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Transcranial Direct Current Stimulation for the Treatment of Refractory Symptoms of Schizophrenia. Current Evidence and Future Directions

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Abstract: Schizophrenia is a severe and frequent neuropsychiatric disorder. Despite antipsychotic medications, up to 30% of patients with schizophrenia still report disabling treatment-resistant symptoms. Transcranial direct current stimulation (tDCS) has been proposed as a novel method to alleviate such symptoms. Here, we review studies investigating the effects of tDCS on symptoms, cognition, brain activity and cortical plasticity in patients with schizophrenia. We provide an up-to-date and comprehensive overview of the use of tDCS in patients with schizophrenia. More specifically, we first present the effects of tDCS on treatment-resistant symptoms of schizophrenia. We report that tDCS applied over the frontotemporal regions reduced auditory hallucinations, with a mean 34% reduction of symptoms. Moreover, tDCS applied over both prefrontal cortices reduced negative symptoms and catatonia. We discuss the need for further sham-controlled studies to confirm these effects. Second, we present the impact of tDCS on cognitive functions in patients with schizophrenia. Positive effects of tDCS have been reported on learning, working memory, attention and source-monitoring. Third, we review the effects of tDCS on brain activity in patients with schizophrenia. Although only few studies investigated the effects of tDCS using neuroimaging technics, these studies are helpful at identifying the mechanisms of action of tDCS in schizophrenia. Fourth, we present tDCS studies on cortical plasticity showing reduced cortical plasticity in patients with schizophrenia that tDCS may beneficially modulate. Lastly, we discuss the safety aspects of tDCS in patients with schizophrenia and potential directions to improve efficacy for this clinical populations.

Keywords: Schizophrenia, transcranial direct current stimulation, tDCS, auditory hallucinations, negative symptoms, cognition.

INTEREST OF tDCS IN PATIENTS WITH SCHIZOPHRENIA

Schizophrenia is one of the most disabling and devastating illnesses worldwide occurring in about 1% of the general population. The clinical expression of the illness is highly heterogeneous. Symptoms have been classified into five main dimensions: positive (e.g., delusion, hallucinations), negative (e.g., avolition, alogia, emotional withdrawal), disorganization, anxiety/depression, and grandiosity/excitement [1]. Despite some advances in psychopharmacology, up to 30% of individuals with schizophrenia still report symptoms even when treated with antipsychotic medication [2, 3]. The most reported refractory symptoms are auditory hallucinations and negative symptoms. These treatment-resistant symptoms increase distress and negatively impact social integration, which greatly disrupt patient's quality of life. They are also associated with high risk of full-blown relapses and greater number of hospitalization episodes, leading to a pejorative prognosis and costly medico-economic impact. There is thus a need for developing novel alternative approaches to alleviate these treatment-resistant symptoms. One potential non-pharmacological approach is transcranial Direct Current Stimulation (tDCS). It is a relatively novel approach that can safely modulate brain activity *in vivo* in humans and holds clinical promises to reduce symptoms in patients with neuropsychiatric disorders such as major depression [4, 5]. The objective of this review is to summarize and discuss results on the effects of tDCS on symptoms, cognition, brain activity and cortical plasticity in patients with schizophrenia, as well as to provide a detailed and comprehensive overview of the current state of the art and future applications of tDCS in schizophrenia.

General Overview of tDCS

tDCS was investigated in the 1960s and 1970s and was called "brain polarization" (for a review see [6]). Early animal studies showed that applying a polarizing current to the cerebral cortex modulates neuronal firing and the size of evoked potentials. Surface-positive current enhanced evoked potentials, whereas surface-negative current reduced both firing and evoked potentials [7]. These effects were related to a polarization-induced shift of resting membrane-potentials towards de- or hyperpolarization [8]. This brain polarization approach was also tested in humans including patients with major depression and patients with schizophrenia. However, the use of tDCS lost its momentum mainly due to mixed obtained results, probably due to non-optimized stimulation parameters and compelling development of psychopharmacotherapy during this period.

tDCS was reappraised in the turn of the century, with seminal studies by Priori *et al.* [9] and Nitsche and Paulus [10].

tDCS is now used as a technique inducing weak electric currents (classically 1 or 2 mA during 20 or 30 minutes) through two electrodes placed over the scalp [10-13]. The current flows from the anode (positive electrode) to the cathode (negative electrode). The neural effects of tDCS can outlast the stimulation period and be observed within the brain regions under the electrodes as well as in larger network interconnected with the targeted regions [14]. For instance, anodal tDCS applied over the primary motor cortex can enhance motor evoked potentials, whereas cathodal tDCS can re-

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duce them [6, 10, 11]. tDCS applied over the primary motor cortex [15, 16] and the prefrontal cortex [17] can also induce cortical and subcortical changes. Further, anodal tDCS applied over the left prefrontal cortex can modulate functional connectivity of large resting state networks including the Default Mode Network [14]. Importantly, tDCS allows researchers to conduct clinical trials with sham-controlled condition. Sham protocols consist of delivering active stimulation during the first 30 seconds of the tDCS session [18] or to deliver a brief period (less than 60 seconds) of active stimulation followed by no current stimulation during the remaining time of the tDCS session [19]. Other tDCS characteristics such as low rate of side effects make allow reliable blinding of active versus sham tDCS conditions. There is however some side effects that are more often observed with active than sham stimulation (e.g. redness under the anode) [20]. Finally, the use of automated devices delivering active and sham protocols without the awareness of the tDCS operator optimizes the integrity of the blinding.

General Overview of tDCS in Schizophrenia

Protocols of tDCS in patients with schizophrenia have been mostly based on neuroimaging literature reporting impaired brain functions. Main findings include fronto-temporal dysconnectivity [21] and hyperactivity in the left temporoparietal region during auditory hallucinations [22], as well as abnormalities in the prefrontal cortices that have been associated with negative symptoms [23]. Based on these lines of work, two tDCS protocols have been proposed to reduce treatment-resistant auditory hallucinations and negative symptoms. One electrode montage tests the hypothesis that anodal tDCS over the left prefrontal cortex (presumably hypoactive) combined with cathodal tDCS over the left temporoparietal junction (presumably hyperactive) alleviates auditory hallucinations and reduces negative dimension [24]. The other electrode montage tests the hypothesis that bi-frontal tDCS with the anode placed over the left prefrontal cortex and the cathode over the right supraorbital region reduces negative symptoms [25]. Results from these electrode montages are discussed in the following sections.

CURRENT DATA OF TDCS IN PATIENTS WITH SCHIZOPHRENIA

A literature review was conducted on PubMed database with "tDCS" AND "schizophrenia" as keywords from the first date available until December 2014 (please see Fig. **1** for the Flowchart). This search resulted in 45 peer-reviewed publications and was completed by a manual search on ScienceDirect database yielding 7 new publications. Reviews, studies evaluating other conditions than schizophrenia and studies not dealing with tDCS were excluded, leading to 32 articles on the use of tDCS in patients with schizophrenia. Among these 32 articles, most studied the clinical effects of tDCS on auditory hallucinations and/or negative symptoms and some articles investigated the impact of tDCS on cognitive functions, brain activity and cortical plasticity.

Effects of tDCS on Symptoms (Table I)

Most studies investigating the clinical effect of tDCS in schizophrenia focused on treatment-resistant auditory hallucinations targeting the fronto-temporal network. These studies delivered 10 sessions of tDCS at an intensity of 2 mA for 20 minutes using 7*5 cm (35 cm²) electrodes with the center of the anode placed over the left prefrontal cortex (F3 or between F3 and FP1) and the cathode over the left temporoparietal junction (between T3 and P3) based on the 10/20 international EEG system (Fig. **2**).

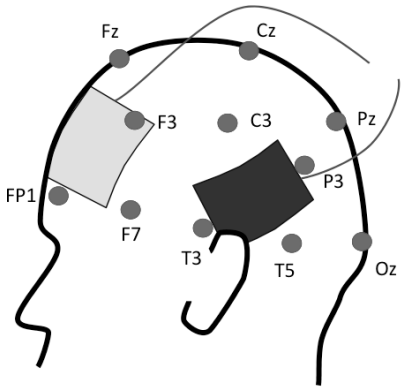

Fig. (2). Electrode montage of the fronto-temporal tDCS protocol used in Brunelin *et al.* [26]. The anode (in grey) is placed over the left prefrontal cortex between the F3 and FP1 of the 10/20 international EEG electrode placement system; and the cathode (in black) is placed at the left temporoparietal junction, between the T3 and P3.

In the first double blind randomized sham controlled trial, Brunelin *et al.* (2012) reported a significant decrease of treatment-resistant auditory hallucinations of 30% following active fronto-temporal tDCS as compared to sham tDCS [26]. Ten tDCS sessions were delivered twice daily on five consecutive days in 30 patients with schizophrenia. Auditory hallucinations were assessed using the Auditory Hallucination Rating Scale (AHRS) [27]. Reduction of auditory hallucinations was associated with a significant 13% reduction of general symptoms as assessed by the Positive and Negative Syndrom Scale (PANSS). The effect of tDCS on auditory hallucinations remained significant 3 months after the tDCS regimen

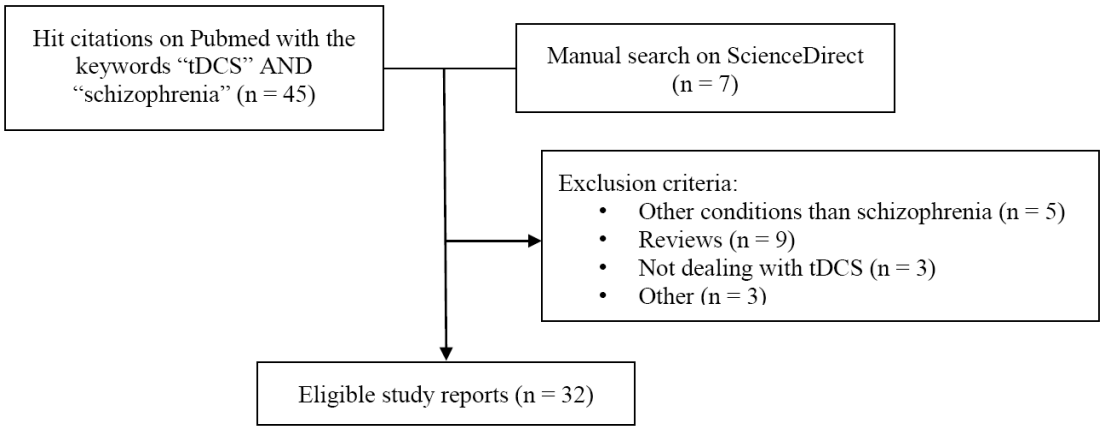

Fig. (1). Flow chart depicting the selection process for studies included in the review.

[26]. These results were replicated in two open labeled studies and 12 case-reports with similar 30% reduction of auditory hallucinations [28, 29] (see Table **I**). Three of the 12 case-reports observed complete remission of auditory hallucinations after patients received tDCS [30-32]. Moreover, two case studies reported efficacy and safety of maintenance tDCS sessions [32, 33]. Andrade (2013) found clinical improvement in a patient with clozapine-resistant symptoms who received daily or twice daily tDCS sessions for 3 years [33]. However, attempts to reduce the number of tDCS sessions resulted in rapid relapse of symptoms. Shivakumar *et al.* (2014) also reported a case of complete remission of auditory hallucinations of a patient who received 10 sessions of tDCS over 5 consecutive days [32]. Three months later the patient relapsed, and then two maintenance sessions were delivered during a single day, leading to a sustained reduction of auditory hallucinations. Additional maintenance sessions were subsequently delivered every 3 months for 7 months resulting in sustained clinical improvement for one year. Remarkably, among studies reporting alleviated auditory hallucinations, some observed a decrease in general symptoms of schizophrenia [24, 26, 33, 34], negative symptoms [24, 26, 28, 35] and insight into the illness [29-31].

Negative findings have also been published. A randomized sham controlled study failed to report clinical effects of active tDCS as compared to sham tDCS on auditory hallucinations in 24 patients with schizophrenia [36]. Fifteen tDCS sessions were delivered once a day during 3 consecutive weeks. Each patient received either the left fronto-temporal electrode montage (with the anode over F3 and the cathode over the T3-P3) or the bilateral fronto-temporal electrode montage (with two anodes over F3 and F4 and two cathodes over T3-P3 and T4-P4).

In sum, the articles reviewed here on auditory hallucinations used the fronto-temporal tDCS montage. A total of 80 patients with schizophrenia received active stimulation and the mean reported effect on auditory hallucinations was 34%. A total of 40 patients received sham tDCS and the mean effect on auditory hallucinations was 6%. Thus, results are encouraging but further sham-controlled studies on acute and long-term effects of fronto-temporal tDCS on auditory hallucinations are needed.

Visual hallucinations were also investigated. Shiozawa *et al.* (2013) observed a reduction in severity of visual hallucinations as well as auditory hallucinations in a patient with schizophrenia [37]. The patient received 10 sessions with the anode over F3 and the cathode over the occipital region (Oz) followed by 10 sessions with the anode over F3 and the cathode over the temporoparietal cortex (T3-P3).

Other symptoms of schizophrenia have been studied with tDCS. For instance, Palm *et al*. (2013) reported that tDCS with the anode placed over the left prefrontal cortex (F3) and the cathode electrode placed over the right supraorbital region (FP2) reduced treatment-resistant negative and positive symptoms in a patient with schizophrenia [25]. A randomized sham controlled trial with 20 patients with negative symptoms who received active or sham tDCS was conducted [38]. tDCS was delivered once a day for 10 consecutive days. Active as compared to sham tDCS decreased negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) and general symptoms as assessed by the PANSS. These beneficial clinical effects were maintained at the 2-week follow-up period. Finally, Shiozawa *et al.* (2013) conducted a case study in a patient suffering from medication- and electroconvulsive therapy-resistant catatonic schizophrenia [39]. The patient received 10 sessions with the anode over F3 coupled with the cathode over F4. The authors reported reduced severity of catatonic symptoms after the end of the tDCS regimen. Moreover, there was a complete remission from 30 to 120 days after the end of the tDCS regimen [39].

Effects of tDCS on Cognition (Table II)

Several studies reported that tDCS can improve cognitive processes in healthy volunteers (e.g., [40]). Some of these cognitive processes are known to be impaired in schizophrenia. This line of work has yielded scientists to explore whether tDCS may also improve cognitive functions in patients with schizophrenia. Among the 32 articles reviewed here, five investigated the effects of tDCS on associative learning, working memory, spatial attention and source-monitoring in patients with schizophrenia (see Table **II**).

In the first study, Vercammen *et al.* (2011) [41] investigated the effects of a single session of tDCS on probabilistic association learning in 20 patients with schizophrenia. They applied the anode over F3 and the cathode over FP2. Probabilistic association learning was defined as the ability to implicitly learn an association between a cue and an outcome. This process has been repeatedly reported impaired in schizophrenia. The authors found no significant effect of active tDCS as compared to sham tDCS on probabilistic association learning. They however found that active tDCS had a facilitating effect in a sub-group of patients with schizophrenia, those who displayed the best learning abilities before stimulation [41].

In another study, Hoy *et al*. (2014) [42] showed beneficial effect of the same electrode montage (anode over F3 coupled with the cathode over the FP2) on working memory in 18 patients with schizophrenia. They found that active as compared to sham tDCS improved working memory. These effects last up to 40 minutes after the end of the stimulation period. Another study investigated verbal memory in 14 patients with schizophrenia using transcranial slow oscillatory stimulation (so-tDCS) during sleep. Göder *et al*. (2013) [43] delivered a sinusoidal current at a frequency of 0.75 Hz at intensity of 0.3 mA during phase 2 of sleep. The electrodes (8 cm^2) were placed over both F3 and F4 and both mastoids. Patients better retained verbal information after active than sham stimulation.

Ribolsi *et al*. (2013) [44] investigated the effects of tDCS on visuospatial attention, more specifically on pseudo-neglect [45]. Pseudo-neglect can be tested with a bisection task in which subjects are invited to mark the middle of a series of horizontal lines. Healthy subjects typically display pseudo-neglect as shown by a preference for the left part of horizontal lines. This pseudo-neglect indicates a predominant role of the right hemisphere, especially of the right posterior parietal cortex, in visuospatial attention. Patients with schizophrenia do not tend to show this left sided preference, but instead display a right-sided preference. This has been proposed to reflect that the right posterior parietal cortex is impaired in schizophrenia. Interestingly, a single session of tDCS with the anode over the right parietal (P4) and cathode over the left shoulder reduced this right-sided bias [44].

Finally, one double-blind sham-controlled study tested the effects of tDCS on source-monitoring in 28 patients with schizophrenia suffering from treatment-resistant auditory hallucinations [46]. Source-monitoring was defined as the ability to discriminate between internally generated words and externally produced words. The anode was placed over F3 and the cathode over the T3-P3. Patients were better at recognizing internally generated words after active than sham tDCS. In addition, frequency of treatment-resistant auditory hallucinations was reduced. Finally, increased recognition of internally generated words was negatively correlated with reduced frequency of auditory hallucinations.

In sum, tDCS may improve cognitive functions in schizophrenia however the number of studies remains limited. Future studies using tDCS in schizophrenia should integrate both clinical and cognitive outcomes.

Effects of tDCS on Brain Activity

The mechanisms of action of tDCS in schizophrenia have yet to be identified. Until now, only few studies investigated the effects of

Table I. Clinical effects of tDCS in patients with schizophrenia.

STUDY							tDCS PARAMETERS					RESULTS
Author Date	**Design**	**n**	**Age (years)**	**Sex**	**Medication (mg/day)**	**Scale**	**Anode/ Cathode**	**Electrode Size (cm²)**	**n session (n/day)**	**I (mA)**	**Duration (min)**	
Clinical interest of fronto-temporal tDCS for auditory hallucinations												
Homan *et al*. 2011 [34]	Case	1	44	M	Haloperidol: 5 Olanzapine: 20	PANSS HCS	FP2/ T3P3	35	10 (1/d)	1	15	Reduction of AH (-60 %) and general symptoms (-20 %). Reduction of rCBF in the TPJ. Clinical improvement maintained at 6-weeks follow-up.
Brunelin *et al*. 2012 [26]	RCT parallel	30 (15 A/ 15 S)	37.7	22M 8F	Cpz eq: 1101 (SD 856)	PANSS AHRS/HCS	F3FP1/ T3P3	35	10 (2/d)	2	20	Reduction of AH (-31 %) and general symptoms (-13 %). Sustained effect at 1 and 3 months.
Brunelin *et al*. 2012 [24]	Case	2	37.5	M	Cpz eq: Patient 1: 1245 Patient 2: 900	PANSS AHRS/HCS	F3FP1/ T3P3	35	10 (2/d)	2	20	Reduction of AH (Patient 1: -77 %; Patient 2: -48 %) and general symptoms (Patient 1: -20 %; Patient 2: -49 %). Sustained effect at 1 and 3 months.
Rakesh *et al*. 2013 [30]	Case	1	24	M	Drug free	AHRS	F3FP1/ T3P3	35	10 (2/d)	2	20	Complete remission of AH. Improvement in insight into the illness.
Shivakumar *et al*. 2013 [31]	Case	1	28	F	Risperidone: 6 Trihexyphenidyl: 4 Clonazepam: 1 Aripriprazole: 5 started after 2 sessions	AHRS IRS	F3FP1/ T3P3	35	10 (2/d)	2	20	Complete remission of AH. Improvement in insight into the illness. Near-total improvement of symptoms at 4-week follow-up (global assessment functioning score of 90).
Shiozawa *et al*. 2013 [37]	Case	1	31	M	Clozapine: 900	PANSS	F3/Oz F3/T3P3	35	10 (1/d) 10 (1/d)	2	20	Reduction of visual and auditory hallucinations (-20 %). Reduction of positive symptoms.
Andrade 2013 [33]	Case	1	24	F	Clozapine: 200-300 Fluoxetine: 20 Aripiprazole: 15 during mainte-nance	Clinical rating	F3/ T3P3	25	1 to 2/d for 3 years	1 to 3	20-30	At home tDCS during 3 years. Reduction of AH and general symptoms.
Nawani *et al*. 2014 [62]	Case	1	31	M	Clozapine: 400 Amisulpride: 800	AHRS	F3/ T3P3	35	10 (2/d)	2	20	Reduction of AH (-30 %). Enhancement of cortical neuroplasticity
Nawani *et al*. 2014 [47]	Case	5	33.2	2M 3F	Cpz eq: 483.3 (SD 189.5)	AHRS	F3FP1/ T3P3	35	10 (2/d)	2	20	Reduction of AH (-30 %). Modulation of corollary discharge dysfunction.

(Table 1) Contd….

STUDY							tDCS PARAMETERS					RESULTS
Author Date	**Design**	**n**	**Age (years)**	**Sex**	**Medication (mg/day)**	**Scale**	**Anode/ Cathode**	**Electrode Size (cm^2)**	**n session (n/day)**	**I (mA)**	**Duration (min)**	
Bose *et al*. 2014 [29]	Open	21	33.1	9M 12F	Cpz eq: 718.7 (SD 354.2)	PSYRATS SAI	F3FP1/ T3P3	35	10 (2/d)	2	20	Reduction of AH (-32.7 %). Increase in insight (-156 %). Correlation between both.
Ferrucci *et al*. 2014 [28]	Open	6	41 to 66	ND	ND	PANSS CAPS	F3FP1/ T3P3	ND	10 (2/d)	2	20	Reduction of AH (frequency: -33 %; distress: -40 %) and negative symptoms (-24 %).
Shivakumar *et al*. 2014 [32]	Case	1	42	F	Haloperidol: 20 Iloperidone: 18 Trihexyphenidyl: 16 Levothyroxine: 100 Fluoxetine: 40	PSYRATS	F3FP1/ T3P3	35	10	2	20	Complete remission of AH for 1 year. Beneficial effect was maintained with 2 sessions at relapse.
Fitzgerald *et al*. 2014 [36]	RCT	24	39.3	15M 9F	ND	PANSS SANS	F3/T3P3 (N=11) / F3+F4/T3P3+T4P4 (N=13)	35	15 (1/d)	2	20	No significant reduction of AH (unilateral: -17 %; bilateral: -14 %) compared to sham (-7 % ; -3%). No effect on other symptoms.
Narayanaswamy *et al*. 2014 [35]	Case	1	22	F	Trifluoperazine: 15 Triheyphenidyl: 1	AHRS SANS	F3FP1/ T3P3	35	10 (2/d)	2	20	Sustained reduction of AH and negative symptoms.
Clinical interest of bi-frontal montage for other symptoms												
Shiozawa *et al*. 2013 [39]	Case	1	65	F	Clozapine: 400	BFS	F3/ F4	35	10 (1/d)	2	20	Reduction of catatonic symptoms until complete remission (4 months after tDCS sessions).
Palm *et al*. 2013 [25]	Case	1	19	M	Olanzapine: 20	PANSS	F3/ FP2	35	10 (1/d)	2	20	Reduction of negative and positive symptoms.
Palm *et al*. 2014 [38]	RCT parallel	20 (10 A / 10 S)	36.1	15M5F	Cpz eq: 520.1 (SD 264.1)	PANSS SANS	F3/ FP2	35	10 (1/d)	2	20	Reduction of negative and positive symptoms.
Safety and tolerability studies												
Mattai *et al*. 2011 [66]	RCT	12	15.4	5M 7F	At least Clozapine: 200	SAPS	FP1 & FP2 or T3 & T4	25	10 (1/d)	2	20	Safety and tolerability of tDCS, no symptoms worsening.
Shiozawa *et al*. 2013 [68]	Case	1	31	M	ND	Safety	F3/Oz	25	10 (1/d)	1.5	20	Safety and tolerability of tDCS in patients with comorbid vitiligo.

(Table 1) Contd….

STUDY							tDCS PARAMETERS					RESULTS
Author Date	**Design**	**n**	**Age (years)**	**Sex**	**Medication (mg/day)**	**Scale**	**Anode/ Cathode**	**Electrode Size (cm²)**	**n session (n/day)**	**I (mA)**	**Duration (min)**	
Shenoy *et al*. 2015 [67]	Case	1	25	F	Iloperidone: 12	PSYRATS + sonography	F3FP1/ T3P3	35	10 (2/d)	2	20	Safety and tolerability during pregnancy. Reduction of AH (-25 %; and -95 % 4 months after tDCS sessions).
Clinical interest of tRNS (100 -640 Hz)												
Palm *et al*. 2013 [72]	Case	1	29	M	Clozapine: 150 Haloperidol: 10 Lamotrigine: 200 Pregabaline: 375	PANSS SANS	F3/ FP2	35	20	2	20	Reduction of negative symptoms, disorganization and depression/anxiety.
Haesebaert *et al*. 2014 [73]	Case	1	26	F	Drug free	PANSS SANS	F3FP1/ T3P3	35	10 (2/d)	2	20	Reduction of AH and increase in insight.

A: active; S: sham; AH: Auditory Hallucinations; AP: antipsychotic medication; I: Intensity; Cpz eq: Chlorpromazine equivalent dose; M: Male; F: female; n: number of subjects; ND: Not done; RCT: Randomized controlled trial; tDCS: transcranial Direct Current Stimulation.

Scales: AHRS: Auditory Hallucination Rating Scale; HCS: Hallucination Change Score; PANSS: Positive and Negative Syndrome Scale; SAI: Schedule for Assessment of Insight (David, 1990); CAPS: Cardiff Anomalous Perceptions Scale; BFS: Bush Francis Scale.

Electrodes placement according to 10/20 EEG system: F3: left Dorsolateral Prefrontal Cortex; F4: right Dorsolateral Prefrontal Cortex; FP2: right supraorbital region; FP1: left supra-orbital region; T3P3: left temporo-Parietal junction; T3: left temporal region (10/20 EEG system); T4: right temporal region.

Table II. Cognitive effects of tDCS in patients with schizophrenia.

STUDY							tDCS PARAMETERS					RESULTS
Author Date	**Design**	**n**	**Age (years)**	**Sex**	**Medication (mg/day)**	**Scale**	**Anode/ Cathode**	**Electrode Size (cm²)**	**n session (n/day)**	**I (mA)**	**Duration (min)**	
Vercammen *et al*. 2011 [41]	Cross-over	20	37.6	10M 10F	Cpz eq: 898 (SD 817)	Probabilistic learning (WPT)	F3/ FP2	35	1	2	20	No tDCS effects on the whole sample. Adequate performers at baseline showed a significant improvement of their performances.
Ribolsi *et al*. 2013 [44]	Cross-over	15	34.3	11M 4F	ND	Spatial pseudo neglect (Line Bissection)	P3 or P4/ contralat shoulder	35	1	1	10	P4 anodal stimulation corrected hyper pseudo neglect bias.
Göder *et al*. 2013 [43]	Cross-over	14	33	ND	Stable AP medication	Verbal memory (RAVT), procedural learning (MT)	F3 or F4 / Mastoïde	Spherical 8 mm diameter	1	0,3	5 x 5	so-tDCS (0.75Hz) delivered during sleep stage 2 enhance learning of verbal material.
Hoy *et al*. 2014 [42]	Cross-over	18	42.2	12M 6F	Atypical AP (N=18) AD (N=9)	Working memory (n-back)	F3/ FP2	35	1	0; 1 and 2	20	tDCS improves working memory performances until 40 minutes after tDCS session.
Mondino *et al*. 2014 [46]	RCT parallel	28 (15 A / 13 S)	36.5 39.2	6M/9F 6M/7F	Olanzapine eq: 30.4 (SD 26.0)	Internal source-monitoring	F3FP1/ T3P3	35	10 (2/d)	2	20	AH reduction correlated with improvement in source monitoring performances (decrease of externalization bias)

A: active; S: sham; AH: Auditory Hallucinations; AD: Antidepressant medication; AP: antipsychotic medication; I: Intensity; Cpz eq: Chlorpromazine equivalent dose; M: Male; F: female; n: number of subjects; ND: Not done; RCT: Randomized controlled trial; tDCS: transcranial Direct Current Stimulation.

Cognitive tasks: RAVT: Rey Auditory verbal Learning Test; WPT: Weather Prediction Test; MT: Mirror Tracing.

Electrodes placement according to 10/20 EEG system: F3: left Dorsolateral Prefrontal Cortex; F4: right Dorsolateral Prefrontal Cortex; FP2: right supraorbital region; FP1: left supra-orbital region; T3P3: left temporo-parietal junction; P3: left parietal region (10/20 EEG system); P4: right parietal region.

tDCS on brain activity in schizophrenia using neuroimaging, specifically fMRI and EEG.

Studies have combined tDCS with resting state fMRI in schizophrenia. In a single case study from Homan *et al*. (2011) [34], auditory hallucinations and BOLD signals were compared before and after 10 sessions of tDCS with the cathode over the left temporoparietal junction and the anode over the right supraorbital region [34]. The authors found reduced auditory hallucinations as well as decreased BOLD signal in the left temporoparietal junction. This work thus supports the hypothesis that tDCS applied over the left temporoparietal region reduces auditory hallucinations by modulating brain activity, specifically by suppressing activity in the left temporoparietal region. Palm *et al.* (2013) [25] investigated the effect of 10 sessions of bi-frontal tDCS on symptoms and on resting state functional connectivity in a patient with schizophrenia. The authors found that tDCS decreased positive symptoms by 37 % and negative symptoms by 25 % as measured by PANSS scores. This clinical improvement was accompanied by reduced functional connectivity in the anterior part of the Default Mode Network (DMN). In a larger sample including 20 patients with schizophrenia, the same group of authors reported that the clinical improvement in negative symptoms observed after patients received tDCS was accompanied by significant deactivated clusters in the regions of nucleus accumbens, subgenual cortex and striatum [38].

Using EEG, Nawani *et al.* [47] investigated the effect of tDCS on auditory hallucinations and the N100 amplitude of auditory evoked potential while patients were presented with speech stimuli as compared to when they were asked to produce speech. In healthy volunteers, the N100 amplitude is typically augmented when they listen to speech as compared to when they speak. In patients with auditory hallucinations, this modulation of N100 amplitude is not observed and is assumed to reflect abnormalities in corollary discharge. This impairment has been associated with left temporal cortex abnormalities [48] and fronto-temporal dysconnectivity [49] observed in these patients. In their study, Nawani *et al.* [47] described no difference in N100 amplitude between speak and listen conditions before tDCS. Following tDCS, they reported that auditory hallucinations were reduced and the N100 amplitude was significantly smaller in the speak condition as compared to listen. These effects of tDCS on temporal cortex reactivity linked to abnormal corollary discharge function may also in part explain the effect of tDCS on auditory hallucinations and source-monitoring performance [46]. One can hypothesize that tDCS efficacy on auditory hallucinations and source-monitoring result from a direct modulating effect on frontal and temporal activity, which are both involved in auditory hallucinations and source-monitoring performance. However, it is difficult to draw any definitive conclusions about the efficacy of the anode or the cathode or both electrodes on the observed symptoms and cognitive improvement. The reported effects may result from the combination of the local impact of both electrodes and/or a global action of tDCS on a larger and distributed fronto-temporal network including interconnected distant areas [17, 50, 51].

Effects of tDCS on Cortical Plasticity

Another line of work using tDCS investigated cortical plasticity in patients with schizophrenia. Cortical plasticity is linked to long-term-potentiation (LTP) and long-term-depression (LTD), mediated by the N-Methyl-D-Aspartate (NMDA) receptor activity [6]. Hasan *et al.*, conducted a series of experiments investigating the effects of tDCS on cortical excitability in patients with schizophrenia. They measured transcranial magnetic stimulation (TMS)-induced motor-evoked potential (MEP) with single-pulse and paired-pulse paradigms. In the first study, the authors assessed cortical plasticity in healthy subjects, patients with multi-episode schizophrenia and patients with recent-onset schizophrenia before and after tDCS applied with the anode over the left primary motor cortex (M1) and the cathode over the right supraorbital region [52]. After tDCS, higher MEPs were observed controlaterally to the stimulation site in all groups, but significantly smaller MEPs were found in patients with multi-episode schizophrenia compared to healthy subjects and patients with recent-onset schizophrenia. Moreover, greater Short-latency Intra-Cortical Inhibition (SICI) was observed after tDCS in patients with recent-onset schizophrenia compared to patients with multi-episode schizophrenia. Hasan *et al*., (2012) also investigated the effects of tDCS applied with the cathode over the left M1 and the anode over the right supraorbital region on cortical excitability in patients with schizophrenia and healthy subjects [53]. They reported smaller MEP amplitude and prolonged Cortical Salient Period (CSP) after tDCS in healthy subjects, but not in patients with schizophrenia. In another study, Hasan *et al.* (2012) investigated the effects of tDCS applied with the cathode over the left M1 and the anode over the right supraorbital region on MEP of both hemispheres [54]. After tDCS, healthy subjects showed reduced MEP amplitude in both hemispheres whereas patients with schizophrenia displayed reduced MEP amplitude only in the stimulated hemisphere. Hasan *et al.* (2013) also compared the effects of tDCS applied with the cathode over the left M1 and the anode over the right supraorbital region on MEP of both hemispheres between healthy subjects, non-psychotic first-degree relatives of patients with schizophrenia and patients with schizophrenia [55]. After receiving tDCS, healthy subjects showed reduced MEP amplitude in both hemispheres, whereas non-psychotic first-degree relatives and patients with schizophrenia displayed no change in MEP size in the left hemisphere and non-psychotic first-degree relatives had greater MEPs in the right hemisphere [55]. In 2013, Hasan *et al.* compared the effects of unilateral tDCS (cathode over the left M1 and anode over the contralateral supraorbital region) and bilateral tDCS (cathode and anode over the left and right M1, respectively) on cortical excitability in healthy subjects and patients with schizophrenia [56]. Healthy subjects showed an increase in MEP amplitude after bilateral tDCS on the right but not on the left hemisphere and a reduction in MEP amplitude after unilateral tDCS on the left but not on the right hemisphere. Patients with schizophrenia showed no modulation of MEP amplitude after unilateral or bilateral tDCS on the left or right hemispheres [56].

Altogether, these findings suggest an impaired LTP-like and LTD-like plasticity in patients with schizophrenia and an association between impaired plasticity and connectivity. Reduced plasticity in patients with schizophrenia seems to be associated with an inhibitory deficit and a dysfunctional equilibrium between NMDA and GABA receptors and is at least partially responsible for pathophysiological symptoms, emerging from reduced signal-to-noise ratio and disturbed filter function [57]. The connection of LTD to signal-to-noise ratio and information processing is currently discussed and there seems to be strong relationship between LTD and LTP activity in information processing pathways [53, 58, 59]. Another explanation for the alteration of NMDA and GABA receptor function during the disease course may point to a neurodegenerative process with disturbed or inhibited cortical plasticity [60, 61].

Nawani *et al.* (2014) [62] investigated the effects of tDCS on auditory hallucinations and EEG signals. They measured modulation of the N100 amplitude evoked by an auditory odd-ball task before and after a titanic block in the frontal region. The authors reported that 10 sessions of tDCS over the fronto-temporal region reduced auditory hallucinations and enhanced modulation of the N100. Results from this work indicate that tDCS may enhance cortical plasticity in patients with schizophrenia.

Computational Model of the Fronto-Temporal Montage

Brunoni *et al.* (2014) [63] proposed a computational model predicting how the electrical current flows into the brain when applying a fronto-temporal montage. They found that the current was diffused under and between the 2 electrodes and the current density

is at its maximum at the cortical level but may also reach deeper structures including the basal ganglia, the hippocampus, the insula and the cingulate cortex. The model also predicts current flow to the cortical surface: inward current flow induced by the anode and outward current flow induced by the cathode. As inward current flow is associated with pyramidal neuron somatic depolarization and outward current flow is associated with pyramidal neuron somatic hyperpolarization, regions of presumed excitation/inhibition are predicted under the anode and the cathode respectively. The model also predicts tangential current between the two electrodes. The role of this current remains has yet to be revealed, but it may induce synaptic reinforcement. In sum, tDCS computer modeling suggests that fronto-temporal tDCS may enhance excitability in the prefrontal cortex, reduce excitability in the temporoparietal junction, and modulate connectivity between these areas, which may be beneficial for patients with schizophrenia.

SAFETY GUIDELINES ON THE USE OF TDCS IN PATIENTS WITH SCHIZOPHRENIA

In the articles reviewed here, more than 250 patients with schizophrenia received at least one session of tDCS. The duration of one tDCS session varies from 9 to 30 minutes and the intensity of stimulation from 0.3 and 3 mA. No study reported premature ending of delivering tDCS for safety issues. No adverse event has been reported in patients with schizophrenia, but some have been reported in healthy subjects, such as skin lesion [64]. Sensation of tingling or itching under the electrodes and sleepiness are the most common reported side effects of tDCS in patients with schizophrenia. These side effects are also the most common reported in healthy volunteers [65]. Patients with childhood-onset schizophrenia (mean age 15 years old; range 10-17) also reported good tolerability of receiving tDCS [66] as well as patients during pregnancy [67]. Also, a case report was conducted in a patient with schizophrenia and vitiligo, a skin condition [68]. The patient received ten daily sessions of tDCS. No skin lesion was observed under the anode electrode that was applied over the vitiligo skin area.

Importantly, reviewed studies reported no worsening of symptoms. However, there is still a need for studies including large samples and long follow up to be conducted to propose safety guidelines and potential concerns of tDCS for the treatment of schizophrenia. The potential of tDCS for home use was suggested in one patient with schizophrenia [33]. It could constitute an important progress for patients with great handicap, however national health authorities have to establish recommendations before any use in clinical practice [69].

FUTURE DIRECTIONS FOR THE USE OF TDCS IN SCHIZOPHRENIA

Optimizing Stimulation Parameters

The use of tDCS in schizophrenia is still in its early years. Numerous factors remain to be explored and identified including optimal stimulation parameters in terms of the intensity, duration, number of sessions, intervals between sessions, and sites of stimulation. In regard to the stimulation intensity, it appears that intensities inferior to 2 mA are less effective than 2 mA on reducing clinical symptoms and improving cognitive functions in schizophrenia [33, 42]. There are interesting data using 3 mA, however they were collected in a single patient [33]. More studies are needed to establish the optimal intensity to apply as well as the safety and tolerance of delivering 3 mA in patients with schizophrenia. In regard to duration, most studies delivered stimulation during 20 minutes except two case reports, one delivering current during 15 minutes [34] and another delivered the current during 30 minutes [33]. Both studies reported reduced auditory hallucinations and general symptoms without side effects. Regarding the number of sessions, 10 sessions delivered twice daily seem to be efficient in improving clinical outcome. The only study that tested the effects of 15 sessions of tDCS delivered once daily failed to report a significant effect on auditory hallucinations [36]. In order to improve efficacy of tDCS, some authors have proposed to increase the number of sites of stimulation. The number of electrodes (e.g., two versus four electrodes) is assumed to play a role on the neural effects of tDCS. A recent randomized study reported that compared to sham, daily session delivered over 3 consecutive weeks (15 sessions, 5 sessions per week from Monday to Friday) of tDCS was not efficient to reduce symptoms of schizophrenia [36]. In this study, tDCS was delivered bilaterally with two anodes places over the left and right prefrontal regions (F3 and F4 according to 10/20 EEG international system) and two cathodes placed over the left and right temporoparietal junctions (between T3 and P3 and between T4 and P4 respectively). It is however not possible to conclude about the efficacy of this bilateral approach based on a single study.

In sum, little is known regarding the optimal stimulation parameters (e.g., intensity, duration, the number of sessions, the interval between sessions, and the electrode montage) for reducing symptoms of schizophrenia but most evidence up to now suggest that 10 sessions of 20-minute tDCS conducted twice daily at 2 mA may lead to beneficial outcomes. Novel protocols of tDCS have been used and could reveal to be effective in treating symptoms of schizophrenia. These protocols consist in delivering oscillatory instead of constant direct current stimulation. We discussed above that patients with schizophrenia showed improved performance on declarative memory when they received slow oscillatory (so)-tDCS during their stage 2 sleep [43]. This kind of paradigm using low frequency stimulation (0.75 Hz) could be of interest for clinical application. Another protocol is the *transcranial random noise stimulation* (tRNS). This method entails of delivering an oscillatory unidirectional or alternative current with a variable frequency [70]. It was proposed that tRNS may have stronger effects on cortical excitability and greater clinical benefits for some populations. This has been shown in patients with tinnitus [71]. Two studies have applied tRNS in patients with schizophrenia. The current delivered was unidirectional with high frequencies, ranging between 100 and 640 Hz. Palm *et al.* (2013b) [72] targeted the frontal cortex applying the anode over the left dorsolateral prefrontal cortex and the cathode over the right supraorbital cortex during twenty sessions and observed decreased negative symptoms, disorganization and depression/anxiety. Haesebaert *et al.* (2014) [73] targeted the fronto-temporal network during ten sessions and reported reduced severity of auditory hallucinations and improved insight into the illness. This technique appears interesting and future studies are needed to further explore its effects in schizophrenia.

Combining tDCS with other Approaches

Future work should also prioritize to investigate combination of tDCS with pharmacologic treatments in schizophrenia. To date, there is no available data on the interaction between antipsychotic pharmacologic treatment and tDCS in patients with schizophrenia. Neurophysiological studies have demonstrated that dopaminergic, serotonergic and GABAergic agents affect tDCS effects on motor cortex excitability in healthy humans [74, 75]. For instance, sulpiride can diminish the induction of tDCS after-effects in healthy volunteers [74]. Many patients with schizophrenia included in tDCS studies suffered from treatment-resistant symptoms and were generally polymedicated with molecules of distinct pharmacological classes such as typical, atypical antipsychotics and selective serotonin reuptake inhibitors. Future work investigating the effect of tDCS should determine the best association between pharmacology and tDCS protocols. As an example, benzodiazepine drugs have a detrimental effect on bifrontal tDCS efficacy in major depression [4] and the same pattern of response could be observed in patients with schizophrenia. Another line of work to further reduce symptoms may consist in combining existing cognitive remediation therapy for schizophrenia [76, 77] with tDCS, which has also been reported to improve cognitive functions [40, 78].

Predictive Markers

Clinical characteristics that might affect beneficial outcome, such as age or chronicity, should also be investigated. Studies with repetitive transcranial magnetic stimulation (rTMS) revealed that long duration of illness and severity of the psychosis are predictors of poor outcome [79, 80]. Future studies should test whether these clinical markers also predict tDCS responses. It should be acknowledged that the state-of-the-art for clinical applications in schizophrenia is much more established with rTMS [80, 81] (encompassing data from the last 25 years; see [79, 80]), whereas most tDCS studies have been phase I and phase II. tDCS might offer great clinical interest as it is affordable, portable, easy to use and without adverse events being reported so far [82].

CONCLUSION

Here, we reviewed and discussed studies investigating the effects of tDCS on symptoms, cognition, brain activity and cortical excitability in patients with schizophrenia. Although research in this area is in its early days, studies showed promising results in reducing symptoms such as auditory hallucinations and general symptoms of schizophrenia with tDCS. Further sham-controlled trials with larger sample are still needed to investigate the clinical usefulness of tDCS in schizophrenia. The international interest in using tDCS in patients with schizophrenia is still growing, as evidenced by results of a search on clinicaltrials.gov website (December 2014) database yielding to 18 ongoing studies investigating the clinical interest of tDCS in schizophrenia (8 in North America, 6 in Europe, 2 in Australia and 1 in South America, Africa and Middle East).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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