A randomized clinical trial of the therapeutic effect of Transcranial direct current stimulation on working Memory in recent-0nset Schizophrenia

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Introduction: Significant cognitive impairments are common in patients with schizophrenia even in the initial recognizable episodes. Brain imaging in these patients also confirms the presence of a defect in the frontal cortex, which is closely related to impaired cognitive functions such as attention and memory (1, 2).

Working memory, as a cognitive feature, is impaired in many neurological and psychological disorders such as Alzheimer disease, Parkinson disease, major depression, and schizophrenia (2, 3). Working memory is characterized as the ability to temporarily store and manipulate information in the brain, which leads to an increase in one's ability to think and perform complex functions (3). It is also essential for several key processes such as language comprehension, learning, and long-term memory (4). The neural circuitry involved in the working memory is located in the dorsolateral prefrontal cortex (DLPFC), which corresponds to the 9th and 46th Brodmann areas. According to the pathophysiology of schizophrenia, impaired memory function is consistent with defects in the DLPFC region (1).

Numerous studies have examined the association between DLPFC and working memory in patients with schizophrenia. For example, by examining the relationship between this area and working memory by fMRI, it was found that patients with schizophrenia suffered from working memory impairment not due to hypo or hyper-frontality but due to a defect in the DLPFC area (5). The cognitive functions' impairment of these patients has a significant impact on their prognosis because they are strongly related to their ability in psychosocial interactions, independent living, and career outcomes (6).

Several strategies have been used to treat cognitive impairment caused by schizophrenia. Some studies suggest that the use of drug therapy, such as the use of antipsychotic drugs particularly the new generation of antipsychotics, improves cognitive function in schizophrenia (7, 8). However, other studies have shown limited effects of these medications for improving cognitive functions or preventing its degradation in these patients (9, 10). In recent years, more studies have focused on non-pharmacological interventions, especially cognitive remediation therapy, for improving cognitive functions. These interventions improve the patient's functioning in daily life, although the amount of this effect has been reported to be low to moderate and further studies are needed (11).

Recent studies have examined new non-invasive techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to modulate the activity of different areas of the brain and neuronal cycles. tDCS refers to a therapeutic tool that aims to change the electrical excitability of brain cells by weak electric current in the range of 25-80 with low intensity through installed electrodes on the scalp. Administration of tDCS has many benefits including low cost, ease of execution, non-invasiveness, and painlessness. Various studies have confirmed the potential therapeutic effects of tDCS such as the recovery of motor function, improvement of speech, learning, and attention functions, etc. (12).

In this study, the therapeutic effect of brain stimulation by tDCS on the working memory of schizophrenic patients has been investigated.

Methods: Adult Patients (>18 years old) with a definite diagnosis of schizophrenia based on standard semi-structured interviews who were not under treatment with any medications unless receiving a stable dose of drugs associated with schizophrenia were included. Patients with a history of overt epilepsy, circulatory disorders, metabolic, hormonal, and other neurological disorders, left-handed, any degree of mental disability (IQ below 75), or those who were receiving drugs that affect the central nervous system were excluded. The study was conducted based on the declaration of Helsinki. Written informed consent was obtained from each patient. The patients were randomly allocated into two groups of intervention or control. In the intervention group, all participants were treated with tDCS with the specifications explained in Table 1 for three sessions with 72-hour intervals. The letter-number sequencing test was checked before and after each treatment session in order to evaluate working memory and the results were recorded.

The treatment protocol in this study was based on previous studies in which anodal tDCs were used on the DLPFC region of healthy individuals and patients with stroke and Parkinson's disease (13, 14).

Group	Pretest	DC Stimulation	Posttest 1
tDCS	WM Task	Online protocol Lt Anodal/ Rt.supra orbital area:Cathodal DLPFC Stim 30 min 1.2 up to 2µA (5_x5=25cm2) Based On 10/20system(F3)	WM Task 5min after Stim Starting
Sham	WM Task	20 min Sham Stim 15sec ramp up 1.2µA at start and off	WM Task 5min after Sham Stim Starting

Table 1: Treatment specifications in study groups

WM= Working memory

The sham group was treated with the same sequence as the intervention (Table 1), and the measurements were the same as the intervention group.

The analysis was performed using independent and paired T-test, repeated measures ANOVA and ANCOVA tests by SPSS version 22.

Results: Among 40 cases, 4 patients (10%) were female and the mean age was 44.12 ±11.20. 20 patients received tDCS and 20 patients received a sham procedure. No significant difference was seen in age and sex between two groups (p>0.05 for each). Baseline letter-number sequencing test scores did not have significant differences between tDCS and control groups (Figure 1, p=0.174)

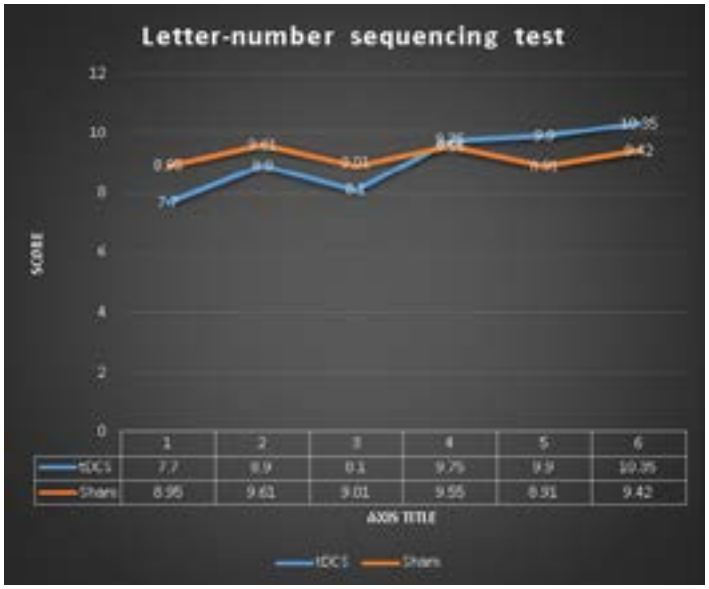

Figure 1: The result of treatment in study groups using letter-number sequencing. Points: 1 before first session, 2 after first session, 3 before second session, 4 after second session, 5 before third session, 6 after third session

Comparison of patients' performance in letter-number sequencing test conducted before and after tDCS showed that their performance improved significantly in all three sessions of tDCS (in the first sessions, from 7.70 ± 2.27 to 8.90 ± 2.49, in the second sessions, from 8.10 ± 2.49 to 9.75 ± 1.75, and In the third sessions, from 9.90 ± 2.01 to 10.35 ± 1.72, p = 0.001).

Comparison of patients' performance in tests conducted in sham group showed that their performance did not change significantly in all three sessions of the sham procedure (in the first sessions, from 8.95 ± 1.56 to 9.61 ± 1.01, in the second sessions, from 9.01 ± 1.19 to 9.55 ± 2.15, and In the third sessions, from 8.91 ± 1.42 to 9.42 ± 1.06, p = 0.216).

Comparisons between the performance of the patients before and after tDCS demonstrated their scores were significantly improved after treatment (mean difference= 3.3, 95%CI= 2.3 – 4.3, p=0.001). However, no significant changes was seen in control group comparing before and after sham procedure (mean difference= 0.51, 95%CI= 0.10 – 0.91, p=0.216). Between-group comparisons using ANCOVA test with controlling for baseline characteristics demonstrated a significant difference (p=0.001).

Conclusion: The result of our study demonstrates treatment with tDCS can improve the working memory of the patients with schizophrenia.

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