EXPERT REVIEWS

Understanding tDCS effects in schizophrenia: a systematic review of clinical data and an integrated computation modeling analysis

Expert Rev. Med. Devices Early online, 1–12 (2014)

Andre R Brunoni*[1–3], Pedro Shiozawa[4], Dennis Truong[5], Daniel C Javitt[6], Hélio Elkis[1], Felipe Fregni[7] and Marom Bikson[5]

[1]*Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil*
[2]*Service of Interdisciplinary Neuromodulation (SIN) and Interdisciplinary Center for Applied Neuromodulation (CINA), University of São Paulo, São Paulo, Brazil*
[3]*Laboratory of Neurosciences (LIM-27), Institute of Psychiatry, University of São Paulo, São Paulo, Brazil*
[4]*Laboratory of Clinical Neuromodulation, Santa Casa Medical School, São Paulo, Brazil*
[5]*Department of Biomedical Engineering, The City College of New York (CCNY), The City University of New York (CUNY), NY, USA*
[6]*Division of Experimental Therapeutics, Department of Psychiatry, Columbia College of Physicians and Surgeons, NY, USA*
[7]*Laboratory of Neuromodulation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA*
**Author for correspondence:*
Tel.: +55 113 091 9241
Fax: +55 113 091 9241
brunoni@usp.br

Although recent clinical studies using transcranial direct current stimulation (tDCS) for schizophrenia showed encouraging results, several tDCS montages were employed and their current flow pattern has not been investigated. We performed a systematic review to identify clinical tDCS studies in schizophrenia. We then applied computer head modeling analysis for prediction of current flow. Out of 41 references, we identified 12 relevant studies. The most employed montage was anode and cathode over the left dorsolateral prefrontal and temporoparietal cortex, respectively. Computational model analysis predicted activation and under-activation under the anode and the cathode, respectively, occurring in areas respectively associated with negative and positive symptoms. We also identified tDCS-induced electrical currents in cortical areas between the electrodes (frontoparietal network) and, to a lesser extent, in deeper structures involved in schizophrenia pathophysiology. Mechanisms of tDCS effects in schizophrenia and the usefulness of computer modeling techniques for planning tDCS trials in schizophrenia are discussed.

KEYWORDS: auditory hallucinations • computer based modeling • non-invasive brain stimulation • schizophrenia • transcranial direct current stimulation

Schizophrenia is a common psychiatric disorder, with an overall prevalence of 0.5–1.5% and a chronic course through life [1]. Its symptoms can be grouped into three relatively distinct phenomenological presentations: positive symptoms (hallucinations and delusions); negative symptoms (impairment in sociability, emotional blunting and abulia); and cognitive dysfunction [2]. Positive symptoms often occur within the first 10–15 years of the disease, while negative and cognitive symptoms exhibit a more chronic, persistent, and sometimes, progressive presentation through life [3]. For this reason, patients with schizophrenia have, in general, low functionality in performing daily life activities, lower quality of life and greater incidence of comorbidities, such as depressive symptoms, substance-related disorders, suicidal behavior and cardiovascular risk [4,5].

Currently, several antipsychotics are available for schizophrenia treatment. According to a recent multiple-treatment meta-analysis that analyzed 212 controlled trials, clozapine is the most effective antipsychotic, displaying superior effect sizes than amisulpride, olanzapine, risperidone and others [6]. Nonetheless, the difference in efficacy between the three most effective drugs is small, and therefore, clozapine use should outweigh its common adverse effects such as weight gain and sedation [6] as well as its rarer albeit severer effects such as neutropenia and agranulocytosis [7,8]. In fact, clozapine is the first-line drug for patients with treatment-resistant schizophrenia, that is, after failure of two adequate antipsychotic trials, as well as for patients with suicidality [9,10]. In addition, up to 30% of patients under treatment with clozapine respond partially and are called super-refractory or resistant to clozapine [7,10]. In such cases, there are two main alternatives: combination therapy with other pharmacological agents

 10.1586/17434440.2014.911082 ISSN 1743-4440

(e.g., lamotrigine, lithium, topiramate) – this approach has limited evidence and in fact may also increase drug-related adverse effects – and non-pharmacological therapies, for instance, electroconvulsive therapy particularly for catatonia and repetitive transcranial magnetic stimulation (rTMS) particularly for persistent auditory hallucinations [9,10]. Evidence is also limited for non-pharmacological therapies; however, recent rTMS meta-analyses have shown promising results for auditory verbal hallucinations [11] and negative symptoms [12].

In the past decade, transcranial direct current stimulation (tDCS) is another non-pharmacological intervention that has shown promising results in several neuropsychiatric disorders [13]. This technique is based on the induction of a weak, direct current that flows from the anode to the cathode. These electrodes are placed over the scalp, with the goal of, respectively, increasing and decreasing cortical excitability [14]. In fact, such effects were observed mainly from studies evaluating motor cortex excitability. These effects of tDCS on the motor cortex may not translate to other cortical areas [15]. In addition, the effects of tDCS are likely modified by other factors such as stimulation intensity or nature of ongoing activity [16]. Although the exact mechanisms of action of tDCS are still being investigated, tDCS produces low-intensity electric field (<1 V/m) [17] in the brain, leading to small changes (<1 mV) [18] in the membrane potential, thus influencing the frequency of spike timing and modifying net cortical excitability [19]. Plastic changes by tDCS are presumed to occur at the synaptic level. For instance, *N*-methyl-D-aspartate (NMDA)-antagonist drugs abolish tDCS after-effects, while NMDA agonists enhance such effects [20,21]. In addition, in an experimental animal study, Fritsch *et al.* [22] also demonstrated that DCS promotes brain-derived neurotrophic (BDNF)-dependent synaptic plasticity. This is important because BDNF is associated with synaptic plasticity and its dysfunction is associated with several neuropsychiatric disorders, including schizophrenia [23]. In fact, experimental studies have suggested that schizophrenia is associated with reduced neuroplasticity [24]. Finally, the clinical effects of tDCS are also enhanced when associated to serotoninergic drugs and decreased with benzodiazepines [25,26].

In the clinical setting, tDCS is comparable to rTMS as both are non-invasive, relatively focal brain stimulation techniques that ameliorate clinical symptoms by inducing cortical excitability changes inasmuch as rTMS is already used in clinical settings, whereas tDCS studies are Phase II and III yet. Nonetheless, tDCS could theoretically have some advantages over rTMS such as lower cost – rTMS devices are more expensive to purchase and maintain than tDCS devices [27]; ease of use – rTMS requires more training for use than tDCS as tDCS can be applied by technicians whereas rTMS can only be applied by trained physicians and, further, optimal rTMS results usually require neuroimaging guidance [28] and electromyography devices for motor threshold determination [29]; portability – tDCS devices are portable and could be potentially used in primary care and even home use and safety and tolerability – direct tDCS effects are mild and well-tolerated [30], whereas direct rTMS effects cause facial twitching that can be unpleasant; in addition, rTMS can rarely induce seizures [31], whereas this severe adverse effect was not ever described for tDCS.

For these reasons, tDCS has gained increased interest in clinical psychiatry over the past decade. The purpose of this review is to summarize the recent advancements of tDCS as a therapy for schizophrenia as well as to discuss its underlying pathophysiological mechanisms and perspectives in the field. We therefore performed a systematic review of all available clinical reports using tDCS as a therapy for schizophrenia. In this context, we also used a high-resolution MRI-derived computer head model to predict the intensity of current flow through the brain using the different electrode montages evaluated in the revised articles. The significance of this overall approach lies in the combination of clinical outcomes with computer models to investigate the mechanisms of action of tDCS in schizophrenia.

Methods

Systematic review

A systematic review was conducted for articles published from the first data available to 1 March 2014 in the following databases: Medline, Scopus, Web of Science and Google Scholar.

The following search strategy was used in MEDLINE in three steps:

- to identify tDCS-relevant articles – we used the keywords 'transcranial direct current stimulation' OR 'tDCS' OR 'brain polarization' OR 'galvanic stimulation' OR 'direct current (DC) stimulation'. This search yielded 1667 references.
- to identify schizophrenia-relevant articles – we used the keywords 'schizophrenia' OR 'psychosis'. This search yielded 122,187 references.
- After that, these terms (from first and second steps) were searched together using the Boolean terms 'AND'. We then identified 41 references.

We also looked for articles in the reference lists of retrieved articles and contacted experts in the field for additional articles.

We excluded review studies, editorials and studies investigating other techniques – for instance, a study investigating the clinical effects of transcranial random noise stimulation in schizophrenia [32]. We also excluded preclinical (animal) studies. Therefore, we included all articles that evaluated tDCS use in humans, regardless of its design (i.e., from case reports to randomized clinical trials [RCTs]).

From each retrieved article, we extracted data regarding demographic and clinical characteristics (such as sample size, age, gender); characteristics of the stimulation (anode and cathode positioning, intensity, duration of stimulation, number of sessions); assessment of schizophrenia, including methods for diagnosing and measuring severity and outcomes, describing each study main results. Anticipating that the number of studies would be heterogeneous and low, we did not plan quantitative analyses, that is, meta-analysis and techniques of meta-regression.

Computational modeling

Finite element method models of two commonly used tDCS montages for schizophrenia were created from a previously

segmented adult male based on a T1 MRI scan with a 1 mm isotropic resolution [33]. Models of sponges and electrodes (5 × 7 cm) were positioned and resampled into the image volume before a voxel-based volumetric mesh was generated using ScanCAD and ScanIP (Simpleware Ltd., Exeter, UK). This mesh was imported into a FEM solver (COMSOL 3.5a, Dassault Systèmes Corp., Waltham, MA, USA) modeling electrostatic physics. One of nine conductivities were assigned to the various materials: skin (0.465S/m), fat (0.025S/m), skull (0.01S/m), cerebrospinal fluid (1.65S/m), gray matter (0.276S/m), white matter (0.126S/m), air (1e-15S/m), electrode (5.99e7) and saline-soaked sponge (1.4) [34,35]. The field equation (Laplace, $\nabla \cdot (\sigma \nabla V) = 0$) was solved with boundary conditions set to: insulated on the skin surface, ground on the cathode surface and 1 mA inward current density on the anode surface. The resulting solution was then scaled for 2 mA of stimulation.

Results

Overview

Our search criteria yielded 41 references. Of those, 11 references were selected according to the eligibility criteria. Since Mattai *et al.* [36] reported two RCTs; we reviewed 12 studies – three RCTs, one case series and eight case reports, as described below. (Supplementary Material [supplementary material can be found online at www.informahealthcare.com/suppl/10.1586/17434440.2014.911082] and Table 1).

Randomized clinical trials

Brunelin *et al.* [37] investigated tDCS for the treatment of auditory hallucinations in schizophrenia by randomizing 30 patients with persistent auditory hallucinations to receive either active or sham tDCS. The cathode was placed on the left temporoparietal region and the anode on the left dorsolateral prefrontal cortex (DLPFC). The rationale was to simultaneously perform an inhibitory stimulation over the area related to positive symptoms and an excitatory stimulation over the area correlated with negative symptoms. tDCS was applied twice daily for 5 days. The authors showed an important, large effect in terms of improvement of auditory hallucinations after the end of stimulation, with sustained clinical response after 1 and 3 months of treatment. The results were also large and significant for the improvement of negative symptoms.

Mattai *et al.* [36] investigated the safety and tolerability of tDCS in childhood-onset schizophrenia in 12 adolescent (10–17 years) patients. Two double-blinded, randomized, sham-controlled trials were carried out with different tDCS setups (bilateral anodal prefrontal stimulation for cognitive improvement and bilateral cathodal temporoparietal stimulation for hallucinatory control, both with an extra-cephalic reference). The treatment was well tolerated with mild adverse effects such as tingling, itching and fatigue sensation that, although frequent (30–50%), presented similar rates in both active and sham groups. The authors did not report clinical outcomes.

Case series

Nawani *et al.* [38] investigated the clinical and neurophysiological effects of tDCS (anode over the left DLPFC, cathode over the left temporoparietal region) in five patients with refractory auditory verbal hallucinations. After 5 days of tDCS performed twice daily, there was a significant improvement in these symptoms. Moreover, the authors found that tDCS induced a modulation of the evoked related potential N100 that was tested during a corollary discharge paradigm, a neurophysiological test that is abnormal in patients with schizophrenia.

Case reports

Homan *et al.* [39] described a patient with refractory auditory verbal hallucinations who underwent tDCS treatment, with the cathode positioned over the 'Wernicke area' (left temporoparietal cortex) and the anode over the right supraorbital cortex. After 10 consecutive daily sessions of 1 mA/20 min of stimulation, the patient improved not only in positive, but also negative and global symptoms. This was also accompanied by regional decreasing of cerebral blood flow indexed by arterial spin labeling. In another report, Rakesh *et al.* [40] used tDCS in monotherapy to treat a full-blown paranoid schizophrenia in an outpatient basis. The cathode was positioned over the left temporoparietal junction and the anode over the left DLPFC; tDCS was applied twice daily at 2 mA/20 min for 5 consecutive days. The authors reported full cessation of verbal hallucinations.

Nawani *et al.* [41]. and Shivakumar *et al.* [42] used similar treatment protocols (5 days of tDCS, two sessions per day, with cathode over the left temporoparietal junction and the anode over the left DLPFC, describing improvement in auditory hallucinations). Particularly in the report of Shivakumar *et al.* [42], the patient presented complete cessation of hallucinations after 5 days of tDCS, effects that persisted over 4 weeks.

Shiozawa and colleagues explored tDCS in severe forms of schizophrenia in two case reports. In one case [43], tDCS (anode over the left and cathode over the right DLPFC, 2 mA/20 min, 10 consecutive sessions) was used to treat a severe catatonic, schizophrenic patient refractory to clozapine and electroconvulsotherapy. Improvement was remarkable, with virtually full remission of catatonia after 30–60 days of tDCS onset. In another study, Shiozawa *et al.* [44] used cathodal stimulation consecutively over the occipital cortex and the temporoparietal cortex (anode over the left DLPFC) to treat visual and auditory hallucinations, with partial response that nevertheless enhanced global functioning.

Palm *et al.* [45] performed tDCS (anode over the left DLPFC, cathode over the right supraorbital area) in a 19-year-old patient with paranoid, treatment-resistant schizophrenia, observing a global improvement of symptoms after 10 sessions of tDCS. The authors also found changes in functional connectivity after tDCS, with reduced functional connectivity in the anterior part of the default-mode network, which might be biologically related to the improvement of depressive and negative symptoms.

The Andrade study [46] explored the long-term use of tDCS (cathode over the left temporoparietal cortex, anode over the left DLPFC), with once- to twice-daily tDCS sessions for

doi: 10.1586/17434440.2014.911082

doi: 10.1586/17434440.2014.911082

Table 1. Summary of included studies in the present review.

Study (year)	Characteristics							tDCS						Ref.
	Design	*Sample size*	*Mean age*	*Sex*	*Diagnosis assessment*	*Main results*	*Follow-up*	*mA*	*min*	*Days*	*Anode*	*Cathode*	*Reported adverse effects*	
Shiozawa *et al.* (2013)	Case report	1	31	M	PANSS	VH/AH improvement	1 month	2	20	20	F3	T3P3 and Oz	None	[44]
Shiozawa *et al.* (2013)	Case report	1	65	F	Bush–Francis Scale	Catatonia improvement	4 months	2	20	10	F3	F4	None	[43]
Andrade (2013)	Case report	1	24	F	Clinical	Long-term improvement	36 months	1–3	20–30	3 years	F3	T3P3	Tingling	[46]
Rakesh *et al.* (2013)	Case report	1	24	M	AHRS	AH improvement	5 days	2	20	5 2×/day	Between F3 and FP1	T3P3	None	[40]
Homan *et al.* (2011)	Case report	1	44	M	AHRS/PANNS	AH improvement	10 days	1	15	10	Right SO	'Wernicke's area'	None	[39]
Shivakumar *et al.* (2013)	Case report	1	28	F	AHRS	AH improvement	4 weeks	2	20	5 2×/day	Between F3 and FP1	T3P3	None	[42]
Nawani *et al.* (2014)	Case report	1	31	M	AHRS	AH improvement	5 days	2	20	5 2×/day	F3	T3P3	None	[41]
Palm *et al.* (2013)	Case report	1	19	M	PANSS	Global improvement	2 weeks	2	20	10	F3	RSO	Not reported	[45]
Nawani *et al.* (2014)	Case series	5	33.2	60% F	AHRS	AH improvement	5 days	2	20	5 2×/day	F3	T3P3	None	[38]
Brunelin *et al.* (2012)	RCT	30	37.7	26.6% F	Clinical/PANNS	Global improvement	3 months	2	20	5 2×/day	Between F3 and FP1	T3P3	Tingling	[37]
Mattai *et al.* (2011)	RCT	8	15.6	40% F	Clinical/SAPS	Safety/ tolerability	2 weeks	2	20	10	See text		Tingling, itching, fatigue	[36]
	RCT	5	15.4	58.3% F	Clinical/SAPS	Safety/ tolerability	2 weeks	2	20	10	See text		Tingling, itching, fatigue	

AH: Auditory hallucinations; AHRS: Auditory hallucination rating scale; F: Female; F3: Left dorsolateral prefrontal cortex; M: Male; PANSS: The positive and negative syndrome scale; RCT: Randomized clinical trial; SAPS: Schedule for the assessment of positive symptoms; T3P3: Left temporoparietal area; tDCS: Transcranial direct current stimulation; VH: Visual hallucinations.

nearly 3 years, with sustained improvement, in a clozapine-refractory patient with schizophrenia. Interestingly, when the sessions were performed in alternate days, the benefits attenuated or were lost.

Computer head modeling

We predicted current flow based on two commonly employed montages: anode over the left DLPFC and cathode over the left temporoparietal junction or the occipital cortex (Figure 1). The current intensity used was 2 mA, as employed in almost all reviewed trials.

Consistent with previous modeling studies using other pad-based tDCS montages, stimulation produces relatively diffuse current flow under and between the electrodes, that is, between the temporoparietal (or occipital) cortex and the DLPFC. Current density is maximal (0.21 A/m^2 at 0.77 V/m) at the cortex but also reaches deeper brain structures (such as the basal ganglia, the hippocampus, the insula and the cingulate cortex) in a montage-specific manner (Figure 1, rows D and E). A role for concurrent neuromodulation of deeper structures thus becomes feasible and evidence for modulation of at least hippocampal excitability by direct current exists from animals [47].

In addition to (directionless) electric field magnitude (Figure 1A), we also predicted current flow normal to the cortical surface (i.e., inward and outward relative to the cortical sheet; Figure 1B) and current flow tangential to the cortical surface (i.e., along the cortical sheet, Figure 1C).

Inward current flow (induced by the anode) is associated with pyramidal neuron somatic depolarization and therefore increased excitability, while outward current flow (induced by the cathode) is associated with pyramidal neuron somatic hyperpolarization and therefore deceased excitability [15,18]. Regions of presumed excitation/inhibition are predicted under the electrodes (i.e., excitability increasing over the left DLPFC and decreasing over the left temporoparietal cortex or the occipital cortex); however due to idiosyncratic cortical folding, alternating regions of presumed excitation/inhibition are also observed between electrodes.

Tangential current (Figure 1C) is predicted between electrodes (as current flow across the brain), the role of which in synaptic modulation (connectivity) remains under investigation, although probably it translates into synaptic strengthening [15].

Discussion

In this systematic review, we identified three randomized, sham-controlled clinical trials (although only one trial reporting efficacy data that enrolled 30 patients), one case series and eight case reports investigating the use of tDCS – an affordable, easy-to-use and portable device – for the treatment of schizophrenia. All clinical studies reported improvement of symptoms and were primarily focused in auditory hallucinations, although improvement of negative symptoms was also reported. Effects were relatively long-lasting, with maintained improvement of more than 6 weeks after 5–10 consecutive daily sessions. Side effects were low, and tDCS was well tolerated even in a case report when daily sessions were applied for almost 3 years. The main tDCS setup used was anode over the left DLPFC and cathode over the left tempoparietal cortex, inspired by findings from neuroimaging studies and results from rTMS trials. In addition, MRI-derived computer models predicted current flow between the left DLPFC and the left temporoparietal cortex or the occipital cortex, particularly corroborating the rationale excitability decreasing over the cathode and increasing over the anode, but also revealing that current flows normal to these cortical regions (therefore inducing changes in cortical excitability) and also tangential to these regions, leading to synaptic strengthening. Finally, the computer models predicted that, with the commonly used tDCS setups, current also reaches deep brain structures involved in the pathophysiology of schizophrenia. These findings are discussed below.

All reviewed studies, except for Homan *et al.* [39], and one of the trials of Mattai *et al.* [36] performed anodal stimulation over the left DLPFC, aiming to increase regional cortical excitability of this area, which is associated with negative/cognitive impairment in schizophrenia. This is in line with several neuroimaging studies, which have revealed that schizophrenia is associated with gray matter reductions in the prefrontal cortex and white matter integrity changes in the deep frontal and temporal regions [48–50], whereas functional neuroimaging studies showed reduced DLPFC activation during working memory tasks in these patients [51,52]. In fact, even during rest, hypoactivity of the prefrontal cortex is observed [53]. Another line of evidence for DLPFC stimulation derives from rTMS clinical trials, which at first yielded mixed findings [54], although more recent meta-analyses showed that high-frequency rTMS was effective in the treatment of negative symptoms, especially when using a frequency of stimulation of 10 Hz and/or in studies with longer duration [55]. Finally, rTMS/tDCS studies observed working memory improvement in healthy subjects [56] and also in patients with DLPFC dysfunction such as major depression [57] and schizophrenia [58].

In most reviewed studies, including the RCT of Brunelin *et al.* [37], the cathode was applied over the left temporoparietal cortex, which was associated with amelioration of auditory hallucinations. This is in line with findings from rTMS, as low-frequency, inhibitory rTMS is applied over this region to effectively treat auditory hallucinations as demonstrated by recent several meta-analyses [54,59,60]. Neuroimaging studies also point out that the left temporal cortex is critical in the pathophysiology of positive symptoms [61], with activation of a specific left temporal area – the Heschl's gyrus – during auditory hallucinations [62]. Interestingly, the right temporal cortex does not seem to be overactive during auditory hallucinations [63], although both temporal lobe volumes are smaller in patients with schizophrenia versus controls [64]

Shiozawa *et al.* [44] also used, in a single report, cathodal stimulation over the occipital cortex for ameliorating visual hallucinations. The pathophysiology of this symptom – which has, in fact, high prevalence in chronic patients with schizophrenia [65] but is

doi: 10.1586/17434440.2014.911082

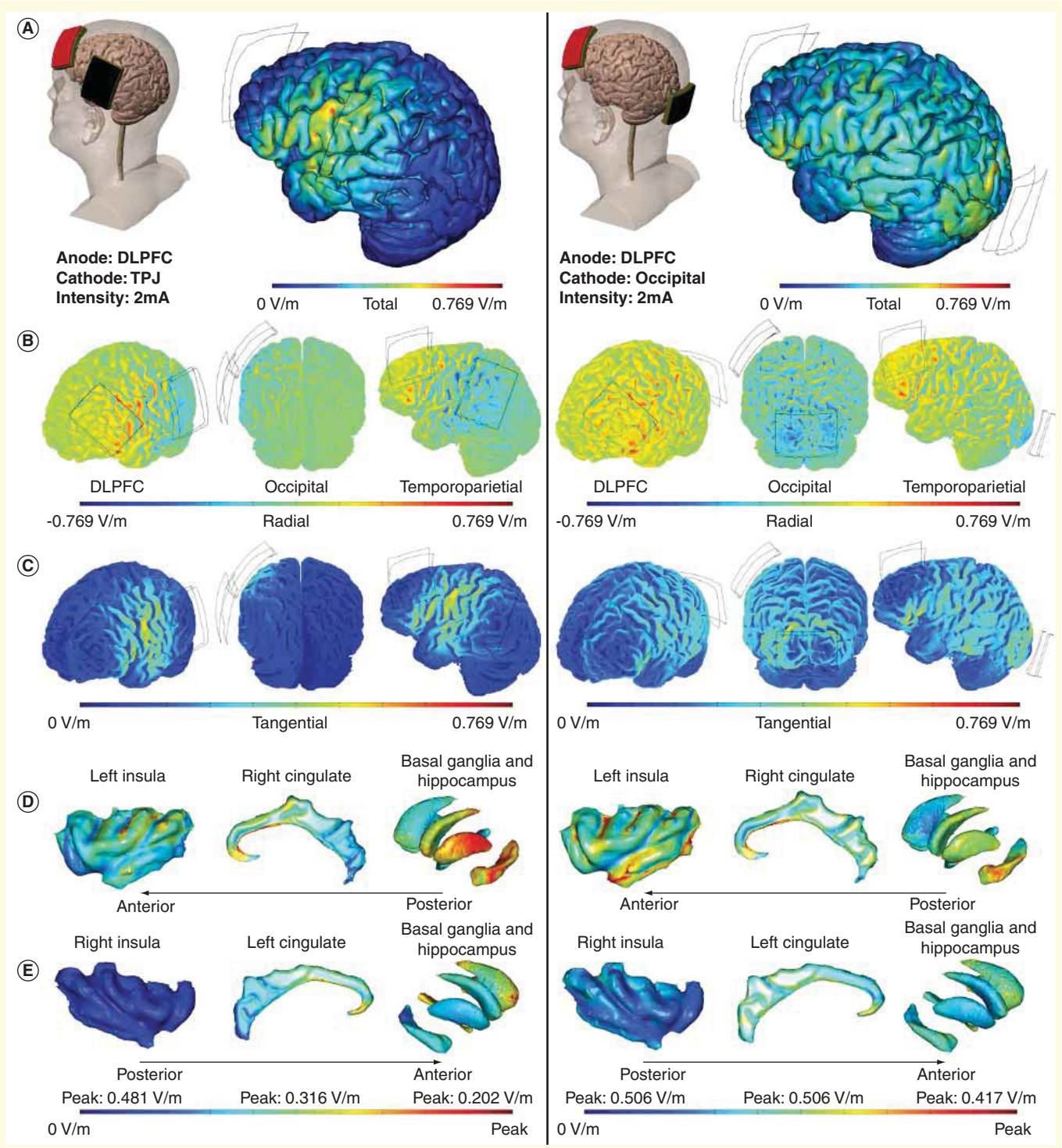

Figure 1. High-resolution computational models predict current flow during tDCS based on two commonly employed montages: anode over the left DLPFC and cathode over the left temporoparietal junction (left) or the occipital cortex (right). Rows describe **(A)** electric field magnitude, **(B)** electric field normal to the cortical surface, **(C)** electric field tangential to the cortical surface and **(D and E)** electric field in deeper cortical structures.
DLPFC: Dorsolateral prefrontal cortex; TPJ: Temporoparietal junction.

also found in other psychiatric and neurologic disorders [66] – is less understood, but it probably involves increased activity in the ventral occipito-temporal lobe [67]. Regarding rTMS, there are only two case reports using low-frequency rTMS over the occipital cortex (localized using anatomical references [68] and functional neuroimaging [69]), both describing amelioration of the visual symptoms.

A case report also described tDCS for the treatment of catatonia-related schizophrenia [43]. The prefrontal cortex seems to play a critical role in catatonia according to neuroimaging studies [70–72] and the observation that benzodiazepines might treat some catatonic symptoms by activating GABAergic neurons of this area [73]. Interestingly, the few rTMS cases for catatonia have also targeted the prefrontal areas [74–76], suggesting that this might be a suitable area for catatonia treatment, especially in the context of schizophrenia.

Regarding adverse effects, the reviewed studies described only mild adverse effects (with similar frequency in active vs sham groups) associated to tDCS such as tingling, itching and fatigue, similarly as observed in literature [30,77], thus demonstrating that tDCS was well tolerated also for patients with schizophrenia. Particularly, Andrade [46] performed, over a period of almost 3 years, once- to twice-daily tDCS sessions, describing only mild adverse effects during the entire treatment course.

Considering the time length of clinical benefits induced by tDCS, the RCT of Brunelin and colleagues [37] observed that the effects of tDCS persisted 3 months after the application of five consecutive tDCS sessions. In addition, the case reports of Homan *et al.* [39]. and Shiozawa *et al.* [43,44] reported long-lasting effects for 6 weeks to 4 months after 5–10 daily tDCS sessions. These studies suggest that even a relatively short course of tDCS sessions can induce relatively long-lasting clinical effects for both positive and negative effects. Conversely, Andrade [46] observed rapid deterioration of symptoms when the frequency of sessions (once- to twice-daily) was decreased. Due to the paucity of data, more trials are necessary to determine the predictors of maintained response for tDCS in schizophrenia.

Limitations

The present review has some limitations. First, most studies reviewed were case reports; therefore some of the clinical benefits could have occurred due to a placebo effect. Case reports are also particularly prone to publication bias, as negative findings are less likely to be published for this type of study. Nonetheless, we included these studies in our systematic review, considering that they are hypothesis-driven for further controlled trials and, although not providing robust evidence regarding tDCS effectiveness in schizophrenia, their findings are useful for designing future studies. We also included these studies considering one of our review aims that were to summarize available data to further perform computer modeling analyses.

Another limitation is that our tDCS computer modeling is not patient specific, and therefore the precise distribution of current flow is determined by individual idiosyncratic anatomy. Still, our aim was to verify whether the general assumptions regarding electrode positioning in schizophrenia would be corroborated in computer models.

Finally, much of the knowledge regarding the physiological basis of tDCS derives from within-subjects, single-session studies performed in healthy volunteers in whom the electrodes were placed over the motor cortex (for a review see Stagg and Nitsche [78]) – thus, it is unclear to what extent findings originated from these studies are transferable to other cortical areas, such as the left DLPFC and temporoparietal cortex, and to patients with neuropsychiatric disorders. For instance, Jacobson *et al.* [79] found, in a meta-analytic review, that the anodal-excitation/cathodal-inhibition effects of tDCS were generally found in neurophysiological studies evaluating motor areas, although the cathodal-inhibition effects were not ubiquitously observed in cognitive studies evaluating non-motor areas, possibly due to compensatory processes as complex cognitive functions are supported by wider brain networks. In fact, this notion reinforces the role of computational modeling and mechanistic studies when investigating non-motor montages and/or complex neuropsychiatric disorders such as schizophrenia.

Schizophrenia as a dysconnectivity disorder: the role of tDCS

Although the reviewed studies provide a useful framework indicating that cathodal stimulation would hyperpolarize the temporal cortex, inhibiting the auditory hallucinations, whereas anodal stimulation would increase DLPFC activity, ameliorating negative and cognitive symptoms, it should be noted that schizophrenia involves additional brain regions [80] and that anodal/cathodal tDCS is expected to have more complex effects on cortical activity than simply 'increasing/decreasing' excitability, modulates multiple regions through diffuse current flow and modulates the strength of connections between regions through synapse polarization [15,81].

Recent studies using resting-state MRI observed that patients with schizophrenia versus controls presented dysconnectivity of the frontoparietal network, which encompasses the DLPFC, temporoparietal regions and the basal ganglia [82] and also of the cingulo-opercular network, which involves cortico-striatal pathways and might be related to negative symptom severity and dopaminergic dysfunction [83]. Another evidence of impaired connectivity comes from measures of cortical motor excitability, which revealed impairment in inhibitory interhemispheric connections, a condition probably related to dysfunctions in glutamatergic and GABAergic activity [84].

In turn, hypo- and hyperpolarizing tDCS effects occur in different cell elements (e.g., soma, dendrites and axons) regardless of the type of stimulation and mainly dependent on the angle of the axis vis-à-vis electrode positioning – for current flow normal to the cortical surface, pyramidal neurons would be polarized (current flow parallel to the somatodendritic access), but for current flow tangential (along) the cortical surface afferent synaptic pathways would be polarized. Whereas the radial current flow is consistent with local changes in

doi: 10.1586/17434440.2014.911082

excitability, tangential flow implies changes in connectivity [15]. This implies that the tDCS montage mostly used for schizophrenia presents effects that occur in the frontoparietal network, not only leading to activation in the frontal areas and underactivation in the temporal areas but also to changes in synaptic connectivity in this network. In addition, while tDCS is often assumed to affect superficial cortical regions, reduced current intensities are evident in deeper structures. While the role of this deeper current flow in neurophysiological changes is not clear, they are implicated in the pathophysiological mechanisms of schizophrenia, and therefore part of the tDCS effects clinically observed could have occurred due to the modulation of these areas.

The two mechanisms hereby observed – local excitability changes by radial currents and synaptic changes induced by tangential currents – are also observed in *in vitro* and *in vivo* animal studies assessing tDCS mechanisms. The polarity-dependent effects of radial DCS has been observed in earlier animal studies [19,85,86], which is consistent with somatic membrane polarization by radial cortical electric current flow [15,18]. In fact, Rahman *et al.* [15] demonstrated, using rat cortical slices, that purely inward currents (relative to the cortical surface, without a tangential component) induced polarity-dependent changes in membrane excitability – that is, anodal DC facilitated and cathodal DC inhibited synaptic efficacy.

Notwithstanding, tDCS also generates tangential fields, which are in fact larger than the radial fields [15]. Although tangential fields do not polarize the somatic neuronal component [18,87], it influences axons and synaptic terminals [88]. Rahman *et al.* [15] also demonstrated that the direction of terminal polarization depends on the morphology of the afferent pathway. This finding, observed *in vitro*, should be further addressed in complex cortical structures with several types and morphologies of neurons. This means that the direction of the effects of tangential fields on synaptic efficacy, although not negligible, is not easily predictable and warrants further investigation.

Neurobiological aspects

The clinical effects of tDCS in schizophrenia can also be conceptualized in a neurobiological level, as tDCS influences the two basic mechanisms of synaptic plasticity, namely long-term depression (LTD) and long-term potentiation (LTP). Fritsch *et al.* [22] showed that anodal DCS over mouse M1 slices induces a long-lasting LTP mechanism, which is polarity- and NMDA-dependent. Moreover, this finding was not observed in mutant mice knocked-out for TrkB (BDNF receptor) and motor skill acquisition was impaired when the BDNF Val66Met polymorphism was present, suggesting that BDNF has a key role in this phenomenon. In another study, Ranieri *et al.* [89] further investigated the effects of anodal and cathodal DCS in the synapses between the CA3 and CA1 regions of the hippocampus (a well-studied model of synaptic plasticity). They found that anodal DC stimulation increased LTP, whereas cathodal stimulation reduced it.

Both LTP and LTD mechanisms are abnormal in schizophrenia. Hasan *et al.* [90] evaluated whether cathodal tDCS decreased motor cortical excitability in schizophrenia, compared to matched controls and in accordance with previous reports on healthy individuals [14]. They found that cathodal tDCS failed to decrease cortical excitability and also increase GABAergic and glutamatergic activity, which could be compensatory mechanisms to the abolished LTD-like plasticity. Also, Hasan *et al.* [91] found that patients with multiple psychotic episodes presented a significant deficient LTP-like plasticity, as significantly lower motor evoked potentials were elicited after anodal tDCS in this group, compared to healthy controls and patients with recent-onset schizophrenia.

In this context, the findings of our review suggested that cathodal tDCS over the temporoparietal area might have induced LTD-like phenomena, due to the decrease in auditory hallucinations, whereas anodal tDCS over the left DLPFC could have induced LTP-like phenomena, as some studies identified an improvement in negative symptoms. Although in apparent contrast with previous studies, it should be emphasized that tDCS clinical studies placed the electrodes in non-motor areas, and performed daily tDCS for several days.

Final remarks

The RCT, the case series and several case reports included in this systematic review positioned the anode over the left DLPFC and the cathode over the left temporoparietal area (based on hypoactivity and hyperactivity of these brain areas in schizophrenia, respectively), observing ameliorating of auditory hallucinations and, in some studies, improvement in negative symptoms as well. Computer models predicted underactivation and activation over the cathode and the anode, respectively, and also activation of cortical regions between these areas and, to a lesser extent, neuromodulation of deeper brain structures. Therefore, tDCS, by simultaneously modulating two distinct brain areas as well as connectivity between temporoparietal and prefrontal regions, might be an interesting neuromodulatory treatment tool for schizophrenia, a disorder in which dysconnectivity between several brain areas is observed. Further, the use of computer modeling techniques provides a framework to be applied in future studies exploring different tDCS montages in the treatment of positive and negative symptoms of schizophrenia.

Expert commentary

tDCS is a relatively novel non-pharmacological intervention that has been increasingly investigated in the treatment of mental disorders. tDCS has important advantages over other brain stimulation interventions, such as ease of use, portability, low cost and a benign profile of adverse effects. Its mechanisms of action in complex brain disorders, such as schizophrenia, are still elusive. We here reviewed the use of computed head modeling analysis to predict electric flow between electrodes according to the most commonly employed montages in schizophrenia. We identified that this computer simulation model is able to predict electric flow in several cortical and subcortical brain areas, aiding in the interpretation of clinical outcomes derived from RCTs. The use of computational

models of brain current flow can be also helpful in planning novel tDCS clinical trials in schizophrenia and other mental disorders.

Five-year view

Computational models of brain current flow are already being increasingly used to understand and optimize tDCS clinical trials. They might prove particularly useful for complex mental disorders that present functional impairment in several brain areas as to predict optimal positioning of the anode(s) and cathode(s) electrodes over the head. In 5 years, whether the use of these computational models becomes more readily accessible to clinical researchers (perhaps through open-source or web-based softwares), these tools will be broadly used in the design of tDCS trials. In addition, given the results presented in this study, we expect that tDCS will be increasingly used and tested for the treatment of schizophrenia.

Acknowledgements

The authors would like to thank the three anonymous reviewers for their comments and suggestions that significantly improved this manuscript.

Financial & competing interests disclosure

D Javitt is supported by NIMH grants R01MH049334 and P50MH086385. AR Brunoni was supported in part by the following grants: 2013 NARSAD Young Investigator from the Brain & Behavior Research Foundation (Grant Number 20493), 2013 FAPESP Young Researcher from the São Paulo State Foundation (Grant Number 20911-5) and National Council for Scientific and Technological Development (CNPq, Grant Number 470904). M Bikson has equity in Soteriz Medical Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Transcranial direct current stimulation (tDCS) is a non-pharmacological intervention that changes cortical excitability according to the parameters of stimulation. It has been increasingly used in the treatment of mental disorders, such as major depression and schizophrenia.
- An important question is to determine optimal anode (excitability-increasing) and cathode (excitability-decreasing) positioning. tDCS trials determine electrode positioning according to neuroimaging findings regarding brain activity, although this approach might be difficult to apply in complex mental disorders such as schizophrenia.
- We performed a systematic review of all clinical studies using tDCS for the treatment of schizophrenia. Based on these studies, we identified the tDCS montages mostly used in these studies and thereafter performed computer head modeling simulation to predict electric flow between electrodes.
- Predicted current flow between these areas corroborated the rationale excitability decreasing over the cathode and increasing over the anode, but also revealed that current flows normal to these cortical regions (therefore inducing changes in cortical excitability) and also tangential to these regions, leading to synaptic strengthening. Current also reaches the deep brain structures involved in the pathophysiology of schizophrenia.
- tDCS, by simultaneously modulating two distinct brain areas as well as connectivity between temporoparietal and prefrontal regions, might be an interesting neuromodulatory treatment tool for schizophrenia, a disorder in which dysconnectivity between several brain areas is observed.
- In addition, the use of computer modeling techniques provides a framework to be applied in future studies exploring different tDCS montages in the treatment of positive and negative symptoms of schizophrenia and also in other mental disorders.

References

1. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67-76
2. Wong AH, Van Tol HH. Schizophrenia: from phenomenology to neurobiology. Neurosci Biobehav Rev 2003;27(3):269-306
3. Andreasen NC. Symptoms, signs, and diagnosis of schizophrenia. Lancet 1995; 346(8973):477-81
4. Bensenor IM, Brunoni AR, Pilan LA, et al. Cardiovascular risk factors in patients with first-episode psychosis in Sao Paulo, Brazil. Gen Hosp Psychiatry 2012;34(3):268-75
5. Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry 2010;196(2):116-21
6. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;382(9896):951-62
7. Elkis H. Treatment-resistant schizophrenia. Psychiatr Clin North Am 2007;30(3): 511-33
8. Brunoni AR, Kobuti Ferreira LR, Gallucci-Neto J, et al. Lithium as a treatment of clozapine-induced neutropenia: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(8):2006-7
9. Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010;36(1):94-103
10. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of

doi: 10.1586/17434440.2014.911082

schizophrenia and the management of treatment resistance. World J Biol Psychiatry 2012;13(5):318-78

11. Slotema CW, Blom JD, van Lutterveld R, et al. Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. Biol Psychiatry 2013; Epub ahead of print
12. Shi C, Yu X, Cheung EF, et al. Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: a meta-analysis. Psychiatry Res 2014;215(3):505-13
13. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 2014;85 Pt 3:948-60
14. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633-9
15. Rahman A, Reato D, Arlotti M, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J Physiol 2013;591(Pt 10):2563-78
16. Batsikadze G, Moliadze V, Paulus W, et al. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;591(Pt 7): 1987-2000
17. Datta A, Bansal V, Diaz J, et al. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul 2009;2(4):201-7
18. Radman T, Ramos RL, Brumberg JC, Bikson M. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul 009;2(4): 215-28.228 e211-213
19. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 1965;28:166-85
20. Nitsche MA, Jaussi W, Liebetanz D, et al. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology 2004;29(8): 1573-8
21. Nitsche MA, Fricke K, Henschke U, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 2003;553(Pt 1):293-301
22. Fritsch B, Reis J, Martinowich K, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 2010;66(2):198-204
23. Favalli G, Li J, Belmonte-de-Abreu P, et al. The role of BDNF in the pathophysiology and treatment of schizophrenia. J Psychiatr Res 2012;46(1):1-11
24. Hasan A, Falkai P, Wobrock T. Transcranial brain stimulation in schizophrenia: targeting cortical excitability, connectivity and plasticity. Curr Med Chem 2013;20(3):405-13
25. Brunoni AR, Valiengo L, Baccaro A, et al. The Sertraline versus Electrical Current Therapy for Treating Depression Clinical Study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 2013; 70(4):383-91
26. Brunoni AR, Ferrucci R, Bortolomasi M, et al. Interactions Between Transcranial Direct Current Stimulation (tDCS) and Pharmacological Interventions in the Major Depressive Episode: findings from a naturalistic study. Eur Psychiatry 2013; 28(6):356-61
27. Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? Brain Stimul 2009;2(4):241-5
28. Ahdab R, Ayache SS, Brugieres P, et al. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. Neurophysiol Clin 2010;40(1):27-36
29. Westin GG, Bassi BD, Lisanby SH, Luber B. Determination of motor threshold using visual observation overestimates transcranial magnetic stimulation dosage: safety implications. Clin Neurophysiol 2014;125(1):142-7
30. Brunoni AR, Amadera J, Berbel B, et al. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011;14(8):1133-45
31. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008-39
32. Palm U, Hasan A, Keeser D, et al. Transcranial random noise stimulation for the treatment of negative symptoms in schizophrenia. Schizophr Res 2013; 146(1-3):372-3
33. Villamar MF, Wivatvongvana P, Patumanond J, et al. Focal modulation of the primary motor cortex in fibromyalgia using 4x1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. J Pain 2013;14(4):371-83
34. Wagner TA, Zahn M, Grodzinsky AJ, Pascual-Leone A. Three-dimensional head model simulation of transcranial magnetic stimulation. IEEE Trans Biomed Eng 2004; 51(9):1586-98
35. Gabriel C, Gabriel S, Corthout E. The dielectric properties of biological tissues: I. Literature survey. Phys Med Biol 1996; 41(11):2231-49
36. Mattai A, Miller R, Weisinger B, et al. Tolerability of transcranial direct current stimulation in childhood-onset schizophrenia. Brain Stimul 2011;4(4): 275-80
37. Brunelin J, Mondino M, Gassab L, et al. Examining Transcranial Direct-Current Stimulation (tDCS) as a Treatment for Hallucinations in Schizophrenia. Am J Psychiatry 2012;169(7):719-24
38. Nawani H, Bose A, Agarwal SM, et al. Modulation of Corollary Discharge Dysfunction in Schizophrenia by tDCS: preliminary Evidence. Brain Stimul 2014; Epub ahead of print
39. Homan P, Kindler J, Federspiel A, et al. Muting the voice: a case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. Am J Psychiatry 2011; 168(8):853-4
40. Rakesh G, Shivakumar V, Subramaniam A, et al. Monotherapy with tDCS for Schizophrenia: a case report. Brain Stimul 2013;6(4):708-9
41. Nawani H, Kalmady SV, Bose A, et al. Neural Basis of tDCS effects on auditory verbal hallucinations in schizophrenia: a case report evidence for cortical neuroplasticity modulation. J ECT 2014;30(1):e2-4
42. Shivakumar V, Bose A, Rakesh G, et al. Rapid improvement of auditory verbal hallucinations in schizophrenia after add-on treatment with transcranial direct-current stimulation. J ECT 2013;29(3):e43-4
43. Shiozawa P, da Silva ME, Cordeiro Q, et al. Transcranial direct current stimulation (tDCS) for catatonic schizophrenia: a case study. Schizophr Res 2013;146(1-3):374-5
44. Shiozawa P, da Silva ME, Cordeiro Q, et al. Transcranial Direct Current Stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations

in schizophrenia: a case study. Brain Stimul 2013;6(5):831-3

45. Palm U, Keeser D, Blautzik J, et al. Prefrontal transcranial direct current stimulation (tDCS) changes negative symptoms and functional connectivity MRI (fcMRI) in a single case of treatment-resistant schizophrenia. Schizophr Res 2013;150(2-3):583-5
46. Andrade C. Once- to twice-daily, 3-year domiciliary maintenance transcranial direct current stimulation for severe, disabling, clozapine-refractory continuous auditory hallucinations in schizophrenia. J ECT 2013;74(11):e1054-8
47. Bikson M, Inoue M, Akiyama H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol 2004;557(Pt 1): 175-90
48. Busatto GF. Structural and Functional Neuroimaging Studies in Major Depressive Disorder With Psychotic Features: a Critical Review. Schizophr Bull 2013;39(4):776-86
49. van Haren NE, Schnack HG, Cahn W, et al. Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry 2011;68(9):871-80
50. Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res 2009; 108(1-3):3-10
51. Potkin SG, Turner JA, Brown GG, et al. Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study. Schizophr Bull 2009;35(1):19-31
52. Kuhn S, Gallinat J. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr Bull 2013;39(2):358-65
53. Andreasen NC, O'Leary DS, Flaum M, et al. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 1997; 349(9067):1730-4
54. Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophr Res 2009; 108(1-3):11-24
55. Dlabac-de Lange JJ, Knegtering R, Aleman A. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. J Clin Psychiatry 2010;71(4):411-18
56. Fregni F, Boggio PS, Nitsche M, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005; 166(1):23-30
57. Oliveira JF, Zanao TA, Valiengo L, et al. Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neurosci Lett 2013;537:60-4
58. Barr MS, Farzan F, Rajji TK, et al. Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. Biol Psychiatry 2013;73(6):510-17
59. Prikryl R. Repetitive transcranial magnetic stimulation and treatment of negative symptoms of schizophrenia. Neuro Endocrinol Lett 2011;32(2):121-6
60. Demeulemeester M, Amad A, Bubrovszky M, et al. What is the real effect of 1-Hz repetitive transcranial magnetic stimulation on hallucinations? Controlling for publication bias in neuromodulation trials. Biol Psychiatry 2012;71(6):e15-16
61. Suddath RL, Casanova MF, Goldberg TE, et al. Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. Am J Psychiatry 1989;146(4):464-72
62. Dierks T, Linden DE, Jandl M, et al. Activation of Heschl's gyrus during auditory hallucinations. Neuron 1999;22(3):615-21
63. Homan P, Kindler J, Hubl D, Dierks T. Auditory verbal hallucinations: imaging, analysis, and intervention. Eur Arch Psychiatry Clin Neurosci 2012; 262(Suppl 2):S91-5
64. Olabi B, Ellison-Wright I, McIntosh AM, et al. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiatry 2011;70(1):88-96
65. Bracha HS, Wolkowitz OM, Lohr JB, et al. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. Am J Psychiatry 1989;146(4):526-8
66. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain 1998;121(Pt 10):1819-40
67. Muller PA, Pascual-Leone A, Rotenberg A. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with pathologic positive sensory phenomena: a review of literature. Brain Stimul 2012; 5(3):320-9.e327
68. Merabet LB, Kobayashi M, Barton J, Pascual-Leone A. Suppression of complex visual hallucinatory experiences by occipital transcranial magnetic stimulation: a case report. Neurocase 2003;9(5):436-40
69. Meppelink AM, de Jong BM, van der Hoeven JH, van Laar T. Lasting visual hallucinations in visual deprivation; fMRI correlates and the influence of rTMS. J Neurol Neurosurg Psychiatry 2010;81(11): 1295-6
70. Northoff G, Kotter R, Baumgart F, et al. Orbitofrontal cortical dysfunction in akinetic catatonia: a functional magnetic resonance imaging study during negative emotional stimulation. Schizophr Bull 2004; 30(2):405-27
71. Northoff G, Steinke R, Nagel DC, et al. Right lower prefronto-parietal cortical dysfunction in akinetic catatonia: a combined study of neuropsychology and regional cerebral blood flow. Psychol Med 2000;30(3):583-96
72. Scheuerecker J, Ufer S, Kapernick M, et al. Cerebral network deficits in post-acute catatonic schizophrenic patients measured by fMRI. J Psychiatr Res 2009;43(6):607-14
73. Richter A, Grimm S, Northoff G. Lorazepam modulates orbitofrontal signal changes during emotional processing in catatonia. Hum Psychopharmacol 2010; 25(1):55-62
74. Saba G, Rocamora JF, Kalalou K, et al. Catatonia and transcranial magnetic stimulation. Am J Psychiatry 2002;159(10): 1794
75. Kate MP, Raju D, Vishwanathan V, et al. Successful treatment of refractory organic catatonic disorder with repetitive transcranial magnetic stimulation (rTMS) therapy. J Neuropsychiatry Clin Neurosci 2011;23(3): E2-3
76. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Catatonia treated with transcranial magnetic stimulation. Am J Psychiatry 1998;155(11):1630
77. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007;72(4-6): 208-14
78. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17(1):37-53
79. Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2012;216(1):1-10
80. Busatto GF, Kerwin RW. Schizophrenia, psychosis, and the basal ganglia. Psychiatr Clin North Am 1997;20(4):897-910
81. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS):

doi: 10.1586/17434440.2014.911082

challenges and future directions. Brain Stimul 2012;5(3):175-95

82. Tu PC, Lee YC, Chen YS, et al. Schizophrenia and the brain's control network: aberrant within- and between-network connectivity of the frontoparietal network in schizophrenia. Schizophr Res 2013;147(2-3):339-47
83. Tu PC, Hsieh JC, Li CT, et al. Cortico-striatal disconnection within the cingulo-opercular network in schizophrenia revealed by intrinsic functional connectivity analysis: a resting fMRI study. Neuroimage 2012;59(1):238-47
84. Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Cortical Inhibition, Excitation, and Connectivity in Schizophrenia: a Review of Insights From Transcranial Magnetic Stimulation. Schizophr Bull 2013; Epub ahead of print
85. Creutzfeld D, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neural 1962;5:436-52
86. Jefferys JG. Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices. J Physiol 1981;319: 143-52
87. Bikson M, Radman T, Datta A. Rational modulation of neuronal processing with applied electric fields. Conf Proc IEEE Eng Med Biol Soc 2006;1:1616-19
88. Basser PJ, Roth BJ. New currents in electrical stimulation of excitable tissues. Annu Rev Biomed Eng 2000;2:377-97
89. Di Lazzaro V, Manganelli F, Dileone M, et al. The effects of prolonged cathodal direct current stimulation on the excitatory and inhibitory circuits of the ipsilateral and contralateral motor cortex. J Neural Transm 2012;119(12):1499-506
90. Hasan A, Nitsche MA, Herrmann M, et al. Impaired long-term depression in schizophrenia: a cathodal tDCS pilot study. Brain Stimul 2012;5(4):475-83
91. Hasan A, Nitsche MA, Rein B, et al. Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by transcranial direct current stimulation. Behav Brain Res 2011;224(1):15-22