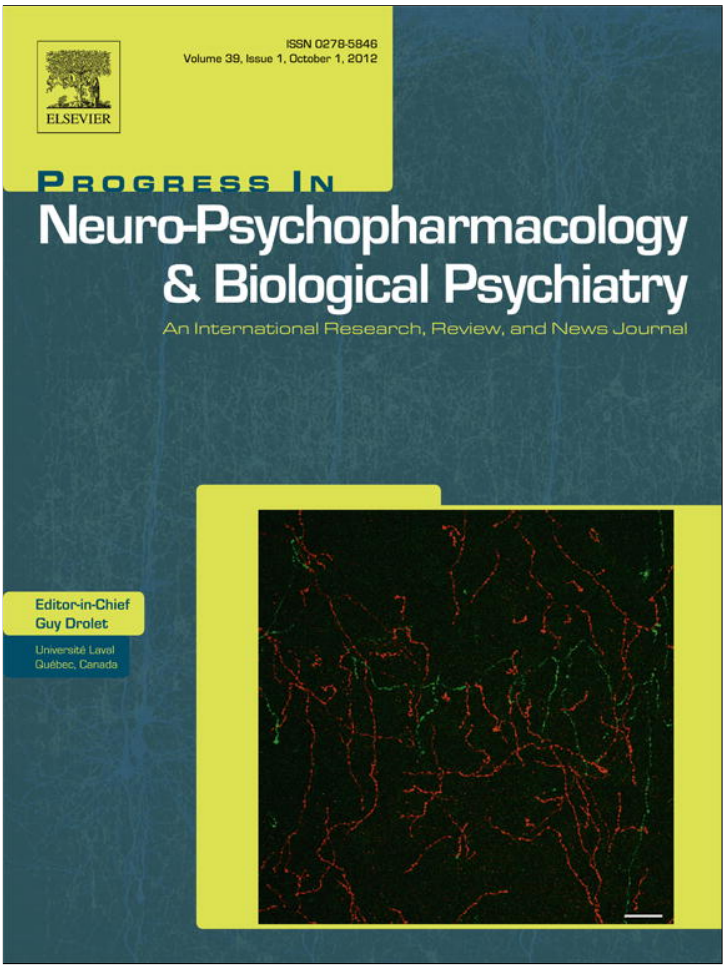

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Review article

Transcranial direct current stimulation for the treatment of major depressive disorder: A summary of preclinical, clinical and translational findings

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ABSTRACT

Major depressive disorder (MDD) is a common psychiatric illness, with 6–12% lifetime prevalence. It is also among the five most disabling diseases worldwide. Current pharmacological treatments, although relatively effective, present important side effects that lead to treatment discontinuation. Therefore, novel treatment options for MDD are needed. Here, we discuss the recent advancements of one new neuromodulatory technique – transcranial direct current stimulation (tDCS) – that has undergone intensive research over the past decade with promising results. tDCS is based on the application of weak, direct electric current over the scalp, leading to cortical hypo- or hyper-polarization according to the specified parameters. Recent studies have shown that tDCS is able to induce potent changes in cortical excitability as well as to elicit long-lasting changes in brain activity. Moreover, tDCS is a technique with a low rate of reported side effects, relatively easy to apply and less expensive than other neuromodulatory techniques — appealing characteristics for clinical use. In the past years, 4 of 6 phase II clinical trials and one recent meta-analysis have shown positive results in ameliorating depression symptoms. tDCS has some interesting, unique aspects such as noninvasiveness and low rate of adverse effects, being a putative substitutive/augmentative agent for antidepressant drugs, and low-cost and portability, making it suitable for use in clinical practice. Still, further phase II and phase III trials are needed as to better clarify tDCS role in the therapeutic arsenal of MDD.

Contents

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1. Introduction

Major depressive disorder (MDD) is a severe, chronic and prevalent psychiatric illness, with community-based surveys showing a lifetime prevalence ranging from 6 to 12%, and an annual prevalence of 3–11% worldwide (Andrade et al., 2003; Kessler et al., 2005; Waraich et al., 2004). It is expected to be the second most disabling condition by 2020 (Murray and Lopez, 1997). In addition, nearly 80% of patients relapse after one antidepressant treatment (Anderson et al., 2008) and almost 33% of patients fail to achieve remission after two or more antidepressant trials — a condition named treatment-resistant depression (Berlim and Turecki, 2007). Moreover, antidepressant side effects such as weight gain; sexual dysfunction and somnolence can significantly decrease patient compliance of maintenance treatment in MDD (Brunoni et al., 2009; Zajecka, 2000). Therefore, the development of new therapeutic interventions for the treatment of this psychiatric illness is needed.

In fact, one field under intensive investigation is neuromodulation. From electroconvulsive therapy (ECT) to novel clinical and preclinical techniques, such as transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and transcranial direct current stimulation (tDCS), these techniques aim to develop novel non-pharmacological interventions for the treatment of neuropsychiatric disorders. Neuromodulation can be either invasive, for instance, Deep Brain Stimulation (DBS), a technique that implants electrodes in subcortical areas aiming the treatment of conditions such as Parkinson's disease and, more recently, MDD (George and Aston-Jones, 2010); or non-invasive, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (Fig. 1).

RTMS uses a coil positioned over the scalp as to generate a potent, pulsatile electromagnetic field (up to 3 T), secondarily inducing an electric current flow inside the brain. Conversely, tDCS is based on the application of weak (0.5–2 mA), direct electric current into the brain through relatively large electrodes placed over the scalp (George and Aston-Jones, 2010). For MDD, rTMS has been more investigated than tDCS hitherto, with dozens of phase-II trials and at least two phase-III trials showing its efficacy — in fact, rTMS has been ultimately approved for the treatment of MDD by regulatory agencies and is being increasingly used worldwide (Brunoni et al., 2010). Nevertheless, this technique has some drawbacks, such as (1) cost: application of rTMS usually costs US$ 300.00 per session, which is expensive in most settings (Simpson et al., 2009); (2) clinical applicability: rTMS is a non-portable device that can be used only in hospital and/or ambulatory settings, obligating patients to perform daily visits to the clinic; (3) availability: rTMS is a relatively expensive device applied only by trained physicians. These issues greatly limit rTMS availability (Priori et al., 2009). One possible solution is developing handheld rTMS devices, which are in fact currently under investigation (George and Aston-Jones, 2010). Another solution would be a device that combines the non-pharmacological advantages of rTMS with low-cost, easiness of use and portability; in fact, these characteristics are present in tDCS devices. Currently, tDCS research on MDD has experimented significant advancement, with some clinical trial showing promising results (Boggio et al., 2008a; Brunoni et al., 2011b; Ferrucci et al., 2009b; Fregni et al., 2006a). The aim of this review is, therefore, to summarize the main aspects and challenges of tDCS as a novel treatment for major depression.

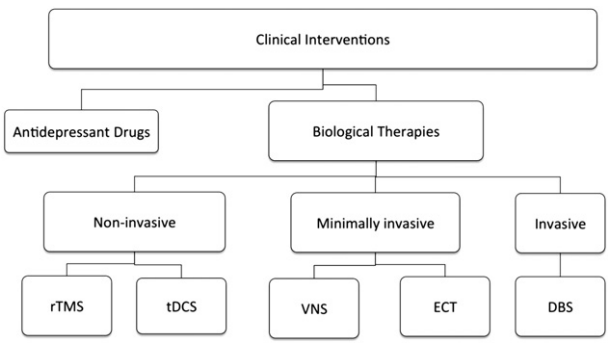

Fig. 1. The biological therapies for the treatment of major depressive disorder.rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation; VNS = vagus nerve stimulation; ECT = electroconvulsive therapy; DBS = deep brain stimulation.

2. Historical remarks

Reports of brain stimulation through electric currents have existed since the Ancient time; with observations by Greek and Roman physicians that the electric "torpedo fish" delivered electric discharges that could relieve headache (Largus, 1529). After the introduction of the electric battery in the 18th century, some physicians started to use these galvanic batteries to perform electric brain stimulation in selected subjects (Zago et al., 2008), although these interventions were uncontrolled and received with skepticism by academics of the epoch. In fact, controlled, systematic research using brain electric stimulation only began in the 1950s and 1960s with the classic studies of Purpura and McMurtry and Bindman and colleagues, who showed in experimental animals that anodal and cathodal cortical stimulation could increase and decrease cortical activity, respectively (Bindman et al., 1964; Purpura and McMurtry, 1965). During 1964–1974 a few clinical trials using tDCS for MDD were also conducted, although with overall mixed results (Nitsche et al., 2009a). However, during the 1970s and 1980s tDCS research faded, possibly due to the advancement and initially positive results of psychopharmacology. The technique of tDCS was only reappraised at the turn of this century, with the seminal studies of Priori et al. (1998) followed by Nitsche and Paulus (2000) who showed that DC stimulation delivered transcranially could modify cortical excitability in a polarity-dependent and intensity-dependent manner. From then onwards, several studies investigated tDCS in basic and applied research, using this technique either as a tool to investigate specific cortical brain areas or as a novel treatment for neuropsychiatric disorders (Brunoni et al., 2011d).

3. Technical aspects and mechanisms of action

tDCS devices are essentially composed by four main components: electrodes (usually one anode and one cathode), power supply (usually 9 V batteries), an amperemeter (for measurement of the intensity of the electric current) and a potentiometer (to allow adjustment of the electric current). One electrode is necessarily placed over the scalp, above the cortical area aimed to be stimulated. The other electrode can be also positioned over the scalp, or, alternatively, on an extra-cephalic position (e.g., deltoid muscle). For MDD, the anode is placed over the area corresponding to the left dorsolateral prefrontal cortex (F3 according to the EEG 10/20 system). Two main protocols are used regarding cathode placement: one places it over the right dorsolateral prefrontal cortex

(F4 area) and the other, over the left supraorbital region (F8 area). The former strategy takes advantage of the prefrontal cortex asymmetry theory for MDD (discussed later), aiming to restore the left-to-right imbalance to "normal" activity. The rationale for the second strategy is that most studies consider the F8 area as neutral or at least less critical given tDCS modulation, therefore assuming any physiological or clinical effect solely due to the anodal stimulation over F3. However, this assumption is not necessarily true, for instance, studies using simulated models show that there is brain activation in the areas beneath the cathode (Miranda et al., 2006). Also in Boggio et al. (2008a) study, when authors changed the DLPFC electrode to the occipital area but kept the supraorbital (F8) electrode, it induced a larger effect compared to sham stimulation, although this strategy was associated with smaller effects than the DLPFC-supraorbital montage (Fig. 2).

When tDCS is turned on, a weak (0.5–2 mA) and direct electric current flows from the anode (positive pole) to the cathode (negative pole). As a result, brain areas close to the anode become hypo-polarized and those near to the cathode are hyper-polarized. It is important to underscore that tDCS per se does not trigger action potentials (this is one fundamental difference between this technique and rTMS); rather, it facilitates or inhibits spontaneous neuronal network activity — thus tDCS is more properly considered a neuro*modulatory* (instead of a neuro*stimulation*) technique (Priori et al., 2009). This is because the membrane potentials are hyperpolarized or depolarized by only a few mV with the electric currents applied in tDCS protocols, which is much lower than the necessary threshold for eliciting action potentials: for instance, a 2 mA current can change the membrane potential in approximately 0.8 mV, whereas at least 20 mV is necessary to trigger action potentials (Ruohonen and Karhu, 2012). In fact, tDCS might act on spike timing, modulating net cortical excitability (Radman et al., 2009).

In addition, tDCS can also induce effects beyond the period of stimulation (a single session can generate long-lasting effects for up to 90 min) (Brunoni et al., 2011d). This indicates that tDCS not only changes neuronal membrane potential but also induces synaptic changes. In fact, studies using tDCS coupled with NMDA-antagonist drugs showed abolishment of tDCS after-effects, whereas association of tDCS with NMDA-agonists enhanced its aftereffects (Nitsche et al., 2003, 2004). As NMDA receptors are post-synaptic glutamatergic receptors that play a critical role in long-term potentiation (LTP) and synaptic strengthening, this evidence endorses tDCS as a promising tool to induce neuroplasticity. Moreover, monoaminergic drugs also modify tDCS effects — for instance, citalopram, a SSRI (selective serotonin reuptake inhibitor) enhances anodal tDCS effects, pergolide (a dopamine agonist) enhances cathodal tDCS effects, amphetamines enhance anodal tDCS effects and sulpiride (a post-synaptic dopamine blocker) abolishes tDCS effects (Stagg and Nitsche, 2011).

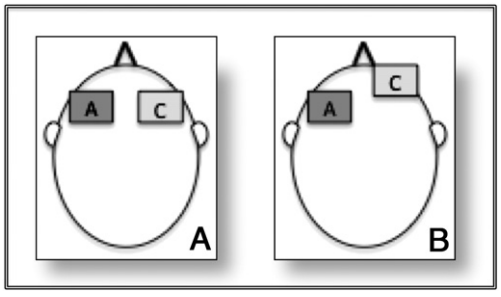

Fig. 2. Montage of transcranial direct current stimulation.The figures show the main montages used for major depression: in both, the anode is positioned over the left dorsolateral prefrontal cortex. The cathode can be either placed over the right dorsolateral prefrontal cortex (figure A) or the right supraorbital area (figure B).

4. tDCS for major depressive disorder

4.1. Putative mechanisms of action

Among several biological hypotheses for explaining MDD, one specially appealing to the field of neuromodulation is the neural system hypothesis, which understands depression as a condition related to dysfunction in several cortical and subcortical areas, specially (as shown by neuroimaging and EEG studies) the dorsolateral and ventromedial areas of the prefrontal cortex (PFC), the amygdala and the hippocampus (Campbell et al., 2004; Hamilton et al., 2008), which are associated with symptoms such as psychomotor retardation and executive dysfunction (related to PFC) as well as anhedonia and feelings of guilt and hopelessness (related to subcortical areas) (Brunoni et al., 2010). Moreover, patients with MDD have interhemispheric imbalance, with lower activity in the left hemisphere and higher activity in the right cortex. This functional asymmetry is supposed to be related to differential emotional judgment towards negative aspects (Vanderhasselt et al., 2009). This neural system hypothesis also agrees with classic observations of MDD being related to monoaminergic deficiencies and a hyperactive hypothalamic-pituitary-adrenal (HPA) axis. The monoamine hypothesis is based on pharmacological studies that show that tricyclics and SSRIs are effective for depression. In fact, noradrenergic, serotoninergic and dopaminergic neurons project from subcortical regions such as the locus ceruleus, raphe nuclei and the nucleus accumbens, respectively, to cortical areas, especially the PFC. Thus, monoaminergic impairment consequently results in cortical–subcortical dysfunction. The HPA hyperactivation is another classic observation in MDD studies during the 1980s. In fact, as higher cortical areas modulate the HPA system, dysfunction of the cortical–subcortical system is also reflected in greater HPA activity.

According to these frameworks, the aim of anodal simulation over the left dorsolateral PFC is to increase cortical activity in this area. Neuropsychological studies modulating the left dorsolateral PFC showed an improvement of executive functioning in working memory tests as well as enhancement of identification of positive visual material (Boggio et al., 2009; Fregni et al., 2005). Daily, repeated tDCS sessions are, thus, supposed to modulate this cortical area and also, via top-down modulation, other subcortical areas. For instance, Beeli et al. (2008) used cathodal tDCS over the right PFC in a visual task, achieving modulation of skin conductance, thus indicating indirect tDCS modulation of subcortical areas.

Besides left dorsolateral PFC stimulation and top-down modulation, tDCS could also act in depression via "left-to-right" modulation — i.e., using the anode electrode over the left PFC and the cathode electrode over the right PFC. In this "bifrontal" setup, one aims to simultaneously enhance left PFC activity, as anodal stimulation increases spontaneous neural activity, while right PFC activity is inhibited as cathodal stimulation decreases neural activity (Ferrucci et al., 2009b).

Lastly, the LTP-deficiency hypothesis of depression proposes that focal deficits in neuroplasticity in certain brain areas could be the final common pathway underlying the clinical and biological characteristics of depression. For instance, depressed subjects present deficits in declarative memory consolidation, enhanced fear acquisition and impaired visual discrimination, suggesting deficits in LTP mechanisms in the hippocampus, amygdala and the visual system (Nissen et al., 2010; Normann et al., 2007) and in addition, overall decreased levels of BDNF (Brunoni et al., 2008). Moreover, a chronic-stress, animal model of depression showed that the antidepressant fluvoxamine prevented the facilitation of long-term depression (LTD) and it also increased LTP in the hippocampus, corroborating this hypothesis. Interestingly, an animal study using direct current stimulation showed that this technique induces BDNF-dependent synaptic plasticity (Fritsch et al., 2010) and studies exploring the electrophysiology of tDCS also demonstrate that tDCS induces neuroplasticity (Stagg and Nitsche, 2011).

Therefore, another putative mechanism of action for tDCS would be to induce neuroplasticity that is impaired in depression.

4.2. Empirical evidence from rTMS

Another bulk of evidence comes from the almost fifty randomized controlled trials conducted using rTMS as a treatment for MDD. Two recent meta-analyses showed that either high-frequency, left or low-frequency or right dorsolateral PFC stimulation is an effective antidepressant strategy (Schutter, 2009, 2010). This framework can be transposed to tDCS, since anodal stimulation increases whereas cathodal decreases cortical excitability, analogously to high-frequency and low-frequency stimulation, respectively.

4.3. Preclinical studies

Although available animal tDCS studies did not specifically evaluate experimental models for depression, they provide interesting insights. For instance, two studies in healthy Sprague–Dawley rats used active anodal tDCS over the rat cortex as to evaluate functional magnetic resonance imaging (Takano et al., 2011) and cerebral blood flow (Wachter et al., 2011) changes before and after stimulation. The studies observed an increase in brain activity and blood flow, respectively. Likewise, experimental animal studies also showed that cathodal stimulation decreased cerebral blood flow (Wachter et al., 2011) and reduced pain (Nekhendzy et al., 2004). These studies demonstrated the polarity-dependent effects of tDCS and therefore further support "bifrontal" montages in MDD aiming for simultaneous, differential brain activation (for a review of tDCS animal studies see (Brunoni et al., 2011c)).

4.4. Relevant findings in studies with healthy volunteers

Several studies in healthy volunteers support the notion that tDCS modifies brain activity. One class of studies used TMS as a tool to index cortical excitability, showing a modulation of the motor-evoked potentials and/or intracortical excitability (Brunoni et al., 2011d; Nitsche et al., 2005).

Particularly considering the stimulation of the left dorsolateral PFC, various tDCS studies have shown interesting results. For instance, Fregni et al. (2005) evaluated working memory using a 3-back test (a neuropsychological test in which the subject should identify the same target – usually a letter – that was presented 3 positions earlier) in 15 healthy volunteers. Those that received active tDCS presented a higher number of correct responses and also fewer errors. Another study using the same experiment in patients with Parkinson's disease presented similar results (Boggio et al., 2006). In addition, Fregni et al. (2006b) evaluated cognitive functioning using several tests (Mini-Mental Status Examination, digit span, Stroop test, symbol digits and five-point test) in patients with depression, showing increased performance in all assessed domains after 5 sessions of anodal tDCS stimulation over the left dorsolateral PFC. The findings of these studies are interesting for depression for two reasons: first, as MDD is related to executive impairment, tDCS could be used to restore cognitive deficits in these patients; second, since dorsolateral PFC activity is both linked to MDD and working memory, these studies serve as an index of dorsolateral PFC modulation, thus providing further evidence for tDCS clinical trials on MDD.

Transcranial DC stimulation over the left dorsolateral PFC can also modulate cognitive functioning. For instance, Kincses et al. (2004) used the "probabilistic classification learning" test that evaluates implicit learning. They showed that anodal tDCS over the left dorsolateral prefrontal cortex (but not over the occipital cortex or cathodal stimulation) improved performance in this test, in contrast to sham and cathodal stimulation. Also, Boggio et al. (2008b) used a go/no-go affective visual test in subjects receiving active or sham tDCS, finding that those receiving active anodal stimulation presented better outcomes. Therefore, as MDD is related to impairment in affective processing, tDCS could be used to restore normal affective processing as well as a putative tool for treating depression.

Recently, neuroimaging studies have been used to determine tDCS effects. Rango et al. (2008) used proton magnetic resonance spectroscopy to evaluate brain activity after active or sham tDCS in 10 healthy volunteers. They showed that only active tDCS was associated with an increased myoinositol production. They observed that active tDCS increased brain phospholipid metabolism. Also, Lang et al. (2005) used a PET-scan to show increased rest blood cerebral flow after active anodal tDCS. However, Antal et al. (2011) measured BOLD activity (using functional magnetic resonance imaging) during anodal tDCS stimulation and a finger-tapping test, observing paradoxically decreasing of BOLD activity during the task.

5. Clinical studies

From 2006 onwards, at least 19 clinical studies with different methodologies (such as case reports; open-label trials; randomized, controlled trials; and meta-analysis) have been published exploring tDCS effects on depression (Table 1). We further discuss their main findings and limitations.

5.1. Randomized clinical trials

Fregni et al. (2006a) were the first of the "present era" of tDCS (i.e., apart from the earlier trials conducted from 1964 to 1974) to show that tDCS could have antidepressant properties. In a pilot randomized, sham-controlled, double-blind trial, 10 patients with mild to moderate depression and medication free were randomly assigned to receive either 5 days of active or sham stimulation. They showed positive results with an improvement of 60% in the active vs. only 12% in the sham group. Fregni et al. (2006b), in another randomized clinical trial, used the same tDCS protocol with 18 depressed subjects who were also medication free for 3-months, also finding significant improvement in the active vs. sham group (58.5% vs. 13.1%, respectively). Later on, Boggio et al. (2008a) enrolled 40 MDD subjects with different degrees of refractoriness (but medication-free) and randomized them to 10 sessions of active dorsolateral prefrontal cortex tDCS, active occipital tDCS or sham tDCS. They found that the active DLPFC tDCS group presented a superior, significant improvement in HDRS scores compared with the other groups (improvement of 40% in active left PFC vs. 20% in the occipital group and 10% in the sham group).

Nonetheless, Loo et al. (2010) and Palm et al. (2011) reported discrepant findings. The first group enrolled 40 patients with severe MDD, in a double-blinded, sham-controlled study but failed to demonstrate significant difference between groups in this phase (similar improvements of approximately 19%); tDCS was only more effective during the open-label phase in which patients received additional five sessions. However, this study had some limitations: the dose applied was relatively low (1 mA), and only five stimulation sessions were held, which were alternated, i.e., performed every other day (or second daily), whereas other studies used consecutive sessions (except for the first pilot study that included patients with mild to moderate depression (Fregni et al., 2006a)). Moreover, patients with axis II disorders were excluded, an issue that could have increased sample heterogeneity. Palm et al. (2011) randomized 22 patients to receive 1 or 2 mA for 20 min/day per 2 weeks, in a cross-over trial, observing that the groups were not superior to sham stimulation (14.6%, 16.7% and 9%, for 1 mA, 2 mA and sham, respectively). The authors considered that possible reasons for this finding were the high degree of treatment-resistance and the concomitant use of antidepressant medications. In the most recent randomized, controlled trial published hitherto, Loo et al. (2012), in contrast with their previous study, found positive results in a larger trial with 64 patients that were randomized to receive 3-week active or

Table 1
Summary of transcranial direct current stimulation clinical studies for major depressive disorder.

Author			Protocol						Improvement (change in scores)		
	Sample size	Depression scale	A	C	Current density (A/m^2)	Session duration (min)	Number of sessions	Frequency	Active	Control	Endpoint (from 1stday of treatment)
Randomized, double-blind, controlled trials											
Fregni et al. (2006a)	10	HDRS	F3	R SO	0.28	20	5	Every other weekday	60%	12%	2 weeks
Fregni et al. (2006b)	18	HDRS	F3	R SO	0.28	20	5	Every other weekday	58.50%	13.10%	2 weeks
Boggio et al. (2008a)	40	HDRS	F3	R SO	0.57	20	10	Consecutive weekdays	40.40%	10.40%	6 weeks
Loo et al. (2010)	40	MADRS	F3	R SO	0.28	20	5	Every other weekday	19.50%	19.20%	2 weeks
Palm et al. (2011)	22	HDRS	F3	R SO	0.28/ 0.57	20	10	Consecutive weekdays	14.6%/16.7%	9%	2 weeks
Loo et al. (2012)	64	MADRS	F3	R SO	0.57	20	15	Consecutive weekdays	28.40%	15.90%	2 weeks
Open-label studies											
Ferrucci et al. (2009b)	14	HDRS/BDI	F3	F4	0.57	20	10	2×/day (one weekday)	32.10%	–	5 weeks
Ferrucci et al. (2009a)	32	HDRS/BDI	F3	F4	0.57	20	10	2×/day (one weekday)	27.70%	–	5 weeks
Brunoni et al. (2011b)	31	HDRS/BDI	F3	F4	0.57	20	10	2×/day (one weekday)	45.2%(*)	–	5 weeks
Dell'osso et al. (2011)	23	HDRS/MADRS	F3	F4	0.57	20	10	2×/day (one weekday)	31.30%	–	2 weeks
Martin et al. (2011)	11	MADRS	F3	R arm	0.57	20	20	Consecutive weekdays	43.80%	–	4 weeks
Case reports											
									Comment		
Palm et al. (2009)	1	HDRS/BDI	F3	R SO	0.28	20	16	Consecutive weekdays	Treatment-resistant depression modestly improved after tDCS		
Arul-Anandam et al. (2010)	1	MADRS	F3	R SO	0.28	20	5	Consecutive weekdays	Transient hypomania episode that started after 3-sessions and resolved spontaneously		
Baccaro et al. (2010)	1	YMRS	F3	F4	0.8	30	10	Consecutive weekdays	Transient hypomania episode that started after 6-sessions and resolved spontaneously		
Brunoni et al. (2011f)	1	YMRS	F3	F4	0.8	30	6	Consecutive weekdays	Full-blown manic episode after 6-sessions of tDCS + sertraline requiring pharmacological intervention		
Bueno et al. (2011)	1	MADRS	F3	F4	0.8	30	10	Consecutive weekdays	Post-stroke depression that markedly improved after tDCS		
Galvez et al. (2011)	1	MADRS	F3	R arm	0.57	20	20	2×/day (one weekday)	Hypomanic episode in a bipolar depressed patient after frontoextracephalic tDCS		
Others											
Rigonatti et al. (2008)	11	HDRS	F3	R SO	0.57	20	10	Consecutive weekdays	tDCS and fluoxetine had similar improvement rates at endpoint, tDCS was superior at 2 weeks		
Kalu et al. (2012)	176	Effect Size of Depression Scales	F3	R SO	0.28/ 0.57	20	5/10/15	Daily/every other day	The first tDCS meta-analysis showed an ES of 0.74 favoring active vs. sham group although between-sample heterogeneity was important		

HDRS, Hamilton Depression Rating Scale, MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; BDI, Beck Depression Inventory; A, anode; C, cathode; F3, left dorsolateral prefrontal cortex; F4, right dorsolateral prefrontal cortex; R SO, right supraorbital area; R arm, right arm; ES, effect size. (*) Improvement in bipolar depression group.

sham anodal tDCS (2 mA/20 min), showing an improvement of 28.4% in the active group vs. 15.9% in the sham group. In this trial, the sample was composed of bipolar and unipolar depressed patients, mostly (67%) on antidepressant treatment and with chronic, treatment-resistant depression.

Kalu et al. (2012) performed a meta-analysis of these studies, showing an effect size of 0.74 (95% Confidence Interval 0.21–1.27) favoring the active vs. sham group; therefore suggesting that tDCS indeed has antidepressant effects. On the other hand, these authors also stated that study results differed more than expected by chance, which was suggestive of between-sample heterogeneity. Interestingly, as seen in Table 1, tDCS protocols can be considered quite homogeneous, since all studies performed anodal stimulation over F3 with the cathode over the right supraorbital cortex. All studies used current densities of 0.57 A/m^2 (although Palm et al. (2011) also stimulated with 0.28 A/m^2), and all sessions lasted 20 min each. Therefore, the different results are probably related to the number of sessions, which ranged from 5 to 15 (although there is no clear number-of-sessions/response relationship), relatively small sample sizes (which increase false-positive and false-negative findings), and sample heterogeneity — for instance, Fregni et al. (2006b) and Boggio et al. (2008a) enrolled medication-free samples whereas Loo et al. (2010) and Palm et al. (2011) did not. Future phase II trials could have their designs optimized by adopting stricter eligibility criteria and could also test different tDCS parameters regarding, for example, electrode placement, current density and number of sessions. In addition, alternative clinical trial designs such as select-drop design may allow investigation of a wider range of parameters.

Nevertheless, further phase III tDCS is also warranted, investigating tDCS efficacy for MDD in larger samples. Along these lines, Brunoni et al. (2011e) are conducting an ongoing 2×2 factorial study in which 120 patients with MDD are being enrolled and randomized to receive tDCS, sertraline, both interventions in combination or double-placebo, in a factorial design. The results of this study combined with others will provide more definite conclusions regarding the efficacy of tDCS for MDD.

5.2. Open-label studies and case reports

Some non-randomized, open-label studies have also investigated tDCS effects in MDD. Ferrucci et al. (2009b) stimulated 14 patients with severe MDD using 2 mA for 20 min for 5 days twice a day (total 10

sessions), showing 32.1% depression improvement in 5 weeks. In another study with 32 patients, Ferrucci et al. (2009a) used the same tDCS protocol and observed a similar (27.7%) improvement. In this study, the effects seemed to be more robust in more severe patients. Later on, Brunoni et al. (2011b) showed that the same protocol was effective in bipolar patients, with 45% improvement in 5 weeks. Finally, Dell'osso et al. (2011), also using the same tDCS protocol, observed 31.3% improvement after 5 weeks of treatment onset in 23 patients with refractory depression. All the abovementioned studies also employed a particular tDCS montage in which the anode is placed over F3 and the cathode over F4. Theoretically, this could be a better strategy as some studies suggest that subjects with depression may exhibit prefrontal cortex asymmetry (hyperactivation on the right and hypoactivation on the left prefrontal cortex (Koenigs and Grafman, 2009)) and therefore, this protocol can act simultaneously in both areas. In contrast to these studies, Martin et al. (2011) performed frontal-extracephalic stimulation, i.e., anode over F3 and cathode in an extracephalic position (in this case, the right arm) in 11 patients with depression, with positive results (43.8% improvement after 4 weeks of daily weekday stimulation, total of 20 sessions). In fact, open-label trials also act as proof-of-concept studies, being useful to test new tDCS protocols, especially when there is no ethical approval to perform sham-controlled trials, though it is debatable whether there is enough evidence to rule out equipoise of a tDCS trial using a sham tDCS group as a control.

Also, Rigonatti et al. (2008) performed an open-label follow-up study in a similar population but testing fluoxetine 20 mg/d for 6-weeks and comparing with 10 weekday sessions of active tDCS (from patients of Boggio's study). They observed similar depression improvement at 6 weeks, although tDCS showed superior improvement than fluoxetine at 2 weeks.

Four of 6 case reports described episodes of treatment-emergent (hypo)mania. Three cases (Arul-Anandam et al., 2010; Baccaro et al., 2010; Galvez et al., 2011) reported hypomanic episodes that were generally benign and directly associated with the tDCS course. Brunoni et al. (2011f), however, described a severe manic, psychotic episode after 6 treatment days concomitant use of tDCS and sertraline that required pharmacological intervention. The other two cases described tDCS effects in special situations: Bueno et al. (2011) reported dramatically improvement of a woman with post-stroke depression after tDCS whereas Palm et al. (2009) described moderate depression improvement and significant cognitive improvement in a patient with treatment-resistant depression. These case reports are useful as they highlight the occurrence of side effects (notably, mania) and tDCS antidepressant effects in different populations, therefore generating hypotheses for new studies.

5.3. Safety and tolerance

One recent animal safety study has showed that current parameters used in clinical studies are probably safe, since brain lesions were only experimentally induced when rats received cathodal tDCS stimulation almost one hundred times higher than being used in clinical studies (Liebetanz et al., 2009). Likewise, a recent review did not observe serious adverse effects associated with tDCS (Brunoni et al., 2011a). Nonetheless, most studies only applied single-sessions of tDCS in healthy volunteers, whereas clinical use of tDCS involves repeated, daily tDCS sessions. Such stimulation protocol might induce adverse effects associated either with daily stimulation, for instance, skin irritation and skin burn (Palm et al., 2008) or with the disorder — e.g., hypomanic switch (Arul-Anandam et al., 2010; Baccaro et al., 2010; Brunoni et al., 2011f) or paradoxical depression worsening.

Still, mild adverse effects of tDCS are relatively common, such as tingling, burning and itching sensations over the electrode site (Brunoni et al., 2011a). Such effects can be greatly attenuated using sponges embedded with saline (15 to 140 mM) solutions and/or anesthetic creams (Brunoni et al., 2011d; Nitsche et al., 2008). Nevertheless, future research should still inquire for adverse effects during tDCS sessions.

6. Future directions

Although the abovementioned results are promising, there are important issues related to tDCS clinical research. We discuss three of them.

6.1. tDCS and pharmacotherapy

One important issue is the association of tDCS with pharmacotherapy. Pharmacological studies have shown that drugs can not only enhance but also abolish tDCS effects (Brunoni et al., 2011g; Stagg and Nitsche, 2011). Although this evidence comes from preliminary, single-session tDCS studies that stimulated the motor cortex (not the PFC) of healthy volunteers, it is important to investigate whether and which drug therapies could modify tDCS effects, specially considering that patients with MDD commonly use a plethora of medicines of different classes, such as antidepressants, anti-epileptics, antipsychotics, lithium and benzodiazepines. In fact, it is unknown how tDCS effects are modified by chronic use of psychopharmacological drugs, an issue to be resolved when applying tDCS in clinical settings. Remarkably, Nitsche et al. (2009b) explored the effects of citalopram on tDCS-induced plasticity. After a single dose of 20 mg citalopram or placebo, they measured motor cortical excitability before and after anodal or cathodal tDCS, in healthy volunteers. They observed that citalopram enhanced and prolonged the facilitation induced by anodal tDCS whereas it turned cathodal tDCS inhibition into facilitation. Therefore, it would be interesting to explore whether antidepressant effects of tDCS combined with antidepressants (particularly serotoninergic) are augmented.

6.2. tDCS and easiness of use

As mentioned earlier, tDCS is less expensive and user-friendlier than rTMS. Still, it requires daily 20–40 min sessions for 5 to 15 days, demanding frequent visits to the clinic center, which might be cumbersome and lead to treatment discontinuation. One interesting alternative could be the manufacture of portable tDCS devices that would allow home application of tDCS after training the patient how to use it (using tailored head caps could help the patient to place the electrodes only at the correct spots).

6.3. tDCS and long-term follow-up

A third issue is how tDCS should be used after achieving remission — i.e., as a maintenance treatment. With pharmacotherapy, this succeeds immediately after the remission, usually maintaining the same drug dosage for several months. In non-invasive neuromodulation therapies, however, the maintenance treatment is still under dispute. Long-term treatment rTMS studies have followed patients who achieved remission and thereafter used antidepressant drugs as a maintenance treatment; using rTMS as an adjuvant, rescue therapy (Demirtas-Tatlidede et al., 2008). Another alternative would be to maintain frequent (e.g. weekly or bi-weekly) rTMS sessions during the remission phase. Although such approach would theoretically avoid depression relapse, it has not been sufficiently investigated (Li et al., 2004). Both alternatives could be interesting strategies for prospective, long-term tDCS studies.

7. Conclusion

tDCS has a wide range of potential applications, including treatment of major depressive disorder, as preclinical and clinical studies showed that it elicits potent neuromodulatory effects. tDCS has some interesting, unique aspects such as noninvasiveness and low rate of side effects, being a putative substitutive/augmentative agent for antidepressant drugs, and low-cost and portability, making it suitable for use in clinical practice.

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