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Short communication

Preliminary findings of four-week, task-based anodal prefrontal cortex transcranial direct current stimulation transferring to other cognitive improvements in schizophrenia

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ABSTRACT

Most transcranial Direct Current Stimulation (tDCS) trials of schizophrenia administer few sessions and do not assess transfer effects to other cognitive domains. In a randomized, double-blind, sham-controlled, parallel groups trial, we determined the extent to which 4-weeks of 2 mA tDCS at 20 min/day totalling 20 tDCS sessions administered during a spatial working memory test, with anodal right dorsolateral prefrontal cortex (DLPFC) and cathodal left tempo-parietal junction (TPJ) placement, as an adjunct to antipsychotics reduced auditory hallucinations and improved cognition in 12 outpatients with schizophrenia. Anodal tDCS significantly improved language-based working memory after 2 weeks and verbal fluency after 2 and 4 weeks. Thus, four weeks of tDCS appears to be safe and elicits transfer benefits to other prefrontal-dependent cognitive abilities in schizophrenia.

1. Introduction

Schizophrenia is a severe mental illness often characterized by refractory auditory hallucinations and cognitive impairment for which antipsychotics are ineffective. Up to 75% of patients with schizophrenia experience auditory verbal hallucinations (Nayani and David, 1996) which are treatment resistant in 25% of patients (Shergill et al., 1998). Repetitive transcranial magnetic stimulation over the left temporal-parietal junction (TPJ) reduces auditory hallucinations in schizophrenia (Aleman et al., 2007; Freitas et al., 2009). Conversely, the core cognitive deficits in schizophrenia (e.g., working memory and executive function) (Weickert et al., 2000) are related to abnormal dorsolateral prefrontal cortex (DLPFC) activity in schizophrenia (Callicott et al., 2003). Transcranial Direct Current Stimulation (tDCS) reduces auditory hallucinations (Brunelin et al., 2012; Lee et al., 2018; Mondino et al., 2018; Kim et al., 2019; Lindenmeyer et al., 2019) and improves cognition in schizophrenia (Orlov et al., 2017a; Vercammen et al., 2011). Since all prior tDCS cognitive treatment trials in schizophrenia administered tDCS for 12 days or less (mode 1 day) and many trials (11/13) did not assess tDCS transfer effects to other cognitive domains, this trial aimed to determine the extent to which 20 sessions across 4-weeks of anodal tDCS over the right DLPFC during a spatial working memory test along with cathodal tDCS over the left TPJ will transfer to benefits on other PFC dependent abilities and reduce auditory hallucinations in schizophrenia.

2. Methods

2.1. Patients

Sixteen patients (18–50 years old) with schizophrenia or schizoaffective disorder were recruited, 15 were randomized to active or sham treatment and three patients discontinued. Diagnosis, determined at the baseline visit and made by a psychologist and confirmed by a psychiatrist or another psychologist, was based on the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2007). One

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Table 1
Demographics and clinical characteristics of active and sham tDCS groups.

		Group Active	Sham	Statistical test T/U/χ2 (df)	*p*-value
	n	6	6		
	Age (years)	45.5 (1.9)	31.3 (3.6)	3.47 (10)	0.01
	Sex (n)	M: 2, F: 4	M: 4, F:2	0.33 (1)	0.56
	Education (years)	12.2 (1.1)	12.0 (0.3)	0.15 (5.8)	0.88
	Illness onset (years)	21.8 (3.2)	22.5 (1.8)	0.21 (10)	0.84
	Illness duration (years)	22(0.9)	8.3 (3.4)	6	0.07
	Chlorpromazine equivalent (mg/day)	555 (248.9)	1009.3 (261.0)	1.26 (10)	0.24
	WAIS-III FSIQ	93.8 (2.7)	104.6 (5.1)	1.22 (10)	0.25
	WTAR score	104.4 (4.8)	106.4 (3.5)	0.12 (10)	0.91
Diagnosis (n)	schizophrenia	4	4	–	–
	Schizoaffective bipolar	1	2	–	–
	Schizoaffective depressed	1	0	–	–
PANSS	Positive	16.2	16.7	0.20 (7.2)	0.85
	Negative	12.8	13.0	0.06 (10)	0.95
	General	30.5	34.0	1.21	0.23
	Total	59.5	65.3	1.30	0.19
Antipsychotics (n)					
	Clozapine	1	1	–	–
	Olanzapine	2	1	–	–
	Risperidone	0	1	–	–
	Clozapine + Amilsupride	2	1	–	–
	Clozapine + zuclopenthixol	0	1	–	–
	Quetiapine + trifluoperazine	1	0	–	–
	Quetiapine + paliperidone	0	1	–	–
Antidepressants (n)					
	Clomipramine	0	2	–	–
	Duloxetine	2	0	–	–
	Mirtazapine	0	1	–	–
	Escitalopram	1	0	–	–
	None	3	3	–	–

Notes: Means with SD in parentheses unless specified otherwise. WAIS-III = Wechsler Adult Intelligence Scale - Third Edition; WTAR = Wechsler Test of Adult Reading; PANSS = Positive and Negative Syndrome Scale.

participant was not randomized to treatment due to hospitalization prior to beginning the trial. Three participants discontinued (two early in the trial, one due to substance abuse and one due to symptom exacerbation which was determined to be unlikely to be due to treatment, and one later in the trial due to an unwillingness to participate further). Thus, twelve patients (6 females) with a diagnosis of schizophrenia ($n = 8$) or schizoaffective disorder ($n = 4$) completed the trial. All participants were receiving antipsychotic medication for at least one year prior to entry into the study and (see Table 1 for antipsychotics administered). Potential participants were excluded if they: were receiving carbamazepine, had a history of substance abuse/dependence within one year of the trial, had a concomitant neurological disorder or were pregnant. Participants provided informed written consent prior to the trial. The trial was approved by the University of New South Wales Human Research Ethics Committee (10,102) and was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12611000731998).

2.2. Procedure

This was a four-week, randomised, double-blind, sham-controlled, parallel groups design trial of either active or sham tDCS administered as an adjunctive treatment to each patient's usual antipsychotic and antidepressant treatment. Participants were randomly assigned into active tDCS (asymmetrical stimulation set at 2 mA of anodal tDCS for 20-minutes to the right DLPFC and cathodal tDCS to the left TPJ) or sham tDCS (using the same electrode montage as the active condition; however, stimulation was initially ramped up to 2 mA over 15 s and then immediately down over the next 15 s) during weekdays as an adjunctive treatment to each patient's current medications including antipsychotics. tDCS was administered using a battery driven, constant current stimulator (Eldith, NeuroConn, Germany) and two conductive rubber electrodes (7 cm x 5 cm; 35 cm^2) covered by a saline-soaked synthetic sponge and restrained with a headband. The 10/20 international electroencephalography (EEG) positioning system was used with an EEG cap to locate the anodal and cathodal sites. The anode was placed on the F4 electrode site (right DLPFC) and the cathode was placed midway between T3-P3 electrode sites (left TPJ). A psychiatrist or psychologist administered tDCS, arranged and implemented the blind, and did not reveal the treatment assignment to research assistants administering the cognitive and symptom assessments, researchers performing analyses, and participants, all of whom were blind to active and sham conditions.

Since concurrent cognitive engagement and tDCS yields enhanced effects (Andrews et al., 2011), participants simultaneously performed a computerized 2-back spatial working memory test (Brain Workshop, version 4.8.1) for 20-minutes during each tDCS session (details of the task can be found at http://brainworkshop.sourceforge.net/details.html). At the baseline visit, the Weschler Test of Adult Reading (WTAR) (Wechsler, 2001) was administered as an estimate premorbid intellectual level and a 4-subtest version of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) (Wechsler, 1997) was administered as an estimate of current intellectual ability. All patients were assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB) (Nuechterlein et al., 2008), the self-rated Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) at baseline and after 2 and 4 weeks of treatment.

2.3. Statistics

Demographic and clinical characteristics were compared between the active and sham groups at baseline using one-tailed independent

samples t-tests, Mann-Whitney U, or chi-square tests as appropriate. Data that were not normally distributed were log transformed to obtain normality. Non-parametric tests were used for data that did not attain a normal distribution after log transformation. Mean difference scores after 2- and 4-weeks of tDCS were calculated relative to baseline (in active and sham conditions separately) and the mean difference scores were compared between active and sham conditions using one-tailed, independent t-tests or Mann-Whitney U tests as appropriate. Effect sizes were calculated as Cohen's *d*. The 2-back data were analysed using a repeated measures ANOVA with treatment group as the grouping factor and percent correct across each 5-day testing block as the repeated measures dependent variable. Mean substitution was applied to one participant's data at the 4-week assessment due to their discontinuation from the trial. Due to insufficient number of alternate forms, NAB mazes were not administered at the week 2 assessment and due to computer malfunction, CPT data were not included in analyses. Two-back data were unavailable for 2 patients from the active and 3 patients from sham treatments due to computer malfunction; thus, 2-back data were available for 7 patients (4 in the active and 3 in the sham condition). All statistical analyses were performed using Statistical Package for Social Sciences version 24.

3. Results

3.1. Baseline comparisons between groups

The active and sham patient groups did not differ significantly on demographic or clinical factors at baseline assessment with the exception of age in which the active treatment group was significantly older than the sham group (see Table 1). Both groups displayed mild to moderate symptom severity. There were no significant differences between active and sham tDCS groups on the basis of MCCB and AHRS scores at baseline assessment (see Table 2); however, AHRS reality and total scores showed significant trends.

3.2. tDCS treatment effects

There were significant transfer effects of active tDCS on language (category fluency) after two, $t(10) = 3.16$, $p = 0.01$, Cohen's $d = 1.84$, and four weeks, $U = 7.0$, $p = 0.05$, Cohen's $d = 0.85$, and on verbal working memory (Letter Number Span) after two weeks, $t(10) = 1.92$, $p = 0.04$, Cohen's $d = 1.09$, see Fig. 1A–C and Table 3. Performance following tDCS relative to baseline was significantly greater in the active versus the sham conditions. There were no other significant differences between active and sham conditions on any other cognitive assessment, see Table 3. There were no significant differences between active and sham tDCS on auditory hallucinations; however, there were some trends after 4 weeks, see Table 3. There were no significant differences between active and sham tDCS with respect to PANSS symptom severity scores, see Table 3. See Fig. 2 for the results of the 2-back test performance during active and sham tDCS. For the 2-back test administered during tDCS, a repeated measures ANOVA showed a significant main effect of trial block, $F(1.8) = 5.6$, $p = 0.01$, no significant main effect of treatment group, $F(1.0) = 0.02$, $p = 0.91$, and no significant treatment group by trial block interaction, $F(1.8) = 0.22$, $p = 0.79$.

Table 2
Baseline MCCB and AHRS scores in active and sham tDCS groups.

	Active	Sham	t/U (df)	*p* value
Category fluency	22.8 (1.7)	27.5 (2.2)	$U = 1.29$	0.20
BACS-SC	49.3 (3.8)	47.0 (2.4)	0.52 (10)	0.62
TMT	38.8 (4.7)	30.3 (2.6)	1.60 (10)	0.14
LNS	13.2 (1.4)	14.0 (1.1)	0.45 (10)	0.66
HVLT-R	21.8 (1.7)	19.2 (2.2)	$U = 1.38$	0.17
BVMT	20.3 (3.5)	21.8 (1.6)	0.39 (10)	0.71
NAB mazes	12. 3 (3.1)	15.3 (3.2)	0.67 (10)	0.52
MSCEIT	1.1 (0.1)	1.0 (0.1)	0.53 (10)	0.61
AHRS frequency	0.4 (0.2)	4.4 (1.7)	$U = 1.5$	0.13
AHRS reality	3.4 (0.7)	4.6 (0.2)	$U = 1.77$	0.07
AHRS loudness	2.0 (0.7)	3.0 (0.3)	1.37 (10)	0.22
AHRS number	2.6 (0.8)	3.2 (1.0)	0.47 (10)	0.65
AHRS length	2.0 (0.6)	2.2 (0.5)	0.27 (10)	0.80
AHRS attention	3.4 (0.7)	4.0 (0.5)	0.68 (10)	0.51
AHRS arousal	2.4 (0.6)	3.4 (0.8)	1.03 (10)	0.33
AHRS total	16.2 (3.3)	24.8 (2.9)	1.94 (10)	0.08

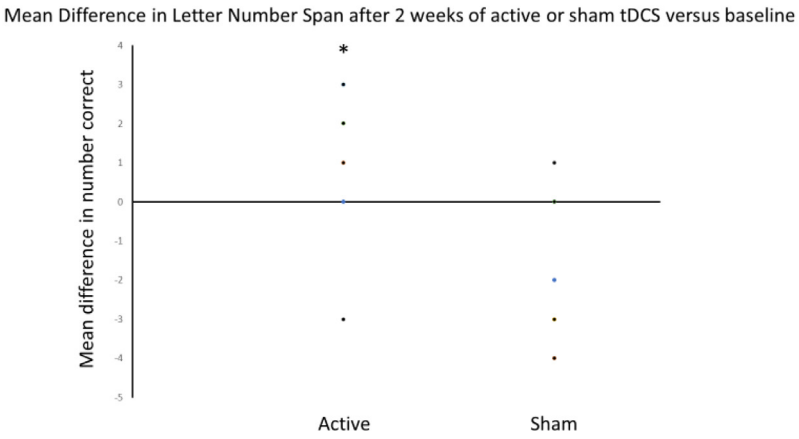
Notes: Means with SEM in parentheses. BACS-SC = Brief Assessment of Cognition in Schizophrenia Symbol Coding Subtest. TMT = Trail Making Task, Part A. LNS = Letter-Number Span Test. HVLT-*r* = Hopkins Verbal Learning Test-revised. BVMT = Brief Visuospatial Memory Test. NAB mazes = Neuropsychological Assessment Battery Mazes subtest. MSCEIT = The Mayer Salovey Caruso Emotional Intelligence Test. AHRS = Auditory Hallucinations Rating Scale.

4. Discussion

Two weeks of active anodal tDCS over the DLPFC concurrent with a DLPFC dependent spatial working memory task transferred to significant improvements in non-trained language-based working memory and verbal fluency tests relative to the sham condition and significant verbal fluency improvement was maintained after 4 weeks of treatment. Others have shown DLPFC anodal tDCS cognitive benefits, demonstrating robust reliability of tDCS to elicit cognitive improvement. However, the majority of these trials (7/12) administered only a single tDCS treatment (Hoy et al., 2014, 2015, 2016; Impey et al., 2017; Papazova et al., 2018; Schretlen et al., 2017; Vercammen et al., 2011) while two trials (generating 3 reports) administered two tDCS treatments (Orlov et al., 2017a; Orlov et al., 2017b; Schwippel et al., 2018), one trial administered 5 tDCS treatments (Smith et al., 2015), two trials administered 10 tDCS treatments (Bose et al., 2018; Jeon et al., 2018), and one case study administered 12 tDCS treatments (Tarur Padinjareveettil, et al., 2015). The present trial was the first to administer 20 tDCS treatments over 4 weeks and showed benefits after 2 and 4 weeks. These preliminary results demonstrate that tDCS benefits transfer to other PFC dependent cognitive domains and are sustained with extended treatment. Meta-analysis has shown right lateralization in the frontal cortex for spatial working memory (Wager and Smith, 2003) and we administered a spatial working memory task during anodal tDCS to the right DLPFC. Thus, improvement in spatial working memory would be expected with right DLPFC tDCS. However, although language-based tasks and production are generally considered to be left-lateralized in healthy, right-handed adults, reduced left hemispheric lateralization for language in schizophrenia is well-documented (Ocklenburg et al., 2013). Thus, improvement in the language domain with right anodal tDCS may also be expected in patients with schizophrenia.

Unlike other trials showing tDCS reduced auditory hallucinations in schizophrenia (Brunelin et al., 2012), our small trial showed only trends towards beneficial tDCS effects on auditory hallucinations. While our study administered tDCS once daily during weekdays for 4-weeks, other studies (Brunelin et al., 2012; Lindenmeyer et al., 2019) showing beneficial effects of tDCS to reduce auditory hallucination severity administered tDCS twice daily. Our small sample size is a limitation which may be related to the difficulty for patients, who generally have low motivation, to commit to daily tDCS treatment for 4 weeks. Another potential limitation pertains to the non-significant, longer illness duration in the active tDCS treatment group. A longer illness duration would generally be expected to diminish the effect of a treatment (in this case tDCS) rather than to enhance the effect of a treatment to both improve cognitive deficits and/or reduce symptom severity. Our results showed that the active tDCS group (with a non-significantly longer illness duration) had a significantly greater improvement in cognitive abilities than the sham tDCS treatment group. Regarding higher doses

A



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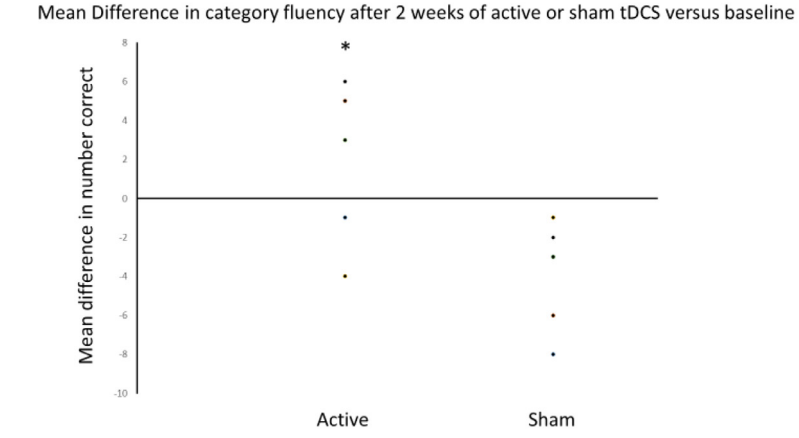

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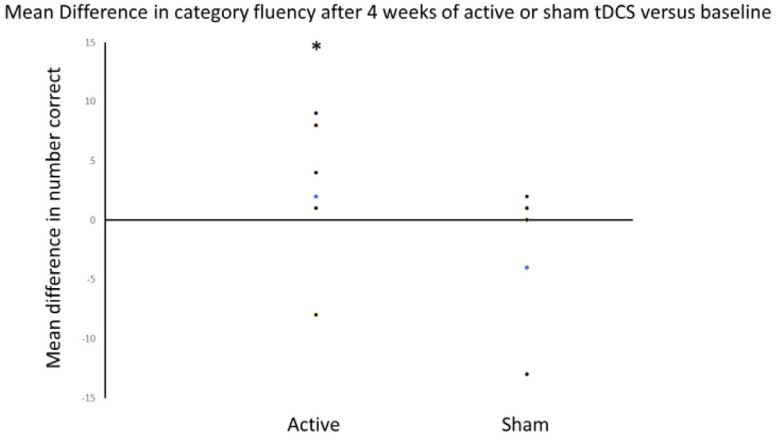

Fig. 1. Transfer effects to (A) verbal working memory after 2 weeks ($p = 0.04$, Cohen's $d = 1.09$) and (B) language fluency after 2 weeks ($p = 0.01$, Cohen's $d = 1.84$) and (C) 4 weeks ($p = 0.05$, Cohen's $d = 0.85$) of 2 mA active versus sham transcranial Direct Current Stimulation to the dorsolateral prefrontal cortex concurrent with a spatial working memory test in patients with schizophrenia (correct difference from baseline performance after 2 and 4 weeks of treatment displayed in the active and sham groups). * = $p \leq 0.05$.

of antipsychotics, a higher dose of antipsychotics may be expected to interfere with the treatment; however, in this case the active tDCS treatment group was receiving a non-significant, lower dose of antipsychotic medication (based on the mean daily chlorpromazine equivalent dose) relative to the sham tDCS treatment group. Thus, the non-significant, lower dose of antipsychotic medication would not be expected to interfere with the tDCS treatment in the patients receiving active tDCS. Future studies should assess continued cognitive benefits post treatment. Thus, in summary, four weeks of anodal tDCS over the DLPFC appears to produce sustained beneficial effects on cognition in schizophrenia that transfers to other prefrontal dependent cognitive domains.

Table 3
Effects of active versus sham tDCS during a working memory test after 2 and 4 weeks of treatment (mean difference scores versus baseline) on other cognitive tests and auditory hallucinations in patients with schizophrenia.

	Two weeks Mean difference Active	Sham	t/U (df)	*p* value	Four weeks Mean difference Active	Sham	t/U (df)	*p* value
Category fluency	2.4	−3.8	3.16 (10)	0.01	2.7	−2.3	*U* = 7	0.05
BACS-SC	4.3	2.8	0.44 (10)	0.34	−0.1	2.4	0.85 (10)	0.41
TMT	−5.8	−1.6	0.94 (10)	0.18	−5.8	−4.5	0.27 (10)	0.40
LNS	1.0	−1.3	1.92 (10)	0.04	0.4	0.3	0.11 (10)	0.46
HVLT-R	−0.6	−0.8	*U* = 16.5	0.81	−2.4	−0.8	0.57 (10)	0.58
BVMT	−2.9	−0.8	0.73 (10)	0.48	−5.3	3.0	1.91 (10)	0.09
NAB mazes	–	–	–	–	−2.5	5.1	2.04 (10)	0.68
MSCEIT	1.3	3.4	0.9 (10)	0.39	−1.7	4.4	1.48 (10)	0.17
AHRS frequency	−0.1	−0.7	*U* = 14.0	0.59	0.1	−1.7	*U* = 7.5	0.09
AHRS reality	1.0	0.2	*U* = 13.5	0.49	−0.9	−0.6	0.41 (10)	0.35
AHRS loudness	0.6	−0.4	1.63 (10)	0.13	−0.3	0	*U* = 21.0	0.35
AHRS number	−0.4	0.2	0.73 (10)	0.24	−0.6	−1.0	*U* = 13.5	0.49
AHRS length	0.7	0.2	*U* = 14.5	0.59	−1	0.3	1.64 (10)	0.06
AHRS attention	0.9	0.2	0.75 (10)	0.47	−0.9	0.5	*U* = 26.5	0.09
AHRS arousal	0.8	0.4	0.45 (10)	0.66	−0.2	0.9	*U* = 28.0	0.06
AHRS total	3.6	−4.1	*U* = 10	0.24	1.5	0.3	*U* = 20.0	0.82
PANSS positive	4.2	0.5	*U* = 17	0.94	−1.8	−1.3	0.26 (10)	0.40
PANSS negative	1.2	0	0.54 (5)	0.61	1.4	2.2	0.44 (10)	0.67
PANSS general	−0.3	−0.2	0.04 (10)	0.49	−2.9	0.2	0.62 (10)	0.28
PANSS total	5.1	0.3	0.66 (10)	0.52	−3.3	−0.53	0.39 (10)	0.35

Notes: BACS-SC = Brief Assessment of Cognition in Schizophrenia Symbol Coding Subtest. TMT = Trail Making Task, Part A. LNS = Letter-Number Span Test. HVLT-*r* = Hopkins Verbal Learning Test-revised. BVMT = Brief Visuospatial Memory Test. NAB mazes = Neuropsychological Assessment Battery Mazes subtest. MSCEIT = The Mayer Salovey Caruso Emotional Intelligence Test. AHRS = Auditory Hallucinations Rating Scale. PANSS = Positive and Negative Syndrome Scale.

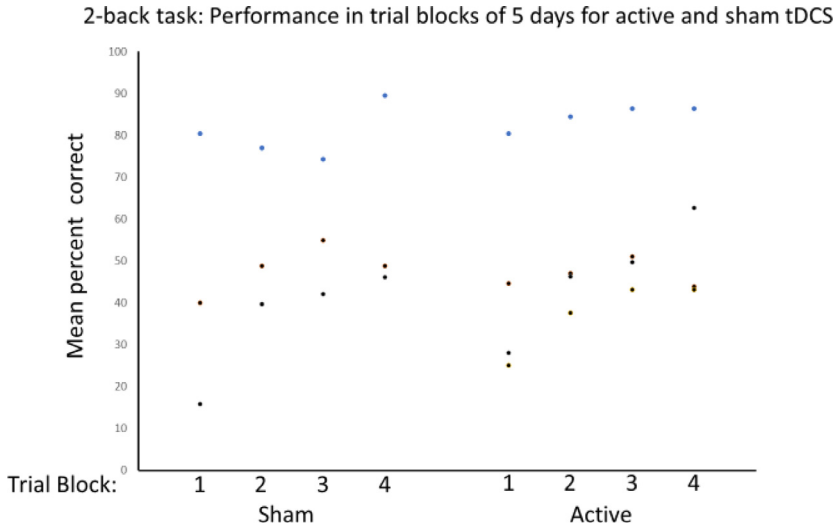

Fig. 2. Working memory performance during tDCS sessions at the end of each 5-day trial block in the active and sham tDCS treatment groups of patients with schizophrenia.

Declaration of Competing Interest

All authors declare that they have no competing financial or other conflict of interest in relation to the work described in this report.

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