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INVITED REVIEW

tDCS for the treatment of depression: a comprehensive review

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Abstract Transcranial direct current stimulation (tDCS) has been investigated for the treatment of major depressive disorders in recent years. Here, we review the implications of current research for the clinical use of tDCS in the treatment of major depressive disorder. Meta-analyses, randomized, placebo-controlled clinical trials, open-label trials, case reports and review articles were identified through a systematic search of the literature database of the National Institutes of Health (USA). Available articles were evaluated with regard to their clinical relevance. Results of tDCS efficacy are inconsistent due to the small sample sizes, the heterogeneous patient samples and the partially high treatment resistance in some studies. Overall, tDCS has very low side effects. Meta-analyses suggest some efficacy of tDCS in the treatment of acute depressive disorder with moderate effect size, and low efficacy in treatment-resistant depression. A general statement about the efficacy of tDCS as a therapeutic tool in major depression seems to be premature. tDCS is considered as a safe therapeutic option and is associated with only minor side effects. The effectiveness of tDCS decreases with resistance to treatment. Psychotropic drugs may attenuate or amplify its effects. The use of 2 mA current strength over 20 min per day over a short time span can be considered as safe.

Keywords Noninvasive brain stimulation · tDCS · Major depressive disorder · Treatment resistance

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Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique with application of weak direct current to the brain over sponge electrodes. Deriving from the results of Bindman et al. [1] published in 1964 that direct current modulates spontaneous neuronal activity in the rat brain in a polarity-dependent manner, several studies with direct current application in animals and humans followed in the 1960s and 1970s. Those early studies from the 1960s suggested some efficacy of DC stimulation to reduce symptoms in depression, but mixed results and development of psychotropic drugs led to an early abandonment of this technique [2]. This research direction was reactivated by Nitsche and Paulus [3] at the beginning of the twenty-first century with the examination of distinct patterns of motor cortex excitability after anodal and cathodal polarization. Contrarily to transcranial magnetic stimulation (TMS) where single magnetic pulses lead to action potentials by the exceeding the depolarization threshold of neurons, tDCS does not exceed the threshold due to the weak and constant polarization. In a simplified model, tDCS shifts neuronal resting membrane potentials toward depolarization after anodal stimulation (= excitatory) and toward hyperpolarization after cathodal stimulation (= inhibitory; tonic changes in resting membrane potential). This finally leads to a facilitation or inhibition of the neuronal firing rate, depending on polarization [4]. Thus, the effect of tDCS is considered to be neuromodulatory. Aftereffects of excitatory tDCS last from several minutes up to one and a half hours and can be measured with amplitude changes in motor evoked potentials by single pulses of TMS over the cortical representation area of the abductor digiti minimi, abductor pollicis brevis or first digitus interosseous muscle [5]. The change in MEP amplitudes is a surrogate for a change in neuroplasticity,

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i.e., the activity-dependent change in neuronal information processing.

The rationale for the use of tDCS in major depressive disorders has been based on the positive results of studies using TMS in depressed patients and the evidence that depressed patients show functional and also structural changes in several cortical regions, especially the left dorsolateral and ventromedial cortex, the amygdala and the hippocampus [6–8]. Furthermore, neuroimaging studies have shown the left dorsolateral prefrontal cortex (DLPFC) to be hypoactive and the right DLPFC to be hyperactive during depressive disorder. This finding led to the hypothesis of a so-called hypofrontality [9] and has been connected to a change in emotional processing toward negative aspects [10]. However, this hypothesis of hypofrontality is discussed controversially as there is also contrary evidence to this so-called interhemispheric frontal imbalance [11, 12] as syndromal differences in psychopathology, cormorbidities and possible influences of subcortical structures such as the amygdala, the hippocampus, the subgenual cortex and their mutual networks have to be considered. Therefore, tDCS has been supposed to normalize cortical activity by excitatory stimulation of the left DLPFC and the inhibitory stimulation over the right orbit in early studies, respectively, over the right DLPFC in recent studies. In healthy volunteers, changes in cortical activity following anodal tDCS over the left DLPFC have been demonstrated to result in a reduction in EEG delta activity in left subgenual prefrontal cortex [13] and by connectivity changes in the frontal–parietal resting state networks (FPN) and default mode network in resting state functional connectivity magnet resonance imaging (fcMRI) [14]. To date, it remains elusive if changes in the resting state network connectivity are responsible for the obtained improvements of depression and cognition following tDCS interventions. Furthermore, it remains unclear whether anodal/cathodal tDCS stimulation alone is responsible for symptom improvement or whether it is a combination of both polarizations.

In this review, we provide a systematic literature overview including not only controlled trials, but also open-label studies and case reports which are not reflected in meta-analyses, but may provide help for the decision on tDCS treatment in patients with non-response to pharmacotherapy, concomitant states (e.g., pregnancy) or diseases, or need for maintenance treatment. Furthermore, we provide information and guidance on actual stimulation parameters as well as on regulatory affairs.

Methods

Literature search was performed from the year 2002 (first publication dates of seminal tDCS studies following actual good clinical practice standards) until mid-October 2015 by the National Institutes of Health (USA) search engine *Pubmed* with the cross-combination of the terms "tDCS," respectively, "transcranial direct current stimulation" and "depression," respectively, "major depressive disorder." Only publications of meta-analyses, double-blind, randomized, placebo-controlled trials, open-label studies and case reports with clinical and therapeutic focus were considered. Studies with the main focus on other clinical aspects (e.g., neurology or other psychiatric disorders) and only concomitant treatment of depression or depressive symptoms were excluded as well as congress proceedings. References of retrieved literature were searched for further relevant publications. Study design, number of participants, age, treatment resistance, electrode size and placement, current intensity, duration of stimulation, frequency of stimulation and total number of stimulation were assessed. In addition, study results and side effects were assessed.

Results

The Pubmed search retrieved 245 hits for the combination "tDCS + depression," 95 hits for "tDCS + major depressive disorder," 241 hits for "transcranial direct current stimulation + depression" and 95 hits for "transcranial direct current stimulation + major depressive disorder." Only studies published in English and describing the study population, methods and study design were included. The first publication on tDCS and major depressive disorder appeared in 2006, and thus, research in this field appears to have lasted a decade.

Studies and protocols

Therapeutic application of tDCS in depressive disorders was first described in the 1960s and 1970s, however abandoned quickly [2]. The new era of systematic tDCS research started in the early twenty-first century and application in depressive disorders was first described in 2006 by Fregni et al. [15, 16] in two double-blind, randomized trials. Since then, 11 double-blind, randomized, placebo-controlled clinical trials [15–25] (Table 1), nine open-label studies [26–35] (Table 2) and eight case reports [36–44] (Table 3) were published. While controlled clinical trials and open-label studies reported on tDCS treatment in different patient samples (e.g., concomitant pharmacotherapy, treatment resistance, unipolar versus bipolar depression) and with different aims (e.g., add-on treatment, comparison to pharmacotherapy, long-term treatment, comparison of different stimulation protocols), case reports reported mainly on side effects (induction of mania/hypomania). Apart from these studies and case reports, tDCS for

Table 1 Double-blind, placebo-controlled studies

Authors	Study design	*N* Mean age	MDD/BD Mean (Ø) treatment resistance	Medication	Electrode position	Reference electrode	Current intensity Electrode size	Frequency/day Total number of stimulations and total duration	Results[a] Depression rating scale RS = response (%) RM = remission (%)
Fregni et al. [15]	Double blind, randomized, placebo controlled (each of 9 patients active/sham)	$N = 18$ 47 ± 10 years	MDD, no treatment resistance	No antidepressant treatment in the last 3 months	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	1 × 20 min/day 5 stimulations in 1 week	HAMD n/a (significant improvement of cognition and mood after active tDCS)
Fregni et al. [16]	Double blind, randomized, placebo controlled (each of 5 patients active/sham)	$N = 10$ 46 ± 9 years	MDD, no treatment resistance	No antidepressant treatment in the last 3 months	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	1 × 20 min/day 5 stimulations in 1 week	HAMD n/a (significant improvement of depressive symptoms after active tDCS)
Boggio et al. [17]	Double blind, randomized, placebo controlled (20 patients active, 10 occipital, 10 sham)	$N = 40$ 49 ± 7 years	MDD, Ø 1.7 inefficient treatments	No antidepressant treatment in the last 2 months	F3 (anodal) [occipital: 2 cm above inion (anodal)]	Supraorbital right (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 10 stimulations in 2 weeks	HAMD RS (active) = 38 RS (sham) = 20 RM (active) = 23 RM (sham) = 0
Rigonatti et al. [18]	Double blind, randomized, placebo controlled (21 patients active, 10 sham, 11 fluoxetine 20 mg/day. fluoxetine group not blinded)	$N = 42$ 49 ± 7 years	MDD, Ø 1.6 inefficient treatments in active group versus 1.2 in fluoxetine group and 1.5 in sham group	No antidepressant treatment in the last 2 months	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 10 stimulations in 2 weeks	HAMD n/a (active conditions superior to sham, no difference after 6 weeks)
Loo et al. [19]	Double blind, randomized, placebo controlled. 5× active or sham followed by 5× active (open label) (20 active → 19 active 20 sham → 15 active)	$N = 40$ 48 ± 10 years (active) 45 ± 12 years (sham)	MDD, Ø 1.0 inefficient treatments in active group versus 1.7 in sham group	With/without antidepressant medication, stable dose >4 weeks	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	1 × 20 min/ day 3×/week 5 stimulations per condition, each in 1.5 weeks	MADRS RS (active/active) = 30 RS (sham/active) = 20 RM (active/active) = 25 RM (sham/active) = 15
Loo et al. [20]	Double blind, randomized, placebo controlled	$N = 64$ 47 ± 12 years (active) 48 ± 12 years (sham)	MDD, Ø 1.7 inefficient treatments in active group, 1.8 in sham group	With/without antidepressant medication, stable dose >4 weeks	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 15 stimulations in 3 weeks	MADRS RS (active) = 12 RS (sham) = 13 RM (active) = 3 RM (sham) = 3

Table 1 continued

Authors	Study design	*N* Mean age	MDD/BD Mean (Ø) treatment resistance	Medication	Electrode position	Reference electrode	Current intensity Electrode size	Frequency/day Total number of stimulations and total duration	Results[a] Depression rating scale RS = response (%) RM = remission (%)
Palm et al. [21]	Double blind, randomized, placebo controlled, crossover design: 10 days active → 10 days sham versus 10 days sham → 10 days active	$N = 22$ 56 ± 12 years (active) 58 ± 12 years (sham)	20 MDD, 2 BD, Ø 2.9 inefficient treatments in active group versus 2.91 in sham group	With antidepressant medication, stable dose >3 weeks	F3 (anodal)	Supraorbital right (cathodal)	10 patients: 1 mA, 35 cm^2, 12 patients: 2 mA, 35 cm^2	1 × 20 min/day 10 stimulations per condition, changing every second week	HAMD RS (active) = 9 RS (sham) = 9 RM (active) = 9 RM (sham) = 9
Blumberger et al. [22]	Double blind, randomized, placebo controlled	$N = 24$ 45 ± 12 years (active) 49 ± 9 years (sham)	MDD, Ø 4.3 inefficient treatments in active group versus 4.1 in sham group	With antidepressant medication, stable dose >4 weeks	F3 (a nodal)	F4 (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 15 stimulations in 3 weeks	HAMD RS (active) = 7 RS (sham) = 9 RM (active) = 7 RM (sham) = 9
Brunoni et al. [23]	Double blind, randomized, placebo controlled. 4 parallel groups with active/sham tDCS x active/placebo–sertraline (Phase 1 of the SELECT-TDCS study)	$N = 120$ 18–65 years	MDD, 0–1 inefficient treatments in 56 %, >2 inefficient treatments in 22 %	Sertraline 50 mg, respectively, placebo, no further medication except benzodiazepines	F3 (anodal)	F4 (cathodal)	2 mA 25 cm^2	1 × 30 min/day 10 stimulations in 2 weeks + each 1 stimulation in week 3 and 4	MADRS RS (active) = 43 RS (sham) = 16 RM (active) = 40 RM (sham) = 13
Bennabi et al. [24]	Double blind, randomized, placebo controlled	$N = 24$ 61 ± 16 years	MDD, treatment resistance II°	Escitalopram 10–20 mg since 4 weeks	F3 (anodal)	Supraorbital right (cathodal)	2 mA 35 cm^2	2 × 30 min/day 10 stimulations in 1 week	MADRS RS (active) = 44 RS (sham) = 22 RM (active) = 22 RM (sham) = 0

MDD major depressive disorder, *BD* bipolar depression, *n/a* not available

[a] Response is defined as >50 % improvement of the respective depression rating scale, and remission is an absence of clinically relevant depression symptoms, usually defined as a cutoff in the respective depression rating scale

the treatment of depression has been evaluated in several review articles and meta-analyses, e.g., [45–49].

The original research articles present overall congruent parameters for the application of tDCS in terms of electrode placement (anode over left DLPFC, cathode over right orbit or over right DLPFC), electrode size (sponge electrode, 7 × 5 cm = 35 cm^2) and duration of stimulation (20 min) [45]. While in early tDCS studies 1 mA current strength was used due to the unknown impact of tDCS [15, 16], recent studies used 2 mA after the safety of this parameter was first reported by Boggio et al. [17]. Duration of stimulation remained the standard at 20 min/day for 2–3 weeks over several years until enhanced protocols with twice daily stimulation (2 × 20 min/day) or prolonged duration time (30 min) were evaluated in recent years to achieve more pronounced results in neuroplasticity. Most studies used an electrode size of 35 cm^2, a few studies used smaller areas, and some studies used extra-cephalic reference electrodes with an area of 100 cm^2 (Tables 1, 2). Positioning of the excitatory electrode (anode) over the left DLPFC (EEG: F3—international 10–20 system) and the reference electrode at the right hemisphere is based on the above-mentioned hypothesis on functional anatomy of depressive disorders. The placement of the cathodal reference electrode over the right orbit was frequently used in early tDCS studies and probably exerts no own antidepressant effects; however, it is not neurophysiological inert. Recent studies used the EEG point F4 for cathodal reference to improve therapeutic efficacy by transcallosal effects of a directly opposite modulation of both hemispheres [26]. Two studies used an extra-cephalic reference electrode on the right upper arm to reach remote and deeper brain structures by a more fanned current flow.

The effect of alternative electrode position on depressive symptoms was investigated by Ho et al. [34], first by generating a computer model for the positions frontal–occipital and frontal–cerebellar and then in an open-label study with 14 patients with major depressive disorder in a 4-week treatment (2 mA, 20 min, 20 treatments). *Montgomery-Åsberg Depression Rating Scale* (MADRS) showed a reduction by 44 % for frontal–occipital montage, however only 16 % for the frontal–cerebellar montage. This points to a higher activation of the anterior cingulate in the frontal–occipital montage than in frontal–occipital montage, whereas the left DLPFC was not affected by frontal–occipital stimulation in the computer model. The authors discuss that the left DLPFC might not be the main target for the improvement of depression and corroborate their hypothesis with a further open-label study in four patients with comparison of bitemporal to extra-cephalic electrode position [35]. Recently, a study comparing F3–F4 and F3–Fp2 montage to sham stimulation showed that the F3–F4 montage significantly reduced vigilance to threatening stimuli and the concomitant attentional bias, and the F3–Fp2 montage showed a numerical trend [50]. These results could cautiously point to a superiority of the F3–F4 montage.

Effect sizes of tDCS in the treatment of depression

Kalu et al. [46] included six randomized placebo-controlled trials by Fregni et al. [15, 16], Boggio et al. [17], Loo et al. [19, 20] and Palm et al. [21] in a meta-analysis. Further studies of Table 1 were excluded due to partially overlapping patient samples. They calculated an effect size (Hedges' g) for the improvement of the *Hamilton Rating Scale for Depression* (HAMD) of $g = 0.74$ (95 % CI 0.21–1.27; $p = 0.006$) in favor of active tDCS compared with sham tDCS, however, with a variance of the results above hazard ratio. This was explained by a high heterogeneity of the samples concerning depression severity, degree of treatment resistance and different stimulation parameters. A meta-regression between depression severity at enrollment, concomitant antidepressant intake, used current strength and total number of stimulations showed no correlations. Berlim et al. [47] repeated this meta-analysis in the light of response and remission rates and added the newly published study by Blumberger et al. [22] (see Table 1 for percentage response and remission rates). Response rates (defined as ≥50 % HAMD improvement compared with baseline) showed no superiority of active tDCS (pooled odds ratio 1.97; 95 % CI 0.85–4.56; $z = 1.59$; $p = 0.11$). Remission rates (defined as score ≤7 on the HAMD-17, respectively, ≤8 on the HAMD-21 scale) showed no superiority of active tDCS (pooled odds ratio 2.13; 95 % CI 0.64–7.06; $z = 1.24$; $p = 0.22$) at study end. Neither the total number of applied stimulations (less than 5 versus more than 10) nor the current intensity (1 vs. 2 mA) had an impact on efficacy. The authors discuss that the intake of mood stabilizers/antiepileptic drugs could have hampered tDCS effects. Furthermore, the effect of tDCS as an add-on to stable medication could have been lower than in monotherapy. Another factor not discussed by the authors could be the high treatment resistance in the samples of Palm et al. (average 2.9 ineffective treatments before add-on tDCS) and Blumberger et al. (average 4.2 ineffective treatments before add-on tDCS). These two studies are in contrast to the mainly positive studies without treatment-resistant patient samples reported in Table 1. Two newer meta-analyses pointed out this fact: Meron et al. [48] calculated a random effects model on 11 studies (393 participants included), which showed that active tDCS was superior to sham ($g = 0.30$, 95 % CI 0.04–0.57; $p = 0.027$). However, antidepressant co-medication, regardless of the substance class, and cognitive control training appeared to attenuate tDCS effects. Hence, the authors state that tDCS may be efficacious for the treatment of depression, but it is

Table 2 Open-label studies

Authors	Study design	*N* Mean age	MDD/BD mean (Ø) treatment resistance	Medication	Electrode position	Reference electrode	Current intensity Electrode size	Frequency/day Total number of stimulations and total duration	Results[a] Depression Rating Scale RS = response (%) RM = remission (%)
Ferrucci et al. [25]	Open label, no placebo control	$N = 14$ 52 ± 2 years	MDD, treatment resistance after several attempts (no further information)	Antidepressant medication in stable dose >4 weeks	F3 (anodal)	F4 (cathodal)	2 mA, 32 cm^2	2 × 20 min/day 10 stimulations in 1 week	HAMD RS = 12 RM = 6
Ferrucci et al. [26]	Open label, no placebo control	$N = 32$ 49 ± 12 years	13 mild/moderate MDD, 19 severe MDD, treatment resistance in 19 patients (2 inefficient treatments)	Antidepressant medication in stable dose	F3 (anodal)	F4 (cathodal)	2 mA, 35 cm^2	2 × 20 min/day 10 stimulations in 1 week	HAMD RS (mild) = 5 RS (severe) = 33 RM (mild) = 5 RM (severe) = 16
Brunoni et al. [27]	Open label, no placebo control	$N = 31$ 54 ± 11 years	17 MDD (14 treatment resistant), 14 BD (11 treatment resistant), no further information	Various drugs except for 2 patients, stable dose >2 weeks	F3 (anodal)	F4 (cathodal)	2 mA, 35 cm^2	2 × 20 min/day 10 stimulations in 1 week	HAMD RS = 28 RM = 21
Martin et al. [28]	Open label, no placebo control	$N = 11$ 46 ± 13 years	9 MDD, 2 BD, moderately treatment resistant (Ø 2.6 inefficient treatments)	With/without drugs, stable dose >4 weeks	F3 (anodal)	Supraorbital right (cathodal, 35 cm^2) right upper arm (cathodal, 100 cm^2)	2 mA, 35 cm^2	1 × 20 min/day 20 stimulations in 4 weeks	MADRS RS = 18 RM = 0
Dell'Osso et al. [29]	Open label, no placebo control	$N = 23$ 51 ± 13 years	15 MDD, 8 BD, (Ø 1 inefficient treatment, no further information)	Various drugs, stable dose >4 weeks	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	2 × 20 min/day 10 stimulations in 2 weeks	HAMD, MADRS RS = 17 RM = 13
Knotkova et al. [30]	Open label, no placebo control	$N = 10$ 52 ± 6	10 MDD with HIV infection	With/without stable antidepressant medication, all with antiretroviral medication	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 25 cm^2	1 × 20 min/day 10 stimulations in 2 weeks	HAMD, MADRS n/a (significant changes in HAMD and MADRS)
Brunoni et al. [31]	Open label, no placebo control	$N = 82$ 54 ± 12 years	63 MDD, 19 BD, no information on treatment resistance	Various drugs, stable dose >4 weeks	F3 (anodal)	F8 (cathodal)	2 mA, 35 cm^2	2 × 20 min/day 10 stimulations in 2 weeks	HAMD RS = 31 RM = 18

Table 2 continued

Authors	Study design	*N* Mean age	MDD/BD mean (Ø) treatment resistance	Medication	Electrode position	Reference electrode	Current intensity Electrode size	Frequency/day Total number of stimulations and total duration	Results[a] Depression Rating Scale RS = response (%) RM = remission (%)
Martin et al. [32]	Open label, no placebo control. Follow-up from 2 other studies	$N = 26$ 47 ± 14 years (study 1) 54 ± 16 years (study 2)	MDD, Ø 1.4 inefficient treatments in study 1, Ø 1.1 inefficient treatments in study 2)	With/without stable or new antidepressant medication	F3 (anodal)	F8 (35 cm^2) or right upper arm (100 cm^2) (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 1×/week for 3 months, or 1×/2 weeks for 3 months	MADRS RS = 69 RM = 0
Valiengo et al. [33]	(Phase 2 + 3 of the SELECT-TDCS study) Phase 2: open label: 10 active stimulations for sham-non-responder from Phase 1 Phase 3: open-label: tDCS-/sertraline maintenance treatment for active tDCS responder from Phase 1 + 2	Phase 2: $N = 25$ Age not reported Phase 3: $N = 42$ 43 ± 13 years	MDD, treatment resistance as in Phase 1 of the SELECT-TDCS study. Phase 3 only for tDCS responder	Continuation of sertraline 50 mg if patient had active medication in Phase 1, otherwise no medication except benzodiazepines	F3 (anodal)	F4 (cathodal)	2 mA, 25 cm^2	Phase 2: 1 × 30 min/day 10 stimulations in 2 weeks Phase 3: 1 × 30 min/day 2×/month over 3 months, 1×/month over 3 months	MADRS Phase 2: RS = 52 (Phase 3: higher relapse rate (40 %) in the first 3 months of second-weekly tDCS than after 6 months (53 %). Higher relapse rates in case of higher treatment resistance at the beginning of Phase 1)
Ho et al. [34]	Open label, no placebo control (7 patients fronto-occipital tDCS, 7 patients fronto-cerebellar tDCS)	$N = 14$ 45 ± 9	MDD, treatment resistance (Maudsley) 7.4, respectively, 6.3	With/without medication, stable dose >4 weeks	Supraorbital left (anodal)	O1-O2 (cathodal) Cerebellum (cathodal)	2 mA, 35 cm^2 frontal, 100 cm^2 occipital, 50 cm^2 cerebellar	1 × 20 min/day 20 stimulations in 4 weeks	MADRS RS = 57 RM = 14
Ho et al. [35]	Open label, no placebo control	$N = 4$ 47 ± 9	MDD, at least one ineffective treatment	With various antidepressants, stable dose >4 weeks	F3/F7 (anodal)	F8/extracephalic (cathodal)	2–2.5 mA, 35 cm^2 in patient 1, 16 cm^2 in patients 2–4	20–30 min/day 15–20 stimulations in 2–3 weeks	MADRS RS = 75 RM = 25

MDD major depressive disorder, *BD* bipolar depression

[a] Response is defined as >50 % improvement of the respective depression rating scale, and remission is an absence of clinically relevant depression symptoms, usually defined as a cutoff in the respective depression rating scale

not recommended in treatment-resistant depression or as an add-on to medication. The second recently published meta-analysis was performed by Brunoni et al. [49] and included the individual patient data of all published randomized controlled trials up to 2015, resulting in a total sample size of six studies with at least ten participants per group (289 patients included). This analysis showed that active tDCS was superior to sham tDCS in terms of depression improvement, clinical response and remission for the acute depressive episode (as measured by the HAMD or the MADRS score). However, high treatment resistance again appeared to hamper tDCS efficacy. Furthermore, correlational analyses revealed a possible dosage dependency of the aftereffects of tDCS treatments.

Overall, meta-analyses suggest that a differentiated view on tDCS has to take into account treatment resistance as well as tDCS use in monotherapy or add-on to pharmacologic treatment and the potential weakening of tDCS effects by mood stabilizers/antiepileptic drugs or benzodiazepines [51].

tDCS versus antidepressants

Most of the earlier studies investigated tDCS as a monotherapy in medication-free patients or as an add-on to stable antidepressant medication over 3–4 weeks. A direct comparison of efficacy between tDCS and antidepressants has been made in two studies so far: Rigonatti et al. [18] compared three treatment arms of active tDCS, sham tDCS and fluoxetine 20 mg in a double-blind, randomized trial and were able to show a quicker improvement in the active tDCS group than in the fluoxetine group. Six weeks after beginning, active tDCS group and fluoxetine group showed the same improvement in the Beck Depression Inventory (BDI) and were significantly superior to the sham tDCS group. The largest study up to now, the SELECT-TDCS study by Brunoni et al. [23] compared sertraline 50 mg and tDCS in a four-arm factorial trial. One hundred and twenty patients were randomized to either receive sertraline + tDCS, placebo–sertraline + tDCS, sertraline + sham tDCS and placebo–sertraline + sham tDCS. The combined treatment sertraline + tDCS was superior to all other groups. While both groups with one active agent (sertraline or tDCS) did not differ, they were superior to the placebo–sertraline + sham tDCS group. A potential mechanism of this adjunctive effect could be tDCS-elicited modulations in cortical structures with network-dependent changes also in deeper brain structures such as thalamus, amygdala and striatum, whereas antidepressant medication also influences serotonergic and noradrenergic structures of the brainstem and its projections to amygdala and ventral striatum. Thus, a combined treatment might reach all cortico-limbic neuronal circuits which are affected during depressive disorders.

tDCS and relapse rates

Martin et al. [32] conducted an open-label study to assess the probability of surviving without relapse and the time to relapse as primary outcome parameters. They demonstrated a higher relapse rate after changing from weekly to biweekly maintenance tDCS, with an increase in relapse rate of 16 % during weekly tDCS over 3 months to 49 % during biweekly tDCS over further 3 months. Also Valiengo et al. [33] conducted an open-label follow-up of the SELECT-TDCS study with relapse as the primary outcome parameter, defined by two consecutive MADRS > 12, any MADRS > 15, suicidal attempt, severe suicidal ideation or psychiatric hospitalization. They reported an increased relapse rate of 40 % during biweekly tDCS in the first 3 months of the follow-up compared with a total rate of 53 % in the whole follow-up period of 6 months with monthly tDCS in the last 3 months. In addition, the relapse rate was increased if treatment resistance was registered at enrollment. Valiengo et al. subsumed that response during acute treatment period was only transient and especially patients with treatment resistance need maintenance treatment in high frequency. Regarding long-term effects of tDCS, an open-label observational study by dell'Osso et al. showed positive aftereffects for 3 months after end of stimulations in nearly a half of the included patients. However, there was a progredient loss of study adherence due to several reasons (e.g., therapeutic changes, poor compliance, worsening of symptoms) [52]. Overall, there is an urgent need of long-term data to optimize acute and maintenance treatment protocols.

Improvement of cognition

The improvement of working memory, learning and long-term memory by tDCS has been shown in healthy volunteers in a variety of studies [53]. In the treatment studies in depressed patients, mentioned in Tables 1, 2 and 3, cognitive tasks were performed irregularly. Improvement of working memory could be shown by Fregni et al. [16] in the Digit Span Test and Boggio et al. [54] in the Go-Nogo Task, whereas other studies did not find significant differences in working memory [20–22, 26, 29]. Improvement of cognition during treatment of post-stroke depression [40] and improvement of verbal fluency in treatment-resistant depression [36] have been reported in single cases. Overall, data on improvement of cognition during treatment with tDCS as an antidepressant are sparse, based on a variety of neuropsychological tasks and therefore more heterogeneous than in healthy volunteers, and also there is a converse

Table 3 Case reports

Authors	Design	Age (years)	MDD/BD Mean (Ø) treatment resistance	Medication	Electrode position	Reference electrode	Current intensity Electrode size	Frequency/day Total number of stimulations and total duration	Results
Palm et al. [36]	Open label, no placebo control	66	MDD, two ineffective treatments	Various drugs, stable dose >6 weeks	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	1 × 20 min/day 16 stimulations in 4 weeks	Moderate improvement in HAMD/BDI
Arul-Anandam et al. [37]	Double blind, randomized. First 5× sham tDCS, then change to active tDCS	57	MDD, no ineffective treatment	No medication	F3 (anodal)	Supraorbital right (cathodal)	1 mA, 35 cm^2	1 × 20 min/day 5 sham tDCS, then 3 active tDCS, in 1.5 weeks	Hypomania after third stimulation
Baccaro et al. [38]	Open label. Pilot phase of the SELECT-TDCS study	58	MDD, 1 inefficient treatment	Sertraline 50 mg	F3 (anodal)	F4 (cathodal)	2 mA, 35 cm^2	1 × 30 min/day 5 stimulations in 1 week	Hypomania after fifth stimulation
Brunoni et al. [39]	Double blind, randomized. In active tDCS group of the SELECT-TDCS study	62	MDD, 1 inefficient treatment	Sertraline 50 mg	F3 (anodal)	F4 (cathodal)	2 mA, 25 cm^2	1 × 30 min/day 5 stimulations in 1 week	Mania with psychotic symptoms after fifth stimulation
Bueno et al. [40]	Open label, no placebo control	48	Post-stroke-depression, 1 inefficient treatment	Fluoxetine 40 mg	F3 (anodal)	F4 (cathodal)	2 mA, 35 cm^2	1 × 30 min/day 10 stimulations in 2 weeks	Improvement of post-stroke-depression and cognition
Galvez et al. [41]	Open label, no placebo control	33	Bipolar-II-disorder, no treatment resistance	Lithium 750 mg, desvenlafaxine 100 mg	F3 (anodal)	Right upper arm (cathodal) (100 $cm^{2)}$	2 mA, 35 cm^2	2 × 20 min/day 14 stimulations in 3 weeks	Hypomania after 14th stimulation
Shiozawa et al. [42]	Open label, no placebo control	92	MDD since 3 years, > 1 inefficient treatment	Escitalopram 10 mg	F3 (anodal)	Right deltoid muscle (cathodal) (size not reported)	2 mA, size not reported	1 × 30 min/day 10 stimulations in 2 weeks	94 % decrease in HAMD, up to 3 weeks after tDCS
Shiozawa et al. [43]	Open label, no placebo control	66	MDD, 1 inefficient treatment	No medication	F3 (anodal)	F4 (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 5 stimulations in 1 week	Worsening of depressive symptoms due to right hemispheric dominance
Palm et al. [44]	Open label, no placebo control	64	BD, multiple ineffective treatments. Concomitant PRES	Various drugs	F3 (anodal)	Supraorbital right (cathodal)	2 mA, 35 cm^2	1 × 20 min/day 2 × 25, 1 × 30 stimulations in 2 × 5 resp. 6 weeks	Improvement during tDCS, deterioration after end of series. No neurologic complication

MDD major depressive disorder, *BD* bipolar depression

study reporting no enhancement of implicit learning after active tDCS in antidepressant-free patients, but after sham tDCS [55]. Recently, several studies were published with the main focus on improvement of cognitive symptoms in depressed patients. Improvement of working memory [56, 57] and affective processing [58] could be shown after single tDCS sessions, as well as a change in negative biasing and affective processing in patients by anodal stimulation after a single session of tDCS of the left DLPFC [59]. A study by Brunoni et al. [60] could show greater improvement of depressive symptoms after combination of cognitive control training with a series of ten active tDCS compared with sham tDCS. In a sub-analysis of the aforementioned study, Vanderhasselt et al. [61] investigated the effects of tDCS on rumination showed no differences in the Paced Auditory Serial Addition Task (PASAT) in after a series of ten active tDCS compared with sham tDCS. Compared with the preliminary finding of a dose–effect relation in the treatment of depressive disorders, amelioration of cognitive tasks does not seem to depend straight proportionally from stimulation intensity and duration, as two studies with comparison of 1 and 2 mA and durations up to 40 min could show in healthy volunteers [62, 63]. Yet it remains elusive whether these results from healthy volunteers are transferable to depressed patients with their disease-related dysfunction of neuronal networks. However, there seems to be some evidence that combining a psychotherapeutic intervention with tDCS improves depressive symptoms [64]. In this three-arm study, tDCS and cognitive control training were compared to either sham tDCS and cognitive control training or tDCS and sham cognitive control training (i.e., non-therapeutic peripheral vision training). Although all three groups showed improvement as each group had at least one active intervention, tDCS and cognitive control training group showed sustained improvement.

Overall, there is a need for further studies elucidating the effect of tDCS on neuropsychological testing and psychotherapeutic interventions. In this context, a consensus in study design is needed, on which depression-related neuropsychological impairments future studies on healthy controls and patients with depressive disorder might focus to enable comparability between studies.

Safety

tDCS is deemed safe and well tolerable. The current intensities are a multiple below the thresholds which could cause injury of brain tissue [65]. Although excitatory stimulation provokes a tonic change in the resting membrane potential toward depolarization, no action potential is triggered contrarily to transcranial magnetic stimulation. This is the main reason for the lack of seizure risk under tDCS; however, one case of seizure was reported after tDCS in a patient with a history of epilepsy [66]. In recent years, skin burns under the anode [21, 67] and under the cathode were reported [68]. This adverse event is probably due to drying out of the water-soaked sponge electrodes with concomitant increase in impedance at the interface between sponge electrode and skin. The impedance-dependent accumulation of current density leads to local temperature rise in the tissue, followed by thermic damage. If sponge electrodes are soaked with sodium chloride solution, evaporation of the contact medium seems to be lower and skin lesions appear more rarely [21]. In any case, appliers should take care of a sufficient wetting of the sponge electrodes and adverse effects/events should assessed systematically by questionnaires, e.g., the Comfort Rating Questionnaire (http://www.researchgate.net/publication/266023737_CRQ-ComfortRatingQuestionnaire_English_Version). Another adverse event being reported in single case reports [37–39, 41] and two clinical studies report [20, 24] is the induction of hypomania/mania after monotherapy of tDCS or in combination with antidepressants, as well in patients with unipolar and bipolar disorder. The SELECT-TDCS trial by Brunoni et al. [23] reported three cases of hypomania and two cases of mania during combined treatment with tDCS + sertraline and also one case of hypomania each during tDCS + placebo–sertraline and sham tDCS + sertraline, respectively. It remains unclear whether patients with bipolar disorder have a higher risk of induction of hypomania/mania by tDCS than patients with unipolar depression. Overall, the safety of the method is well documented over years and also currently used stimulation parameters with increased current strength (2 mA) and duration of stimulation (2 × 20, 2 × 30 min) are deemed safe. Recently, a case series was published suggesting safety of twice daily 30 min tDCS over longer periods [69].

Sham control and validity check

Four of the randomized placebo-controlled trials (Table 1) report on blinding integrity [19–22]. Overall, there was no difference in correct guesses between active and sham tDCS. However, in the SELECT-TDCS study by Brunoni et al. [23], patients were able to correctly guess active tDCS and active sertraline. Blinding of tDCS was deemed safe and feasible over years when the stimulator was placed behind the patient and switched off without his knowledge for sham stimulation or when programmable automatic switching off was used. Recent studies challenged this notion [70, 71] by proving that higher current intensities (e.g., 2 mA) provoke more uncomfortable skin sensations (itching, tingling, burning) and increased reddening of the skin than sham stimulation. This might lead to unblinding in crossover studies and could be prevented by covering

the stimulation areas or applying skin crème. If crossover designs are used, there should be a 2- to 3-week interval between conditions to fade patients' memories of side effects and to prevent potential overlap effects from the first condition to the second.

Modulation of tDCS treatment

Throughout the assessed literature, placement of electrodes as well as current intensity, duration of application, frequency of tDCS applications and intervals between them have been discussed to influence tDCS effects. Very long distance between electrodes, e.g., extra-cephalic reference, might cause a so-called fanning of the current flow which supposedly affects deeper and more distant brain areas, but also might lose focality. The placing parameters currently used (i.e., cathodal electrodes are placed on the skull surface) are already thought to exert distinct changes in deeper brain structures, e.g., subgenual cortex and anterior cingulate [36], and might also contribute to change in cortical *resting state networks* [13, 14, 72, 73]. Aside from that, anatomical conditions such as size and shape of the skull and brain morphology (anomalies, tissue scars, hematomas, etc.) have been discussed to modulate direction, fanning and depth of penetration. Computer-based modeling of intracranial current flow may appear to be helpful for future assessments of optimal electrode placements and current strengths [74].

Another tool for modulation of tDCS effects is the combined use with psychotropic drugs: Citalopram, amphetamines and D-cycloserine have been shown to prolong and/or enhance the aftereffects of anodal tDCS, whereas carbamazepine, lamotrigine, pregabaline, acetylcholine, sulpiride and nicotine appeared to abolish them [75]. Other agents such as L-Dopa, ropinirole and rivastigmine might have a modulating effect on anodal or cathodal tDCS depending from their dosage [75]. Such experimental approaches might turn out to be useful for the establishment of an individual treatment of neuropsychiatric disorders with a combined therapy with tDCS and medication.

Regulatory considerations

There is still no international guideline on the use of tDCS in depressive disorders. A guideline from a European expert panel has gathered available evidence until mid-2014 and publication of this guideline is expected in early 2016 (Lefaucheur et al., in preparation). The National Institute for Health and Care Excellence (NICE) in Great Britain evaluated tDCS efficacy and stated in its consultation that the total number of patients treated with tDCS is low, that no study has a follow-up over 24 weeks and that different electrode positions hamper the comparability of the studies (https://www.nice.org.uk/guidance/ipg530/documents/transcranial-direct-current-stimulation-tdcs-for-depression-consultation). Although tDCS was considered safe, there was "some evidence of efficacy but there are uncertainties about the specific mode of administration, the number of treatments needed and the duration of effect." It was suggested that further studies should be conducted and the application of tDCS required strict indication and expert monitoring. The United States Food and Drug Administration (FDA) has not yet considered approval of tDCS in psychiatric and neurologic disorders [76]; however, the off-label use of tDCS is possible in the USA.

Future directions

The most important challenge for future research will be to collect unequivocal evidence for the acute and long-term efficacy of tDCS in larger RCTs. This requires a parallel optimization of stimulation protocols in terms of current strength, positioning of electrodes, electrode size, duration of stimulation, frequency of daily stimulations, interval between stimulations, total number of stimulations and maintenance treatment. Particularly, the frequency and the interval between stimulations could be a main factor for the consolidation of neuroplasticity changes. In addition, potentiation of tDCS-elicited neuroplasticity changes by several psychotropic agents could be a promising tool for a combined and finally standardized tDCS + antidepressant treatment. This could lead to quicker and more sustained improvement of depressive disorders and might also improve patient's adherence due to less side effects compared with drug interactions under polypharmacy. The positive cost–benefit ratio of tDCS could entail economizations in the treatment of depressive disorders, and costs of inpatient care could be reduced if patients were enabled to apply stimulation at home with their personal device after technical briefing. For this purpose, small home-use tDCS devices with predefined current strength, duration, frequency and number of daily stimulations are currently investigated.

There is still a need for large and multi-centric clinical trials to investigate the future directions mentioned above and to imply tDCS in the routine treatment under naturalistic conditions. The collection of pilot data in small-sized proof-of-principle studies seems to be exhausted. Thus, there are several studies going on, e.g., to investigate (1) escitalopram versus tDCS in a triple-arm, sham-controlled study in 240 MDD patients [77], (2) tDCS in a double-blind, sham-controlled study in 60 bipolar patients with depression [78], (3) tDCS + escitalopram/citalopram in an open-label study in 100 patients (http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00008009), (4) tDCS and serotonin reuptake inhibitor in a double-blind,

sham-controlled study with 152 patients (http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02530164) and (5) tDCS as add-on in treatment-resistant bipolar/unipolar depression with 120 patients (http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01644747).

Preliminary recommendations

There are currently no standardized guidelines or certificate of qualification for applying persons. Therefore, tDCS and especially enhanced protocols with increased current strength and higher frequency over longer periods should only be performed in specialized centers with sufficient scientific expertise. It is suggested to use devices with CE certification (in Europe) or with "investigational device exemption" (USA). Operators should insure sufficient wetting of the sponge electrodes and a proper contact of the sponges to the skin without too intensive pressure. Routine inspection of the skin after each stimulation and the use of skin care products can decrease the rate of adverse effects. In case of skin irritation and skin burns, stimulation series should be interrupted or discontinued.

Concerning the positioning of the reference electrode, there is no direct evidence so far that F4 positioning is clearly superior over supraorbital positioning. The use of extra-cephalic reference electrodes is currently investigated. Maintenance treatment after a series of tDCS over 2 or 3 weeks should be carried out weekly as biweekly stimulation seems to increase the relapse risk. There are no data about tolerability, neuroplasticity changes and efficacy of long-term treatment exceeding 6 months. Therefore, treatment decision has to be made carefully and individually.

Concomitant pharmacotherapy can influence neuroplasticity effects of tDCS: mood stabilizers/antiepileptic agents abolish tDCS-elicited excitability changes by blockade of voltage-gated sodium and calcium channels; benzodiazepines have probably modulating action and can provoke unexpected tDCS effects. Preliminary data suggest that patients with a high degree of treatment resistance probably have only insufficient benefit of a short tDCS series. For this group of patients, enhanced protocols have to be developed, including optimization of intervals, duration and total number of stimulations, frequency of maintenance treatment and pharmacologic enhancement of tDCS effects.

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