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Review

Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases

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ABSTRACT

Neuroplasticity, which is the dynamic structural and functional reorganization of central nervous system connectivity due to environmental and internal demands, is recognized as a major physiological basis for adaption of cognition, and behavior, and thus of utmost importance for normal brain function. Pathological alterations of plasticity are increasingly explored as pathophysiological foundation of diverse neurological and psychiatric diseases. Non-invasive brain stimulation techniques (NIBS), such as repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS), are able to induce and modulate neuroplasticity in humans. Therefore, they have potential to alter pathological plasticity on the one hand, and foster physiological plasticity on the other, in neuropsychiatric diseases to reduce symptoms, and enhance rehabilitation. tDCS is an emerging NIBS tool, which induces glutamatergic plasticity via application of relatively weak currents through the scalp in humans. In the last years its efficacy to treat neuropsychiatric diseases has been explored increasingly. In this review, we will give an overview of pathological alterations of plasticity in neuropsychiatric diseases, gather clinical studies involving tDCS to ameliorate symptoms, and discuss future directions of application, with an emphasis on optimizing stimulation effects.

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Introduction

Dynamic alterations of connections between neurons are an important feature of the central nervous system. These neuroplastic changes of brain connectivity are the foundation of various cognitive, motor, and behavioral processes. Moreover, during the last years it became increasingly clear that pathological alterations of neuroplasticity

Abbreviations: AD, Alzheimer's disease; DLPFC, dorsolateral prefrontal cortex; ERCP, endoscopic retrograde cholangio-pancreaticography; LTD, long term depression; LTP, long term potentiation; NIBS, non-invasive brain stimulation; OCD, obsessive compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; TPC, temporoparietal cortex.

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are involved in various neuropsychiatric diseases. Therefore, modification of such pathological plasticity, or enhancing beneficial plasticity in these diseases, might be an interesting new therapeutic option.

Alterations of synaptic connections as a basis of cognitive functions were first proposed by Hebb (1949), and demonstrated by Bliss and Lomo (1973). Fast rhythmic stimulation of the hippocampus enhances (long-term potentiation (LTP)), and slow rhythmic stimulation decreases (long term depression (LTD)) excitability for hours (Dunwiddie and Lynch, 1978). Both, LTP and LTD, can be induced at glutamatergic, GABAergic, dopaminergic, and other synapses, and in virtually all areas of the central nervous system. Apart from having been shown in slice preparations, they are also present in in vivo animal models (for an overview see Malenka and Bear (2004)). Their functional relevance was demonstrated by motor learning in rats (Rioult-Pedotti et al., 1998, 2000) and in sensory, and more complex memory formation (Feldman, 2009). Consequently, pathological alterations of plasticity are suggested to influence neuropsychiatric diseases, including, but not restricted to, learning and memory deficits.

In analogy to animal studies, plasticity can be induced or modified in the human central nervous system by non-invasive brain stimulation (NIBS) approaches. Numerous stimulation protocols have been developed which allow the induction of long-lasting cortical excitability alterations. Transcranial direct current stimulation (tDCS) is one of these stimulation protocols. It induces plasticity via generation of a sub-threshold, stimulation polarity-dependent alteration of membrane potentials modifying spontaneous discharge rates. This results in enhanced/reduced cortical excitability during stimulation, which can outlast the stimulation for over 1 h, if tDCS is performed in the range of minutes (Kuo et al., 2008b; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003c). The resulting plasticity involves glutamatergic synapses, and is calcium-dependent (Nitsche et al., 2003a, 2004b; Stefan et al., 2002; Wolters et al., 2003).

Plasticity induction with NIBS has been shown to have functional effects. Learning in different modalities (Floel et al., 2008; Kincses et al., 2004; Nitsche et al., 2003d), working memory performance (Fregni et al., 2005a), as well as other cognitive processes are modulated by NIBS (Guse et al., 2010; Kuo and Nitsche, 2012). These respective functions are pathologically altered in many neuropsychiatric diseases, and in some instances, associated modifications of plasticity have been identified. Therefore, counter-acting these pathological alterations of plasticity by NIBS is a potentially interesting new therapeutic venue (Nitsche et al., 2012).

DC stimulation was systematically studied in the 1960s as a tool to induce neuroplastic alterations of cortical excitability in animal models (Bindman et al., 1964; Nitsche et al., 2003b). Stimulation for 10 min induces prolonged and stimulation polarity-dependent alterations of cortical activity for hours (Bindman et al., 1964). Later it was probed as a therapeutic tool mainly for depression. Due to mixed results at that time, when compared to pharmacotherapy, it was not implemented into clinical routine treatment (for overviews see Lolas, 1977; Nitsche et al., 2003b, 2009a). In the last years however, new stimulation protocols were developed mainly based not only on reliable modulation of motor cortex excitability, but also on functional effects in healthy subjects (Nitsche et al., 2003b, 2008). Consequently, tDCS was re-evaluated for the treatment of neuropsychiatric diseases, with promising results in various pilot studies.

This review gives an overview about the state of the art of application of tDCS in psychiatric diseases with the addition of pain, and tinnitus, which include neurological as well as psychiatric components, including an outlook, in which options to enhance the efficacy of stimulation in future studies are discussed (Table 2). Application of tDCS for treatment of neurological diseases will be covered by another review in this issue (Flöel et al., in press).

Therapeutic application of tDCS

Pain

Different interwoven cortico-subcortical pain-related networks cover perceptual, affective, and vegetative aspects of pain processing. The main components of the perceptual pain processing network are the spinothalamic tract, the lateral thalamus, the somatosensory areas, and the posterior insula. Pain-associated affections have been related to the anterior insular, and cingulate cortices, as well as the prefrontal areas. Vegetative, and neuroendocrine effects of pain perception are closely linked to various subcortical regions (Zaghi et al., 2009). Neuroplastic alterations of connectivity between these areas might contribute to chronification of pain.

Cortical stimulation to reduce central pain has been shown to be effective (Zaghi et al., 2009). The two major targets are the primary motor, and the dorsolateral prefrontal cortex (Marlow et al., 2012). Primary motor cortex stimulation interferes with perceptual processing of pain via suppressing lateral thalamic activity (Canavero and Bonicalzi, 2007; Garcia-Larrea et al., 2006; Nizard et al., 2012; Plow et al., 2012b), while stimulation of the dorsolateral prefrontal cortex modulates primarily the affective reaction to painful experiences. Invasive motor cortex stimulation is an established method for pain treatment (Tsubokawa et al., 1991) and its replacement by non-invasive tDCS is one of the most promising methods of NIBS in this type of therapy.

With the exception of one study, in which a single-blinded approach was chosen, all studies in which the effect of tDCS was applied for pain reduction were double-blinded, which is of special importance, given the relatively large placebo effects related to pain treatment (for an overview, see Table 1). Anodal M1 tDCS for five consecutive days resulted in a reduction of pain ratings after spinal cord injury for at least 24 h after stimulation (Fregni et al., 2006a). A similar effect was described for chronic pelvic pain (Fenton et al., 2009), chronic neuropathic pain in multiple sclerosis (Mori et al., 2010), and pain of different origin (Antal et al., 2010). In the two latter studies, pain reduction after 5 days of daily stimulation lasted for several weeks. Anodal tDCS over M1 improved also pain ratings in fibromyalgia (Fregni et al., 2006c; Riberto et al., 2011; Valle et al., 2009). Interestingly, anodal tDCS over M1 combined with transcutaneous electrical stimulation (TENS) for treating chronic neurogenic pain of the upper limb had better effects than tDCS alone (Boggio et al., 2009a). It might therefore be speculated that combined stimulation approaches affecting different modalities are suited to optimize efficacy of stimulation. For prefrontal stimulation, negative results after five sessions of stimulation (Fregni et al., 2006d) are opposed to a positive impact of 10 daily (Valle et al., 2009), or weekly sessions on pain ratings (Riberto et al., 2011), and another study, in which a single session of orbitofrontal tDCS was conducted for pain reduction in fibromyalgia (Mendonca et al., 2011). Moreover, combined anodal left prefrontal and cathodal tDCS of the gut representation area of the right somatosensory cortex reduced analgetic drug consumption, sleep disturbance, and ratings of acute pain after ERCP (Borckardt et al., 2011).

In migraine, whose pathophysiology differs from that of other pain syndromes,10 sessions of motor cortex anodal tDCS over four weeks resulted in a marginal improvement of pain evolving with a delay of about 120 days (Dasilva et al., 2012). Although anodal M1 tDCS for 20 consecutive days generated a reduced attack frequency, drug consumption, and pain intensity in another study (Auvichayapat et al., 2012), anodal M1 tDCS does not appear conceptually as well suited as in chronic pain. An alternative concept pursues the attenuation of visual cortex hyperexcitability by inhibitory cathodal tDCS in migraine patients both during and between attacks (Antal et al., 2005; Chadaide et al., 2007), which was applied over the occipital cortex (15 sessions over 6 weeks), and resulted in a reduction of the intensity of migraine attacks (Antal et al., 2011).

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Table 1
tDCS for pain treatment.

Studies	Design		Patients	Stimulation protocol							Outcome	
	Placebo-controlled	Blinding		Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm^2)	Duration (min)	Current density (mA/cm^2)	Effects	Side-effects
Fregni et al. (2006a)	Yes	Double	Traumatic spinal cord injury	A/S	C3/C4	Contralateral orbit	2	35	20 min (5 consecutive days)	0.06	Pain reduction, cumulative effect, effects present for at least 24 h	None
Fregni et al. (2006c)	Yes	Double	Fibromyalgia	A/S	C3/F3	Contralateral orbit	2	35	20 min (5 consecutive days)	0.06	Pain reduction after motor cortex stimulation, significant 3 weeks after stimulation	Redness of skin, itching, sleepiness, headache
Valle et al. (2009)	Yes	Double	Fibromyalgia	A/S	C3/F3	Contralateral orbit	2	35	20 min (10 consecutive days)	0.06	Pain reduction after motor cortex, and prefrontal stimulation, significant 6 weeks after motor cortex stimulation	Redness of skin, tingling
Fenton et al. (2009)	Yes	Double	Chronic pelvic pain	A/S	C3/C4	Contralateral orbit	1	35	20 min (2 consecutive days)	0.04	Significant reduction of pain	Sleepiness, reddening and numbness under electrode
Boggio et al. (2009a)	Yes	Double	Chronic neurogenic pain of upper limb	A/S	C3/C4	Contralateral orbit	2	35	30	0.06	Significant reduction of pain by real tDCS, larger in combination with TENS	Headache
Mori et al. (2010)	Yes	Double	Chronic neuropathic pain in multiple sclerosis	A/S	C3/C4	Contralateral orbit	2	35	20 (5 consecutive days)	0.06	Anodal tDCS reduced pain for up to 4 weeks after stimulation	None
Antal et al. (2010)	Yes	Double	Chronic pain of different origin	A/S	Motor cortex	Contralateral orbit	1	16 (motor cortex), 50 (return)	20 (5 consecutive days)	0.06	Pain reduction after anodal tDCS for 3 to four weeks after tDCS	Tingling, fatigue, headache, sleep disturbance
Antal et al. (2011)	Yes	Double	Migraine	C/S	Oz	Cz	1	35	15 (3 times per week over 6 weeks)	0.04	Pain intensity reduced	Itching, tingling, fatigue, headache
Borckardt et al. (2011)	Yes	Double	Post-ERCP pain	A/S	A: left prefrontal C: gut representation right sensory cortex	n.a.	2	16	20	0.125	Less hydromorphine use, less sleep disturbance, less throbbing pain	Tingling, itching under electrodes
Mendonca et al. (2011)	Yes	Double	Fibromyalgia	A/C/S	Supra-orbital, M1	Shoulder	2	16 (stimulation); 80 (return)	20	0.125	Pain reduction by cathodal and anodal supraorbital tDCS	Tingling
Riberto et al. (2011)	Yes	Double	Fibromyalgia	A/S	C3	Contralateral orbit	2	35	20 (once weekly for 10 weeks)	0.06	Reduced pain after anodal tDCS	None
Dasilva et al. (2012)	Yes	Single	Chronic migraine	A/S	Motor cortex	Contralateral orbit	2	35	20 (10 sessions over 4 weeks)	0.06	Reduced pain after anodal tDCS evolving with a delay (120 days after tDCS)	Tingling, skin redness, sleepiness
Auvichayapat et al. (2012)	Yes	Double	Chronic migraine	A/S	C3	Contralateral orbit	2	35	20 (20 consecutive days)	0.06	Attack frequency, pain intensity and medication reduced	Tingling, headache, reddening under electrode, first degree skin burn, tiredness

Shown are studies dedicated to treatment of central pain of different origin. Patient, and study characteristics, details of the stimulation protocols as well as effects of stimulation, including side effects, are shown. A = anodal tDCS, C = cathodal tDCS; TENS = transcutaneous electrical nerve stimulation; S = sham tDCS. Stimulation target areas are described according to the international 10–20 system.

Table 2
tDCS for treatment of tinnitus.

Studies	Design		Patients	Stimulation protocol							Outcome	
	Placebo-controlled	Blinding		Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm^2)	Duration (min)	Current density (mA/cm^2)	Effects	Side-effects
Fregni et al. (2006d)	Yes	Partially	Chronic unilateral	A/C/S	Left temporoparietal area	Contralateral orbit	1	35	3	0.04	Anodal tDCS induces short-lasting reduction of tinnitus	None
Vanneste et al. (2010)	No	Open	Chronic unilateral and bilateral	A/C	F3/F4	n.a.	1.5	35	20	0.04	Right anode/left cathode reduces tinnitus intensity, and tinnitus-related distress	Not reported
Vanneste et al. (2012)	No	Open	Chronic unilateral and bilateral	A/C	A right, C left	n.a.	1.5	35	20	0.04	Higher gamma band activity in right auditory cortices, and parahippocampus, increased functional connectivity in responders	Not reported
Garin et al. (2011)	Yes	Double	Chronic, unilateral and bilateral	A/C/S	Left temporoparietal area	Between T4 and F8	1	35 (left); 50 (right)	20	0.04	Reduction of tinnitus intensity immediately after anodal tDCS, heterogeneous long-lasting effects	In some patients tinnitus worsening after cathodal tDCS
Frank et al. (2012)	No	Open	Chronic, unilateral and bilateral	A/C	A right, C left	n.a.	1.5	n.a.	30 (6 sessions, 2 times per week)	n.a.	Reduced loudness, unpleasantness, and discomfort	Skin lesions, burning, headache
Faber et al. (2012)	Yes	Double	Chronic bilateral	A/C	Left/right DLPFC	Contralateral DLPFC	1.5	35	20 (6 sessions, 2 times per week)	0.04	Reduced tinnitus annoyance by both tDCS protocols	None
Shekhawat et al. (2013)	No	Open	Chronic, unilateral and bilateral	A	Left temporoparietal area	Contralateral frontal	1.2	35 (left); 50 (right)	10, 15, 20	0.04–0.06	Intensity-, and duration-dependent effects, 2 mA 20 min most effective	Headache

Shown are studies dedicated to treatment of tinnitus. Study characteristics, details of the stimulation protocols as well as effects of stimulation, including side effects, are shown. A = anodal tDCS; C = cathodal tDCS; S = sham tDCS. Stimulation target areas are described according to the international 10–20 system.

In general, tDCS, and here most clearly anodal tDCS over the primary motor cortex, seems well suited to reduce pain. With regard to stimulation intensity, and repetition rate, a diversity of protocols has been explored, but approaches in which these parameters are titrated systematically are missing. However, in patients suffering from fibromyalgia, stimulation over 10 days seems to be more effective than stimulation for 5 consecutive days (Fregni et al., 2006d; Valle et al., 2009), which claims for enhanced efficacy of intensified protocols. Moreover, combination of stimulation approaches such as tDCS and TENS might be a promising approach. Furthermore it seems plausible that optimal stimulation areas differ between syndromes, as suggested by the migraine studies. Interestingly, side effects, if present at all, were minor, which is remarkable in this patient group. Although most of the studies were double-blinded and sham-controlled, the rate of placebo effects is relatively high in pain studies. Also recently the effective blinding of 2 mA studies was challenged (O'Connell et al., 2012). Therefore, despite the positive effects of most of the above-mentioned studies, there is a need for rigorously double-blinded studies in this field. In the ClinicalTrials.gov (http://clinicaltrials.gov/) registry, currently 11 active studies are listed, which encompass the comparison of different tDCS repetition rates (NCT01599767), the efficacy of anodal tDCS with that of rTMS (NCT01800136), the efficacy of tDCS on other pain syndromes, such as corneal pain, and pain after burn injury (NCT01575002, NCT01795079), and the superiority of a combination of tDCS with other stimulation approaches, such as electroacupuncture (NCT01747070), or transcranial ultrasound (NCT01404052). These studies might help to increase the efficacy of tDCS, and to broaden its application for pain treatment.

Tinnitus

The pathophysiological basis of tinnitus is still not sufficiently clear. One line of concepts argues for a deafferentation-induced compensatory spontaneous hyperactivity of auditory cortices within certain frequency representations, leading to maladaptive plasticity. The left temporoparietal area seems to be specifically involved, and disruption of its activity has been shown to reduce tinnitus (Plewnia, 2011). Therefore, neuromodulation via tDCS might be suited to alter this pathological pattern of cortical activity. In two double-blinded, sham-controlled studies it was indeed shown that a single session of anodal tDCS of this area results in a short-lasting reduction of symptoms in patients suffering from tinnitus, whereas cathodal stimulation had no effects (Fregni et al., 2006d; Garin et al., 2011). At first sight, it sounds counter-intuitive that excitability-enhancing stimulation should reduce tinnitus in case of spontaneous hyperactivity of this area. However, this might be caused by stimulation-induced mimicking of physiological activation of a broader range of sound-representing areas, which could reduce pathological activity by induction of cortical noise. Beyond this area, the prefrontal cortex seems to be involved in tinnitus symptoms (Vanneste and De Ridder, 2012), and may control for attentional or annoyance aspects. In accordance, bilateral prefrontal tDCS reduced tinnitus annoyance, but interestingly not intensity, independent from stimulation polarity, in another double-blinded sham-controlled study (Faber et al., 2012). In these studies, primarily acute effects of tDCS on tinnitus were explored, or obtained, thus they allow no conclusions about a clinically relevant prolonged impact of tDCS. A couple of open studies could replicate these findings for right anodal/left cathodal stimulation of the dorsolateral prefrontal cortex (Frank et al., 2012; Vanneste et al., 2010). In the only study, which explored the impact of tDCS intensity and duration on the efficacy of stimulation, the longest and strongest stimulation tested (2 mA for 20 min) had the best efficacy (Shekhawat et al., 2013). Relative short breaks between stimulation sessions in this study require further investigation of a possible impact of cumulative stimulation effects on increased efficacy (Monte-Silva et al., in press). Taken together, knowledge about clinically meaningful effects on the impact of tDCS on tinnitus, which requires double-blinded sham-controlled studies including longer observation periods following stimulation protocols aimed for the induction of those long-term effects, i.e. repetitive stimulation, is scarce. One currently ongoing study, which is suited to solve this problem at least partially, because it includes repetitive tDCS for the treatment of tinnitus, and prolonged observation periods, is however listed in the ClinicalTrials.gov registry (NCT01575496).

Psychiatric diseases

The cortical allocation of brain areas involved in psychiatric diseases provides a better accessibility for transcranial stimulation than subcortical neurological diseases such as Parkinson's disease. Abnormal brain activity, plasticity and functional connectivity have been identified as probable underlying causes in many psychiatric diseases (Knable et al., 2002; Spedding et al., 2003; Uhlhaas and Singer, 2010). The majority of therapeutic options remain pharmacological to date. NIBS including tDCS has been recently introduced as adjuvant tool for the treatment of psychiatric disorders, especially for refractory or treatment-resistant conditions. Most studies conducted so far are dedicated to the treatment of depression. One reason for this might be that reduced activity of the dorsolateral prefrontal cortex (DLPFC), which is located at the convexity of the brain, provides optimal prerequisites for successful NIBS (Fitzgerald et al., 2006). Therapeutic options for schizophrenia, addiction, and dementia are more difficult due to a lack of similar simple location targets.

Depression

In addition to left hemispheric hypoactivity, right hemispheric hyper-activation is suggested to be a key substrate of depression. Moreover, dysfunctional plasticity including deficient LTP seems to play a role (Normann et al., 2007; Spedding et al., 2003). In accordance, serotonin reuptake inhibitors enhance LTP-like plasticity in healthy humans, and re-establish LTP-like plasticity in patients suffering from major depression (Nitsche et al., 2009a; Normann et al., 2007). Therefore, therapeutic strategies of NIBS to treat depression have focused on enhancing left DLPFC activity and LTP-like plasticity, and/or decreasing right DLPFC activity (Schonfeldt-Lecuona et al., 2010).

The application of tDCS for the treatment of depression can be traced back to the 1960s. Bilateral anodal prefrontal stimulation was conducted in those trials with the return electrode positioned at the knee. Since physiological effects of this stimulation protocol were not explored, it is unknown what kind of alteration of brain excitability was induced. Clinical effects of these studies were mixed (for details see Lolas, 1977; Nitsche et al., 2009a).

With regard to “modern” tDCS protocols, excitability-enhancing anodal tDCS of the left DLPFC with the return electrode positioned over the contralateral orbit has turned out to be efficient to ameliorate clinical symptoms in major depression. In a double-blinded, sham controlled study, anodal tDCS for five consecutive days in newly diagnosed patients resulted in a significant improvement of clinical symptoms (Fregni et al., 2006b). Increase of stimulation intensity to 2 mA, and number of sessions up to 15 resulted in clinical effects stable for up to one month after tDCS in two other double-blinded sham-controlled studies (Boggio et al., 2008a; Loo et al., 2012), and in an open study performed in HIV-patients suffering from depression (Knotkova et al., 2012). The magnitude of these effects was similar to the treatment with 20 mg fluoxetine, but evolved earlier than the pharmacological intervention (Rigonatti et al., 2008). In contrast, anodal prefrontal tDCS was not superior as compared to placebo stimulation in two other trials, where somewhat weaker and less frequent stimulation was conducted and more severely affected patients were treated (Loo et al., 2010; Palm et al., 2012) (see Table 3).

Bifrontal tDCS with the anode on the left and the cathode on the right DLPFC in order to reestablish the balance between right and left DLPFC was not effective in another double-blinded sham-controlled study (Blumberger et al., 2012). Patients with greater disease severity

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Table 3
tDCS for the treatment of psychiatric diseases.

Studies	Design		Patients	Stimulation protocol								Outcome	
	Placebo-controlled	Blinding		Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm^2)	Duration (min)	Session(s)	Current density (mA/cm^2)	Effects	Side-effects
Depression													
Fregni et al. (2006b)	Yes	Double	MD	A/S	L DLPFC	Contralateral orbit	1	35	20	Daily session for 5 alternate days	0.03	Improvement of symptoms	None
Boggio et al. (2008a)	Yes	Double	MD	A/S	L DLPFC or occipital (active control)	Contralateral orbit	2	35	20	5 daily sessions/ week for 2 weeks	0.06	Improvement of HDRS with DLPFC tDCS for up to 1 month	Headache, itching, redness of skin
Rigonatti et al. (2008)	Yes	Double	MD	A/S	F3	Contralateral orbit	2	35	20	daily session for 5 days	0.06	Improvement of symptoms, similar to fluoxetine	Not reported
Ferrucci et al. (2009)	No	Open	MD with treatment resistance	A	L DLPFC	R DLPFC	2	35	20	2 sessions/day for 5 days	0.06	Improvement of HDRS and BDI, and subjective mood ratings	None
Loo et al. (2010)	Yes	Double	MD	A/S	L DLPFC	Contralateral orbit	1	35	20	Daily session for 5 alternate days	0.06	Improvement of symptoms in both active and sham groups	Skin redness, itching, tingling, headache, ringing in the ear, altered vision, tiredness, euphoria, hypomania, nausea, disorientation, anxiety, insomnia, swallowing problems
Brunoni et al. (2011)	No	Open	MD and BPD	A	L DLPFC	R DLPFC	2	35	20	2 sessions/day for 5 days	0.06	Both groups show reduction in HDRS and BDI for up to 1 month	None
Dell'Osso et al. (2012)	No	Open	MD with treatment resistance	A	L DLPFC	R DLPFC	2	35	20	2 sessions/day for 5 days	0.06	13–30% of patients showed reduction of HDRS and remission up to 1-week follow-up	Redness of skin under electrodes
Martin et al. (2011)	No	Open	MD (who showed inadequate response after bifrontal tDCS)	A	L DLPFC	R upper arm	2	35	20	5 daily session/ week for 4 weeks	0.06	Greater treatment response compared to bifrontal tDCS	Not reported
Palm et al. (2012)	Yes	Double	MD with treatment resistance	A/S	L DLPFC	Contralateral orbit	1–2	35	20	5 daily session/ week for 2 weeks	0.03–0.06	No significant difference in depression score, but improvement in subjective mood ratings	Headache, itching under electrodes
Loo et al. (2012)	Yes	Double/ open	MD and BPD	A/S	L DLPFC	F8	2	35	20	5 daily session/ week for 3 weeks followed by additional 3 weeks active tDCS	0.06	Improvement in mood	One patient with bipolar disorder became hypomanic after active tDCS
Blumberger et al. (2012)	Yes	Double	MD with treatment resistance	A/S	F3	F4	2	35	20	5 daily session/ week for 3 weeks	0.06	No difference in remission rate between active and sham group	Tingling, headache
Martin et al. (2013)	No	Open	MD	A	L DLPFC	R upper arm or Contralateral orbit	2	35	20	Once a week for 3 months, and then once every other week for 3 months	0.06	Prevention of relapse for up to 6 months	Tingling/itching, skin redness, dizziness, headache, fatigue, nausea, blurred vision

Q3

Brunoni et al. (2012)	No	Open	MD and BPD	A	F3	F4	2	35	20	2 sessions/day for 5 days	0.06	Improvement in BDI and HDRS	None
Brunoni et al. (2013)	Yes	Double	MD	A/S	F3	F4	2	25	30	10 daily session, and 2 sessions every other week	0.08	Improvement in MADRS, better effect of tDCS/sertraline combination than tDCS or sertraline alone	Skin redness, hypomania or mania in 7 patients, 5 under combined treatment, one under tDCS, and sertraline only
Knotkova et al. (2012)	No	Open	HIV-MD	A	F3	Contralateral orbit	2	35	20	Once daily for 10 consecutive weekdays	0.06	Improvement in HDRS and subjective ratings	None
Schizophrenia													
Brunelin et al. (2012)	Yes	Double	SCZ with auditory hallucination	A/S	Left DLPFC	Left tempo-parietal cortex	2	25	20	2 sessions/day for 5 days	0.08	- reduction of auditory hallucinations for up to 3 months - improvement of positive/negative symptoms	Tingling/itching
Addiction													
Boggio et al. (2010b)	No	Single	Marijuana (after 24 h abstinence)	A/C/S	F3/F4	F4/F3	2	35	10	Single	0.06	Reduction of craving after F4 anodal/F3 cathodal tDCS	None
Boggio et al. (2008b)	Yes	Double	Alcohol (after detoxification)	A/C/S	F3/F4	F4/F3	2	35	20	Single	0.06	Reduction of craving by both active tDCS conditions	
Fregni et al. (2008)	No	Double	Nicotine	A/C/S	F3/F4	F4/F3	2	35—active/ 100—return	20	Single	0.06	Reduction of cue-induced craving after both active tDCS conditions	Scalp burning, headache and local itching, no difference between groups
Boggio et al. (2009c)	No	Double	Nicotine	A/S	F3	F4	2	35—active/ 100—return	20	Daily session for 5 days	0.06	Reduction of craving and cigarette consumption	Scalp burning, headache and local itching; no difference between real and sham tDCS
Dementia													
Ferrucci et al. (2008)	Yes	Double	AD	A/C/S	L					temporo-parietal cortex		Contralateral orbit	2
35	20	Single	0.06		Improvement of recognition memory with anodal tDCS; worsening with cathodal	Itching under electrodes							
Boggio et al. (2009b)	No	Double	AD	A	R DLPFC	L				temporo-parietal cortex	2	35	30
Single	0.06		Improvement of visual recognition memory	None									
Boggio et al. (2012)	Yes	Double	AD	A/S	Bilateral temporal cortex	Right deltoid muscle	2	35	30	Daily session for 5 days	0.06	Improvement of visual recognition memory for four weeks after stimulation	None
Huey et al. (2007)	Yes	Double	FTD	A/S	F3	Contralateral orbit	2	25	40	Single session	0.08	No effect on verbal fluency	Not reported

Shown are studies dedicated to treatment of psychiatric diseases. Patient, and study characteristics, details of the stimulation protocols as well as effects of stimulation, including side effects, are shown. A = anodal tDCS; BDI = Beck depression inventory; BPD = bipolar disorder; C = cathodal tDCS; DLPFC = dorsolateral prefrontal cortex; HRDS = Hamilton depression rating scale; MD = major depression; S = sham tDCS; SCZ = schizophrenia. Stimulation target areas are described according to the international 10–20 system.

and numerous patients under benzodiazepines, which might have reduced the efficacy of tDCS (Nitsche et al., 2004c), may have contributed to the negative result. A recently published large-scale double-blinded sham-controlled study, in which bilateral stimulation of the dorsolateral prefrontal cortex was conducted, compared the effects of tDCS, sertraline, and combination of both agents in 120 patients suffering from unipolar depression. 2 mA stimulation for 30 min was performed for 10 days, and then repeated every other week once. In this study, tDCS alone improved depression ratings significantly, and to a similar extent as antidepressant medication. Interestingly, combination of tDCS and sertraline had larger effects on the respective symptoms than each of the interventions alone (Brunoni et al., 2013). Additionally, some open label studies applying bifrontal tDCS were clinically effective (Brunoni et al., 2011, 2012; Dell'Osso et al., 2012). Moving the right frontal return electrode to an extra-cephalic position showed a better initial treatment response in patients resistant to bifrontal stimulation (Martin et al., 2011). Furthermore, additional "boosting sessions" showed remission rates of about 80% after 3, and 50% after 6 months with weekly or second-weekly extra sessions after initial daily tDCS (Martin et al., 2013).

With regard to manic symptoms in bipolar disorder, which might be associated with a converse pattern of prefrontal activation disbalance, i.e. right hypo- and left hyperactivity, anodal tDCS over the right DLPFC has been demonstrated to induce fast alleviation of acute symptoms in one study (Schestatsky et al., in press).

In general, stimulation in most studies was applied with current intensities between 1 and 2 mA and duration of 20 min. However, a number of treatment sessions, the interval between sessions, electrode positions, and disease severity vary considerably between these studies. So far most studies have shown a potential of tDCS to alleviate depressive symptoms. Stronger stimulation, more stimulation sessions, and tDCS in less severely affected patients might generate larger effects, as implied by the results of the study by Brunoni et al. (2013). Moreover this study is in favor for a superior efficacy of combined tDCS and pharmacological intervention, which makes sense, given the deficient LTP hypothesis of depression, the positive impact of both agents alone on symptoms, and the strengthening of tDCS-induced LTP-like plasticity by application of serotonin reuptake-inhibitors (Nitsche et al., 2009b). tDCS seems to be relatively well tolerated, however, hypomania, and manifest mania were described in relatively rare cases (see Table 3), which might hint to the importance of "dosed" stimulation. Future studies should be designed to identify optimally suited stimulation protocols with regard to the above-mentioned parameters, and, given the positive results of the study by Brunoni et al. (2013), it might make sense to conduct a large multi-center double-blinded sham-controlled trial. The ClinicalTrials.gov registry shows a relatively large amount of 35 studies, 14 of them are recruiting subjects currently. Some of these studies aim to further elucidate the interaction of tDCS with antidepressant medication or medication known to improve the efficacy of anodal tDCS, such as D-cycloserine (Nitsche et al., 2004b), combine tDCS with cognitive training of prefrontal functions, compare the efficacy of different electrode positions, test the impact of remote "boosting" sessions of tDCS on the maintenance of therapeutic effects, broaden the application of tDCS to specific depression syndromes, such as post-stroke depression, and explore the cognitive effect of tDCS in more detail. The results of these studies might help to identify optimized stimulation protocols, to learn more about the cognitive impact of tDCS in depression, and suitable patient groups. With regard to treatment of manic symptoms in bipolar disorders, currently no active studies are registered.

Addiction

Substance abuse or dependence remains difficult to treat and relapse rates are high. It is related to abnormal reinforcement of the brain reward circuitry, and prefrontal cortical networks including the DLPFC exert a crucial role in inhibitory control mechanisms involved in addiction (Bechara, 2005; Koob and Volkow, 2010). Indeed, prefrontal tDCS can modify decision-making processes, which may share some common mechanisms with impulsive behavior in addiction, as shown in healthy subjects (Boggio et al., 2010a; Fecteau et al., 2007a,b; Knoch et al., 2008). In accordance, decision-making in a risk-taking task similar to the ones applied in the above-mentioned studies was modulated in chronic marijuana users via bilateral DLPFC tDCS, and a significant reduction of craving following right-anodal/left-cathodal tDCS was observed in these patients (Boggio et al., 2010b). Similar acute effects of bilateral tDCS (single session) were reported for decreasing craving in alcohol-dependent patients (Boggio et al., 2008b), and cigarette smokers (Fregni et al., 2008). In the latter study, tDCS reduced additionally the amount of smoked cigarettes. In a follow-up study, the authors performed 5 consecutive days of bilateral DLPFC stimulation (anodal—left/cathodal—right), which resulted in decreased cigarette consumption in addition to reduced craving (Boggio et al., 2009b).

In summary, tDCS over DLPFC seems to be suited to reduce substance craving in addiction. It seems that bilateral stimulation with both polarities is equally effective, except for the study with marijuana users, in which only anodal tDCS over right DLPFC diminished craving. The therapeutic effect of tDCS on substance abuse could be related to the disruption of the existing, balanced reward circuits within and between left and right DLPFCs. However, further exploration of the underlying mechanisms with optimized stimulation protocols and experimental designs is required. Importantly, so far in most studies only acute effects of the stimulation have been explored, but long-lasting effects would be needed to make these clinically relevant. This shortcoming of the currently available studies might at least be partially overcome by active studies registered in ClinicalTrials.gov, in which one study aims to evaluate extended effects of tDCS on smoking cessation (NCT01710410), and two other ones are testing the effects of extended stimulation protocols on alcohol, and crack-cocaine dependence (NCT01337297, NCT01330394).

Schizophrenia

Schizophrenia is a chronic mental disorder characterized by dysfunctions of perception of reality, emotion and cognition. Clinical manifestations include positive (hallucinations, delusions, thought disorders, and bizarre behavior) and negative (affective flattening, anhedonia, alogia, and attention impairment) symptoms, which are associated with dysregulation of several neuromodulatory transmitters, consequently leading to pathological alterations of cortical activity and plasticity. Deficits of both, excitability-enhancing, and -diminishing neuroplasticity induced by anodal and cathodal tDCS were demonstrated in schizophrenia patients (Hasan et al., 2011, 2012a,b). Since tDCS-induced cortical plasticity is dependent on NMDA receptors and is modulated by dopaminergic transmission (Monte-Silva et al., 2010b), this observation can be explained by a disbalance of the glutamatergic and dopaminergic systems in schizophrenia (Goto and Grace, 2007; Javitt, 2010).

For the impact of tDCS on deficient cognitive functions in schizophrenia, one study demonstrated that patients with schizophrenia, as compared to healthy controls, show a more rightward bias in a line bisection task, which was partially corrected by parietal tDCS (Ribolsi et al., 2012). However, in another study probabilistic associative learning in schizophrenia was not improved by simultaneous anodal tDCS over left DLPFC, with the exception of a subset of patients with relatively good baseline performance (Vercammen et al., 2011). These results suggest that tDCS may be able to facilitate cognitive functions in schizophrenia, yet more studies are needed to delineate the specific modulatory effects of tDCS on different aspects of cognition, with consideration to timing or connectivity between related cortical areas, and more specific and optimized stimulation protocols.

Regarding the therapeutic application of NIBS in schizophrenia, inhibiting activity of the left temporoparietal cortex (TPC) to reduce auditory hallucinations, a frequent positive symptom, is one potentially relevant target of stimulation. For improvement of negative symptoms, enhancement of left DLPFC activity, which is dysfunctional

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in schizophrenia, is a common approach. Some rTMS studies have demonstrated beneficial effects of respective rTMS protocols (for review, see Freitas et al., 2009). Brunelin and co-workers explored the efficacy of tDCS to ameliorate auditory hallucinations, and improve negative symptoms, by a bipolar stimulation approach (Brunelin et al., 2012). They applied tDCS in schizophrenic patients within a sham-controlled, double-blinded design, in which excitability of the left DLPFC was enhanced by anodal stimulation, and excitability of the left TPC was reduced by cathodal tDCS (2 mA for 20 min each session, 2 sessions per day for 5 consecutive days). The authors describe a significant reduction of auditory hallucinations together with reduced negative symptoms accomplished by active tDCS relative to sham stimulation. This effect lasted for up to 3 months after treatment. In a case report, in accordance with this result, cathodal tDCS over the left TPC reduced auditory hallucinations after 10 consecutive daily sessions with 1 mA intensity and 15 min duration (Homan et al., 2012). Regional cerebral blood flow measured by arterial spin labeling further confirmed a significant reduction of blood flow under the cathode after each session and also during the treatment course, which might serve as neurobiological explanation for the beneficial effect of tDCS. Taken together, the results of these pilot studies are promising, but need confirmation by future studies. Furthermore, nothing is known about optimally suited tDCS protocols for the treatment of schizophrenia. Five active monocentric studies are registered in ClinicalTrials.gov, which encompass the treatment of schizophrenia by tDCS. Three of these studies are dedicated to the improvement of negative symptoms, including cognition, in schizophrenia, and two other studies aim to treat negative as well as positive symptoms, one of those in childhood-onset schizophrenia. These studies are well-suited to improve the evidence of an effect of tDCS on clinical symptoms, and to broaden its application range to children. Moreover, some of the studies include measures of physiological effects of tDCS in schizophrenia, which seems to be especially important in this disease because alterations of the glutamatergic, and dopaminergic systems have a profound impact on tDCS-induced plasticity (Monte-Silva et al., 2009, 2010b; Nitsche et al., 2012). In none of the studies however systematic titration of tDCS parameters is planned to explore optimally efficient stimulation protocols.

Anxiety disorders

Anxiety disorders represent another major category of psychiatric diseases. Neuroimaging studies revealed abnormal patterns of cortical and subcortical activation as well as functional connectivity in OCD patients. Striatal dysfunction mainly of the caudate nucleus is thought to result in insufficient thalamic gating, and hyperactivity of orbitofrontal, and anterior cingulate cortices, resulting in intrusive thoughts, and anxiety. Moreover, the connectivity of the ventral striatum with prefrontal cortices seems to be enhanced in these patients (Del Casale et al., 2011; Sakai et al., 2011). Recently, an interhemispheric disbalance with left hyper- and right hypo-activation was suggested by functional imaging in a case report (Volpato et al., 2012). In this single case study, 2 mA 20 min tDCS (cathode-F3/anode-posterior neck) did not alter OCD symptoms, although the balance of cortical activity between the two hemispheres was restored, and depression and anxiety were improved (Volpato et al., 2012). No currently ongoing studies are listed in ClinicalTrials.gov for the treatment of OCD or other anxiety disorders, which is surprising, because the physiological background of these diseases is promising with regard to the application of tDCS, especially since tDCS has been shown to have an impact on functional cortico-subcortical networks including cortico-striatal, and cortico-thalamic loops (Polania et al., 2012b), which are involved in the respective diseases.

Dementia

Since tDCS has been shown to improve cognitive functions in numerous studies in healthy humans (Kuo and Nitsche, 2012), it can be speculated to exert possible beneficial effect in dementia. From the multitude of dementia syndromes, the impact of tDCS has been so far only explored for Alzheimer's disease, and fronto-temporal degeneration, in a limited number of studies.

The main physiological substrates of Alzheimer's disease seem to be temporo-parietal hypo-activity (Fernández et al., 2002) caused by cholinergic, GABA-ergic, and glutamatergic dysfunction (Iwakiri et al., 2005; Parameshwaran et al., 2008; Schliebs and Arendt, 2011; Yamin, 2009), amongst others, leading to impaired plasticity, and oscillatory activity, and thus causing cognitive deficits. Therefore, improving plasticity by tDCS is a conceptually promising approach to diminish cognitive decline. Indeed, in a double-blinded sham-controlled study, one session of anodal tDCS of the left temporoparietal area enhanced performance in a word recognition task, while cathodal tDCS worsened it, and sham stimulation had no effect (Ferrucci et al., 2008). Another double-blinded study revealed a positive effect of single-session anodal tDCS of the left DLPFC and temporal cortices on performance in a visual recognition memory task (Boggio et al., 2009b). In a follow-up study of the same group, bilateral temporal anodal tDCS over five consecutive days improved visual memory for at least four weeks after stimulation (Boggio et al., 2012).

The impact of tDCS on cognitive functions, specifically verbal fluency, in frontotemporal degeneration (FTD) was explored in a double-blinded, sham-controlled study, in which 2 mA anodal stimulation of the left dorsolateral prefrontal cortex was applied for 40 min. tDCS had no effect on performance in these subjects (Huey et al., 2007). Possible reasons for this negative result might be increased distance between brain and electrodes due to cerebral atrophy, co-commitment CNS-active medication, as well as the pathology of the disease itself, which includes degeneration of glutamatergic neurons, which might have abolished any efficacy of tDCS, as shown in healthy subjects, in which tDCS-induced plasticity was absent under an NMDA receptor antagonist (Nitsche et al., 2003a).

In general, the number of studies exploring the effects of tDCS on dementia is limited, especially with regard to clinically meaningful long-term effects, and nothing is known about optimally suited stimulation protocols. In the ClinicalTrials.gov registry, four active studies are listed, one of them exploring the effect of tDCS on apathy in Alzheimer's disease, and the remaining ones exploring the impact of tDCS on language performance, and memory consolidation, in patients suffering from mild cognitive impairment, and thus at a relatively early stage of cognitive decline.

Optimizing stimulation protocols

One critical aspect of the future impact of tDCS is the optimization of stimulation frequency, duration, and strength. In the following we provide an overview about optimized stimulation protocols at M1. It is not completely clear if the results of motor cortex stimulation can be transferred completely to other cortical areas, however no better data are available at present.

For anodal tDCS, stronger and longer-lasting stimulation resulted in larger effects, as shown by varying stimulation intensity between 0.2 and 1 mA, and stimulation duration between 1 and 5 min (Nitsche and Paulus, 2000). On this basis, increase of stimulation duration and stimulation intensity has been extended in many clinical studies, as compared to the initial protocols. For stimulation intensity, tDCS with 2 mA for 10 min resulted in effects similar to stimulation with 1 mA (Kuo et al., 2012). Extending the stimulation duration to 20 min with 2 mA current strength reverses the effects of cathodal tDCS from excitability diminution to enhancement (Batsikadze et al., 2013). Moreover, prolongation of anodal tDCS (1 mA, electrode size 35 cm^2) to 26 min generates excitability diminution (Monte-Silva et al., in press). These results reveal a non-linear relationship between stimulation duration, intensity, and the direction of after-effects, which limits simple extension of stimulation duration to obtain stronger and longer-lasting after-effects. It should however be taken into account that in some studies longer anodal tDCS durations have been performed in neuropsychiatric

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patients with a positive outcome on clinical symptoms, most probably due to excitability-enhancing effects of stimulation. Boggio et al. (2009a) describe a reduction of pain symptoms by 30 min anodal stimulation, Frank et al. (2012) describe improvement of tinnitus, and Brunoni et al. (2013) describe reduction of depression symptoms by the same stimulation duration and polarity. Similar results have been obtained in some studies conducted in neurological diseases (Flöel et al., in press). Thus a one-to-one translation of the physiological results obtained in healthy young subjects, as in the study conducted by Monte-Silva et al. (in press) might be questionable. Specific conditions of the brain state in the target population, such as compromised LTP-like plasticity in depressed subjects, might broaden the range for excitability-enhancing effects of tDCS. However, possible non-linear effects of stimulation on excitability should be taken into account with regard to the implementation of intensified stimulation protocols. Increasing tDCS intensity is furthermore restricted due to the induction of pain sensations at current strengths of about 3 mA and a blinding problem at 2 mA (with electrode sizes between about 20 and 35 cm^2 (O'Connell et al., 2012)). Repetition of stimulation can enhance the after-effects of tDCS. The physiological effects of repetitive stimulation on the after-effects of tDCS have been evaluated for relatively short (3 and 20 min), and long (3 and 24 h) inter-tDCS intervals (1 mA, 35 cm^2 electrodes, 9 min cathodal/13 min anodal tDCS) (Monte-Silva et al., 2010a; Monte-Silva et al., in press). Specifically the short intervals prolonged the after-effects for at least 24 h after anodal tDCS (Monte-Silva et al., 2012). These results are in accordance with late-phase plasticity induction procedures in animal slice preparations, where a critical time window of about 30 min was described (Reymann and Frey, 2007). Another option to prolong and strengthen the after-effects of tDCS is the combination of stimulation with pharmacological interventions. The partial NMDA receptor agonist D-cycloserine, amphetamine, and serotonin all have been demonstrated to enhance the efficacy of anodal tDCS (Nitsche et al., 2004a,b, 2009b), whereas application of L-dopa, as well as dopamine agonists extends the after-effects of cathodal stimulation (Kuo et al., 2008a; Monte-Silva et al., 2009, 2010b; Nitsche et al., 2006). The latter effects have been shown to be non-linearly dosage-dependent. Combination of pharmacological intervention with stimulation might be especially well-suited for diseases in which the specific drugs are applied for therapeutic reasons, e.g. application of serotonin reuptake inhibitors with anodal tDCS for treatment of depression (Brunoni et al., 2012).

For combination of tDCS with task performance, which plays no major role in psychiatric applications so far, but is of importance for the implementation of tDCS in rehabilitative settings with regard to neurological diseases, e.g. motor rehabilitation after stroke (Flöel et al., in this issue), timing of the stimulation in relation to performance might be important. For most rehabilitation protocols, stimulation and rehabilitation therapy were so far conducted simultaneously, but optimal timing has not been systematically evaluated in patients. In healthy subjects, with regard to a sequential motor learning task, anodal tDCS of the primary motor cortex during, but not before learning improved performance, and premotor cortex stimulation, which did not improve performance during learning, resulted in improved outcome when applied during REM sleep, during which this area is involved in reconsolidation processes (Nitsche et al., 2003d, 2008, 2010). For a visuo-motor consolidation task, however, anodal tDCS improved performance when applied not only during, but also before learning (Antal et al., 2004, 2008). In the latter condition, also cathodal tDCS improved performance. Thus it might be speculated that anodal tDCS during learning boosts task-related plasticity via the addition of stimulation-induced plasticity, maybe mediated via activity-dependent calcium influx, while anodal stimulation before performance might gate task-related plasticity, and cathodal tDCS before performance might improve it via homeostatic mechanisms (Ziemann and Siebner, 2008). In contrast, a recently conducted study showed superior effects of anodal stimulation, when applied before performance of an implicit visual perceptual learning task (Pirulli et al., in press). However in this study a repetitive tDCS protocol with relatively short stimulation durations was performed, which makes it difficult to speculate about the net impact of this protocol on cortical excitability (Fricke et al., 2011). Although conceptually it makes sense that for learning tDCS during performance should be more effective, due to not only NMDA receptor-, but also calcium channel-mediated intracellular calcium increase, the latter induced by tDCS-dependent membrane depolarization, clearly more systematic studies are needed to explore this topic further. For cognitive processes, which might not require the induction of neuroplasticity, e.g. working memory, or attentional processes, similarly most studies have been performed with tDCS during performance, but systematic studies comparing differently timed stimulation protocols are missing (for an overview see Kuo and Nitsche, 2012).

With regard to the focality of tDCS, the conventional bipolar electrode arrangement with large electrodes delivers a relatively non-focal stimulation (Nitsche et al., 2008). More focal effects can be achieved by reducing stimulation electrode size, or increasing the size of the return electrode, thus enabling a functional monopolar stimulation (Nitsche et al., 2007). Moreover, the return electrode can be placed at remote areas distant from the head, although tDCS might be less efficient with this electrode arrangement (Moliadze et al., 2010). This does not imply that an extracephalic return electrode position makes stimulation functionally ineffective, as shown by studies in which tDCS for pain reduction (Mendonca et al., 2011), and depression (Boggio et al., 2012; Martin et al., 2011) was applied. Statements about the relative clinical efficacy of cephalic versus extracephalic return electrode positions are not possible, because no studies have been conducted which compare these protocols directly. Furthermore, it cannot be decided if different neuronal populations due to different current flow, and electrical field orientation, are affected by these protocols. A principal problem of an extracephalic return electrode position might be the activation of brainstem structures, however, possible problematic vegetative effects have not been present in a recently conducted study (Vandermeeren et al., 2010). Another option to focalize the effects of tDCS might be the so-called high definition (HD) tDCS. Here a relatively small central stimulation electrode is surrounded by four return electrodes, which are thought to be functionally inert. Modeling suggests that this electrode arrangement results in more focal effects than the conventional electrode arrangement (Bikson et al., 2012; Kuo et al., 2012). Moreover, it is effective at the physiological and functional levels (Borckardt et al., 2012; Kuo et al., 2012). Physiological validation of increased focality of the effects however is missing so far. It waits to be shown if more focal stimulation is more efficient for the treatment of neuropsychiatric diseases. Better-targeted stimulation might result in less side effects. However, in some diseases relatively large areas would be preferentially aimed to be modulated. Therefore, benefits and shortcomings of focal stimulation with regard to clinical application of tDCS should be discussed thoroughly for each project.

Whereas the focus of tDCS effects so far was dedicated to regional effects under the stimulation electrodes, it also modulates the activity within and between different cortical networks. Primary motor cortex stimulation has been shown to increase the connectivity of cortico-cortical, and cortico-subcortical motor network components, including premotor, and parietal areas, as well as thalamic nuclei, and the caudate nucleus, in the resting human brain, as shown by fMRI. An EEG study demonstrated similar effects of tDCS on motor networks in the gamma frequency range. Here tDCS increased respective motor task-related activations (Polania et al., 2011, 2012a,b,c). Beyond the motor cortex, prefrontal tDCS affects resting network connectivity (Keeser et al., 2011), and anodal stimulation of the inferior frontal gyrus, an area critically involved in language production, resulted in increased connectivity of this area with other major hubs of the language network in the resting brain. Interestingly, in this study tDCS improved word retrieval, suggesting a functional relevance of the respective network activation (Meinzer et al., 2012). So far, only relatively acute effects of tDCS on

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functional connectivity in healthy humans have been demonstrated. It remains to be shown if combined stimulation of disease-relevant connected areas have better effects than stimulation of a single structure.

Concluding remarks

This review gathers the clinical trials conducted for the treatment of neuropsychiatric diseases via "modern" tDCS protocols, i.e. stimulation protocols which have been physiologically validated in most cases at M1. In general, the results from most of the studies are promising, demonstrating the efficacy of stimulation in a variety of neuropsychiatric diseases accompanied by pathological alterations of cortical excitability and activity. In principal, two groups of studies can be discerned: early pilot experiments, which are dedicated primarily to the evaluation of principal efficacy of tDCS to improve symptoms, and later controlled trials, which aim to induce clinically relevant effects. For the latter, a limited number of diseases were explored so far. Relatively clear, also clinically relevant effects seem to be achieved in pain syndromes with regard to neurological diseases discussed in the present paper, and for depression with regard to psychiatric diseases. Importantly, side effects so far are rare, and mild. Before tDCS can be implemented into clinical practice, however, larger multi-center studies are also needed for these relatively well explored diseases. One important aspect to clarify before conduction of these studies is the definition of optimized stimulation protocols. Here interesting approaches exist, which are however only available for stimulation in healthy subjects so far. The transferability of the respective results to patient populations awaits yet to be investigated.

Uncited references

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Stafstrom, 2006

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