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Therapeutic effects of transcranial direct current stimulation on ketamine-induced schizophrenia-like behaviors and oxidative stress

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Abstract

Schizophrenia is a serious neuropsychiatric disorder that affects 1% of the world's population. It plays an important role in psychiatric symptoms, including major depression and schizophrenia. However, it is also known that one of the main reasons underlying the pathogenesis of schizophrenia is oxidative stress. Transcranial direct current stimulation (tDCS) has recently been a promising method for modifying neuronal membrane stimulation, cognition, and behavioral function. Our aim in this study is to explore the effects of 0.5 mA anodal tDCS stimulation on schizophrenia-like behaviors and oxidative stress in a ketamine-induced schizophrenia model. 30 male Balb/C mice were divided into 3 groups as control, schizophrenia, and schizophrenia+tDCS. The schizophrenia model was created by administering 25mg/kg/day ketamine for 7 days. tDCS treatment was performed by giving 0.5 mA anodal tDCS stimulation for 7 days. On day 14 of the experiment, SCZ-like behaviors were assessed using a novel object recognition test (NOR), open field test (OF), and tail suspension test (TST), and also oxidative stress in hippocampus and prefrontal tissues was estimated. Results showed that locomotor activity, depressive and anxiety-like behaviors of the schizophrenia group increased significantly compared to the control group and decreased after tDCS stimulation ($p<0.05$). In addition, it was investigated that tDCS stimulation also significantly increased learning that decreased after schizophrenia ($p<0.05$). All together, it was observed that the total antioxidant capacity of the schizophrenia group decreased while the total oxidant capacity of the schizophrenia group rose in the prefrontal cortex and hippocampus tissues compared to the control group ($p<0.05$). Otherwise, 0.5 mA anodal tDCS stimulation increased the total antioxidant capacity of the schizophrenia+tDCS group compared to the schizophrenia group, while it decreased total oxidant capacity ($p<0.05$). Based on our results displayed that 0.5 mA anodal tDCS stimulation for 30 minutes for 7 days reduced schizophrenia-like behaviors and oxidative stress by modulation of N-methyl-D-aspartic acid (NMDA) receptors in the glutamatergic pathway in a ketamine-induced, NMDA antagonist, schizophrenia model.

Keywords: tDCS, schizophrenia, oxidative stress

Introduction

Schizophrenia is a serious and persistent, overwhelming neuropsychiatric disorder that affects 1% of the world's population. Schizophrenia is identified by three groups of symptoms: positive (eg, hyperactivity, hallucinations), negative (eg, flattening of emotion, aversion) and cognitive (eg, learning and memory impairments, impaired executive functions) symptoms [1]. Schizophrenia is a multifaceted disease that usually begins before the age of 25, disrupts interpersonal and occupational functioning, and has a chronic course. The most obvious symptoms of schizophrenia are; delusions, hallucinations, disorganized speech and behavior, inappropriate affect, cognitive deficits, and impairments in psychosocial

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functioning [2]. The results of radiological imaging and the detection of functional and structural disorders in brains of people with schizophrenia suggested that a neurodegenerative process that leads to progressive loss of neuron functions continues during disease. When the etiology of schizophrenia is examined, there is evidence that it is a hereditary disease, although the exact cause has not yet been determined [3]. Genetic, environmental factors, neurotransmitters, hormones, urban life, migration, trauma, substance use and nutrition are also effective in the formation of schizophrenia [4]. When the effects of neurotransmitters are examined, it is stated that the decrease in glutamate receptors causes exacerbation of psychotic symptoms, excessive dopamine production causes the formation of positive symptoms, deterioration in serotonin causes cognitive problems such as memory, and the increase in gamma aminobutyric acid A receptor (GABA-A) concentration causes sleep disturbance [5,6]. Psychosis is a psychiatric disorder with symptoms such as delusions, hallucinations, alogy, disgust, bad taste, and memory deficit [7]. Ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, is preferred in rodents to induce psychosis leading to various behavioral changes seen in some psychotic patients [7]. Studies have shown that there is a link between psychosis and hypofunction of NMDA receptors [8 9]. NMDA receptor antagonists act through modulation of the neurotransmitter system in the different regions of brain, particularly GABAergic, glutamatergic, cholinergic, serotonergic and dopaminergic, which are essential in the development of psychosis [10,11]. Increased GABA release is controlled by inhibition of dopaminergic neurotransmission by NMDA receptors responsible for abnormal dopaminergic activity [12]. It is effective in the psychosis of dopaminergic dysfunction in the frontal cortex and limbic system [13]. Hyperdopaminergic and hypodopaminergic transmissions, reduction of GABAergic inhibitory neurons, hypofunctionality of NMDA glutamatergic receptors in subcortical and cortical brain regions play a vital role in pathophysiology of schizophrenia [14]. In addition, chronic administration of NMDAR antagonist causes oxidative stress and neuroinflammation in animals [15]. Chronic administration of NMDAR antagonists has been found to cause several behavioral changes, including stereotyped behaviors, hyperlocomotor activity on the actophotometer, increased immobility time in depression test, and reduced latency deceleration in learning test. These changes show cognitive symptoms of psychosis [9]. Schizophrenia, a serious mental illness identified by misinterpretation of reality, affecting more than 50 million people worldwide; It is a biological disorder that occurs in brain and causes deterioration in brain structure and function [16]. Oxidative stress causes damage to brain and its gray matter, causing difficulties in people's daily functioning [16]. While oxidative stress increases in patients with acute schizophrenia, antioxidant activity decreases [17]. Oxidative stress is the result of abnormal redox in which free radical reactive oxygen species (ROS) overrun antioxidant capacity at cellular levels. However, oxidative stress, sudden rise in toxicity and cellular metabolism, or changed antioxidant gene expression may also be the result of decreased antioxidant defense system and/or dietary antioxidants [18]. Brain is particularly susceptible to oxidative stress as it is highly susceptible to degradation and relatively low levels of antioxidant enzymes, with high oxidative metabolic activity and oxygen consumption [19]. Although normal levels of ROS are necessary in physiological conditions, excess levels of ROS can cause detrimental effects on important macromolecules such as proteins, DNA, lipids [20]. This overgrowth of ROS can affect DNA, cause mutations and alter gene expression [21]. Reactive oxygen species can also reasen peroxidative harmful to lipids, damaging the cell membrane and membranes of cellular organelles. Abnormally increased ROS levels may provide to etiology of schizophrenia via the oxidative stress pathway (Figure 1) [22]. Since schizophrenia is a chronic disease that affects every aspect of life, the aim of treatment is; to reduce or eliminate the symptoms of the disease, to rise quality of life of patient and to reduce the complications of the disease as much as possible [23]. The most effective treatment; it is a multidisciplinary approach that includes medication, psychotherapy, and sociotherapy [24]. Haloperidol is a typical antipsychotic drug that improves symptoms of psychosis and has extra-pyramidal side effects [9]. Olanzapine, on the other hand, is an atypical antipsychotic drug that is beneficial in positive, negative, depressive or cognitive symptoms of psychosis, as well as having some side effects (e.g. weight gain and diabetes) [7]. Unfortunately, despite the effectiveness of antipsychotic drugs, it is limited due to partial side effects and risk of psychotic relapse [25]. Because of these side effects, researchers are looking for alternative methods in the treatment of neuropsychiatric diseases.

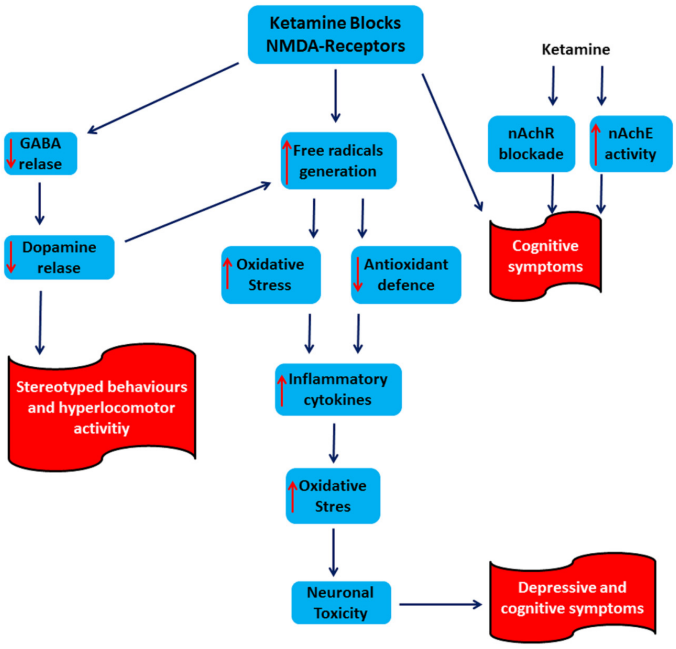

Figure 1. Ketamine-induced schizophrenia model and its molecular damage mechanism [7]

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In recent years, transcranial direct current stimulation (tDCS) neuromodulation therapies have been applied in the treatment of psychological diseases such as schizophrenia [26]. tDCS is a non-invasive method of brain stimulation that can alter the excitability of neuronal activity in the cerebral cortex [26]. The neuromodulatory effects of tDCS have been demonstrated as a therapeutic effect in rat models of focal epilepsy, memory, Parkinson's disease, depression, and stroke [26,27]. tDCS exerts its effect through the activation of Na+-Ca²+ dependent ion channels and changes over NMDA receptor activity [26]. tDCS is inexpensive and easy to use, but has almost no adverse side effects [26,28]. In studies conducted with tDCS, mild itching, transient headache, weakness, nausea were observed in the applied area in some people after tDCS treatment, and no other significant side effects were observed, and neuronal damage was not reported in safety studies [26]. The current passing through the brain tissue produces increased or decreased excitable effects in the cortical region [26]. Excitability is determined by the intensity of the current and the polarity with anodal excitation or cathodal excitation [26]. While anodal stimulation depolarizes the soma of pyramidal cells with an excitatory effect, cathodal stimulation produces a hyperpolarized response with an inhibitory effect (Figure 2.) [26].

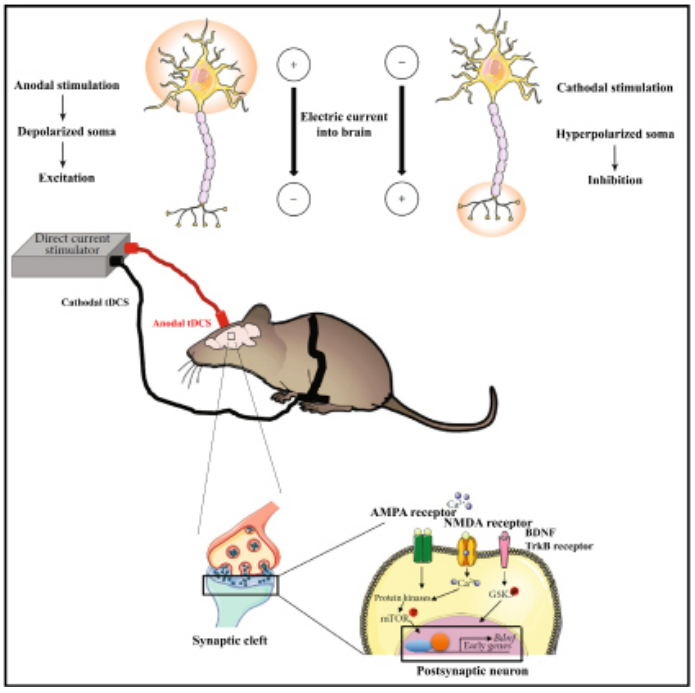

Figure 2. Schematic representation of tDCS. While A-tDCS increases excitability by acting on the neuronal membrane potential by depolarizing, C-tDCS decreases excitability by affecting hyperpolarization. A-tDCS depolarizes the presynaptic neuronal membrane and glutamate, and glutamate binds to AMPA and NMDA receptors. Adapted from Cavaleiro et al. [29].

Depending on the stimulus type, the tDCS method modulates the stimulus causing anodal tDCS depolarization and cathodal tDCS hyperpolarization in structures such as cortico-striatal and thalamocortical [26]. In our study, it was aimed to investigate the therapeutic effects of tDCS stimulation on the oxidative stress pathway in mice with schizophrenia model.

Material and Methods

This study was performed in Erciyes University Experimental Animals Unit. Mice obtained from Erciyes University Experimental Animals Application and Research Center with the approval of Erciyes University Animal Experiments Local Ethics Committee (Decision No 22/253) were used in the study.

Experimental Groups and Protocol

Experiments were carried out by dividing Balb/C male mice, 2 months old, weighing 25-30 g, into 3 groups:

1. Control Group: 1.0mL/kg/day saline was administered i.p. during 7 days (n=10),
2. Schizophrenia Group: Induced by ketamine i.p. 25mg/kg/day during 7 days (n=10),
3. Schizophrenia+tDCS Group: Ketamine-induced schizophrenic mice received 0.5 mA tDCS stimulation for 30 min during 7 days after schizophrenia was induced (n=10) (Figure 3).

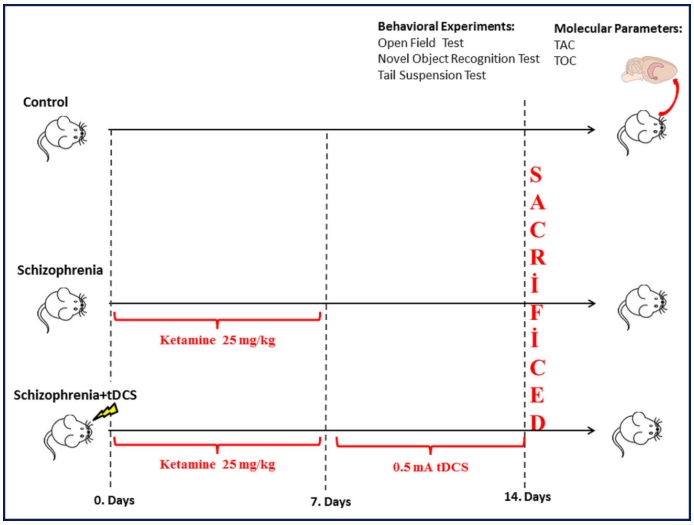

Figure 3. Experimental schedule

Schizophrenia Model

The ketamine-induced schizophrenia model induced by ketamine dissolved in saline administered i.p. 25 mg/kg/day during 7 days [30].

tDCS Application

For tDCS application, Animal DCS Stimulator (model 2100) device with temporal resolution of 1 min was used [27]. In our study, mice in the schizophrenia+tDCS group were fed 30 minutes a day for 7 days starting from the 7th day of the experiment. 0.5mA anodal tDCS was applied. During the tDCS

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application, a superficial disc electrode was used, the maximum current intensity was ±1000μA, and the current resolution was set as 0.01mA.

Behavioral Experiments

Open Field (OF) Test

Locomotor activity measured in OF test. OF experiments were performed in a square-shaped apparatus with a 40x40cm base, with a black matte base. The area was divided into 16 equal small circles of 10cm². At the beginning of the experiment, the mice were left in the middle of this area one by one and their movements were examined for 3 minutes. For each mouse, the total distance (cm) and the velocity (cm/s) measured [27].

Novel Object Recognition Test (NOR)

The Novel Object Recognition Test (NOR) test is particularly effective in measuring attention or short-term memory studies and has three stages: habituation, training and retention. During the practice phase, the mice will be placed in the center of the 40 cm high, 40x40 cm arrangement and allowed to wander for 5 minutes without any objects in the environment. During the training phase, the mice will be released from the center to the field and given 5 minutes to examine the two objects placed in the environment. In the recall phase, one of the objects will be replaced with a novel object and the behavior of the mice will be recorded for 5 minutes. Mice are expected to spend more time examining the novel object in this process [31]. In the NOR test, the discrimination index and the time spent in the novel object (sec) values will be analyzed. Discrimination Index = ((Time Spent at Novel Object-Time Spent at Old Object)/Total Time)*100.

Tail Suspension Test (TST)

In Tail Suspension Test (TST), each mouse will be placed approximately 1 cm from the tip of the tail and hung 30 cm above the floor using adhesive tape. In the last 4 minutes of 6 minutes, the total time of inactivity, which can be defined as a restless suspension without any strain, shall be recorded. Mice that climb on their tails during tests will be excluded from the experiments [32].

Biochemical Method

Determination of Total Antioxidant Capacity

TAC in tissues was evaluated using the OxiSelect™ TAC Assay kit. This method is based on the principle that the hydroxyl radical, a potent radical formed by the Fenton reaction, reacts with a colorless substrate, o-dianisidine, to form a bright yellow-brown colored dianisyl radical. The addition of hydroxyl radical to the supernatants initiates oxidative reactions and this reaction is suppressed by antioxidants and color change is prevented. In this process, the effective measurement of "Total Antioxidative Capacity" in the tissue has been achieved.

Determination of Total Oxidant Capacity

Determination of TOC in tissues was measured using the OxiSelect™ ROS/RNS Assay Kit. In this method, the oxidative reaction is accelerated by adding a catalyst to the oxidants in the sample. After a short time, the oxidation reaction was allowed to proceed with the prepared dichlorodihydrofluorescein probe. The tissues were fluorometrically measured against a hydrogen peroxide or 7'-dichlorodihydrofluorescein standard. The free radical content of oxidant molecules present in the sample was determined by comparison with a predetermined 7'-dichlorodihydrofluorescein or hydrogen peroxide standard curve.

Statistical Analysis

Statistical analysis of the results was performed using SPSS 20.0 software. The results were given as mean±standard error (SEM) and statistical significance was accepted as $p<0.05$. OF, NOR and TST datas were evaluated with one-way analysis of variance (ANOVA) and Tukey test was used as posthoc test.

Results

Behavioral experiments of the groups were measured in locomotor activity in the OF, learning in NOR and depression in TST (Figure 4). The total distance and velocity in OF in schizophrenia group was significantly rised compared with that in control group ($p<0.05$) (Figure 4.A and Figure 4.B). After tDCS application, a significant reduce was observed in locomotor activities of schizophrenia+tDCS group compared to schizophrenia group ($p<0.05$) (Figure 4.A and Figure 4.B). The short-term memory experiments of groups reduce evaluated in NOR test (Figure 4.C). While it was observed that there was a significant reduce in learning of schizophrenia group compared to control group ($p<0.05$), there was a significant increase in schizophrenia+tDCS group compared to schizophrenia group ($p<0.05$). Depression behaviors of experimental groups were evaluated in TST (Figure 4.D). It was determined that there was a significant increase in immobility time of schizophrenia group compared to control group ($p<0.001$), while a significant decrease was found in schizophrenia+tDCS group compared to schizophrenia group ($p<0.05$).

In the hippocampus and frontal cortex tissues, a significant reduce was observed in total antioxidant capacity of schizophrenia group compared to control group ($p<0.05$) (Figure 5.A and Figure 5.B), while a significant rise was observed in TOC ($p<0.05$) (Figure 5.C and Figure 5.D). After tDCS stimulation, there was a significant rise on TAC of hippocampus and prefrontal cortex tissues of schizophrenia+tDCS group compared to schizophrenia group ($p<0.05$) (Figure 5.A and Figure 5.B). In addition, a significant reduce was found in TOC of hippocampus and prefrontal cortex tissues of schizophrenia+tDCS group compared to schizophrenia group ($p<0.05$) (Figure 5.C and Figure 5.D).

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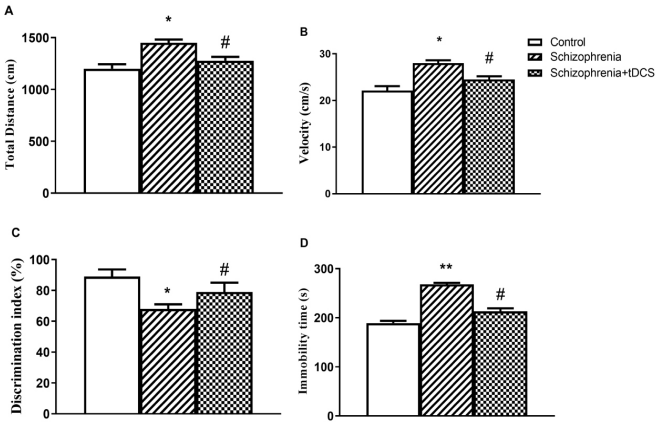

Figure 4. Behavioral test results of experimental groups. A) Total distance (cm) in OF, B) Velocity (cm/s)) in OF, C) Discrimination index in NOR, DI) Immobility time in TST . (n=10, for each group; * p<0.05, ** p<0.001 shows the difference compared to the control group, # p<0.05 shows the difference compared to the schizophrenia group, one-way ANOVA test, followed by Tukey post hoc test). All data are presented as means ± s.e.m

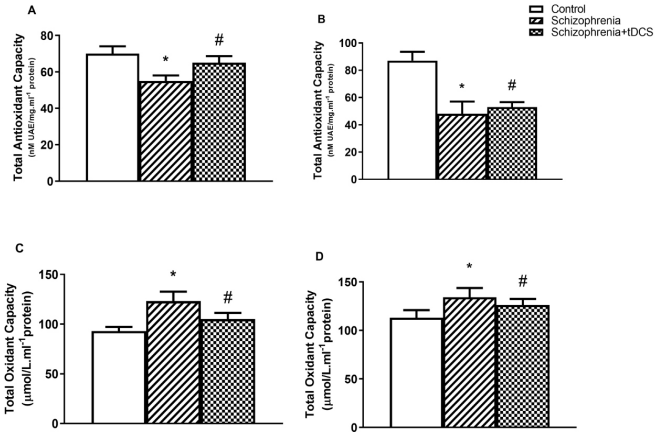

Figure 5. Oxidative stress results. A) Total antioxidant capacisity levels in hippocampus tissue, B) Total antioxidant capacisity levels in prefrontal cortex tissue, C) Total oxidant capacisity levels in hippocampus tissue, D) Total oxidant capacisity levels in prefrontal cortex tissue (n=10, for each group; * p<0.05 shows the difference compared to the control group, # p<0.05 shows the difference compared to the schizophrenia group, one-way ANOVA test, followed by Tukey post hoc test). All data are presented as means ± s.e.m

Discussion

Schizophrenia is a psychiatric disease in which psychotic symptoms such as hallucinations and cognitive disorders are also seen, although it affects approximately 1% of the world's population [14]. Although the underlying cause of schizophrenia is still unclear, it is thought to result from dysregulation of neurochemicals such as dopamine, serotonin, and glutamate [14]. Although typical antipsychotic and conventional atypical antipsychotic drugs such as dopamine D2 receptor antagonist, serotonin 5-HT2A antagonist are used in the treatment of schizophrenia, these drugs are not effective in all symptoms of schizophrenia and have serious side effects. On the other hand, since the treatment of schizophrenia with antipsychotic drugs also causes oxidative stress, therapeutic and protective agents with less side effects are needed. tDCS is a non-invasive method of brain stimulation that can alter excitability of neuronal activity in cerebral cortex [26]. tDCS is inexpensive and easy to use, but has almost no adverse side effects [28]. The neuromodulatory effects of tDCS have been skowed as a therapeutic effect in rat models of focal epilepsy, memory, depression, and stroke [26]. tDCS exerts its effect through the activation of Na+-Ca²+ dependent ion channels and changes over NMDA receptor activity [26]. While anodal stimulation depolarizes the soma of pyramidal cells with an excitatory effect, cathodal stimulation produces a hyperpolarized response with an inhibitory effect. Anodal tDCS exerts its effects by modulation of both GABAergic (short-range intracortical inhibition) and glutaminergic (intracortical facilitation) synapses, whereas cathodal tDCS exerts its effects only by modulation of glutaminergic synapse [26].

This article investigated the effect of tDCS treatment to ameliorate ketamine-induced SCZ-like behavior in mice and oxidative stress factors. Our findings showed that tDCS contributed to the following outcomes: 1) reduction in ketamine-induced depressive and anxiety-like behaviors, 2) reduction in ketamine-induced memory deficits, and 3) oxidant system decreased and antioxidant defense system improved in prefrontal cortex and hippocampus of mice. Ketamine-induced schizophrenia model is widely used to experimentally mimic schizophrenia symptoms. Similarly, du Bois et al. (2009) reported that administration of NMDA antagonist caused anxiety and depressive behaviors in mice and also increased NMDA receptor in the hippocampus [33]. In our results, it was observed that locomotor activity increased, learning was impaired, and anxiety-depression-like behaviors increased in ketamine-induced schizophrenia model. In OF test, in which locomotor activity was evaluated, it was determined that schizophrenia group mice had an increase in locomotor activity parameters, distance and velocity, compared to control group. In addition, in NOR test, it was observed that the learning of the schizophrenia group was impaired, and there was an increase in depression behaviors according to the results of TST. These results are consistent with other studies in the literature [33-35]. It was observed that 0.5 mA anodal tDCS treatment, which we applied for 7 days, reduced locomotor activity and depression-like behaviors and learning disability caused by ketamine-induced schizophrenia. Smith et al. (2020) reported that tDCS stimulation applied to schizophrenic patients for 2 weeks increased cognitive functions and neuroplasticity [36]. Adam et al. (2021) also reported that 2mA 20-minute anodal tDCS stimulation in 24 schizophrenia patients caused significant changes in plasticity [37]. Moghaddam et al. (2021), in their study on a ketamine-induced schizophrenia model, reported that they found similar results to our study, and that they reduced the increased locomotor activity and depression-like behaviors after schizophrenia with antioxidant curcumin treatment [34]. They also reported that curcumin treatment increased antioxidant capacity and decreased oxidant capacity.

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Oxidative stress, which occurs as a result of imbalance between ROS production activities and antioxidant defense mechanism, plays a vital role in pathophysiology of schizophrenia [14]. Akosman et al. (2021) reported that schizophrenia decreased total antioxidant capacity and increased total oxidant capacity in MK-801-induced schizophrenia mouse model [35]. Similar to the studies of Akosman et al. (2021), Mogheddam et al. (2021) reported that the total antioxidant capacity increased and the total oxidant capacity decreased in their study [34]. In our study, it was observed that ketamine-induced schizophrenia decreased the total antioxidant capacity and increased the total oxydant capacity. It was determined that the tDCS treatment we applied in our study increased the decreased total antioxidant capacity and decreased the increased total oxidant capacity. In some experimental studies, it was reported that antioxidant treatments after schizophrenia significantly increased the total antioxidant capacity and decreased the total oxidant capacity [14,34,35]. In addition, it has been stated that schizophrenia will increase oxidative stress via the glutamatergic pathway and may have an effect on NMDA and dopamine receptors. NMDARs in different brain regions play a vital role in anxiety and depression as well as learning and memory. NDMA blockade by ketamine lowers dopamine levels predominantly in prefrontal cortex, resulting in cognitive symptoms [38]. In this context, other studies have appered that rise in free radicals during SCZ may be associated with severity of symptoms [39]. In our results, it was determined that oxidative stress rised in hippocampus and prefrontal regions. In fact, oxidative stress can also affect neurotransmitter and cause behavioral disorders such as learning and memory. According to our results and results of previous studies, ketamine-induced schizophrenia leads to changes in locomotor activity, memory impairment and depression-like behavior. In addition, it causes an increase in oxidative stress over total antioxidant and oxidant balance. In our study, although it can be said that tDCS stimulation may have a therapeutic effect on behavioral changes and oxidative stress caused by schizophrenia, more molecular studies are needed.

Conclusion

In summary, this article shed light on the fact that tDCS stimulation has a potent therapeutic effect against ketamine-induced SCZ-like behavior and oxidative damage in mice. Therefore, tDCS therapy can be considered a promising formulation for prevention and treatment of SCZ, which needs further research.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Our study was carried out in Erciyes University Experimental Animals Unit. Mice obtained from Erciyes University Experimental Animals Application and Research Center with the approval of Erciyes University Animal Experiments Local Ethics Committee (Decision No 22/253) were used in the study.

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