Review

Treatment of depression with transcranial direct current stimulation (tDCS): A Review

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ABSTRACT

Major Depression Disorder (MDD) is usually accompanied by alterations of cortical activity and excitability, especially in prefrontal areas. These are reflections of a dysfunction in a distributed cortico-subcortical, bihemispheric network. Therefore it is reasonable to hypothesize that altering this pathological state with techniques of brain stimulation may offer a therapeutic target. Besides repetitive transcranial magnetic stimulation, tonic stimulation with weak direct currents (tDCS) modulates cortical excitability for hours after the end of stimulation, thus, it is a promising non-invasive therapeutic option. Early studies from the 1960s suggested some efficacy of DC stimulation to reduce symptoms in depression, but mixed results and development of psychotropic drugs resulted in an early abandonment of this technique. In the last years tDCS protocols have been optimized. Application of the newly developed stimulation protocols in patients with major depression has shown promise in few pilot studies. Further studies are needed to identify the optimal parameters of stimulation and the clinical and patient characteristics that may condition response to tDCS.

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Contents

Introduction

Major depression is a common psychiatric disease with a lifetime prevalence of about 15% and a 12-month prevalence of about 7% (Kessler et al., 2003) that generates a large socio-economic burden. Although antidepressant drug treatment has improved during the last decades, symptoms in about 20% of the patients are not in remission two years after initiation of pharmacological intervention (Rush et al.,

2006). Thus alternative or adjunctive therapies are needed, and in this context, brain stimulation approaches may play a prominent role. Electroconvulsive therapy (ECT) is the therapy of choice for pharmaco-resistant patients (Pagnin et al., 2004), but alternative approaches like magnetic seizure therapy, vagal nerve and deep brain stimulation show also some promising results (for an overview see Kennedy and Giacobbe, 2007).

Beyond these fairly non-focal and/or invasive stimulation protocols, non-invasive brain stimulation, especially repetitive transcranial magnetic stimulation (rTMS), has gained interest in recent years for the treatment of depression, shown encouraging results despite some limitations (Lam et al., 2008; Daskalakis et al., 2008), and Neuronetics has recently achieved approval from the Food and Drug Administration

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for their Neurostar® TMS therapy for a subset of medication-refractory depression. The common rationale of rTMS protocols dedicated to the treatment of depression is to modulate the excitability of the prefrontal cortex. However mechanism of action is certainly not proven. It has been demonstrated that the activity of the prefrontal cortex is pathologically altered in major depression and some studies suggest an imbalance between right and left DLPFC activity as an important causal factor for major depression (Grimm et al., 2008). This imbalance of activation is not restricted to the dorsolateral prefrontal cortex, but might affect also orbitofrontal areas (Altshuler et al., 2008). A causal relationship between hemispheric imbalance of function and depression is suggested by lesion studies, but far from conclusively proven. Tumors, ischemia and epileptogenic zones of the left hemisphere are frequently accompanied by depressed mood, while tumors and epileptogenic zones of the right hemisphere cause euphoria (Belyi, 1987; Perini, 1986; Robinson and Lipsey, 1985). Both, excitability enhancement of the left DLPFC or excitability reduction of the right DLPFC to treat depression have been studied, and both approaches show promise. Indeed, a PET study has shown that both rTMS protocols had the desired effects on prefrontal activity and related effects on depressive symptoms (Speer et al., 2000). However, it should be noted that there is no definite evidence that the mechanism of action of rTMS in depression is indeed via modulation of prefrontal excitability. Such neuromodulatory effects could be epiphenomena or simply one aspect of the neurobiologic impact of rTMS that leads to therapeutic benefits in depression. Nonetheless, other neuromodulatory methods are also associated with changes in cortical excitability. VNS does, for instance, enhance cortical inhibition and affect hippocampal plasticity (Di Lazzaro et al., 2004; Zuo et al., 2007). Interestingly, also ECT has been demonstrated to increase cortical inhibition (Bajbouj et al., 2006). In this context though it is important to consider that ECT and rTMS are primarily neuro-stimulatory techniques, rTMS tends to have short-lived effects, VNS requires surgery and benefits are often discrete, and ECT induces cognitive side-effects and involves anaesthesia and the induction of a convulsive seizure (Wagner et al., 2007). Therefore, the use of non-invasive, safe, brain stimulation protocols eliciting longer-lasting effects and exerting purely neuromodulatory influences is desirable (Wagner et al., 2007). One of these techniques is transcranial direct current stimulation (tDCS). The following sections of the paper will be dedicated to discuss the effects and mechanisms of action of tDCS, the clinical studies performed with tDCS in depression so far, and to propose future areas of research.

Direct current stimulation as a tool to modulate cortical excitability

Transcranial direct current stimulation encompasses the induction of a relatively weak constant current flow through the cerebral cortex via scalp electrodes (Fig. 1). Dependent on stimulation polarity, this results in a modulation of cortical excitability and spontaneous neural activity.

The technique was established in the 1950s and 1960s primarily in animals. In these early studies it was shown that subthreshold DC stimulation increases spontaneous neuronal activity if the anode is placed above or within the cortex, while exposure to cathodal polarity results in reduced activity (Bindman et al., 1964; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). This is caused by a subthreshold membrane depolarization by anodal and a hyperpolarization by cathodal stimulation (Purpura and McMurtry, 1965; Scholfield, 1990). However, it was also shown that these effects were not absolutely homogenous: while there was an average, dominant net shift of cortical activation dependent on stimulation polarity as described, some neurons were modulated in the opposite direction. For example, in the cat motor cortex, neurons situated in deep cortical layers were often de-activated by anodal and activated by cathodal stimulation (Creutzfeldt et al., 1962). It was argued that these neurons were
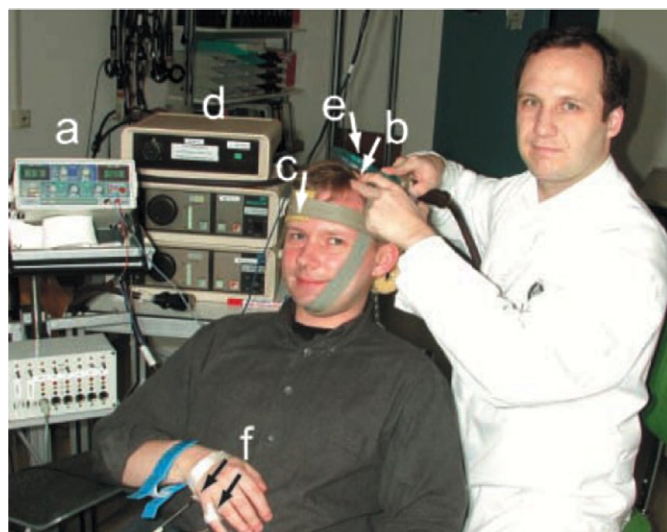
Fig. 1. Illustration of the conduction of tDCS in humans. Experimental setup of tDCS for inducing and recording excitability modifications for the example of the primary motor cortex. Current source is a constant current stimulator (a). The stimulator is connected with a stimulation electrode over the motor cortex (b), and a reference electrode positioned over the contralateral orbit (c). The impact of tDCS on cortical excitability is monitored by transcranial magnetic stimulation (TMS, d − stimulator, e − coil) of the representation area of the abductor digiti minimi muscle. Muscle evoked potentials are recorded from this muscle via surface electromyography electrodes (f).

spatially oriented in a way that reversed current flow direction through the neuron compared to the dominant type of neuron. Moreover, the type of neurons modulated by DC stimulation seems to depend on stimulation strength: whereas weak stimulation modulates predominantly non-pyramidal cells, higher intensities were necessary to change spontaneous activity of pyramidal neurons (Purpura and McMurtry, 1965). Apart from changes of spontaneous discharge rate, subthreshold DC stimulation was shown to modulate the cortical response to thalamic stimulation in the cat: anodal stimulation enhanced the positive and reduced the negative component of the respective electro-cortico potentials, whilst cathodal stimulation resulted in opposite changes (Landau et al., 1964; Purpura and McMurtry, 1965). Conversely, with regard to sensory-evoked potentials in the rat, anodal stimulation decreased the positive waves, while increasing the negative ones; again, cathodal stimulation resulted in reverse effects (Bindman et al., 1964). Because stimulation intensities were similar in both cases and the position of the reference electrode was demonstrated not to be critical (Bindman et al., 1964; Purpura and McMurtry, 1965), these discrepancies may be due to spatially differently organized cortices of the species. Taken together, these animal studies showed that *during* cortical DC stimulation, spontaneous neuronal activity and processing of afferent signals is modulated by polarity-specific shifts of resting membrane potential in a de- or hyperpolarizing direction. The direction of change depends on an interaction of current flow and neuronal orientation in space, the type of neurons involved, and stimulation intensity.

Apart from the acute effects of DC stimulation, early animal experiments already demonstrated the capability of DC stimulation to induce long-lasting after-effects on neuronal excitability and activity. Bindman et al. (1964) showed that anodal stimulation of the rat sensorimotor cortex induces long-lasting increases in the negative wave amplitude of sensory-evoked potentials and spontaneous discharge rates, whereas cathodal stimulation results in reverse effects. These shifts were stable for at least some hours after the end of stimulation. Substantially shorter after-effect durations (about 20 s) were seen in the cat (Purpura and McMurtry, 1965), however, the duration of stimulation in this study was also much shorter (minutes vs. seconds). Further animal experiments revealed some of the

physiological foundations for these effects. They do not appear to be solely electrical phenomena, since intermittent complete cortical inactivation by cooling or application of KCl does not eliminate them (Gartside, 1968a). Instead protein-synthesis-dependent mechanisms have been proposed to also play a role (Gartside, 1968b). As revealed by histological studies, anodal stimulation modifies intracellular cAMP-level dependent on noradrenaline and increases the intracellular calcium level as well as early gene expression (Hattori et al., 1990; Islam et al., 1995, 1997).

Most of the effects and mechanisms of DC stimulation, as explored in these animal studies, seem to be similar or identical to those found to account for the tDCS effects in humans. Anodal tDCS enhances, while cathodal tDCS reduces cortical excitability. These effects evolve during stimulation, but outlast it for an hour or longer given a sufficiently long stimulation duration of some minutes (Antal et al., 2004; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a). As in animal experiments, the primary mechanism of tDCS of the human cerebral cortex appears to be a subthreshold modulation of neuronal resting membrane potential, since blocking voltage-dependent ion channels pharmacologically abolishes any effect of depolarizing anodal tDCS on cortical excitability, but does not influence the impact of hyperpolarizing cathodal tDCS (Nitsche et al., 2003b). Whereas the primary effects of tDCS on neuronal excitability during stimulation are sufficiently explained by neuronal membrane polarization shifts, these cannot fully explain the after-effects. It was demonstrated in humans that the after-effects of tDCS depend on modifications of NMDA receptor-efficacy. The after-effects of tDCS are blocked by the NMDA receptor antagonist dextrometorphan, but prolonged by the partial NMDA receptor-agonist D-cycloserine (Liebetanz et al., 2002; Nitsche et al., 2003b, 2004a). This tDCS polarity-dependent alteration of NMDA receptor function seems to be initiated by the respective membrane potential shift and probably by the accompanying cortical activity modification, because it is prevented by the sodium channel-blocker carbamazepine. Intraneuronal calcium concentration also contributes, since calcium channel antagonists eliminate the excitability-enhancing after-effects of anodal tDCS (Nitsche et al., 2003b).

With regard to the focality of tDCS, it is limited by the relatively large stimulation electrodes ($35 cm^2$ each) and the bipolar cortical stimulation electrode arrangement used in current studies. However, the direct functional effects of tDCS seem to be restricted to the area under the electrodes, since moving the electrodes a few centimetres shifts the efficacy of tDCS dramatically (Nitsche et al., 2003c), and the electrical field strength is relatively homogenous under the electrodes, but diminishes exponentially with distance from it (Miranda et al., 2006; Rush and Driscoll, 1968). Regardless, widespread remote effects of tDCS on different cortical and subcortical areas were revealed in a PET study, which might be connectively driven (Lang et al., 2005).

Most of the initial tDCS studies in humans were performed targeting the motor cortex, because here cortical excitability changes can be easily monitored by TMS-evoked motor evoked potentials (MEPs). However, the efficacy of tDCS is not restricted to this area. Of specific importance for the treatment of depression are the effects of tDCS to modulate prefrontal function. Although electrophysiological measures are not available for this cortical region, it was shown that tDCS of the DLPFC is able to influence working memory, decision making, risk-taking behaviour, impulsiveness, and emotions responsive to visual material in healthy humans (Beeli et al., 2008; Boggio et al., 2008; Fecteau et al., 2007a,b; Fregni et al., 2005). Likewise, tDCS of the frontopolar cortex was demonstrated to affect performance in a probabilistic classification learning task (Kincses et al., 2004). Therefore, it has been convincingly shown that tDCS can affect prefrontal functions.

Safety of tDCS in humans

With regard to the safety of tDCS, current knowledge is still limited, especially with regard to the limits of stimulation strength and duration, which determine the magnitude and duration of the effects. However, currently applied stimulation protocols (typically 1–2 mA intensity, electrode size between 25 and $35 cm^2$, stimulation for up to 20 min per session) should be regarded as safe, as shown by behavioural measures, EEG, serum neuron-specific enolase concentration, and diffusion-weighted and contrast-enhanced MRI measures (Nitsche and Paulus 2000, 2001; Nitsche et al., 2003a, 2004b; Iyer et al., 2005). Most studies have used two cephalic electrodes, and less experience is available with non-cephalic electrode placements. Furthermore, electrode positions above cranial foraminae and fissures should be avoided because these could increase effective current density, and thus safety of stimulation may no longer be guaranteed. Within these limits, no major adverse events had been reported so far for about 2000–3000 subjects in laboratories worldwide. However, slight tingling under the electrodes, headache, fatigue and nausea might occur (Poreisz et al., 2007).

tDCS in depression

Since the 1960s, attempts have been made to explore the effects of tDCS on mood and depressive symptoms in humans. However, the experimental protocols applied in early studies differ fundamentally from the currently used ones. For instance, bifrontal stimulation electrodes and a reference electrode positioned at the knee were used. It was reported that depending on the polarity of the stimulation, alertness and mood were antagonistically modulated in healthy subjects. Anodal stimulation caused increased alertness and elevated mood, whereas under cathodal stimulation subjects became silent, slightly retarded, and withdrawn (Lippold and Redfearn, 1964). It was speculated that these effects might have been accomplished by brainstem stimulation caused by the passage of current from the stimulation to the reference electrodes. In a subsequent open pilot study and a placebo-controlled double-blind clinical trial, the effect of anodal bifrontal tDCS on depressive subjects was explored (Costain et al., 1964; Redfearn et al., 1964). As compared to currently available protocols, a relative strong, long-lasting stimulation was performed with stimulation being performed up to 8 h per day for several days (Table 1). Severity of depression was reportedly reduced, especially with regard to anxiety, agitation and somatic symptoms (Costain et al., 1964; Redfearn et al., 1964). However, only the assessment performed by the nurses and psychiatrists showed significant changes, while the patients themselves experienced no change (Costain et al., 1964; Redfearn et al., 1964). Positive effects of tDCS in depression were confirmed by some subsequent open pilot studies and clinical observations of other groups (Baker, 1970; Carney et al., 1970; Herjanic and Moss-Herjanic, 1967; Nias and Shapiro, 1974; Ramsay and Schlagenhauf, 1966). However, a controlled study performed by Arfai and colleagues (1970) could not replicate these findings. Thus taken together, the results about the clinical potential of these early tDCS protocols to treat depression are mixed. The same holds true for the mood-altering effects of tDCS in healthy subjects, which could not be replicated in later studies (Koenigs et al., 2009; Sheffield and Mowbray, 1968). One possible reason for such mixed findings is large variability in patient populations. For example, more severely depressed individuals are likely to be more resistant to tDCS. Moreover, a common problem of these studies was the lack of consideration of interhemispheric asymmetries. For example, several studies used bifrontal anodal tDCS, which may simply upregulate activity in both hemispheres without modulating hemispheric balance. In general the authors of these early studies favoured an effect of the stimulation on brainstem function, which might be true, given the current flow between the frontal and the knee electrodes; however it is also expected that current between the two electrodes be diffuse and ultimately not able to induce significant biological effects in the brainstem. In addition, taking into account current knowledge about pathological activity alterations in depression, it is

Table 1
tDCS studies conducted for antidepressive treatment.

Study	Type of study	Patients	Medication	Current strength (mA)	Electrode size (cm^2)	Stimulation electrode	Reference electrode	Stimulation duration per session (min)	Number of sessions	Effects
Arfai et al., 1970	Randomized, double-blinded, sham-controlled	Depression	n.a.	0.25	n.a.	Frontal bilateral	Thigh	480	12	No effects
Baker, 1970	Clinical observation	Depression	Tricyclic antidepressants	0.4	1	Frontal bilateral	Arm	300	Max. 6	Reduction of depressive symptoms
Boggio et al., 2007	Randomized, double-blinded, sham-controlled	Major depression	None	2	35	F3	Contralateral supraorbital	20	1	Increased correct identification of affective positive pictures
Boggio et al., 2008	Randomized, double-blinded, sham-controlled	Major depression	None	2	35	F3	Contralateral supraorbital	20	Once daily over 10 days	Reduction of depressive symptoms, stable for 1 month after treatment
Carney et al., 1970	Clinical observation	depression	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	Reduction of depressive symptoms
Costain et al., 1964	Sham-controlled, double-blinded, cross-over	Major depression (?)	n.a.	0.25	0.5 (proposed)	Frontal bilateral	knee	480	Once daily over 12 days	Reduction of depressive symptoms
Fregni et al., 2006	Randomized, double-blinded, sham-controlled	Major depression	none	1	35	F3	Contralateral supraorbital	20	Once daily over 5 days	Reduction of depressive symptoms
Herjanic and Moss-Herjanic, 1967	Clinical observation	Bipolar depression, depressed state	diverse	n.a.	n.a.	Frontal bilateral	Knee	1–8	Once daily over 3–12 days	Reduction of depressive symptoms
Nias and Shapiro, 1974	Case study, placebo-controlled, double-blinded	Depression	Antidepressives, lithium	0.4–0.5	n.a.	Frontal bilateral	Knee	240–320	20 trials, randomized with placebo	One pat. Improved with anodal, another with cathodal stimulation
Ramsay and Schlagenhauf, 1966	Open pilot study	Various	n.a.	0.15–0.3	?	Frontal bilateral	Knee?	42–300 h	Consecutive days	Reduction of depressive symptoms
Redfearn et al., 1964	Open pilot study	Depression	None reported	0.02–0.25	0.5 (proposed)	Frontal bilateral	Knee	Maximum 480 min	For weeks	reduction of depressive symptoms
Rigonatti et al., 2008	Randomized, double-blinded, sham-controlled	Major depression	none	2	35	F3	Contralateral supraorbital	20	Once daily over 5 days	Reduction of depressive symptoms, similar to fluoxetine

Displayed are the type of study, patients included, details of the stimulation protocols, such as current strength, electrode position, electrode size, duration of stimulation sessions, number of sessions and effects of tDCS. Note that the protocols differ relevantly between early and recently conducted studies.

unclear if brainstem modulation can affect depressive symptoms. Whilst clinical impact on the severity of depression was indeed the goal of the studies, the small sample size and the variability in patient populations, make the results unreliable.

In the mid 1970s and 80s, tDCS as well as its therapeutic application in depression was nearly forgotten due to the initial mixed results and development of psychotropic drugs. However, it was re-evaluated and optimized as a powerful tool to induce prolonged neuroplastic cortical excitability changes recently (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003a). In comparison to the above-mentioned studies, the currently performed protocols differ relevantly with regard to current density, electrode position, and stimulation duration (Table 1), and their efficacy to modify excitability has been proven neurophysiologically. Given such methodologic improvements and the promising results of rTMS in depression, scientists were encouraged to re-evaluate the use of tDCS for the treatment of major depression. Hereby, the common rationale of the respective studies is to modify activity in the prefrontal cortex and also to re-establish the balance of left and right prefrontal cortex activation, i.e. to enhance excitability of the hypoactive left prefrontal

cortex and to reduce excitability of the right hyperactive prefrontal cortex. However, it is worth remembering that such therapeutic rationales are purely hypothetical, likely overly simplistic, and the lack of empirical proof of the pathogenetic link between such neurophysiologic abnormalities and the clinical symptoms of depression should be kept in mind.

In a first randomized, double-blinded, sham-controlled study, the effect of tDCS on depression was explored in 10 patients with newly diagnosed major depression without a past or ongoing antidepressive medication treatment (Fregni et al., 2006). In this study depressive symptoms were significantly reduced after 5 sessions of tDCS with one mA for 20 min once daily, but not after sham stimulation, as shown by the Hamilton depression score (HAM) and the Beck depression inventory (BDI). Four out of five subjects under real stimulation had a benefit from tDCS, and the mean reduction in the depression scores were between 60 and 70%, relative to baseline values. In a follow-up study, Boggio et al. demonstrated that a single prefrontal tDCS session, but not occipital or sham tDCS, improved performance in an affective go–non-go task in patients with major depression. Prefrontal tDCS enhanced identification accuracy of
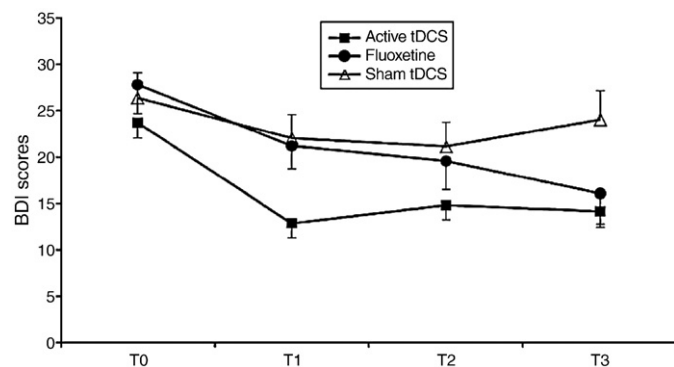
emotionally positive visual material (Boggio et al., 2009), providing some evidence that prefrontal tDCS might improve depression by an alteration of emotion-connected information processing. This effect was not correlated with the reduction of depressive symptoms in these patients after 10 days of tDCS. Nevertheless, this does not rule out that "affective priming" by tDCS is important for the efficacy of stimulation, because the effect of 10 days of stimulation might differ from that of a single stimulation session. In a subsequent study the number of sessions was extended to 10 days and stimulation intensity was increased to 2 mA. The main focus of this study was to explore the long-lasting effects of the antidepressive effects of tDCS (Boggio et al., 2008b). Forty patients with moderate to severe major depression without current use of antidepressive medication were included and randomly assigned to prefrontal (21 patients), occipital (9 patients) or sham stimulation (10 patients). Depressive symptoms were evaluated by the Hamilton depression rating scale and the Beck depression inventory before, immediately after, 15 and 30 days after stimulation. Only prefrontal tDCS reduced depressive symptoms significantly — to about 40% of baseline ratings, and these effects were stable 30 days after the last stimulation session. As compared to sham and occipital stimulation, the number of responders was significantly larger in the prefrontal stimulation group (8 vs. 2 vs. 0, respectively), and only in the prefrontal stimulation group remissions were achieved (5 patients). In a companion study, the antidepressive effects of prefrontal tDCS were compared with those of a six-week treatment with 20 mg fluoxetine and sham tDCS (Rigonatti et al., 2008). Both, real tDCS and fluoxetine reduced depressive symptoms considerably, while sham tDCS had no effect. The overall effects of real tDCS were similar to those of fluoxetine. However, whereas the effects of tDCS were maximal immediately after the end of stimulation and stable for the following four weeks, the effects of fluoxetine were delayed and reached their maximum peak at 6 weeks after the start of treatment (Fig. 2). The results of this study are important in at least two aspects: (i) the size of clinical improvement delivered by tDCS was shown to be similar to the beneficial effects of antidepressant medication in a similar patient population, and, (ii) the effects of tDCS were faster than those of pharmacological treatment.

Taken together, the recently conducted pilot studies deliver clear evidence for an antidepressive effect of prefrontal tDCS. Importantly, the size of the effect seems to be in the range of antidepressant medication, is clinically relevant, occurs early, and is stable for some weeks after the end of stimulation.

Future directions of research

The above-mentioned studies suggest a clinically relevant potential of tDCS to treat depression as performed in the recently conducted studies. Moreover, as compared to drug treatment, the immediate impact of tDCS on depressive symptoms might make it a promising approach to bridge the first weeks of medical treatment, until the pharmacologic benefits manifest themselves. However, results have to be replicated in multi-center studies with larger patient groups, before they can be considered reliable and be entertained for use in clinical practice.

Future studies should explore various aspects likely relevant for the efficacy of tDCS.

For example, it is not clear which brain areas should be directly targeted with tDCS to achieve optimal antidepressant efficacy. Stimulation of the prefrontal cortex results in clinically relevant effects, however, if these are caused by left dorsolateral prefrontal excitability enhancement, right frontopolar excitability reduction, or both – as performed in all of the above-mentioned recently conducted studies – is not clear. Stimulation of both prefrontal cortices was effective in rTMS studies. Thus it might be assumed that the combined stimulation of both areas causes the comparatively large effects of tDCS. However, since not only prefrontal cortices, but also other areas display pathologically altered activity in depression, it might be worth to look systematically for alternative targets of brain stimulation in depression. Likewise, it is not clear what is the optimal stimulation protocol to achieve maximum stability of the antidepressant effects of tDCS. For example, it would be important to know if stimulation once daily is best suited to gain a stable improvement of depressive symptoms, how many sessions are needed to achieve stable effects, and, if effects diminish over time, when to apply additional sessions to boost these. Additionally, long-term follow-ups are needed to evaluate the stability of the effects longer than for four weeks after stimulation.

All of the studies reported so far were accomplished in relatively new diagnosed depression with mild to moderate symptoms. It would be of interest to know if tDCS does also work well in more severe and longer-lasting depressive disorders. Likewise, all patients under study were without antidepressant medication. Since the effects of tDCS are influenced substantially by neuromodulators like dopamine and acetylcholine (Kuo et al., 2007, 2008), it is essential to study whether tDCS would also work in patients on stable antidepressive medication. Since one important aspect of tDCS is its immediate efficacy, which could make it well suited to bridge the gap between start of antidepressive medication and its clinical effects, it would be important to clarify this aspect.

Finally, our understanding about the mechanisms of action of tDCS and the relation between prefrontal neuromodulation and clinical antidepressant impact remains sketchy. A better understanding might improve the efficacy of the stimulation, maybe by combination with psychotherapeutic approaches. Future research approaches in this field should thus address this topic.

Altogether, tDCS could evolve as a promising approach for treating major depression. The positive initial results justify further research efforts to optimize the effects and enhance our understanding of mechanisms of action of tDCS in depression. The results of these studies might lead to an integration of tDCS into the arsenal of antidepressant therapeutics.

Fig. 2. Effects of tDCS on symptoms in major depression, as compared with fluoxetine. Depression scores (as indexed by the Beck Depression Inventory (BDI)) change over time. BDI scores were assessed at baseline (T0) and after 2, 4 and 6 (T1–3) weeks of the treatment onset. Each point represents mean and error bars represent S.E.M (Rigonatti et al., 2008).

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