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ORIGINAL RESEARCH

Effects of transcranial direct current stimulation on brain changes and relation to cognition in patients with schizophrenia: a fMRI study

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Abstract

We studied brain changes during an N-back task before and after 10 sessions of transcranial direct current stimulation (tDCS) and its relation to cognitive changes. This was a double-blind, sham-controlled, randomized study of tDCS in 27 patients with schizophrenia. They performed an N-back task in a 3 T scanner before and after receiving the 10 tDCS sessions. Cognitive performance outside the fMRI session was assessed using the MATRICS Consensus Cognitive Battery and other tests at baseline and several time points after 10 sessions of tDCS. During the N-back task performed during fMRI scans, comparing the 0-back vs. the 2-back task, the active tDCS group demonstrated a significantly increased activation in the right fusiform, left middle frontal, left inferior frontal gyrus (opercular part) and right inferior frontal gyrus (triangular part) and reduced activation in the left posterior cingulum gyrus with most of these results primarily due to increases in activation during the 0-back rather than 2-back task. There were also significant positive or negative correlations between some of the brain changes and cognitive performance. tDCS modulated prefrontal activation at low working memory load or attention mode, but default mode network at higher working memory load. Changes in brain activation measured during the N-back task were correlated with some dimensions of cognitive function immediately after 10 tDCS sessions and at follow-up times. The results support tDCS could offer a potential novel approach for modulating cortical activity and its relation to cognitive function.

Keywords Transcranial direct current stimulation · Cognitive deficits · Schizophrenia · fMRI

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Introduction

Cognitive deficits, including impairments in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Nuechterlein et al., 2004), are considered a core feature of schizophrenia (Keefe, 2008; Wilk et al., 2005). These deficits may be seen in childhood and precede the onset of schizophrenia (Reichenberg et al., 2010) or even persist after stabilization of the illness (Horan et al., 2014). Transcranial direct current stimulation (tDCS), using weak currents to modulate cortical excitability and modify plasticity (Bestmann & Walsh, 2017), has been utilized as a potential alternative to improve cognition in schizophrenia. Previous research by our own group (Smith et al., 2015, 2020) and others (Ciullo et al., 2020; Hoy et al., 2014; Lindenmayer et al., 2019; Smith et al., 2015, 2020; Weickert et al., 2019) provide evidence that tDCS may improve some aspects of cognitive function in schizophrenia, either immediately after a series of tDCS sessions and/or in several week or months follow-up after the end of treatment.

The underlying brain changes involved in these effects of tDCS in patients with schizophrenia have not been extensively investigated. Although findings from neuroimaging studies are not consistent, dysfunctional activation of the DLPFC may play a major role in the pathophysiology of cognitive dysfunction (Hill et al., 2004; Johnsen et al., 2020; Minzenberg et al., 2009; Sheffield & Barch, 2016). Because of its essential role in the pathophysiology of schizophrenia, the left DLPFC has been a promising target for studies investigating tDCS for the treatment of cognitive deficits. One recent study using functional magnetic resonance imaging (fMRI) (Orlov et al., 2017) did examine brain changes induced by tDCS administered with the anode overt the DLPFC during an on-line N-back task and the relation of some of these brain changes to subsequent cognitive function changes in patients with schizophrenia. In this study, during the working memory task, anodal tDCS was associated with increased activation in the medial frontal gyrus and reduced activation in the left cerebellum. Furthermore, there was a positive correlation between working memory performance and increased activation in the medial frontal gyrus. During the executive function task, there was reduced activation in the anterior cingulate gyrus, which was associated with improved performance on the executive function task. These results showed that tDCS could modulate functional activation in both in local task-related regions and in more distal nodes in the network.

In the current study we investigated the brain functional activation patterns at different working memory loads, using an N-back tasks during fMRI scans, before and after the administration of 10 tDCS sessions in patients with schizophrenia with the anode placed over the Left DLPFC. We examined the cognitive effects of tDCS and the correlation of changes in brain activation patterns with the cognitive effects of tDCS.

Methods

Study design and patients

This is a sub-analysis of a double-blind, sham-controlled randomized study of tDCS in patients with schizophrenia (Smith et al., 2020) of 27 patients in this larger study who also completed 2 fMRI brain scans during which they performed an N-back task. We recruited right-handed patients diagnosed with schizophrenia who were hospitalized at the Shanghai Mental Health Center. In the original larger sample study (Smith et al., 2020) patients were randomly assigned to either active or sham tDCS (Supplementary material). The study design and inclusion/exclusion criteria and procedures have been described in detail in a larger behavioral study (Smith et al., 2020). In brief, patients with a total score of < 85 on the Repeatable Battery for Neuropsychological Status (RBANS) and completed 10 sessions of active or sham tDCS once a day over 2 weeks and were evaluated at baseline, immediately (1–2 days) post-treatment, and 2 and 4 weeks post-treatment using the Chinese version (Shi et al., 2015) of the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008), the Paced Auditory Serial Addition Task (PASAT) (Gronwall, 1977), and the CogState Battery (CS) using CS tasks (identification task, N-back task). Each patient included in this study signed a written informed consent form for a protocol approved by the Institutional Review Board of Shanghai Mental Health Center (Approval number 2015-09R2).

tDCS treatment

We used the same tDCS stimulation protocol as our previous published study (Smith et al., 2015). A Chattanooga Ionto System stimulator was used for tDCS stimulation with two 5.08×5.08 cm^2 sponge electrodes soaked in a saline solution (0.9% NaCl). The anode was placed over the left DLPFC (F3) and the cathode over the right supraorbital area (Fp2), according to the 10–20 electrode placement system. Ten stimulation sessions were conducted once a day over 2 weeks. Active stimulation level was set at 2 mA for 20 min, whereas sham stimulation was applied for 40 s only at 2 mA, though the electrodes remained in place for 20 min.

Behavioral cognitive data analysis

The methods of analysis of the effects of tDCS on cognitive evaluations outside the fMRI procedures in this sub-sample of 27 subjects were the same as those used for the complete sample (45 subjects) presented in our earlier publication (Smith et al., 2020). The purpose was to evaluate whether the cognitive effects of tDCS in this sub sample was representative of the larger sample. It used the same statistical procedures as in the original paper with the full sample (Smith et al., 2020), an intention-to-treat analysis using all subjects who had at least one post-baseline values on the variable of interest. The mixed procedure of SAS 9.4 was used to handle missing data. Details of the statistical analysis procedures are found in our previous paper (Smith et al., 2020) and are also presented in the supplementary data.

Working memory task

The working memory task (N-back task) has been described elsewhere in full detail (Cohen et al., 1994). In this study, we used the 0-back and 2-back tasks to activate brain regions. The 0-back task has a low load task which may primarily involve attention functions, while the 2-back task has a higher moderate working memory load. The working memory task consisted of seven repetitions of each task lasting 34 s each, resulting in a 238 s 0-back period and a 238 s 2-back period. Each repetition consisted of 20 trials with a stimulus lasting for 1700 ms. In addition, a fixation condition (cross-hair), lasting 1000 ms, was presented between trails. During the 0-back task, patients viewed a series of numbers (1–4) and were asked to press a button with the right index finger if the number "1" appeared; otherwise, they were asked to use the right middle finger. During the 2-back task, patients viewed the same number series (1–4) and were asked to press a button with the right index finger if the currently presented number matched the number that presented two trials previously; otherwise, they were asked to use the right middle finger. Patients could view the numbers which were projected onto an overhead screen through a mirror located on the scanner's head coil. Numbers were presented and results were recorded using E-prime software (Psychology Software Tools, Pittsburgh, PA, USA). Before each scan, patients were trained on each task to ensure that they understood the rules. The N-back paradigm is shown in Supplementary Fig. 1.

fMRI data acquisition

Structural and fMRI scans were acquired on a SIEMENS MAGNETOM Verio syngo MR B17 3 T scanner at the Shanghai Mental Health Center. A 32-channel head coil was used for signal reception. We instructed patients to remain still and placed foam padding around the head to minimize the effects of movement. Functional data were collected over a 10-min period using an echo planar imaging sequence (repetition time, 1,400 ms; echo time, 30 ms; flip angle, 80°; field of view, 224 mm; matrix, 112 × 112, 64 slices; acquisition voxel size, 2.0 × 2.0 × 2.0 mm). A T1-weighted magnetization prepared rapid acquisition gradient echo sequence was obtained from each subject using brain-volume imaging (repetition time, 2,500 ms; echo time, 3.5 ms; inversion time, 1,200 ms; flip angle, 88°; field of view, 256 mm; matrix, 256 × 256; voxel size = 1.0 × 1.0 × 1.0 mm).

Functional MRI analysis

The preprocessing was performed with Statistical Parametric Mapping 12 (SPM12) (www.fil.ion.ucl.ac.uk/spm) and NIT (Dong et al., 2018) in MATLAB R2018a (https://uk.mathworks.com/) with the following steps: slice-timing, motion corrected, spatially realigning to the mean image from the series and resliced, then spatial normalization into Montreal Neurological Institute (MNI) template and smoothing the data with an 8 mm Gaussian Kernel. A first-level analysis was conducted using the General Linear Model (GLM) for each subject individually; only the correctly trials were included in analysis. Contrasts were estimated for each load (0-back, 2-back and 0-back vs. 2-back) level. In order to produce the hemodynamic response for each experimental condition (sustained activity over the whole blocks), the vectors were convolved with a canonical hemodynamic response function using a box-car function. The resulting single-subject images were taken to a second-level random effects analysis. The repeated 2 (between-group: Active and Sham group) *2 (within-group: pre-treatment and post-treatment) ANOVAs were performed to obtain the effect of treatment on task related network activation, controlling the age, gender and illness duration. The post hoc test was calculated by paired t-test (within-group) and two sample t-test(between-group). We assessed the relationship between change in brain activation and change in cognitive performance using spearman correlations.

Results

Patients' characteristics

Of the recruited 49 patients with schizophrenia, 45 provided at least one evaluable cognition data. Of these 45 subjects, 27 patients successfully completed an fMRI scan with the N-back (0-back and 2-back) working memory task before and after tDCS treatment. There were no differences between the active vs. sham groups in terms of demographic and clinical characteristics (Table 1).

Table 1 Patients' characteristics

Characteristic	tDCS Active (N = 16)	tDCS Sham (N = 11)	Test
Age, years	43.56 ± 13.20	46.91 ± 11.53	T = 0.680, DF = 25, P = 0.52
Sex (Male/Female)	4/12	3/8	FET P = 1.00
RBANS Total	74.81 ± 7.99	73.27 ± 9.58	T = -0.454, DF = 25, P = 0.65
PANSS Total	58.94 ± 15.64	56.73 ± 10.86	T = -0.405, DF = 25, P = 0.69
PANSS Positive	11.38 ± 5.00	10.82 ± 3.74	T = -0.313, DF = 25, P = 0.76
PANSS Negative	19.68 ± 6.04	18.27 ± 5.71	T = -0.611, DF = 25, P = 0.55
Duration of illness, years	17.91 ± 11.61	19.52 ± 10.25	T = 0.367, DF = 24, P = 0.72
Type of Antipsychotic (first generation/ second generation/ combined 1st and 2nd generation), n	1/13/2	0/9/2	FET P = 1.00
On Clozapine, n	3	3	FET P = 0.66
On Antidperessant, n	1	1	FET P = 1.00
On Mood Stabilzier, n	4	2	FET P = 1.00
On Benzodiazepine, n	1	4	FET P = 0.13

Abbreviations: tDCS, transcranial direct current stimulation; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; PANSS, Positive and Negative Syndrome Scale. FET = Fishers' Exact Test. T = t-test

Results of cognitive tests performed outside of fMRI scans

The cognitive effects of tDCS in the subsample of 27 patients who underwent fMRI scanning were very similar those reported for the complete sample of 45 subjects in our published paper (Smith et al., 2020). There were no significant differences in cognitive tests directly after 10 sessions of tDCS (Supplementary Table 1), but there was significant improvement Matrics domain score on speed of processing and CogState 1-back scores at 2 weeks after the last tDCS session, and a trend ($P < 0.10$) for improvement in Matrics reasoning and problem solving domain at 4 weeks (Table 2). These results show that the sub-sample who participated in fMRI study were representative, in its cognitive effects of tDCS, to the full enlarged sample, and may support a suggestion that the fMRI results for this sub-sample, discussed below, may be consistent with results if we were able to scan all the subjects who participated in the study.

fMRI analyses

Subjects performed reasonably well on the N-back task during fMRI scan, with high accuracy (about 90%) in the 0-back and 2-back (about 70%) (Supplementary Table 2). During the 0-back task at baseline, the active group showed increased activation in the bilateral cerebellum and left triangle inferior frontal gyrus. The sham group mainly found the decreased activation in the default mode network (DMN). After tDCS treatment, the active group showed significant activation in the bilateral DLPFC whereas the sham group almost no activation (Supplementary Fig. 2). The activation pattern after 2-back was less consistent with our expectations. During 2-back task, the active group at baseline showed increased positive activation in the right hippocampus/parahippocampus, bilateral calcarine, middle cingulate cortex, and left middle frontal gyrus (MFG) and the sham group at baseline mainly showed increased positive activation in sub-cortices. After treatment, the active group only displayed the increased positive activity in the posterior DMN regions and cerebellum. And the sham group displayed the positive activity in the visual-related regions (Supplementary Fig. 3). These results suggest that, in this sample, tDCS may have modulated functional activation at very low working memory load, engaging primarily attention function, but not at moderate working memory load. Thus, in current study, the activation of 2-back was set as baseline. The results of repeated ANOVA in 0-back minus 2-back showed significant interaction effect in the right fusiform gyrus, bilateral MFG, bilateral inferior frontal gyri (IFG) and left posterior cingulate cortex (PCC). Furthermore, compared to the pre-treatment, the active group showed significant increased activation in the right fusiform, left MFG, left IFG (opercular part) and right IFG (triangular part) after tDCS treatment, and displayed significant decreased activation in the left PCC. There was no significant change of task-related activation within the sham group (Fig. 1).

We explored whether there were significant correlations between the difference in brain activation during the N-back task, comparing baseline and after 10 sessions of tDCS (0 back vs 2-back activation differences) and cognition scores measured outside of the fMRI session. There were significant correlations between some fMRI measures

Table 2 Effects of tDCS on cognition up to one-month follow-up

Measure	tDCS	After 10 tDCS Sessions	2 weeks after 10 tDCS Sessions	4 weeks after 10 tDCS Sessions	Mixed-model ANCOVA, Group * Time Effect (F_{GT})			Mixed-model ANCOVA, Group Effect (F_G)			Mixed-model ANCOVA, Time Effect (F_T)			Effect Size	POW
MATRICS Battery					F	DF	P	F	DF	P	F	DF	P		
Overall Composite	Active	1.93 ± 1.16	6.86 ± 1.35	6.53 ± 1.63	3.70	2,25	0.039	0.66	1,25	0.424	11.88	2,25	< 0.001	0.33	0.13
	Sham	2.47 ± 1.53	3.17 ± 1.58	4.80 ± 1.99											
Speed of Processing	Active	5.51 ± 1.15	**9.63 ± 1.61** [*A]	10.6 ± 1.91	1.76	2,25	0.193	6.36	1,25	0.018	6.87	2.25	0.004	1.03	0.73
	Sham	2.09 ± 1.40	**2.17 ± 1.85**	6.06 ± 2.21											
Attention Vigilance	Active	4.22 ± 1.81	3.99 ± 2.29	3.13 ± 2.13	2.21	2,25	0.131	0.57	1,25	0.457	1.11	2,25	0.345	0.31	0.12
	Sham	1.84 ± 2.33	-1.04 ± 2.62	3.72 ± 2.51											
Spatial Working Memory	Active	0.31 ± 1.41	3.90 ± 1.92	4.59 ± 2.06	5.84	2,25	0.008	0.11	1,25	0.746	1.55	2,25	0.231	0.14	0.06
	Sham	4.78 ± 1.72	0.27 ± 2.20	5.78 ± 2.33											
Verbal Learning	Active	-8.46 ± 2.49	3.22 ± 2.97	-2.26 ± 2.09	0.96	2,25	0.395	0.74	1,25	0.398	14.28	2,25	< 0.001	0.35	0.14
	Sham	-3.22 ± 3.03	4.47 ± 3.41	-0.23 ± 2.44											
Visual Learning	Active	4.66 ± 1.79	6.35 ± 2.38	5.66 ± 2.57	0.25	2,25	0.780	3.86	1,25	0.061	0.60	2,25	0.558	0.80	0.51
	Sham	0.24 ± 2.23	1.39 ± 2.81	-1.40 ± 2.92											
Reasoning-Problem Solving	Active	3.45 ± 1.50	4.88 ± 1.98	**9.08 ± 2.01** [†]	0.65	2,25	0.532	4.32	1,25	0.048	2.75	2,25	0.084	0.85	0.56
	Sham	-0.00 ± 1.86	1.18 ± 2.31	**2.04 ± 2.27**											
Social Cognition	Active	-0.02 ± 1.20	-1.36 ± 1.41	0.36 ± 2.12	0.27	2,25	0.763	0.25	1,25	0.621	0.44	2,25	0.646	0.20	0.08
	Sham	0.29 ± 1.49	0.58 ± 1.62	1.28 ± 2.49											
PASAT															
Number Correct	Active	2.47 ± 1.45	1.82 ± 2.27	4.86 ± 2.56	1.27	2,25	0.298	0.04	1,25	0.843	5.54	2,25	0.010	0.08	0.05
	Sham	-0.63 ± 1.76	1.63 ± 2.67	6.38 ± 2.98											
COGSTATE															
Identifcation Task, LgRT	Active	-0.05 ± 0.01	-0.06 ± 0.01	-0.04 ± 0.01	3.12	4,25	0.033	1.71	1,25	0.203	1.55	4,25	0.218	0.53	0.26
	Sham	-0.02 ± 0.02	-0.04 ± 0.02	-0.04 ± 0.02											
1-Back Memory Task, ASCR	Active	**0.14 ± 0.04** [†]	**0.16 ± 0.03** [*]	0.11 ± 0.05	2.63	4,25	0.059	3.27	1,25	0.083	0.85	4,25	0.506	0.74	0.45
	Sham	**0.04 ± 0.05**	**0.02 ± 0.04**	0.06 ± 0.04											
2-Back Memory Task, ASCR	Active	0.07 ± 0.04	0.16 ± 0.05	0.13 ± 0.04	2.22	4,24	0.098	0.52	1,24	0.478	4.28	4,24	0.009	0.30	0.12
	Sham	0.16 ± 0.05	0.13 ± 0.06	0.20 ± 0.05											

[†] $P < 0.10$, * $P < 0.05$ ** $P < 0.01$

Abbreviations: N = 27, Active tDCS = 16, sham tDCS = 11. Each number represents estimated mean ± s.e.m. ANCOVA = (mixed-model) Analysis of covariance of difference score with baseline score as covariate. PASAT, Paced Auditory Serial Addition Task; LgRT, Log10 of reaction time to correct responses; ASCR, arcsine transformation of the square root of the proportion of correct responses; DF, degree of freedom; POW, observed (post-hoc) power (α = 0.05). BH corrected significance levels taking into account the three time-point comparisons for most measures, and five time point comparisons for cogstate measures: [A] significant at (α = 0.05)

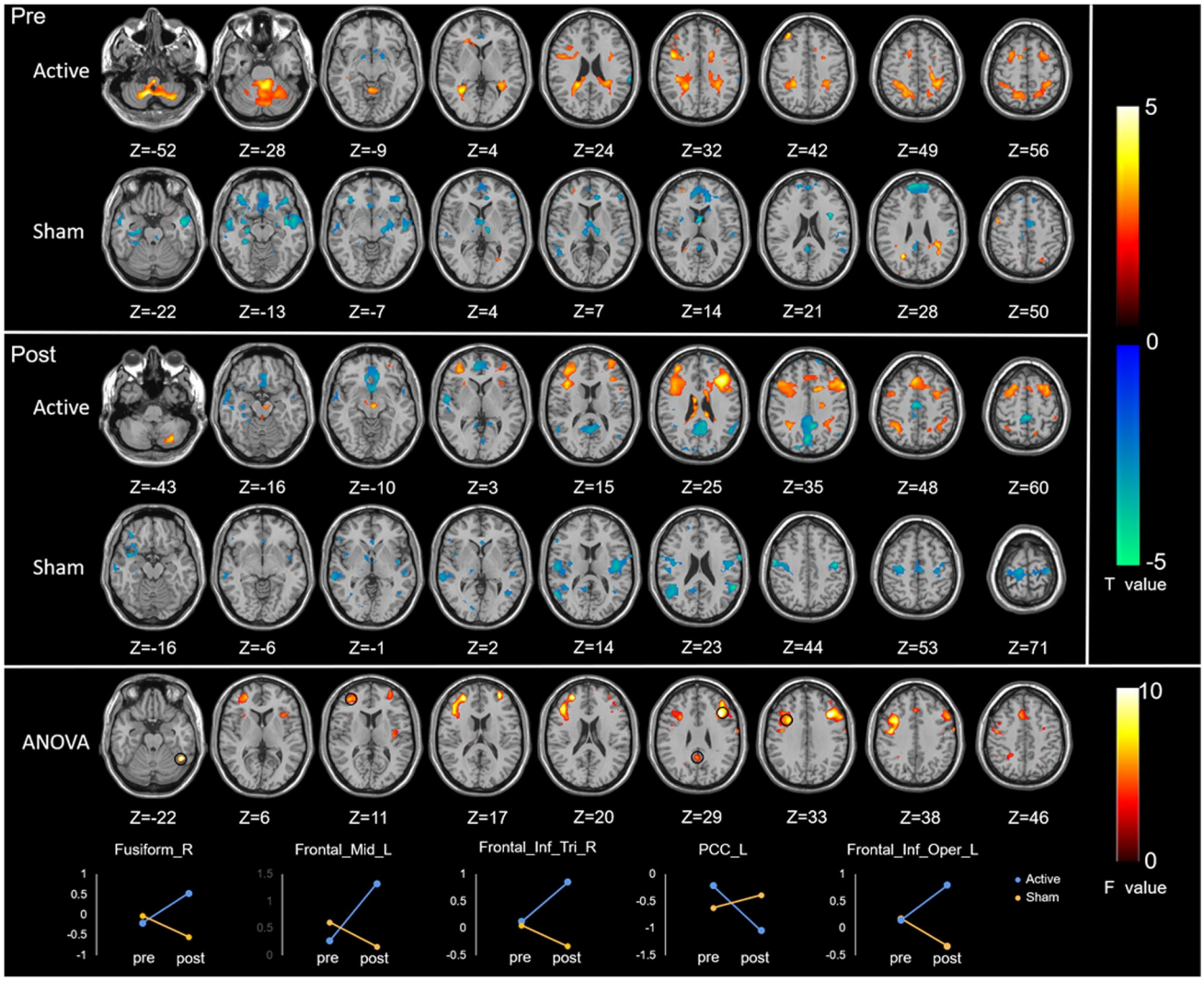

Fig. 1 Changes in neuronal activity during N-back task before(pre) and after(post) tDCS treatment: main effects of treatment (ANOVA) (active versus sham) contrasting 0 versus 2-back, $p < 0.005$ (uncorrected), for illustration purposes, controlling the age, gender and illness duration. Post points in the bottom graphs are significantly different ($P < 0.005$) for active vs sham

during the N-back task and changes in cognition tested immediately after the 10 tDCS sessions. To examine this the β for 0-back vs. 2-back was extracted and we found a significant correlation between the decreased activation in left PCC and better performance in MATRICS speed of processing domain in the active tDCS group (rho = -0.72, P = 0.003) (Fig. 2). Furthermore, we also found a significant correlation between the increased activation in the left IFG (opercular part) and better performance in the CogState in the active tDCS group (LgRT of Identification Task: rho = 0.56, P = 0.047; ASCR of 1-Back Task: rho = 0.63, P = 0.020) (Fig. 3). In our behavioral cognitive analysis, we and others (Smith et al., 2020; Weickert et al., 2019) have found beneficial effects of tDCS on some measures of cognition occurring weeks after the last tDCS session, which may be related to changes in neuroplasticity induced by 10 treatment sessions. Therefore, we also explored whether changes in functional brain activity, in the fMRI N-back task, were related to cognitive measures we tested 2 or 4 weeks after the last tDCS session. Several correlations showed statistically significant effects. Two weeks after the end of tDCS increased activation in the left IFG (opercular part) was associated with better social cognition (rho = 0.92, $P < 0.05$, Supplementary Fig. 4A) and increased activation in the right fusiform gyrus was associated with better visual learning (rho = 0.82, $P < 0.05$, Supplementary Fig. 4B). However, at this time point there was also a significant negative correlation between spatial working memory and the increased activation in the right fusiform gyrus (rho = -0.81, $P < 0.05$, Supplementary Fig. 4C). At the 4 week time point there were negative correlations between spatial working memory and

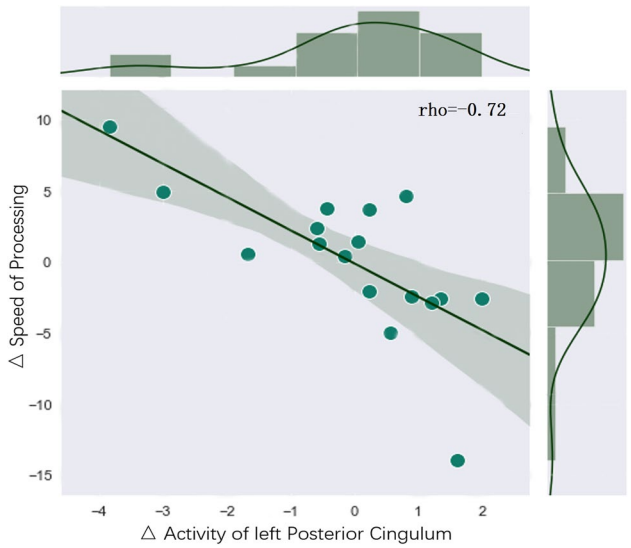

Fig. 2 Spearman's correlation between change in brain activity in the PCC and change in performance in the MCCB processing speed domain, in the group who received active tDCS, in cognitive assessment immediately after 10 TDCS sessions (rho = -0.72, P = 0.003)

the increased activation in the left IFG (opercular part) (rho = -0.76, P < 0.05, Supplementary Fig. 5A) and verbal learning and the increased activation in the right IFG (triangular part) (rho = -0.81, P < 0.05, Supplementary Fig. 5B) However, at this time point there were also positive correlations which showed that increased activation in the right fusiform gyrus was associated with better social cognition (rho = 0.76, P < 0.05, Supplementary Fig. 5C) and visual learning (rho = 0.86, P < 0.05, Supplementary Fig. 5D).

Discussion

The effects of tDCS on cognitive measures in this sub-sample of patients with schizophrenia showed improved cognition on several measures at the 2-week or 4-week time point, but no immediate effect after 10 sessions of tDCS, which is consistent with our earlier published results of the total sample (Smith et al., 2020). Some previous studies, including our early study in schizophrenic patients in the US population (Smith et al., 2015) and a meta-analysis (Narita et al., 2019), have found more consistent effects of tDCS on improving working memory, although some have found effects at later time points but not immediately after tDCS (Jeon et al., 2018). In a more recent meta-analysis (Liu et al., 2021), we found no effects of tDCS on working memory tested immediately after completion of tDCS sessions in patients with schizophrenia, but weak evidence for positive effects when working memory was assessed at later time points.

The fMRI results showed that tDCS produced increased activation in areas relevant to the DLPFC such as the bilateral MFG as IFG during the 0-back but not the 2-back task; even at baseline the 2-back did not produce the full panoply of expected increase in activation in frontal cortex working memory related networks. Although our subjects' performance on cognitive tests assessed immediately after 10 sessions of tDCS showed no differences between active vs sham, there were significant correlations with between changes in brain measures related to activation (0 back vs 2 back) and Matrics speed of processing and N-back measures at this time point. Additionally, there were multiple significant correlations between changes in brain activation measures and cognitive performance 2 weeks or 4 weeks after the end of tDCS.

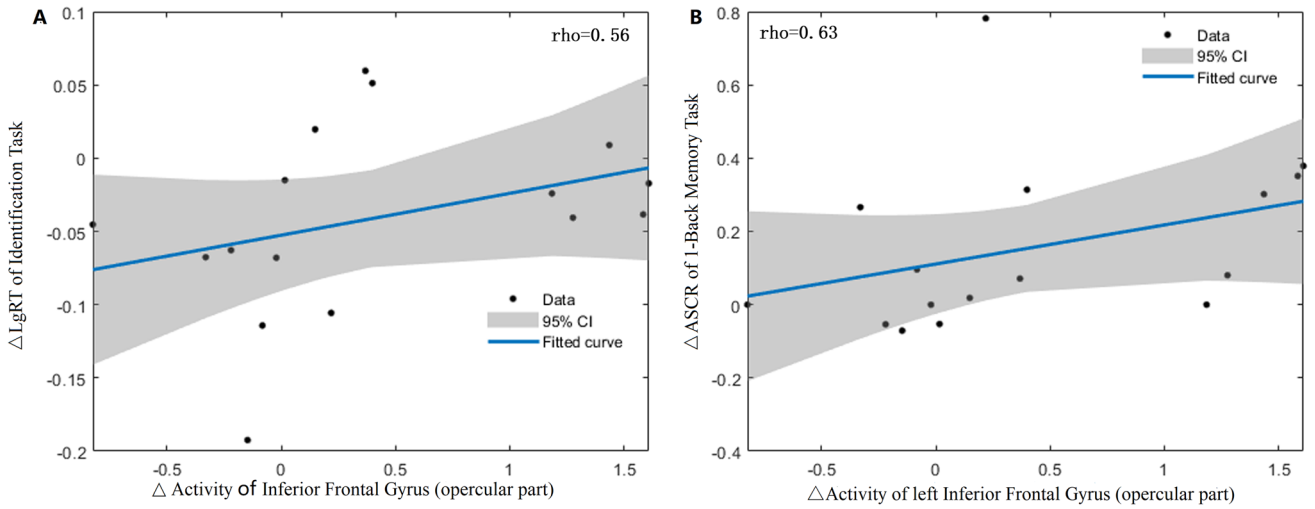

Fig. 3 Spearman's correlations between change in brain activity in the left IFG (opercular part) and change in performance in the CogState, in the group who received active tDCS, in cognitive assessment immediately after 10 tDCS sessions. LgRT, Log10 of reaction time to correct responses; ASCR, arcsine transformation of the square root of the proportion of correct responses. (**A**) △LgRT of Identification Task (rho = +0.56, P = 0.047); (**B**) △ASCR of 1-Back Memory Task (rho = +0.63, P = 0.020)

Schizophrenia is characterized as a "disconnection syndrome" marked by abnormal communication between brain networks (Fan et al., 2020; Uhlhaas & Singer, 2012), and shows global hyperconnectivity at rest, which leads to inflexibility in changing the activation patterns as per task demands (Whitfield-Gabrieli et al., 2009). Recent investigations of intrinsic brain connectivity networks using resting state fMRI have shown a number of disruptions in functional connectivity for schizophrenia-most notably in the fronto-parietal control network, which is commonly associated with higher order goal directed performance, and the default mode network (DMN), which is increasingly implicated in spontaneous cognition (Baker et al., 2014; Zhou et al., 2021).

Several studies have explored the effects of tDCS on changes in the connectivity of brain networks in resting state. Palm and colleagues found preliminary evidence for changes in DLPFC connectivity within frontal-thalamic-temporo-parietal networks; specifically, after one tDCS session, the active group showed changes of functional connectivity of the left DLPFC seed with the left posterior cingulate/left precuneus and the left thalamus than the sham group (Palm et al., 2016). Meanwhile, one study had also studied the effects of tDCS on the brain activation in the DLPFC during working memory task; it reported results from working memory task that were completed with concomitant active/sham tDCS and showed increased brain activation in the medial frontal cortex during an N-back task (Orlov et al., 2017). Similar to the findings of previous studies, our current results showed that tDCS could modulate prefrontal activation during 0-back. Previous studies have demonstrated the consistency of the hypo-activation of the DLPFC during a working memory task in patients with schizophrenia compared to controls and our study demonstrated that tDCS could increase prefrontal activation, accompanied by improved cognitive function.

The lack of effect of anticipated brain changes in the 2-back task and the effect on tDCS on increasing activation only at the 0-back and not the 2-back is inconsistent with some of our expectations and with data from some previous studies. One study in China (Li et al., 2019), using a dual N-back task comparing schizophrenics with controls, showed more activation in DLPFC related areas in both group on the 2-back task, although schizophrenics had significantly lower activation in 2-back vs 0 back compared to control subjects. Some studies have proposed an inverted U shape for brain activation, especially in the frontal lobe associated with areas of DFPFC, in working memory tasks, as memory load increases in the higher levels of N-back. Patients with schizophrenia have been reported to show both increased or decreased brain activation compared to healthy control on the 2-back level tasks, and showed less brain activation than controls at some higher memory loads (Callicott et al., 2003; Wu & Jiang, 2020). But most prior studies show that schizophrenics have some degree of increased activation in the frontal lobes areas related to working memory circuits during a 2-back task. A potential explanation of our anomalous results on the 2-back task, might be that 2-back task was too difficult for the schizophrenic patients in this study to perform, so that subjects didn't really try to attend to it. However, this is not consistent with their actual performance on the 2-back task during the fMRI; the active tDCS group have about 70% accuracy which is similar to that found for 2-back in the Callicot study (Callicott et al., 2003). Furthermore, our schizophrenics also showed reasonable accuracy on the 1-back and 2-back versions of the CogState N-back task evaluated separately outside the fMRI session. Therefore, we do not have a clear explanation for the lack of increased brain activation in the relevant frontal lobes circuits with the 2-back during fMRI scan in this set of patients, especially after the 10 sessions of tDCS.

Interestingly, we also found an increased activation in the left PCC under the condition of active tDCS during the 2-back working memory task, which we hypothesized should show decreased activation during a working memory task. The PCC is a component of the DMN (Raichle, 2015). Some studies had revealed consistently decreased deactivations in the PCC in patients with schizophrenia compared to the healthy controls, and it was accompanied by working memory deficits (Wu & Jiang, 2020). These results suggest that the abnormal activity patterns in patients with schizophrenia are restricted to the working memory activation network and exhibit a dysregulation of the DMN, implying that these networks work together to perform certain cognitive functions. Dynamic suppression of the DMN network is thought to be necessary for the accurate behavioral performance of cognitively demanding tasks such as higher loads in working memory tasks. Our findings suggested that PCC may play a role in modulating the dynamic interaction between the working memory activation network and DMN. Overall, the present study showed that tDCS modulated prefrontal activation or DMN under different types of working memory load could provide a valuable perspective for understanding the tDCS effect between brain network and cognitive function.

We found significant correlations with the measures extracted from the difference between 0-back vs 2-back brain activation patterns in the active tDCS group and cognitive changes measured immediately after 10 sessions of tDCS as well as some cognitive changes measured 2 weeks and 4 weeks later. Immediately after the 10 sessions there were positive correlation of some cognitive performance measures with decreased activation in PCC and increased activation in left IFG. At 2 and 4 weeks after the last tDCS session there were both positive and negative correlations of cognitive performance at these time points with brain

activation changes during the fMRI N-back task completed weeks earlier. One possible explanation of the correlations at the 2 and 4 week time points, could be that the BOLD response represents persistent changes in synaptic activity (Attwell & Iadecola, 2002) with the effect that tDCS might increase the longer term neuroplasticity (Kronberg et al., 2017), and these effects could last two weeks or longer after a series of tDCS sessions.

There are several limitations associated with our study. Our blinding procedures were only partially successful and the way to ask the guess question may need to be redesigned. However, this did not substantially bias our results for some reasons (Smith et al., 2020). Although our main imaging results in 0 back versus 2 back comparisons (Fig. 1) were significant at the $P < 0.005$ level, none of them survived significance following FWE or FDR corrections. Although others (Guse et al., 2013; Wang et al., 2016) have published imaging results at similar uncorrected significance levels, there is less certainty about the replicability of findings with uncorrected significance levels and a greater chance of type I error. The lack of a multiple load levels in our working memory task (without 1-back and 3-back) makes it harder to discern the reasons for the lack of expected brain region activation in the 2-back task in our study group. Although our results demonstrated significant correlations between brain activation during the fMRI N-back task and cognition measured directly after 10 tDCS sessions and also weeks later, the functional meaning of these correlations as well as their relationships to the underlying brain circuits needs further exploration. The sample size of this study is relatively small, and the smaller number of subjects at the 2 and 3 weeks' time points may make the robustness of some of the correlations less certain. But it still adds some new evidence of the brain dynamics and behavioral changes from fMRI data of tDCS in schizophrenia.

Conclusion

In summary our study showed that 10 sessions of tDCS had effects on brain activation in patients with schizophrenia in an N-back task, primarily showing effects in the lowest load 0-back version, and that changes in brain activation during this fMRI task correlated with changes in cognitive performance assessed within a day after 10 Sessions of tDCS as well 2 and 4 weeks later. This suggests that brain changes induced by tDCS may persist and influence behavior weeks later. However, additional studies are needed to replicate these findings. Using an N-back task with more load gradations for working memory performance, and comparing the effects of tDCS on brain changes during N-back in patients with schizophrenics vs. controls would help clarify the robustness and substantive interpretation of these results.

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Author contribution CBL, RS and CL designed this study. WL, YRW and JLJ acquired the data. YL and HCL analyzed the data, assisted by XYC. YL, HCL and WL drafted the manuscript. THZ, YYT, DZY and JJW discussed the data. RS, CL and CBL reviewed the manuscript and all the authors approved the final version for submission.

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Availability of data and materials Not applicable.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to Publish Not applicable.

Competing interests None of the authors have a conflict of interest to declare.

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