (tDCS) for treatment of major depressive disorder

In brief

- **Non-invasive tDCS relieves symptoms in depressed patients by modulating cortical excitability through a weak current**
- **tDCS can be used both as a monotherapy or as an adjunct to antidepressant medication and psychotherapy**
- **Meta-analyses have found active tDCS treatment to be significantly superior to sham tDCS in depressed patients**
- **tDCS is well tolerated, and no serious side effects have been reported**

Major depressive disorder (MDD) has an estimated lifetime prevalence of 8–12% and is associated with significant morbidity and mortality.[1] Standard treatments for MDD include psychological therapies and antidepressant medication, which are often only moderately effective and may have adverse effects. Furthermore, the applicability of non-pharmacological brain stimulation options such as repetitive transcranial magnetic stimulation (rTMS) or electroconvulsive therapy (ECT) are limited either by cost or significant safety issues.[2,3] Non-invasive transcranial direct current stimulation (tDCS) is a safe, effective, and affordable therapeutic option for several psychiatric disorders.[4] Importantly, tDCS can be used either as a monotherapy or as an adjunct to increase the effect of conventional antidepressant medication and psychotherapy.[5,6]

Mode of action

Brain stimulation with tDCS can be used to induce changes in neuronal excitability in a polarity-dependent manner: positive anodal stimulus increases cortical excitability (depolarization) without triggering action potentials, whereas negative cathodal stimulus decreases excitability (hyperpolarization)[4] (Figure 1). To date, several studies have demonstrated hypoactivity of the left dorsolateral prefrontal cortex (DLPFC) in depressed patients.[7,8] Accordingly, the antidepressant effects of tDCS may be due to the increased excitability of the DLPFC, which further balances the left-right prefrontal activity and subsequently leads to symptom relief in depressed patients.[3]

Neurobiological studies have demonstrated that tDCS mediates a cascade of events at a cellular and molecular level, including effects on the N-methyl-D-aspartate receptors.[9,10] In addition to acute transient membrane potential changes that can last up to one hour, tDCS is associated with longer-lasting synaptic changes.[11–12] Further studies elucidating the detailed mechanism of tDCS in therapeutic neuromodulation are currently ongoing.

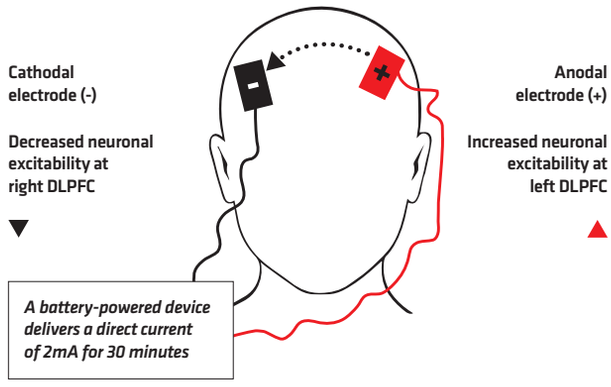


Figure 1. Mode of action. The neuromodulatory effect of tDCS is based on a weak constant current delivered through electrodes. The positive stimulus from the anodal electrode increases neuronal excitability at the left DLPFC, which is found to be hypoactive in depressed patients. The current flows from the positive to the negative electrode, and balances the activity in the prefrontal cortex.[4,14]

Method

During the tDCS procedure, the patient remains awake and alert. A low-intensity, direct current of 2mA is applied directly to the scalp through saline-soaked electrodes (Figure 1). The electrodes are placed on the scalp over the left and right DLPFC.[13,14] This forms a circuit for the current flow, which modulates neuronal excitability in the frontal lobe. In addition to the polarity and location of the electrodes, the current intensity, stimulation duration, and the electrode size affect the total charge delivered in the procedure.[4] One daily session typically lasts 20 to 30 minutes, and the procedure is usually repeated up to 15 times during the acute treatment period.[13,14]

Efficacy and safety

The National Institute for Health and Care Excellence (NICE) in the United Kingdom published interventional procedure guidance "*Transcranial direct current stimulation (tDCS) for depression*" in August 2015. The guidance is based on an interventional procedure overview of about 2000 patients including a meta-analysis (consisting of seven randomized control trials, RCTs), a systematic review, an open-label follow-up study, and a case report.[13,14] Furthermore, the Canadian network for Mood and Anxiety Disorders (CANMAT) added tDCS to their "Clinical Guidelines for the Management of Adults with Major Depressive Disorder" in September 2016.[15]

Efficacy

A systematic review and individual patient data (IPD) meta-analysis from 2016 of six RCTs enrolling 289 patients demonstrated a significantly greater improvement in patients treated with active vs. sham tDCS.[16] tDCS was used either as a monotherapy or an adjunct to conventional therapy in patients suffering from moderate-degree treatment-resistant depression. The relative strength of standardized treatment effects for each study is shown in Figure 2. The researchers found that "tDCS presents similar efficacy to antidepressant drugs and rTMS" based on comparisons with the outcomes in meta-analyses of antidepressant drugs and rTMS.

In agreement with the meta-analyses, an RCT of 120 patients comparing the treatment efficacy of active vs. sham tDCS, combined either with sertraline (50mg/day), a selective serotonin reuptake inhibitor (SSRI), or placebo drug, reported a significant reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) scores in patients treated with active tDCS vs. sham tDCS, regardless of sertraline administration.[6] Analysis of the active tDCS+placebo vs. sham tDCS+sertraline groups revealed comparable efficacies. Furthermore, the greatest efficacy was achieved in the active tDCS+sertraline group, and this effect was demonstrated to be additive.

Response

The meta-analysis of 259 patients demonstrated significantly higher response rates in active vs. sham tDCS (odds ratio, [OR] 2.44, 95% confidence interval, [CI] 1.38 to 4.32).[16] Similar outcomes were observed in the RCT of 120 patients (Figure 3), where only 16.7% of the placebo group but 43.3% of the patients treated with active tDCS (OR=8.6, 95% CI 2.5 to 29.1, $P<0.001$) and 63.3% of active tDCS+sertraline-treated patients (OR=3.8, 95% CI 1.1 to 12.7, $P=0.03$) responded.[6] Response was defined as >50% improvement in depression scores from baseline.

Remission

Significantly higher remission rates were reported in active vs. sham tDCS in the meta-analysis (OR=2.38, 95% CI 1.22 to 4.64, $P=0.002$).[16] In the RCT of 120 patients, a significantly larger number of active tDCS-treated patients also achieved remission compared to sham tDCS (Figure 3).[6] Remission was defined either as a score <8 in the Hamilton Depression Rating Scale, or a score ≤10 in MADRS.

Relapse

A mean response duration of 11.7 weeks was demonstrated in an open-label follow-up study of 42 patients who were responders in the initial study phase and continued to receive treatment. The sustained response rate at 24 weeks was 47% (95% CI 27 to 64). Lower sustained response rates were observed in patients with treatment-resistant depression than in patients with non-refractory disease (10% vs. 77%, OR 5.52, $P<0.01$).[17]

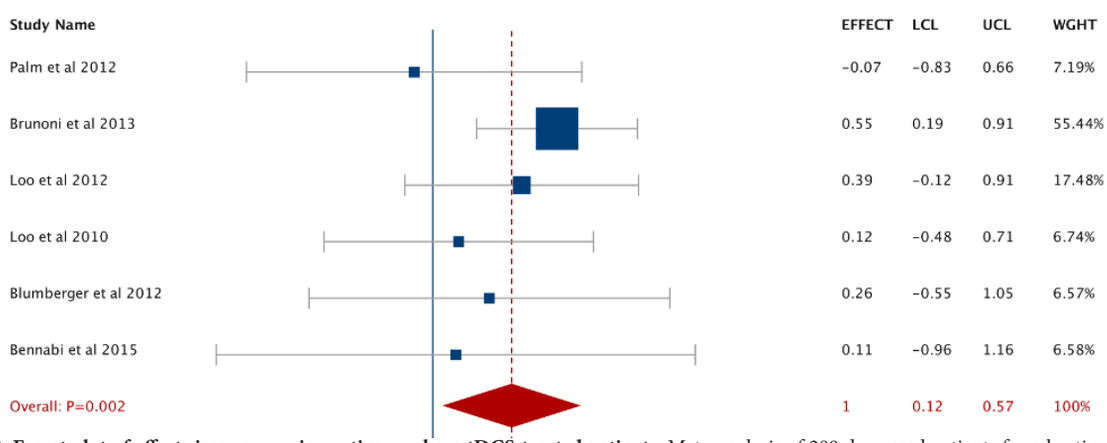


Figure 2. Forest plot of effect sizes comparing active vs. sham tDCS-treated patients. Meta-analysis of 289 depressed patients found active tDCS to be significantly superior to sham tDCS treatment. β was used as the measure of effect size to standardize different depression scales. The level of heterogeneity was not significant between the studies. The Figure is adapted from Brunoni et al. (2016).

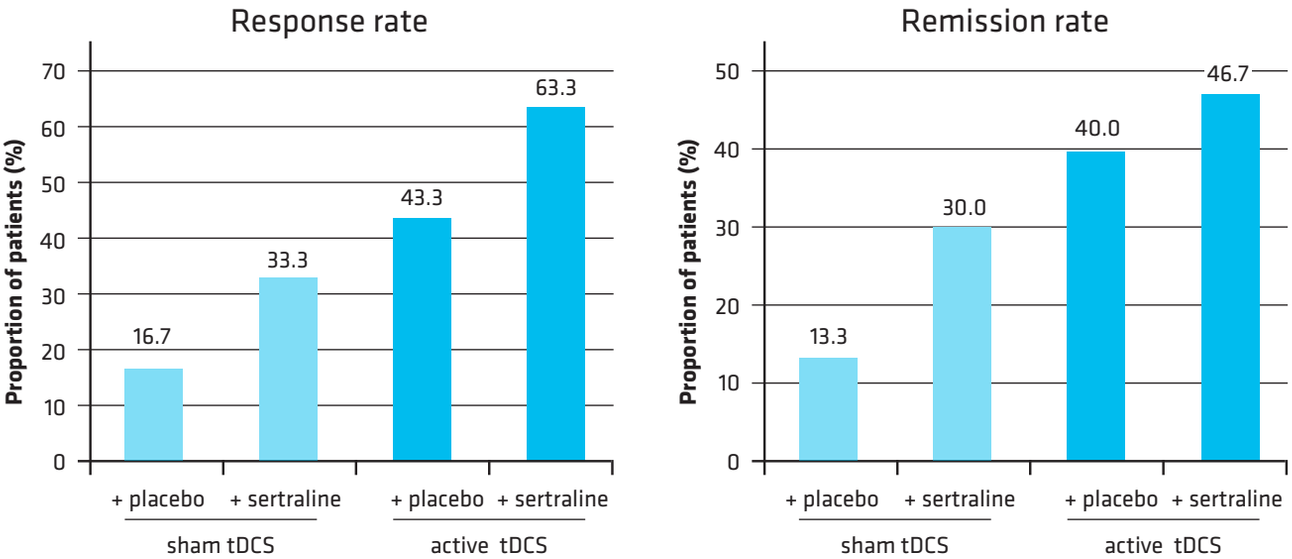


Figure 3. Response and remission rates according to MADRS scores in active vs. sham-treated depressed patients (n=120). An RCT found significantly higher response (P <0.001) and remission (P=0.03) rates in active tDCS vs. sham tDCS-treated patient groups 6 weeks after treatment initiation. tDCS was combined with either sertraline (50mg/day) or placebo drug treatment. Response was defined as a MADRS score change >50% from baseline, and remission as a score ≤10. Data is adapted from Brunoni et al. (2013).

Similarly, a follow-up study of initial responders (n=26) reported cumulative probabilities of disease remission to be 83.7% at 3 months (maintenance tDCS once weekly) and 51.1% at 6 months (maintenance tDCS once every two weeks). This study also found medication resistance to be the only predictor of relapse during maintenance tDCS treatment (hazard ratio, [HR]=1.61, 95% CI 1.10 to 2.36, P <0.05).[18]

Acceptability

No difference in treatment acceptability was found in the meta-analysis when comparing active vs. sham tDCS treatment. The dropout rate was 10.1% for active tDCS and 12.2% for sham tDCS treated patients (OR=0.78, 95 % CI 0.33 to 1.82, P=0.57).[14]

Safety

Mild local adverse events such as transient skin redness, itching, or skin lesions were reported both after active and sham tDCS treatment. According to the NICE guidelines, the difference between the groups was not statistically significant.[14] Part of this safety evaluation was based on a large meta-analysis of tDCS-related adverse events, which included both healthy volunteers and patients (n=1851).[19]

The frequency of adverse events or the effect on cognitive capabilities did not differ between the different treatment groups in the RCT of 120 patients.[6] However, this RCT reported six episodes of hypomania or clinical mania: five in the combined treatment group, and one in the active tDCS+placebo group. Accordingly, the risk of switching to mania should be considered when using tDCS in depressed patients.

Sooma tDCS™ for treatment of MDD

Sooma offers a fixed tDCS procedure that is indicated for adult patients suffering from unipolar depression. Sooma tDCS™ is easy-to-use and cost-effective, which makes it ideal for routine clinical practice. This system can be used as a monotherapy or as an adjunct to conventional treatments such as antidepressant medication and psychotherapy. Importantly, it is a viable option for patients who do not tolerate or benefit from antidepressant medication. An overview of the Sooma tDCS™ device and the treatment procedure is presented in Figure 4. Case studies and open-label data of Sooma tDCS patients is available in separate white papers.

Sooma tDCS™ holds a CE mark and complies with the EU medical device directive. The device is composed of a lightweight, battery-driven stimulator that delivers a constant current of 2mA to the electrodes. The headcap positions the electrodes at the defined areas of the scalp: the anode on the left F3 region, and the cathode on the right F4 region. Prior to treatment, the electrodes are placed inside disposable sponge pouches, which are soaked with saline solution.

In the standard treatment protocol, Sooma tDCS™ is used on weekdays for 2–4 weeks, followed by a maintenance period of one session per week as required for up to 6 months (Figure 4). After an initial consultation with a psychiatrist, Sooma tDCS™ can be delivered by a psychotherapist during a psychotherapy session, or by a trained nurse. Contraindications for the Sooma tDCS™ include metal implants (excluding dental implants) and implanted devices in the head area, cardiac pacemakers, and acute eczema in the stimulation area.

Figure 4. Sooma tDCS™ treatment. The Sooma tDCS™ medical device consists of a small, battery-powered stimulator, electrodes with saline-soaked sponges, and a headcap with pockets for correct electrode positioning. Each session delivers a constant current of 2 mA for 30 minutes, which is repeated on each weekday for 2 to 4 weeks. After the acute treatment phase, the sessions can be continued once a week up to 6 months.

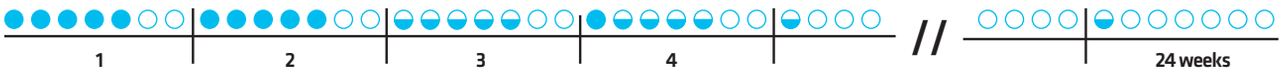
Sooma tDCS™ session:

2mA direct current for 30 minutes

Acute treatment:
1 session per day,
5 days a week
for 2 to 3 weeks

Maintenance treatment:
1 session per week up to
6 months or as required

standard protocol as required



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About Sooma

Sooma Oy is a Finnish medical device manufacturer, which develops innovative neuromodulation technology for treating depression. Sooma tDCS™ is a CE-marked device that is affordable, easy to use, and easily adaptable to various clinical routines. Sooma Oy holds ISO13485 and ISO9001 Quality Management Systems certificates, holds international patents and has additional patents pending.

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