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REVIEW ARTICLE

The application of tDCS for the treatment of psychiatric diseases

Min-Fang Kuo[a], Po-See Chen[b,c] and Michael A. Nitsche[a,d]

[a]Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany; [b]Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [c]Addiction Research Centre, National Cheng Kung University, Tainan, Taiwan; [d]Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

ABSTRACT

Neuroplasticity represents the dynamic structural and functional reorganization of the central nervous system, including its connectivity, due to environmental and internal demands. It is recognized as a major physiological basis for adaption of cognition and behaviour, and, thus, of utmost importance for normal brain function. Cognitive dysfunctions are major symptoms in psychiatric disorders, which are often associated with pathological alteration of neuroplasticity. Transcranial direct current stimulation (tDCS), a recently developed non-invasive brain stimulation technique, is able to induce and modulate cortical plasticity in humans via the application of relatively weak current through the scalp of the head. It has the potential to alter pathological plasticity and restore dysfunctional cognitions in psychiatric diseases. In the last decades, its efficacy to treat psychiatric disorders has been explored increasingly. This review will give an overview of pathological alterations of plasticity in psychiatric diseases, gather clinical studies involving tDCS to ameliorate symptoms, and discuss future directions of application, with an emphasis on optimizing stimulation effects.

Introduction

The prevalence of psychiatric diseases has increased rapidly in the last decades to almost one third of the global population having experienced a mental disorder at some time during their lifetimes (Steel et al., 2014). This growing incidence also exacerbates the burden for healthcare systems in both social and financial aspects. Therefore, a main focus of neuropsychiatric research is to elucidate pathophysiology underlying psychiatric diseases, and on this foundation to develop effective treatment methods.

During the last years it became increasingly evident that dysfunctional neuroplasticity is involved in various neuropsychiatric disorders. Neuroplasticity encompasses dynamic alterations of neuronal connections in the central nervous system. It serves as the foundation for various brain functions, including cognitive processes such as learning and memory formation. Plasticity of synaptic connections was first proposed by Hebb (1961) and later demonstrated in hippocampal slices as long-term potentiation (LTP) and long-term depression (LTD) of excitability after fast or slow rhythmic stimulation, respectively (Bliss

& Lømo, 1973; Dunwiddie & Lynch, 1978). In addition to glutamatergic synapses in the hippocampus, both LTP and LTD can be induced in other synaptic connections including GABAergic and dopaminergic neurons in virtually all areas of the central nervous system *in vitro* and *in vivo*, which has been revealed by extensive investigations in the last three decades (for review, see Malenka and Bear (2004)). Furthermore, physiological plasticity has been linked to learning and memory processes, as demonstrated in different modalities such as sensory and motor learning, as well as more complex memory formation (McGann, 2015; Rioult-Pedotti, Friedman, & Donoghue, 2000; Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998; Whitlock, Heynen, Shuler, & Bear, 2006). On the other hand, disruption of long-term plasticity or aberrant plasticity has been shown to compromise learning and memory processing (McNaughton & Morris 1987). Such cognitive deficits are commonly observed in psychiatric diseases.

Neuroplasticity can be induced in humans by non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS). Brain stimulation with direct current was first shown in animal

models to elicit long-lasting alterations of cortical excitability, possibly via generation of sub-threshold, stimulation polarity-dependent alteration of neuronal membrane potentials, which modifies spontaneous firing rates (Bindman, Lippold, & Redfearn, 1964). For an overview, see Nitsche, Liebetanz, et al., (2003). During the last decade, non-invasive transcranial direct current stimulation of the human brain has been introduced following the development of methods that allow probing its neurophysiological effects (e.g. transcranial magnetic stimulation, TMS, and functional magnetic resonance imaging, fMRI). It has become established as a technique that reliably induces and modulates neuroplasticity in the human cerebral cortex, in order to elicit prolonged and, thus, neuroplastic, but yet reversible shifts of cortical excitability (Nitsche & Paulus, 2000, 2001, 2011; Nitsche et al., 2008). The respective excitability alterations are bi-directional within certain limits, as excitatory and inhibitory effect can be induced by anodal and cathodal tDCS, respectively, and the after-effects can outlast the stimulation for over 1 h or longer when the stimulation is continued in the range of minutes (Nitsche & Paulus, 2000, 2001; Nitsche, Nitsche, Klein, et al., 2003). The resulting plasticity is associated with N-methyl-D-aspartate (NMDA) receptors of glutamatergic synapses and calcium channels, as well as protein synthesis, and thus shares common features with LTP and LTD (Nitsche, Fricke, et al., 2003; Nitsche, Liebetanz, et al. 2004).

In addition to the neurophysiological effects, as demonstrated primarily by changes of excitability in the human motor system, tDCS can also modulate cognitive functions such as working memory and learning processes in different modalities (Kuo & Nitsche, 2012; Shin, Foerster, & Nitsche, 2015). Therefore, it provides the possibility to counteract cognitive dysfunction observed in psychiatric diseases, and to serve as alternative and adjuvant therapeutic option to conventional pharmaceutic treatment. Extensive investigation in both basic and clinical studies has revealed promising results and facilitated the development of effective stimulation protocols (for review, see Woods et al. (2016)). Here we will review the current state of tDCS application in psychiatric diseases, and provide an outlook based on the up-to-date evidence for the improvement of its efficacy in future studies.

tDCS in psychiatric diseases

In psychiatry, pharmacological intervention remains the first choice of therapeutic option to date. Non-invasive brain stimulation techniques including tDCS have recently been introduced as adjuvant treatment, especially for refractory or treatment-resistant patients. Earlier applications of tDCS in psychiatry were mainly focused on depression, but the field of application has gradually extended to other diseases such as addiction, schizophrenia, anxiety, and obsessive-compulsive disorder (OCD), which will be discussed separately in the following sections.

Depression

Most tDCS studies conducted in psychiatry so far are dedicated to the treatment of depression, possibly due to the underlying pathophysiology, which includes reduced activity of the left dorsolateral prefrontal cortex (DLPFC), which is located at the convexity of the brain, and, thus, provides optimal pre-requisites for stimulation efficacy (Fitzgerald et al., 2006). In addition, right hemispheric hyper-activation is also suggested to be involved in depression, which supports the focus of therapeutic strategies to enhance left DLPFC activity, and/or to decrease right DLPFC activity (Schönfeldt-Lecuona, Cárdenas-Morales, Freudenmann, Kammer, & Herwig, 2010). Furthermore, anodal tDCS facilitates LTP-like plasticity, which has been shown to be compromised in depression (Normann, Schmitz, Fürmaier, Döing, & Bach, 2007; Spedding, Neau, & Harsing, 2003). Consistent with the hypothesis that reduced LTP plays a role in depression, an important effect of antidepressant serotonin re-uptake inhibitors might be its enhancing impact on LTP-like plasticity in healthy humans and patients suffering from major depression (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009; Normann et al., 2007).

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 combined with an extra-cephalic return electrode. These studies revealed mixed results, and, since physiological effects of such stimulation protocols were not explored, it is unclear what kind of cortical excitability alteration was induced (for details see Lolas (1977) and Nitsche, Boggio, et al. (2009)).

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. tDCS improved the pathological attentional bias for emotional cues during working memory tasks in patients with depression (Wolkenstein & Plewnia, 2013). 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, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006). Increasing stimulation intensity to 2 mA for up to 15 sessions resulted in stable clinical effects lasting for up to 1 month after tDCS, as shown in two other double-blinded sham-controlled studies (Boggio, Rigonatti, et al., 2008; Loo, Alonzo, Martin, Mitchell, Galvez, & Sachdev, 2012). The tDCS efficacy in these studies was similar to the treatment with 20 mg fluoxetine, but evolved earlier than the pharmacological intervention (Rigonatti et al., 2008). In other trials, anodal prefrontal tDCS was not superior as compared to placebo stimulation, possibly due to the application of weaker and less frequent stimulation, and the inclusion of more severely affected patients (Bennabi et al., 2015; Loo et al., 2010; Palm et al., 2012). However, it was observed in the latter study that trend-wise more patients in the active tDCS group achieved the response and remission criteria after treatment, as compared to the sham group (Bennabi et al., 2015). Furthermore, additional 'boosting sessions' following two studies with left-DLPFC tDCS (Loo et al., 2010; Martin et al., 2011) revealed beneficial effects, e.g. one study showed remission rates of ∼80% after 3, and 50% after 6 months, with weekly or second-weekly extra sessions after initial daily tDCS (Martin et al., 2013) (see Table 1).

Bi-frontal tDCS with the anode over the left and the cathode over the right DLPFC, in order to re-establish the balance between right and left DLPFC activation, was demonstrated first to be effective in some open-label studies (Brunoni, Ferrucci, et al., 2013; Brunoni, Ferrucci, Bortolomasi, Vergari, Tadini, Boggio, et al., 2011; Dell'Osso et al., 2012). The clinical improvement lasted for up to 3 months in half of the patients receiving tDCS (Dell'Osso et al., 2014). However, less promising results were obtained in a double-blinded sham-controlled study (Blumberger, Tran, Fitzgerald, Hoy, & Daskalakis, 2012). Factors like patients with higher disease severity and numerous patients under benzodiazepines, which might have reduced the efficacy of tDCS (Nitsche, Liebetanz, et al., 2004), may have contributed to this negative result (Brunoni, Ferrucci, et al., 2013). It was also demonstrated that moving the right frontal return electrode to an extra-cephalic position resulted in a better initial treatment response in patients resistant to bifrontal stimulation (Martin et al., 2011). In a recently published large-scale double-blinded sham-controlled study, bi-frontal tDCS was applied in 120 patients diagnosed with unipolar depression, and the effects of tDCS or sertraline alone, and combination of both agents was compared (Brunoni, Valiengo, et al., 2013). DC stimulation with 2 mA for 30 min was performed for 10 days, and then repeated every other week once. The results revealed that 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. In phase II of the same trial the non-responders of the sham tDCS groups received a 10-day tDCS course and more than half of these responded to active tDCS (Valiengo et al., 2013). Moreover, in the same study another group including all active-tDCS responders were recruited for a follow-up phase-III trial, in which a 24-week tDCS treatment regimen was administered, with a maximum of nine tDCS sessions performed every other week for 3 months and then once monthly for the subsequent 3 months. The results demonstrated an average response duration of 11.7 weeks within the 24-week treatment course (Valiengo et al., 2013). Alternative electrode arrangements in addition to the above-mentioned montages have also been tested. Both fronto-occipital and bi-temporal tDCS were reported to be effective in four or 14 patients, respectively, with major depression (Ho et al., 2015; Ho et al., 2014).

With regard to combined treatment approaches, not only tDCS applied during antidepressant medication, but also a combination of tDCS with cognitive therapy has been investigated, based on the rationale that tDCS-induced LTP-like plasticity could further improve cognitive function such as therapy-related learning processes, which are associated with cortical plasticity. Ten-session adjunctive bi-frontal tDCS combined with cognitive behavioural therapy in a patient with refractory major depression improved therapeutic endurance, as compared to tDCS alone (D'Urso, Mantovani, Micillo, Priori, & Muscettola, 2013). In a sham-controlled study, in which bifrontal tDCS was combined with cognitive control therapy, real tDCS was, however, not superior to sham control (Brunoni et al., 2014). In contrast, a clinical benefit was reported when the return electrode was placed over the right supra-orbital area, and tDCS was applied with lower current density and shorter treatment sessions (Segrave, Arnold, Hoy, & Fitzgerald, 2014).

With regard to manic symptoms in bipolar disorder, which might be associated with a converse pattern of imbalanced prefrontal activation, i.e. right

Table 1. tDCS for depression. Shown are studies dedicated to treatment of depression in chronological order.

Depression	Design		Patients	Stimulation protocol								Outcome
Studies	Placebo-controlled	Blinding		Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm²)	Duration (min)	Session(s)	Current density (mA/cm²)	
Fregni et al. (2006)	Yes	Double	MD	A/S	L DLPFC	R supraorbital	1	35	20	Daily session for 5 alternate days	0.03	Improvement of symptoms
Boggio, Rigonatti, et al. (2008)	Yes	Double	MD	A/S	L DLPFC or occipital (active control)	R supraorbital	2	35	20	5 daily sessions/week for 2 weeks	0.06	Improvement of HDRS with DLPFC tDCS for up to 1 month
Rigonatti et al. (2008)	Yes	Double	MD	A/S	F3	R supraorbital	2	35	20	5 daily session/week	0.06	Improvement of symptoms, similar to fluoxetine
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
Loo et al. (2010)	Yes	Double	MD	A/S	L DLPFC	R supraorbital	1	35	20	Daily session for 5 alternate days	0.06	Improvement of symptoms in both active and sham groups
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
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
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
Dell'Osso et al. (2012) (follow-up in Dell'Osso et al (2014))	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; maintained for 3+ months in half of the patients
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
Palm et al. (2012)	Yes	Double	MD with treatment resistance	A/S	L DLPFC	R supraorbital	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
Knotkova et al. (2012)	No	Open	HIV-MD	A	F3	R supraorbital	2	35	20	Once daily for 10 consecutive weekdays	0.06	Improvement in HDRS and subjective ratings
Brunoni, Ferrucci, et al. (2013)	No	Open (blinded rater)	MD	A	L DLPFC	R DLPFC	2	25	20	2 sessions/day for 5 days	0.08	Improvement in depression symptoms; patients using BZD showed worse outcome
Brunoni, Valiengo, et al. (2013)	Yes	Double	MD	A/S	L DLPFC	R DLPFC	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

Table 1. Continued

| Depression | Design | | | | Stimulation protocol | | | | | | | |
Studies	Placebo-controlled	Blinding	Patients	Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm²)	Duration (min)	Session(s)	Current density (mA/cm²)	Outcome
D'Urso et al. (2013)	No	Open	MD with treatment resistance	A (with or without CBP)	F3	F4	1.5	/	/	5 daily session/week for 2 weeks	/	Improvement in depression symptoms post tDCS, and complete remission at 12-month follow-up with tDCS + CBT
Martin et al. (2013)	No	Open	MD	A	L DLPFC	R upper arm or R supraorbital area	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
Valiengo et al. (2013) (PHASE II of Brunoni, Valiengo, et al. (2013))	No	Open	MD	A	L DLPFC	R DLPFC	2	25	30	5 daily sessions/week for 2 weeks	0.08	Improvement in depression symptoms post tDCS (patients are the non-responders with sham tDCS in Brunoni, Valiengo, et al. (2013))
Valiengo et al. (2013) (PHASE III of Brunoni, Valiengo, et al. (2013))	No	Open	MD	A	L DLPFC	R DLPFC	2	25	30	9 sessions (1 per week for 6 alternative weeks, then 1 per month for 3 months)	0.08	No relapse in half of the sample for 24+ weeks; mean response duration: 11.7 weeks (patients are from active tDCS group in Brunoni, Valiengo, et al. (2013) and from PHASE II)
Brunoni et al. (2014)	Yes	Double	MD	A/S (both combined with CCT)	F3	F4	2	25	30	5 daily session/week for 2 weeks	0.08	tDCS + CCT was not superior to sham + CCT; both groups showed improvement post tDCS
Ho et al. (2014)	No	Open	MD	A	R prefrontal area	Oz or Cerebellum	2	35/100 (Oz) or 50 (cerebellum)	20	5 daily session/week for 4 weeks	0.06	Improvement in depression symptoms only with fronto-occipital tDCS
Segrave et al. (2014)	Yes	Double	MD	tDCS + CCT; sham tDCS + CCT; tDCS + sham CCT	L DLPFC	R supraorbital	2	35	24	5 daily session/week	0.06	tDCS + CCT showed most effective result with delayed onset
Bennabi et al. (2015)	Yes	Double	MD	A/S	L DLPFC	R supraorbital	2	35	30	2 sessions/day for 5 days	0.06	No superior effect of active tDCS in depression symptoms
Ho et al. (2015)	No	Open	MD	A	L fronto-temporal	R fronto-tempoal	2.5	35/16	20	5 daily session/week for 4 weeks	0.07–0.09	Improvement in depression symptoms post tDCS
Schestatsky et al. (2013)	No	Open	BPD with acute mania	A	R DLPFC	L supraorbital	2	35	20	5 daily session/week	0.06	Improvement in symptoms after the 3rd day of tDCS

A: anodal; BDI: Beck Depression Inventory; BPD: bipolar disorder; CCT: cognitive control therapy; DLPFC: dorsolateral prefrontal cortex; HDRS: Hamilton Depression Rating Scale; L: left; MD: major depression; R: right; S: sham; tDCS: transcranial direct current stimulation.

hypo- and left hyper-activity, preliminary results from a patient showed that anodal tDCS over the right DLPFC induced fast alleviation of acute symptoms (Schestatsky et al., 2013).

Stimulation in most studies was applied with current intensities between 1–2 mA and durations between 20–30 min. However, the number of treatment sessions, the interval between sessions, electrode positions, and disease severity vary considerably between 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, Valiengo, et al. (2013). Moreover this study is in favor of 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 or noradrenaline reuptake-inhibitors (Kuo et al., 2016; Nitsche, Boggio, et al., 2009). tDCS seems to be relatively well tolerated; however, hypomania, and manifest mania were described in relatively rare cases, 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 studies by Brunoni, Valiengo, et al. (2013) and Valiengo et al. (2013), it would make sense to conduct large multi-centre double-blinded sham-controlled trials. Apart from this, it might, furthermore, make sense to explore the potential of tDCS by elucidating the interaction of tDCS with antidepressant medication or medication known to improve the efficacy of anodal tDCS, such as D-cycloserine and reboxetine (Kuo et al., 2016; Nitsche, Jaussi, et al., 2004), combining tDCS with cognitive training of prefrontal functions, comparing the efficacy of different electrode positions directly, testing the impact of remote 'boosting' sessions of tDCS on the maintenance of therapeutic effects, broadening the application of tDCS to specific depression syndromes, such as post-stroke depression, and exploring 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.

Schizophrenia

Schizophrenia is a chronic mental disorder characterized by dysfunction of perception of reality, emotion and cognition. Clinical manifestations include positive (hallucinations, delusions, thought disorders, and bizarre behaviour) 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 excitatory and inhibitory neuroplasticity, induced by anodal and cathodal tDCS, respectively, were demonstrated in schizophrenia patients (Hasan, Aborowa, et al., 2012; Hasan, Nitsche, et al., 2012; Hasan, Nitsche, Rein, Schneider-Axmann, Guse, Gruber, et al., 2011). Since tDCS-induced cortical plasticity is dependent on NMDA receptors and is modulated by dopaminergic transmission (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010), this observation can be explained by the imbalance of the glutamatergic and dopaminergic systems in schizophrenia (Goto & 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., 2013). However, in another study, probabilistic associative learning was not improved by simultaneous anodal tDCS over the left DLPFC, with the exception of a sub-set of patients with relatively good baseline performance (Vercammen et al., 2011). These results suggest that tDCS may be able to facilitate cognitive function in schizophrenia, yet more studies are needed to delineate the specific modulatory effects of tDCS on different aspects of cognition, with regard to timing or connectivity between related cortical areas, and to more specific and optimized stimulation protocols.

Regarding the clinical application of tDCS in schizophrenia, inhibiting activity of the left temporo-parietal cortex (TPC) to reduce auditory hallucinations (AH), a frequent positive symptom associated with enhanced left-TPC activity, is one potentially relevant target of stimulation. For negative symptoms, which are characterized by dysfunctionally reduced frontal cortex activation, enhancement of this activity by intervention might be a promising approach (Andreasen et al., 1997). Clinical studies using other non-invasive brain stimulation protocols, such as repetitive transcranial magnetic stimulation (rTMS), have demonstrated beneficial effects of respective targeted excitability alterations (for review, see Freitas, Fregni, and Pascual-Leone (2009)). Brunelin,

Mondino, et al. (2012) explored the efficacy of tDCS to ameliorate auditory verbal hallucinations, and to improve negative symptoms, by a bipolar stimulation approach. 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 aimed to be 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 AHs together with reduced negative symptoms accomplished by active tDCS as compared to sham stimulation, and the effect lasted for up to 3 months after treatment (Brunelin, Mondino, Gassab, et al., 2012). Similar amelioration of AH together with improvement of the deficit in identifying self-generated mental events was also reported in the extended follow-up study (Mondino, Haesebaert, Poulet, Suaud-Chagny, & Brunelin, 2015). Furthermore, the reduction of AH was correlated with a reduction of resting-state functional connectivity (rs-FC) between the left TPC and the left anterior insula (Mondino et al., 2016). A case report with cathodal tDCS over the left TPC describes reduced AH after 10 consecutive daily sessions with 1 mA intensity and 15 min duration of tDCS (Homan et al., 2011). Regional cerebral blood flow measured by arterial spin labelling confirmed a significant reduction of blood flow under the cathode after each session, which might serve as a neurobiological explanation for the effect of tDCS. Persistent AH were also significantly improved in three open-label studies applying the same tDCS montage (Bose et al., 2014; Brunelin, Hasan, Haesebaert, Nitsche, & Poulet, 2015; Shivakumar et al., 2015). It should be noted that tDCS seems to be more beneficial in non-smoking patients when targeting auditory verbal hallucinations, which could be due to the comorbid plasticity decline observed in long-term smokers present under acute nicotine deprivation (Grundey et al., 2012; Thirugnanasambandam et al., 2011). Furthermore, patients carrying the catechol-O-methyltransferase (COMT) Val158Met polymorphism seem to be more responsive (Brunelin et al., 2015; Shivakumar et al., 2015).

Efficacy of tDCS in schizophrenia is further suggested by several case studies (Brunelin, Mondino, Haesebaert, et al., 2012; Jacks, Kalivas, Mittendorf, Kindt, & Short, 2014; Nawani, Bose, et al., 2014; Nawani, Kalmady, et al., 2014; Shenoy et al., 2015) (Table 2). In single-case studies applying twice daily tDCS for 5 consecutive days, an improvement or even

total cessation of AH was shown immediately after the first day of two-session tDCS, and complete cessation after day 5 (Narayanaswamy et al., 2014; Rakesh et al., 2013). Moreover, sustained therapeutic effects were maintained for up to 1 year with six add-on boosting sessions after 5-day treatment (Shivakumar et al., 2014). Another study reported improvement at the end-point of 10 sessions of tDCS, although 6 days later the symptom rating scores returned to baseline (Praharaj, Behere, & Sharma, 2015). Prolonged treatment courses over years might be more beneficial (Bose et al., 2015). On the other hand, a negative result was reported by a recent study implementing 5 days once-daily tDCS sessions targeting the same cortical regions, however with a different electrode arrangement, which might have contributed to the lack of clinical effects (Frohlich, Burrello, Mellin, Cordle, Lustenberger, Gilmore, et al., 2016).

A different stimulation protocol was developed targeting visual hallucinations (VH) and AH simultaneously (Shiozawa, da Silva, Cordeiro, Fregni, & Brunoni, 2013b). Here the cathode was placed over the occipital region with the anode over the left DLPFC for the first 10 sessions in 5 days, and then the occipital electrode was switched to the left TPC for another 5 days. The results revealed improved VH and AH, as well as other negative and positive symptoms (Shiozawa et al. 2013b). On the other hand, an electrode montage with the cathode placed over the right TPC and anode over the left TPC did not result in clinical improvement (Shiozawa, Santos, et al., 2014). Interestingly, tDCS with the anode over the left DLPFC and return electrode over the right supraorbital area also resulted in positive outcomes on both positive and negative symptoms, including catatonia, following 10 treatment sessions (Gomes, et al., 2015; Palm et al., 2013; Shiozawa et al., 2013a), but no effect after only five sessions (Smith et al., 2015). A beneficial effect was also reported when the cathode was moved to an extra-cephalic region, but only for negative symptoms (Kurimori, Shiozawa, Bikson, Aboseria, & Cordeiro, 2015) (Table 2).

Taken together, the results of these pilot studies are promising, but need confirmation by larger multicentre trials. Furthermore, nothing is known about optimally suited tDCS protocols for the treatment of schizophrenia. A number of active mono-centre studies are registered in ClinicalTrials.gov, encompassing the treatment of schizophrenia with tDCS. Some of these studies are dedicated to the improvement of negative symptoms, including cognition, in schizophrenia, and two other studies aim to treat negative

Table 2. tDCS for schizophrenia. Shown are studies dedicated to treatment of schizophrenia in chronological order.

	Design			Stimulation protocol								Outcome
Schizophrenia Studies	Placebo-controlled	Blinding	Patients	Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm²)	Duration (min)	Session(s)	Current density (mA/cm²)	Effects
Homan et al. (2011)	No	Open	SCZ with AH	C	L TPC	Right supra-orbital area	1	35	15	5 daily sessions/week for 2 weeks	0.03	Reduction in AH; maintained for at least 6 weeks.
Brunelin, Mondino, Gassab, et al. (2012)	Yes	Double	SCZ with AH	A/S	L DLPFC	L TPC	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
Brunelin, Mondino, M., Haesebaert, et al. (2012b)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days	/	Reduction in AH; maintained for at least 3 months
Palm et al. (2013)	No	Open	SCZ	A	L DLPFC	Right supra-orbital area	2	/	20	5 daily sessions/week for 2 weeks	/	Improvement in positive and negative symptoms post tDCS
Rakesh et al. (2013)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	35	20	2 sessions/day for 5 days	0.06	Complete cessation of AH post tDCS
Shiozawa et al. (2013a)	No	Open	SCZ with catatonia	A	L DLPFC	R DLPFC	2	35	20	5 daily sessions/week for 2 weeks	0.06	Improvement in catatonic symptoms during tDCS course; remained asymptomatic at 4-month follow-up
Shiozawa et al. (2013b)	No	Open	SCZ with AH/VH	A	L DLPFC	Occipital area then TPC	2	/	20	fronto-occipital: 5 daily sessions/ week for 2 weeks -> 5-day break -> fronto-temporal: 5 daily sessions/week for 2 weeks	/	First increase in AH/VH during tDCS, but reduction post tDCS; maintained for 2+ months; improvement in negative and positive symptoms after tDCS
Bose et al. (2014)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	35	20	2 sessions/day for 5 days	0.06	Reduction in AH post-tDCS.
Jacks et al. (2014)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days	/	Improvement in delusions, AH, blunted affect, emotional withdrawal, and general PANSS score post tDCS, but no change in positive or negative PANSS subscale scores
Narayanaswamy et al. (2014)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days	/	Improvement in negative symptoms; reduction in AH; maintained for 6+ months
Nawani, Bose, et al. (2014)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days	/	Reduction in AH post tDCS
Nawani, Kalmady, et al. (2014)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days	/	Reduction in AH post tDCS
Shiozawa, Santos, et al. (2014)	No	Open	SCZ	A	L TPC	R TPC	2	35	20	2 sessions/day, 5 days/week for 2 week	0.06	No improvement in schizophrenic symptoms
Shivakumar et al. (2014)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days; plus 6 booster sessions over 1 year (2 sessions/day)	/	Complete cessation of AH after tDCS; maintained for 3 months; boosting sessions controlled relapses over 1 year

Table 2. Continued

| Studies | Design | | Patients | Stimulation protocol | | | | | | | Outcome |
Schizophrenia	Placebo-controlled	Blinding		Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm²)	Duration (min)	Session(s)	Current density (mA/cm²)	Effects
Bose et al. (2015)	No	Open	SCZ with AH	A/C	L/R DLPFC	R/L DLPFC	2	35	20	2 sessions/day for 9 consecutive days (anodal L DLPFC), then changed to anodal R DLPFC (2 sessions/day for 10 consecutive days)	0.06	No improvement in symptoms after anodal L DLPFC tDCS, but reduction in AH after anodal R DLPFC tDCS
Brunelin et al. (2015)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	35	20	10 sessions (unknown frequency)	0.06	Reduction in AH post tDCS
Gomes et al. (2015)	Yes	Double	SCZ	A/S	L DLPFC	R DLPFC	2	/	20	5 daily sessions/week for 2 weeks	/	Improvement in negative but not positive symptoms post active tDCS
Kurimori et al. (2015)	No	Open	SCZ	A	L DLPFC	R deltoid	2	/	20	5 daily sessions/week for 2 weeks	/	Improvement in negative but not positive symptoms post tDCS
Mondino, Haesebaert, Poulet, Saoud, et al. (2015), Mondino, Haesebaert, Poulet, Suaud-Chagny, et al. (2015)	Yes	Double	SCZ with AH	A/S	L DLPFC	L TPC	2	35	20	2 sessions/day for 5 days	0.06	Reduction in AH after active vs sham tDCS
Praharaj et al. (2015)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	25	20	5 daily sessions/week	0.08	Reduction in AH post tDCS, but symptoms returned to baseline levels 6 days after tDCS
Shenoy et al. (2015)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	/	20	2 sessions/day for 5 days	/	Reduction in AH post tDCS with further improvement for 1+ month
Shivakumar et al. (2015)	No	Open	SCZ with AH	A	L DLPFC	L TPC	2	35	20	2 sessions/day for 5 days	0.06	Reduction in AH post tDCS
Smith et al. (2015)	Yes	Double	SCZ	A/S	L DLPFC	Right supra-orbital area	2	5.08	20	5 daily sessions/week	0.39	No improvement in schizophrenic symptoms
Frohlich et al. (2016)	Yes	Double	SCZ with AH	A/S (with two separate stimulators)	L DLPFC	L TPC	2	35	20	5 daily sessions/week	0.06	Active tDCS was not superior to sham in reduction of AH; no effect in negative symptoms
Mondino et al. (2016)	Yes	Double	SCZ with AH	A/S	L DLPFC	L TPC	2	35	20	2 sessions/day for 5 days	0.06	Reduction in AH and negative symptoms after active tDCS; reduction of AH was correlated with reduction of rs-FC between L TPC and L ACC

A: anodal; ACC: anterior cingulate cortex; AH: auditory hallucination; C: cathodal; DLPFC: dorsolateral prefrontal cortex; L: left; PANSS: Positive And Negative Syndrome Scale; R: right; rs-FC: resting-state functional connectivity; S: sham; SCZ: schizophrenia; tDCS: transcranial direct current stimulation; TPC: temporoparietal cortex; VH: visual hallucination.

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; Monte-Silva, Liebetanz, et al., 2010; Nitsche, Müller-Dahlhaus, Paulus, & Ziemann, 2012). Systematic titration of tDCS parameters exploring optimally efficient stimulation protocols is needed for more efficient application in schizophrenia.

Addiction

Substance abuse or dependence remains difficult to treat and relapse rates are high. Addiction 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 (Bechara, 2005; Koob & Volkow, 2010). Indeed, prefrontal tDCS can modify decision-making processes, which may share some common mechanisms with impulsive behaviour in addiction, as shown in healthy subjects (Boggio, Campanhã, et al., 2010; Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007; Knoch, Nitsche, Fischbacher, Eisenegger, Pascual-Leone, & Fehr, 2008). Accordingly, 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 (R-anodal/L-cathodal) tDCS, and a significant reduction of craving following tDCS was observed in these patients (Boggio, Zaghi, et al., 2010). Similar acute effects of single-session bilateral tDCS were reported for decreasing craving and cigarette consumption in smokers (Fregni et al., 2008). In a follow-up study, the authors performed 5 consecutive days of bilateral DLPFC stimulation with the same montage, which resulted in not only decreased cigarette consumption but also reduced craving (Boggio, Liguori, Sultani, Rezende, Fecteau, & Fregni, 2009). Similarly, a single tDCS session with the same bilateral DLPFC montage reduced cravings in alcohol-dependent patients (Boggio, Sultani, et al., 2008). In a study aiming for a therapeutic effect, it was documented that five weekly sessions of tDCS with the anode positioned over the left DLPFC and the cathode over the right supradeltoid region significantly suppressed craving in alcoholism after tDCS, and in

accordance reduced a respective pathological increase of the amplitude of cue-related evoked potentials (da Silva et al., 2013; Nakamura-Palacios, et al., 2012). However, in the latter study the active group also showed a higher tendency to relapse as compared to sham controls (da Silva et al., 2013). In contrast, application of an intensified stimulation protocol with opposite polarity (bilateral DLPFC tDCS, L-cathodal/R-anodal, 10 twice-daily sessions) showed no effect on craving scores, but a significant decrease in relapse after treatment (Klauss et al., 2014).

The therapeutic potential of tDCS in other substance abuse disorders, such as crack-cocaine addiction, was also explored. Bilateral DLPFC tDCS (R-anodal/L-cathodal) for five sessions resulted in a significant reduction of craving, and also a higher abstinence rate at the 3-month follow-up assessment, as compared to the sham group (Batista, Klauss, Fregni, Nitsche, & Nakamura-Palacios, 2015; Conti & Nakamura-Palacios, 2014). For methamphetamine addicts, single-session tDCS with the anode over the right DLPFC and cathode over the contralateral supra-orbital area showed a state-dependent modulation: tDCS reduced craving during rest, but increased the craving rate when exposed to substance-related cues (Shahbabaie et al., 2014).

In summary, tDCS over the DLPFC shows a potential to reduce substance craving in addiction (Table 3). Bilateral stimulation with both polarities has been shown to be effective, but effects might differ between specific substances, and addiction-related symptoms. In the study with marijuana users, only anodal tDCS over the right DLPFC diminished craving, while L-anodal/R-cathodal tDCS showed no effect (Boggio, Zaghi, et al., 2010). In alcoholism, however, left-DLPFC anodal tDCS (with return electrode over right supradeltoid) reduced craving, but trend-wise increased relapse, while bilateral DLPFC tDCS (R-anodal/L-cathodal) showed opposite effects (da Silva et al., 2013; Klauss et al., 2014). This double dissociation may imply different mechanisms underlying addiction symptoms in alcoholism, and differences between effects of tDCS in different substance disorders. The principal therapeutic effect of tDCS on substance abuse could be related to disruption of reward circuits within and between left and right DLPFC. It may also be associated with modulation of ventromedial PFC (vmPFC) activity via DLPFC tDCS, as suggested in a study showing increased diffusion tensor imaging (DTI) parameters, and, thus, enhanced structural connections between vmPFC and nucleus accumbens following DLPFC tDCS treatment

Table 3. tDCS for addiction. Shown are studies dedicated to treatment of substance addiction in chronological order.

Addiction	Design		Patients	Stimulation protocol								Outcome
Studies	Placebo-controlled	Blinding		Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm²)	Duration (min)	Session(s)	Current density (mA/cm²)	Effects
Boggio, Zaghi, et al. (2010)	No	Single	Marijuana (after 24 h abstinence)	A/C/S	F3/F4	F4/F3	2	35	10	Single	0.06	Reduction of craving after R-anodal/L-cathodal tDCS
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
Boggio et al. (2009)	No	Double	nicotine	A/S	F3	F4	2	35 (active)/100 (return)	20	5 daily sessions/week	0.06	Reduction of craving and cigarette consumption
Boggio, Sultani, et al. (2008)	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
Nakamura-Palacios et al. (2012)	Yes	Single	Alcohol	A/S	L DLPFC	R supradeltoid	1	35	10	Single	0.03	No reduction in alcohol craving after active tDCS as compared to sham
da Silva et al. (2013)	Yes	Single	Alcohol	A/S	L DLPFC	R supradeltoid	2	35	20	5 daily sessions/week	0.06	Reduction in alcohol craving after active vs sham tDCS; but trend for relapse during active tDCS
Klauss et al. (2014)	Yes	Double	Alcohol	A/S	R DLPFC	L DLPFC	2	35	13	2 sessions/day (with 20-min interval) for 5 consecutive days	0.06	No reduction in alcohol craving after active tDCS, but patients with active tDCS group showed more resistence to relapse for at least 6 months
Conti and Nakamura-Palacios (2014)	Yes	Double	Crack-cocaine	A/S	R DLPFC	L DLPFC	2	35	20	5 daily sessions/week	0.06	No difference in relapse rates between active and sham tDCS during the treatment; more patients with active tDCS maintained abstinence at 3-month follow-up
Batista et al. (2015)	Yes	Double	Crack-cocaine	A/S	R DLPFC	L DLPFC	2	35	20	5 daily sessions/week	0.06	Reduction in crack-cocaine craving after active tDCS vs sham; maintained for 1+ week.
Shahbabaie et al. (2014)	Yes	Double	methamphetamine	A/S	R DLPFC	L supraorbital	2	35	20	Single	0.06	Reduction in craving at rest, but increase in cue-induced craving during active tDCS

A: anodal; C: cathodal; DLPFC: dorsolateral prefrontal cortex; L: left; R: right; S: sham; tDCS: transcranial direct current stimulation.

(Nakamura-Palacios et al., 2016). However, further exploration of the pathophysiological mechanisms with optimized stimulation protocols and experimental designs is required for a more effective therapeutic application.

Anxiety disorders

Anxiety disorders, including OCD and general anxiety disorder (GAD), represent another major category of psychiatric diseases. Neuroimaging studies have revealed abnormal patterns of cortical and sub-cortical 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 inter-hemispheric imbalance with left hyper- and right hypo-activation was suggested by functional imaging in a case report, in which 2 mA 20 min tDCS (cathode - F3/anode - posterior neck) did not alter OCD symptoms, but restored the balance of cortical activity between the two hemispheres, and improved depression and anxiety (Volpato et al., 2013). OCD-associated abnormal hyperactivities in the orbitofrontal-subcortical network, including DLPFC, orbitofrontal cortex (OFC), the anterior cingulate gyrus, the supplementary motor area (SMA), and the basal ganglia, have been shown in neuroimaging studies (Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005). In a case study, cathodal tDCS over the left OFC with the anode over the right occipital region was applied twice daily for 5 days, and resulted in reduced OCD symptoms (Mondino, Haesebaert, Poulet, Saoud, & Brunelin, 2015). It was also described that 20 sessions of tDCS with the anode positioned over the left pre-SMA/SMA and the cathode over the right supraorbital area significantly improved OCD scores in two patients. This effect was sustained for up to 2 months (Narayanaswamy et al., 2015). In contrast, worsened symptoms were recorded following the same stimulation protocol (but with an extra-cephalic cathode) in another study. However, in this case report, the reversed electrode montage with cathodal tDCS over the right preSMA/SMA for another 10 sessions resulted in reduction of symptom scores for 3 months after treatment (D'Urso et al., 2016).

Regarding tDCS effect on general anxiety disorder, tDCS was shown to be effective in a case report with cathodal tDCS over the right DLPFC (anode over the left deltoid, 2 mA 30 min daily for 3 weeks), and this improvement lasted for up to 1 month (Shiozawa, Leiva, et al., 2014). It was also described that anorexia nervosa was ameliorated after 10 sessions of tDCS with the anode over the left DLPFC and the cathode positioned on the right arm (Khedr, Elfetoh, Ali, & Noamany, 2014) (Table 4).

To sum up, the application of tDCS for anxiety disorders might be promising, but results to date are preliminary. One mechanisms of action might be stimulation-induced alteration of dysfunctional cortico-subcortical networks including cortico-striatal, and cortico-thalamic loops (Polanía, Paulus, & Nitsche, 2012c), which are involved in the pathophysiology of anxiety disorders.

Outlook: optimizing therapeutic effects of tDCS

One critical aspect of the future application of tDCS in psychiatric diseases is the optimization of stimulation frequency, duration, and strength, as well as electrode position, to achieve optimal clinical effects. In the following section, we will discuss future optimized stimulation protocols based primarily on results of primary motor cortex stimulation, as this area has been studied most thoroughly based on advanced understanding of underlying neurophysiology. In addition, study designs including treatment course and concomitant therapy will also be covered in this section.

Stimulation intensity and duration

For anodal tDCS, stronger and longer-lasting stimulation results in larger effects, as shown by varying stimulation intensity between 0.2–1 mA, and stimulation duration between 1–5 min (Nitsche & Paulus, 2000). On this basis, 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., 2013). Extending the stimulation duration to 20 min with 2 mA current strength reversed, however, the effects of cathodal tDCS from excitability diminution to enhancement (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). Moreover, prolongation of 1 mA anodal tDCS to 26 min generated excitability diminution (Monte-Silva et al., 2013). These results, obtained in the motor cortex of healthy humans, revealed a non-linear relationship between

Table 4. tDCS for anxiety disorders. Shown are studies dedicated to treatment of anxiety in chronological order.

Studies	Placebo-controlled	Blinding	Patients	Polarity	Stimulation electrode position	Reference electrode position	Current strength (mA)	Electrode size (cm²)	Duration (min)	Current density (mA/cm²)	Session(s)	Effects
Volpato et al. (2013)	No	Open	OCD	C	L OFC	R occipital cortex	2	35/100	20	0.06	5 daily sessions/week for 2 weeks	Improvement in OCD symptoms; maintained for 1 month
Narayanaswamy et al. (2015)	No	Open	OCD	A	L pre-SMA/SMA	R supraorbital	2	35	20	0.06	2 sessions/day for 10 consecutive days	Improvement in OCD symptoms; maintained for 1–2 months
D'Urso et al. (2016)	No	Open	OCD	A/C	L pre-SMA/SMA	R deltoid	2	35	20	0.06	5 daily sessions/week for 4 weeks	Improvement in OCD symptoms with anode over L pre-SMA; worsening with the other polarity
Shiozawa, Leiva, et al. (2014)	No	Open	GAD	C	R DLPFC	L deltoid	2	25	30	0.08	5 daily sessions/week for 3 weeks	Improvement in anxiety symptoms during tDCS; maintained for 1 month post tDCS
Khedr et al. (2014)	No	Open	anorexia nervosa	A	L DLPFC	R arm	2	24/100	25	0.08	5 daily sessions/week for 2 weeks	Improvement in symptoms; maintained for 1 month post tDCS

A: anodal; C: cathodal; DLPFC: dorsolateral prefrontal cortex; GAD: general anxiety disorder; L: left; OCD: obsessive-compulsive disorder; OFC: orbitofrontal cortex; R: right; SMA: supplementary motor area; tDCS: transcranial direct current stimulation.

stimulation parameters and the direction of after-effects, which constrains 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 patients with a positive outcome on clinical symptoms, most probably due to excitability-enhancing effects of stimulation, and the pathophysiological nature of the disease. Brunoni and colleagues reported reduction of depression symptoms by 30 min anodal stimulation, and clinical benefits have also been described in other psychiatric disorders with the same or alike stimulation protocols (Brunoni, Valiengo, et al., 2013; Shiozawa, Leiva, et al., 2014, Shiozawa, Santos, et al., 2014; Valiengo et al., 2013). Similar results have been obtained in some studies conducted in neurological diseases (Floel, 2014). Thus, a one-to-one translation of the physiological results obtained in healthy young subjects (Monte-Silva et al., 2013) 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 considered with regard to the implementation of intensified stimulation protocols. Increasing tDCS intensity is, furthermore, restricted due to the induction of pain sensation at current strengths of ∼3 mA and a blinding problem at 2 mA with electrode sizes between ∼20–35 cm², which could be at least partially prevented by the application of topical anaesthetics over the stimulation area (Batsikadze et al., 2013; O'Connell et al., 2012).

Treatment course

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 cm² electrodes, 9 min cathodal/13 min anodal tDCS) (Monte-Silva et al., 2013; Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010). Specifically, the short intervals prolonged the after-effects for at least 24 h after anodal tDCS (Monte-Silva et al., 2013). These results are in accordance with late-phase plasticity induction procedures in animal slice preparations, where a critical time window of ∼30 min was described (Reymann & Frey, 2007). The treatment course with tDCS in patient studies typically ranged from 5–20 sessions so far. Most studies applied 10 sessions for 2 weeks, with

5 consecutive days each week (see Tables 1–4). When compared, 10 sessions of stimulation, either once or twice daily, show more benefits than only five sessions, as least in schizophrenia (Gomes et al., 2015; Shiozawa, et al. 2013a; Smith et al., 2015). It has, furthermore, been shown in depression that, after the 2-week treatment, a follow-up stimulation protocol with five sessions per week for 6 alternating weeks and then three monthly sessions consolidated and prolonged the clinical effects (Valiengo et al., 2013). In general, study courses with repeated sessions reported so far are restricted to at most 5 days per week, with a 2-day break between each stimulation week. It remains unclear whether continuous long-term treatment with tDCS will generate better therapeutic effects, and results from rTMS studies suggest that even current prolonged tDCS protocols might be too short. The development of home-based tDCS interventions, whose feasibility has been tested in other chronic diseases (Kasschau et al., 2016; O'Neill, Sacco, & Nurmikko, 2015), may enable the investigation and establishment of more advantageous treatment protocols.

Electrode montage

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, Doemkes, Karakose, Antal, Liebetanz, Lang, 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, Antal, & Paulus, 2010). This does not imply that an extracephalic return electrode position makes stimulation functionally ineffective, as shown by studies in which tDCS for depression (Martin et al., 2011), schizophrenia (Kurimori et al., 2015), and anxiety (Shiozawa, Leiva, et al., 2014) was applied. Statements about the relative clinical efficacy of cephalic vs extracephalic return electrode positions are not possible at present, because no studies have been conducted to compare these protocols directly. Furthermore, different neuronal populations due to different current flow, and electrical field orientation, might be 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, Jamart, & Ossemann, 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 presumed to be functionally inert. Modelling suggests that this electrode arrangement results in more focal effects than the conventional electrode arrangement (Bikson, Rahman, & Datta, 2012; Kuo et al., 2013). Moreover, it is effective at physiological and functional levels (Borckardt et al., 2012; Kuo et al., 2013). Physiological validation of increased focality of the effects, however, is missing so far. It waits to be seen 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 targeted for modulation. 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, Paulus, & Nitsche, 2011, 2012a, 2012b, 2012c). 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).

Pathophysiological alteration of neural network connectivity associated with psychiatric symptoms has been revealed by neuroimaging techniques (for review, see Narr & Leaver (2015) and Northoff (2016)). For example, abnormal resting-state functional connectivity, which revealed a pathological pattern of connectivity within a fronto-temporal network, has been related to AH in schizophrenia (Hoffman & Hampson, 2011).

Recently it has been shown that tDCS decreased the functional connectivity of the left TPC with the left anterior insula and the right inferior frontal gyrus, and increased connectivity of the left TPC with the left angular gyrus, the left dorsolateral prefrontal cortex, and the precuneus in patients with auditory verbal hallucinations (Mondino, Haesebaert, Poulet, Saoud, et al., 2015; Palm et al., 2013). Moreover, the improvement of clinical symptoms was correlated with respective tDCS-induced changes of functional connectivity within this disease-related network (Mondino et al., 2016). In a study investigating tDCS effect on drug addicts, bilateral DLPFC tDCS increased connectivity between vmPFC and nucleus accumbens, as shown with DTI, and the alteration of DTI parameters was associated with craving reduction (Nakamura-Palacios et al., 2016). These results suggest a modulating effect of tDCS on the symptom-associated cortical networks and connectivity beyond the stimulation sites, which could hint at future applications of tDCS with combined stimulation of disease-relevant connected areas rather than stimulation of a single structure.

Concurrent therapy

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, serotonin, and reboxetine all have been demonstrated to enhance the efficacy of anodal tDCS (Kuo et al., 2016; Nitsche, Jaussi, et al., 2004, Nitsche, Grundey, et al., 2004, Nitsche, Kuo, et al., 2009), whereas application of L-dopa, as well as dopamine agonists extend the after-effects of cathodal stimulation (Fresnoza et al., 2014; Kuo, Paulus, & Nitsche, 2008; Monte-Silva et al., 2009, Monte-Silva, Liebetanz, et al., 2010; 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 re-uptake inhibitors with anodal tDCS for treatment of depression (Brunoni, Valiengo, et al., 2013).

For combination of tDCS with cognitive therapy in psychiatric disorders, three studies have explored the effect of combining tDCS and cognitive training in patients with depression, and mixed results have been described (Brunoni et al., 2014; D'Urso et al., 2013; Segrave et al., 2014). It is not clear whether the timing of tDCS and cognitive training may contribute to the results in the respective studies. A relevance of timing was observed for the combination of tDCS and behavioural/motor task performance in rehabilitative settings with regard to neurological diseases, e.g. motor rehabilitation after stroke (Floel, 2014). For most rehabilitation protocols, stimulation and rehabilitation therapy were so far conducted simultaneously. 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, Liebetanz, et al., 2003, 2008; Nitsche et al., 2010). For a visuo-motor consolidation task, however, anodal tDCS improved performance when applied not only during, but also before learning (Antal, Begemeier, Nitsche, & Paulus, 2008; Antal et al., 2004). In the latter condition, cathodal tDCS also 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 & 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, Fertonani, & Miniussi, 2013). However in this study a repetitive tDCS protocol with relatively short stimulation duration 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 increases, 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)).

Conclusion

This review gathers clinical trials conducted for the treatment of psychiatric diseases via 'modern' tDCS

protocols, i.e. stimulation protocols which have been physiologically validated. In general, the results from most studies are promising, demonstrating effects of stimulation in a variety of psychiatric 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 was explored so far. Relatively clearly, clinically relevant effects seem to be achieved in depression and schizophrenia. Importantly, side-effects so far are rare and mild, if any. Before tDCS can be implemented into clinical practice, however, larger multi-centre studies are needed also for these relatively well-explored diseases. One important aspect to clarify is the definition of optimized stimulation protocols. Here, interesting new approaches do exist, which are, however, based mostly on stimulation results in healthy subjects so far. The transferability of the respective results to patient populations is yet to be investigated.

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