Transcranial current direct stimulation for improving working memory in patients with recent onset schizophrenia

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Transcranial current direct stimulation for improving working memory in patients with recent onset schizophrenia: An ARAS study

Dear Editor:

The deficit in Working memory (WM) is a core feature of schizophrenia and plays a role in several tasks ranging from simple daily life activities and social functioning up to the outcome of functional recovery in patients with schizophrenia [1]. Available pharmacological treatments have limited effect and cognitive remediation approaches result in valuable, yet modest improvements [2]. Therefore, interests emerged to find other approaches, such as direct modulations to the dorsolateral prefrontal cortex (DLPFC), the region that plays a central role in several cognitive capabilities.

Transcranial direct current stimulation (tDCS) is a non-invasive therapeutic modality that is proposed as a non-invasive modality for getting better responses in treatment of schizophrenia. Results of a recent meta-analysis supported the notion that tDCS is effective and safe in improving WM in schizophrenia, but findings from different trials were inconsistent [3]. Discrepancy of results is ascribed to factors related to the disorder, patient characteristics, the intervention and measurements. To this end, we conducted a double blind, sham controlled randomized clinical trial nested within the context of ARAS cohort study [4] that is a prospective cohort of the first episode psychosis in Iranian population. The protocol was approved by the ethical committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1395.1142) and registered with the Iran Registry for Clinical Trials (IRCT20160528028118N2).

Adult patients with a diagnosis of recent onset schizophrenia based on DSM5, and taking stable doses of antipsychotic medication of any kind at least for the last month were enrolled. The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of clinical symptoms as positive and negative symptoms. History of seizure attack for any reason, history of substance abuse, neurological, metabolic, hormonal disease or blood circulation dysfunction, left handedness, intellectual quotient under 90 or taking antiepileptic or benzodiazepines resulted in exclusion. Those who did not complete the trial for any reason were replaced by another patient.

After giving written informed consent by the patients and their legal caregivers, patients were randomized to receive either 2 mA anodal tDCs for 30 min, or a sham intervention, with no standard blinding assessment. A bilateral montage was used in this trial, with the anode over the left prefrontal cortex or F3 and cathode electrode placed on the right supraorbital area. Electrode size was *25cm2*. At the beginning of each session, current was ramped up over 10 seconds until 2 mA was reached and was ramped down with same speed at the end of stimulation. The procedure was repeated in three sessions with 72-h intervals. The sham-tDCS group received only 15sec ramp of 1.2μA at the first seconds of the procedure, and the rest of the sham intervention was continued with no current. Adverse effects were probed.

The letter-number sequencing (LNS) task was used to measure WM before and after each session of tDCS. The task involved hearing a series of random letters and digits, and then participants were asked to report them back with the letters in alphabetical order and digits in ascending numerical order.

Data about participants are given in the table. Lost to follow up was 6 in tDCS group and 7 in sham-tDCS group. Tingling and itching were reported by nine and seven patients in tDCS and sham-tDCS groups respectively. None of patients stopped the trial because of adverse effects. Performance of patients on the WM task were not different in the first assessment ($p = 0.27$).

Demographics and measurements

		tDCS		Sham-tDCS		p	Total
Age (years)		38.57 ± 8.41		38.50 ± 9.02		0.97	38.53 (±8.64)
Sex	Male	26 (90%)		25 (83.3%)		1.00	36 (90%)
	Female	4 (13.3%)		5 (16.7%)			4 (10%)
Educational level	Lower	13 (43.3%)		9 (30.0%)		0.46	22 (36.7%)
	Middle	15 (50.0%)		17 (56.7%)			32 (53.3%)
	Higher	2 (6.7%)		4 (13.3%)			6 (10.0%)
Marital status	Single	6 (20.0%)		7 (23.3%)		0.75	13 (21.7%)
	Married	24 (80.0%)		23 (76.7%)			47 (78.7%)
PANSS scales	Positive	16.76 (4.91)		15.90 (4.32)		0.471	16.33 (4.60)
	Negative	10.60 (4.32)		9.43 (3.25)		0.243	10.02 (3.84)
Session 1		7.80 ± 2.09	9.07 ± 2.49	8.57 ± 3.13	8.90 ± 2.87		
Session 2		8.07 ± 1.87	9.80 ± 1.84	8.37 ± 2.98	9.17 ± 3.11		
Session 3		9.30 ± 2.02	10.40 ± 1.58	8.33 ± 2.89	8.50 ± 2.88		

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All of the measured scores were evaluated by repeated measures ANOVA test. Mauchly's Test of Sphericity indicated that the assumption of sphericity has been violated, $p < 005$. Since sphericity is violated ($\varepsilon > 0.75$), Huyn-Feldt corrected results are reported. Results indicated that performance of patients in WM task was significantly different between the two groups [$F(4.629,268.454) = 19.582$, $p < 0.001$] and the score improved by tDCS compared to sham-tDCS.

The intervention did not improve or aggravate the clinical symptoms of schizophrenia. No significant change was observed in the positive (16.33 vs. 16.08, $p = 0.12$) or negative score of PANSS (10.01 vs. 9.88, $p = 0.22$) after receiving the intervention in both groups.

By this double-blind controlled trial study, we investigated the effect of tDCS on WM of patients with recent onset schizophrenia. We found that tDCS can improve the WM capability in these participants. We could not replicate the positive results on hallucinations or delusions. There was no worsening of the positive or negative symptoms. The score of WM task had a mean increase of 34.7% from the baseline measurement that might be clinically significant. We did not have a measure to show the impact of this changes on social functioning of participants, that should be addressed in further researches.

WM capacity improved slightly in the second measurement of each session. Interestingly, there was not a learning effect in the sham group that might also increase the validity of results in the intervention group. In terms of technical differences, some show that patients perform better during an online (the ongoing changes occurring during stimulation) tDCS session [5], but cross-over counterbalanced sham-controlled experiments showed that offline stimulations over DLPFC improved verbal and spatial WM tasks [6]. We implemented this method and thus were able to replicate the findings from the offline tDCS (post stimulation effects).

The current study was limited with absence of a follow up measurement to evaluate lasting of the effect. Further, the duration of the intervention was short (3 sessions, during one week), but these results might add valuable data to the evidence about efficacy of tDCS. Especially when feasibility of a short duration intervention and ease of access gets into account too. However, our study size was larger compared to similar studies. The results should also be considered with the fact that we did not use any standard toll for blinding assessment. This limitation should also be addressed in further studies.

A most noted addition of our study is, unlike previous studies, in the inclusion of patients with first episode of psychosis. Recent evidences indicate that early and intensive treatment of first episode psychosis ameliorate clinical outcomes [7]. Therefore, interventions targeting cognitive functioning of these patients have an exceptional value in the program of multidisciplinary early intervention teams. Promising results of this study should be followed by studies improving its limitations to get closer to an effective intervention for patients in the early stage of schizophrenia.

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CRediT authorship contribution statement

Sara Farhang: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ali Reza Shafiee-kandjani:** Writing – review & editing, Data curation, Conceptualization. **Arash Mohagheghi:** Writing – review & editing, Resources, Project administration, Conceptualization. **Maryam Moghaddam:** Writing – review & editing, Software, Investigation, Conceptualization. **Fatemeh Ranjbar:** Writing – review & editing, Conceptualization. **Behrooz Z. Alizadeh:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **Wim Veling:** Writing – review & editing, Validation, Methodology, Data curation, Conceptualization. **Richard Bruggeman:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

Authors have no conflict of interests to declare.

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