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The limited effect of neural stimulation on visual attention and social cognition in individuals with schizophrenia

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ABSTRACT

Background: Research demonstrates a relationship between faulty visual attention and poorer social cognition in schizophrenia. One potential explanatory model suggests abnormal neuromodulation in specific neural networks may result in reduced attention to socially important cues, leading to poorer understanding of another's emotional state or intentions.
Objective: The current study experimentally manipulated neural networks using tDCS to examine this potential causal mechanism. The primary aim was to determine whether stimulation to the right temporoparietal junction (rTPJ) improves visual attention, and secondary aims were to determine whether 1) stimulation improves social cognitive performance and 2) visual attention moderates this improved performance.
Method: Using a double-blind crossover design, 69 individuals with schizophrenia underwent both active and sham stimulation to either the rTPJ of the ventral attention network (n = 36) or the dorsomedial prefrontal cortex of the social brain network (dmPFC; n = 33). Following stimulation, participants completed tasks assessing emotion recognition and mentalizing. Concurrent eye tracking assessed visual attention, measuring proportion of time spent attending to areas of interest.
Results: For emotion recognition, stimulation failed to impact either visual attention or social cognitive task accuracy. Similarly, neurostimulation failed to affect visual attention on the mentalizing task. However, exploratory analyses demonstrated that mentalizing accuracy significantly improved after stimulation to the active comparator, dmPFC, with no improvement after stimulation to rTPJ.
Conclusion: Results demonstrate limited effect of a single stimulation session on visual attention and emotion recognition accuracy but provide initial support for an alternate neural mechanism for mentalizing, highlighting the importance of executive functions over visual attention.

1. Introduction

Social cognition, or the ability to recognize and interpret social information, is a distinct area of dysfunction in schizophrenia (Green et al., 2019; Savla et al., 2013) related to poorer functional outcomes (Halverson et al., 2019). The etiology of social cognitive deficits is unclear but may have a neural basis rooted in both hypoactivation of key nodes of social cognitive networks (Sugranyes et al., 2011; Vucurovic et al., 2020) and reduced functional connectivity within these networks (e.g., (Bitsch et al., 2019). Faulty connectivity within and between neural networks may also disrupt simple perceptual and cognitive processes that likely contribute to successful social cognition and the development of adaptive social behaviors (Green et al., 2019).

One potentially important perceptual process is visual attention. Individuals with schizophrenia demonstrate atypical visual behaviors (Beedie et al., 2011) that may create additional challenges in social situations, attending less to salient social information like facial features (Gordon et al., 1992; Loughland et al., 2002; Nikolaides et al., 2016; Sasson et al., 2016; Williams et al., 2003). Further, aberrant gaze patterns correlate with mentalizing ability (Roux et al., 2014), as more normative visual attention relates to better performance (Simpson et al., 2013). Established cross-sectional correlations between visual attention and social cognition might be explained through cascading deficits, i.e., lower-level deficits preventing appropriate and adaptive evaluation of

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social cues.

In examining neural correlates of social cognition and visual attention, the temporoparietal junction (TPJ) stands out as a potentially important area, with associations to ventral attention (Vossel et al., 2014) and social brain (Mitchell, 2008) networks, as well as additional connections to lower order visual areas (Donaldson et al., 2015). This places the TPJ at the nexus of several streams (Carter and Huettel, 2013), thus being conceptualized as a neural "circuit breaker" for ongoing cognitive activity, important in halting sustained attention and reorienting attention to unexpected but relevant, external stimuli (Corbetta et al., 2008; Donaldson et al., 2015). Additionally, the TPJ may integrate new information into contextual understanding of situations (Geng and Vossel, 2013). Individuals with schizophrenia display reduced activation in this region in both simple visual tasks (Jimenez et al., 2016) as well as social tasks such as detecting biological motion (Hashimoto et al., 2014), and fail to increase activation of the broader ventral attention network when viewing social images compared to healthy controls (Bjorkquist and Herbener, 2013). These results suggest that reduced activation of the TPJ within individuals with schizophrenia may lead to aberrant visual attention, and specifically a failure to attend to salient visual stimuli, that may then prevent accurate social cognitive processes.

The current study examined this proposed mechanistic model by experimentally increasing activity within the TPJ via transcranial direct current stimulation (tDCS) which allows for noninvasive excitation (anodal) or depression (cathodal) of neural responses through the administration of low-level electrical signals into targeted cortical areas (Nitsche and Paulus, 2000; Priori et al., 2009). In contrast to jolting the entire system artificially, tDCS lowers thresholds for activation to allow signals to freely propagate as needed within the network. In this way, tDCS allows for direct examination of behaviors that result from potentially under activated regions or networks (Keeser et al., 2011; Meinzer et al., 2012).

Use of tDCS on healthy individuals has produced limited, but promising results highlighting the role of the TPJ in social cognition. Cathodal stimulation of the TPJ, lowering the probability of neural firing, results in decreased accuracy in mentalizing and empathy tasks (Mai et al., 2016), as well as decreased intensity of empathic responses, specifically perceiving pain of others (Coll et al., 2017). Anodal stimulation of the TPJ, aimed at increasing the probability of neural firing, led to improved control over imitating and taking the visual perspective of others (Martin et al., 2019; Santiesteban et al., 2012, 2015), as well as improved lie detection (Sellaro et al., 2016).

Interestingly though, anodal stimulation has been ineffective in improving recognition of more complex emotional cues, like expressions of pain, or higher-level aspects of social understanding such as ToM in healthy individuals (Coll et al., 2017; Mai et al., 2016; Santiesteban et al., 2015). As acknowledged by each of these researchers, failures to improve social cognition and social perception through anodal stimulation in healthy individuals may not be a failure of neurostimulation, but instead could be due to healthy individuals performing well on these tasks independent of stimulation. As many social cognitive tasks are designed to detect deficits in a clinical population, this may limit the ability to measure improvement in a healthy population.

Within schizophrenia research, few studies have targeted social cognition using tDCS interventions. Rassovsky et al. (2015) used tDCS to bilaterally stimulate DLPFC and showed a somewhat limited effect, improving emotion recognition on static faces, but not more complex ToM tasks. Dunn et al. (2016) reported concurrent EEG data for the same dataset, noting modulation of the mismatch negativity (MMN) signal, a neural marker of attentional response to changing stimuli. In follow-up to their preliminary study discussed above (Rassovsky et al., 2015), Rassovsky et al. (2018) noted that a single session of bilateral stimulation to the DLPFC may not have been sufficient to impact their measures of neurocognition, social cognition, and neurophysiological (i.e., EEG) responses, despite having previous success with a similar montage. These studies examining the efficacy of tDCS on social cognition within schizophrenia have focused on activating top-down executive control over these processes, instead of targeting other mechanism(s), namely bottom-up perceptual processes, that may drive observed deficits. It may be that automatic processes, such as visual attention and eye gaze are more amenable to single session stimulation than complex social cognitive processes. This study draws upon these discrete but converging lines of research to examine the TPJ's role in reorienting visual attention as a mechanism for social cognitive performance.

The primary aim of this study was to examine whether anodal tDCS over the TPJ in individuals with schizophrenia would increase the proportion of time spent attending to salient social stimuli as measured via eye-tracking. As visual attention may be lateralized to the right side (Horiguchi et al., 2016; Vossel et al., 2014), we applied neurostimulation to the right TPJ (i.e., anodal tDCS to rTPJ) and utilized eye tracking technology to directly assess how neural activity impacts visual attention to visual stimuli and subsequent social cognitive performance. In doing so, a key consideration was to address whether observed changes were specific to stimulation of the rTPJ, and thus, we used an alternate stimulation site as a comparator. The dorsal medial prefrontal cortex (dmPFC) was determined to be ideal, as it has a principal role within the social brain network (Ferrari et al., 2016), but, unlike the TPJ, should not directly be involved in visual attention. To limit practice effects, we randomly assigned matched pairs of participants to receive active and sham conditions to either the rTPJ or dmPFC and used stimulation site as a between subjects factor. Comparisons across stimulation site should further strengthen claims of dissociable effects of improved visual attention from stimulation to specific neural regions.

A secondary aim of this study was to assess performance on social cognitive tasks and to determine: 1) whether stimulation results in improved performance, and 2) whether increases in visual attention to socially and contextually relevant regions mediate this effect. In order to support the overarching idea that abnormal visual attention stems from dysregulated neural systems, we hypothesized that participants would better regulate eye movements (i.e. show a higher percentage of fixations in designated areas of interest) after anodal stimulation of the rTPJ relative to sham, and compared to either active or sham stimulation of the dmPFC. We also anticipated that participants would demonstrate improved social cognitive performance (i.e. increased accuracy) after anodal stimulation of the rTPJ relative to sham, and compared to either active or sham stimulation of the dmPFC. Finally, we predicted that improved performance on social cognitive tasks after anodal stimulation of the rTPJ would be mediated by improved visual attention (i.e. the proportion of fixations within designated areas of interest). Mediation would need to be specific to stimulation of the rTPJ, and any potential improvements in social cognitive performance after stimulation of the dmPFC would not be expected to show the same mediation effect.

2. Methods

2.1. Registration of study

This study was registered to clinicaltrials.gov in March 2019 prior to data collection. Identifier: NCT03880227.

2.2. Participants

Eighty-one participants diagnosed with schizophrenia spectrum disorders, aged 18–60, were recruited. Six individuals were removed due to incomplete data ($n = 4$) or poor data quality ($n = 2$), and one withdrew due to an adverse event deemed not study related. At enrollment, participants were matched in pairs based upon key demographic factors (i.e., age, race, gender, and education), and pairs were randomly assigned to stimulation condition, resulting in separate rTPJ ($n = 37$) and dmPFC ($n = 37$) stimulation groups. Matching groups based on these key factors should mitigate any known differential effects of tDCS

(i.e., gender or age-related effects) between the groups. Five subjects were later identified as outliers (±3 SD on three or more eye-tracking and/or behavioral measures), resulting in final sample of 36 participants in the rTPJ stimulation group and 33 in the dmPFC stimulation group. Supplemental materials provide a priori power analyses, participant exclusion criteria, and results with outliers included.

2.3. Design

Participants completed two visits (average 8.7 days between visits). Demographic information, medication dosing, and premorbid IQ (*Wide Range Achievement Test*, WRAT (Wilkinson and Wide Range, 1993); were assessed at the initial visit, as well as confirmation of psychiatric diagnoses (*Mini International Neuropsychiatric Interview* (Sheehan et al., 1998); and *Structured Clinical Interview for DSM Disorders - Psychosis Module*; (First et al., 2007). Symptom severity was assessed at both visits via the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987). No participants reported a change in antipsychotic medications between the two visits, and written informed consent was obtained prior to any study specific tasks.

2.3.1. Stimulation procedure

Following symptom assessment, subjects were administered assigned neurostimulation procedure using neuroConn's programable Direct Current stimulator. Electrodes were affixed to the subject's head to target the designated stimulation location according to the international 10–20 EEG placement system with Modified Combinatorial Nomenclature. For those assigned to the rTPJ region, the anode was placed between P6 and CP6. The cathode was placed contralaterally on the left bicep to draw the current through the midline and increase the likelihood of full stimulation of targeted region. For those assigned to the dmPFC location, the anode was placed at AFz, with the cathode placed on the opposite side of the skull, approximately 1 cm below Iz. This location was favored to ensure current flows through the targeted dmPFC region.

Active and sham stimulation were counterbalanced for all participants, and NeuroConn machine's preprogrammed "study mode" administered stimulation condition in a double-blinded fashion. Active stimulation consisted of 2 mA for 20 min (15s ramp up and ramp down). In the pre-programmed sham condition, direct current was only administered for 30 s, but the machine performed impedance control checks during the remainder of the 20-min assessment so neither participant nor administrator were aware of which condition the machine was administering. Following neurostimulation, participants were asked to wait quietly for 30 min to allow tDCS effects to work through the neural network.

2.3.2. Post-stimulation assessments

Following stimulation, participants completed a series of social cognitive tasks. Poststimulation tasks were counterbalanced to reduce the impact of order effects. Tasks were administered in the same counterbalanced order following both active and sham stimulation for each individual. During task completion, eye movements recorded via Gazepoint desktop eye tracker were utilized to measure the time visually fixating to researcher identified areas of interest (AOIs) relative to total item time, labeled "propAOI".

Facial emotion recognition accuracy was assessed with the *Emotion Recognition-40* (ER40; Kohler et al., 2003)which uses static faces and results in a total accuracy score of correctly identified emotions out of 40. Important AOIs for this task were core features of the face, namely the eyes, nose, and mouth of the actors exhibiting the emotions. Additionally, emotion choices were listed for participant's reference on the right side of the screen, and these regions were identified as important AOIs for task performance.

The *Bell Lysaker Emotion Recognition Task* (BLERT; Bryson et al., 1997) assessed emotion recognition in a dynamic audio/visual format, resulting in a total accuracy score of correctly identified emotions out of 21. In this task, important AOIs were similar to static faces in the ER40, namely the core features of the actor's face (i.e., eyes, nose, and mouth), and emotion choices listed on the right side of the screen.

Mentalizing was assessed via *The Awareness of Social Inferences Test* (TASIT Form A; McDonald et al., 2006). Participants watch vignettes of complex social situations and must answer questions regarding the understanding of intentions, beliefs, and meanings of speakers in the scene. Scores are total correct out of 64. Important AOIs were similar to the previous two tasks, namely core features of the actors' faces and bodies. Additionally, important contextual AOIs were specific to each scene, and included clues embedded in the scene necessary to understanding intent in each scenario. Examples of contextually important cues include scribbles in a book, an empty wallet, or an incomplete crossword puzzle.

2.3.3. Additional eye-tracking variables

While proportion of time attending to AOIs was the primary eye-tracking index, secondary eye-tracking variables were also calculated and analyzed. These analyses were intended to more fully assess visual strategies utilized by patients with schizophrenia and are available in supplemental materials.

2.3.4. Additional measures

The following measures were performed to assess factors that could theoretically impact neurostimulation or eye-tracking, as well as assessing potential adverse events. State depression (Maryland Trait and State Depression Scale, MTSD-S; Chiappelli et al., 2014), state anxiety (State-Trait Anxiety Inventory; STAI-S; Spielberger et al., 1983), and nicotine dependency (Fagerström Test for Nicotine Dependence, FTND; Heatherton et al., 1991) were assessed at both visits. Self-reported auditory hallucinations (Auditory Hallucinations Rating Scale, AHRS; Hoffman et al., 2003) were assessed before and after stimulation, and an exit questionnaire (adapted from Brunoni et al., 2011) was included to assess adverse effects. For each measure, higher scores indicate a stronger presence of the symptom assessed. At the end of each appointment, participants and raters were asked to independently guess if they received active or sham stimulation to verify success of double-blinding.

2.3.5. Statistical plan

To test the study's first hypothesis, we ran three separate 2x2 mixed ANOVAs on the proportion of time spent attending to researcher defined areas of interest (propAOI) on static faces (ER-40), dynamic videos (BLERT), and social situations (TASIT), with location (rTPJ vs. dmPFC) as a between-subjects' factor and stimulation condition (active vs. sham stimulation) as a within-subject factor. No direct comparisons between tasks were performed as we did not have hypotheses regarding the effects of stimulation exceeding one social cognitive task versus any other. To adjust for multiple comparisons, a Bonferroni correction was applied, with significant alpha $\leq$0.017 for each test run.

To test our second hypothesis, we repeated 2x2 mixed ANOVAs on total scores of the individual social cognitive tasks (ER40, BLERT, and TASIT) with location (rTPJ vs dmPFC) as a between-subjects' factors and stimulation condition (active versus sham stimulation) as a within-subjects' factor. As above, tasks were not directly compared, and an alpha correction was applied, with significant alpha $\leq$0.017 for each test run.

To test the third hypothesis (H3), we planned moderated mediation analyses using multilevel structural equation modeling. However, as discussed in the results below, these analyses were ultimately not warranted due to nonsignificant findings regarding eye tracking behavior on each of the social cognitive tasks.

3. Results

3.1. Sample characteristics

Demographic makeup and comparisons of stimulation groups are listed in Table 1. Mean symptom severities of the sample at each visit are listed in Table 2. Participants in the rTPJ stimulation group and the dmPFC stimulation group were well matched and did not differ on any demographic characteristics or symptom severity (see supplemental materials). Additionally, none of these variables differed significantly between stimulation condition (active vs. sham; see supplemental materials); therefore, none of these variables were included as covariates in subsequent analyses.

3.2. Social cognitive tasks

3.2.1. ER40

Attention. The 2x2 mixed ANOVA on proportion of time visually attending to researcher defined AOIs (i.e., propAOI) throughout the ER40, revealed no main effects for condition (active vs. sham), $F(1,67) = 2.954$, $MSE = 0.008$, $p = .090$, $\eta_p^2 = 0.042$, or location (rTPJ vs. dmPFC), $F(1,67) = 0.647$, $MSE = 0.033$, $p = .424$, $\eta_p^2 = 0.010$. Additionally, there were no interaction between condition and location, $F(1,67) = 0.978$, $MSE = 0.008$, $p = .326$, $\eta_p^2 = 0.014$. Means and standard deviations are listed in Table 2.

Accuracy. A 2x2 mixed ANOVA revealed no main effects for condition, $F(1,67) = 1.301$, $MSE = 4.763$, $p = .258$, $\eta_p^2 = 0.019$, or location, $F(1,67) = 0.933$, $MSE = 34.691$, $p = .337$, $\eta_p^2 = 0.014$, and no interaction effect for condition and location, $F(1,67) = 0.060$, $MSE = 4.763$, $p = .808$, $\eta_p^2 = 0.001$ (Table 2).

Table 1
Participant demographic and clinical characteristics.

	rTPJ sample ($n = 36$)	dmPFC sample ($n = 33$)			
	n(%)	n(%)	X^2	p	
Sex			0.323	0.570	
Male	21 (58.3)	17 (51.5)			
Female	15 (41.7)	16 (48.5)			
Race			2.514	0.473	
Caucasian	15 (41.7)	11 (33.3)			
African American	21 (58.3)	20 (60.6)			
Asian	0 (0.0)	1 (3.0)			
Native American	0 (0.0)	1 (3.0)			
Ethnicity			0.022	0..882	
Hispanic	5 (13.9)	5 (15.2)			
Non-Hispanic	31 (86.1)	28 (84.8)			
Number currently on Antipsychotics	34 (94.4)	29 (87.9)	0.935	0.334	
	M(*SD*)	M(*SD*)	t	p	d
Age	41.22 (10.51)	40.97 (11.49)	0.095	0.924	0.023
Education (years)	12.58 (2.43)	12.70 (2.33)	−0.198	0.844	0.050
WRAT-3	93.94 (12.31)	94.76 (13.73)	- 0.259	0.796	0.063
CPZ equivalent	196.39 (230.67)	261.51 (299.68)	−0.877	0.385	0.249

Note: Groups did not differ on any key demographic or clinical characteristics. Abbreviations: rTPJ, right temporoparietal junction; dmPFC, dorsomedial prefrontal cortex; WRAT-3, Wide Range Achievement Test - Reading recognition subtest; CPZ equivalent, chlorpromazine equivalent of oral antipsychotic treatment.

Table 2
Means and standard deviations for sham and active visits broken down by stimulation location.

	rTPJ sample ($n = 36$)		dmPFC sample ($n = 33$)	
	Sham Visit M(*SD*)	Active Visit M(*SD*)	Sham Visit M(*SD*)	Active Visit M(*SD*)
MTSD	25.50 (17.63)	23.19 (16.03)	24.67 (19.41)	24.39 (17.49)
STAI	39.75 (11.95)	40.11 (11.86)	39.18 (15.73)	40.33 (14.10)
FTND	2.83 (2.68)	2.94 (2.62)	2.36 (2.71)	2.48 (2.83)
$AHRS_{pre}$	8.94 (10.47)	7.56 (8.83)	7.70 (9.15)	6.82 (7.72)
$AHRS_{post}$	4.50 (6.85)	5.06 (8.60)	4.06 (6.03)	3.73 (4.89)
PANSS (5 Factor)				
Positive Symptoms	19.03 (7.53)	19.58 (7.21)	19.21 (8.00)	18.79 (7.97)
Negative Symptoms	14.86 (5.36)	14.47 (4.90)	14.15 (5.62)	13.94 (5.69)
Disorganization	18.24 (6.15)	18.03 (5.44)	18.53 (5.64)	18.42 (6.62)
Excitement	14.09 (4.61)	14.08 (3.57)	13.92 (3.65)	14.42 (5.06)
Emotional Distress	20.83 (7.78)	21.33 (7.55)	21.00 (7.78)	20.97 (7.17)
Exit Questionnaire	3.94 (5.07)	4.28 (4.05)	3.55 (4.01)	3.12 (2.97)
ER40				
Total	31.00 (4.57)	31.33 (4.10)	31.88 (4.87)	32.39 (4.21)
propAOI	0.53 (0.15)	0.54 (0.15)	0.53 (0.14)	0.58 (0.13)
BLERT				
Total	13.89 (4.00)	13.78 (3.83)	15.21 (2.92)	14.97 (3.70)
propAOI	0.46 (0.11)	0.47 (0.12)	0.47 (0.12)	0.47 (0.12)
TASIT				
Total[†]	47.22 (6.61)	46.67 (7.44)	45.27 (7.29)	47.24 (6.46)
propAOI	0.23 (0.07)	0.22 (0.06)	0.25 (0.06)	0.26 (0.07)

Note: Groups did not differ on any clinical characteristics, and only marginally significant differences observed between groups on TASIT total scores, $F(1,67) = 5.181$, $MSE = 10.596$, $p = .026$, $\eta_p^2 = 0.072$ (p > corrected alpha value, 0.017). Abbreviations: rTPJ, right temporoparietal junction; dmPFC, dorsomedial prefrontal cortex; MTSD, Maryland Trait and State Depression Scale; STAI, The State portion of the State-Trait Anxiety Inventory; FTND, Fagerström Test for Nicotine Dependence; $AHRS_{pre}$ and $AHRS_{post}$, Auditory Hallucinations Rating Scale pre-stimulation and 24–36 h post-stimulation; PANSS, Positive and Negative Syndrome Scale; ER40, Emotion Recognition-40; BLERT, Bell Lysaker Emotion Recognition Task; TASIT, The Awareness of Social Inferences Test; propAOI, proportion of time attending to researcher defined areas of interest (AOI).

Moderated Mediation. Although moderate relationships between visual attention and social cognitive performance were shown at both the active, $r = 0.386$, $p = .001$, and sham visit, $r = 0.343$, $p = .004$, neither attention nor task accuracy was meaningfully impacted by active neurostimulation. Therefore, we did not run the planned analyses to determine whether a moderated mediation relationship existed between stimulation, eye movement behavior, and performance on the ER40.

3.2.2. BLERT

Attention. Results for visual attention on the BLERT are similar to those reported for ER40, with the 2x2 mixed ANOVA resulting in no significant main effects for condition, $F(1,67) = 0.026$, $MSE = 0.007$, $p = .872$, $\eta_p^2 < 0.001$, or location, $F(1,67) = 0.033$, $MSE = 0.020$, $p = .855$, $\eta_p^2 < 0.001$, no significant interaction between condition and location, $F(1,67) = 0.271$, $MSE = 0.007$, $p = .604$, $\eta_p^2 = 0.004$. Means and standard deviations are listed in Table 2.

Accuracy. Similar to results from ER40, analyses revealed no significant main effects for either condition, $F(1,67) = 0.512$, $MSE = 2.102$, $p = .477$, $\eta_p^2 = 0.008$, or location, $F(1,67) = 2.217$, $MSE = 24.559$, $p = .141$, $\eta_p^2 = 0.032$, and no interaction between condition and location, F

(1,67) = 0.071, *MSE* = 2.102, $p = .791$, $\eta_p^2 = 0.001$ (Table 2).

Moderated Mediation. For BLERT data, no significant relationship was observed between visual attention and accuracy during the active visit, $r = .171$, $p = .161$, and only a small relationship during the sham visit, $r = 0.246$, $p = .041$. Fisher's *Z* indicated that these correlations did not significantly differ, $Z = -1.143$, p = .257. As neither attention nor social cognitive performance were meaningfully impacted by neurostimulation, we forewent mediation analyses.

3.2.3. TASIT

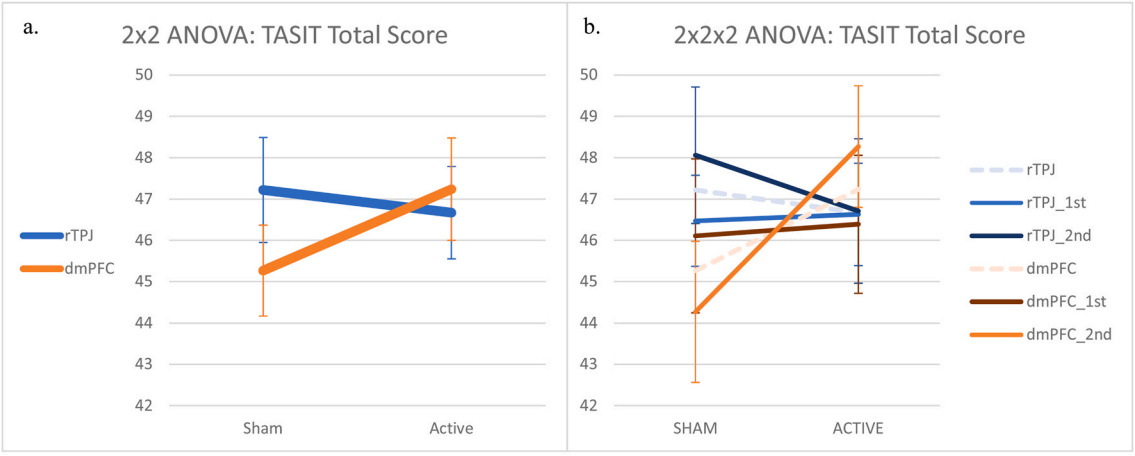
Attention. 2x2 mixed ANOVA on propAOI for TASIT revealed no main effects for condition, $F(1,67) = 0.002$, $MSE = 0.003$, $p = .967$, $\eta_p^2 < 0.001$, nor an interaction between condition and location, $F(1,67) = 1.447$, $MSE = 0.003$, $p = .233$, $\eta_p^2 = 0.021$. There was a significant main effect for location, $F(1,67) = 6.492$, $MSE = 0.006$, $p = .013$, $\eta_p^2 = 0.088$, with the dmPFC group attending to more researcher defined AOIs on average across condition and stimulation order, despite stimulation condition. Means and standard deviations listed in Table 2.

Accuracy. For TASIT accuracy, 2x2 mixed ANOVA revealed no significant main effect for condition, $F(1, 67) = 1.625$, $MSE = 10.596$, $p = .207$, $\eta_p^2 = 0.024$, or location, $F(1, 67) = 0.188$, $MSE = 86.491$, $p = .666$, $\eta_p^2 = 0.003$. There was a marginally significant interaction effect of stimulation and location, $F(1, 67) = 5.181$, $MSE = 10.596$, $p = .026$, $\eta_p^2 = 0.072$, with those in the dmPFC group improving their performance from sham to active stimulation, while average performance for those in the rTPJ group decreased from sham to active. (Table 2).

Based upon previous work within our own lab demonstrating that receiving active stimulation may result in an unintentional carry-over effect up to a week post stimulation (paper in preparation), we repeated these analyses in an exploratory fashion, including the order of stimulation (whether subject received active or sham stimulation first) as an additional between subject's factor to better characterize observed relationships between variables. The 2 × 2 × 2 mixed ANOVA for accuracy on the TASIT revealed no significant main effects for condition, $F(1,65) = 2.056$, $p = .156$, $\eta_p^2 = 0.031$, location, $F(1,65) = 0.194$, $p = .661$, $\eta_p^2 = 0.003$, or order, $F(1,65) = 0.069$, $p = .794$, $\eta_p^2 = 0.001$. There were no significant two-way interactions between condition and order, $F(1,65) = 1.058$, $p = .308$, $\eta_p^2 = 0.016$, or location and order, $F(1,65) = 0.064$, $p = .802$, $\eta_p^2 = 0.001$. The two-way interaction between condition and location, $F(1,65) = 6.478$, $p = .013$, $\eta_p^2 = 0.091$, was strengthened, and was better explained by a three-way interaction between condition, location, and order, $F(1,65) = 5.923$, $p = .018$, $\eta_p^2 = 0.084$.

This interaction reveals that those in the dmPFC group who received active stimulation at their second visit showed the greatest increase in accuracy when comparing sham, $M = 44.27$, $SD = 6.62$, to active stimulation, $M = 48.27$, $SD = 5.27$. Those who received active stimulation first in both the dmPFC and TPJ groups had, on average, minimally higher scores after active stimulation, $dmPFC_{1st}$:$M = 46.39$, $SD = 7.09$, $rTPJ_{1st}$:$M = 46.63$, $SD = 7.61$, compared to sham, $dmPFC_{1st}$:$M = 46.11$, $SD = 7.90$, $rTPJ_{1st}$:$M = 46.47$, $SD = 7.19$. Finally, the rTPJ group who received active stimulation at their second visit showed an overall decrease in accuracy after active stimulation, $M = 46.71$, $SD = 7.48$, compared to the sham condition, $M = 48.06$, $SD = 6.01$ (Fig. 1).

Moderated Mediation. Although we observed an effect of neurostimulation on accuracy for this task, we failed to establish an impact of neurostimulation on visual attention. Additionally, for both the rTPJ and dmPFC groups, there were no significant relationships between visual attention and accuracy following active (rTPJ:$r = -0.035$, $p = .838$; dmPFC:$r = -0.109$, $p = .548$) or sham stimulation (rTPJ:$r = 0.235$, $p = .168$; dmPFC:$r = 0.191$, $p = .287$). As visual attention was neither significantly impacted by single session neurostimulation nor related to accuracy, our planned moderated mediation models were not performed.



c.

	rTPJ Active 1st (*n*=19)		rTPJ Active 2nd (*n*=17)		dmPFC Active 1st (*n*=18)		dmPFC Active 2nd (*n*=15)	
	Sham Visit *M*(*SD*)	Active Visit *M*(*SD*)	Sham Visit *M*(*SD*)	Active Visit *M*(*SD*)	Sham Visit *M*(*SD*)	Active Visit *M*(*SD*)	Sham Visit *M*(*SD*)	Active Visit *M*(*SD*)
Order	2nd	1st	1st	2nd	2nd	1st	1st	2nd
TASIT Total*	46.47 (7.19)	46.63 (7.61)	48.06 (6.01)	46.71 (7.48)	46.11 (7.90)	46.39 (7.09)	44.27 (6.62)	48.27 (5.69)

Fig. 1. Interaction plots and means for TASIT total scores. Participants were randomly assigned to stimulation group and to which visit they received active stimulation. (a.) 2x2 mixed ANOVA with stimulation condition (active versus sham) as within subjects' factor and stimulation location (rTPJ versus dmPFC) as a between subjects' factor. Results show dmPFC group improving from sham to active, while the rTPJ group scored lower at active compared to sham. (b.) 2 × 2 × 2 mixed ANOVA interaction adding stimulation order (whether active stimulation was administered at first visit or at second visit) as an additional between subjects' factor. These results demonstrate that dmPFC improvement from 2x2 ANOVA driven by those that received active stimulation at their second visit, with the sham acting as a true potential baseline. However, those in the rTPJ group that received active at second visit had a higher baseline than all other groups, and accuracy decreased during active stimulation. (c.) Means standard deviations for sham and active visits broken down by stimulation location and order of administration. Note: Second visits/administrations are in shaded columns.

3.3. Double-blind check

Post stimulation participant check of double-blind efficacy resulted in only 20 of 69 participants, 29.0%, correctly guessing the stimulation condition, which did not differ by stimulation location, $X^2(1,N = 69) = 0.090$, $p = .764$. Similarly, post stimulation experimenter check of double-blind efficacy resulted in 28 of 69 participant assignments, 40.6%, correctly guessing stimulation condition. This, too, did not differ by stimulation location, $X^2(1,N = 69) = 0.037$, $p = .848$. Thus, both participants and experimenters were largely unaware of experimental condition.

4. Discussion

The current study utilized tDCS to test a causal model of social cognitive deficits within individuals diagnosed with schizophrenia spectrum disorders. Through the use of double-blind neurostimulation administered to targeted neural regions, we predicted that active stimulation to the rTPJ would be sufficient to improve visual attention to salient cues, and thus improve social cognitive performance on static and dynamic emotion recognition tasks, as well as a complex mentalizing task. Our results failed to support hypotheses across the three tasks but provide valuable insights into the limited impact and utility of single-session neurostimulation in social cognitive research in schizophrenia. The few observed effects hint at an alternate model of mentalizing deficits that can be beneficial for hypothesis generation.

4.1. Emotion Recognition

Neurostimulation failed to produce significant change in either visual attention or social cognitive accuracy on tasks of emotion recognition (i.e., the ER40 and BLERT). Multiple factors may have inadvertently impacted results. First, it is possible that the proposed model is inaccurate, and that visual attention and emotion recognition are not intrinsically tied. Instead, corollary relationships in current and past research could be due to the visual nature of emotion recognition tasks. Similarly, the targeted regions, rTPJ and dmPFC, may serve more supplemental roles and may not be critically involved in either visual attention processes or successful performance for these two tasks. Although individuals with schizophrenia show altered activation in these regions (Kronbichler et al., 2017; Mukherjee et al., 2016), patients may benefit from stimulating alternate or compensatory neural regions rather than the regions targeted here. Further research critically examining links between perceptual and behavioral abnormalities, as well as disrupted neural activity, can continue to disentangle these relationships.

It is also possible that the causal nature of neural activation is reversed, and for individuals with schizophrenia, learned behavior over time trains neural regions to engage and disengage differently than healthy individuals. In this model, behavior would dictate neural activity, and therefore, brief neurostimulation may not be sufficient to override compensatory neural signatures or behaviors.

Our results could also be indicative of a suboptimal dose, with a single stimulation being insufficient to illicit the types of behavioral changes measured (Berryhill et al., 2014). Our protocol also involved offline testing, in which measures of social cognition were administered after completion of the neurostimulation procedure. Benefits of online training (performing tasks during neurostimulation procedure) versus offline testing are not currently known, but it is possible that unknown factors mitigated the effects of tDCS between the time of stimulation and testing (Horvath et al., 2014). Pairing task performance with concurrent neurostimulation may direct optimal recruitment of neural networks in real time and strengthen connectivity of those networks (Bikson et al., 2018). Since tDCS is still a relatively novel research technique, optimal protocols have not yet been established (Bikson et al., 2018). Few studies have specifically targeted social cognition with tDCS, demonstrating mixed results (Dunn et al., 2016; Rassovsky et al., 2015, 2018); none have specifically targeted the TPJ to impact visual attention within this population. Thus, future studies examining efficacy of different stimulation protocols are encouraged.

4.2. Mentalizing

The current study challenges our hypotheses for mentalizing ability and indicate that visual attention and rTPJ may not play a substantial role. Our results reveal no significant impact of neurostimulation on visual attention, and we failed to observe a significant relationship between visual attention and accuracy, replicating recent work identifying independence of visual behaviors and performance on the TASIT within schizophrenia (Patel et al., 2020). However, participants demonstrated marginal improvement in task accuracy after stimulation to the active comparator (dmPFC), not the target region (rTPJ). These results support an alternate neural mechanism of mentalizing suggesting accurate performance may rely more heavily on executive functions rather than visual attention. This interpretation is consistent with recent meta-analyses revealing moderate associations between ToM and executive functions, specifically abstraction, or the ability to combine concrete information into a bigger, abstract picture (Thibaudeau et al., 2020), and the dmPFC may serve a unique role in abstraction (Baetens et al., 2017). Although exploratory results require replication, these results are hypothesis generating, suggesting the dmPFC may be a suitable stimulation target to improve the ability to process and integrate cues necessary for interpreting mental states of others.

Importantly, these results should be interpreted with caution. Current findings seem to be driven by participants in the dmPFC group who received active stimulation at the second visit and showed a significant improvement from baseline. Based upon work in our lab, administering sham at initial visits may be preferential, as it allows for true assessments of baseline, and active stimulation may demonstrate carryover effects weeks later. The current results are further complicated by the rTPJ group that received active stimulation at the second visit scoring much higher than all other groups after sham stimulation, with a reduction in performance after active stimulation. This pattern resulted in a large discrepancy between sham performance for the rTPJ and dmPFC groups who received active simulation second. Given that groups were matched on key demographic factors (i.e., age, race, gender, and education) and there were no discernible differences in clinical symptoms, baseline performance differences are difficult to explain. Further, the level of antipsychotic treatment and nicotine use were similar across groups, and location/condition assignments were randomized and counterbalanced, reducing the likelihood that results are solely due to sample sorting. Recent work has questioned whether sham stimulation is truly inert (Nikolin et al., 2018), indicating a crucial need for combined stimulation and neuroimaging trials to confirm neural activation concurrent to stimulation conditions.

Although group equivalences should strengthen the confidence in these results, there may still be unknown individual differences that impact the receptibility and efficacy of tDCS (Berryhill et al., 2014). Therefore, current study results, as well as dmPFC montage used, should be validated through replication before accepting an alternate model. Further, it would be beneficial to examine the generalizability of results to other ToM tasks.

5. Conclusions

The current study is, to our knowledge, the first study to target the rTPJ within schizophrenia for the purposes of testing a causal model of social cognitive deficits, namely that bottom-up visual attention deficits lead to inaccurate emotion recognition and mentalizing. Although our results failed to support this model, and single-session neurostimulation failed to impact visual attention, the current study provides initial support for an alternate model of social cognitive deficits. Specifically,

active stimulation of dmPFC, but not rTPJ, improved mentalizing task accuracy, suggesting that increased executive functioning, rather than visual attention, may support mentalizing performance.

Many limitations have been discussed, highlighting much of what is still unknown with regards to best practices in implementing tDCS in both healthy and clinical populations. Notably, the current study also suffers from montage design based upon theoretical excitation of targeted regions and was not confirmed with a priori current modeling. Although current models present only estimations of the true path that tDCS anodal stimulation takes in an average individual, these models provide support that neural targets were activated. Schizophrenia potentially arises out of dysconnectivity within and between neural networks (Friston et al., 2016), which may present unique challenges in accurate current models (however, see Brunoni et al., 2014 for a retrospective review of current flow within two common montages used within schizophrenia research). Future researchers are encouraged to use concurrent neuroimaging to confirm a priori current modeling and verify its accuracy within this population. Thus, we express caution with this result and encourage replication before accepting this model. For our study, we believe that the use of a comparator group is a major strength and an example of leveraging comparators to inform both mechanistic and treatment-oriented research. Further, we believe that these results may be hypothesis generating of not only neural mechanisms underlying social cognitive deficits, but also considerations in implementing stimulation research within clinical populations. Experimental trials utilizing multiple tDCS neurostimulation sessions, possibly with concurrent task training, and validation of neurostimulation through neuroimaging will help clarify whether current results are simply a dosage failure or are truly independent and/or resistant to neurostimulation.

Credit author statement

Hans Klein: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, writing – original, review, and editing, Visualization. Sven Vanneste: Resources, Supervision, writing - review., Amy Pinkham: Resources, Writing – review & editing, Methodology, Supervision.

Declaration of competing interest

The authors report no conflict of interests as it relates to the current manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2021.107880.

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