Psychiatry Research 344 (2025) 116308

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Transcranial direct current stimulation (tDCS) enhances cognitive function in schizophrenia: A randomized double-blind sham-controlled trial

Lorena García-Fernández [a,b,c,*], Verónica Romero-Ferreiro [c,d,e], Sergio Padilla [a,f,g], Rolf Wynn [h,i], Bartolomé Pérez-Gálvez [a,b], Miguel Ángel Álvarez-Mon [j,k,l], Ángeles Sánchez-Cabezudo [e], Roberto Rodriguez-Jimenez [c,e,m]

[a] Clinical Medicine Department, Universidad Miguel Hernández, Investigador. Cibersam isciii, Crta. Nacional 332 s/n, Alicante 03550, Spain
[b] Psychiatry Department, Hospital Universitario de San Juan, Alicante, Spain
[c] CIBERSAM-ISCIII (Biomedical Research Networking Centre for Mental Health), Spain
[d] European University of Madrid, Madrid, Spain
[e] Health Research Institute Hospital 12 de Octubre (imas12), Madrid, Spain
[f] Infectious Diseases Unit, Hospital General Universitario de Elche, Alicante, Spain
[g] CIBER de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain
[h] Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[i] Department of Education, ICT and Learning, Østfold University College, Halden, Norway
[j] Department of Medicine and Medical Specialities. University of Alcala, Alcala de Henares, Spain
[k] Department of Psychiatry and Mental Health. Hospital Universitario Infanta Leonor, Madrid, Spain
[l] Ramón y Cajal Institute of Sanitary Research (IRYCIS), Madrid 28034, Spain
[m] Complutense University of Madrid (UCM), Madrid, Spain

ARTICLE INFO

Keywords:
Schizophrenia
Transcranial direct current stimulation (tDCS)
Cognition
Neurocognition
Working memory
Subjective perception

ABSTRACT

This study aimed to examine the cognitive effects of tDCS and the subjective cognitive improvement perceived by patients with schizophrenia. A total of 173 outpatients diagnosed with schizophrenia were recruited for this double-blind, randomized, placebo-controlled trial. Two different stimulation modes were applied: 2 mA 20 minutes active tDCS and sham tDCS. Ten daily sessions over 10 consecutive weekdays were applied, using a bifrontal montage (F3/F4). The Positive and Negative Syndrome Scale for Schizophrenia and the MATRICS Consensus Cognitive Battery (MCCB) were administered at baseline. The MCCB and a scale designed for measuring subjective cognitive improvement were administered to evaluate the outcomes. Post hoc comparisons revealed significant effects between the two types of interventions in Working Memory (EMM difference = 2.716, $p < .001$) and Neurocognition (EMM difference = 1.289, $p = .007$. Chi-squared tests demonstrated a significant association between subjective improvement and the treatment group, χ^2 (2) = 10.413, $p = .005$, Cramer's V = 0.295. A higher proportion of patients in active tDCS (68.6%) reported cognitive improvement compared to sham tDCS (31.4%). We concluded that tDCS can enhance cognition and generate a satisfactory perception of cognitive improvement in patients with schizophrenia.

1. Introduction

Schizophrenia is a disabling brain disorder that impairs crucial brain regions necessary for daily functioning (Świtaj et al., 2012). It is also one of the most common mental disorders, affecting nearly 1% of the global population (Lauriello, 2020; Faden, and Citrome, 2023). Schizophrenia typically begins in late adolescence or early adulthood and follows a chronic course in which up to two-thirds of patients exhibit some degree of cognitive dysfunction despite treatment (Tandon et al., 2013; American Psychiatric Association, 2013).

Schizophrenia affects emotions, perception, thinking, social interaction, behavior and information processing, resulting in a disorder with a wide range of affected symptom domains (Carpenter, and Buchanan, 1994). Among all these clinical manifestations, cognitive deficits have traditionally been considered as part of the core symptoms of schizophrenia (McCutcheon et al., 2023). These deficits typically appear at

* Corresponding author.
E-mail address: lorena.garciaf@umh.es (L. García-Fernández).

https://doi.org/10.1016/j.psychres.2024.116308
Received 12 July 2024; Received in revised form 26 November 2024; Accepted 30 November 2024
Available online 2 December 2024

early stages of the disorder and remain stable throughout its course (Fioravanti et al., 2012). They are relatively unaffected by the different phases of the disease and are regarded as the main determinants of prognosis (Marwaha and Johnson, 2004; Yamada et al., 2019)

Cognitive dysfunction in schizophrenia has traditionally been linked with deficits in neurocognition, which encompasses the brain processes related to evaluating and processing information (Fakra et al., 2015; Gebreegziabher et al., 2022). This includes domains such as attention, memory, executive functions, and language. Most patients with schizophrenia exhibit impairments across multiple cognitive domains, with cognitive performance typically falling between 1 and 2 standard deviations below that of the general population (Rodriguez-Jimenez et al., 2019).

A wide range of pharmacological approaches have been attempted to address cognitive symptoms in schizophrenia, including those targeting glutamatergic, cholinergic, and nicotinic receptors, but these have demonstrated limited effectiveness so far (Keefe and Fenton, 2007; Keefe et al., 2013; Yang and Tsai, 2017; Zink and Correll, 2015; Koola, 2021). Consequently, there has been an increased focus on non-pharmacological therapies aimed at enhancing cognition. Among these, cognitive behavioral therapy, neurocognitive remediation and non-invasive brain stimulation (NIBS) techniques have demonstrated promising benefits in improving cognitive performance (Best and Bowie, 2017; García Fernández et al., 2019; Bowie et al., 2020; Cella et al., 2023).

Transcranial direct current stimulation (tDCS), a NIBS technique, uses low-intensity electric currents delivered via scalp electrodes over specific cortical areas to induce sustained changes in membrane potential and cortical cell and fiber excitability (Lefaucheur et al., 2017; Cella et al., 2023). In addition to modulating cortical activity, tDCS induces neurochemical and hormonal changes through selective stimulation of specific brain regions, which, depending on the applied protocol, can increase or decrease neuronal excitability (Kronick et al., 2022). These modifications in membrane potential, mediated by calcium and the activity of N-methyl-D-aspartate (NMDA) receptors, induce neuroplastic and structural changes (Boudewyn et al., 2020). They also modulate GABAergic and glutamatergic transmission (Das et al., 2016), both of which are implicated in the pathophysiology of schizophrenia. tDCS has been tested in patients with schizophrenia in the last decade suggesting its efficacy in addressing treatment resistant hallucinations, catatonic symptoms, and negative symptoms (Pelletier and Cicchetti, 2014). The safety and tolerability of the technique have been established, including in pediatric populations (Stagg et al., 2013).

Studies conducted across various neuropsychiatric disorders indicate a modest trans-diagnostic effect on working memory and attention/vigilance following tDCS (Rossi et al., 2009; Cheng et al., 2020; Begemann et al., 2020). Effects on other cognitive domains are statistically non-significant and often limited in size and duration (Dedoncker et al., 2016; Hill et al., 2016). Research focusing exclusively on individuals with schizophrenia also reports positive effects on working memory (Smith et al., 2015; Kostova et al., 2020; Fregni et al., 2021). However, the findings have been inconsistent as some randomized controlled trials have shown no reliable cognitive improvement following treatment with tDCS in patients suffering from schizophrenia (Vercammen et al., 2011; Hyde et al., 2022; Li et al., 2024). Additionally, these studies show mixed results regarding benefits in the attention domain, adding further complexity to the overall findings (Smith et al., 2015; Sloan et at., 2021; Li et al., 2024). Moreover, due to the limited number of studies, small sample sizes, and heterogeneity in study design, stimulation intensity, session duration, and the total number of sessions, the research results should be interpreted with caution.

Therefore, to shed light on the potential of tDCS for enhancing cognitive function in schizophrenia, the aim of this double-blind, randomized, placebo-controlled study is to evaluate the cognitive effects of tDCS in a large group of schizophrenia outpatients. We hypothesize that anodal tDCS applied over the left DLPFC, with the cathode at the right contralateral area, may improve cognitive performance. Additionally, as no prior studies have explored the subjective sense of improvement perceived by patients following tDCS, we have addressed this gap focusing on assessing patients' perceived cognitive enhancement following the intervention.

2. Material and methods

2.1. Subjects

A total of 173 outpatients diagnosed with schizophrenia were recruited from San Juan´University Hospital in Alicante, Spain, for this double-blind, randomized, placebo-controlled trial. All patients were diagnosed by an independent psychiatrist according to the Structured Clinical Interview for DSM-5 Disorders (SCID-5-CV) (Shabani et al., 2021).

Participants were included if they met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) criteria for schizophrenia, were aged between 18 and 50 years old and had been clinically stable outpatients for at least the last month. Stability was defined as the absence of significant clinical changes in symptomatology as recorded in the patient's medical file, along with no modifications in treatment and no hospitalizations.

Participants over 50 years old were excluded, aiming to prevent the inclusion of patients with cognitive deterioration from other causes than the psychotic disorder. Exclusion criteria also included people with neurosensory deficits that impeded reading or executing the selected instruments and those with previously diagnosed intellectual dysfunction as estimated by an IQ < 70 on the Wechsler Adult Intelligence Scale (WAIS-IV) (Weschler, 1955). Participants who have received electroconvulsive therapy in the past year, those with a history of organic brain damage, including epilepsy, tumors, and traumatic brain injuries, and those with specific contraindications for tDCS, such as metal implants or intracranial devices were also excluded.

All participants provided written informed consent. The study was approved by the research ethics committee for medical products of the General University Hospital of Elche.

2.2. Instruments

The Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987) is considered the gold standard test for assessing symptom severity and monitoring treatment response. This assessment consists of 30 items scored from 1 "absent" to 7 "extreme" allowing the subdivisión into three subscales (positive, negative and general psychopathology).

The MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008; Kern et al., 2011) is a standardized tool designed to evaluate cognitive function in patients with schizophrenia. It assesses seven cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition. This study used the published and approved translation of the MCCB for Spain and the Spanish normative and standardized data correction published by our group (Rodriguez-Jimenez et al., 2015). This version, in addition to covering different domains, provides a global neurocognitive variable called Neurocognition. This variable offers a composite score based on all the neurocognitive domains of the MCCB, excluding Social Cognition.

The Subjective Cognitive Improvement Likert Scale was designed for the present study. It evaluates patients' perceived cognitive changes on a 3-point Likert scale: 1 "I feel worse," 2 "I have noticed no difference," and 3 "I have improved." Participants indicate their subjective perception of cognitive changes based on these categories, providing insights into their perceived improvements once the intervention has concluded. Participants were not asked about their improvement expectations or their guessed group assignment.

The Visual Analog Scale (VAS) (Delgado et al., 2018) is a 10 cm horizontal line used to measure subjective experiences, such as pain. It ranges from 0 "no pain" to 10 "worst pain", and respondents mark their experience on the line, giving a quantitative score based on the distance from one end.

2.3. Procedures

Participants were randomly assigned to either the active tDCS group or the sham tDCS group. Random assignment was conducted by the clinical staff responsible for administering the tDCS, using an online random assignment generator platform (https://www.random.org/). The results of the randomization were safeguarded by this clinical staff, blinding both the patients and the study evaluators until the study's completion.

Once consent was obtained, prior to randomizing the patients and initiating any study procedures, a tolerability test for the tDCS technique was conducted. This involved a 5-minute sham tDCS application during which quantitative pain assessment was performed using the VAS (Delgado et al., 2018). Patients scoring 8 or higher (severe pain) on the VAS were excluded from the study.

The study comprised 12 visits. A baseline assessment visit (V0), ten consecutive weekdays, excluding weekends, following the protocol proposed by Orlov (Orlov et al., 2017) and a final visit (V1).

At visit V0, the PANSS was administered to evaluate the clinical psychopathological state, along with the MCCB to assess cognitive performance. The MCCB was administered again at V1, following the completion of the 10 tDCS sessions to evaluate the efficacy of tDCS on cognitive performance. In V1, since the MCCB includes alternative forms for repeated measures, these alternative forms were presented in a counterbalanced manner. Furthermore, upon completion of the intervention, participants were asked to evaluate the perceived cognitive benefit of tDCS using a 3-point Likert scale.

Failure to attend two or more sessions out of the 10 scheduled sessions was considered as treatment failure.

2.4. tDCS parameters

To generate the electric current, a transcranial direct current stimulation (tDCS) device, DC-Stimulator@ (NeuroConn@; Ilmenau, Germany), was used. This device holds the EU Declaration of Conformity as a Class IIA medical product in accordance with Directive 93/42/EEC. Following the International 10-20 system for electroencephalographic electrode placement (Klem et al., 1999), the anode (with a surface area of 35 mm2) was applied to the left dorsolateral prefrontal cortex (DLPFC) (F3) (Kennedy et al., 2018), while the cathode (with a surface area of 35 cm2) was applied to the right DLPFC (F4) (Gomes et al., 2018), known as bifrontal montage (F3/F4). The electrodes were inserted into sponges soaked in saline solutions (0.9% NaCI) prior to placement.

Two different stimulation modes were applied based on patient assignment: i) tDCS stimulation consisting in 2 mA for 20 minutes (Gomes et al., 2018) plus an additional ramp-up and ramp-down period of 30 seconds each and, ii) sham stimulation consisted of a ramp-up stimulation phase (30 seconds), followed by a brief period of 30 seconds of stimulation to mimic the typical tingling sensation experienced at the beginning of stimulation. Subsequently, the current was discontinued, with the last 30 seconds of the session being a ramp-down phase. Stimulation took place once a day on ten consecutive weekdays (Brunoni et al., 2017).

2.5. Statistical analysis

Failure to attend two or more sessions out of the 10 scheduled has been considered as treatment failure in the intention-to-treat analysis. Data were analyzed with IBM® SPSS v.29.0 (IBM Corp.). Basal values were compared between groups using independent samples t-test for continuous variables, and chi-squared tests for categorical variables (i.e. gender distribution or active working). Raw scores from each test of MCCB were entered into the MCCB Computer Scoring Program to produce age- and gender-corrected T-scores.

For the primary aim, a mixed-effect model was conducted to analyze the tDCS effects. Intervention (active tDCS vs. sham tDCS) and the seven domains of the MCCB were modelled as fixed effects, whereas variance across participants was modelled as a random effect to account for individual differences in the dependent variables. The difference scores (post-treatment minus pretreatment) of the seven domains of the MCCB were included as the dependent variable. The intervention (active tDCS vs. sham tDCS) was included as the between-groups factor. The MCCB x group interaction was analyzed with an estimated marginal means (EMM) post hoc analysis with the Bonferroni adjustment. Baseline differences between groups in the cognitive domain being analyzed were included as covariates in the analysis.

For the second aim, the distribution of responses in the The Subjective Cognitive Improvement Likert Scale in both groups was compared using the chi-squared test. In this case, only responses from those who completed at least eight treatment sessions were analyzed.

A p-value less than predetermined alpha (0.05) was considered a statistically significant result.

3. Results

3.1. Participant selection and dropout

Throughout the study period, a total of 173 patients were selected. Thirty-four of these patients were excluded: 14 declined to participate, 12 did not meet the inclusion criteria, and 8 scored 8 or higher (severe pain) on the pain assessment scale before starting any study procedure.

Finally, a total of 139 patients were randomized into one of two comparison groups (71 patients received tDCS and 68 received sham tDCS). Nine patients in the tDCS group and ten patients in the sham group did not complete the minimum of eight sessions required for treatment completion and were thus classified as lost to follow-up. Fig. 1 presents the flow diagram of participants throughout the study, illustrating their allocation, intervention, follow-up, and analysis stages. Consequently, of the 139 included participants, 120 completed all the study visits. Thus, only 6.8% of the overall data were missing. Analysis revealed that missing data was completely at random (MCAR) (Little MCAR test: $\chi 2\ (10) = 12.39$, $p = 0.26$). Despite the small percentage of missing data, missing values were imputed. Intention-to-treat (ITT) analyses were performed following Newman's guidelines (Newman, 2014), using Maximum Likelihood (ML) estimation method.

3.2. Baseline comparisons

No significant baseline differences between the active tDCS and sham tDCS groups were observed regarding gender, age, disease duration in years, educational level of the patient or their family (calculated as the average years of education of the mother and father), active employment and chlorpromazine equivalent doses (although the active tDCS group showed slightly lower average chlorpromazine equivalent doses) as Table 1 shows.

Nor were any baseline differences detected in clinical psychopathology scale scores measured with the PANSS. However, a trend toward significance was observed in MCCB Speed Processing and Working Memory, although theses did not reach statistical significance. On the other hand, significant baseline differences in some cognitive domains assessed bythe MCCB. Specifically, differences between groups were found in MCCB Reasoning Problem-Solving $t(137) = 2.298$, $p = .023$ and in MCCB Neurocognition $t(137) = 2.095$, $p = .038$. For this reason, these variables were included as covariates in the analysis. Clinical features are described in Table1.

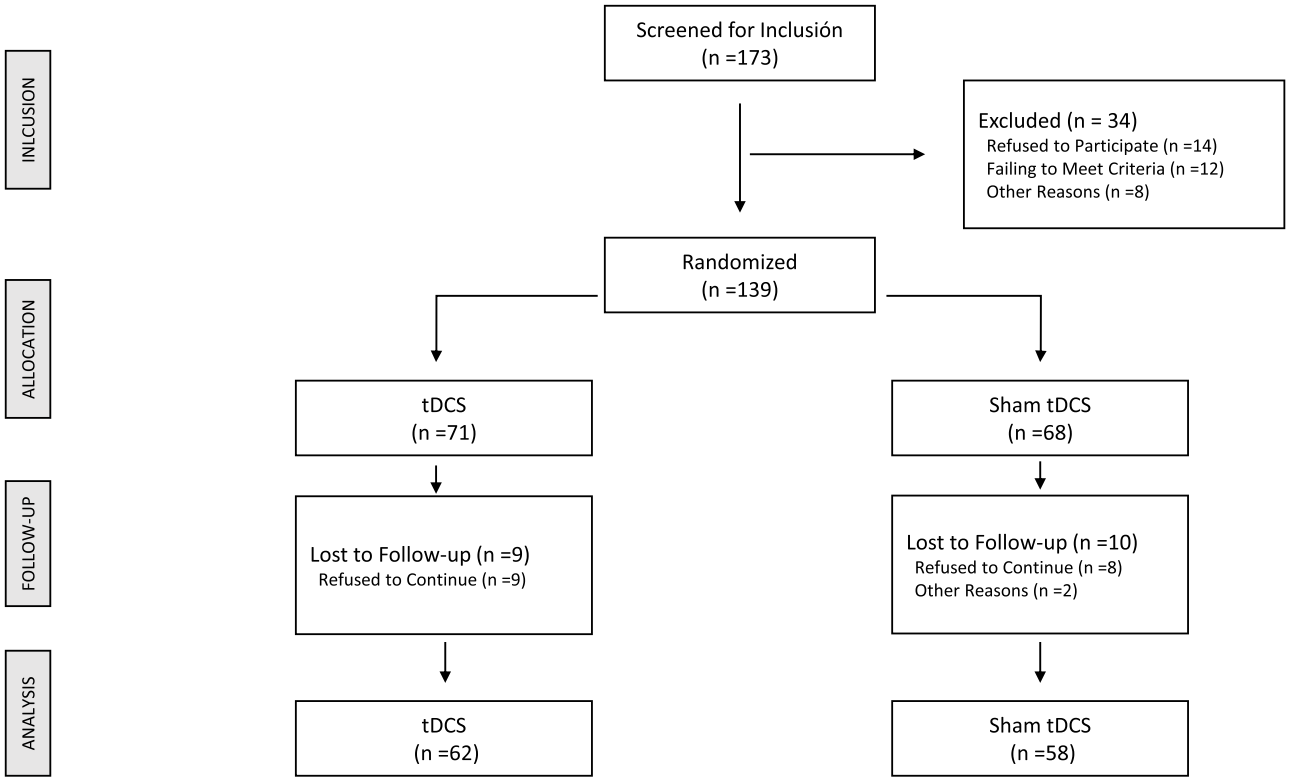

Fig. 1. Flow Diagram of Participants (Cobos-Carbó, 2005).

3.3. tDCS effects on cognition

The result of the mixed-effect model showed a main effect of MCCB domains [$F(8, 226.8) = 10.074$, $p < .001$]. Regarding the between-subjects factor, there was a significant effect of the intervention [$F(1, 190.9) = 5.361$, $p = .022$] and also, a significant MCCB x intervention interaction [$F(8, 226.8) = 4.056$, $p < .001$].

Post hoc comparisons revealed a significant effect between the two types of interventions (Fig. 2) in the following MCCB domains: Working Memory [EMM difference = 2.716, $p < .001$; M (SD) pre tDCS 45.6 (10.9); post tDCS 49.3 (11.0) vs. M (SD) pre sham tDCS 42.1 (12.4); post sham tDCS 43.2 (12.6)]; and Neurocognition [EMM difference = 1.289, $p = .007$; M (SD) pre tDCS 41.5 (10.5); post tDCS 42.5 (9.8) vs. M (SD) pre sham tDCS 37.6 (11.8); post sham tDCS 37.4 (11.1)] as shown in table 2.

3.4. Subjective perception of the cognitive effect of tDCS

Chi-squared tests showed an association between the subjective improvement and the treatment group $\chi^2(2) = 10.413$, $p = .005$, Cramer's V = 0.295. The proportion of patients who responded 3 "I have improved" was superior in the active tDCS group (68.6%) compared to the sham tDCS group (31.4%).

4. Discussion

This study aims to evaluate the cognitive effects of tDCS in a large cohort of schizophrenia outpatients. Regarding the first hypothesis, our findings indicate that 10 tDCS sessions, administered once a day over 10 consecutive weekdays, have been effective in improving working memory and therefore, neurocognition in stable outpatients with schizophrenia, immediately after the intervention had finished. No significant improvement in other cognitive domains were achieved.

Despite the growing interest in neuromodulation as a potential strategy for enhancing cognition in patients with schizophrenia, research has yielded mixed and heterogeneous results regarding the technique's efficacy (Sloan et al., 2021). These inconsistencies have been attributed to small sample sizes of most of the studies (Gomes et al., 2018; Chang et al., 2019), individual and clinical differences (Bulubas et al., 2021), as well as variations in devices and parameters used (Shiozawa et al., 2013; Mondino et al., 2015; Moffa et al., 2018).

Regarding the observed enhancement of working memory and neurocognition performance, which was not evident for other cognitive domains, our study highlights the potential of anodal tDCS applied to the left DLPFC in enhancing working memory and neurocognition in patients with schizophrenia. This approach has been suggested as an innovative treatment tool for cognitive improvement (Martin et al., 2014; Filmer et al., 2014; Smith et al., 2015; Hoy et al., 2015), particularly for working memory (Andrews et al., 2011; Valiengo et al., 2020). The left DLPFC has been proposed as a target area to improve working memory due to its crucial role in mental representation and abstraction (Arnsten, 2013). The DLPFC shows reduced gray matter volume (Arnsten, 2013) and decreased activation (Hill et al., 2004), indicating lower resting-state blood flow (Andreasen et al., 1997) in patients with schizophrenia. Additionally, while the DLPFC itself shows specific deficits in patients with schizophrenia, the disconnection of the prefrontal cortex (PFC) from other brain regions is also associated with cognitive impairments (Zhou et al., 2015). Moreover, the DLPFC is the brain region most implicated in working memory (Levy and Goldman, 2000; Cannon et al., 2005), therefore, targeting the DLPFC through tDCS, as our study has done, may mitigate cognitive deficits by enhancing its function and connectivity and could partly explain why a significant improvement is observed in these cognitive domains but not in others.

Regarding montage, placing the anode at the left DLPFC (F3) appears essential for cognitive improvement, while the location of the cathode might be less critical as prior studies have suggested that the benefits in working memory have persisted despite variations in cathode placement (Rassovsky et al., 2018; Papazova et al., 2018; Meiron et al., 2021; Fathi Azar et al., 2021; Lisoni, 2022).

These findings underscore the importance of optimizing tDCS

Table 1
Patient demographic and clinical baseline data per treatment group.

	Active tDCS (N=71)	Sham tDCS (N=68)	Stats	p-value
Age, years (M, SD)	32.4 (11.2)	31.9 (10.8)	t(137) = 0.266	0.791
Gender (male, %)	62.0%	72.1%	1.596	0.214
Illness duration (M, SD)	10.4 (9.2)	9.5 (9.0)	t(137) = 0.623	0.534
Level of education, years attending school (M, SD)				
Patient	13.2 (3.5)	13.1 (3.6)	t(137) = 0.153	0.879
Family	12.1 (3.9)	10.8 (4.3)	t(137) = 0.904	0.059
Functioning, % active employment	19.7	14.7	0.611	0.504
Chlorpromazine equivalent doses (M, SD)	445.8 (264.8)	535.8 (298.5)	t(137) = -0.884	0.062
PANSS score (M, SD)				
Positive	15.1 (5.5)	14.6 (5.7)	t(137) = 0.551	0.582
Negative	21.7 (5.9)	20.9 (4.5)	t(137) = 0.840	0.402
General psychopatology	40.0 (10.2)	39.4 (8.3)	t(137) = 0.426	0.671
MCCB score* (M, SD)				
Speed of processing	40.4 (9.3)	37.5 (8.7)	t(137) = 1.865	0.064
Attention vigilance	41.9 (9.7)	39.1 (1.,4)	t(137) = 1.577	0.117
Working memory	45.6 (10.9)	42.1 (12.4)	t(137) = 1.757	0.081
Verbal learning	44.8 (13.6)	42.1 (11.9)	t(137) = 1.326	0.187
Visual learning	43.1 (12.2)	41.5 (13.9)	t(137) = 0.689	0.492
Reasoning problem solving	46.5 (10.9)	42.0 (12.1)	t(137) = 2.298	**0.023**
Social Cognition	37.9 (12.6)	39.4 (14.3)	t(137) = -0.635	0.572
Neurocognition	41.5 (10.5)	37.6 (11.8)	t(137) = 2.095	**0.038**

Bold font indicates statistical significance ($p < .05$). *MCCB age- and gender-corrected T-scores
M: mean; SD: standard deviation

protocols to maximize cognitive outcomes in clinical settings. However, we cannot disregard clinical trials with comparable tDCS intensities and session frequencies that did not find cognitive benefits. These divergent outcomes, notwithstanding similar methodologies, may be attributed to sample characteristics. Our study primarily involves young patients with a median age under 32 years old, an average disease duration of about 10 years and low psychopathological scores indicative of clinical stability. In contrast, other studies with contradictory findings included older patients with longer illness durations (Irani et al., 2011; Chang et al., 2019), those with higher levels of general psychopathology (Gomes et al., 2018), or samples predominantly comprising patients with negative symptoms (Bulubas et al., 2021).

Our results demonstrate significant cognitive benefits with 2 mA tDCS administered in 20-minute sessions daily over 10 consecutive days, indicating that this intensity and frequency may be adequate to induce

Table 2
Post-treatment and Estimated Marginal Means (EMM) in MCCB domains for the post-pre difference and post hoc significances per treatment group.

		Active tDCS Mean (SD)	**Sham tDCS** Mean (SD)	Difference (SD), p-value
Speed of processing	Post-treatment	40.4(8.9)	37.7(8.7)	
	EMM Post-Pre diff	0.126 (0.182)	0.104 (0.186)	0.023(0.262), $p = .931$
Attention vigilance	Post-treatment	41.4(9.3)	39.1 (11.4)	
	EMM Post-Pre diff	-0.381 (0.324)	-0.29 (0.331)	-0.352(0.464), $p = .449$
Working memory	Post-treatment	49.3 (11.0)	43.2 (12.6)	
	EMM Post-Pre diff	3.746 (0.391)	1.030 (0.399)	2.716(0.559), $p < .001$
Verbal learning	Post-treatment	45.6 (12.2)	42.7 (11.0)	
	EMM Post-Pre diff	0.675 (0.286)	0.339 (0.292)	0.337(0.410), $p = .413$
Visual learning	Post-treatment	43.4 (11.3)	41.8 (11.7)	
	EMM Post-Pre diff	0.408 (0.219)	0.207 (0.224)	0.201(0.315), $p = .523$
Reasoning problem solving	Post-treatment	46.7 (10.4)	42.7 (11.8)	
	EMM Post-Pre diff	0.309 (0.349)	0.677 (0.357)	-0.368(0.500), $p = .463$
Social Cognition	Post-treatment	37.1 (11.9)	38.5 (12.6)	
	EMM Post-Pre diff	-0.911 (0.606)	-0.803 (0.593)	0.108(0.848), $p = .899$
Neurocognition	Post-treatment	42.5(9.8)	37.4 (11.1)	
	EMM Post-Pre diff	1.084 (0.328)	-0.205 (0.335)	1.289(0.469), $p = .007$

M: mean; SD: standard deviation; EMM: estimated marginal means.

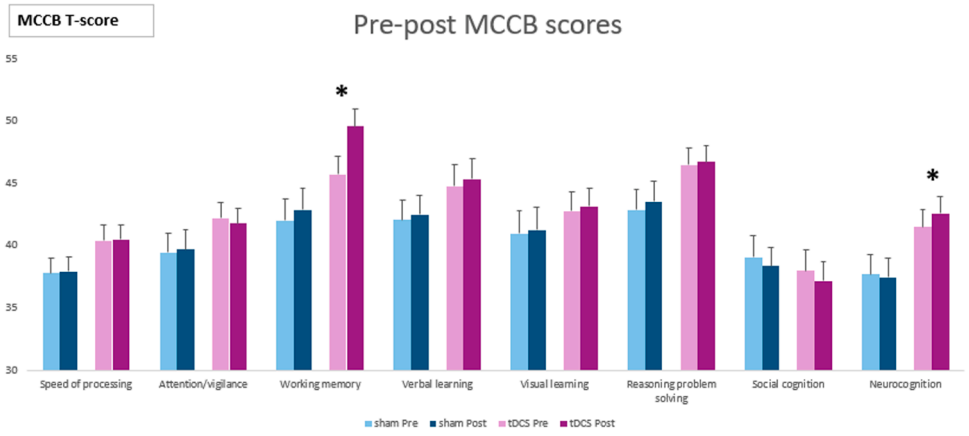

Fig. 2. Change in cognitive performance across MCCB domains after tDCS and sham tDCS in the study groups.

cognitive improvements. This aligns with previous research suggesting that increased session frequency and intensity, along with a higher number of sessions, are associated with more pronounced treatment effects (Mondino et al., 2015; Kim et al., 2019; Yu et al., 2020; Hyde et al., 2022).

Furthermore, regarding the second objective of this study, an aspect that has been relatively understudied in previous research is the subjective perception of cognitive improvement reported by the patients following the intervention (Womg et al., 2011; Grycuk et al., 2021). Our results indicate that a greater number of patients in the active tDCS group perceive a sense of cognitive enhancement post-treatment compared to those in the sham tDCS group. This subjective improvement is crucial as it provides insights into the real-world applicability and patient-centered outcomes of the treatment. Additionally, the positive perception of tDCS experienced by patients is essential for treatment adherence, perceived quality of care, and overall patient satisfaction. These factors highlight the importance of considering patient opinions when evaluating the effectiveness of tDCS in clinical settings. Understanding these subjective experiences complements objective measures, such as the MCCB, and underscores the holistic benefits of tDCS in enhancing cognitive functions in patients with schizophrenia.

Given the limited efficacy of pharmacological treatments for the cognitive symptoms of schizophrenia, there has been a need for other treatments that could address these symptoms. tDCS has shown promise, but prior studies have shown differing results (Begemann et al., 2020). The present study finds that tDCS can enhance cognitive functioning in patients suffering from schizophrenia, and has some significant strengths. We conducted a study with one of the largest sample of patients with schizophrenia receiving tDCS, to date. Participants were assessed using the MCCB, an established tool for evaluating cognition in schizophrenia. Additionally, we applied a montage specifically designed for cognitive enhancement and, for the first time, assessed participants' subjective perception of improvement following tDCS. As a limitation, we note the significant differences between groups in the two baseline cognitive domains (reasoning problem-solving and neurocognition), which we addressed by including this variable as a covariate in the analysis. While our findings provide promising insights into the potential cognitive benefits of tDCS over a short two-week period in people with schizophrenia, caution must be exercised in their interpretation due to the chronic nature of the condition. Nevertheless, our results shed light on a treatment avenue that may enhance cognition and thereby improve the overall well-being of patients with schizophrenia. Future research with longer follow-up periods is essential to validate our findings and further explore this promising therapeutic approach.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Lorena García-Fernández: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Verónica Romero-Ferreiro:** Data curation, Formal analysis, Writing – review & editing. **Sergio Padilla:** Methodology, Writing – review & editing. **Rolf Wynn:** Writing – review & editing. **Bartolomé Pérez-Gálvez:** Resources, Writing – review & editing. **Miguel Ángel Álvarez-Mon:** Writing – review & editing. **Ángeles Sánchez-Cabezudo:** Writing – review & editing. **Roberto Rodriguez-Jimenez:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

Dr. R. Rodriguez-Jimenez has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/BMD-2422 AGES; S2017/BMD-3740; P2022/BMD-7216), JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen-Recordati, Angelini, Rovi. All other authors declare that they have no competing interests.

Acknowledgment

N/A.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. Arlington, VA.

Andreasen, N.C., O'Leary, D.S., Flaum, M., Nopoulos, P., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D., 1997. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naïve patients. Lancet 349 (9067), 1730–1734. https://doi.org/10.1016/s0140-6736(96)08258-x.

Andrews, S.C., Hoy, K.E., Enticott, P.G., Daskalakis, Z.J., Fitzgerald, P.B., 2011. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul. 4 (2), 84–89. https://doi.org/10.1016/j.brs.2010.06.004.

Arnsten, A.F., 2013. The neurobiology of thought: the groundbreaking discoveries of Patricia Goldman-Rakic 1937-2003. Cereb. Cortex (New York, N.Y.: 1991) 23 (10), 2269–2281. https://doi.org/10.1093/cercor/bht195.

Begemann, M.J., Brand, B.A., Ćurčić-Blake, B., Aleman, A., Sommer, I.E., 2020. Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. Psychol. Med. 50 (15), 2465–2486. https://doi.org/10.1017/S0033291720003670.

Best, M.W., Bowie, C.R., 2017. A review of cognitive remediation approaches for schizophrenia: from top-down to bottom-up, brain training to psychotherapy. Expert. Rev. NeurOther 17 (7), 713–723. https://doi.org/10.1080/14737175.2017.1331128.

Boudewyn, M.A., Scangos, K., Ranganath, C., Carter, C.S., 2020. Using prefrontal transcranial direct current stimulation (tDCS) to enhance proactive cognitive control in schizophrenia. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 45 (11), 1877–1883. https://doi.org/10.1038/s41386-020-0750-8.

Bowie, C.R., Bell, M.D., Fiszdon, J.M., Johannesen, J.K., Lindenmayer, J.P., McGurk, S. R., Medalia, A.A., Penadés, R., Saperstein, A.M., Twamley, E.W., Ueland, T., Wykes, T., 2020. Cognitive remediation for schizophrenia: an expert working group white paper on core techniques. Schizophr. Res. 215, 49–53. https://doi.org/10.1016/j.schres.2019.10.047.

Brunoni, A.R., Moffa, A.H., Sampaio-Junior, B., Borrione, L., Moreno, M.L., Fernandes, R. A., Veronezi, B.P., Nogueira, B.S., Aparicio, L.V.M., Razza, L.B., Chamorro, R., Tort, L.C., Fraguas, R., Lotufo, P.A., Gattaz, W.F., Fregni, F., Benseñor, I.M., ELECT-TDCS Investigators, 2017. Trial of electrical direct-current therapy versus escitalopram for depression. N. Engl. J. Med. 376 (26), 2523–2533. https://doi.org/10.1056/NEJMoa1612999.

Bulubas, L., Goerigk, S., Gomes, J.S., Brem, A.K., Carvalho, J.B., Pinto, B.S., Elkis, H., Gattaz, W.F., Padberg, F., Brunoni, A.R., Valiengo, L., 2021. Cognitive outcomes after tDCS in schizophrenia patients with prominent negative symptoms: Results from the placebo-controlled STARTS trial. Schizophr. Res. 235, 44–51. https://doi.org/10.1016/j.schres.2021.07.008.

Cannon, T.D., Glahn, D.C., Kim, J., Van Erp, T.G., Karlsgodt, K., Cohen, M.S., Nuechterlein, K.H., Bava, S., Shirinyan, D., 2005. Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. Arch. Gen. Psychiatry 62 (10), 1071–1080. https://doi.org/10.1001/archpsyc.62.10.1071.

Carpenter Jr, W.T., Buchanan, R.W., 1994. Schizophrenia. N. Engl. J. Med. 330 (10), 681–690. https://doi.org/10.1056/NEJM199403103301006.

Cella, M., Tomlin, P., Robotham, D., Green, P., Griffiths, H., Stahl, D., Valmaggia, L., 2023. Virtual Reality Supported Therapy for the Negative Symptoms of Schizophrenia: The V-NeST Feasibility RCT. National Institute for Health and Care Research.

Chang, C.C., Kao, Y.C., Chao, C.Y., Chang, H.A., 2019. Enhancement of cognitive insight and higher-order neurocognitive function by fronto-temporal transcranial direct current stimulation (tDCS) in patients with schizophrenia. Schizophr. Res. 208, 430–438. https://doi.org/10.1016/j.schres.2018.12.052.

Cheng, P.W.C., Louie, L.L.C., Womg, Y.L., Womg, S.M.C., Leung, W.Y., Nitsche, M.A., Chan, W.C., 2020. The effects of transcranial direct current stimulation (tDCS) on clinical symptoms in schizophrenia: a systematic review and meta-analysis. Asian J. Psychiatr. 53, 102392. https://doi.org/10.1016/j.ajp.2020.102392.

Cobos-Carbó, A., CONSORT group, 2005. Ensayos clínicos aleatorizados (CONSORT) [Randomized clinical trials (CONSORT)]. Med. Clin. (Barc) 125 (Suppl 1), 21–27. https://doi.org/10.1016/s0025-7753(05)72205-3.

Das, S., Holland, P., Frens, M.A., Donchin, O., 2016. Impact of transcranial direct current stimulation (tDCS) on neuronal functions. Front. Neurosci. 10, 550. https://doi.org/10.3389/fnins.2016.00550.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.A., 2016. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 9 (4), 501–517. https://doi.org/10.1016/j.brs.2016.04.006.

Delgado, D.A., Lambert, B.S., Boutris, N., McCulloch, P.C., Robbins, A.B., Moreno, M.R., Harris, J.D., 2018. Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. J. Am. Acad. Orthop. Surg. Glob. Res. Rev. 2 (3). https://doi.org/10.5435/JAAOSGlobal-D-17-00088.

Faden, J., Citrome, L., 2023. Schizophrenia: one name, many different manifestations. Med. Clin. North Am. 107 (1), 61–72. https://doi.org/10.1016/j.mcna.2022.05.005.

Fakra, E., Belzeaux, R., Azorin, J.M., Adida, M., 2015. Symptômes négatifs, émotions et cognition dans la schizophrénie [Negative symptoms, emotion and cognition in schizophrenia]. Encephale 41 (6 Suppl 1), 6S18–6S21. https://doi.org/10.1016/S0013-7006(16)30005-7.

Fathi Azar, E., Hosseinzadeh, S., Nosrat Abadi, M., Sayad Nasiri, M., Haghgoo, H.A., 2021. Impact of psychosocial occupational therapy combined with anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex on the cognitive performance of patients with schizophrenia: a randomized controlled trial. Hong Kong J. Occup. Therapy: HKJOT 34 (2), 121–131. https://doi.org/10.1177/15691861211065155.

Fioravanti, M., Bianchi, V., Cinti, M.E., 2012. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. BMC. Psychiatry 12, 64. https://doi.org/10.1186/1471-244X-12-64.

Fregni, F., El-Hagrassy, M.M., Pacheco-Barrios, K., Carvalho, S., Leite, J., Simis, M., Brunelin, J., Nakamura-Palacios, E.M., Marangolo, P., Venkatasubramanian, G., San-Juan, D., Caumo, W., Bikson, M., Brunoni, A.R., Group, Neuromodulation Center Working, 2021. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. Int. J. Neuropsychopharmacol. 24 (4), 256–313. https://doi.org/10.1093/ijnp/pyaa051.

García-Fernández, L., Cabot-Ivorra, N., Rodríguez-García, V., Pérez-Martín, J., Dompablo, M., Pérez-Gálvez, B., Rodriguez-Jimenez, R., 2019. Computerized cognitive remediation therapy, REHACOM, in first episode of schizophrenia: A randomized controlled trial. Psychiatry Res. 281, 112563. https://doi.org/10.1016/j.psychres.2019.112563.

Gebreegziabhere, Y., Habatmu, K., Mihretu, A., Cella, M., Alem, A., 2022. Cognitive impairment in people with schizophrenia: an umbrella review. Eur. Arch. Psychiatry Clin. Neurosci. 272 (7), 1139–1155. https://doi.org/10.1007/s00406-022-01416-6.

Gomes, J.S., Trevizol, A.P., Ducos, D.V., Gadelha, A., Ortiz, B.B., Fonseca, A.O., Akiba, H. T., Azevedo, C.C., Guimaraes, L.S.P., Shiozawa, P., Cordeiro, Q., Lacerda, A., Dias, A. M., 2018. Effects of transcranial direct current stimulation on working memory and negative symptoms in schizophrenia: a phase II randomized sham-controlled trial. Schizophr. Res. Cogn. 12, 20–28. https://doi.org/10.1016/j.scog.2018.02.003.

Grycuk, L., Moruzzi, F., Bardjesteh, E., Gaughran, F., Campbell, I.C., Schmidt, U., 2021. Participant experiences of transcranial direct current stimulation (tDCS) as a treatment for antipsychotic medication induced weight gain. Front. Psychol. 12, 694203. https://doi.org/10.3389/fpsyg.2021.694203.

Hill, A.T., Fitzgerald, P.B., Hoy, K.E., 2016. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul. 9 (2), 197–208. https://doi.org/10.1016/j.brs.2015.10.006.

Hoy, K.E., Bailey, N.W., Arnold, S.L., Fitzgerald, P.B., 2015. The effect of transcranial direct current stimulation on gamma activity and working memory in schizophrenia. Psychiatry Res. 228 (2), 191–196. https://doi.org/10.1016/j.psychres.2015.04.032.

Hyde, J., Carr, H., Kelley, N., Seneviratne, R., Reed, C., Parlatini, V., Garner, M., Solmi, M., Rosson, S., Cortese, S., Brandt, V., 2022. Efficacy of neurostimulation across mental disorders: systematic review and meta-analysis of 208 randomized controlled trials. Mol. Psychiatry 27 (6), 2709–2719. https://doi.org/10.1038/s41380-022-01524-8.

Irani, F., Kalkstein, S., Moberg, E.A., Moberg, P.J., 2011. Neuropsychological performance in older patients with schizophrenia: a meta-analysis of cross-sectional and longitudinal studies. Schizophr. Bull. 37 (6), 1318–1326. https://doi.org/10.1093/schbul/sbq057.

Kay, S.R., Fizbein, A., Opler, L.A., 1987. The Positive and Negative Symptom Scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Keefe, R.S., Fenton, W.S., 2007. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr. Bull. 33 (4), 912–920. https://doi.org/10.1093/schbul/sbm046.

Keefe, R.S., Buchanan, R.W., Marder, S.R., Schooler, N.R., Dugar, A., Zivkov, M., Stewart, M., 2013. Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far? Schizophr. Bull. 39 (2), 417–435. https://doi.org/10.1093/schbul/sbr153.

Kennedy, N.I., Lee, W.H., Frangou, S., 2018. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. Eur. Psychiatry: J. Assoc. Eur. Psychiatrists 49, 69–77. https://doi.org/10.1016/j.eurpsy.2017.12.025.

Kern, R.S., Gold, J.M., Dickinson, D., Green, M.F., Nuechterlein, K.H., Baade, L.E., Keefe, R.S., Mesholam-Gately, R.I., Seidman, L.J., Lee, C., Sugar, C.A., Marder, S.R., 2011. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. Schizophr. Res. 126 (1-3), 124–131. https://doi.org/10.1016/j.schres.2010.11.008.

Kim, J., Iwata, Y., Plitman, E., Caravaggio, F., Chung, J.K., Shah, P., Blumberger, D.M., Pollock, B.G., Remington, G., Graff-Guerrero, A., Gerretsen, P., 2019. A meta-analysis of transcranial direct current stimulation for schizophrenia: "Is more better?". J. Psychiatr. Res. 110, 117–126. https://doi.org/10.1016/j.jpsychires.2018.12.009.

Klem, G.H., Lüders, H.O., Jasper, H.H., Elger, C., 1999. The ten-twenty electrode system of the international federation. The International Federation of Clinical Neurophysiology. Electroencephalography and clinical neurophysiology. Supplement 52, 3–6.

Koola, M.M., 2021. Alpha7 nicotinic-N-methyl-D-aspartate hypothesis in the treatment of schizophrenia and beyond. Hum. Psychopharmacol. 36 (1), 1–16. https://doi.org/10.1002/hup.2758.

Kostova, R., Cecere, R., Thut, G., Uhlhaas, P.J., 2020. Targeting cognition in schizophrenia through transcranial direct current stimulation: A systematic review and perspective. Schizophr. Res. 220, 300–310. https://doi.org/10.1016/j.schres.2020.03.002.

Kronick, J., Sabesan, P., Burhan, A.M., Palaniyappan, L., 2022. Assessment of treatment resistance criteria in non-invasive brain stimulation studies of schizophrenia. Schizophr. Res. 243, 349–360. https://doi.org/10.1016/j.schres.2021.06.009.

Lauriello, J., 2020. Prevalence and impact of relapse in patients with schizophrenia. J. Clin. Psychiatry 81 (2), MS19053BR1C. https://doi.org/10.4088/JCP.MS19053BR1C.

Lefaucheur, J.P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M.A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Paulus, W., 2017. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin. Neurophysiol.: Off. J. Int. Fed. Clin. Neurophysiol. 128 (1), 56–92. https://doi.org/10.1016/j.clinph.2016.10.087.

Li, X., Dai, J., Liu, Q., Zhao, Z., Zhang, X., 2024. Efficacy and safety of non-invasive brain stimulation on cognitive function for cognitive impairment associated with schizophrenia: a systematic review and meta-analysis. J. Psychiatr. Res. 170, 174–186. https://doi.org/10.1016/j.jpsychires.2023.12.003.

Lisoni, J., Baldacci, G., Nibbio, G., Zucchetti, A., Butti Lemmi Gigli, E., Savorelli, A., Facchi, M., Miotto, P., Deste, G., Barlati, S., Vita, A., 2022. Effects of bilateral, bipolar-nonbalanced, frontal transcranial direct current stimulation (tDCS) on negative symptoms and neurocognition in a sample of patients living with schizophrenia: Results of a randomized double-blind sham-controlled trial. J. Psychiatr. Res. 155, 430–442. https://doi.org/10.1016/j.jpsychires.2022.09.011.

Martin, D.M., Liu, R., Alonzo, A., Green, M., Loo, C.K., 2014. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Exp. Brain Res. 232 (10), 3345–3351. https://doi.org/10.1007/s00221-014-4022-x.

Marwaha, S., Johnson, S., 2004. Schizophrenia and employment - a review. Soc. Psychiatry Psychiatr. Epidemiol. 39 (5), 337–349. https://doi.org/10.1007/s00127-004-0762-4.

McCutcheon, R.A., Keefe, R.S.E., McGuire, P.K., 2023. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol. Psychiatry 28 (5), 1902–1918. https://doi.org/10.1038/s41380-023-01949-9.

Meiron, O., David, J., Yaniv, A., 2021. Left prefrontal transcranial direct-current stimulation reduces symptom-severity and acutely enhances working memory in schizophrenia. Neurosci. Lett. 755, 135912. https://doi.org/10.1016/j.neulet.2021.135912.

Moffa, A.H., Brunoni, A.R., Nikolin, S., Loo, C.K., 2018. Transcranial direct current stimulation in psychiatric disorders: a comprehensive review. Psychiatr. Clin. North Am. 41 (3), 447–463. https://doi.org/10.1016/j.psc.2018.05.002.

Mondino, M., Brunelin, J., Palm, U., Brunoni, A.R., Poulet, E., Fecteau, S., 2015. Transcranial direct current stimulation for the treatment of refractory symptoms of schizophrenia. Current evidence and future directions. Curr. Pharm. Des. 21 (23), 3373–3383. https://doi.org/10.2174/1381612821666150619093648.

Newman, D.A., 2014. Missing data: five practical guidelines. Organ. Res. Methods 17, 372–411. https://doi.org/10.1177/1094428114548590.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese 3rd, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165 (2), 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042.

Orlov, N.D., Tracy, D.K., Joyce, D., Patel, S., Rodzinka-Pasko, J., Dolan, H., Hodsoll, J., Collier, T., Rothwell, J., Shergill, S.S., 2017. Stimulating cognition in schizophrenia: A controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 10 (3), 560–566. https://doi.org/10.1016/j.brs.2016.12.013.

Papazova, I., Strube, W., Becker, B., Henning, B., Schwippel, T., Fallgatter, A.J., Padberg, F., Palm, U., Falkai, P., Plewnia, C., Hasan, A., 2018. Improving working memory in schizophrenia: Effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophr. Res. 202, 203–209. https://doi.org/10.1016/j.schres.2018.06.032.

Pelletier, S.J., Cicchetti, F., 2014. Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. Int. J. Neuropsychopharmacol. 18 (2), pyu047. https://doi.org/10.1093/ijnp/pyu047.

Rassovsky, Y., Dunn, W., Wynn, J.K., Wu, A.D., Iacoboni, M., Hellemann, G., Green, M.F., 2018. Single transcranial direct current stimulation in schizophrenia: Randomized, cross-over study of neurocognition, social cognition, ERPs, and side effects. PLoS. One 13 (5), e0197023. https://doi.org/10.1371/journal.pone.0197023.

Rodriguez-Jimenez, R., Dompablo, M., Bagney, A., Santabárbara, J., Aparicio, A.I., Torio, I., Moreno-Ortega, M., Lopez-Anton, R., Lobo, A., Kern, R.S., Green, M.F., Jimenez-Arriero, M.A., Santos, J.L., Nuechterlein, K.H., Palomo, T., 2015. The MCCB impairment profile in a Spanish sample of patients with schizophrenia: effects of diagnosis, age, and gender on cognitive functioning. Schizophr. Res. 169 (1-3), 116–120. https://doi.org/10.1016/j.schres.2015.09.013.

Rodriguez-Jimenez, R., Santos, J.L., Dompablo, M., Santabárbara, J., Aparicio, A.I., Olmos, R., Jiménez-López, E., Sánchez-Morla, E., Lobo, A., Palomo, T., Kern, R.S., Green, M.F., Nuechterlein, K.H., García-Fernández, L., 2019. MCCB cognitive profile in Spanish first episode schizophrenia patients. Schizophr. Res. 211, 88–92. https://doi.org/10.1016/j.schres.2019.07.011.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol.: Off. J. Int. Fed. Clin. Neurophysiol. 120 (12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016.

Shabani, A., Masoumian, S., Zamirinejad, S., Hejri, M., Pirmorad, T., Yaghmaeezadeh, H., 2021. Psychometric properties of structured clinical interview for DSM-5 disorders-clinician version (SCID-5-CV). Brain Behav. 11 (5), e01894. https://doi.org/10.1002/brb3.1894.

Shiozawa, P., da Silva, M.E., Cordeiro, Q., Fregni, F., Brunoni, A.R., 2013. Transcranial direct current stimulation (tDCS) for catatonic schizophrenia: a case study. Schizophr. Res. 146 (1-3), 374–375. https://doi.org/10.1016/j.schres.2013.01.030.

Sloan, N.P., Byrne, L.K., Enticott, P.G., Lum, J.A.G., 2021. Non-invasive brain stimulation does not improve working memory in schizophrenia: a meta-analysis of randomised controlled trials. Neuropsychol. Rev. 31 (1), 115–138. https://doi.org/10.1007/s11065-020-09454-4.

Smith, R.C., Boules, S., Mattiuz, S., Youssef, M., Tobe, R.H., Sershen, H., Lajtha, A., Nolan, K., Amiaz, R., Davis, J.M., 2015. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr. Res. 168 (1-2), 260–266. https://doi.org/10.1016/j.schres.2015.06.011.

Stagg, C.J., Lin, R.L., Mezue, M., Segerdahl, A., Kong, Y., Xie, J., Tracey, I., 2013. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J. Neurosci.: Off. J. Soc. Neurosci. 33 (28), 11425–11431. https://doi.org/10.1523/JNEUROSCI.3887-12.2013.

Świtaj, P., Anczewska, M., Chrostek, A., Sabariego, C., Cieza, A., Bickenbach, J., Chatterji, S., 2012. Disability and schizophrenia: a systematic review of experienced psychosocial difficulties. BMC. Psychiatry 12, 193. https://doi.org/10.1186/1471-244X-12-193.

Tandon, R., Gaebel, W., Barch, D.M., Bustillo, J., Gur, R.E., Heckers, S., Malaspina, D., Owen, M.J., Schultz, S., Tsuang, M., Van Os, J., Carpenter, W., 2013. Definition and description of schizophrenia in the DSM-5. Schizophr. Res. 150 (1), 3–10. https://doi.org/10.1016/j.schres.2013.05.028.

Valiengo, L.D.C.L., Goerigk, S., Gordon, P.C., Padberg, F., Serpa, M.H., Koebe, S., Santos, L.A.D., Lovera, R.A.M., Carvalho, J.B., van de Bilt, M., Lacerda, A.L.T., Elkis, H., Gattaz, W.F., Brunoni, A.R., 2020. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia: a randomized clinical trial. JAMa Psychiatry 77 (2), 121–129. https://doi.org/10.1001/jamapsychiatry.2019.3199.

Vercammen, A., Rushby, J.A., Loo, C., Short, B., Weickert, C.S., Weickert, T.W., 2011. Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr. Res. 131 (1-3), 198–205. https://doi.org/10.1016/j.schres.2011.06.021.

Wechsler, D., 1955. Manual for the Wechsler Adult Intelligence Scale. Psychological Corporation, New York.

Womg, M.M., Chen, E.Y., Lui, S.S., Tso, S., 2011. Medication adherence and subjective weight perception in patients with first-episode psychotic disorder. Clin. Schizophr. Relat. Psychoses. 5 (3), 135–141. https://doi.org/10.3371/CSRP.5.3.3.

Yamada, Y., Inagawa, T., Sueyoshi, K., Sugawara, N., Ueda, N., Omachi, Y., Hirabayashi, N., Matsumoto, M., Sumiyoshi, T., 2019. Social cognition deficits as a target of early intervention for psychoses: a systematic review. Front. Psychiatry 10, 333. https://doi.org/10.3389/fpsyt.2019.00333.

Yang, A.C., Tsai, S.J., 2017. New targets for schizophrenia treatment beyond the dopamine hypothesis. Int. J. Mol. Sci. 18 (8), 1689. https://doi.org/10.3390/ijms18081689.

Yu, L., Fang, X., Chen, Y., Wang, Y., Wang, D., Zhang, C., 2020. Efficacy of transcranial direct current stimulation in ameliorating negative symptoms and cognitive impairments in schizophrenia: a systematic review and meta-analysis. Schizophr. Res. 224, 2–10. https://doi.org/10.1016/j.schres.2020.10.006.

Zink, M., Correll, C.U., 2015. Glutamatergic agents for schizophrenia: current evidence and perspectives. Expert. Rev. Clin. Pharmacol. 8 (3), 335–352. https://doi.org/10.1586/17512433.2015.1040393.

Zhou, Y., Fan, L., Qiu, C., Jiang, T., 2015. Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia. Neurosci. Bull. 31 (2), 207–219. https://doi.org/10.1007/s12264-014-1502-8.