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Original article

Modulation of brain activity with transcranial direct current stimulation: Targeting regions implicated in impaired illness awareness in schizophrenia

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ABSTRACT

Background: Impaired illness awareness or insight into illness (IIA) is a common feature of schizophrenia that contributes to medication nonadherence and poor clinical outcomes. Neuroimaging studies suggest IIA may arise from interhemispheric imbalance in frontoparietal regions, particularly in the posterior parietal area (PPA) and the dorsolateral prefrontal cortex (dlPFC). In this pilot study, we examined the effects of transcranial direct current stimulation (tDCS) on brain regions implicated in IIA.
Methods: Eleven patients with schizophrenia with IIA (≥3 PANSS G12) and 10 healthy controls were included. A crossover design was employed where all participants received single-session bi-frontal, bi-parietal, and sham stimulation in random order. For each condition, we measured (i) blood oxygen level-dependent (BOLD) response to an illness awareness task pre- and post-stimulation, (ii) regional cerebral blood-flow (rCBF) prior to and during stimulation, and (iii) changes in illness awareness.
Results: At baseline, patients with schizophrenia showed higher BOLD-response to an illness awareness task in the left-PPA compared to healthy controls. Bi-parietal stimulation reduced the interhemispheric imbalance in the PPA compared to sham stimulation. Relatedly, bi-parietal stimulation increased rCBF beneath the anode (21% increase in the right-PPA), but not beneath the cathode (5.6% increase in the left-PPA). Bi-frontal stimulation did not induce changes in rCBF. We found no changes in illness awareness.
Conclusion: Although single-session tDCS did not improve illness awareness, this pilot study provides mechanistic justification for future investigations to determine if multi-session bi-parietal tDCS can induce sustained changes in brain activity in the PPA in association with improved illness awareness.

1. Introduction

Impaired illness awareness or insight into illness (IIA) – having partial or complete lack of conscious awareness of one's illness, its symptoms, and the need for treatment – is a common feature of schizophrenia [1,2]. IIA is of high clinical relevance as it contributes to antipsychotic medication nonadherence and poor treatment outcomes [3,4].

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IIA is prototypically associated with right hemisphere brain damage secondary to stroke, but it is also encountered in other neuropsychiatric conditions [5]. IIA is proposed to arise from interhemispheric imbalance, primarily in frontoparietal regions [6,7]. This imbalance may result from right hemisphere damage in "structural", lesion-based disorders (e.g., right hemisphere stroke, neurodegeneration) [8,9] or left hemisphere overactivity in "functional" disorders, such as schizophrenia [10,11].

Support for the interhemispheric imbalance model in patients with schizophrenia comes from functional neuroimaging studies that found increased blood oxygen level-dependent (BOLD) response to an illness awareness task in the left posterior parietal area (PPA) [6], and increased default-network connectivity with the left-PPA in patients with IIA [12]. Although findings from structural neuroimaging studies are mixed, right hemisphere deficits in patients with IIA have been reported [13–15], including our own study that found reduced right dorsolateral prefrontal cortex (dlPFC) and PPA volumes relative to the left hemisphere [7].

Frontoparietal regions contributing to interhemispheric imbalance provide suitable neural targets for non-invasive brain stimulation, such as transcranial direct-current stimulation (tDCS). tDCS applies a weak electric current through anodal and cathodal electrodes placed on the scalp, which have been proposed to increase and decrease cortical excitability, respectively [16]. Recent studies suggest tDCS may be an efficacious treatment for schizophrenia [17–19], including studies that showed improvements in illness awareness [20–22].

A number of neuroimaging studies in healthy participants examined the effects of tDCS on regional cerebral blood flow (rCBF), a surrogate marker of neural activity [23]. Zheng et al. (2011) showed anodal stimulation to the right motor cortex increased rCBF beneath the electrode, whereas cathodal stimulation over the contralateral supraorbital region caused a slight increase in rCBF that decreased after tDCS cessation [24]. Stagg et al. (2013) showed that anodal stimulation of the left dlPFC increased rCBF in this region compared to cathodal stimulation of the same area [25]. Whether similar changes occur in patients with schizophrenia, and the clinical implications of such alterations, remain unclear.

In this pilot study, we investigated the effects of single-session tDCS on the frontoparietal regions associated with IIA by measuring BOLD-response to an illness awareness task and changes in rCBF. We used two electrode placements, i.e., bi-parietal and bi-frontal tDCS to target the PPA and the dlPFC, respectively. We hypothesized that single-session tDCS would:

(i) Increase BOLD-response in the right-PPA and/or decrease BOLD-response in the left-PPA to an illness awareness task to restore the interhemispheric balance. Our hypothesis was specific to the PPA based on the consistency of this region in relation to IIA in our prior functional neuroimaging studies [6,12].
(ii) Increase rCBF beneath the anode, but not cathode, during bi-parietal and bi-frontal stimulation.
(iii) Transiently improve illness awareness in patients with schizophrenia.

2. Methods

2.1. Study design

A crossover design was employed where all participants received each of the three conditions separated by at least one week: bi-parietal, bi-frontal, and sham stimulation. The order of stimulation was randomized via a computer-generated list and counterbalanced. During each visit, participants received the following: (i) task-based fMRIs pre- and post-tDCS; (ii) bi-parietal, bi-frontal, or sham stimulation; and (iii) serial arterial spin labeling (ASL) scans prior to and during stimulation to measure rCBF (Fig. 1). Both raters and participants were blind to the stimulation condition. After each stimulation, participants were asked to guess which stimulation condition they received. Randomized allocation concealment and blinding were maintained until all participants completed the study.

2.2. Participant criteria

Twelve patients with schizophrenia and 11 healthy control participants (HC) were recruited from the Centre for Addiction & Mental Health (CAMH). The study was approved by the Research Ethics Board and was conducted between 2013 and 2016. Capacity

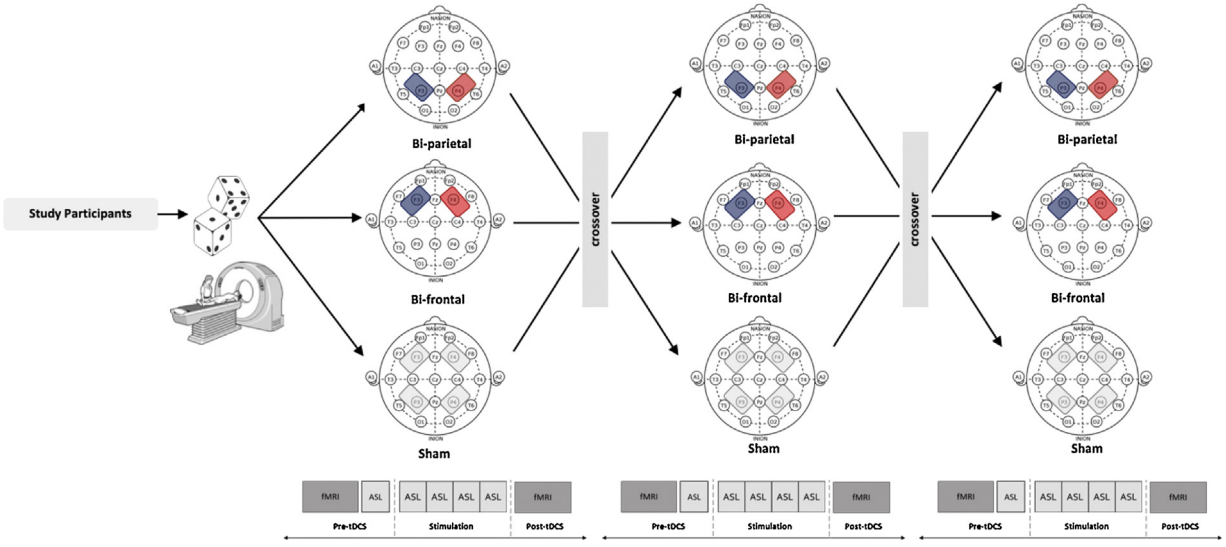

Fig. 1. Participants were randomly assigned to receive each of the three single-session tDCS conditions in the scanner: bi-parietal, bi-frontal, and sham stimulation. The order of stimulation was randomized and counterbalanced. During each condition, participants received the following: (i) illness awareness task-based fMRIs pre- and post-tDCS; (ii) bi-parietal, bi-frontal, or sham stimulation; and (iii) serial arterial spin labeling (ASL) sequences prior to and during stimulation. For the bi-parietal condition, the anode and cathode were placed over P4 and P3, respectively. For the bi-frontal condition, the anode and cathode were placed over F4 and F3, respectively. For the sham condition, the electrodes were placed at the site of active treatment (half of the participants P3 and P4 and the other half F3 and F4).

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to consent to participate in the study was confirmed with the MacArthur Test of Competence [26]. Inclusion criteria for patients were: Inpatients or outpatients ≥18 years of age; DSM-IV diagnosis of schizophrenia or schizoaffective disorder; and IIA (≥3 on PANSS G12). Exclusion criteria included: Serious, unstable medical illness, or concomitant medical or neurological illness; acute suicidal or homicidal ideation; formal thought disorder rating >2 on the Scale for the Assessment of Positive Symptoms (SAPS); DSM-IV substance dependence (except caffeine and nicotine) within the past month; pregnant; positive urine drug screen; taking antiepileptics; contraindications to MRI; and a score <32 on the Wide Range Achievement Test-III (WRAT-III) [27].

Inclusion and exclusion criteria for HCs were the same as patients, with the exception of the following requirements for inclusion: No current or past psychiatric disorder; and no first-degree relatives with a primary psychotic disorder.

Of the included participants, one schizophrenia and one HC participant dropped out after receiving sham stimulation due to withdrawal of consent because the MRI sessions were described as too long. For task-based fMRI analyses, post-tDCS data for one schizophrenia participant was excluded due to excess head movement. For rCBF, two schizophrenia and three HC participants were missing rCBF data for bi-frontal stimulation. These participants received stimulation outside the scanner because the MR-compatible electrode wires were damaged by the user. Lastly, some participants were missing data from the last 5-min rCBF interval. This occurred for one schizophrenia participant during bi-parietal and sham stimulation, and three schizophrenia participants during bi-frontal stimulation.

2.3. Study measures

Illness awareness was measured with the VAGUS self-report (VAGUS-SR) and clinician-rated versions (VAGUS-CR) [28], and fMRI paradigm scores (higher percentage of items answered correctly represents greater illness awareness). Symptom severity was assessed with the SAPS and the Scale for the Assessment of Negative Symptoms (SANS) [29]. The Beck Cognitive Insight Scale (BCIS), composed of the self-reflectiveness and self-certainty subscales, was used to measure cognitive insight [30]. A composite-index score is derived from subtracting the self-certainty from the self-reflectiveness subscale score [30]. The WRAT-III reading subtest was used to measure premorbid IQ [27]. The Edinburgh Handedness Inventory was used to measure laterality [31]. Chlorpromazine antipsychotic dose equivalents (CPZ equivalence) were calculated using a previously reported method [32,33]. Self-reported smoking status was also collected.

2.4. Statistical analyses

Statistical analyses were carried out using SPSS Statistics v23.0 (IBM Corporation). Independent samples t-tests were used to examine group differences in demographic and clinical characteristics between schizophrenia and HC participants. Linear mixed effects model analyses were performed to examine differences in VAGUS (-SR and -CR), BCIS composite and subscale, and SAPS scores pre- and post-tDCS. A threshold of $p<0.008$ (i.e., 0.05/6) was used. Linear mixed effects modeling was preferred as it has the capacity to handle missing data by using maximum likelihood estimation (See Supplemental Material 1A). Subsequent exploratory paired t-tests were performed to examine differences in pre- and post-tDCS scores for each stimulation condition.

2.5. tDCS parameters

tDCS was performed using the programmable DC-Stimulator Plus (NeuroConn, GmbH). MR-compatible rubber electrodes (7×5 cm) were placed with the long-edge in the anterior-posterior direction using conduction paste and secured with a rubber strap around the head. For the bi-parietal condition, the anode and cathode were placed over P4 and P3, respectively. For the bi-frontal condition, the anode and cathode were placed over F4 and F3, respectively [34]. For the active conditions, a 2 mA constant current was applied for 20-min. For the sham condition, the electrodes were placed at the site of active stimulation (half of the participants at P3/P4 and the other half at F3/F4), and a 1 mA current was applied for 15 s with a fade in-and-out of 15 s. SimNIBS 2.1.2 (http://simnibs.de/) was used for electric field modeling of bi-parietal and bi-frontal tDCS (Supplemental Material 2 and 3) [35].

2.6. Illness awareness task

Each participant completed a task in the scanner designed to confront participants with their beliefs about their illness. The same paradigm was employed in a prior study by our group [6]. The task consisted of a bank of "yes/agree" or "no/disagree" items derived from four categories: general illness awareness, symptom awareness, awareness of the need for treatment, and illness-independent/control. For symptom awareness, the statements were tailored to each participant's experience. The statements for other categories were common across all participants. The paradigm for HCs was similar consisting of stimuli derived from the same four categories.

Each participant was outfitted with an MR-compatible button-box. An adjustable mirror located above the participant's eyes was used to view the stimuli projected onto a screen placed at the head of the bed. Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA). Each statement was presented for 4 s with an interstimulus interval of 2 s. Participants could respond up to 5 s following the presentation of each stimulus (Supplemental Material 4).

2.7. MRI data acquisition

MRI scans were performed on a Discovery MR750 3.0 T GE scanner (Milwaukee, WI, USA). See Supplemental Material 5A for detailed acquisition parameters.

Using T1-weighted images, cerebrospinal fluid (CSF) to total brain volume (TBV) ratio was calculated as a global measure of cerebral atrophy (Supplemental Material 5B).

2.8. Task-based fMRI analyses

2.8.1. Task-based fMRI: preprocessing

Similar to the analysis performed in our original study to identify the neural correlates of IIA [6], first-level contrasts were created using random-effect analyses between total illness awareness (i.e., general illness awareness, symptom awareness, and awareness of the need for treatment combined) and illness-independent/control stimuli, and also between each illness awareness category and illness-independent/control stimuli. These contrast images were then used for second-level analyses. See Supplemental Material 6 for a detailed description.

2.8.2. Task-based fMRI: whole brain analyses

Two sample t-tests were used to investigate differences in BOLD-response between schizophrenia and HCs pre- and post-tDCS. As the left-PPA was our a priori region of interest (ROI), our statistical analyses were confined to the PPA (10 mm sphere around the peak -46,-70,+36) [12]. The cluster was reported as significant if the peak survived a threshold of family-wise error (FWE) $p<0.05$ within this region.

2.8.3. Task-based fMRI: ROI analyses

ROI analyses were performed using the same a priori ROI for the whole brain analysis (10 mm sphere around the peak

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-/+46,−70,+36) was defined using the Talairach Daemon atlas with WFU-Pickatlas software [36–38]. The mean BOLD-response in each hemisphere was extracted using the REX toolbox (http://web.mit.edu/swg/software.htm).

Linear mixed effects models were used to examine the difference in baseline interhemispheric imbalance between patients with schizophrenia and HCs (i.e., left minus right BOLD-response in the PPA using baseline scans from all visits), as well as the change in interhemispheric imbalance with bi-parietal compared to sham tDCS (See Supplemental Material 1B).

For exploratory purposes, we examined the correlation between left minus right BOLD-response in the PPA and the VAGUS scores. We did not expect to observe any associations due to the limited range in illness awareness scores as all patients included had moderate-to-severe illness awareness impairment.

2.9. Regional CBF analyses

2.9.1. Regional CBF: preprocessing

See Supplemental Material 6 for a detailed description.

2.9.2. Regional CBF: whole brain analyses

Two sample t-tests were performed to examine changes in rCBF following 20-min (or if missing, 15-min) of bi-parietal, bi-frontal, and sham stimulation compared to baseline. A cluster was reported as significant if the peak survived a threshold of FWE $p<0.05$ [39].

2.9.3. Regional CBF: ROI analyses

We extracted rCBF from the PPA (10 mm sphere around the peak -/+46,−70,+36) [12] and the dlPFC (10 mm sphere around the peak -/+27,+49,+24) [7] using the REX toolbox. Linear mixed effects models were used to measure rCBF differences from baseline between conditions. rCBF was defined as mL of blood per 100 mg of tissue per min (mL/100 mg/min). The significance level was established at $p<0.025$ (i.e., 0.05/2). Linear contrasts were used to explore rCBF differences between baseline and each 5-min interval (See Supplemental Material 1C). Regression analyses were performed to explore the effects of clinical characteristics, including CSF-to-TBV ratio and CPZ equivalence, on the changes in rCBF following 20-min (or if missing, 15-min) of tDCS.

Table 1
Participant demographic and clinical characteristics at baseline.

	SCZ (n = 12) Mean (SD)	HC (n = 11) Mean (SD)	*p*-value
Age, range (years)	45.0 (12.1), 28-64	40.7 (12.9), 23-64	0.442
Gender (male/female, %male)	7/5, 58.3%	8/3, 72.7%	0.667
Education (years)	13.6 (2.3)	16.0 (1.3)	0.007*
IQ (WRAT-3)	109.4 (8.9)	111.9 (8.2)	0.493
Tobacco use (smokers/non-smokers, % smokers)	4/8, 33.3%	3/8, 27.3%	1.000
Cigarettes per day	27.5 (19.4)	9.3 (6.0)	0.185
EHI score	77.6 (16.2)	83.3 (20.6)	0.467
Grey matter	700.3(75.2)	710.3 (55.1)	0.721
White matter	502.5 (63.9)	512.6 (54.5)	0.688
CSF	378.0 (35.2)	356.3 (33.0)	0.142
TBV (cm^3)	1580.9 (162.5)	1579.3 (133.4)	0.980
CSF / TBV	0.24 (0.01)	0.22 (0.01)	0.019*
Illness onset (years)	25.4 (10.1)	–	
Illness duration (years)	19.6 (12.9)	–	
CPZ equivalent dose (mg/day)	492.1 (184.9)	–	
Duration of current primary antipsychotics (years)	4.2 (2.6)	–	
SAPS			
Composite score	19.5 (12.4)	–	
Global score	3.1 (2.0)	–	
SANS			
Composite score	21.9 (13.8)	–	
Global score	6.2 (3.2)	–	
PANSS G12	4.8 (1.3)	–	
VAGUS-CR average score	5.5 (2.1)	–	
VAGUS-SR average score	4.9 (2.0)	–	
BCIS composite score	3.7 (8.0)	–	
BCIS self-reflectiveness	12.0 (6.2)	–	
BCIS self-certainty	8.3 (3.9)	–	
Condition response time (s)			
Total illness awareness	2.7 (0.9)	2.3 (0.7)	0.432
General illness awareness	2.4 (0.7)	2.1 (0.7)	0.056
Symptom awareness	3.0 (1.0)	2.1 (0.7)	0.026*
Awareness of the need for treatment	2.7 (0.9)	2.6 (0.6)	0.260
Illness-independent/control	1.7 (0.7)	1.7 (0.7)	0.824
Total illness awareness minus control	1.0 (0.5)	0.9 (0.3)	0.549
General illness minus control	0.6 (0.3)	0.4 (0.1)	0.200
Symptom awareness minus control	1.3 (0.6)	0.4 (0.2)	< 0.001*
Awareness of the need for treatment minus control	1.0 (0.5)	0.9 (0.3)	0.549
Antipsychotics[1]	Risperidone (n = 2) Olanzapine (n = 2) Perphenazine (n = 1) Clozapine (n = 6) Quetiapine (n = 1)		

SCZ, schizophrenia spectrum disorder; HC, healthy control; IQ, Intelligence Quotient; EHI, Edinburgh Handedness Inventory; CSF, cerebrospinal fluid; TBV, total brain volume; CPZ, chlorpromazine; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; PANSS G12, Positive and Negative Syndrome Scale Insight and Judgement Item; BCIS, Beck's Cognitive Insight Scale. [1]One participant was taking more than one antipsychotic medication. * $p\leq0.05$.

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3. Results

3.1. Participant characteristics

Table 1 presents participant demographic and clinical characteristics. Compared to HCs, patients with schizophrenia had fewer years of education (t(21)=3.02, p=0.007) and higher CSF-to-TBV ratios (t(21)=-2.55, p=0.019). The fMRI task condition response times for symptom awareness and symptom awareness minus illness-independent/control items were significantly longer in the schizophrenia compared to HCs. Supplemental Material 7 includes a list of antipsychotic and concomitant medications.

3.2. Clinical effects

Linear mixed effects model analyses showed a main effect of time (i.e., pre- and post-tDCS) on BCIS-composite (F=15.41, p<0.001), self-reflective (F=11.45, p=0.002), and self-certainty scores (F=8.44, p=0.006). Subsequent exploratory paired t-tests showed differences in BCIS composite scores with bi-frontal (t(10) =-2.8, p=0.019) and sham stimulation (t(11)=-2.51, p=0.029), and self-certainty scores with bi-frontal stimulation (t(10)=3.01, p=0.013). There were no differences in the VAGUS or SAPS scores (Supplemental Material 8). Participants' guess as to which stimulation condition they received did not differ between conditions. The mean percentage of participants guessing they received active stimulation for the bi-frontal, bi-parietal, and sham conditions was 61%, 75%, and 65%, respectively.

3.3. Task-based fMRI results

3.3.1. Task-based fMRI: whole brain analyses

At baseline, a whole brain analysis comparing the schizophrenia and HC groups using the contrast total illness awareness > illness independent/control stimuli revealed a peak BOLD-response in the left-PPA (-44,-62,+40) (t=3.34, p=0.025, FWE corr.) (Fig. 2A). Post-tDCS, there were no suprathreshold clusters between the groups. Supplemental Material 9 shows the results from other contrasts.

3.3.2. Task-based fMRI: ROI analyses

At baseline, linear mixed effect model analysis showed a significant difference in the left minus right PPA BOLD-response (for the contrast total illness awareness > illness-independent/control stimuli) in patients with schizophrenia compared to HCs (F=6.07, p=0.022), suggesting that patients with impaired illness awareness have higher interhemispheric imbalance in the PPA (schizophrenia, left vs. right t(35)=4.26, p<0.001; HC, t(29)=0.05, p=0.959).

Linear mixed effect model analysis showed a significant interaction effect of group (i.e., schizophrenia and HCs), stimulation (sham and bi-parietal tDCS), and time (pre and post-tDCS) (F=6.32, p=0.016). Bi-parietal compared to sham tDCS reduced the interhemispheric imbalance in patients with schizophrenia (F=4.42, p=0.046), but not in HCs (F=2.40, p=0.137). Supplemental Material 10 shows the exploratory results from other contrasts.

Interhemispheric imbalance was correlated with one of the subdomains of the VAGUS, specifically the negative consequences domain (r(12)=-0.632, p=0.028), but not with the VAGUS average (r (12)=-0.247, p=0.438) or other domain scores (illness awareness, r (12)=-0.220, p=0.492; symptom attribution, r(12)=0.345, p=0.272; and need for treatment domain, r(12)=-0.233, p=0.466). Following bi-parietal tDCS, we found no significant correlations between interhemispheric imbalance and VAGUS average or subdomain scores.

3.4. Regional CBF results

3.4.1. Regional CBF: whole brain analyses

Whole brain analyses comparing rCBF at 20-min of bi-parietal, bi-frontal, and sham stimulation to baseline in both the schizophrenia and HC groups revealed no peak activation that survived FWE corr. Fig. 2C-E show the areas of activation with bi-parietal, bi-frontal, and sham stimulation in all participants using a liberal threshold of p<0.05, uncorr. Supplemental Material 11 and Supplemental Material 12 show areas of activation for each of the conditions for the HC and schizophrenia groups, respectively.

3.4.2. Regional CBF: ROI analyses

3.4.2.1. Baseline rCBF. At baseline, HCs had higher rCBF in the PPA (t (21)=2.61, p=0.016) and the dlPFC (t(21)=3.15, p=0.005) compared to the schizophrenia group. Exploratory analyses showed an association between baseline rCBF and CSF-to-TBV ratio in the PPA (F(1,22)=8.46, p=0.008) (Supplemental Material 13) and the

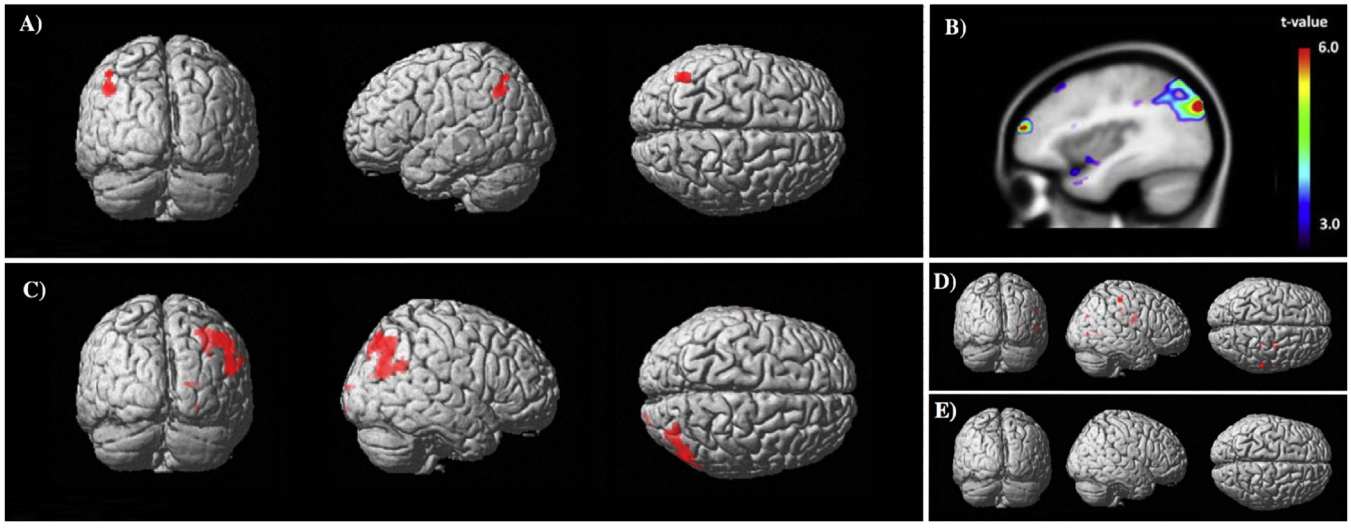

Fig. 2. (A) BOLD-response in the left posterior parietal area (PPA) for the contrast total illness awareness > illness-independent/control stimuli in the schizophrenia compared to the healthy control group. A low threshold of p < 0.01 was used to reveal all brain activity (peak voxel -44, -60, 40). (B) BOLD-response for the contrast total illness awareness > illness-independent/control stimuli in patients with IIA compared to patients with intact illness awareness. Reproduced from our previous study [6]. Regional cerebral blood flow beneath the anode with 20-min of (C) bi-parietal, (D) bi-frontal, (E) and sham tDCS compared to baseline. A low threshold of p<0.05 was used to reveal all regions affected.

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dlPFC (F(1,22)=16.81, p=0.001) suggesting cerebral atrophy was related to lower rCBF. There was no association between CPZ equivalence and baseline rCBF.

3.4.2.2. Changes in rCBF with bi-parietal tDCS.

There was a significant main effect of group on rCBF beneath the anode (F=8.11, p=0.009), where HCs had higher overall rCBF. There was a significant main effect of stimulation (F=9.05, p=0.007), time (F=5.37, p<0.001), and an interaction effect of stimulation by time (F=3.20, p=0.015). Exploratory analyses showed increased rCBF at 5-min (t=2.52, p=0.013), 10-min (t=3.14, p=0.002), 15-min (t=2.82, p=0.005), and 20-min (t=2.29, p=0.023) of bi-parietal compared to sham stimulation. This corresponded to a 21.0% increase in rCBF in the right-PPA with 20-min of bi-parietal stimulation compared to baseline (Fig. 3).

There was a significant main effect of group on rCBF beneath the cathode (F=1.68, p=0.010) where HCs had higher overall rCBF. No other main or interaction effects survived correction for multiple comparisons. Compared to baseline, there was a 5.6% increase in rCBF in the left-PPA at 20-min.

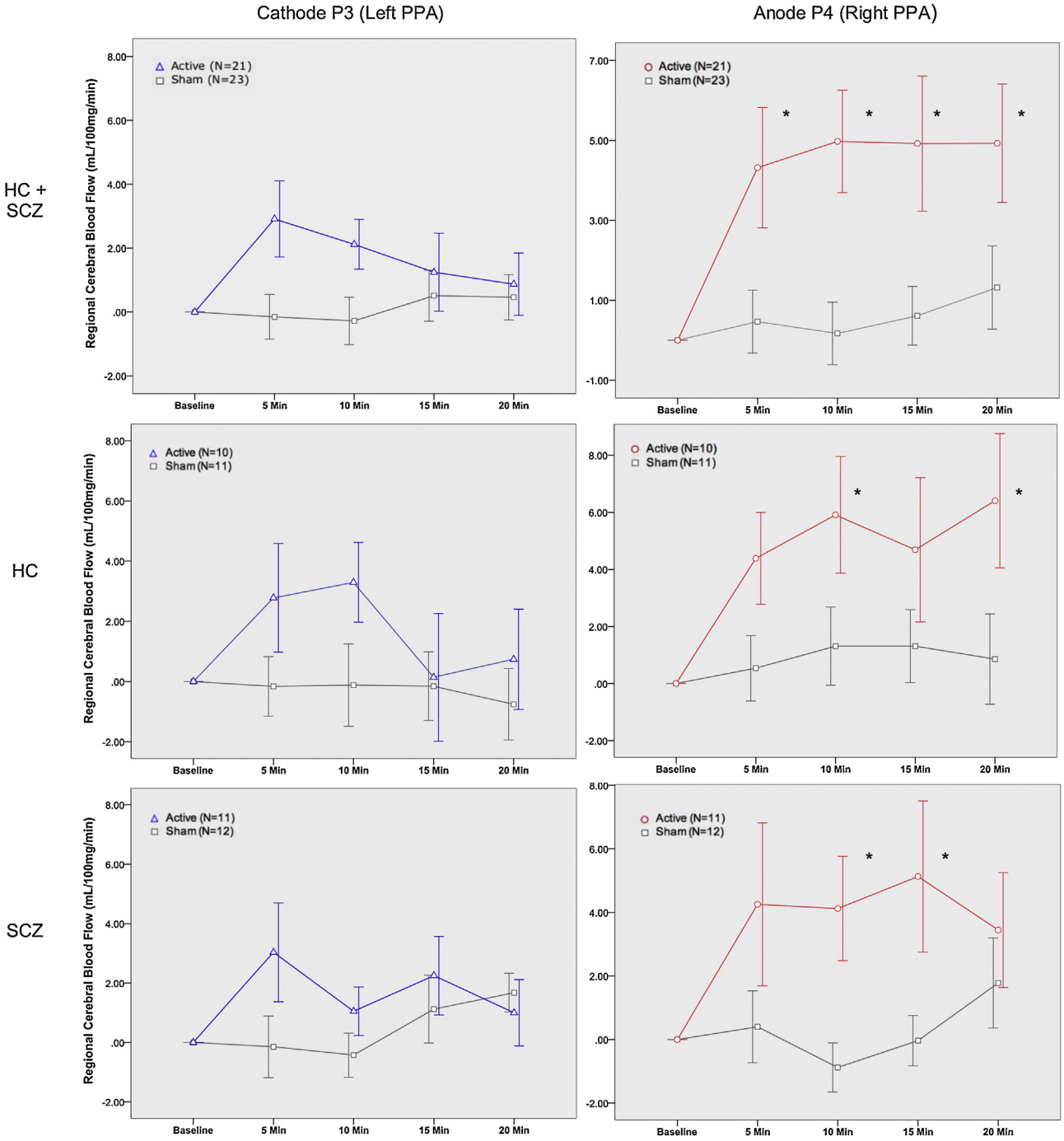

Fig. 3. Change in regional cerebral blood flow ±1 standard error beneath the cathode (left) and anode (right) at each 5-min interval of bi-parietal compared to sham stimulation. *p<0.05 for subsequent pairwise comparisons. Schizophrenia, schizophrenia spectrum disorder; HC, healthy control.

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Exploratory regression analyses showed an association between CPZ equivalence and rCBF change beneath the anode ($F(1,10) = 7.89$, $p = 0.020$) (Fig. 4). Cerebral atrophy and smoking status were not associated with changes in rCBF. Supplemental Material 14 shows the extracted rCBF data.

3.4.2.3. Changes in rCBF with bi-frontal tDCS.

There was asignificant main effect of group on rCBF beneath the anode ($F = 6.81$, $p = 0.016$) and the cathode ($F = 9.07$, $p = 0.006$) where HCs had higher overall rCBF. There were no other main or interaction effects. Supplemental Material 14 shows the extracted rCBF data.

4. Discussion

This study examined the effects of single-session tDCS on fMRI BOLD-response to an illness awareness task and rCBF. Bi-parietal stimulation significantly reduced the interhemispheric imbalance in the PPA, and relatedly, increased rCBF beneath the anode in the right-PPA. Bi-frontal stimulation did not induce changes in rCBF in the dlPFC. Taken together, the results of this pilot study suggest that single-session bi-parietal tDCS can modulate brain regions implicated in IIA. However, multi-session tDCS may be required to observe clinical effects [40].

The fMRI illness awareness task employed in this study was designed to assess brain activity at the moment of illness acceptance/denial. In a previous study by our group, the illness awareness task was used to compare patients with impaired versus intact illness awareness. Specifically, we aimed to identify differences in BOLD-response between patients that *incorrectly deny* having an illness and patients that *correctly accept* having an illness [6]. The current study is the first to use the illness awareness task in HCs. We wished to build on our previous work by aiming to identify the differences in BOLD-response between patients that *incorrectly deny* having an illness and HCs that *correctly deny* having an illness. The increased BOLD-response in the left-PPA was consistent across both studies (Fig. 2A,B). The consistency of our results between related, but distinct comparison groups support the role of the PPA in IIA in patients with schizophrenia.

The reduction in left-PPA BOLD-response with bi-parietal stimulation suggests that single-session tDCS may transiently resolve the interhemispheric balance associated with IIA. Moreover, this occurred in relation to increased rCBF beneath the anode in the right-PPA (Fig. 2C). However, changes in brain activity with single-session tDCS did not directly correspond with clinical improvements in illness awareness. This is expected as tDCS effects may be delayed and are more likely to be cumulative [17,40–43]. Three recent studies, including two open-labelled [20,21] and one randomized-sham controlled [22], showed that multi-session tDCS improves illness awareness in patients with schizophrenia. Bose et al. (2014) and Chang et al. (2018) applied twice-daily tDCS for 5 days with cathodal stimulation to the left temporoparietal junction (i.e., between T3 and P3) and anodal stimulation in the left prefrontal cortex (i.e., between F3 and FP1) [20,22]. Sreeraj et al. using high-definition tDCS, a more focal method of electrical stimulation, showed that twice-daily cathodal stimulation to the left temporoparietal junction for 5-days improved illness awareness [21]. Taken together, the results of these studies suggest that multi-session cathodal stimulation of the left parietal area improves illness awareness, possibly by reducing the overactivation in this region. However, it remains unclear if anodal stimulation to the right parietal area provides greater benefit than left parietal cathodal stimulation alone. Further, additional studies are needed to determine the effects of modifications to other tDCS parameters (e.g., intensity, frequency and duration) on tDCS response [44].

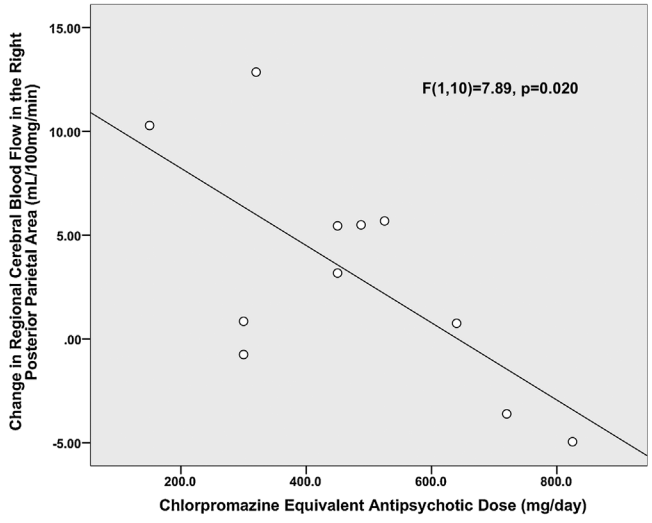

Fig. 4. Correlation between chlorpromazine equivalent antipsychotic dose and change in regional cerebral blood flow in the right posterior parietal area (PPA) with anodal stimulation in schizophrenia participants.

While the results of our study demonstrate that single-session bi-parietal stimulation induces a stable increase in rCBF beneath the anode (Fig. 3), changes in rCBF appeared to be influenced by antipsychotic drug CPZ equivalence. Patients with schizophrenia with higher CPZ equivalence had lower rCBF changes beneath the anode. Interactions between antipsychotic drugs and responses to tDCS in patients with schizophrenia have been reported previously. Agarwal et al. (2016) found that patients taking antipsychotics with lower affinity for dopamine 2 (D_2) receptors were more likely to have a favorable response to tDCS in reducing auditory hallucinations [45]. With our current sample, we are unable to comment on the possible effect of D_2 receptor affinity as only 2 of the 12 participants were prescribed high D_2 receptor affinity antipsychotic drugs. Notably, 6 of the 12 participants were on clozapine. Further studies are needed to tease out the effect of antipsychotic medications on tDCS response.

Previous investigations have reported on the cognitive benefits of single-session tDCS, particularly in improving working memory and learning in patients with schizophrenia [46–48]. Although we did not observe a main effect of tDCS in improving cognitive insight, post-hoc exploratory analyses showed that bi-frontal stimulation reduced 'self-certainty' subscale scores (Supplemental Material 8). This reduction in self-certainty, a core component of cognitive insight as measured with the BCIS, represents a generalized increase in mental flexibility, which according to cognitive insight theorists, may be necessary for improvement in clinical insight [30,49]. However, this finding from our study should be interpreted with caution, especially given we did not observe a change in rCBF in the dlPFC with bi-frontal tDCS. It is possible that our results were underpowered to detect a difference as data from two schizophrenia and three HC participants were missing. Alternatively, methodological (e.g., inaccurate electrode placement) or other patient-specific factors may have hampered the effects of bi-frontal tDCS. Previous studies have shown that the electric fields of frontal tDCS are highly variable due to greater variation in cortical folding patterns in comparison with other brain regions [50,51]. Furthermore, other anatomical differences, such as skull thickness and composition, subcutaneous fat levels, and shunting effects may hamper the effects of tDCS [52,53]. Further studies to assess the distribution of electric fields may be useful to understand, and potentially account for, the inter-subject variability in response to tDCS [54–56].

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Our pilot study has several limitations. First, our sample size was small, limiting multi-level statistical analyses. Relatedly, due to the loss of ASL data during bi-frontal stimulation, we likely did not have enough statistical power to detect changes in rCBF. Second, it is important to note that "sham" tDCS may have some neuromodulatory activity due to the fade-in and fade-out of the stimulus and possible current leakage from the device [57]. Third, although participants' guess as to which stimulation condition they received did not differ between conditions, it is possible that blinding was not maintained given the crossover study design. Third, other factors, such as tobacco and nicotine use, may have influenced the results [58]. Fourth, there is an unavoidable heterogeneity in our schizophrenia sample that may have influenced our results, including treatment responsiveness and antipsychotic drug regimens. Relatedly, given that some participants were taking concurrent medications, the individual and combined pharmacological effects on rCBF remain unclear and require further investigation [59].

5. Conclusion

Overall, this study showed that single-session bi-parietal tDCS can modulate BOLD-response to an illness awareness task and rCBF in the PPA, a brain region implicated in IIA. This pilot study provides mechanistic justification for future investigations to determine if multi-session bi-parietal tDCS can induce sustained changes in brain activity in the PPA in association with improved illness awareness. Additionally, the effects of tDCS on cognitive insight require further exploration as bi-frontal tDCS may enhance mental flexibility. This has implications for the use of tDCS in combination with psychotherapy (e.g., cognitive behavioral therapy for psychosis) to facilitate patients' re-evaluation of their anomalous experiences.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurpsy.2019.06.007.

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