

Potential Delayed Positive Effects of tDCS on Improving Introspective Accuracy in Social Cognition in Schizophrenia

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Background and Hypothesis: Impairments in introspective accuracy (IA) are prominent among schizophrenia patients and detrimentally affect daily functioning, making IA a potential therapeutic target. Recent research highlights the role of the right rostrolateral prefrontal cortex (rLPFC) in IA and suggests that transcranial direct current stimulation (tDCS) to this region may improve it. Therefore, we tested whether applying tDCS to the right rLPFC could enhance IA for schizophrenia patients and explored the potential order/delayed effects.

Study Design: A randomized, double-blind, sham-controlled crossover design was used. Patients with a schizophrenia spectrum disorder ($N = 40$) underwent 2 tDCS sessions targeting right rLPFC (one was active stimulation and the other was sham) about a week apart. After each session, participants completed executive function and emotion recognition tasks for evaluating IA.

Study Results: When ignoring order effects, tDCS did not affect performance, IA, or confidence ratings across 3 tasks, except for increased confidence ratings in the cognitive task after active stimulation versus sham. However, considering order effects revealed significant interaction effects between condition and order for both task performance and IA. The group receiving active stimulation at visit 1 (Active First) generally improved over time in both cognitive and social cognitive task performance and in social cognitive IA, specifically for emotion recognition ability. In contrast, the group receiving sham stimulation at visit 1 (Sham First) showed no change in performance or IA over time.

Conclusions: Our findings provide preliminary evidence for potential positive, but delayed, effects of tDCS in improving task performance and IA in schizophrenia.

Key words: introspective accuracy; schizophrenia; neuromodulation; transcranial direct current stimulation; social cognition.

Introduction

Introspective accuracy (IA) refers to how well individuals directly evaluate their own abilities and performance.¹ As a component under the umbrella of metacognition and insight, IA centers on the self-perception of one's performance and ability. Meanwhile, clinical insight pertains to how well patients understand their mental illness, and cognitive insight addresses the difficulties individuals face in forming self-concepts or questioning their own beliefs.² Impairments in IA are evidenced by discrepancies between how an individual rates their abilities and their actual performance in those domains, and recent work provides evidence of IA deficits in schizophrenia that span judgments of neurocognitive impairment,^{3–5} social cognitive impairment,^{6,7} and functional abilities.^{8,9} While the majority of individuals with schizophrenia tend to overestimate their abilities, a substantial portion of individuals underestimate them, demonstrating that IA impairments are bidirectional.^{10–12} Regardless of direction, such inaccuracies are likely to have adverse consequences for everyday functioning. Indeed, deficits in both cognitive and social cognitive IA have been found to be more strongly predictive of clinician-rated deficits in everyday functioning than objective performance on neurocognitive or social cognitive tasks.^{10,12} Thus, IA deficits offer a promising new lead in the search for determinants of real-world functional outcomes and represent a novel treatment target.

Recent work demonstrates that IA can be improved via behavioral training^{13,14}; however, these programs are not widely integrated into clinical services and are unlikely to be available to many individuals who receive standard care. Pharmacological efforts are also suboptimal, primarily due to limited evidence of efficacy. For example, acute administration of haloperidol in healthy individuals has shown mixed effects, decreasing overconfidence in errors in 1 study¹⁵ but also decreasing IA more broadly in another.¹⁶ More optimistically, noradrenergic blockade in healthy individuals did significantly improve IA¹⁷; however, this has not been tested in individuals with schizophrenia. The only study to examine patients thus far found that the administration of oxytocin had no impact on IA.¹⁸ A need therefore exists for novel, easy-to-use interventions that demonstrate efficacy in individuals with schizophrenia.

Clear neurobiological underpinnings of IA have recently been identified in healthy individuals that suggest potential neural targets for intervention. Specifically, previous work highlights activation of the right rostrolateral prefrontal cortex (rLPFC), a region adjacent to and just inferior to the dorsolateral prefrontal cortex (DLPFC), as critical for intact IA.¹⁹ The rLPFC is also involved in higher-order cognitive function; however, it demonstrates specificity for metacognition,²⁰ with greater activation during these tasks relative to control tasks.²¹ Importantly, we have recently found reduced activation of the right rLPFC during a social cognitive task of IA in patients with schizophrenia as compared to healthy controls.²² Furthermore, the amount of IA-specific activation within this region was positively correlated with IA ability in healthy controls.²² Together, these findings suggest that increasing activity of the rLPFC in individuals with schizophrenia may result in improved IA, which may then lead to better functional outcomes.

To this end, transcranial direct current stimulation (tDCS) may offer promise. tDCS is a form of noninvasive neurostimulation that applies a constant, low-intensity current directly to the brain using 2 electrodes, denoted as the anode and cathode. Anodal current is thought to increase cortical excitability, with cathodal stimulation decreasing excitability,^{23,24} and within schizophrenia, anodal stimulation of left DLPFC has yielded small positive effects in the cognitive domains of attention and working memory²⁵ as well as significant improvements in cognitive insight,^{26,27} a construct related to IA. While no studies to date have used tDCS to specifically target IA in schizophrenia, previous work has applied anodal tDCS to right DLPFC in healthy older adults and found selective improvements in error awareness compared to anodal stimulation of left DLPFC and cathodal stimulation of right DLPFC.²⁸ Combined with these studies implicating that the PFC is an important target for cognitive function and the aforementioned evidence for the critical role of rLPFC in IA, further investigation into modulating the

functioning of rLPFC and examining its effects on IA in schizophrenia is warranted.

Thus, the current study sought to test the hypothesis that stimulating the right rLPFC via tDCS would improve IA for both cognitive and social cognitive task performance in individuals with schizophrenia. Using a randomized double-blind, sham-controlled crossover design, 40 individuals with a schizophrenia spectrum illness participated in 2 tDCS sessions occurring approximately 1 week apart. Following stimulation at both sessions, participants completed tasks of executive function and emotion recognition that were expanded to also allow for assessments of IA. We hypothesized that (1) active stimulation would result in improved IA relative to sham and (2) cognitive ability indexed by standard task performance would be unaffected by active stimulation. This tentative second hypothesis is driven by previous research showing that while the rLPFC is involved in cognitive functions (eg, reasoning,²⁹ planning,³⁰ abstract thinking³¹), a single session of tDCS in this area may not be sufficient to improve such fundamental functions.³² This pattern of dissociative results would support the specificity of stimulating rLPFC for IA; however, if such specificity is not revealed, it would suggest that the tDCS effects impact not only IA but also cognitive abilities regulated by rLPFC.

Of note, recent experimental trials of tDCS that utilize both active stimulation and a control condition of sham stimulation suggest that the order of stimulation conditions influences stimulation effects. For example, applying tDCS to the DLPFC among patients with internalizing pathologies effectively reduced anxiety, depression, and valence and arousal ratings for negative affects only in participants who received active stimulation first rather than those receiving sham first.³³ Such order effects may be linked to the varying short-term and long-term impacts of neuromodulation, in that the active first condition could enhance long-term synaptic plasticity,³⁴ extending beyond the waiting period and preparing individuals for subsequent tasks that facilitate long-term gains. To examine the possibility of order effects in the current study, we also tested the post hoc, exploratory hypothesis that participants receiving active stimulation first would show greater improvement in IA (Hypothesis 3).

Methods

Participants

Sample size estimation with G*Power 3.1³⁵ yielded a sample size of 34 participants (paired samples *t*-tests, $d_z = 0.5$, power = 0.80, $\alpha = .05$, 2-tailed). Anticipating potential attrition due to the repeated-stimulation nature of the study, we intentionally overrecruited and increased the target to 40 participants. The original sample included 41 participants with schizophrenia or schizoaffective disorder; however, 1 individual was lost to follow-up, resulting in a final sample of 40 individuals.

Table 1. Participant Demographic and Clinical Characteristics

Characteristic	Full sample (<i>n</i> = 40)		Active First (<i>n</i> = 21)		Sham First (<i>n</i> = 19)		P
	<i>N</i>	%	<i>n</i>	%	<i>n</i>	%	
Male	24	60	10	48	14	74	.09
Race							.33
Caucasian	23	57.5	14	67	9	47.4	
African American	16	40	7	33	9	47.4	
Other	1	2.5	0	0	1	5.2	
Ethnicity							.84
Hispanic	12	30	6	29	6	32	
Non-Hispanic	28	70	15	71	13	68	
Diagnosis							.03
Schizophrenia	14	35	4	19	10	53	
Schizoaffective	26	65	17	81	9	47	
Medication type							.25
Typical	4	10	1	5	3	16	
Atypical	28	70	16	76	12	63	
Combination	2	5	0	0	2	10.5	
No antipsychotic	6	15	4	19	2	10.5	
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	39.50	10.36	39.43	11.05	39.58	9.84	.96
Education (years)	12.34	2.41	12.33	2.82	12.34	1.93	.99
Maternal education (years) ^a	12.29	4.00	11.24	4.35	13.28	3.46	.13
Paternal education (years) ^b	11.97	4.85	11.86	4.38	12.07	5.40	.91
WRAT-3	96.73	10.98	98.95	11.58	94.26	10.01	.18
CPZ equivalent	358.43	343.19	271.05	309.91	456.08	361.11	.11
PANSS, Visit 1							
Positive total	17.95	5.83	17.19	5.97	18.79	5.72	.39
Negative total	13.65	4.34	13.52	4.09	13.79	4.70	.85
General total	33.60	9.12	34.43	10.40	32.68	7.64	.55
PANSS, Visit 2							
Positive total	16.68	6.14	16.52	6.62	16.84	5.73	.87
Negative total	13.50	4.10	13.14	4.95	13.89	2.98	.57
General total	32.20	8.04	33.57	8.90	30.68	6.89	.26

^aMaternal education information was missing for 4 individuals in the Active First group and 1 individual in the Sham First group.

^bPaternal education information was missing for 7 individuals in the Active First group and 4 individuals in the Sham First group.

Abbreviations: CPZ, Chlorpromazine; PANSS, Positive and Negative Syndrome Scale; WRAT, Wide Range Achievement Test.

Written informed consent was obtained from all participants prior to any study procedures, and the project was preregistered at ClinicalTrials.gov (NCT03370341). Participants were recruited from Metrocare Services, a nonprofit mental health services provider in Dallas County, TX, and diagnoses were confirmed via clinical interview with the MINI³⁶ and SCID Psychosis Module.³⁷ To be eligible, participants had to be between the ages of 18 and 55, be clinically stable (ie, no hospitalizations for at least 8 weeks) and be on a stable medication regimen for at least 6 weeks, have no history of medical, cardiac, or neurological illness that could affect brain function (eg, stroke, seizures, etc.), and have no sensory limitations that would interfere with assessment. Participants with histories of pervasive developmental disorder, estimated IQ < 70 as measured by the Wide Range Achievement Test–Reading recognition subtest 3 (WRAT-3),³⁸ or common contraindications for tDCS (eg, implanted

devices, pregnancy)³⁹ were excluded. Demographic and clinical characteristics of the study sample are presented in [Table 1](#).

Procedures

Participants completed 2 visits, approximately 1 week apart (Mean_{days} = 8.15, SD_{days} = 3.62) and were randomly assigned to receive either active neurostimulation at visit 1 followed by sham stimulation at visit 2 or vice versa. Diagnostic interviews were conducted only at visit 1, but symptom and cognitive assessments were administered at both visits before stimulation (see [Figure 1](#) for the whole study procedure).

tDCS was delivered via neuroConn's programmable Direct Current Stimulator Plus (model-no: 0021) that allowed pre-programming of the condition to render both participants and research assistants blind to the study

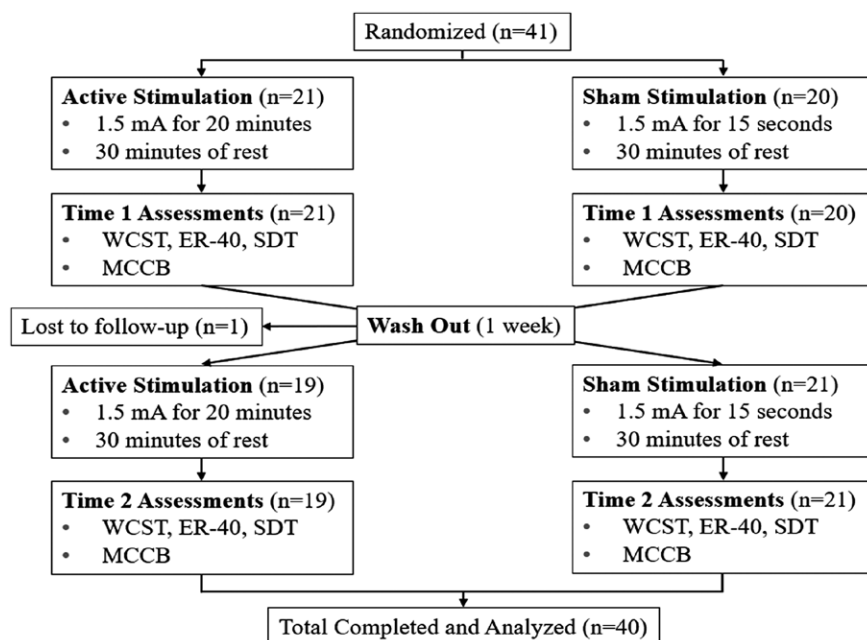


Figure 1. The Flowchart of the Study Design. WCST, Wisconsin Card Sorting Task; ER-40, the Penn Emotion Recognition Test; SDT, the signal detection theory task; MCCB, The MATRICS Consensus Cognitive Battery.

condition. Post-session inquiries regarding the suspected condition indicated that both participants and researchers (those conducting the stimulation and those conducting assessments) were unaware of the stimulation condition (58.75% and 55%, respectively), indicating that blinding procedures were successful. The Active First (64%) and Sham First (53%) groups did not differ significantly in their accuracy of guessing the condition [$\chi^2(1) = 0.75$, $P = .386$].

Active stimulation involved 20 minutes of neurostimulation at 1.5 mA as used in our previous protocol,^{40,41} with the anode placed at the right rIPFC (Montreal Neurological Institute coordinates: 36, 44, 28), and the cathode placed extracortically on the left bicep. Direct current was delivered via a saline-soaked pair of rectangular conductive rubber electrodes. Both electrodes were 5 cm × 7 cm in size (35 cm²), producing a current density of 0.0429 mA/cm². Electrodes were identically placed for the sham condition; however, stimulation was limited to 45 seconds in total, with 15 seconds of gradual stimulation leading up to 15 seconds of full stimulation, followed by 15 seconds of gradual ramping down. The parameters selected for sham stimulation align with those used in our previous work⁴⁰ and were chosen based on literature indicating that the sensations perceived on the skin (eg, tingling) typically diminish within the first 30 seconds of tDCS.⁴² The assigned neurostimulation procedure was then administered for a total of 20 minutes. Stimulation was followed by a 30-minute waiting period where the participant browsed through magazines quietly. All patients successfully underwent the brain stimulation procedure and experienced no adverse effects.

After the waiting period, participants completed the Wisconsin Card Sorting Task (WCST), the Penn Emotion Recognition Test (ER-40), and a novel emotion recognition task based on the signal detection theory (SDT) framework in a counterbalanced order as detailed below.

Measures

Symptom Severity. This was assessed with the Positive and Negative Syndrome Scale.⁴³

Neurocognitive IA: WCST. Participants completed a computerized version of the WCST⁴⁴ that was modified to allow the measurement of IA (Figure S1A) and that has previously been used to demonstrate IA impairments in schizophrenia and bipolar disorder.⁴⁵ As in the original version, participants were instructed to match 64 individually presented cards to 1 of 4 stimulus cards; however, immediately after making each match, participants rated their confidence in the correctness of their response on a scale from 1 to 5, with higher ratings indicating greater confidence. Feedback regarding the actual correctness of the response was then provided, followed by the next card. Performance was indexed as percent correct.

Social Cognitive IA: ER-40 and SDT task. The well-validated ER-40⁴⁶ was modified to assess IA in an identical manner to the WCST (Figure S1B). Participants viewed 40 individual images of faces and identified which of 5 emotion choices (happy, sad, anger, fear, or no emotion) was displayed on each face. After each emotion

choice, participants rated their confidence in their response from 1 to 5, and feedback was then provided. This approach to assessing IA in both the WCST and ER-40 was modeled directly from Fleming and colleagues,¹⁹ and this version of the ER-40 was identical to that used in our previous imaging paper.²² Performance was indexed as percent correct.

Based on the recommendations of Maniscalco and Lau,⁴⁶ social cognitive IA was also assessed with a novel task that utilizes the SDT framework to assess emotion recognition ability (Figure S1C). Participants viewed 3 different blocks of 60 emotional faces taken from the publicly available University of Pennsylvania Brain Behavior Lab 2D Facial Emotion Stimuli. Emotions included happiness, sadness, fear, anger, and neutral/no emotion. For each block, a target emotion (ie, happy, sad, or anger) was identified, and participants viewed each face and indicated whether the face was or was not displaying the target emotion. Following each decision, participants rated their confidence in the accuracy of that decision on a 4-point scale from “probably wrong” to “probably right.” Each face was shown for 50 ms, and participants could take as much time as needed to respond. There were 18 faces within each block showing the target emotion, with the other 42 faces being distributed as evenly as possible across the 4 other emotion categories. This task was modeled by Tsoi and colleagues⁴⁷ and performance was indexed as *d*-prime (*d'*).

Basic Cognitive Function. The MATRICS Consensus Cognitive Battery⁴⁸ was also administered as a control for the potential tDCS effects, which measures processing speed (Trail Making Test: Part A, Symbol Coding, Animal Naming), working memory (Letter-Number Span), and verbal learning (Hopkin's Verbal Learning Test-Revised; HVLT).

Statistical Analyses

Calculation of IA. For both WCST and ER-40, IA was calculated using Fleming and Lau's⁴⁹ type 2 receiver-operating characteristic (ROC) curve and computing the area under this curve (AUROC2). AUROC2 provides an index of IA that is theoretically free from bias in the overall tendency to report high or low confidence, and as with traditional ROC analyses, higher values indicate better sensitivity, or in this case, IA. For the SDT task, IA was calculated as meta-*d'*, an index of the sensitivity with which one differentiates between their own correct and incorrect judgments that are free from response bias,⁵⁰ and again, higher values indicate better IA.

Analyses for dependent variables. We have 3 dependent variables in this study: actual performance, IA, and confidence ratings. As initially planned, a paired samples

t-test on active versus sham was performed for each task (ie, WCST, ER-40, SDT) and each dependent variable. Additionally, to test the possible effect of stimulation order, repeated-measures ANOVAs were performed as additional analyses for each task and each dependent variable, with condition (active vs. sham) as the within-subject factor and stimulation order (Active First vs. Sham First) as the between-subject factor. Paired samples *t*-tests were performed following significant interaction effects. Note that for the SDT task, results based on the average performance/IA/confidence ratings across the 3 emotions are presented here (see [Supplementary Materials](#) for findings regarding each individual emotion).

Results

Demographics and Symptom Severity

As shown in [Table 1](#), the Active First group and Sham First group did not differ in most demographic variables and clinical characteristics (eg, antipsychotics dosage), except for diagnosis. The Active First group had a higher proportion of participants diagnosed with schizoaffective disorder (81%) compared to the Sham First group (47%).

Results of Primary Analyses

tDCS Effects on Task Performance. Paired samples *t*-test revealed that participants did not differ significantly in performance for WCST [$t(39) = -0.91$, $P = .371$], ER-40 [$t(39) = -0.87$, $P = .390$], or the SDT task [$t(39) = -1.15$, $P = .260$] between the active and sham conditions.

tDCS Effects on IA. Again, there were nonsignificant differences between the active and sham conditions in IA for WCST [$t(39) = 0.582$, $P = .564$], ER-40 [$t(39) = 0.89$, $P = .377$], and the SDT task [$t(39) = -1.94$, $P = .060$].

tDCS Effects on Confidence Rating. Participants reported significantly higher confidence ratings for WCST after active stimulation (Mean_{confidence} = 3.98, SD_{confidence} = 0.72) compared to sham [Mean_{confidence} = 3.71, SD_{confidence} = 0.88; $t(39) = 2.25$, $P = .030$, $d_z = 0.34$]. Their confidence rating did not differ between the active and sham visits for ER-40 [$t(39) = 1.51$, $P = .138$] or the SDT task [$t(39) = -0.46$, $P = .648$].

Results of Post Hoc Analyses Exploring Stimulation Order

tDCS Effects on Task Performance. The interaction term between condition and stimulation order was significant for WCST performance [$F(1, 38) = 4.19$, $P = .048$, $\eta_p^2 = 0.10$; [Figure 2A](#)]. Post hoc sensitivity power analysis revealed an effect size $f = 0.184$, suggesting a small-to-medium estimated effect. Specifically, the Sham First

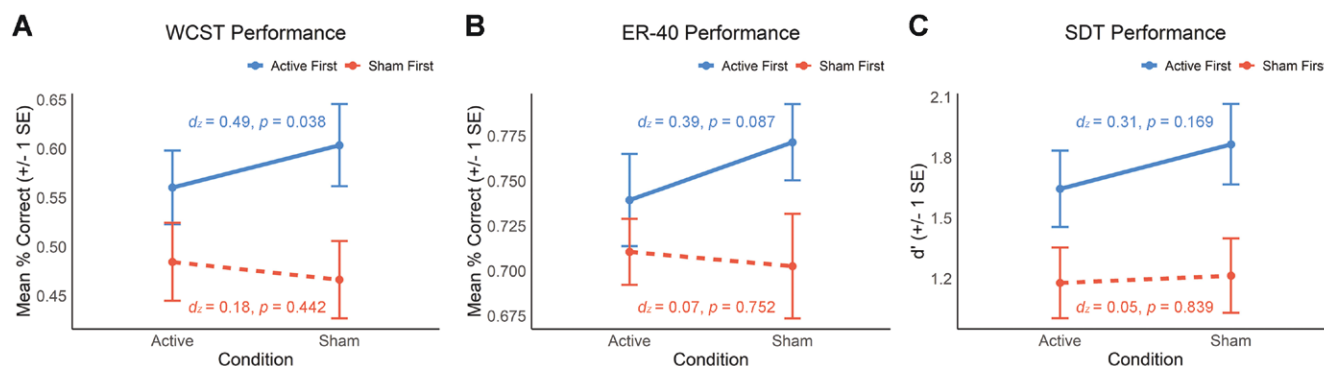


Figure 2. The tDCS Effects on Task Performance. WCST, Wisconsin Card Sorting Task; ER-40, the Penn Emotion Recognition Test; SDT, the signal detection theory task.

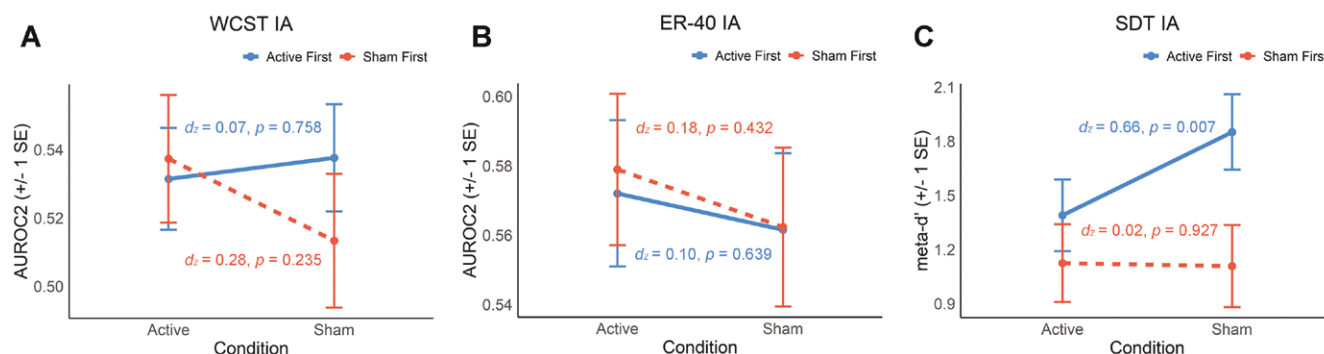


Figure 3. The tDCS Effects on IA. WCST, Wisconsin Card Sorting Task; ER-40, the Penn Emotion Recognition Test; SDT, the signal detection theory task.

group showed no difference in WCST performance across 2 visits [Visit 1: Mean_{correct percentage} = 0.47, SD_{correct percentage} = 0.18; Visit 2: Mean_{correct percentage} = 0.48, SD_{correct percentage} = 0.17; $t(18) = 0.79$, $P = .442$, $d_z = 0.18$], but the Active First group performed better at their second visit [Visit 1: Mean_{correct percentage} = 0.56, SD_{correct percentage} = 0.17; Visit 2: Mean_{correct percentage} = 0.60, SD_{correct percentage} = 0.18; $t(20) = -2.22$, $P = .038$, $d_z = 0.49$], which was actually the sham visit. Notably, this better performance is not likely due to only practice effects because the Sham First group did not improve. Neither the main effect of condition ($P = .408$) nor stimulation order ($P = .056$) was significant.

No interaction effects or main effects were significant for ER-40 ($P_s > .113$; **Figure 2B**). However, for the SDT task, we found a significant main effect of stimulation order [$F(1, 38) = 5.52$, $P = .024$, $\eta_p^2 = 0.13$; **Figure 2C**], such that the Active First group (Mean _{d'} = 1.75, SD _{d'} = 0.85) generally had better SDT task performance than the Sham First group (Mean _{d'} = 1.20, SD _{d'} = 0.63).

tDCS Effects on IA. No interaction effects or main effects were significant for IA on WCST ($P_s > .287$; **Figure 3A**) or ER-40 ($P_s > .378$; **Figure 3B**). However, for the SDT task, the interaction term between condition and stimulation order was significant [$F(1, 38) = 4.21$, $P = .047$, η_p^2

= 0.10; **Figure 3C**]. Post hoc sensitivity power analysis revealed an effect size $f = 0.269$, suggesting a medium estimated effect. The Sham First group showed no difference in meta- d' across the 2 visits [Visit 1: Mean_{meta- d'} = 1.11, SD_{meta- d'} = 1.02; Visit 2: Mean_{meta- d'} = 1.12, SD_{meta- d'} = 1.01; $t(18) = 0.09$, $P = .927$, $d_z = 0.02$], whereas the Active First group showed increased meta- d' at their second/sham visit relative to their first visit [Visit 1: Mean_{meta- d'} = 1.39, SD_{meta- d'} = 0.82; Visit 2: Mean_{meta- d'} = 1.85, SD_{meta- d'} = 0.96; $t(20) = -3.02$, $p = .007$, $d_z = 0.66$]. The main effects of condition ($P = .063$) and stimulation order ($P = .077$) were nonsignificant.

tDCS Effects on Confidence Rating. For WCST, a significant main effect of condition was found for confidence rating [$F(1, 38) = 4.93$, $P = .032$, $\eta_p^2 = 0.12$; **Figure 4A**], such that individuals were more confident in the correctness of their responses on the WCST after active stimulation (Mean_{confidence} = 3.98, SD_{confidence} = 0.72) compared to the sham procedure (Mean_{confidence} = 3.71, SD_{confidence} = 0.88).

No interaction effects or main effects were significant for confidence ratings on ER-40 ($P_s > .115$; **Figure 4B**). The interaction effect between condition and stimulation order was significant again for confidence ratings on the SDT task [$F(1, 38) = 8.08$, $P = .007$,

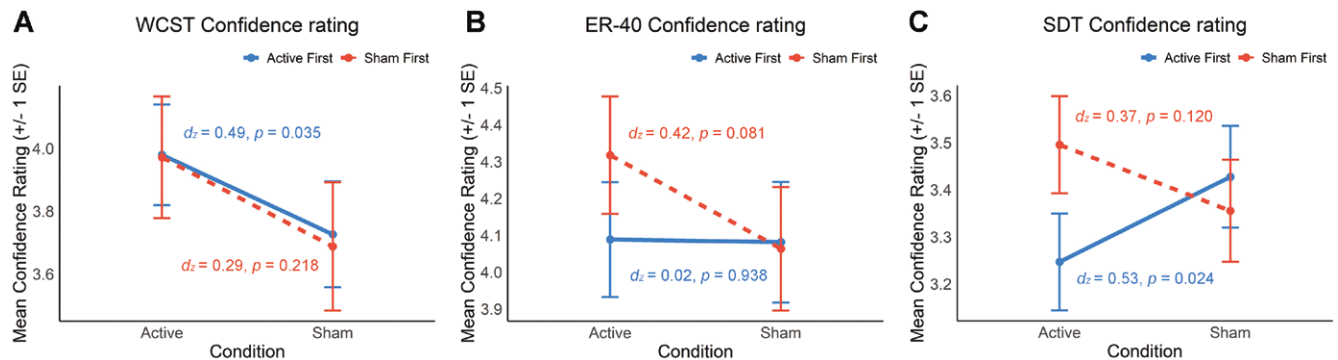


Figure 4. The tDCS Effects on Confidence Rating. WCST, Wisconsin Card Sorting Task; ER-40, the Penn Emotion Recognition Test; SDT, the signal detection theory task.

$\eta_p^2 = 0.18$; **Figure 4C**]. Post hoc sensitivity power analysis revealed an effect size $f = 0.284$, suggesting a medium estimated effect. The Sham First group showed no difference in confidence ratings across the 2 visits [Visit 1: Mean_{confidence} = 3.36, SD_{confidence} = 0.43; Visit 2: Mean_{confidence} = 3.50, SD_{confidence} = 0.42; $t(18) = 1.63$, $P = .120$, $d_z = 0.37$], but the Active First group reported higher confidence ratings at their second/sham visit [Visit 1: Mean_{confidence} = 3.25, SD_{confidence} = 0.51; Visit 2: Mean_{confidence} = 3.43, SD_{confidence} = 0.21; $t(20) = -2.44$, $P = .024$, $d_z = 0.53$].

For the nonsignificant interaction effects across the 3 tasks, post hoc sensitivity power analysis revealed that the effect size f ranges from 0.031 to 0.217, indicating small-to-medium estimated effects.

Discussion

Using a double-blind, sham-controlled crossover design, we found evidence supporting our Hypothesis 1, in that improvements in IA for emotion recognition ability were observed. These enhancements were measured by a rigorous task that utilized the SDT framework to control for potential response bias when estimating IA. Regarding our Hypothesis 2, tDCS-related improvements in cognitive performance were revealed, indicating that the effects of tDCS on the rLPFC may not be limited to IA alone; they could also affect cognitive ability regulated by this area. Intriguingly, in line with our Hypothesis 3, the improvements in IA were all observed in the group of patients who received active stimulation followed by sham stimulation (as opposed to the opposite order) and therefore highlight potentially delayed brain modulation effects. The current study was designed in response to the need for noninvasive and easily administered interventions aimed at improving IA in schizophrenia. To our best knowledge, this is the first study systematically investigating tDCS effects to the right rLPFC on cognitive and social cognitive IA among patients with schizophrenia. It is worth noting that while some forms of IA (eg, discrepancies between the ratings from patients,

clinicians, and objective evaluations) might be available in previous datasets, the current work may represent the first endeavor explicitly designed to target this specific construct a priori. Therefore, this work may lay a foundation for more future work to systematically investigate this field. Interpretations and implications of the current findings are further discussed below.

Improved IA and Confidence Rating in the SDT Task

In line with our hypothesis, the Active First group showed improved IA and increased confidence ratings in their ability to recognize emotions during their second visit, whereas the Sham First group did not demonstrate any significant changes between their 2 visits. This improvement is unlikely to be attributed to practice effects as the Sham First group failed to show similar improvements at their second visit. Therefore, we interpret this effect as a delayed improvement resulting from the tDCS protocol. These findings are compatible with previous neuroimaging studies associating rLPFC with metacognitive ability (the same as IA in the current study)¹⁹ and metacognition,²⁰ as well as our previous work revealing the crucial role of the rLPFC-related networks in social cognitive IA (ie, emotion recognition).²² Our current findings also speak to earlier work reporting that improved metacognitive awareness, achieved through behavioral training, was reflected in the real-time fMRI signal of the rLPFC.⁵¹ Although the rLPFC is key in IA, recent studies have indicated the presence of a related neural network contributing to meta-awareness (eg, dorsal anterior cingulate cortex, superior frontal gyrus, insular, etc.).^{21,22} Therefore, it is possible that the neuromodulation procedure used here activated and regulated the entire IA-related network. Evidence from computational modeling⁵² and empirical work from the language field⁵³ supports the notion that stimulating 1 hub of a network may result in changes across the full network. Future research could benefit from integrating the current tDCS procedure with imaging approaches, particularly fMRI and/or EEG, to map the pathways of the electrical currents

and to identify specific brain regions influenced by this neuromodulation.

Combined with the null effect of tDCS on neurocognitive IA as measured by WCST in this work, the present findings lend support to the notion that IA impairments are domain-specific,^{21,54} and that the rIPFC may be more specifically involved in social cognitive IA rather than in neurocognitive IA. Given the extensive scope of social cognition (eg, Theory of Mind, attributional style, etc.),⁵⁵ further research is warranted to determine if the observed stimulation effects can be generalized across various social cognitive areas. Additionally, it would be informative to explore whether improved IA in social cognition can lead to broader enhancements in interpersonal functioning.

Intriguingly, the tDCS effects on emotion recognition IA were observed exclusively in the SDT task and not in the ER-40, suggesting that the SDT task may be more sensitive at detecting changes related to tDCS compared to the ER-40. This increased sensitivity might be due to the more effective methods of measuring metacognition (meta-*d'*) in the SDT task. Meta-*d'* serves as an indicator of how well a person can distinguish between their correct and incorrect judgments, thereby diminishing their personal response bias (ie, one's own criteria for producing different response levels).⁴⁹ This metric is considered the most effective one for measuring metacognitive sensitivity and has become increasingly popular in recent years.⁴⁹ Another potential factor contributing to these discrepant patterns may be the different cognitive processes underlying the ER-40 and SDT tasks. In ER-40, participants determine which emotion the character is expressing by selecting 1 of 5 options. In contrast, the SDT task involves simpler judgments, as participants only need to decide whether the character is displaying the target emotion (yes or no). Thus, future research should carefully consider measurement approaches.

Improved Performance in WCST

In contrast to the tentative hypothesis that tDCS would have no impact on task performance, the Active First group performed better on the WCST over time, whereas the Sham First group displayed no significant change in performance across 2 visits. These patterns again support the overall interpretation that tDCS to rIPFC shows delayed positive effects. Indeed, the rIPFC has been implicated in processes related to cognitive function, including memory retrieval,⁵⁰ planning,³⁰ reasoning,²⁹ uncertainty-driven exploration,⁵⁶ and the development of abstract thinking.³¹ As such, the present findings are actually compatible with previous tDCS research stimulating the PFC that revealed improvements in working memory and attention in individuals with schizophrenia.^{25,57} These findings may suggest that by improving IA, the current stimulation protocol also enhances task performance on

the WCST, probably because of the similarities between WCST and IA. Given the WCST is a complex task requiring higher-order executive functions (eg, planning, set changing capacity)⁴⁴ that may tap into constructs similar to IA, further research is necessary to systematically determine to what extent they overlap via behavioral and neuroimaging approaches.

Notably, the same pattern of results was found for the 2 emotion recognition tasks. While the improvements over time in the Active First group did not reach statistical significance for these tasks, the results are consistent with a delayed positive effect of tDCS on emotion recognition ability and should be further investigated in future work.

The Potential Delayed Effects of tDCS

The observation that all tDCS effects were consistently found for individuals from the Active First group warrants attention. In line with McAleer's work,³³ order effects also emerged in the current study, which may suggest a potential delayed stimulation effect. As most tDCS work typically anticipates short-term effects, this potential delayed effect might reinforce an intriguing aspect to the field of neuromodulation, which has been documented in several previous studies, particularly in reducing depressive symptoms. For example, an early study applying tDCS to the DLPFC twice daily for 5 consecutive days found a substantial and progressive reduction in depressive symptoms in patients with bipolar disorders, not just after 5 sessions, but also at 1-week and 1-month follow-ups.⁵⁸ These findings suggest that tDCS effects might escalate and can be tracked for up to a month after the procedure. Similarly, another tDCS study followed patients with mood disorders for up to 3 months, and although reductions in depressive symptoms were present after 1 week, 1 month, and 3 months, the most significant decrease was observed at the 1-week assessment, where 95.6% of depressive symptoms were reduced.⁵⁹

More compelling evidence of delayed effects can be observed in a recent work stimulating the primary motor cortex aiming to reduce subjective pain in patients with spinal cord injury. In their Phase I trial, participants did not experience any alterations in pain feelings after the tDCS protocol; however, they reported significantly lower pain ratings 1 week after the brain modulation sessions.⁶⁰ The delayed effects have also been observed in works involving healthy populations. For example, 2 recent studies have found prominent tDCS effects on memory 7 days after the stimulation session.^{41,61}

Therefore, when considering these findings in conjunction with previous studies, it raises the possibility that the delayed effects of tDCS may be attributed to long-term synaptic plasticity³⁴ and even meta-plasticity⁶² rather than merely transient changes in cortical excitability. It is possible that the stimulation alone does not drive the observed effects; rather, the active first condition might

have enhanced plasticity beyond the waiting period and primed individuals for subsequent social cognitive tasks that facilitate learning and long-term gains. In other words, completing the tasks after active stimulation may have created a learning opportunity that was then either partially or fully demonstrated at the second task administration, thereby resulting in better performance and improved IA at the second visit. Future research should continue to investigate the robustness of this delayed tDCS impact in treating IA in schizophrenia. This could be achieved by designing delayed-start trials with three or more visits (eg, active/sham/active, sham/active/sham, etc.), and structuring and comparing visits with versus without post-stimulation social cognitive tasks.

Limitations and Future Directions

In addition to the aforementioned future directions regarding the mechanisms and applicable domains of neuromodulation effects, several other limitations should also be considered in future research. First, although participants were generally unaware of the stimulation condition, it is possible that expectancy effects still exist and may have affected their performance. Future research may wish to explore the potential role of expectancy effects in neuromodulation protocols targeting IA. Second, while the tDCS machine automatically stops when impedance exceeds 10 k Ω to ensure safety and effective current delivery, real-time impedance during stimulation was not recorded. Therefore, we cannot confirm whether the intended amount of current was consistently delivered to each individual. Third, a more detailed examination of the optimal parameters for the current protocol is warranted. Considering that existing research links enhanced outcomes to repeated-stimulation sessions, it is possible that the current protocol might yield more prominent effects right after the stimulation if administered repeatedly (eg, twice daily) over several consecutive days. Fourth, future research should explore integrating the current tDCS protocol with behavioral training approaches, such as metacognitive training⁶³ or metacognitive remediation,⁶⁴ to enhance treatment outcomes for IA. This combination of tDCS with behavioral training has already shown additive benefits for improving attention and working memory in healthy participants⁶⁵ and may be similarly beneficial for IA.

Finally, given that the Active First and Sham First groups differed in diagnosis, this may have influenced our findings. However, results from post hoc repeated-measures ANOVAs on performance, IA, and confidence rating, with condition (active vs. sham) as the within-subject factor and diagnosis (schizophrenia vs. schizoaffective disorder) as the between-subject factor revealed only a significant main effect of diagnosis on WCST performance [$F(1, 38) = 6.48, P = .015, \eta_p^2 = 0.15$], with individuals diagnosed with schizoaffective disorder generally performing better on the WCST than those

with schizophrenia. No other significant findings were revealed for performance on ER-40 or SDT, and perhaps most importantly, there were no significant effects on IA or confidence ratings on any of the 3 tasks. Thus, it seems unlikely that diagnostic differences between groups played a primary role in the positive effects seen here, and particularly those found for IA and confidence; however, this cannot be definitively ruled out, and our results should be considered with this potential caveat in mind.

Conclusions

This project is the first to systematically characterize tDCS effects of rLPFC for improving social cognitive IA in a sizeable sample of patients with schizophrenia. The current study demonstrated potentially delayed positive effects of tDCS for enhancing cognitive performance and social cognitive IA. Subsequent work is warranted to identify clinically relevant or real-world functional correlates of the current tDCS protocol and to optimize the stimulation montage to further support its promising utility as a treatment for schizophrenia.

Supplementary material

Supplementary material is available at [https://academic.oup.com/schizophreniabulletin](https://academic.oup.com/schizophreniabulletin/advance-article/doi/10.1093/schul/sba014/8046652).

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Author contributions

L.F.: Data curation, Formal analysis, Validation, Visualization, Methodology, Writing—original draft, Writing—review & editing. E.B.: Data curation, Project administration. H.K.: Data curation, Project administration. C.S.: Data curation, Project administration. S.V.: Methodology, Resources, Supervision. A.E.P.: Conceptualization, Resources, Supervision, Writing—original draft, Writing—review & editing, Funding acquisition.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could

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Data availability

The data for this study are available upon request to the corresponding author.

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