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Original Article

Effects of transcranial direct current stimulation (tDCS) on positive and negative symptoms in patients with schizophrenia

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Abstract

Introduction: The symptoms that patients with schizophrenia experience during schizophrenia are divided into two positive and negative symptoms. This study aims to evaluate the effectiveness of transcranial direct current stimulation (tDCS) on both positive and negative symptoms in patients with schizophrenia.

Methods: This experimental study was a pretest-posttest plan consisting of patients with schizophrenia in Razi psychiatric hospital in Tabriz, of which 30 patients were selected in a targeted and available manner and randomly assigned to experimental and control groups. The experimental group underwent anodal tDCS treatment for ten sessions of 20 minutes at 72-hour intervals, while the control group underwent dummy treatment in the same manner. The research data were collected using The Positive and Negative Symptom Scale (PANSS) and analyzed using the covariance analysis method with SPSS software.

Results: The results of statistical analysis showed that tDCS has a significant effect on negative and general symptoms of schizophrenia ($P=0.01$) but has no significant effect on positive symptoms ($P\leq0.05$).

Conclusion: To the results of the present study, we concluded that tDCS is a suitable therapeutic tool in the treatment of pathological symptoms of schizophrenia.

Introduction

Schizophrenia is one of the most severe mental disorders, the fundamental nature of which isn't clarified, and for this reason, it is sometimes called a syndrome. Schizophrenia is a clinical syndrome with variable but profoundly debilitating psychopathology that involves cognition, emotion, perception, or other behavioral aspects.[1] In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Schizophrenia spectrum disorders are characterized by abnormalities in one or more of the five areas of delirium, hallucinations, disturbed thinking (speech), highly disturbed or abnormal motor behavior, and negative symptoms.[2]

Schizophrenia is a serious mental disorder because it has the potential to affect a person's ability to manage a productive and satisfying life to a great degree.[3] This severe mental disorder has a lifetime prevalence of one percent.[2] Additionally, approximately 5% of the population in the United States is treated for the disorder, and despite its severity, only about half of all patients with schizophrenia are treated; these patients occupy about 50% of all psychiatric hospital beds and involve 16% of all mentally ill people who receive some form of treatment.[1] Symptoms experienced during the active stage of schizophrenia experienced into positive and negative symptoms. The former consists of exaggerations or distortions of thoughts, emotions, and normal behavior; while the latter includes performance below the normal level of behavior.[3] These symptoms are among the main features of schizophrenia and constitute the diagnostic criteria for this disorder.[2] A major approach for improving the symptoms of schizophrenia is medication, but it is not yet clear whether common and unusual antipsychotics are effective?[4-6] Furthermore, given that antipsychotics have the best response to the positive symptoms of schizophrenia and have less effect on the negative symptoms, self-medication cannot lead to satisfactory results. In very acute situations where a person with schizophrenia may harm himself/herself or others, hospitalization is necessary, although hospitals are now less satisfied with this than before.[7] The emergence of effective antipsychotic drugs and the change in society's attitude towards the treatment of mentally ill patients as well as their rights, have led to a clear change in the hospitalization pattern of patients with schizophrenia.

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However, even with the prescription of antipsychotic drugs, the probability of readmission within two years after the first hospitalization is about 40% to 60%.[1] As a result, the need for non-pharmacological treatments is increasing, and achieving effective and efficient treatments is a priority in schizophrenia research and treatment; on the other hand, the complexity of schizophrenia implies that no single treatment approach is sufficient to address this multifaceted disorder, Therefore, most patients with schizophrenia, a combination of antipsychotic drugs and non-drug complementary therapies are prescribed. A new non-pharmacological treatment model for patients with schizophrenia is Transcranial Direct Current Stimulation of the brain (tDCS).

Recent observations have shown that patients with schizophrenia treated with tDCS of the brain have seen significant improvement. As a rapid and effective treatment, and most importantly, a treatment for various aspects of the symptoms of schizophrenia, tDCS involves auditory symptoms, which are among the most prominent symptoms as well as negative symptoms. tDCS is a non-invasive method in which a weak direct electric current (0.5 up to 2 mA) is applied to the scalp, and long-term changes in cortical polarity are generated following depolarization and hyperpolarization of neurons and their effect on the neuronal receptors. In other words, in this type of electrical stimulation, parts of the head are targeted using weak electrical currents.[8]

Since tDCS involves applying low-intensity currents to the scalp using cathodic and anodic electrodes,, the polarity can either inhibit (cathodic) or facilitate (anodic) this functions.[1] Research shows that tDCS can help improve patients with mental health problems, such as reducing depressive symptoms in patients with major depressive disorder improving cognitive and executive functions, including attention and working memory, in healthy individuals, as well as patients with schizophrenia and neurodevelopmental disorder.[9-13]

In addition, research findings, such as the current research, can be effective in developing treatment protocols in other dimensions of schizophrenia. Thus, considering the importance of schizophrenia as well as its adverse consequences on the life of people and society and the lack of treatments that result in satisfactory improvement of all positive and negative symptoms of schizophrenia, as well as the research gaps in the effectiveness of tDCS on the symptoms of schizophrenia, the present study seeks to answer the question of whether tDCS has a positive effect on both the positive and negative symptoms of schizophrenia?

Methods

The method of the present study is an experimental study with a pretest - posttest design with control group. The statistical population of the present study consisted of all patients with schizophrenia admitted to Razi hospital in Tabriz, from this population, 30 people were randomly selected and divided into two groups: experimental (n = 15) and control (n = 15). Exclusion criteria are Lack of established status and informed consent, drug abuse, co-occurrence of other mental disorders, having neurological or general medical disorders, as well as age over 60 years and under 20. The diagram of the present research plan is provided in the below Table 1.

The Schizophrenia Positive and Negative Symptoms Scale (PANSS) was used to measure the positive and negative symptoms of patients. The scale was developed by Kay et al to measure the symptoms of patients with schizophrenia.[14] It consists of five subscales as follows: (1) Positive symptoms, (2) Negative symptoms, (3) Disintegration, (4) Excitement, and (5) Anxiety and depression. This scale has an acceptable validity and reliability and its Cronbach's alpha coefficient has been reported 0.83.[15] To ensure accurate diagnosis of schizophrenia, a clinical interview was performed by the researcher on all subjects in the admitted hospital based on the DSM-5 diagnostic criteria, which includes the criteria for the signs and symptoms of schizophrenia, the duration criterion, the criterion of clinical discomfort and dysfunction, and the criterion of physiological effects of the drug/no other physical illness.

When the objectives of the study were briefly explained to patients and their informed consent was obtained by the researcher, the sampling and random assignment steps of subjects to groups of 15 were tested and controlled and PANSS was performed individually at the patients' place of hospitalization on all 30 patients by the researcher, and data related to the pre-test stage were collected. The experimental group was then treated with tDCS for 10 sessions, each lasting 20 minutes (with 72 hours' intervals between sessions), while the patients in the control group did not receive any intervention. Finally, after the treatment sessions, the PANSS scale was re-performed individually on all subjects in the experimental and control groups, and thus the post-test data were collected (Table 2).

Finally, the data obtained from the patients was analyzed using descriptive statistical methods and multiple analysis of covariance (MANCOVA) statistical test using the SPSS-18 statistical software, and the significance level in the tests was set at 0.05.

Results

In the present study, 40 patients (4 females and 36 males) with schizophrenia with mean and standard deviation of

Table 1. Diagram of pretest-posttest research plan with control group

Group	Pre-test	Independent variable	Post-test
Experimental	T1	tDCS	T2
Control	T1	-	T2

tDCS, Transcranial direct current stimulation.

44.12 ± 11.20 years were participated, of which 18 patients (45%) had primary education and 22 patients (55%) held a diploma (Table 3).

As shown in the table above, the mean scores of the experimental group in all three variables of positive, negative, and general symptoms have been decreased in the post-test stage, while the mean scores of the pre-test and post-test of the control group differ a little in these variables (Table 4).

Subsequently, to evaluate the significance of the difference between the scores of the pre-test and post-test stages, MANCOVA statistical test is used.

When the distribution of variable scores related to Kolmogorov-Smirnov test and Shapiro-Wilkes test was examined which indicated the normal distribution of scores ($P > 0.05$), Box and Levin tests was also showed the observance of homogeneity assumption of variance/covariance matrices for using MANCOVA parametric test ($P < 0.05$). Finally, the results of regression slope test also showed that, except for the case of negative syndrome, the [independent] variable also did not have a significant interaction with the dependent variable, thus the regression slope assumption has been observed ($P < 0.05$).

According to the results in Table 5, all three indicators of test owner statistics show a significant difference between the experimental and control groups at $P = 0.001$. Therefore, these two groups have significant differences in at least one variable.

As indicated by the results in Table 6, the difference between the adjusted means after controlling the pre-test intervening variable in the experimental and control groups is significant in the post-test stage ($P \leq 0.05$), therefore the effect of tDCS on improving negative and general symptoms of the patients in the experimental group was significant, but it did not significantly improve the positive symptoms ($P \leq 0.05$).

Discussion

The present study aims to evaluate the effectiveness of tDCS on positive and negative signs and symptoms in individuals with schizophrenia. The research findings indicate that tDCS has a positive and significant effect on the general and negative symptoms of schizophrenia, but it does not have a significant effect on the positive symptoms. This finding is consistent with the findings of many studies,[9,11-13,16-21] that show tDCS can be useful in improving mental patients; also, it is consistent with the finding that tDCS can improve cognitive and executive functions, such as attention and working memory in both healthy individuals and patients with schizophrenia and neurological disorders.

In explaining the present study, it can be said that schizophrenia leads to defects in cognitive functions, especially working memory.[1] Additionally, studies have shown that tDCS improves working memory in people with schizophrenia by stimulating brain neurons to create the potential for excitatory action in the FP2 region, which is related to memory function.[12] Also, various studies have shown the effectiveness of tDCS in the DLPFC region on cognitive functions such as memory, language, learning, and attention.[18,19] that is, stimulation of this area may improve cognitive functions because this area is involved with cognitive actions and activities that improves performance in a working memory task in its own place; on the other hand, the study by

Gottlieb[22] shows that cognitive deficits are associated with symptoms of mental disorders such as depression,

Table 2. Summary of research method and process

Group	Posttest 1	DC Stimulation	Posttest 1
S1	PANSS	Online protocol Lt Anodal/Rt. supra orbital Area: Cathodal DLPFC Stim 20 min 1.2 up to 2 μA ($5_x5 = 25$ cm^2) based on 10/20 system (F3)	PANSS after stim starting
S2	PANSS	20 min sham stim 15 sec ramp up 1.2 μA at start and off	PANSS after sham stim starting

PANSS: Schizophrenia Positive and Negative Symptoms Scale.

Table 4. Mean and standard deviation of positive and negative symptom scores of subjects in experimental and control groups in pretest–posttest

Variable	Group	Pretest		Posttest	
		Mean	SD	Mean	SD
Positive symptoms	Experimental	18	3.43	17.50	3.18
	Control	16.55	3.70	16.35	4.03
Negative symptoms	Experimental	10.90	2.59	9.10	1.51
	Control	10.95	2.39	11	2.42
General symptoms	Experimental	21.65	2.98	18.20	2.88
	Control	21.10	3.41	20.90	3.37

Table 3. Demographic characteristics of patients

Variables		Total	Experimental group	Control group	*P* value
Age, Mean (±SD)		44.12 (±8.37)	42.90 (±29.11)	45.35 (±28.11)	0.497
Gender, No. (%)	Male	36 (90)	(90)18	(90)18	
	Female	4 (10)	2 (10)	2 (10)	
Education, No. (%)	Primary	18 (45)	9 (45)	9 (45)	
	High school	22 (55)	11 (55)	11 (55)	

Table 5. Multivariate analysis of covariance of positive and negative symptoms in the experimental and control groups

Test	Value	F	F assumption	*df* error	*P*	Eta squared
Pillai's Trace	0.756	34.012	3	33	0.001	0.756
Wilks' Lambda	0.244	34.012	3	33	0.001	0.756
Hotelling's Trace	3.092	34.012	3	33	0.001	0.756

Table 6. Results of covariance analysis of group membership on memory in the post-test stage

Components	Pre-test Effect		The main effect of the group		Eta squared
	P value	F value	*P* value	F value	
Positive symptoms	0.001	272.23	0.528	0.406	0.011
Negative symptoms	0.307	1.073	0.001	46.059	0.568
General symptoms	0.654	0.206	0.001	37.286	0.516

and the improvement in these deficits is linked to reduced morbidity; Therefore, it can be concluded that in addition to the direct effects of tDCS on improving cognitive function, it can also lead to improvement in other pathological signs and symptoms, such as general and negative symptoms. Also, studies have shown that the negative and general symptoms of schizophrenia, such as social withdrawal, cognitive deficits, superficial emotion, depression, etc. are mostly associated with defects in the serotonergic system, in the form of decreased serotonin levels.[1] hence, the stimulatory effect of tDCS on increasing serotonin levels can improve these signs and symptoms. One possible reason that may explain the ineffectiveness of tDCS on positive symptoms is the low number of sessions in the present study.

Conclusion

As it has been defined, tDCS refers to a therapeutic tool that uses a weak electric current in the range of 25-80 with low intensity and through electrodes installed on the scalp, aiming of change the electrical excitability of brain cells. With the help of this mild current, electricity reaches the surface of the brain and changes the excitability level of its neurons.[23] The process requires time to be completely effective, so the lack of sufficient time can hinder the therapeutic effects; therefore, it is recommended to use that tDCS tools with more sessions in future studies.

Limitations and Recommendations

Like all other studies, the present study had limitations, including the lack of control over other treatments running concurrently with the research, such as medication and the dose of treatment received by each patient that could affect the results. Another limitation of the study was the small number of female participants compared to male, which makes it difficult to control the gender variable. Thus, it is recommended in future studies to control other received treatments, especially the type of medicine and its dose in the study sample, as well as equal sampling between men and women and also comparison of results in the two groups to control and study the effect of gender. Finally, another major limitation of the present study was the lack of a follow-up test due to time constraints, which limits coming to the conclusion about the durability of the therapeutic effect and hence limits reaching wider generalizations as well. Therefore, it is recommended that in the future studies a follow-up test is performed by the interested researchers to evaluate the durability of a possible therapeutic effect. Finally, it is suggested that tDCS can be used alongside other established therapies, especially medication, to facilitate treatment and recovery in the patients with schizophrenia. Additionally, tDCS treatment can be made more widely and effectively available to patients by educating therapists who participate in schizophrenia treatment about this therapy.

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Competing Interests
The authors stated that they had no conflict of interest.

Study Highlights

What is current knowledge?

- tDCS is effective in improvement of auditory hallucinations in patients with schizophrenia. Therefore, more positive symptoms may be relieved by this approach.

What is new here?

- tDCS may be effective on negative symtoms and general health than positive symtoms of schizophrenia.

Ethical Approval

The present study was implemented after the approval of the Ethic Committee (IR.TBZMED.REC.1397.707) in University of Medical Sciences of Tabriz. The study data were collected after completing the written consent. All information in the samples was confidential, and their personal information was not disclosed.

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