Research Paper

Improving causality perception judgments in schizophrenia spectrum disorder via transcranial direct current stimulation

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Background: Deficient causality perception and attribution may underlie key symptoms of schizophrenia spectrum disorder (SSD), such as delusions and ideas of reference. Although transcranial direct current stimulation (tDCS) can increase the influence of spatial information on perceptual causality judgments among healthy participants, its effect among patients with SSD remains unknown. We sought to determine whether tDCS modulates the contribution of stimulus characteristics to perceptual causality judgments among patients with SSD; we predicted that right parietal tDCS would increase the influence of spatial stimulus characteristics on patients' causality perception. **Methods:** Patients with SSD received frontal, parietal, frontoparietal and sham tDCS in 4 separate sessions. Pre- and post-tDCS, patients viewed video clips of ball A colliding with ball B. Spatial linearity (ball B's angle of egress) and temporal contiguity (delay between collision and ball B's movement) varied parametrically. After each launching event, patients rated perceived causality. **Results:** Among 19 patients with SSD, we found a brain region–dependent effect of tDCS regarding sensitivity to violations of spatial linearity. After right parietal anodal tDCS, the influence of angle variations on patients' perceptual causality judgments increased, reflected by a higher probability of perceived causality for stimuli with small angles and a lower probability of perceived causality for stimuli with high angles. **Conclusion:** Transcranial direct current stimulation increased the influence of spatial stimulus characteristics on causality perception among patients with SSD. Future research should explore potential links between tDCS-induced changes in basic perceptual processes and clinical symptoms, such as delusions and ideas of reference.

Introduction

The perception of causality is a fundamental feature of human cognition that allows us to make sense of the environment and our place in the world. Investigating launching events, Michotte[1] found that humans tend to perceive causality directly and automatically, even when observing strikingly simple percepts. In a launching event, a small, 2-dimensional object (A) moves toward another small, 2-dimensional object (B) and makes contact with it. Object A then stops moving and object B starts moving away from object A. Despite the simplicity of such stimuli, the ensuing perception of causality in the observer is strong and immediate.[1–3] Therefore, perceptual causality has been argued to occur at the early stages of visual processing and to be distinct from higher-level cognitive interpretations (e.g., inferring causality).[4–6] Rather, perceptual causality may be regarded as "a basic preattentional cognitive function akin to gestalt-like neurocognitive binding processes."[7] This view is supported by studies showing that the perception of causality emerges in 6-month-old infants.[8–11] The impression of causality when viewing launching events is strongly dependent on spatial and temporal stimulus parameters.[12–14] Importantly, neuroimaging studies have established that perception and attribution of causality in the context of launching events is not instantiated in a universal "causality network."[12,15–17] Rather, the perception of causality depends primarily on the brain networks involved in the perception of spatial and temporal stimulus characteristics.[12,15,17] The processing of spatial stimulus characteristics has been consistently linked to activation of the right parietal cortex.[6,12,17] Moreover, 2 studies have shown that parietal transcranial direct current stimulation (tDCS) increases the influence of spatial stimulus characteristics (i.e., angle variations) on perceptual judgments of causality among healthy participants viewing launching events. The first study found higher perceived causality for trials

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Submitted Oct. 17, 2022; Revised Feb. 11, 2023; Accepted Apr. 2, 2023

Cite as: *J Psychiatry Neurosci* 2023 July 4;48(4). doi: 10.1503/jpn.220184

with small angles after right parietal anodal tDCS, and higher perceived causality for trials with large angles after right parietal cathodal tDCS.[13] Congruently, the second study also showed that participants were less likely to judge causality based on spatial violations after right parietal anodal tDCS.[17]

Patients with schizophrenia show marked deficits in Gestalt-like perceptual organization.[18] This impairment contributes to deficits in the perception and judgment of cause-and-effect relationships, and manifests as delusions,[19] ideas of reference[20] and reduced mentalizing ability.[21] Patients with schizophrenia tend to perceive cause-and-effect relationships where they do not exist (e.g., when jumping to conclusions).[19,22,23] Importantly, this tendency manifests even when patients watch simple animations of geometric shapes.[24] Concerning the perception of causality during the observation of launching events, positive symptoms have been associated with increased judgments of causality, whereas disorganization symptoms have been associated with reduced perceived causality.[7] Moreover, patients with schizophrenia spectrum disorder (SSD) overestimate causality in physical launching contexts and underestimate causality in social launching contexts, while being generally less influenced by spatial and temporal motion parameters.[25] Although tDCS has been successfully applied to increase the influence of spatial motion parameters among healthy participants,[13,17] it remains hitherto unknown whether tDCS could also increase sensitivity to spatial stimulus characteristics among patients with SSD. From a clinical point of view, a nonpharmacological intervention to influence aberrant attribution of cause-and-effect relationships among patients with schizophrenia would be highly valuable.

We sought to test the hypothesis that right parietal tDCS increases the influence of spatial stimulus properties on perceptual causality judgments of patients with SDD watching launching events of 1 ball colliding with another. We predicted that parietal anodal tDCS would increase the sensitivity of patients' causality perception judgments to violations of spatial linearity (i.e., angle of egress) of the second ball's movement. In addition to parietal tDCS, we included frontal, frontoparietal and sham stimulation in the design to control for unspecific tDCS effects.

Methods

Participants

We recruited patients with SSD at the Department of Psychiatry and Psychotherapy, Philipps-University, Marburg, Germany. We collected demographic (age, sex, level of education as measured by the CASMIN classification)[26] and basic neurocognitive data (Multiple-Choice Vocabulary Intelligence Test, Trail Making Test A, Trail Making Test B, Digit Symbol Substitution Test, Scale for the Assessment of Negative Symptoms [SANS], Scale for the Assessment of Positive Symptoms [SAPS]) before the first tDCS application. Diagnoses of SSD were made according to the *International Statistical Classification of Diseases and Related Health Problems, Version 10, German Modification* (ICD-10 GM).

Transcranial direct current stimulation

We applied tDCS to parietal (left parietal cathodal, right parietal anodal [LPC-RPA]), frontoparietal (left frontal cathodal, right parietal anodal, [LFC-RPA]) and frontal (left frontal cathodal, right frontal anodal [LFC-RFA]) cortical areas using the DC-STIMULATOR PLUS (neuroConn GmbH). Frontal electrodes were positioned at F3/F4 and parietal electrodes were positioned at CP3/CP4, according to the 10–20 electroencephalography system. We applied a current of 1.5 mA to the head using saline-soaked sponges (0.9 % NaCl to minimize adverse effects, 5 cm × 7 cm) placed on rubber electrodes, resulting in a current density of 0.043 mA/cm^2.[27,28] Figure 1 shows the electric fields resulting from stimulation, simulated on the cortical surface of a MNI152 template using SimNIBS (version 3.2.1).[29] The duration of stimulation was 10 minutes plus 10 seconds of fade-in or fade-out time. We chose a stimulation dose of 1.5 mA because a multisession tDCS study of healthy participants showed modulation of spatial reorienting after administering 1.5 mA to the right parietal cortex.[30] We limited the stimulation duration to 10 minutes to maximize patient comfort while ensuring tDCS efficacy. All parameters complied with current tDCS safety guidelines.[31,32] We performed sham stimulation using the sinus (HW) mode of the DC-STIMULATOR PLUS, applied for a duration of 30 seconds via frontoparietal (left frontal, right parietal) electrodes.[33,34]

Perceptual causality judgment task

Immediately before and after tDCS, we presented 98 video clips depicting simple launching events to participants on a computer screen (Figure 1). Each stimulus showed the movement of a first (blue) ball toward a second (red) ball, their collision and the subsequent movement of the second ball. The stimuli (duration 2 s, frame rate 60 Hz, resolution 720 × 576 pixels) were constructed using Strata 3D software (Corastar, Inc. dba Strata Software). The balls were shaded to give the impression of 3-dimensional objects and not flat discs. The first ball began to move 400 ms after animation onset; it rolled along a horizontal plane and stopped moving after 1000 ms when it came into contact with the second ball. The delay between the initial contact and the subsequent movement varied between 0 ms and 267 ms (0 ms, 33 ms, 67 ms, 100 ms, 133 ms, 200 ms, 267 ms); the angle of egress of the second ball varied between 0° and 60° (0°, 7.5°, 15°, 22.5°, 30°, 45°, 60°). The speed and length of trajectory were the same for both balls in all conditions. We presented the 49 different stimuli in left-to-right and right-to-left versions, resulting in a total of 98 stimuli (7 different delays, 7 different angles of egress, 2 different directions). Each possible combination of stimulus properties was presented exactly once per run in pseudorandomized order. Each patient viewed a different set of 98 stimuli in each run, with the total number of presentations of each set of pseudorandomized stimuli counterbalanced across patients and conditions. In the first session, we gave participants standardized written and oral task instructions.

They were instructed to rate perceived causality of the launching events as causal or noncausal ("Left click if you believe that the blue ball caused the movement of the red ball. Right click if you don't believe the blue ball caused the movement of the red ball."). We instructed participants that there were no right or wrong answers; that all that mattered was their immediate, individual, intuitive perception; that they would always watch a blue and a red ball; that both balls would always come into contact with each other; that the second ball would always start moving away from the first ball; that movement direction and timing would differ between the video clips; and that they should respond as

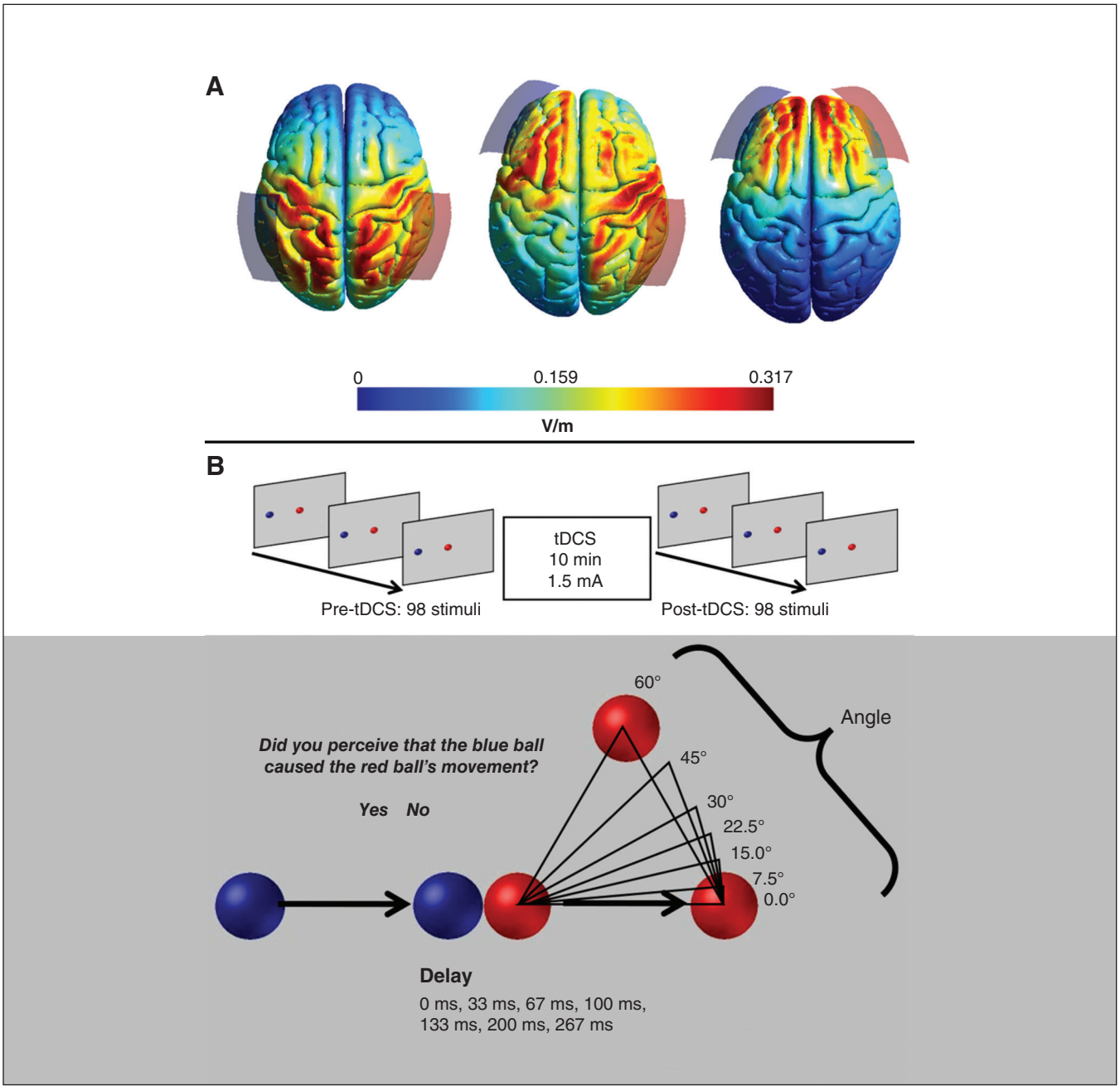

Figure 1: (A) Transcranial direct current stimulation (tDCS) conditions, showing the simulated normalized electric field strengths (in V/m) on the cortical surface for the 3 different tDCS conditions (from left to right: parietal [left parietal cathodal, right parietal anodal], frontoparietal [left frontal cathodal, right parietal anodal] and frontal [left frontal cathodal, right frontal anodal] tDCS). In addition, every patient received 1 session of sham tDCS. (B) Procedure and task. In each session, before and after 10 minutes of 1.5 mA tDCS, 98 stimuli of ball A launching ball B were presented on screen. Each of the 98 possible combinations of stimulus characteristics (7 different angles, 7 different delays, presented right to left and left to right) was presented exactly once, in pseudorandomized order. Immediately after each stimulus, patients judged perceived causality by pressing a button, either yes (causal) or no (noncausal).

quickly as possible after each video clip via mouse click. Importantly, we did not give explicit instructions on how to rate causality (i.e., based on spatial or temporal stimulus characteristics). Thus, participants were not instructed to rate causality based on plausibility (i.e., laws of physics), but were instead instructed to rate causality based on the subjective impression of causality. Instructions were followed by a short practice run. Stimulus presentation, timing and responses were controlled using Presentation software (Neurobehavioural Systems). This experimental paradigm has previously been applied successfully to study perceptual causality in healthy participants[12–17] and patients with schizophrenia.[25]

Experimental design

The current study was part of a larger project investigating the effects of tDCS on perception and cognition in schizophrenia.[35–38] All patients underwent 4 different tDCS conditions on 4 different days. Sessions were performed at least 20 hours apart to ensure that tDCS effects had faded away by the beginning of each new session. To control for effects of order and repetition, the order of stimulation conditions was pseudorandomized and counterbalanced across patients. For the first patient, the order of conditions was 1-2-3-4; for the second patient, it was 2-3-4-1; for the third patient, it was 3-4-1-2; for the fourth patient, it was 4-1-2-3; for the fifth patient, it was 1-2-3-4; and so on. Patients were blinded regarding the stimulation conditions; examiners were blinded regarding the experiment's hypotheses. Immediately before and after 10 minutes of parietal, frontoparietal, frontal and sham tDCS, patients performed the perceptual causality judgment task. Causality judgments (causal or noncausal) and reaction time data were collected for analysis. During stimulation, patients viewed videos of an actor and judged the relationship of speech and cospeech gestures produced by the actor.[36] The administration of this easy online task ensured a consistent behavioural and cognitive activity across the sample, whereas simply instructing participants to rest during stimulation may have led to largely different patterns of activity (e.g., mind wandering, rumination, fidgeting, sleeping, talking with the examiner). Another objective of this task was to make patients more comfortable while undergoing stimulation, diverting their attention away from potential stimulation-associated or sitting-associated sensations of discomfort. After the post-tDCS causality task, patients completed an action outcome monitoring task.[38] At the end of each session, perceived adverse effects were assessed.[36]

Ethics approval

All patients were capable of giving informed consent, as clinically assessed, gave written informed consent before participation and received an expense allowance. The ethics committee at the Philipps-University in Marburg approved the study (registration no. 191/12). The study was carried out in accordance with the latest version of the Declaration of Helsinki.

Statistical analysis

We performed all statistical analyses in R (version 4.0.4). To probe whether tDCS influenced causality judgments, we performed generalized linear mixed models (GLMMs), using a binomial distribution and the logit link function to model the dichotomous causality judgment data. Before analysis, we excluded observations with reaction times 4 or more standard deviations above the mean. We treated angle and delay as continuous variables and centred these variables on the mean before analysis. The main GLMM included fixed effects for time point (pre-tDCS, post-tDCS), location (parietal, frontoparietal, frontal, sham), angle and delay, as well as their interactions. We included participants as a random effect to account for repeated-measures within subjects. We performed Wald tests for statistical inference. We calculated marginal and conditional coefficients of determination using the method by Nakagawa and Schielzeth.[39] We were mainly interested in whether there would be a location- and angle-specific tDCS effect (i.e., an interaction of time point × location × angle or time point × location × angle × delay). To follow up significant interaction effects, we tested whether there were significant pre–post differences for specific angles in specific conditions by performing pairwise comparisons. To this end, for each angle we computed estimated marginal means of full-factorial GLMMs analogous to the main model but without the variable for angle. Likewise, we tested whether there were significant between-location differences in estimated marginal means for specific angles, at pre- and post-tDCS time points. For both series of post hoc tests, we corrected for false discovery rate (FDR) using the Benjamini–Hochberg method, to control for multiple comparisons.

To test whether individual angle sensitivity related to symptomatology, we performed GLMs for each patient individually with pre-tDCS data, including only the main effect for angle to compute individual coefficients for angle. We then calculated Pearson correlation coefficients between these angle coefficients and SAPS scores, scores of the delusions subscale of SAPS and SANS scores. To test for tDCS effects on reaction times, we performed a GLMM analogous to the main GLMM for causality judgments, using the normal distribution with the log link function to model the reaction time data. We performed Wald tests for statistical inference. We used pairwise comparisons with FDR correction to follow up significant interactions.

Results

We recruited 20 patients with SSD. All patients were right-handed, native-level German speakers with normal or corrected-to-normal vision, no hearing deficits and no electric implants. We excluded 1 patient from post hoc analyses because of insufficient compliance with task requirements. The analyzed sample thus consisted of 19 patients (17 males, 2 females; mean age 39.6 years, standard deviation [SD] 11.2 years; Table 1). Twelve patients had diagnoses of paranoid schizophrenia (ICD-10 GM F20.0), 4 patients had diagnoses of schizoaffective disorder (ICD-10 GM F25.0), 1 patient had a diagnosis of residual schizophrenia (ICD-10 GM F20.5),

1 patient had a diagnosis of prodromal schizophrenia (ICD-10 GM F21.0) and 1 patient had a diagnosis of acute and transient psychotic disorder (ICD-10 GM F23.0) with a differential diagnosis of paranoid schizophrenia (ICD-10 GM F20.0). Patients were under stable medication when participating (Appendix 1, Table 1, available at https://www.jpn.ca/lookup/doi/10.1503/jpn.220184/tab-related-content), with 2 patients entirely medication-free. Symptom severity was relatively low (mean SAPS 10.5 [SD 13.0], mean SANS 17.6 [SD 18.2]). Clinical ratings were missing for 2 patients.

Regarding causality judgments, we found strong main effects of angle ($\chi^2_1 = 251.677$, $p < 0.001$) and delay ($\chi^2_1 = 61.101$, $p < 0.001$) on ratings in the main GLMM (Table 2), indicating that patients' perceived causality depended on both spatial and temporal stimulus parameters. Importantly, we found that tDCS has a location-specific effect on the angle sensitivity of causality judgments (Figure 2), as indicated by a significant time point × location × angle interaction ($\chi^2_3 = 24.863$, $p < 0.001$). To explore this interaction effect from the perspective of pre–post differences, we performed pairwise comparisons among estimated marginal means of pre- and post-tDCS causality judgments for each combination of angles and conditions (Table 3). After FDR correction, the pre–post differences for frontoparietal (LFC-RPA) tDCS remained significant at angles of 0° (odds ratio [OR] 0.447, standard error [SE] 0.118, $p_{adjusted} = 0.021$), 7.5° (OR 0.422, SE 0.104, $p_{adjusted} = 0.013$), 45° (OR 1.997, SE 0.504, $p_{adjusted} = 0.043$) and 60° (OR 2.586, SE 0.739, $p_{adjusted} = 0.013$) (Figure 3). Frontoparietal tDCS resulted in a higher probability of causal judgments for 0° and 7.5° angles (probability increases for causal judgments from

Table 1: Sample characteristics

Variable	No. of patients	Minimum	Maximum	Median	Mean ± SD
Sex					
Female	2				
Male	17				
Age	19	20	61	39	39.63 ± 11.24
Education*	19	2	9	6	5.63 ± 1.98
SAPS	17	0	50	7	10.53 ± 13.01
SANS	17	0	57	13	17.65 ± 18.21
MWT-B	19	21	36	32	30.63 ± 3.65
TMT-A	19	19	57	31	32.32 ± 9.67
TMT-B	18	38	115	56	62.44 ± 19.68
DSST	19	22	55	45	43.63 ± 8.43
Chlorpromazine equivalents, mg/d	18	0	1390	517.36	582.96 ± 412.39

DSST = Digit Symbol Substitution Test; MWT-B = Multiple-Choice Vocabulary Intelligence Test; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; TMT-A = Trail Making Test A; TMT-B = Trail Making Test B.
*As measured by the CASMIN classification.

Table 2: Tests of model effects for generalized linear mixed model of causality judgments*

Effect	χ^2	Degrees of freedom	*p* value
(Intercept)	0.849	1	0.357
Time point	2.919	1	0.088
Location	11.710	3	0.008
Angle	251.677	1	< 0.001
Delay	61.101	1	< 0.001
Time point × location	5.230	3	0.156
Time point × angle	0.058	1	0.809
Location × angle	12.507	3	0.006
Time point × delay	1.224	1	0.269
Location × delay	3.258	3	0.354
Angle × delay	0.012	1	0.914
Time point × location × angle	24.863	3	< 0.001
Time point × location × delay	0.824	3	0.844
Time point × angle × delay	0.842	1	0.359
Location × angle × delay	0.632	3	0.889
Time point × location × angle × delay	1.063	3	0.786

*Shown are the results of Wald tests for the fixed effects and interactions of the main generalized linear mixed model for causality judgments. In addition, the random effect of participant was included in the model.

84.9% to 92.6% and from 56.3% to 75.4%, respectively), and in a lower probability of causal judgments for 45° and 60° angles (probability decrease for causal judgments from 17.0% to 9.3% and from 14.8% to 6.3%, respectively), compared with pre-tDCS measurements. Sensitivity to spatial stimulus characteristics thus specifically increased after frontoparietal tDCS. Frontoparietal tDCS increased the relative influence of spatial characteristics on patients' perceived causality, inducing higher perceived causality for stimuli with small violations of spatial linearity (small angles of egress) and lower perceived causality for stimuli with large violations of spatial linearity (large angles of egress). To explore the significant time point × location × angle interaction from the perspective of differences between tDCS locations, we also performed pairwise comparisons among estimated marginal means for the different tDCS locations separately for both time points and the different angles (Appendix 1, Table 2). After FDR correction, 12 comparisons remained significant. Nine of these comparisons were post-tDCS comparisons. Eleven of these comparisons involved right parietal anodal tDCS, and 8 comparisons involved LFC-RPA tDCS. These tests confirmed the influence of right parietal anodal tDCS on causality judgments. We found no modulation regarding the influence of delay on causality judgments; none of the interactions involving delay were significant (time point × location × delay $\chi^2_3 = 0.824$, $p = 0.844$; time point × location × angle × delay $\chi^2_3 = 1.063$, $p = 0.786$). The model fit of the GLMM was acceptable, as indicated by a conditional coefficient of determination of 0.418. Fixed effects explained an important part of the variance, as indicated by a marginal coefficient of determination of 0.201.

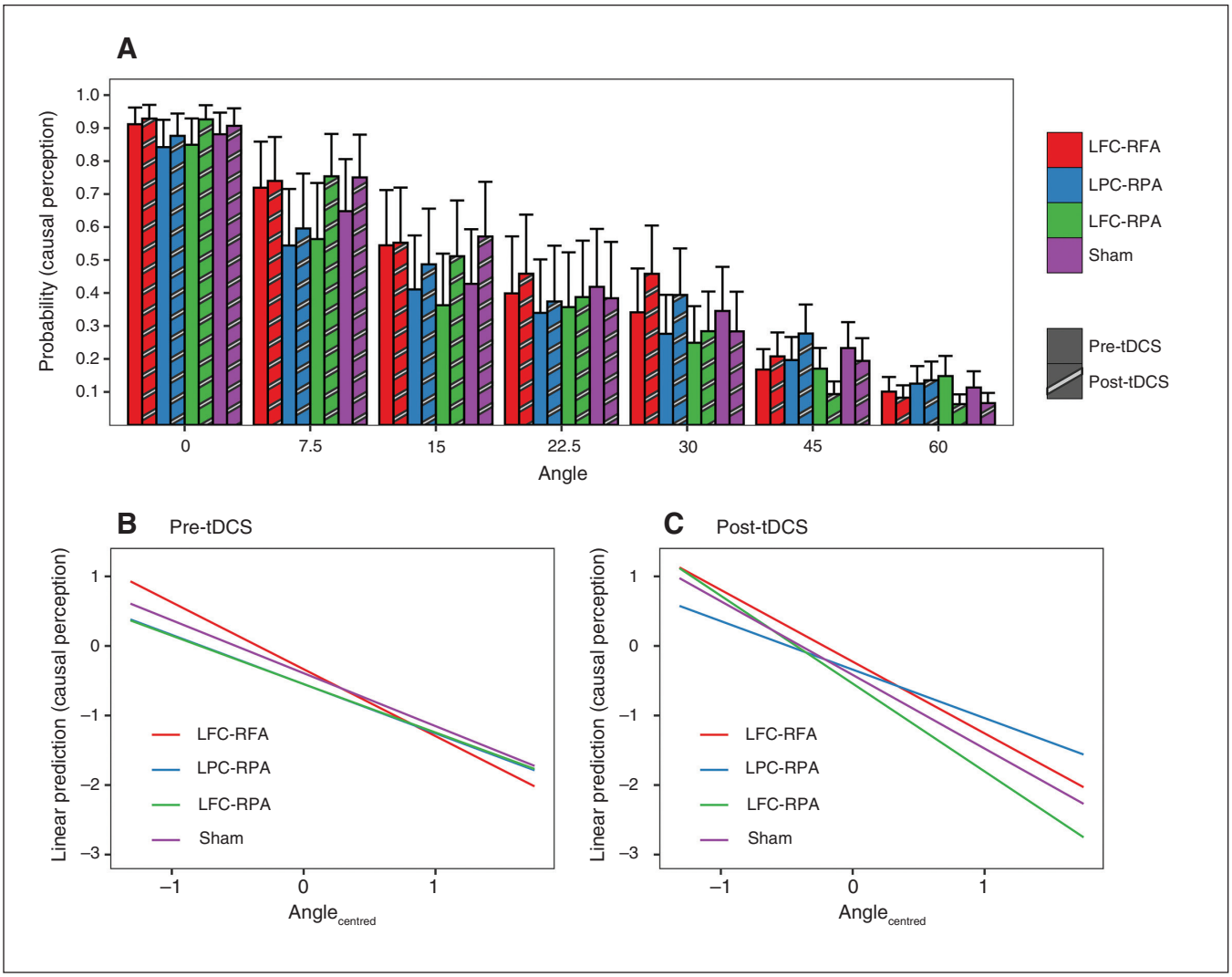

Figure 2: Location-specific effect of transcranial direct current stimulation (tDCS) on angle sensitivity of perceptual causality judgments. (A) The estimated marginal means for the probability of causal perception (i.e., causal judgments) for different angles of egress of the second ball (measured in degrees), for the 4 different tDCS locations, pre- and post-tDCS. Error bars indicate standard errors. (B) Location by angle interaction plots of estimated marginal means (i.e., the linear prediction of the generalized linear mixed models for causal perception based on angle (mean-centred), pre-tDCS and (C) post-tDCS, for the 4 different tDCS locations. LFC-RFA: left frontal cathodal, right frontal anodal tDCS; LFC-RPA: left frontal cathodal, right frontal anodal tDCS; LPC-RPA: left parietal cathodal, right parietal anodal tDCS.

Regarding clinical psychopathology, individual angle-sensitivity, defined as the coefficient for the effect of Angle in individual GLMs including only this single effect, performed on pre-tDCS data, was not correlated with overall SAPS (r = –0.091, p = 0.730) scores, scores of the SAPS delusions subscale (r = –0.095, p = 0.718) or SANS scores (r = –0.148, p = 0.572).

Regarding reaction times, we found no angle- and location-specific tDCS effect. The interaction of time point × location × angle in the GLMM was not significant (χ^2_3 = 0.622, p = 0.891; Appendix 1, Table 3), in contrast to the corresponding interaction in the GLMM for causality judgments. However, there was a significant 2-way interaction effect of time point × location (χ^2_3 = 16.899, p = 0.001; Appendix 1, Figure 1). Pairwise comparisons using FDR correction showed that patients responded significantly faster after tDCS in all conditions (Appendix 1, Table 4). Descriptively, the largest reduction in reaction times was found for LFC-RPA tDCS, but this was found in a context of large differences in pre-tDCS reaction time between conditions (Appendix 1, Figure 1) and cannot be unambiguously interpreted as a tDCS effect.

Discussion

We found that patients' perceptual causality judgments were more strongly influenced by violations of spatial linearity in launching events after frontoparietal tDCS. Right parietal anodal tDCS (combined with left frontal cathodal tDCS) led to greater perceived causality for launching events with small angles of egress, and to less perceived causality for launching events with large angles of egress. More generally, our findings support the prominent role of the parietal lobes for processing movement path information.[40,41] Our results are consistent with those of studies involving healthy participants that showed that sensitivity to angle variation regarding causality perception in launching events was instantiated in the right parietal cortex[12,17] and could be enhanced by right parietal anodal tDCS, in combination with left frontal or left parietal cathodal tDCS.[13,17] We extend these findings, showing that judgments in causality perception may be similarly modulated among patients with SSD. It is encouraging that tDCS increased patients' sensitivity to spatial motion parameters, since patients tend to overestimate causality in physical contexts

Table 3: Pre–post differences of causality judgments by location and angle*

Location	Angle	Odds ratio	SE	z ratio	$p_{adjusted}$ value	$p_{unadjusted}$ value
LFC-RPA	7.5	0.422	0.104	–3.491	0.013	< 0.001
LFC-RPA	60.0	2.586	0.739	3.321	0.013	0.001
LFC-RPA	0.0	0.447	0.118	–3.061	0.021	0.002
LFC-RPA	45.0	1.997	0.504	2.737	0.043	0.006
LFC-RPA	15.0	0.544	0.133	–2.489	0.071	0.013
Sham	15.0	0.561	0.137	–2.372	0.071	0.018
LPC-RPA	30.0	0.587	0.130	–2.400	0.071	0.016
LPC-RFA	30.0	0.613	0.136	–2.209	0.095	0.027
LPC-RPA	45.0	0.638	0.143	–2.002	0.127	0.045
Sham	60.0	1.806	0.523	2.041	0.127	0.041
Sham	7.5	0.612	0.154	–1.952	0.130	0.051
LPC-RPA	15.0	0.735	0.178	–1.274	0.446	0.203
Sham	30.0	1.334	0.304	1.261	0.446	0.207
LPC-RPA	0.0	0.754	0.193	–1.103	0.482	0.270
Sham	0.0	0.763	0.203	–1.015	0.482	0.310
LFC-RFA	22.5	0.783	0.181	–1.056	0.482	0.291
LFC-RFA	45.0	0.770	0.176	–1.143	0.482	0.253
Sham	45.0	1.262	0.280	1.047	0.482	0.295
LFC-RFA	0.0	0.791	0.212	–0.873	0.550	0.382
LPC-RPA	7.5	0.810	0.200	–0.854	0.550	0.393
LFC-RPA	30.0	0.836	0.191	–0.781	0.553	0.435
LFC-RFA	60.0	1.249	0.352	0.787	0.553	0.431
LPC-RPA	22.5	0.860	0.204	–0.638	0.627	0.523
Sham	22.5	1.155	0.270	0.616	0.627	0.538
LFC-RPA	22.5	0.879	0.208	–0.547	0.655	0.585
LFC-RFA	7.5	0.901	0.223	–0.422	0.725	0.673
LPC-RPA	60.0	0.914	0.236	–0.350	0.754	0.727
LFC-RFA	15.0	0.969	0.233	–0.133	0.894	0.894

FDR = false discovery rate, LFC-RFA = left frontal cathodal, right frontal anodal transcranial direct current stimulation; LFC-RPA = left frontal cathodal, right frontal anodal transcranial direct current stimulation; LPC-RPA = left parietal cathodal, right parietal anodal transcranial direct current stimulation; SE = standard error.
*Pairwise comparisons among estimated marginal means of pre- and post-tDCS causality judgments, for each combination of tDCS location and angle, ordered by statistical significance. FDR-adjusted p values were computed using the Benjamini–Hochberg method, to correct for performing 28 tests.

and are generally less influenced by spatial and temporal motion parameters than healthy controls.[25] Whether tDCS led to more accurate causality perception judgments because of more accurate motion information processing, an improvement in visuospatial reasoning or a specific improvement of causality inference remains to be tested in future studies.

Our results support ongoing efforts to develop tDCS into a clinical treatment tool for patients with schizophrenia. By including not only a sham condition but also 2 active tDCS control conditions in our experimental design, as has recently been suggested,[42] we were able to control for unspecific tDCS effects caused by cutaneous stimulation.[42,43] Post hoc tests showed that the effect of tDCS on causality judgments was most pronounced for LFC-RPA tDCS. In contrast, effects of LPC-RPA tDCS were less evident. Effects of left parietal cathodal tDCS may have offset the effects of right parietal anodal tDCS. Another possible explanation could be that left frontal hyperactivity among patients with SSD, observed in relation to dysfunctional perception of causality,[25] was suppressed by cathodal tDCS in our LFC-RPA condition. In any case, despite some previous evidence pointing toward a prominent role of the right parietal lobe in the perception of causality when viewing launching events,[12,13,17] it needs to be stressed that the tDCS effect brought about by frontoparietal stimulation seems to depend on left frontal cathodal stimulation too.[12,13,17] It should also be noted that frontoparietal tDCS may well have had network-modulating effects going far beyond regions that were directly stimulated. Additional neuroimaging studies could provide further mechanistic insights.

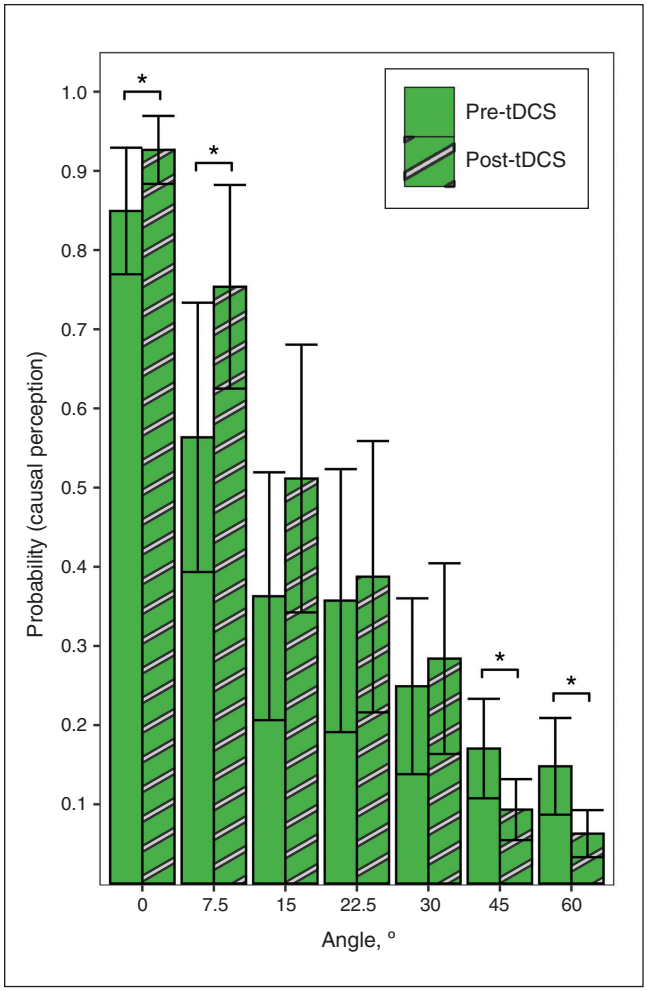

Figure 3: Angle sensitivity of causality judgments after left frontal cathodal, right parietal anodal (LFC-RPA) transcranial direct current stimulation (tDCS); shown are the estimated marginal means for the probability of causal perception (i.e., causal judgments) for different angles of egress of the second ball, pre- and post-tDCS. False discovery rate–adjusted *p* values were computed using the Benjamini–Hochberg method, to correct for performing 28 tests (Table 2). Error bars indicate standard errors. *$p_{adjusted} < 0.05$.

As expected, we did not find delay-specific tDCS effects. Delay sensitivity of perceived causality in launching events has previously been linked to activity in the left putamen, a region not directly affected by the tDCS-induced cortical electrical field.[12] Although we did not observe any angle- and location-specific effect for reaction times, we found a significant interaction of time point × location, with the largest reduction in reaction times observed after LPC-RPA tDCS. It is possible that parietal tDCS improved processing speed in our perceptual causality judgment task, potentially by facilitating assessment of spatial causality in the parietal cortex. However, we cannot make definitive conclusions regarding this reduction in reaction times, since it was found amid considerable pre-tDCS differences in reaction times. In absolute terms, we observed the fastest post-tDCS reaction times after sham tDCS.

We did not find a relationship between current positive or negative symptoms (i.e., SAPS or SANS scores) and angle sensitivity of patients' causality perception. This may be owing to the small sample size or the relatively low SAPS or SANS scores in our sample. Alternately, one could speculate that impaired perceptual causality judgments are not merely an epiphenomenon of current symptomatology but represents a more stable, trait-like feature of SSD.[25] Recently, the potential of tDCS for treating positive[44–46] and negative[36,47–49] symptoms of schizophrenia has received attention. However, studies investigating the clinical utility of tDCS hitherto rarely explored whether tDCS-induced changes in clinical symptoms may be related to or even driven by changes in low-level perceptual processes relevant for the perception and evaluation of causality. For example, one would expect a relationship between tDCS effects on perceptual causality, the jumping-to-conclusions bias and delusions.[19] Notably, jumping to conclusions and overestimation of causality when viewing causal illusions were recently found to correlate among healthy participants.[50] Whether tDCS may remediate patients' impaired perception of causality in social contexts should also be investigated in the future.[21,24,25] Moreover, the causality perception judgment task employed here has not yet been presented to other groups of psychiatric patients, such as patients with bipolar disorder or depression. Future research should test whether impaired causality judgments on this task are indeed specific to patients with schizophrenia or may also be found in other patient populations.

Limitations

Our findings are limited by a relatively small sample size, especially for correlation analyses. It should also be noted that males were over-represented in the sample, considering the global male-to-female ratio of 1.4 for schizophrenia.[51] It is possible that selection bias may have contributed to male over-representation (e.g., male patients may be more likely to volunteer for participation in a brain stimulation study and accept a perceived risk to their physical health). This limits the external validity of our results. Given the low spatial resolution of tDCS, drawing conclusions about specific subregions of the parietal cortex is not possible. Finally, based on our study alone, it is impossible to determine whether tDCS influenced relatively low-level or high-level cognitive processes (i.e., basic visual perception or inferential reasoning), and whether such effects on any of the subprocesses between perception and inference have been narrow and specific (i.e., improved perception regarding the movement direction of small moving circles) or broad and generalizable (i.e., improved causal inferences regarding movements). These issues of interpretation are shared by all similar investigations of perceptual causality.[52] Overall, our data are consistent with a large body of previous work that supports the view that launching events can be used to investigate perceptual causality.[3,5–7,11,17]

Conclusion

We found a brain region–specific effect of tDCS on sensitivity to spatial stimulus characteristics when perceiving causality in launching events among patients with SSD. Right parietal anodal tDCS increased the influence of angle variations on patients' causality perception. Future research should explore whether tDCS-induced changes in perceptual causality judgments may be linked to improvements in SSD symptoms, such as delusions and ideas of reference.

Acknowledgments: The authors thank Lina Eicke-Kanani and Thomas Wallis for their useful comments on the manuscript, Alexei Sirbu and Leona Hömberg for their help with data collection and Bjarne Schülke for his assistance regarding data pre-processing.

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Competing interests: Rasmus Schülke took part in an educational event sponsored by Livanova, a manufacturer of vagus nerve stimulation devices. No other competing interests were declared.

Contributors: Benjamin Straube conceived and supervised the study. Rasmus Schülke was responsible for data acquisition and implementing the experiments. Christina Schmitter recruited patients and performed experiments. Rasmus Schülke performed data analysis. Rasmus Schülke and Benjamin Straube interpreted the data. Rasmus Schülke drafted the manuscript. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Data sharing: The data that support the findings of this study will be made publicly available on Zenodo.

Funding: This work was supported by a research grant from the University Medical Centre Giessen and Marburg (25/2015MR), the German Research Foundation (Ki588/6-2, STR 1146/11-2, STR 1146/8-1, STR 1146/9-1 to Benjamin Straube) and The Adaptive Mind, funded by the Excellence Program of the Hessian Ministry of Higher Education, Science, Research and Art. The funding sources had no role in study design; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the article for publication.

References

1. Michotte AE. *The perception of causality* (T. R. Miles & E. Miles, translators). London: Methuen; 1963.
2. Schlottmann A, Ray ED, Mitchell A, et al. Perceived physical and social causality in animated motions: spontaneous reports and ratings. *Acta Psychol (Amst)* 2006;123:112-43.
3. Moors P, Wagemans J, de-Wit L. Causal events enter awareness faster than non-causal events. *PeerJ* 2017;5:e2932.
4. Scholl BJ, Tremoulet PD. Perceptual causality and animacy. *Trends Cogn Sci* 2000;4:299-309.
5. Blakemore SJ, Fonlupt P, Pachot-Clouard M, et al. How the brain perceives causality: an event-related fMRI study. *Neuroreport* 2001;12: 3741-6.
6. Fugelsang JA, Roser ME, Corballis PM, et al. Brain mechanisms underlying perceptual causality. *Brain Res Cogn Brain Res* 2005;24:41-7.
7. Tschacher W, Kupper Z. Perception of causality in schizophrenia spectrum disorder. *Schizophr Bull* 2006;32:S106-12.
8. Leslie AM. The perception of causality in infants. *Perception* 1982;11: 173-86.
9. Leslie AM, Keeble S. Do six-month-old infants perceive causality? *Cognition* 1987;25:265-88.
10. Saxe R, Carey S. The perception of causality in infancy. *Acta Psychol (Amst)* 2006;123:144-65.
11. Schlottmann A, Ray ED, Surian L. Emerging perception of causality in action-and-reaction sequences from 4 to 6months of age: Is it domain-specific? *J Exp Child Psychol* 2012;112:208-30.
12. Straube B, Chatterjee A. Space and time in perceptual causality. *Front Hum Neurosci* 2010;4:28.
13. Straube B, Wolk D, Chatterjee A. The role of the right parietal lobe in the perception of causality: A tDCS study. *Exp Brain Res* 2011; 215:315-25.
14. Woods AJ, Lehet M, Chatterjee A. Context modulates the contribution of time and space in causal inference. *Front Psychol* 2012;3:371.
15. Blos J, Chatterjee A, Kircher T, et al. Neural correlates of causality judgment in physical and social context-the reversed effects of space and time. *Neuroimage* 2012;63:882-93.
16. Wende KC, Nagels A, Blos J, et al. Differences and commonalities in the judgment of causality in physical and social contexts: an fMRI study. *Neuropsychologia* 2013;51:2572-80.
17. Woods AJ, Hamilton RH, Kranjec A, et al. Space, time, and causality in the human brain. *Neuroimage* 2014;92:285-97.
18. Uhlhaas PJ, Silverstein SM. Perceptual organization in schizophrenia spectrum disorders: empirical research and theoretical implications. *Psychol Bull* 2005;131:618-32.
19. Dudley R, Taylor P, Wickham S, et al. Psychosis, delusions and the "Jumping to Conclusions" reasoning bias: a systematic review and meta-analysis. *Schizophr Bull* 2016;42:652-65.
20. Lindner A, Thier P, Kircher TTJ, et al. Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. *Curr Biol* 2005;15:1119-24.

21. Russell TA, Reynaud E, Herba C, et al. Do you see what I see? Interpretations of intentional movement in schizophrenia. *Schizophr Res* 2006;81:101-11.
22. Garety PA, Freeman D, Jolley S, et al. Reasoning, emotions, and delusional conviction in psychosis. *J Abnorm Psychol* 2005;114:373-84.
23. Moritz S, Woodward TS. Jumping to conclusions in delusional and non-delusional schizophrenic patients. *Br J Clin Psychol* 2005;44:193-207.
24. Blakemore SJ, Sarfati Y, Bazin N, et al. The detection of intentional contingencies in simple animations in patients with delusions of persecution. *Psychol Med* 2003;33:1433-41.
25. Wende KC, Nagels A, Stratmann M, et al. Neural basis of altered physical and social causality judgements in schizophrenia. *Schizophr Res* 2015;161:244-51.
26. Brauns H, Scherer S, Steinmann S. The CASMIN educational classification in international comparative research. In: Hoffmeyer-Zlotnik JHP, Wolf C, editors. *Advances in cross-national comparison: a European working book for demographic and socio-economic variables*. Boston: Springer US; 2003: 221-44.
27. Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. *Clin Neurophysiol* 2007;118:1166-70.
28. Palm U, Feichtner KB, Hasan A, et al. The role of contact media at the skin-electrode interface during transcranial direct current stimulation (tDCS). *Brain Stimul* 2014;7:762-4.
29. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? *Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS* 2015;2015:222–5.
30. Roy LB, Sparing R, Fink GR, et al. Modulation of attention functions by anodal tDCS on right PPC. *Neuropsychologia* 2015;74:96-107.
31. Antal A, Alekseichuk I, Bikson M, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol* 2017;128:1774-809.
32. Iyer MB, Mattu U, Grafman J, et al. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology* 2005;64:872-5.
33. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* 2006;117:845-50.
34. Ambrus GG, Al-Moyed H, Chaieb L, et al. The fade-in–short stimulation–fade out approach to sham tDCS–reliable at 1 mA for naive and experienced subjects, but not investigators. *Brain Stimul* 2012;5:499-504.
35. Schülke R, Straube B. Modulating the assessment of semantic speech–gesture relatedness via transcranial direct current stimulation of the left frontal cortex. *Brain Stimul* 2017;10:223-30.
36. Schülke R, Straube B. Transcranial direct current stimulation improves semantic speech-gesture matching in patients with schizophrenia spectrum disorder. *Schizophr Bull* 2019;45:522-30.
37. Straube B, Schülke R, Drewing K, et al. Hemispheric differences in the processing of visual consequences of active vs. passive movements: a transcranial direct current stimulation study. *Exp Brain Res* 2017;235:3207-16.
38. Straube B, van Kemenade BM, Kircher T, et al. Transcranial direct current stimulation improves action-outcome monitoring in schizophrenia spectrum disorder. *Brain Commun* 2020;2:fcaa151.
39. Nakagawa S, Schielzeth H. A general and simple method for obtaining R2 from generalized linear mixed-effects models. *Methods Ecol Evol* 2013;4:133-42.
40. Wu DH, Morganti A, Chatterjee A. Neural substrates of processing path and manner information of a moving event. *Neuropsychologia* 2008;46:704-13.
41. Battelli L, Alvarez GA, Carlson T, et al. The role of the parietal lobe in visual extinction studied with transcranial magnetic stimulation. *J Cogn Neurosci* 2009;21:1946-55.
42. van Boekholdt L, Kerstens S, Khatoun A, et al. tDCS peripheral nerve stimulation: a neglected mode of action? *Mol Psychiatry* 2021;26:456-61.
43. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nat Commun* 2019;10:266.
44. Brunelin J, Mondino M, Gassab L, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *Am J Psychiatry* 2012;169:719-24.
45. Mondino M, Sauvanaud F, Brunelin J. A review of the effects of transcranial direct current stimulation for the treatment of hallucinations in patients with schizophrenia. *J ECT* 2018;34:164-71.
46. Mondino M, Jardri R, Suaud-Chagny MF, et al. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left Temporo-Parietal junction in patients with schizophrenia. *Schizophr Bull* 2016;42:318-26.
47. Aleman A, Enriquez-Geppert S, Knegtering H, et al. Moderate effects of noninvasive brain stimulation of the frontal cortex for improving negative symptoms in schizophrenia: meta-analysis of controlled trials. *Neurosci Biobehav Rev* 2018;89:111-8.
48. Palm U, Keeser D, Hasan A, et al. Prefrontal transcranial direct current stimulation for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. *Schizophr Bull* 2016;42:1253-61.
49. Lefebvre S, Pavlidou A, Walther S. What is the potential of neurostimulation in the treatment of motor symptoms in schizophrenia? *Expert Rev Neurother* 2020;20:697-706.
50. Moreno-Fernández MM, Blanco F, Matute H. The tendency to stop collecting information is linked to illusions of causality. *Sci Rep* 2021;11:1-3942.
51. Picchioni MM, Murray RM. Schizophrenia. *BMJ* 2007;335:91-5.
52. Choi H, Scholl BJ. Measuring causal perception: connections to representational momentum? *Acta Psychol (Amst)* 2006;123:91-111.