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Short communication

A pilot study investigating the effect of transcranial direct current stimulation on the electrophysiological correlates of working memory in patients with schizophrenia

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ABSTRACT

Transcranial direct current stimulation (tDCS) exerts pro-cognitive effects in various populations. We evaluated the effect of tDCS on cognitive performance and its electrophysiological correlates in schizophrenia patients. Ten participants received 10 sessions of tDCS and performed cognitive performance tasks; error-related negativity and correct response negativity (CRN) were measured before and after tDCS. Verbal performance was improved by tDCS and strongly correlated with a reduced CRN amplitude. Despite the lack of sham control design and possible practice effects of cognitive tasks, we might conclude that CRN could be a modifiable electrophysiological correlate of cognitive improvement by tDCS.

1. Introduction

Working memory (WM) is closely related to real-life functioning and prognosis in schizophrenia patients (Fujii and Wylie, 2003; Green, 1996); however, previous aims to improve WM functioning by various interventions have produced inconclusive results (Guse et al., 2013; Keefe et al., 2007; Wykes et al., 2011).

Transcranial direct current stimulation (tDCS) delivers weak currents over the desired scalp areas to either enhance (anode) or inhibit (cathode) cortical excitability. tDCS is hypothesized to exert differential effects by target region and polarity of stimulation, and has been studied in various populations (for more detail, refer to e-components).

Leading stream of tDCS studies in schizophrenia aims to target refractory auditory hallucinations, while several other studies are conducted to target cognitive deficits. Anodal F3-FP1 (left dorsolateral prefrontal cortex; DLPFC) with cathodal TP3 (left temporo-parietal junction; TPJ) regimen has most widely been used to alleviate hallucinations (Tortella et al., 2015). However, the effect of this protocol on WM of schizophrenia patients has scarcely been studied, considering that the left DLPFC serves as the neuroanatomical correlate of cognitive deficits in schizophrenia (Karlsgodt et al., 2009), and tDCS in temporal regions improved cognitive performances (Brückner and Kammer, 2017).

Regarding cognitive functioning, anodal F3 with cathodal F4 (bifrontal) appear to be frequently used protocols. However, most existing reports have evaluated the effect of one or two sessions of this protocol (Gupta et al., 2018), which introduces the problem of effective dosing. Two studies evaluated the effect of 5 sessions of bifrontal tDCS on cognition and showed mixed results (Shiozawa et al., 2016; Smith et al., 2015). The existing studies appear to vary not only in their tDCS protocols but also in their findings.

Meanwhile, cognitive performance is inevitably affected by practice effects; thus, utilizing neurophysiological markers could be useful. Error-related negativity (ERN) and correct response negativity (CRN) are event-related potential (ERP) components thought to reflect functions related to conflict monitoring (Perez et al., 2012) and have been suggested as possible electrophysiological markers of cognitive function (Lefebvre et al., 2005; Marchand et al., 2006; Miller et al., 2012). In schizophrenia patients, abnormalities, such as a decreased ERN and an anomalously increased CRN amplitude, are associated with cognitive deficits (Bates et al., 2002; Simmonite et al., 2012).

In this pilot study, we investigated the effect of a 10 session (as opposed to 1 to 5 sessions performed in previous studies) protocol of anodal F3-FP1 (left DLPFC)/cathodal TP3 (left TPJ) on WM functions in schizophrenia patients. Additionally, we evaluated the changes in cognitive performances and modifiability of ERN/CRN after 10 sessions

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of tDCS to investigate whether ERN/CRN could be a possible marker of tDCS.

2. Methods

Ten patients with schizophrenia recruited from an outpatient setting completed a series of WM-related tasks and underwent ERP recording before and after 10 sessions of tDCS.

We used a tDCS protocol involving 2 mA stimulation lasting 20 min per session twice daily for 5 consecutive weekdays with the anode placed midway between F3 and FP1 and the cathode placed midway between T3 and P3. This protocol has been shown to be tolerable and effective in previous studies (Kekic et al., 2016).

Various domains of cognitive functioning were measured with the following tasks: the digit span (DS) test; Wisconsin Card Sorting Test (WCST); Trail Making Test, Part B (TMT-B); California Verbal Learning Test (CVLT); and Spatial Working Memory test (SWM).

Participants performed in the flanker task while continuous electroencephalographic (EEG) recordings were acquired. Detailed protocols of the tDCS, flanker task, EEG recordings/preprocessing, and ERN measurements are more fully described in the e-components.

Wilcoxon signed rank test was used to compare the flanker performance and ERP before and after the tDCS, and Spearman's correlation analysis to evaluate the relationship between the change in the ERP amplitude and the change in performances on the WM-related tasks after tDCS with SPSS version 21 (IBM, Armonk, NY, USA).

3. Results

Demographic and clinical characteristics of participants are provided in the e-components (Table S1). Regarding cognitive performances, correct responses and perseverative responses on the WCST, immediate and delayed recall of the CVLT, and the reaction time on the TMT-B were significantly improved after tDCS. Performance on the DS test and SWM task did not show significant changes after tDCS (Table 1). Neither the performances in the flanker task nor the changes in the peak amplitudes and latencies of ERN/CRN reached statistical significance (Table 1). However, the reduction in CRN amplitude at FCz was significantly correlated with improved performance on the delayed recall of the CVLT ($r = 0.710$, $p = 0.021$; Fig. S2[c]) and SWM error response ($r = 0.709$, $p = 0.022$; Fig. S2[b]), after tDCS.

4. Discussion

We investigated the effect of anodal F3-FP1 (over the left DLPFC) and cathodal TP3 (over the left TPJ) tDCS protocols on WM functions of schizophrenia patients. We observed that 10 sessions of tDCS improved measures of the WCST correct and perseverative responses, TMT-B reaction time, and CVLT immediate and delayed recall but did not improve DS task performance and SWM error response.

In addition, we also examined the electrophysiological correlates of cognitive functioning to further support the results of our study. The CRN amplitude is consistently shown to be anomalously increased in schizophrenia patients, and this increase is believed to underlie defective conflict monitoring (Bates et al., 2002). Although we could not find significant changes in the amplitudes and latencies of the ERN/CRN perhaps due to our small sample size, two domains of WM performance (i.e., CVLT delayed recall and SWM error response) were strongly correlated with the CRN amplitude reduction (i.e., normalization) after tDCS.

Left DLPFC is understood as the neurological correlate of cognitive deficits in schizophrenia (Potkin et al., 2008), and left TPJ region as region that correlates with symptoms of auditory hallucinations (Mondino et al., 2015). We observed that verbal and visuospatial functions seemed to be modulated by tDCS, a result that might relate to the functional modulation of the fronto-parietal networks by tDCS. Regarding verbal performances, neuroanatomical correlates of language functions are distributed in large neural networks in the frontal, temporal, and parietal lobes (Binder et al., 2009), and previous studies targeting semantic fluency by tDCS also have stimulated the left DLPFC (Joyal and Fecteau, 2016) or Wernicke's area (Brückner and Kammer, 2017), regions that overlap or close to those used in our study protocols. On visuospatial functions, fMRI studies suggest correlates of such functions are not restricted to the visual sensory areas of the

Table 1
Changes in the Flanker task performance, working memory performance before and after transcranial direct current stimulation (tDCS). Amplitudes and latencies of error-related negativity (ERN) and correct response negativity (CRN) prior to and after tDCS.

	Pre-Tdcs ($N=10$)		Post-tDCS ($N=10$)		Wilcoxon signed rank test	
	Mean	SD	Mean	SD	Z	P
Error rate (%)	23.67	17.03	18.07	13.99	−1.478	0.139
Digit span	10.8	3	10.9	3.1	−0.175	0.861
WCST						
Correct response	54.2	14.6	68.3	13.1	−2.383	0.017*
Perseverative error response	35.4	24.3	21.6	16.2	−2.49	0.013*
TMT-B reaction time	107.4	47.9	80.3	29.3	−2.805	0.005*
CVLT						
Immediate recall	5.6	3.2	8.4	3.3	−2.111	0.035*
Delayed recall	6	3	8.9	12.1	−2.257	0.024*
SWM error response	42.3	22	34	24.3	−1.428	0.153
ERN amplitude (μV)						
Fz electrode site	−2.42	1.57	−2.64	2.31	−0.051	0.959
FCz electrode site	−2.31	1.77	−2.52	2.91	−0.153	0.878
CRN amplitude (μV)						
Fz electrode site	−1.73	1.29	−1.29	1.95	−0.866	0.386
FCz electrode site	−0.76	1.45	−0.60	1.59	−0.561	0.575
ERN latency (ms)						
Fz electrode site	63.5	27.41	59.7	24.05	−0.533	0.594
FCz electrode site	63.2	37.74	62.9	14.46	−0.892	0.373
CRN latency (ms)						
Fz electrode site	45.5	22.21	48.8	24.92	−0.358	0.720
FCz electrode site	58.3	32.89	60.2	32.18	−0.281	0.778

Abbreviations: WCST, Wisconsin Card Sorting Test; TMT-B, Trail Making Test, Type B; CVLT, California Verbal Learning Test; SWM, spatial working memory; ERN, error-related negativity; CRN, correct response negativity; tDCS, transcranial direct current stimulation

* P-value was significant at < 0.05.

occipital region but also in the central executive system of the fronto-parietal networks. Processing integrated chunks of information regarding domains of verbal and visuospatial memory were correlated with neural regions of the prefrontal cortex (PFC) (Prabhakaran et al., 2000), suggesting PFC plays an important role in processing both verbal and visuospatial information. Accordingly, anodal stimulation of the left DLPFC were shown to improve visual memory in other neuropsychiatric disorders (Salehinejad et al., 2015). The results of this study are seemingly consistent with these previous findings, suggesting that simultaneous stimulation of left DLPFC and TPJ may have resulted in improvements of verbal and visuospatial domains, which are closely related to functions of the fronto-parietal networks.

Previous studies utilizing anodal F3-FP1/cathodal TP3 regimen have mainly focused on its effects on reducing hallucinations, and this pilot study contributes to existing literature of tDCS in that we investigated the effect of this regimen with regards to the cognitive aspect of schizophrenia patients. While there are currently no established consensus on which regimen is more fit to target WM deficits, the alternative bifonrtal regimen utilized only small numbers of tDCS stimulation and presented with mixed results (Moffa et al., 2018). Also, although there was one study utilizing anodal F3-FP1/cathodal TP3 protocol with sham-control and sufficient duration of tDCS, the study was conducted in an inpatient setting with 'ultra-treatment-resistant' patients (Lindenmayer et al., 2018), which makes it hard to extrapolate the results to clinically more stable, less severe patients, who may seem more likely to benefit from tDCS.

It should be stated that the lack of sham control and possible impact of practice effects must be taken into account when interpreting the results of this pilot study. However, our results are consistent with existing volume of literatures that tDCS seems to be more effective in improving verbal and visuospatial functions (Naka et al., 2018; Pestalozzi et al., 2018; Schwippel et al., 2018). Because CRN is a measure of automatic neural process that can hardly be practiced, it could be said that the strong correlation observed between the verbal and visuospatial performances and CRN normalization can pose CRN amplitude as possible marker that are correlated with improvement by effective dose of tDCS.

In conclusion, 10 sessions of tDCS over the left DLPFC and TPJ regions seemed to improve verbal and visuospatial performance in schizophrenia patients. Furthermore, CRN amplitude could be a possible objective electrophysiological marker that seems to correlate well with these improvements. Future studies with larger sample size and sham control designs and comparison studies of the two tDCS protocols may be needed.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.12.014.

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