Schizophrenia

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Abstract

This chapter proposes an overview of current evidence and future directions for using tDCS in schizophrenia. To date, the effects of tDCS have been investigated in three main outcomes: (1) to alleviate auditory verbal hallucinations using a frontotemporal tDCS montage (the anode placed over the left dorsolateral prefrontal cortex coupled with the cathode placed over the left temporoparietal junction); (2) to alleviate negative symptoms using a frontal montage (the anode placed over the left dorsolateral prefrontal cortex coupled with the cathode placed over the right dorsolateral prefrontal cortex, the right supraorbital region or extra-cephalically); and (3) to enhance cognitive functions, using different tDCS montages. Promising results have been reported for these three outcomes. tDCS can decrease the severity of symptoms such as auditory verbal hallucinations and negative symptoms by about 30 % and enhance a wide range of cognitive functions (e.g., working memory, self-monitoring, facial emotion recognition). However, most studies to date are case-reports and open labeled studies with small samples. Thus, large randomized controlled studies are needed to confirm the usefulness of tDCS in schizophrenia.

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Introduction

Schizophrenia is a frequent and debilitating psychiatric condition occurring in about 1 % of the general population. The clinical expression of schizophrenia is heterogeneous, and symptoms are usually classified into five main dimensions: positive (e.g., hallucinations, delusions), negative (e.g., flat expression, avolition), depression, disorganization, and grandiosity/excitement. Symptoms of schizophrenia are usually alleviated by psychopharmacological medications. However, up to 30 % of treated patients still report disabling symptoms such as auditory verbal hallucinations, negative symptoms, and cognitive deficits [1, 2]. These treatment-resistant symptoms are associated with a higher risk of relapse and worse prognosis, justifying the need for developing novel alternative approaches.

Over the last decade, various nonpharmacological approaches such as noninvasive brain stimulation (NIBS) techniques have been developed in order to alleviate treatment-resistant symptoms in patients with schizophrenia. NIBS techniques are safe tools to modulate brain activity and connectivity in living humans. These approaches were based on neuroimaging studies that have highlighted some brain correlates of schizophrenia symptoms: auditory verbal hallucinations were associated with hyperactivity in the left temporoparietal region [3] and frontotemporal dysconnectivity [4]; negative symptoms and cognitive deficits were associated with structural and functional abnormalities in the prefrontal cortices [5]. According to their neuromodulatory effects, NIBS techniques were thus proposed to reduce treatment-resistant symptoms in patients with schizophrenia by targeting the brain regions that showed abnormal activities. One of the NIBS techniques recently used in these patients is transcranial direct current stimulation (tDCS).

The first studies investigating the use of tDCS to improve symptoms of schizophrenia have been published in 2011. Since then, a rapid increase in the number of published articles in the field was observed (Fig. 14.1)—in fact, 20 studies investigating the clinical interest of tDCS in schizophrenia were indicated as "ongoing" on clinicaltrials.gov database in September 2015 (ten in North America, four in Europe, two in Middle East, one in Australia, one in South America, one in Africa, and one in East Asia) suggesting the international growing interest of tDCS for schizophrenia.

Two tDCS montages for schizophrenia have been mostly used. The first one, a frontotemporal electrode montage, is proposed to reduce treatment-resistant auditory verbal hallucinations. In this montage, the anode (presumably excitatory) was placed over the left prefrontal cortex and the cathode (presumably inhibitory) was placed over the left temporoparietal junction [6, 7]. The second one is proposed to reduce treatment-resistant negative symptoms and to improve cognitive functions by targeting the left prefrontal region. In this montage, the anode was placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right supraorbital region, the right DLPFC or extra-cephalically [8, 9].

The aim of this chapter was to investigate whether tDCS can alleviate symptoms and improve cognitive functions in patients with schizophrenia. Hence, we reviewed studies investigating the clinical effects of tDCS on auditory verbal hallucinations, negative symptoms and other symptoms of schizophrenia. We also reviewed studies focusing on the effects of tDCS on cognitive functions in patients with schizophrenia. After a description of current evidence regarding the interest of using tDCS in patients with schizophrenia and the brain correlates of clinical and cognitive improvements, we also discussed the safety of this approach and how tDCS parameters can be optimized to improve efficacy.

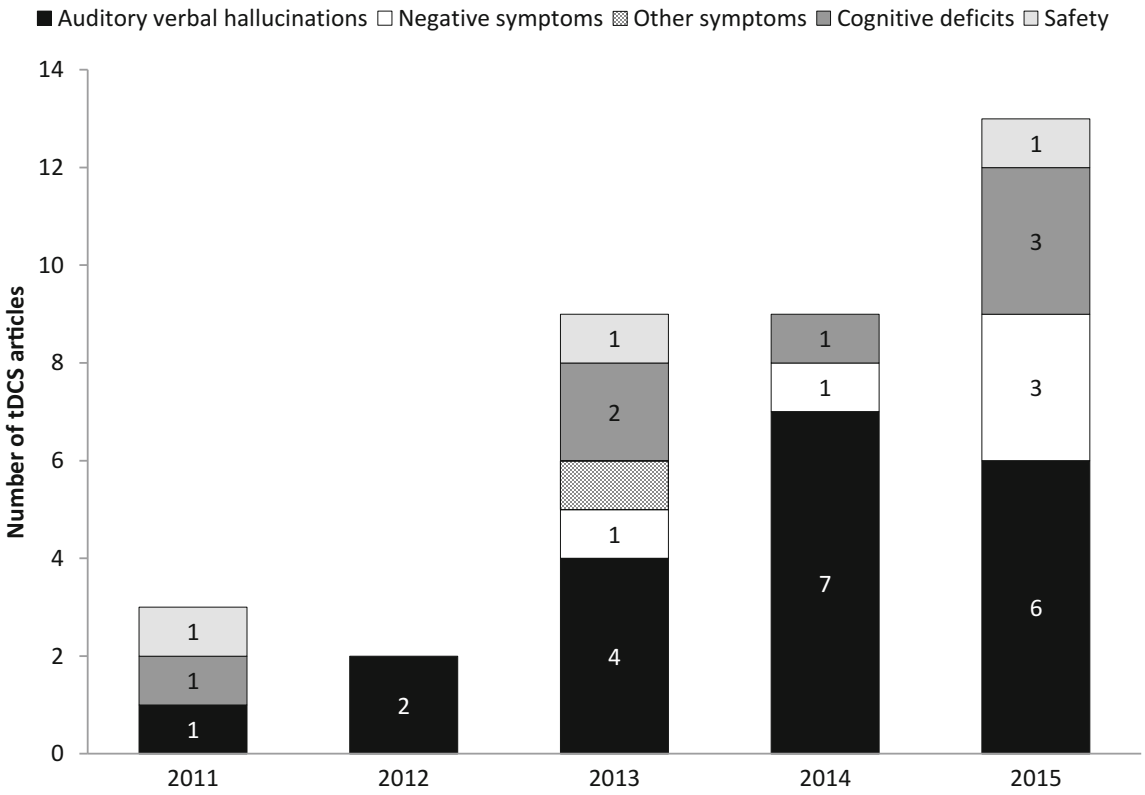

Fig. 14.1 Number of published articles per year examining the effects of transcranial direct current stimulation (tDCS) in patients with schizophrenia. Articles investigating the effects on auditory verbal hallucinations, negative symptoms, other symptoms, cognitive deficits, and safety have been listed (*Source*: PubMed/Medline)

Effects of Frontotemporal tDCS on Auditory Verbal Hallucinations

Twenty-one studies investigated whether tDCS targeting the frontotemporal network can improve the symptoms of treatment-resistant auditory verbal hallucinations in patients with schizophrenia (see Table 14.1). Among them, three randomized sham-controlled studies have reported a significant effect of active tDCS on auditory verbal hallucinations as compared to sham [6, 26, 27]. In the first one [6], 30 patients with schizophrenia received ten sessions of 20 min of either active (2 mA) or sham tDCS delivered twice daily on 5 consecutive days. Electrodes were placed on the scalp based on the 10/20 international EEG system, with the center of the anode placed between F3 and FP1 (assuming to correspond to the left prefrontal cortex) and the center of the cathode placed between T3 and P3 (assuming to correspond to the left temporoparietal junction). Auditory verbal hallucinations were assessed using the Auditory Hallucination Rating Scale (AHRS). Patients receiving active tDCS reported a significant 31 % decrease of their treatment-resistant auditory verbal hallucinations whereas patients receiving sham tDCS reported a nonsignificant 8 % decrease [6]. Remarkably, the effect of tDCS on auditory verbal hallucinations was still significant at 1 and 3-month follow-up [6].

Similar results were reported using the same tDCS protocol in two randomized controlled studies published in 2015 [26, 27]. It is important to stress that samples enrolled in these studies partially overlapped with the study sample of Brunelin et al. [6]. In the first study, Mondino et al. [26] reported a significant 46 % reduction in the frequency of auditory verbal hallucinations assessed by the first item of the AHRS after 10 sessions of

active tDCS, whereas a nonsignificant 10 % decrease was reported in the sham group. In the second one, a significant 28 % decrease in auditory verbal hallucinations measured by the AHRS was reported after the ten sessions of active tDCS, whereas a nonsignificant 10 % decrease was reported in patients receiving sham tDCS [27].

Using the same electrodes montage, promising effects of tDCS for reducing auditory verbal hallucinations were also reported in 4 open labeled studies including 23 [25], 21 [17], 16 [28], and 6 [18] patients with schizophrenia. All studies included patients with schizophrenia receiving ten sessions of 20 min of active 2 mA tDCS delivered twice daily on 5 consecutive days. In the first one, Shivakumar et al. [25] recruited 23 patients and assessed their auditory verbal hallucinations using the "auditory hallucination" subscale of the Psychotic Symptom Rating Scale (PSYRATS). Patients showed a nearly 30 % significant decrease of their treatment-resistant auditory verbal hallucinations after tDCS. Bose et al. [17] recruited 21 patients and assessed the auditory verbal hallucinations, also using the "auditory hallucination" subscale of the PSYRATS. After tDCS, patients showed a significant decrease (32.7 %) in auditory verbal hallucinations. Brunelin et al. [28] recruited 16 patients and assessed their auditory verbal hallucinations using the AHRS. After tDCS, patients showed a significant 20 % decrease in auditory hallucinations. In Ferrucci et al. [18], six patients were included and assessed using the Cardiff Anomalous Perceptions Scale (CAPS). After tDCS, patients showed a 33 % decrease in frequency and a 40 % decrease in distress of auditory verbal hallucinations.

Thirteen case-reports also investigated the effects of frontotemporal tDCS on auditory verbal hallucinations in patients with schizophrenia. Of note, three of them observed a complete remission of auditory verbal hallucinations after tDCS [11, 12, 19]. Indeed, Rakesh et al. [11] and Shivakumar et al. [12] assessing auditory verbal hallucinations with AHRS, reported that ten sessions of 20 min of active 2 mA tDCS delivered twice daily on 5 consecutive days allowed complete remission of auditory verbal hallucinations. Shivakumar et al. [19], assessing auditory verbal hallucinations with the "auditory hallucinations" subscale of the PSYRATS, reported a complete remission of auditory verbal hallucinations for at least 3 months after ten sessions of tDCS delivered twice daily for 20 min at 2 mA. Two case studies also highlighted the efficacy and safety of maintenance tDCS sessions for 1 and 3 years [14, 19]. Shivakumar et al. [19] reported a complete remission of auditory verbal hallucinations assessed with the PSYRATS "auditory hallucinations" subscale during 1 year after ten sessions of tDCS delivered twice daily for 20 min at 2 mA. In fact, the patient presented three relapses within 1 year, which were successfully managed with only two sessions of tDCS (in 1 day). Andrade [14] reported a decrease in auditory verbal hallucinations assessed with clinical scales during 3 years of tDCS delivered domiciliary once then twice daily, for 20 then 30 min at 1–3 mA intensity. Within 2 months, the patient self reported a 90 % improvement.

Finally, a randomized sham controlled study failed to replicate the beneficial clinical effect of tDCS on auditory verbal hallucinations assessed by a single item on the Positive and Negative Syndrome Scale (PANSS) measuring hallucinations severity [20]. In this study, 15 sessions of tDCS (2 mA, 20 min) were delivered once a day during 3 consecutive weeks using either a left frontotemporal montage (with the anode over F3 and the cathode over the T3-P3) in 11 patients with schizophrenia or an original bilateral montage with four electrodes (two anodes over F3 and F4 and two cathodes over T3-P3 and T4-P4) in 13 patients with schizophrenia. In a recent case-report study, Bose et al. [24] reported that 18 sessions of left frontotemporal tDCS (with the anode placed midway between F3 and FP1 and the cathode over the T3-P3) had no effect on auditory verbal hallucinations as assessed by the "auditory hallucination" subscale of the PSYRATS. However, when switching the electrode montage to the right side of the brain with the anode placed over the right DLPFC (between F4 and FP2) coupled with the cathode over the right temporoparietal junction (between T4 and

Table 14.1 Summary of studies investigating the effects of frontotemporal tDCS on auditory verbal hallucinations in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Homan et al. 2011 [10]	Case	1	44	M	FP2/T3P3	10 (1/day)	1	15	1. Decrease in HCS score (−60 %) 2. Decrease in PANSS score (−20 %) 3. Decrease in PSYRATS score (−16 %) 4. Decrease of rCBF in Wernicke's area (BA22), left Heschl's gyrus (BA41/42), and Broca's area (BA44/45) Sustained effect on symptoms at 6-month follow-up
Brunelin et al. 2012a [7]	RCT	30 15A 15S	37.7	22M/8F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−31 %) Sustained effect at 1 and 3-month follow-up 2. Decrease in PANSS score (−13 %)
Brunelin et al. 2012 [6]	Case	2	37.5	M	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (patient 1: −77 %; patient 2: −48 %) 2. Decrease in PANSS score (patient 1: −20 %; patient 2: −49 %) Sustained effects at 3-month follow-up
Rakesh et al. 2013 [11]	Case	1	24	M	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by AHRS 2. Improvement in measured by an increase in IRS from 1 to 5
Shivakumar et al. 2013 [12]	Case	1	28	F	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by AHRS 2. Improvement in insight measured by an increase in IRS from 0 to 5
Shiozawa et al. 2013 [13]	Case	1	31	M	F3/Oz F3/T3P3	10 (1/day) 10 (1/day)	2	20	1. Decrease in AHRS score (−20 %) 2. Decrease in visual hallucinations measured by LSHS score (−20 %) 3. Decrease in general (−29 %), positive (−38 %) and negative symptoms (−27 %) assessed by PANSS
Andrade 2013 [14]	Case	1	24	F	F3/T3P3	1–2/day at home during 3 years	1–3	20–30	1. Decrease in AH and general symptoms measured by clinical ratings
Nawani et al. 2014 [15]	Case	1	31	M	F3/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−30 %) 2. Increased changes in amplitudes of N100 induced by tetanic blocks. These changes were reported only for the frontal electrodes

(continued)

Table 14.1 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Nawani et al. 2014 [16]	Case	5	33.2	2M/3F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS score (−30 %) 2. Modulation of N100 amplitude in the auditory cortex during "talk" and "listen" conditions: before tDCS, no differences between N100 amplitudes in talk and listen conditions After tDCS, smaller N100 amplitude during "talk" as compared to "listen"
Bose et al. 2014 [17]	Open	21	33.1	9M/12F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in PSYRATS AHS scores (−32.7 %) 2. Improvement in insight measured by an increase in SAI scores from 7.8 ± 4.4 to 12.2 ± 4.2 Correlation between the both
Ferrucci et al. 2014 [18]	Open	6	41–66	ND	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in frequency (−33 %) and distress (−40 %) of AH measured by the CAPS. The effects lasted up to 1 month 2. Decrease in PANSS negative symptoms scores (−24 %)
Shivakumar et al. 2014 [19]	Case	1	42	F	F3FP1/T3P3	10 (2/day)	2	20	1. Complete cessation of AH measured by the AHS of PSYRATS during 1 year. 2 sessions at relapse allow maintenance of beneficial effect
Fitzgerald et al. 2014 [20]	RCT	11 13	39.3	15M/9F	F3/T3P3 F3 + F4/ T3P3 + T4P4	15 (1/day)	2	20	1. No significant decrease in PANSS AH score (unilateral: −17 %; bilateral: −14 %) compared to sham (−7 %; −3 %). No effects in total PANSS scores, PANSS positive symptoms and PANSS negative symptoms 2. No effect on SANS
Narayanaswamy et al. 2014 [21]	Case	1	22	F	F3FP1/T3P3	10 (2/day)	2	20	After the ten sessions of tDCS: 1. No changes in AHRS scores 2. No changes in SANS scores During the subsequent 2 weeks: 1. No changes in AHRS scores 2. Decrease in SANS scores (−30 %) At 6-month follow-up: 1. Decrease in AHRS scores (−37 %) 2. Decrease in SANS scores (−60 %)

Shenoy et al. 2015 [22]	Case	1	25	F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHS of PSYRATS (−25 % immediately after the ten sessions and −95 % 4 months after tDCS sessions) 2. Safety and tolerability during pregnancy assessed using sonography
Praharaj et al. 2015 [23]	Case	1	49	M	F3/T3P3	5 (1/day)	2	20	1. More than 90 % decrease in frequency and duration of AH after the 1st session 2. Decrease in PSYRATS AHS score 3. No effect on PSYRATS delusion score 4. Subjective report of reduction in distress associated with AH Symptoms return to baseline 6 days after the last tDCS session
Bose et al. 2015 [24]	Case	1	37	F	F3FP1/T3P3 F4FP2/T4P4	18 (1/day) 20 (1/day)	2	20	After 18 sessions of F3FP1/T3P3 tDCS: 1. No effects on AHS of PSYRATS 2. No effects on "attentional salience" item of the AHRS After 20 sessions of F4FP2/T4P4 tDCS: 1. Decrease in AHS of PSYRATS (−31.4 %) 2. Decrease in "attentional salience" item of the AHRS (from 6 to 4)
Shivakumar et al. 2015 [25]	Open	23	33.4	10M/13F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in PSYRATS AHS after tDCS. Greater decrease in the COMT val/val group ($n=11$) than in the met group (val/met or met/met; $n=12$)
Mondino et al. 2015 [26]	RCT	28 15A 13S	Active: 36.5 Sham: 39.2	9F/6M 7F/6M	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in "frequency" item of the AHRS (−46 %) 2. Improvement in internal source monitoring performances (decrease of externalization bias) Correlation between both

(continued)

Table 14.1 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Mondino et al. 2015b [27]	RCT	23 11A 12S	Active: 36.7 Sham: 37.3	8M/3F 7M/5F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS scores (−28 %) 2. Decrease in PANSS negative score (−17 %). No effects on PANSS positive symptoms and general psychopathology 3. Effects on rs-FC of the left TPJ measured by fMRI: decreased rs-FC of the left TPJ with the left anterior insula and the right inferior frontal gyrus. Increased rs-FC of the left TPJ with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus Correlation between the reduction of AHRS scores and the reduction of the rs-FC between the left TPJ and the left anterior insula
Brunelin et al. 2015 [28]	Open	16	41	6M/10F	F3FP1/T3P3	10 (2/day)	2	20	1. Decrease in AHRS scores (−20 %) Greater decrease in nonsmokers (−46 %) than in smokers (−6 %)

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region; FP1: Left supraorbital region; Oz: Occipital region; T3P3: Left temporoparietal junction; T4P4: Right temporoparietal junction; T3: Left temporal region; T4: Right temporal region

A active, AH auditory hallucinations, *AHRS* auditory hallucination rating scale, *AHS* auditory hallucinations subscale, *BA* Brodmann's area, *CAPS* Cardiff anomalous perceptions scale, *F* female, *fMRI* functional magnetic resonance imaging, *HCS* hallucination change score, *I* intensity, *IRS* insight rating scale, LSHS, Launay–Slade hallucination scale, *M* male, *n* number of subjects, *PANSS* positive and negative syndrome scale, *PSYRATS* psychotic symptom rating scale, *rCBF* regional cerebral blood flow, *RCT* randomized controlled trial, *rs-FC* resting-state functional connectivity, *S* sham, SAI schedule for assessment of insight, *SANS* scale for the assessment of negative symptoms, *tDCS* transcranial direct current stimulation, *TPJ* temporoparietal junction

P4), 20 sessions of tDCS induced a 31.4 % reduction of auditory verbal hallucinations.

In sum, among the studies investigating the effects of frontotemporal tDCS on auditory verbal hallucinations, the intensity of stimulation varied from 1 to 3 mA for a 15- to 30-min duration. The size of the electrodes was mostly 35 cm^2 (7 × 5 cm), but some studies used 25 cm^2 electrodes (5 × 5 cm; [14, 23]). tDCS regimen consisted in 5–20 sessions of tDCS delivered either once or twice daily. Auditory verbal hallucinations were assessed using various standardized multidimensional scales such as the PSYRATS or the AHRS, but also using single item assessments such as the "auditory hallucinations" item of the PANSS [20] or the "frequency" item of the AHRS [26]. These assessments and outcomes may not have the same sensitivity to capture changes in auditory verbal hallucinations. Further studies are needed to confirm promising effects observed on auditory verbal hallucinations following frontotemporal tDCS in patients with schizophrenia.

Effects of Frontotemporal tDCS on Other Symptoms

Remarkably, among studies reporting a reduction of auditory verbal hallucinations in patients with schizophrenia following tDCS, some also observed a decrease in general symptoms of schizophrenia [6, 7, 10, 14], positive symptoms [13], negative symptoms [13, 18, 21, 27], and insight into the illness [11, 12, 17]. In addition, Shiozawa et al. [13] investigated the effect of ten sessions of tDCS with the anode over F3 and the cathode over the occipital region (Oz) followed by ten sessions with the anode over F3 and the cathode over the temporoparietal cortex (T3-P3) on visual and auditory verbal hallucinations in a patient with schizophrenia. They reported that ten sessions of each electrode montage lead to a reduction of hallucinations in both visual and auditory modalities.

Predictive Markers of Response to Frontotemporal tDCS on Auditory Verbal Hallucinations

Two open labeled studies investigated potential predictive markers of response to tDCS [25, 28]. Shivakumar et al. [25] investigated the effects of frontotemporal tDCS in 23 patients with treatment-resistant auditory verbal hallucinations divided into two groups depending on their COMT Val158Met polymorphism. A significant reduction of auditory verbal hallucinations was observed in both groups. However, patients with the val/val COMT polymorphism ($n = 11$) showed a greater reduction in auditory verbal hallucinations than met-allele carriers (val/met or met/met polymorphism; $n = 12$). The COMT Val158Met polymorphism may thus modulate response to tDCS. An excessive dopamine transmission has been implicated in the clinical expression of positive symptoms. The Val variant catabolizes frontal dopamine at up to four times the rate of its methionine counterpart, suggesting that lower extracellular dopamine rates in the frontal region predicts beneficial clinical outcome in patients with AVH.

Brunelin et al. [28] reported a mean 20 % decrease of auditory verbal hallucinations following 10 sessions of frontotemporal tDCS in 16 patients with treatment-resistant auditory verbal hallucinations. In this sample, patients with a comorbid tobacco use disorder showed a nonsignificant 6 % reduction in auditory verbal hallucinations, whereas nonsmokers displayed a significant 46 % reduction in auditory verbal hallucinations. Thus, smoking may prevent the effect of repeated sessions of frontotemporal tDCS in patients with treatment-resistant auditory verbal hallucinations. It has been hypothesized that interactions between antipsychotic medication and nicotine may influence dopamine transmission and in turn modulate tDCS effects on neural plasticity.

Furthermore, one case study suggested that some clinical characteristics such as attentional salience of auditory verbal hallucinations could

influence site-specific response to tDCS. Namely, Bose et al. [24] described the case of a patient with high attentional salience auditory verbal hallucinations that failed to respond to left-sided frontotemporal tDCS but that decreased after right-sided frontotemporal tDCS.

Brain Correlates of the Effects of Frontotemporal tDCS on Auditory Verbal Hallucinations

Several studies used fMRI and EEG to investigate how tDCS modulates the brain when reducing auditory verbal hallucinations in patients with schizophrenia.

In a first single case study, Homan et al. [10], reported that tDCS decreased the regional cerebral blood flow in Wernicke's area (BA22), left Heschl's gyrus (BA41/42), and Broca's area (BA44/45), as well as auditory verbal hallucinations. This work supports the hypothesis that tDCS applied over the left temporoparietal junction reduces auditory hallucinations by normalizing brain activity, specifically by suppressing the hyperactivity observed in the language-related network during auditory verbal hallucinations [3].

In a randomized sham controlled study including 23 patients with schizophrenia, Mondino et al. [27] reported that active tDCS decreased resting state functional connectivity of the left temporoparietal junction with the left anterior insula and the right inferior frontal gyrus and increased resting state functional connectivity of the left temporoparietal junction with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus as compared to sham tDCS. These changes in functional connectivity were accompanied by a reduction of auditory verbal hallucinations. Moreover, there was a correlation between the reduction of auditory verbal hallucinations and the reduction of the resting state functional connectivity between the left temporoparietal junction and the left anterior insula. These results also suggest that the reduction of auditory verbal hallucinations induced by tDCS was associated with a modulation of the brain activity within an auditory verbal hallucinations -related brain network, including brain areas involved in inner speech production and monitoring.

Using EEG, Nawani et al. [16] investigated the effects of ten sessions of left frontotemporal tDCS on auditory verbal hallucinations and on the amplitude of the auditory evoked potential N100 in five patients with schizophrenia. The N100 amplitude was measured when patients were listening to speech stimuli and when they were asked to produce speech. The authors reported that patients with schizophrenia showed no difference at baseline between N100 amplitudes generated in talk and listen conditions. This absence of N100 modulation during talking as compared to listening is suggested to reflect abnormalities in the corollary discharge. After tDCS, the amplitude of N100 was significantly smaller during talking than listening. Thus, tDCS seems to restore the N100 amplitude modulation when reducing auditory verbal hallucinations.

In a case study, Nawani et al. [15] tested whether the same protocol of left frontotemporal tDCS had an effect on cortical plasticity measured by EEG. Namely, they measured the N100 amplitude evoked by an auditory oddball task before and after a tetanic block before and after tDCS. The authors reported that ten sessions of frontotemporal tDCS reduced auditory hallucinations and increased the modulation of the N100 amplitude induced by the tetanic block. This effect was measured in the frontal region only. Since a change in N100 amplitude after tetanic block is considered as an indicator of neuroplasticity, these results suggested that tDCS modulates cortical neuroplasticity in patients with schizophrenia.

Effects of Frontal tDCS on Negative Symptoms and Other Symptoms of Schizophrenia

Five studies investigated the clinical effect of tDCS on treatment-resistant negative symptoms of schizophrenia (see Table 14.2). In these studies, the targeted brain region was the DLPFC, mainly its left part. This brain region was targeted with tDCS by placing the anode over the left DLPFC (F3) and the cathode either over the supra orbital region (FP2), the right DLPFC (F4) or the right

Table 14.2 Summary of studies investigating the effects of frontal tDCS on negative symptoms and other symptoms in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (n/day)	*I* (mA)	Duration (min)	Outcomes and main results
Palm et al. 2013 [8]	Case	1	19	M	F3/FP2	10 (1/day)	2	20	1. Decrease in PANSS total scores (−29 %), negative (−25 %) and positive (−37 %) subscores 2. Decrease in SANS scores (−28 %) 3. Decrease in depression assessed by CDSS (−82 %) Effects on FC measured using fMRI: reduced FC in the subgenual cortex, the anterior cingulate, the medial frontal gyrus, the and superior frontal gyrus 4. Increase in TMT performances 5. Decrease in the number of errors at the SOPT
Palm et al. 2014 [9]	RCT	20	ND	ND	F3/FP2	10 (1/day)	2	20	1. Decrease in SANS scores 2. Decrease in PANSS total scores 3. Effects on FC measured using fMRI: Deactivated cluster in the nucleus accumbens, subgenual cortex and striatum
Kurimori et al. 2015 [29]	Open	9	40.3	3F/6M	F3/Right deltoid	10 (1/day)	2	20	1. Decrease in PANSS negative symptoms scores (−24 %). Decrease in total PANSS scores (−8 %). No change in PANSS positive and general symptoms
Gomes et al. 2015 [30]	RCT	15 7A 8S	A: 43.3 S:34.2	5M/2F 6M/2F	F3/F4	10 (1/day)	2	10	1. Decrease in PANSS negative symptoms scores (−20 %) in the active group (versus −0.5 % in the sham group). Decrease in general and total PANSS scores (−15 % and −12 %) in the active group (0 % in the sham group). No effect on PANSS positive symptoms scores 2. No effect on depression assessed by CDSS 3. No effect on global functioning assessed by GAF
Shiozawa et al. 2013 [31]	Case	1	65	F	F3/F4	10 (1/day)	2	20	1. Decrease of catatonic symptoms assessed by BFS scores until complete remission (4 months after tDCS sessions)

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region

A active, *BFS* Bush–Francis scale, *CDSS* Calgary depression scale, *F* female, *FC* functional connectivity, *fMRI* functional magnetic resonance imaging, *GAF* global assessment of functioning, *I* intensity, *M* male, *n* number of subjects, *PANSS* positive and negative syndrome scale, *RCT* randomized controlled trial, *rs-FC* resting-state functional connectivity, *S* sham, *SANS* scale for the assessment of negative symptoms, *SOPT* self ordered pointing task, *tDCS* transcranial direct current stimulation, *TMT* trail making test

deltoid. In the first study, Palm et al. [8] reported that 10 sessions of tDCS delivered once a day with the anode placed over the left DLPFC (F3) and the cathode electrode placed over the right supra orbital region (FP2) reduced treatment-resistant negative and positive symptoms in a patient with schizophrenia. In a further randomized sham controlled trial with 20 patients with negative symptoms, Palm et al. [9] reported that ten daily sessions of active tDCS 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 assessment.

These beneficial effects of tDCS on negative symptoms were also reported more recently in an open-label study including nine patients with schizophrenia [29] and in a randomized sham-controlled study including 15 patients with schizophrenia [30]. In the first study, patients received ten daily sessions of tDCS with the anode placed over the left DLPFC (F3) and the cathode placed over the right deltoid muscle [29]. After tDCS, patients showed a significant 24 % reduction in negative symptoms assessed by the PANSS negative subscale as compared to baseline. In the second study, patients received ten daily sessions of either active or tDCS with the anode placed over the left DLPFC (F3) and the cathode placed over the right DLPFC (F4) [30]. After tDCS, patients receiving active tDCS showed a significant 20 % reduction in negative symptoms as measured by the PANSS negative subscale whereas patients receiving sham tDCS showed no significant difference. Patients receiving active tDCS also reported a significant 15 % reduction in PANSS general symptoms as compared to patients receiving sham tDCS.

Brain Correlates of the Effects of Frontal tDCS on Negative Symptoms

Only one case study and one randomized controlled study investigated how tDCS modulates the brain when reducing negative symptoms in patients with schizophrenia. In the case study, Palm et al. [8] used fMRI to measure the effects of ten sessions of tDCS with the anode placed over the left DLPFC and the cathode placed over the right supraorbital region (FP2) on resting-state functional connectivity. Following tDCS, the patient showed a reduction in positive and negative symptoms and a reduced functional connectivity in the anterior part of the default mode network including the subgenual cortex, the anterior cingulate, the medial frontal gyrus and superior frontal gyrus. 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 a significant reduced functional connectivity within the nucleus accumbens, the subgenual cortex and the striatum [9].

Effects of Frontal tDCS on Other Symptoms

In a case study, Shiozawa et al. [31] reported a reduction in severity of catatonic symptoms in a patient suffering from treatment- and electroconvulsive therapy-resistant catatonic schizophrenia following ten sessions of tDCS delivered once a day with the anode over F3 and the cathode over F4. After 1 month, the remission of symptoms was complete and lasted for at least 4 months.

Effects of TDCS on Cognitive Functions

Cognitive deficits are a key feature in patients with schizophrenia. Several studies explored whether tDCS could improve cognitive functions in patients with schizophrenia (Table 14.3).

In the first study, Vercammen et al. [32] reported that a single session of active tDCS had a facilitating effect on probabilistic association learning measured by the weather prediction test in patients who displayed the best learning abilities before stimulation. In this study the anode was placed over the left DLPFC (F3) and the cathode over the right supraorbital region (FP2).

Table 14.3 Summary of studies investigating the effects of tDCS on cognitive functions in patients with schizophrenia

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Vercammen et al. 2011 [32]	Cross-over	20	37.6	10F/10M	F3/FP2	1	2	20	1. No effects on probabilistic learning assessed by the WPT in the whole sample. Significant improvement of performances in participants showing adequate performances at baseline
Ribolsi et al. 2013 [33]	Cross-over	15	34.3	4F/11M	P3/Right shoulder P4/Left shoulder	1	1	10	1. Anodal stimulation applied over P4 partially corrected the lack of leftward bias described using a line bisection task
Hoy et al. 2014 [34]	Cross-over	18	42.2	6F/12M	F3/FP2	1	0; 1 and 2	20	After stimulation at 2 mA intensity: 1. Increase in working memory performances assessed by the n-back task until 40 min after tDCS session After stimulation at 1 mA intensity: 1. No effect of 1 mA stimulation on working memory
Rassovsky et al. 2015 [35]	RCT	Anode 12 Cathode 12 12S	45.8 47.8 41.6	2F/10M 6F/6M 4F/8M	FP1/FP2	1	2	20	1. Anodal tDCS increases the identification of facial expressions assessed by the FEIT 2. No effect on social cognition assessed by the MSCEIT 3. No effect on social perception assessed by the PONS 4. No effect on theory of mind assessed by the ASIT 5. No effect on cognitive functions assessed by the MCCB composite score
Smith et al. 2015 [36]	RCT	30 14A 16S	A: 46.7 S: 44.8	14M/3F 10M/6F	F3/FP2	5 (1/day)	2	20	1. Increase in the MCCB composite score, the MCCB working memory score and in attention-vigilance domain scores in the active group as compared to sham 2. No effect on PANSS scores 3. No effect on smoking assessed by self report of cigarettes smoked and breathalyzer CO levels 4. No effect on cigarette dependence assessed with the cigarette dependence scale 4. No effect on craving assessed by the QSU

(continued)

Table 14.3 (continued)

Study					tDCS parameters				
Author, date	Design	*n*	Age (years)	Sex	Anode/cathode	*n* session (*n*/day)	*I* (mA)	Duration (min)	Outcomes and main results
Schretlen et al. 2015 [37]	Cross-over no sham	5 patients 6 first degree relatives	50	6F/5M	F3/F4 F4/F3	1	1.5	30	1. No effect on motor speed assessed by the GPT and the FTT 2. No effect on processing speed assessed by the PCT 3. Increase in novel design production with no changes in world fluency productivity assessed by the CIFA 4. No effect on WMS-III spatial span and WAIS-III digit span forward (assessing attention) 5. Increase in overall backward span test performance (assessing working memory) during anodal versus cathodal tDCS
Hoy et al. 2015 [38]	Cross over	18	42.2	6F/12M	F3/FP2	1	0, 1 and 2 mA	20	After stimulation at 2 mA intensity: 1. Increase in working memory performance measured by the 2-back task at 20 and 40 min post-stimulation 2. Increase in gamma event-related synchronization measured by EEG at 40 min post-stimulation After stimulation at 1 mA intensity: 1. No effect on working memory 2. No effect on gamma event-related synchronization

tDCS electrodes placement was described according to 10/20 EEG system: F3: Left dorsolateral prefrontal cortex; F4: Right dorsolateral prefrontal cortex; FP2: Right supraorbital region; FP1: Left supraorbital region; P3: Left parietal region; P4: Right parietal region

A active, ASIT, awareness of social inference test, *CIFA* calibrated ideational fluency assessment, *CO* carbon monoxide, *EEG* electroencephalography, *F* female, *FEIT* facial emotion identification test, *FTT* finger tapping test, *GPT* grooved pegboard test, *I* intensity, *M* male, *MCCB* MATRICS consensus cognitive battery, *MSCEIT* Mayer–Salovey–Caruso emotional intelligence test; *n* number of subjects, *PANSS* positive and negative syndrome scale, *PCT* perceptual comparison test, *PONS* profile of nonverbal sensitivity, *QSU* questionnaire of smoking urges, *RCT* randomized controlled trial, *S* sham, *tDCS* transcranial direct current stimulation, *WAIS III* Wechsler adult intelligence scale, 3rd ed, *WMS-III* Wechsler memory scale, 3rd ed, *WPT* weather prediction test

In another study, Hoy et al. [34] observed beneficial effects of the same electrode montage on working memory performances measured using the n-back task. These beneficial effects lasted up to 40 min after the end of the stimulation period and were associated with an increase in frontal gamma event related synchronization [38]. Ribolsi et al. [33] reported a reduction of visuospatial attention deficit in patients with schizophrenia after a single session of tDCS where the anode electrode was placed over the right parietal (P4) and cathode over the left shoulder.

Several studies investigated the effects of anodal tDCS applied over the left DLPFC on cognitive functioning of patients with schizophrenia using a standardized battery of cognitive tests. In one of them, Rassovsky et al. [35] tested the effect of a single session of either anodal or cathodal tDCS applied over FP1 or FP2 (with the reference electrode placed over the upper right arm) on social cognition and cognitive functions in 36 patients with schizophrenia. Social cognition was measured using the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) that assesses four components of emotional processing, the Facial Emotion Identification Test (FEIT) that assesses the identification of facial emotion, the Profile of Nonverbal Sensitivity that assesses social perception, and the Awareness of Social Inference Test that assesses theory of mind. Cognitive functions were assessed using the MATRICS Consensus Cognitive Battery (MCCB) composite score. Following anodal tDCS, patients showed a significant improvement in the FEIT only, indicating that a single session of anodal tDCS over the prefrontal cortex might enhance identification of facial emotion in patients with schizophrenia.

In another study, Schretlen et al. [37] compared the effects of two 30-min sessions of tDCS, applied either with the anode over the left and cathode over the right DLPFC or with the reverse montage, on working memory and on a brief battery of cognitive measures in five outpatients with schizophrenia and six first-degree relatives of patients with schizophrenia. No differences were reported between tDCS conditions on motor speed assessed by the Grooved Pegboard Test and the Finger Tapping Test and on processing speed assessed by the Perceptual Comparison Test. No effects of tDCS condition were observed on attention assessed by the Wechsler Adult Intelligence Scale, 3rd Ed. Digit Span and Wechsler Memory Scale, 3rd Ed. Spatial Span. Working memory performances assessed by backward digit and spatial span were shown to be improved during anodal stimulation of the left DLPFC relative to cathodal stimulation. In addition, patients showed an increase in novel design production without alteration of overall productivity at the calibrated ideational fluency assessment during anodal versus cathodal tDCS.

Finally, only few studies investigated the effects of repeated sessions of tDCS on cognition in patients with schizophrenia. For instance, in a randomized double-blind, sham-controlled study, Smith et al. [36] investigated the effects of five sessions of either active or sham tDCS on cognition assessed by the MCCB composite score, psychiatric symptoms assessed by the PANSS, and smoking and cigarette craving in 37 patients with schizophrenia or schizoaffective disorder who were current smokers. tDCS was delivered with the anode placed over F3 and the cathode electrode placed over the right supra orbital region (FP2). Patients receiving active tDCS, as compared to sham, showed a significant improvement in the MCCB composite score, in the MCCB working memory score and in attention-vigilance domain scores. However, no significant effects were observed on clinical symptoms assessed by the PANSS, hallucinations, cigarette craving, and cigarettes smoked.

In a double-blind sham controlled study, Mondino et al. [26] tested the effects of ten sessions of left frontotemporal tDCS on source monitoring performance and treatment-resistant auditory verbal hallucinations in 28 patients with schizophrenia. Source monitoring was defined as the ability to discriminate between internally generated words and externally produced words. After ten sessions of active tDCS, patients performed better at recognizing internally generated words as compared to sham tDCS. In addition, there was a negative correlation between the reduction in the frequency of treatment-resistant

auditory verbal hallucinations and the increased recognition of internally generated words.

Safety of Using tDCS for Treating Schizophrenia

The reviewed articles investigated the impact of at least one tDCS session on more than 300 patients with schizophrenia. The duration of the tDCS session lasted from 10 to 30 min, with the intensity of stimulation ranging from 1 to 3 mA. Among expected adverse events following a session of tDCS [39], patients with schizophrenia more commonly reported tingling or itching sensations under the electrodes as well as sleepiness. No study reported any serious adverse event. In addition, ten sessions of tDCS delivered once or twice daily were well tolerated by specific populations such as patients with childhood-onset schizophrenia (mean age 15 years old; range 10–17) [40], female patients during pregnancy [22], and patients with comorbid skin condition [41]. Importantly, these studies did not observe any worsening of symptoms. An important improvement for patients with severe handicaps would be to have the possibility of tDCS to be delivered at home. Indeed, this was suggested for one patient with schizophrenia [14]. However, to allow this practice, the national authorities should establish recommendations ([42], also discussed in Chap. 26 of this book).

Optimizing tDCS Efficacy on Symptoms of Schizophrenia

Optimizing tDCS Parameters

The use of tDCS in schizophrenia is just at its beginning. There are still numerous unanswered questions including optimal stimulation parameters such as intensity, duration, and the number of sessions. Concerning stimulation intensity, tDCS has been mostly delivered at 1, 1.5, and 2 mA. Some studies comparing 1–2 mA stimulation suggested that 2 mA is the cut off for an optimal efficiency in reducing clinical symptoms and improving cognitive functions in schizophrenia [14, 34]. In that line, an interesting case study reported the safety of a 3 mA stimulation [14]. Concerning the duration of a session, most studies used sessions of a 20-min duration each. However, few studies reported beneficial effects of different session durations. For instance, Homan et al. [10] reported reduced auditory verbal hallucinations following ten sessions of tDCS delivered once daily at 1 mA during 15 min in a patient with schizophrenia. In another single case study, Andrade [14] enhanced tDCS duration from 20 to 30 min without adverse effects. In a randomized controlled study, Gomes et al. [30] reported the effects of ten sessions of tDCS delivered once daily at 2 mA during 10 min on negative symptoms and general symptomatology in 15 patients with schizophrenia. Concerning the number of sessions to deliver, patients with schizophrenia showed improvement after ten sessions delivered once or twice per day. One study, delivering 15 sessions of tDCS once per day, did not show any significant effect on auditory hallucinations [20]. In one case study, delivering five sessions of tDCS once per day induced a substantial reduction of auditory hallucinations that lasted at least 6 days [23]. To sum up, even if there is still much to learn about the tDCS optimal parameters, gathered evidence suggests that ten sessions of tDCS of 20-min duration and at a 2 mA intensity delivered once or twice per day produce a positive outcome such as reducing symptoms and improving cognition in patients with schizophrenia.

Other Modalities of Transcranial Electric Stimulation in Schizophrenia

Other forms of transcranial electric stimulation besides tDCS, such as high frequency oscillatory unidirectional *transcranial random noise stimulation* (tRNS) [43], have been tested in schizophrenia. To date, two studies investigated the effects of unidirectional tRNS with high frequencies ranging from 100 to 640 Hz, in patients

with schizophrenia. Palm et al. [44] reported an improvement in negative symptoms after 20 sessions of tRNS with the anode applied over the left DLPFC cortex and the cathode over the right supraorbital cortex. Haesebaert et al. [45], using the left frontotemporal montage during ten sessions of tRNS, observed a reduced severity of auditory hallucinations and an improved insight into the illness. Moreover, one study investigated the effects of transcranial slow oscillatory direct stimulation applied at a frequency of 0.75 Hz during phase 2 of sleep in 14 patients with schizophrenia [46]. In this study, slow oscillatory tDCS was applied at an intensity of 0.3 mA through two spherical 8 mm diameter electrodes placed bilaterally over F3 and F4 and at the mastoids. Stimulation was delivered for five blocks of 5 min separated by 1-min intervals free of stimulation. The authors reported that patients displayed greater performances to retain verbal information following active as compared to sham stimulation. A significant elevated mood was also observed in the morning after stimulation as compared to the morning after sham stimulation.

Combining tDCS with Other Approaches

tDCS studies most often include patients with schizophrenia suffering from treatment-resistant symptoms, and thus, treated with several medication classes including typical, atypical antipsychotics and selective serotonin reuptake inhibitors. These treatments should be taken into account when studying the impact of tDCS sessions. Indeed, in studies involving healthy subjects, dopaminergic, serotonergic, and GABAergic agents/drugs have been shown to have an impact on motor cortex excitability after tDCS sessions [47, 48]. For example, tDCS aftereffects in healthy subjects are considerably reduced with sulpiride [48]. With this in mind, it seems important that the studies investigating the effect of tDCS in patients with schizophrenia should determine the optimal association between pharmacology and the tDCS protocol. For example, a major depression study showed that bifrontal tDCS efficacy was reduced with concomitant use of benzodiazepine drugs [49]. Such interactions might also occur in patients with schizophrenia. Future work is therefore needed to study the association between tDCS effects, medication, and even nicotine intake [28] with tDCS efficacy in schizophrenia.

Another interesting approach, with the aim to improve tDCS effects on symptoms, could involve combination with neurocognitive strategies such as cognitive remediation therapy [50, 51]. For example, tDCS has been shown to improve working memory [52], therefore it could work with cognitive training as to enhance both cognitive and clinical efficacy. Further studies are needed to determine the optimal associations with the aim of improving clinical outcomes.

Conclusion

In this chapter, we reviewed and discussed studies investigating the usefulness of tDCS to reduce symptoms and improve cognitive functions of patients with schizophrenia. To date, two electrode montages seem to stand out: one frontotemporal montage with the anode placed over the left prefrontal cortex and the cathode placed over the left temporoparietal junction, which may reduce auditory verbal hallucinations; and one frontal montage with the anode placed over the left DLPFC and the cathode placed over the right DLPFC or the right supraorbital region which may also have beneficial clinical outcomes, mainly on negative symptoms. However, as the use of tDCS is quite recent and since most studies reviewed here were case-reports and open labeled studies with small samples, further randomized controlled trials with large samples are needed to confirm the efficacy of tDCS in schizophrenia. Moreover, further investigations have to be conducted to determine biological correlates and the optimal stimulation parameters to use to better impact on the symptoms of schizophrenia.

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