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Enhancement of cognitive insight and higher-order neurocognitive function by fronto-temporal transcranial direct current stimulation (tDCS) in patients with schizophrenia

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ABSTRACT

No studies have examined the effects of fronto-temporal transcranial direct current stimulation (tDCS) on cognitive insight and neurocognitive function in schizophrenia patients and the dynamic interplay between tDCS-induced changes in these two outcomes. In this double-blind, randomized, sham-controlled study, we investigated the effects of fronto-temporal tDCS [anode corresponding to left dorsolateral prefrontal cortex and cathode to left temporo-parietal junction; 2-mA, twice-daily sessions for 5 days] on illness severity, psychosocial functioning, cognitive insight and neurocognitive function in schizophrenia patients (N = 60).

The authors observed significant trends that tDCS ameliorated the severity of total and general psychopathology as measured by the Positive and Negative Syndrome Scale. No significant effects were observed for other psychopathological symptoms and psychosocial functioning. Cognitive insight as measured by the Beck Cognitive Insight Scale (BCIS) was rapidly enhanced by 10-session tDCS ($F = 10.80$, Cohen's $d = 0.44$, $p = 0.002$) but the beneficial effect became borderline significant 1 month after stimulation. A trend-level improvement with tDCS of planning ability ($F = 6.40$, Cohen's $d = 0.339$, $p = 0.014$) as measured by the accuracy in Tower of London task was also observed. In the active tDCS group, the change in cognitive insight from baseline to immediately after tDCS assessment was positively correlated with that in planning ability ($r = 0.46$, $p = 0.015$), which was independent of the corresponding change in illness severity. The promising results regarding the fast-acting beneficial effects of tDCS on cognitive insight and planning ability in schizophrenia require confirmation in future replication studies.

1. Introduction

Impaired insight in schizophrenia is prevalent across different cultures and phases of the illness and predicts poorer medication adherence and functional and clinical outcomes (Lysaker et al., 2018). The mainstream approach of contemporary research focusing on insight impairment in schizophrenia encompasses two forms of insight: clinical insight, which represents awareness of illness/symptoms, treatment need and the consequences of the illness, and cognitive insight, which is a form of cognitive flexibility and encompasses the evaluation and correction of distorted beliefs and misinterpretations. Researchers have suggested that the latter is a prerequisite for the former (Gerretsen et al., 2014) and is of great importance for the following reasons. First, insight into illness involves a cognitive process of conscious reflection and reasoning and the neurocognitive theory of insight posits that cognitive deficits in cognitive self-appraisal mechanisms play a vital role in poor clinical insight of schizophrenia (Cooke et al., 2007). Schizophrenia itself results in a generalized and substantial cognitive impairment (Schaefer et al., 2013). Patients with decline in global cognition, executive function and memory and deficiencies in conceptual organization and flexibility in abstract thinking have increased risk for impaired clinical insight (Aleman et al., 2006; Nair et al., 2014; Shad et al., 2006). Secondly, cognitive insight has been associated with reality processing and declarative memory (Lee et al., 2015) and neurocognition including premorbid IQ and executive function (Lysaker et al., 2018). Patients with good cognitive insight are able to view themselves in perspective requiring intact executive function and distance themselves from their cognitive distortions or highly delusional beliefs, and are pervious to corrective feedback. A lack of cognitive insight in these patients contributes to both impaired clinical insight, and heightened psychopathological symptoms (Lysaker et al., 2018). Finally, research has indicated that cognitive insight can be independent of clinical insight and that the neural correlates of cognitive insight involve a narrower range of brain regions than clinical insight (Xavier

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and Vorderstrasse, 2016). Specifically, patients with poor clinical insight showed widespread gray matter reductions in the prefrontal, temporal and occipital regions and cerebellum and aberrant activity in central midline structures including basal ganglia, prefrontal cortex, cingulate cortex, insula, inferior parietal lobule and the precuneus (Lysaker et al., 2018; Tordesillas-Gutierrez et al., 2018) while patients with poor cognitive insight showed volumetric reductions in frontal, parietal and temporal regions (Xavier and Vorderstrasse, 2016) and decreased activity in dorsolateral prefrontal cortex during reality evaluation task and decreased activity in inferior parietal lobule and posterior cingulate cortex during recognition task (Lee et al., 2015).

Psychological and pharmacological interventions are existing treatments applied to improve insight impairment in schizophrenia (Lysaker et al., 2018), but available resources of psychological intervention are inadequate and most patients have poor adherence in complying with the recommended pharmacotherapy possibly due to their negative attitudes toward accepting these traditional interventions. Thus, researchers are striving to develop novel, low-cost, high-acceptability treatments that target the proposed underlying causes of poor insight (Lysaker et al., 2018). For cognitive impairments in schizophrenia, the modest improvements produced by cognitive remediation which necessitates many hours of intensive cognitive training (Vinogradov et al., 2012) and the lack of efficacy of pharmacological treatments (Kreyenbuhl et al., 2010) also urge the development of novel, effective, easy-to-use treatments for the deficits.

Recent studies reported that fronto-temporal transcranial direct current stimulation (tDCS) protocol, which was first proposed to treat auditory hallucinations (Brunelin et al., 2012), rapidly improved insight impairment in schizophrenia (Bose et al., 2014; Chang et al., 2018). It employs low-intensity electric current that is applied to the brain through two electrodes placed over the scalp with anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation over the left temporo-parietal junction (TPJ), which can shift membrane resting potentials, thereby leading to a rapid increase and decrease in cortical excitability of the brain neurons beneath the electrode, respectively (Nitsche et al., 2003). The acute efficacy of tDCS can be further enhanced and prolonged by repetitive stimulation during specific time intervals via modulation of *N*-methyl-D-aspartate (NMDA) receptor (Nitsche et al., 2008). However, the mechanism by which fronto-temporal tDCS enhanced insight is still undetermined. Given that impaired insight in schizophrenia has been consistently associated with deficits in cognitive performance in tests sensitive to frontal lobe dysfunction and that anodal left DLPFC tDCS has been shown to improve cognitive deficits in schizophrenia patients (Hoy et al., 2014; Smith et al., 2015), researchers proposed that anodal tDCS stimulation of the left DLPFC may facilitate enhancement in insight through improving schizophrenia-specific cognitive deficits. This potential explanation has not been confirmed by research studies so far and the first step is to examine fronto-temporal tDCS-induced changes in both cognitive insight and neurocognitive function and the dynamic interplay between the two outcomes as well.

The primary aim of our study was to investigate the effects of fronto-temporal tDCS on cognitive insight and neurocognitive function, while also investigating the tDCS effects on illness severity and functional outcomes in schizophrenia patients. First, we hypothesized that tDCS would enhance cognitive insight and improve deficits in prefrontal cognitive functions. We also hypothesized that tDCS-induced enhancement in cognitive insight would be correlated with the corresponding improvement in specific cognitive performance.

2. Methods

2.1. Participants

The Institutional Review Board of Tri-Service General Hospital approved the clinical trial (No. of IRB approval: TSGHIRB-2-103-03-002; ClinicalTrials.gov ID:NCT03388554). The current sample overlapped with a previous sample in a randomized double-blind, sham-controlled trial as described elsewhere and a proportion of clinical data were already used (Chang et al., 2018). Patients eligibility criteria were: (1) Subjects aged 20–65 years and diagnosed with DSM-IV-TR schizophrenia or schizoaffective disorder; (2) No current psychiatric comorbidity or active substance use disorder, with the exception of caffeine and/or tobacco; (3) Exhibiting persistent auditory verbal hallucinations in spite of ≧3-month treatment with antipsychotic drugs at an adequate dosage and having a score of Auditory Hallucinations Rating Scale (AHRS) ≧18; (4) No history of seizures; (5) No contraindications for tDCS, e.g., implanted brain medical devices or metal in the head or; (6) No pregnancy at enrollment; (7) Agreement to participate in the study with the expressed purpose of treating auditory verbal hallucinations and provide the written informed consent. Throughout the study period, the participants' antipsychotic medications were kept unchanged. An Eldith DC stimulator (Neuroconn DC Stimulator Plus, GmbH, Ilmenau, Germany) was used for stimulation, with two 7×5 cm^2 sponge electrodes soaked in a 0.9% NaCl saline solution. The middle of the anode located over a point midway between international 10–20 electrode positions F3 and FP1, presumably corresponding to left prefrontal cortex and dorsolateral prefrontal cortex. The cathode was centered at a point midway between T3 and P3, corresponding to left temporo-parietal junction (TPJ). Stimulation was applied at an intensity of 2 mA for 20 min, twice-daily, on 5 consecutive weekdays. The twice daily sessions were separated by at least 3 h. In sham stimulation, the 2 mA current was turned on for 30 s and then ramped down to 0 mA through the remainder of the 20-min time.

2.2. Effectiveness of blinding

Immediately after first stimulation session, all participants were asked to answer the question of whether they received active or sham tDCS treatment. After unblinding of the study, it was noted that 76.7% of patients receiving active tDCS and 70.0% of those receiving sham tDCS guessed they had received active treatment ($p = 0.559$). Therefore, the effectiveness and adequacy of our blinding protocol was shown to be satisfactory.

2.3. Clinical assessments

Illness severity was assessed with the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) rating scales. Clinician-reported insight was measured by the G12 item of the PANSS (lack of judgement and awareness of the disease).

2.4. Assessment of cognitive insight

Cognitive insight was measured by the Taiwanese version of the Beck Cognitive Insight Scale (BCIS), which derives from the original BCIS (Beck et al., 2004), a self-reported instrument comprising 15 items. Our previous studies have reported the reliability and validity of the Taiwanese BCIS (Kao and Liu, 2010; Kao et al., 2011).The Taiwanese BCIS is composed of 2 subscales including reflective attitude (9 items) and certain attitude (6 items). We obtained a R-C (reflective attitude minus certain attitude) index of the Taiwanese BCIS, representing the measurement of cognitive insight by subtracting the score of the certain attitude subscale from that of the reflective attitude subscale. Lower R-C index scores indicate poorer cognitive insight.

2.5. Assessment of functional outcomes

Clinician-rated functional outcome was measured using the Global Assessment of Functioning (GAF) Scale of the DSM-IV, a valid tool for assessing global psychosocial and occupational functioning for schizophrenia patients (Startup et al., 2002). Self-rated functional outcome was measured using the self-reported version of the graphic personal

and social performance scale (SRG-PSP). The SRG-PSP is a self-rating scale of proven validity and reliability (Bai et al., 2014), comprising both male and female versions of cartoon-like pictures that are derived from the narrative text of the four domains of Personal and Social Performance (PSP) scale including the sub-items of socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviour (Wu et al., 2013). The scale contained 22 items on which the patients rated from 1 "seldom" to 3 "always", and the four domain scores were then summed. Higher domain scores indicated better functioning in socially useful activities (A), personal and social relationships (B), and self-care (C), but worse disturbing and aggressive behaviour (D). The global score of the SRG-PSP was calculated by the formula: (A + B + C domain score) - D domain score. Better personal and social functioning was indexed by a higher global score.

2.6. Assessment of neurocognitive function

Neurocognitive function was assessed using standardized tests administered by a well-trained examiner and participants were instructed to abstain from caffeine for at least 24 h before the assessments. Finger Tapping Test (FTT) was used to measure psychomotor speed and the level of motor coordination (Lezak, 1995). The digit span forward and backward subtests of the Wechsler Memory Scale-III (Wechsler, 1997) were used to assess load capacity of working memory. The Trail Making Test, Part A (TMT-A) were used to assess attention and visuomotor processing speed and Part B (TMT-B) to assess attentional set shifting, executive function and visuospatial working memory (Lezak, 1995). Wisconsin Card Sorting Test (WCST) was used to measure executive functions including abstract reasoning ability, cognitive flexibility in response to changing environmental contingencies (Heaton et al., 1993). Connors' Continuous Performance Test –2nd Edition (CPT-II) was performed to assess concentration, sustained attention, response inhibition and impulsivity (Lopez-Luengo et al., 2016). The Tower of London-Drexel University Test 2nd Edition (TOL^{DXtm}) (Garcia-Alba et al., 2017) was administered to assess executive functioning, especially in regard to the ability of planning, processing, and problem-solving skills.

A rater (HAC) who was blind to the group assignment administered the PANSS, CGI and GAF at baseline, immediately after tDCS, and 1 and 3 months after tDCS. The self-rated SRG-PSP and BCIS and examiner-administered neurocognitive tests were undertaken at baseline and at least 2 h after the final session of tDCS. One month after tDCS, the patients also completed the SRG-PSP and BCIS. Patients were reimbursed for transportation fee at each visit.

2.7. Statistical analyses

IBM SPSS Statistics 21.0 software (IBM SPSS Inc., Chicago, IL, USA) was used for analyses. Theχ^2 and Fisher's tests were used to examine between-group differences in discrete variables. For the between-group comparisons of continuous variables, Student's *t*-tests were used for parametric variables, and the Mann-Whitney tests for non-parametric variables. To compare the between-group effects of tDCS on outcome measures over time, a repeated-measures analysis of variance (RMANOVA) was used with time as the within-group factor and treatment as the between-group factor. Adjustment for imbalances at baseline in any of the covariates was undertaken. When significant treatment group-by-time interaction effects were found, post hoc analyses were performed. For the changes in outcome measures before and after tDCS, between-groups comparisons were carried out. An intention-to-treat analysis was performed and missing values were imputed with the last observation carried forward (LOCF) method. G*power version 3.1.9.2. was used to calculate Cohen's d effect sizes and statistical power. Cohen's guidelines (Cohen, 1992; Cohen, 1988) identify 0.2, 0.5, and 0.8 as small, medium, and large effects, respectively. Spearman rank correlation was used to analyze the relationship between the tDCS-induced significant change in cognitive insight and that in neurocognitive function. The independent contribution of the change in neurocognitive function to the variance in cognitive insight was assessed by using hierarchical regression analysis with adjustment for the covariate of change in illness severity. All results are two-tailed and statistical significance was defined as $p < 0.05$ and Benjamin-Hochberg correction was used to adjust for multiple tests, in which only $p < 2.33 \times 10^{-3}$ was considered significant.

3. Results

3.1. Sample characteristics

Sixty patients (all right-handed) were included and 51 of them (85%) had a diagnosis of schizophrenia and 9 (15%) had schizoaffective disorder. Thirty patients were randomly assigned to the active tDCS group and 30 to the sham group. Active tDCS group had longer illness duration, higher general score of PANSS and higher SRG-PSP global score and domain score in social useful activities (Table 1). Other demographic and clinical data did not show any significant between-group difference, and neither did the measures of neurocognitive function at baseline (Table 2). All participants completed 10 sessions of tDCS and none of them dropped out from the study. Six patients (4 in the active group versus 2 in the sham group, $p = 0.39$) missed the final assessment at 3 months after tDCS and the missing data were filled with the last observed non-missing values. The side effects were illustrated in Supplementary Information S1 (table).

3.2. tDCS effects on illness severity and clinician-reported insight

After controlling for baseline covariates, the RMANOVA did not show significant group-by-time interaction for CGI score [$F(3,54) = 1.97$, $p = 0.13$] and PANSS positive [$F(3,54) = 0.53$, $p = 0.66$] and negative [$F(3,54) = 2.05$, $p = 0.12$] score and but showed trends toward significance for PANSS total [$F(3,54) = 2.81$, $p = 0.048$], general [$F(3,54) = 3.81$, $p = 0.015$] and G12 item [$F(3,54) = 3.32$, $p = 0.026$] score. The acute effects of tDCS on PANSS total, general and G12 item score showed small effects compared with the sham group (Table 3) but did not reach statistical significance.

3.3. tDCS effects on cognitive insight

After adjustment for baseline covariates, the RMANOVA showed significant group-by-time interaction for BCIS-R [$F(2,55) = 9.71$, $p = 2.45 \times 10^{-4}$] and borderline significance for R-C index [$F(2,55) = 6.49$, $p = 0.003$] scores but no statistical significance for BCIS-C score [$F(2,55) = 0.79$, $p = 0.46$]. Compared with sham group, the acute effects of tDCS on BCIS-R and R-C index scores showed medium and small effects, respectively (Table 3). Post hoc analyses showed that between-group differences in percent change of BCIS-R score (Fig. 1) and mean change of R-C index score (Fig. 2) from baseline were significant immediately after tDCS but only trended toward significant 1 month after tDCS.

3.4. tDCS effects on functional outcomes

The RMANOVA showed no significant group-by-time interaction for GAF scores [$F(3,56) = 0.62$, $p = 0.61$], SRG-PSP global score [$F(2,57) = 1.93$, $p = 0.16$], scores of social useful activities domain [$F(2,57) = 0.62$, $p = 0.54$], personal and social relationships domain [$F(2,57) = 0.53$, $p = 0.59$], self-care domain [$F(2,57) = 1.87$, $p = 0.16$] and disturbing or aggressive behavior domain [$F(2,57) = 0.84$, $p = 0.44$]. These results were unchanged after co-varying baseline covariates in RMANCOVA.

3.5. tDCS effects on neurocognitive function

In TOL test, there were no significant between-group differences for changes in total time (TOL time) or total rule violations (TOL score). But

Table 1
Baseline demographic and clinical characteristics of the participants.

Characteristics	Active tDCS (N = 30)	Sham tDCS (N = 30)	t/U or χ^2/Fisher's	p-Value
Females (%)	16 (53.30)	17 (56.70)	0.07	0.80
Age, years	46.40 ± 10.29	42.17 ± 10.29	1.46	0.15
Education level, years	13.17 ± 2.57	13.03 ± 2.53	0.20	0.84
BMI, kg/m^2	25.77 ± 3.75	25.29 ± 4.86	0.43	0.67
Smokers (%)	10 (33.33)	4 (13.30)	3.35	0.13
Onset age, years	26.50 ± 8.88	28.27 ± 9.85	−0.73	0.47
Length of illness, years	19.73 ± 10.36	13.90 ± 7.50	2.50	**0.02**
CGI	4.17 ± 0.70	3.93 ± 0.83	371.50	0.21
Positive and Negative Syndrome Scale (PANSS)				
Total score	72.33 ± 13.19	66.73 ± 12.49	1.69	0.10
Positive score	15.83 ± 5.06	14.93 ± 3.96	0.77	0.45
Negative score	19.70 ± 4.74	18.40 ± 4.37	1.11	0.27
General score	36.83 ± 5.99	33.40 ± 5.90	2.24	**0.029**
G12 item score	4.23 ± 1.25	3.73 ± 0.83	333	0.07
BCIS				
BCIS-R	25.37 ± 4.85	24.97 ± 4.36	0.340	0.74
BCIS-C	16.90 ± 3.32	15.47 ± 3.30	1.68	0.10
R-C index	9.07 ± 3.82	9.83 ± 5.32	460.50	0.88
GAF	43.33 ± 10.06	47.00 ± 10.37	540.00	0.17
SRG-PSP				
Social useful activities	12.90 ± 3.06	11.07 ± 3.51	2.16	**0.035**
Personal and social relationships	9.40 ± 3.39	8.00 ± 2.92	1.71	0.09
Self-care	15.43 ± 3.49	13.63 ± 3.76	1.92	0.06
Disturbing and aggressive behavior	6.53 ± 2.43	6.67 ± 2.99	−0.25	0.81
Global score	30.90 ± 8.88	25.70 ± 8.80	2.28	**0.026**

Data are presented as means ± standard deviations, unless otherwise stated; BMI, Body Mass Index (calculated as weight in kilograms divided by height in meters squared); CGI, Clinical Global Impression; BCIS, Beck's Cognitive Insight Scale; BCIS-R, Self-reflectiveness subscale of BCIS; BCIS-C, Self-certainty subscale of BCIS; GAF: Global Assessment of Functioning; SRG-PSP, Self-reported version of the graphic Personal and Social Performance scale. Bold emphasis indicates statistically significance at $p < 01.05$

there was a certain trend toward increased total correct score (TOL accuracy) for patients receiving active tDCS compared with that of patients receiving sham stimulation, showing a small effect (Table 4). No significant effects were observed for other neurocognitive domains.

3.6. Correlation analyses

In the active tDCS group, the changes in self-reflectiveness score ($r = 0.53$, $p = 0.003$) and R-C index score ($r = 0.46$, $p = 0.015$, Fig. 3) from baseline to immediately after tDCS assessment were positively correlated with that in TOL accuracy after adjusting for the corresponding change in symptoms severity (PANSS total and general score). The change in TOL accuracy accounted for the additional variance in the prediction of the change in self-reflectiveness (r^2 change = 32.5%, $F = 13.45$, $p = 0.001$) and R-C index score (r^2 change = 11.3%, $F = 5.06$, $p = 0.033$) after adjusting for the change in symptoms severity [Supplementary Information S2 (table)].

4. Discussion

The present study observed a borderline significant trend that tDCS ameliorated the severity of total and general psychopathology and also improved the impairment of clinical insight as measured by a single-item scale-PANSS item G12. Given that the item G12 is limited to a seven-point clinician-reported scale, a more sensitive measure for clinical insight may have been able to detect more pronounced effect brought about by tDCS. Consistent with this conjecture is the evidence from our recently published article, in which the beneficial effect of fronto-temporal tDCS was demonstrated more clearly when the impairment in clinical insight was measured by the abbreviated version of the Scale to Assess Unawareness in Mental Disorder in schizophrenia (SUMD), which is an expert-rating scale based on a patient interview and comprises 9 items measuring current states of illness awareness, with scores on each item ranging from 0 to 3 (Chang et al., 2018).

Cognitive insight, as distinguished from clinical insight refers to the current capacity of an individual to evaluate anomalous self-experiences and recognize improper interpretations of such experiences which are crucial for correctly reporting one's experience of illness and symptom and was defined as the difference between self-reflectiveness and self-certainty (Beck et al., 2004). Low self-reflectiveness and high self-certainty reflect poor cognitive insight. Our result is pioneering in confirming that tDCS can enhance cognitive insight in schizophrenia patients. In our participants, tDCS intervention resulted in rapid, significant increases in scores of self-reflectiveness and R-C index but did not change scores of self-certainty over time. Thus, the enhancement of overall cognitive insight was mainly driven by the effect of tDCS to heighten the capacity for self-reflectiveness. Neuroimaging studies have suggested that the neural correlates of cognitive insight involve a network of fronto-temporo-parietal brain regions. Specifically, low self-reflectiveness is associated with volumetric reductions in widespread frontal, parietal and temporal cortices and especially ventrolateral prefrontal cortex (VLPFC) (Buchy et al., 2016). Evidence indicated that fronto-temporal tDCS has the potential to correct the hypoactivation of prefrontal cortex and modulate the disintegration of fronto–temporo-parietal network functional connectivity in schizophrenia patients (Brunelin et al., 2012; Mondino et al., 2016). It is possible that tDCS brought about beneficial effects on patients' cognitive insight through augmenting the endogenous effort to compensate for anatomical deficits in neural correlates of self-reflectiveness.

Although not significant after Benjamin-Hochberg correction, the TOL accuracy increased in patients treated with active tDCS. The TOL is a valid measure for planning ability, which belongs to higher-order executive functions requiring the concurrent use of multiple basic executive functions. Research has indicated poorer performance in solving the TOL task in schizophrenia patients relative to healthy controls and concerned the DLPFC as the critical brain structure of the performance (Rasser et al., 2005). The greater activation of the left DLPFC has been related to superior TOL performance (Cazalis et al., 2003). The underlying mechanism involved in tDCS effects on improving patients' TOL accuracy remains to be explored. One possible mechanism is via remodeling brain connectivity networks (Lett et al., 2014). Functional neuroimaging studies in schizophrenia have revealed dysconnectivity of prefrontal cortex to other brain regions, in which reduced functional connectivity of the fronto-parietal control network has been particularly associated

Table 2
Baseline performance of neurocognitive function tests of the participants.

Characteristics	Active tDCS (N = 30)	Sham tDCS (N = 30)	t/U or χ^2/Fisher's	p-Value
Digits forward score	12.13 ± 2.73	11.33 ± 2.92	367.00	0.22
Digits backward score	7.70 ± 2.69	7.43 ± 3.66	0.32	0.75
Finger Tapping Test				
Dominant finger	51.07 ± 12.00	55.52 ± 9.51	522.50	0.28
Non-dominant finger	52.27 ± 11.74	54.97 ± 9.49	483.00	0.63
Trail making test part-A	70.58 ± 23.93	67.98 ± 24.54	0.42	0.68
Trail making test part-B	171.07 ± 67.21	161.32 ± 60.29	409.50	0.55
WCST				
Trials administered (Trials completed)	122.60 ± 14.13	117.97 ± 17.61	1.12	0.27
Total correct (trials correct)	79.37 ± 12.87	79.27 ± 12.55	0.03	0.98
Total errors	43.37 ± 17.10	38.80 ± 18.51	0.99	0.33
% errors	34.57 ± 12.45	31.57 ± 13.00	0.91	0.37
Perseverative responses	21.10 ± 7.85	22.17 ± 11.58	−0.42	0.68
% perseverative responses	16.83 ± 5.55	17.80 ± 7.81	−0.55	0.58
Perseverative errors	18.70 ± 6.31	19.43 ± 9.18	−0.36	0.72
% perseverative errors	14.90 ± 4.42	15.87 ± 6.45	−0.68	0.50
Non-perseverative errors	26.67 ± 13.73	19.37 ± 12.10	1.59	0.12
% non-perseverative Errors	19.53 ± 10.46	15.73 ± 8.97	1.51	0.14
Conceptual level responses	63.73 ± 20.03	66.47 ± 16.43	−0.58	0.57
% conceptual level responses	54.87 ± 18.01	58.33 ± 18.20	−0.74	0.46
Categories completed	3.80 ± 1.75	4.13 ± 1.93	−0.70	0.49
CPT II				
Omission errors (number)	23.73 ± 26.54	15.80 ± 16.93	370.00	0.24
Omission errors (%)	7.35 ± 8.21	4.90 ± 5.25	370.50	0.24
Commission errors (number)	20.17 ± 9.49	20.47 ± 9.98	457.50	0.91
Commission errors (%)	58.02 ± 24.36	56.97 ± 27.50	443.00	0.92
Hit RT (ms)	512.50 ± 125.78	457.32 ± 89.28	325.00	0.07
Hit RT SE	16.44 ± 11.57	11.18 ± 7.86	340.50	0.11
Variability (variability of SE)	32.15 ± 23.67	22.78 ± 19.26	352.00	0.15
Detectability (d′)	0.41 ± 0.34	0.45 ± 0.41	−0.44	0.66
Response style (ß)	0.99 ± 0.88	1.15 ± 1.83	409.50	0.55
Perseverations	3.90 ± 3.65	3.13 ± 5.30	353.50	0.15
Perseverations (%)	1.21 ± 1.13	0.97 ± 1.64	353.00	0.14
Hit RT block change	0.15 ± 0.05	0.01 ± 0.05	353.00	0.54
Hit SE block change	0.01 ± 0.12	0.01 ± 0.14	404.50	0.50
Hit RT ISI change	0.10 ± 0.07	0.06 ± 0.05	312.00	0.05
Hit SE ISI change	0.17 ± 0.20	0.07 ± 0.19	2.05	0.05
Tower of London test (TOL)				
Total correct score (TOL accuracy)	2.53 ± 1.25	3.00 ± 1.98	−1.09	0.28
Total time (TOL time)	477.23 ± 192.87	439.77 ± 173.93	412.00	0.57
Total rule violations (TOL score)	2.87 ± 4.04	1.87 ± 2.84	391.00	0.37

Data are presented as means ± standard deviations, unless otherwise stated; WCST, Wisconsin Card Sorting Test; CPT II, Connors' Continuous Performance Test – Second Edition; RT, reaction time; SE, standard error; ISI, inter-stimulus interval.

with deficits in cognitive control and executive function (Zhou et al., 2015). It is possible that fronto-temporal tDCS has the capacity to increase functional connectivity between left DLPFC and left TPJ (Mondino et al., 2016), thereby beneficially modulating the dysfunctional connectivity of the fronto-parietal network.

Another possible mechanism is that anodal tDCS on a cellular level can produce long-term potentiation (LTP)-like plasticity, which is considered to be the neurochemical correlates of learning and memory and may be modulated by effects on NMDA receptors through glutamatergic influences. It has been suggested that anodal tDCS has the capacity to improve learning- and memory-related cognitive impairment in schizophrenia through enhancement of cortical plasticity (Lett et al., 2014). The idea has been verified in a recent animal study, in which anodal tDCS over prefrontal cortex (PFC) improved cognitive dysfunction via restoration of synaptic plasticity deficit in the PFC (Wu et al., 2017). In healthy individuals, research has indicated that the recruitment of the left DLPFC and its associated neural circuitry can potentiate the learning effect on planning performance in the TOL task by heightening the ability to adapt and generate efficient strategies in the task (Cazalis et al., 2003), possibly through increased cortical excitability which strengthens neuronal synaptic connections, thereby enhancing neural efficiency (Nitsche et al., 2003). Therefore, our participants stimulated with anodal tDCS over left DLPFC may become more efficient in developing specific sets of rules and strategies and solve the TOL problems more accurately.

Furthermore, given that hypoactivation in the left DLPFC plays an important role in schizophrenia-specific deficits in numerous cognitive functions, it is not surprising that a recent review reported small positive effects of anodal tDCS over left DLPFC on working memory and attention in schizophrenia (Mervis et al., 2017). But the reason for the specificity of enhancing effects on planning ability brought about by fronto-temporal tDCS is still unclear. In schizophrenia patients, only a single 2 mA, 20-minute session of anodal left DLPFC tDCS can significantly improve performance on working memory task (Hoy et al., 2014) while 5 sessions of that improved cognitive deficits in both working memory and attention-vigilance domains (Smith et al., 2015). However, 10 sessions of anodal left DLPFC tDCS improved patients' performance in neither working memory nor attention (Gomes et al., 2018). None of patients' neurocognitive function including working memory, attention and planning ability were significantly changed by anodal tDCS over left DLPFC for 15 daily sessions (Fitzgerald et al., 2014). A possible explanation for the conflicting findings is that the observed positive effects of anodal tDCS on different aspects of neurocognitive function depend on the accumulated electrical dose during the study period (i.e., total charge density) delivered to the left DLPFC. The current tDCS dosage may represent a parameter that has the potential to enhance planning ability of schizophrenia patients. It is also possible that fronto-temporal tDCS might significantly improve other neurocognitive domains that are not included in the

Table 3
Mean changes in the illness severity, cognitive insight and functional outcomes after 5 days of tDCS or sham treatment in the participants.

Outcome measures[a]	Active tDCS (N = 30) Mean ± SE[a]	Sham tDCS (N = 30) Mean ± SE[a]	F	p-Value	partial η^2	Effect size
Illness severity						
CGI	−0.28 ± 0.08	−0.12 ± 0.08	2.06	0.157	0.036	0.193
PANSS						
Total score	−2.50 ± 0.54	−0.47 ± 0.54	6.84	**0.011**	0.109	0.350
Positive score	−0.50 ± 0.23	−0.20 ± 0.23	0.86	0.36	0.015	0.123
Negative score	−0.49 ± 0.15	−0.08 ± 0.15	3.69	0.06	0.062	0.257
General score	−1.58 ± 0.33	−0.19 ± 0.32	9.01	**0.004**	0.139	0.402
G12 item score	−0.74 ± 0.14	−0.16 ± 0.14	7.92	**0.007**	0.124	0.376
Cognitive insight						
BCIS						
BCIS-R	5.15 ± 0.73	0.49 ± 0.73	18.78	$\mathbf{6.2 \times 10^{-5}}$	0.251	0.579
BCIS-C	−0.09 ± 0.76	0.83 ± 0.76	0.69	0.41	0.012	0.110
R-C index	4.77 ± 1.16	−0.81 ± 1.16	10.80	**0.002**	0.162	0.440
Functional outcomes						
GAF	1.17 ± 0.51	2.23 ± 0.51	2.05	0.16	0.035	0.190
SRG-PSP						
Social useful activities[b]	0.60 ± 0.61	0.33 ± 0.61	0.09	0.77	0.002	0.045
Personal and social relationships[b]	0.31 ± 0.61	0.30 ± 0.61	0.003	0.96	5.0×10^{-5}	0.007
Self-care[b]	−0.35 ± 0.75	0.56 ± 0.75	0.69	0.41	0.012	0.110
Disturbing and aggressive behavior[b]	−0.45 ± 0.39	−0.05 ± 0.39	0.44	0.52	0.008	0.090
Global score[b]	1.87 ± 1.68	2.20 ± 1.68	0.02	0.90	3.02×10^{-4}	0.0174

SE, Standard Error; tDCS, Transcranial Direct Current Stimulation; CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale; BCIS, Beck's Cognitive Insight Scale; BCIS-R, Self-reflectiveness subscale of BCIS; BCIS-C, Self-certainty subscale of BCIS; GAF: Global Assessment of Functioning; SRG-PSP, Self-reported version of the graphic Personal and Social Performance scale.
[a] Values adjusted for length of illness and baseline PANSS general score.
[b] Additionally adjusted for baseline SRG-PSP global score and social useful activities domain score.

neurocognitive tests of the present study, e.g., probabilistic association learning (Vercammen et al., 2011).

The gain of cognitive insight produced by tDCS in our study are unlikely due to chance alone given that the strong statistical power (0.93 for the outcome of cognitive insight to detect a Cohen's d small effect) has protected the outcome measure against the risk of type I error, and thus has other underlying causes for the occurrence. However, the aforementioned explanation regarding the potential mechanism is speculative because of no functional neuroanatomical or electrophysiological evidence. Our results should be verified in future research with simultaneous fMRI or EEG recording during tDCS intervention. Nevertheless, our study did find the positive correlation between the enhancement of cognitive insight and the improvement of higher-order executive functioning among patients treated with active tDCS. The change in accuracy of planning ability independently accounted for small to moderate amount of variance in the change of cognitive insight and particularly its self-reflectiveness dimension (11.3% and 32.5%, respectively). Our results raise an important question: Did tDCS improve patients' self-reflectiveness domain of cognitive insight through the mechanism of enhancement of their higher-order executive functioning? Research has indicated the differential associations of cognitive insight components with neurocognitive functioning. Specifically, lower levels of R-C index and self-reflectiveness dimension of cognitive insight were correlated with poorer executive functioning, while higher levels of self-certainty were linked to poorer premorbid IQ (Lysaker et al., 2018). In line with these findings and ours, metacognitive training, a novel treatment for poor insight of schizophrenia focusing on improving patients' higher-order executive functioning of problem-solving in

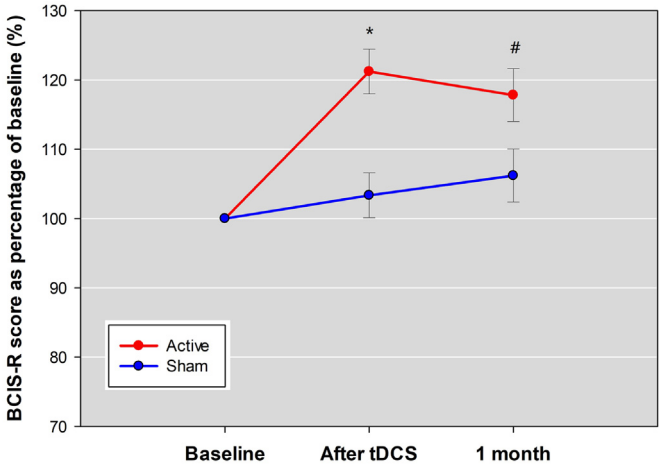

Fig. 1. Score as percentage of baseline in the reflective attitude subscale scores of the Taiwanese version of the Beck Cognitive Insight Scale (BCIS) between active stimulation group and sham group across the three assessments. Error bars indicated the standard error. Post hoc analyses were undertaken to examine between-group difference at each post-baseline assessment with p value < 2.33×10^{-3} considered significant. #p < 0.05; *p < 2.33×10^{-3}.

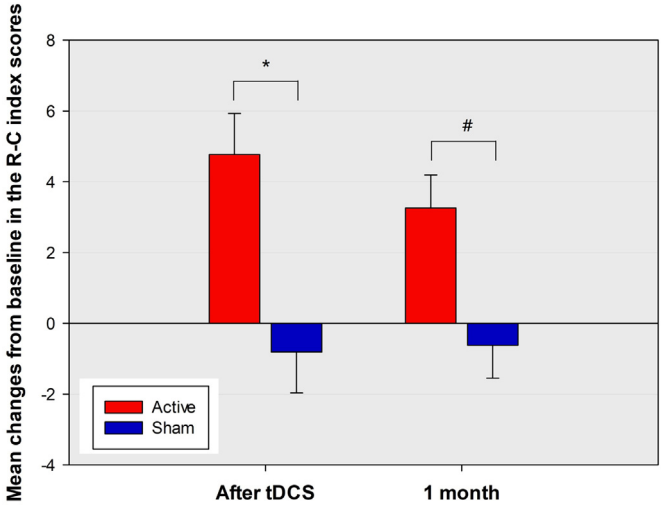

Fig. 2. Mean changes from baseline in the R-C index scores of the Taiwanese version of the Beck Cognitive Insight Scale (BCIS) between active stimulation group and sham group at postbaseline assessments of after tDCS and 1 month after treatment. Other descriptions are as in Fig. 1.

Table 4
Mean change in the performance of neurocognitive function tests after 5 days of tDCS or sham treatment in the participants.

Variables[a]	Active tDCS (N = 30)	Sham tDCS (N = 30)	F	p-Value	Partial η^2	Effect size
Digits forward score	0.56 ± 0.17	0.74 ± 0.17	0.47	0.49	0.008	0.090
Digits backward score	0.96 ± 0.28	0.67 ± 0.28	0.47	0.50	0.008	0.090
FTT dominant finger	−2.98 ± 1.24	−3.54 ± 1.24	0.10	0.76	0.002	0.045
FTT non-dominant finger	−4.86 ± 1.08	−3.36 ± 1.08	0.89	0.35	0.016	0.128
Trail making test part-A	−5.64 ± 4.27	−11.46 ± 4.27	0.86	0.36	0.015	0.123
Trail making test part-B	−20.95 ± 12.38	−24.49 ± 12.38	0.04	0.85	0.001	0.032
WCST						
Trials completed	−19.70 ± 5.26	−13.64 ± 5.26	0.62	0.44	0.011	0.105
Trials correct	−0.35 ± 3.88	0.71 ± 3.88	0.04	0.85	0.001	0.032
% errors	−12.91 ± 2.96	−9.76 ± 2.96	0.52	0.47	0.009	0.095
% perseverative responses	−2.65 ± 2.01	−3.65 ± 2.01	0.12	0.74	0.002	0.045
% perseverative errors	−2.40 ± 1.58	−3.30 ± 1.58	0.15	0.70	0.003	0.055
% non-perseverative errors	−10.52 ± 2.09	−6.55 ± 2.09	1.67	0.20	0.029	0.173
Categories completed	1.69 ± 0.43	1.04 ± 0.43	1.07	0.31	0.019	0.139
CPT II						
Omission errors (number)	2.36 ± 5.17	6.45 ± 5.17	0.29	0.59	0.005	0.071
Commission errors (number)	4.70 ± 1.93	0.57 ± 1.93	2.13	0.15	0.037	0.196
Hit RT (ms)	44.77 ± 27.56	77.46 ± 27.56	0.65	0.42	0.011	0.105
Hit RT SE	3.81 ± 2.48	5.52 ± 2.48	0.22	0.64	0.004	0.063
Variability (variability of SE)	5.74 ± 5.27	8.03 ± 5.27	0.09	0.77	0.002	0.045
Detectability (d′)	−0.07 ± 0.09	0.10 ± 0.09	1.63	0.21	0.028	0.170
Response style (ß)	−0.02 ± 0.24	−0.06 ± 0.24	0.01	0.91	2.17×10^{-4}	0.015
Perseverations	5.97 ± 2.11	7.70 ± 2.11	0.31	0.58	0.006	0.078
Hit RT block change	−0.003 ± 0.01	−0.002 ± 0.01	0.06	0.80	0.001	0.032
Hit SE block change	0.05 ± 0.10	0.12 ± 0.10	0.18	0.67	0.003	0.055
Hit RT ISI change	0.01 ± 0.02	0.03 ± 0.02	0.81	0.37	0.014	0.119
Hit SE ISI change	0.03 ± 0.04	0.09 ± 0.04	0.96	0.33	0.017	0.132
Tower of London test (TOL)						
Total correct score (TOL accuracy)	3.03 ± 0.45	1.37 ± 0.45	6.40	**0.014**	0.103	0.339
Total time (TOL time)	−110.20 ± 24.02	−92.80 ± 24.02	0.24	0.62	0.004	0.063
Total rule violations (TOL score)	−1.53 ± 0.40	−1.57 ± 0.40	0.01	0.94	1.12×10^{-4}	0.011

Data are presented as means ± standard deviations, unless otherwise stated; WCST, Wisconsin Card Sorting Test; CPT II, Connors' Continuous Performance; Test – Second Edition; RT, reaction time; SE, standard error; ISI, inter-stimulus interval.
[a] Values adjusted for length of illness and baseline PANSS general score.

an attempt to enhance reflection on cognitive biases, has also shown promising results on improving self-reflectiveness dimension of cognitive insight (Lam et al., 2015; Ochoa et al., 2017). Our results provide evidence for the previous claim that self-reflectiveness and self-certainty may reflect separate cognitive processes which necessitate targeted interventions (Gonzalez-Blanch et al., 2014) and for the linkage between enhancement of cognitive insight and improvement of higher-order executive functioning among patients treated with fronto-temporal tDCS.

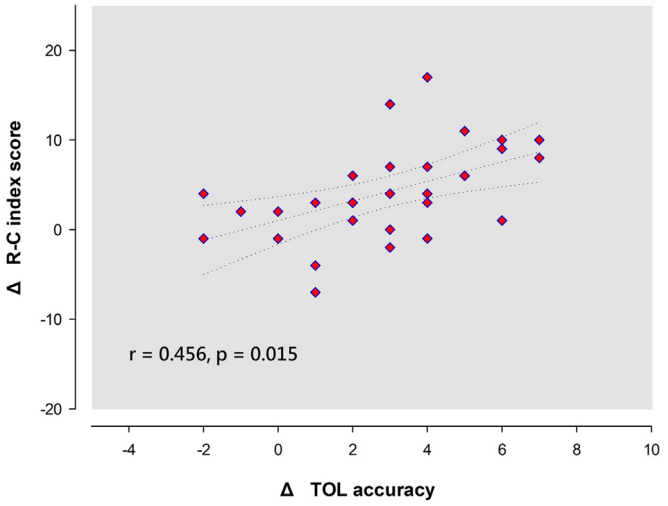

Fig. 3. Correlation between the changes in the R-C index scores of the Taiwanese version of the Beck Cognitive Insight Scale (BCIS) from baseline to immediately after tDCS assessment and that in the accuracy of the Tower of London (TOL) test in patients treated with the active stimulation. The regression line and 95% confidence intervals for the linear regression slope are shown.

Our study has several limitations. First, given that we recruited patients with medication-refractory AVHs who volunteered for this interventional trial, a selection bias may exist. This may preclude patients who had AVHs but with no insight that the AVHs were symptoms of illness and thus would not have agreed to tDCS treatment. Our participants may represent a patient population who would have had some insight into their illness to recognize that their AVHs were symptoms of illness that could be treated. Second, the beneficial effect of fronto-temporal tDCS on cognitive insight became borderline significant one month after stimulation. Compared to the conventional tDCS used in our study, high definition tDCS (HD-tDCS) which targets cortical areas using arrays of electrodes on the scalp can better constrain the electrical current flow to a specific cortical area (Alam et al., 2016). Further studies should investigate whether anodal HD-tDCS over the left VLPFC has a greater potential and a longer duration of after-effect than fronto-temporal tDCS to be a pathophysiological-orientated treatment specifically for poor cognitive insight in schizophrenia. Finally, tDCS did not improve patients' psychosocial functioning. It seems contrary to previous evidence indicating that higher executive function (Cohen et al., 2006) and better cognitive insight (Sumiyoshi et al., 2016) were associated with superior psychosocial functioning. Moreover, in line with the so-called “insight paradox” which posits that patients with heightened insight is associated with increased levels of depression, our previous study has confirmed that better cognitive insight is related to worse depression in schizophrenia patients (Kao et al., 2011). Better cognitive insight has also been identified as a potential risk factor for suicidality in psychosis patients (Lopez-Morinigo et al., 2014). Only three-month follow-up of our study may be too short to reveal the long-term impact of tDCS-enhanced cognitive insight and higher-order executive function on patients' psychosocial functioning and their levels of depression and suicidality.

In summary, we observed beneficial effects of fronto-temporal tDCS on cognitive insight and planning ability in schizophrenia patients. The

promising results require confirmation in future studies. We also found the positive correlations between the enhancement in cognitive insight, particularly its self-reflectiveness dimension and the improvement in planning ability. Future studies should determine whether fronto-temporal tDCS facilitated enhancement in cognitive insight through improving higher-order executive functioning.

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CRediT authorship contribution statement

Chuan-Chia Chang: Writing - original draft, Writing - review & editing. **Yu-Chen Kao:** Conceptualization, Investigation, Methodology. **Che-Yi Chao:** Project administration, Investigation, Data curation. **Hsin-An Chang:** Project administration, Investigation, Methodology, Funding acquisition, Formal analysis, Supervision, Validation.

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None.

Conflict of interest

The authors have no conflicting interests.

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