BRAIN COMMUNICATIONS

Transcranial direct current stimulation improves action-outcome monitoring in schizophrenia spectrum disorder

Benjamin Straube, Bianca M. van Kemenade, Tilo Kircher and Rasmus Schülke

Patients with schizophrenia spectrum disorder often demonstrate impairments in action-outcome monitoring. Passivity phenomena and hallucinations, in particular, have been related to impairments of efference copy-based predictions which are relevant for the monitoring of outcomes produced by voluntary action. Frontal transcranial direct current stimulation has been shown to improve action-outcome monitoring in healthy subjects. However, whether transcranial direct current stimulation can improve action monitoring in patients with schizophrenia spectrum disorder remains unknown. We investigated whether transcranial direct current stimulation can improve the detection of temporal action-outcome discrepancies in patients with schizophrenia spectrum disorder. On 4 separate days, we applied sham or left cathodal/right anodal transcranial direct current stimulation in a randomized order to frontal (F3/F4), parietal (CP3/CP4) and frontoparietal (F3/CP4) areas of 19 patients with schizophrenia spectrum disorder and 26 healthy control subjects. Action-outcome monitoring was assessed subsequent to 10 min of sham/transcranial direct current stimulation (1.5 mA). After a self-generated (active) or externally generated (passive) key press, subjects were presented with a visual outcome (a dot on the screen), which was presented after various delays (0–417 ms). Participants had to detect delays between the key press and the visual consequence. Symptom subgroups were explored based on the presence or absence of symptoms related to a paranoid-hallucinatory syndrome. In general, delay-detection performance was impaired in the schizophrenia spectrum disorder compared to the healthy control group. Interaction analyses showed group-specific (schizophrenia spectrum disorder versus healthy control group) and symptom-specific (with/without relevant paranoid-hallucinatory symptoms) transcranial direct current stimulation effects. *Post hoc* tests revealed that frontal transcranial direct current stimulation improved the detection of long delays in active conditions and reduced the proportion of false alarms in undelayed trials of the passive condition in patients. The patients with no or few paranoid-hallucinatory symptoms benefited especially from frontal transcranial direct current stimulation in active conditions, while improvement in the patients with paranoid-hallucinatory symptoms was predominantly reflected in reduced false alarm rates in passive conditions. These data provide some first evidence for the potential utility of transcranial direct current stimulation in improving efference copy mechanisms and action-outcome monitoring in schizophrenia spectrum disorder. Current data indicate that improving efference copy-related processes can be especially effective in patients with no or few positive symptoms, while intersensory matching (i.e. task-relevant in passive conditions) could be more susceptible to improvement in patients with paranoid-hallucinatory symptoms.

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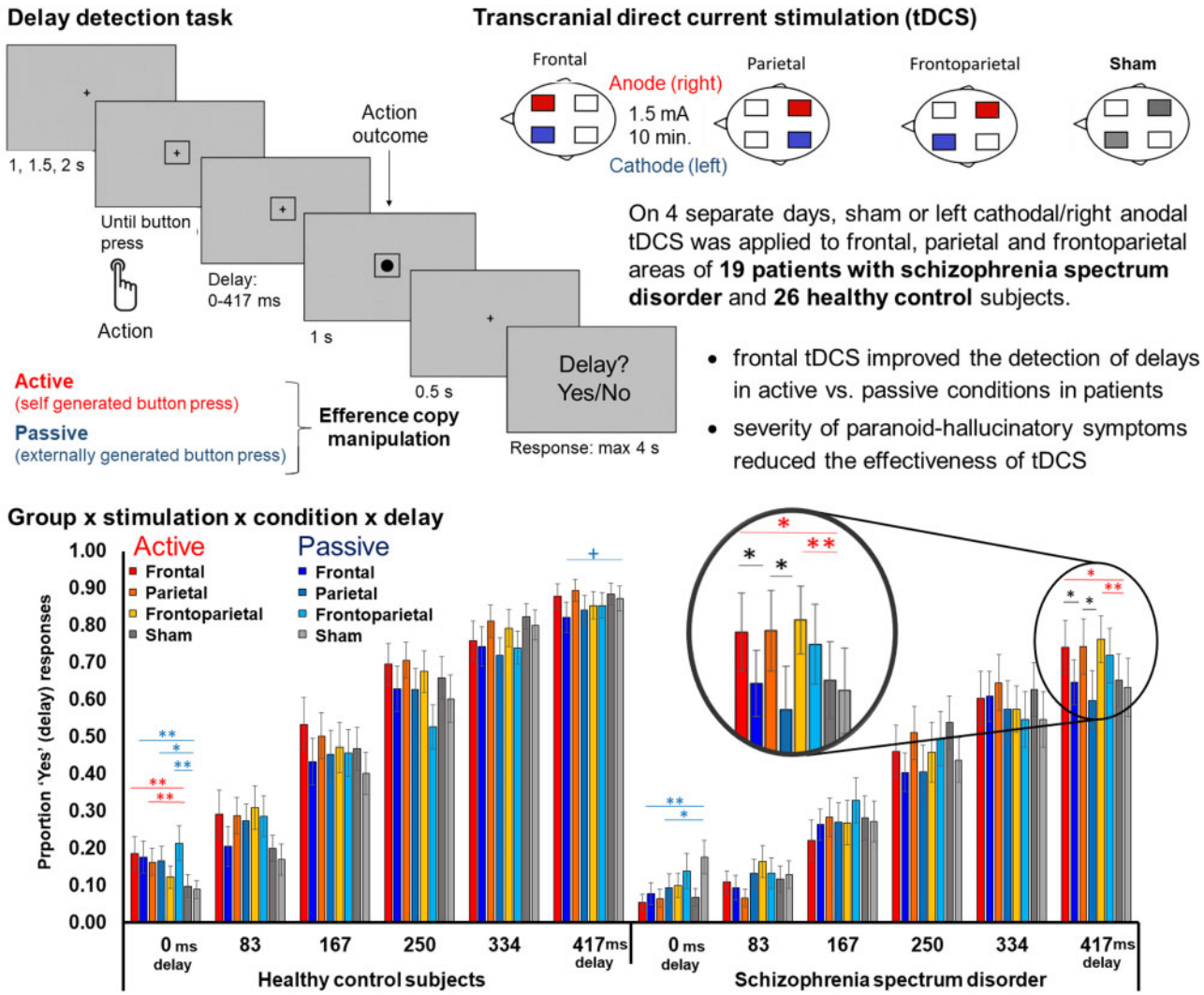
Abbreviations: GEE = generalized equation estimation; GM = German Modification; HC = healthy control; ICD-10 = International Classification of Diseases, Tenth Revision; LFC–RFA = left frontal cathode–right frontal anode; LFC–RPA = left frontal cathode–right parietal anode; LPC–RPA = left parietal cathode–right parietal anode; SSD = schizophrenia spectrum disorder; SSD phs− = patient group without relevant paranoid-hallucinatory symptoms; SSD phs+ = patient group with relevant paranoid-hallucinatory symptoms; tDCS = transcranial direct current stimulation.

Graphical Abstract



Introduction

The sensory outcomes of one's own actions are usually highly predictable, and small temporal violations of expected action-outcome associations can be detected with relative ease by healthy participants (van Kemenade *et al.*, 2016, 2017, 2019*b*; Schmalenbach *et al.*, 2017; Straube *et al.*, 2017*b*; Arikan *et al.*, 2019; Pazen *et al.*, 2020; Uhlmann *et al.*, 2020). These predictive mechanisms allow us to anticipate the future state of both the environment and ourselves to compensate for delays in the transmission of neural signals and to conserve resources by suppressing the processing of self-generated stimuli when they match our predictions (Straube *et al.*, 2017*b*). Furthermore, differences in predictability between self-generated and externally generated sensory information might help to distinguish external events from the sensory consequences of our own actions (Pynn and DeSouza, 2013). Dysfunctions in the processing of one's own action consequences have been linked to the severe symptoms of patients with schizophrenia, such as hallucinations (e.g. hearing internal verbalizations as

external voices) or passivity/ego-disturbances (e.g. feeling that one's own thoughts and actions are implanted or externally controlled; for reviews, see Leube *et al.*, 2008; Pynn and DeSouza, 2013). Therefore, the investigation of interventions influencing the processing of one's own movements has potential for the discovery of new treatments for mental disorders where this type of processing is impaired.

A variety of approaches have been used to investigate the perception of one's own action consequences and related predictive mechanisms (Straube *et al.*, 2017*a*). These comprise the presentation of self-initiated action conditions in which the sensory consequences are spatially remapped, e.g. by rotating visual feedback of the hand (Farrer *et al.*, 2003; Synofzik *et al.*, 2010) or are temporally remapped, e.g. by delaying visual and/or auditory feedback (Blakemore *et al.*, 2001; Hashimoto and Sakai, 2003; Leube *et al.*, 2003, 2010; Farrer *et al.*, 2008; Kurayama *et al.*, 2012; Backasch *et al.*, 2014; van Kemenade *et al.*, 2016, 2017, 2019*b*; Schmalenbach *et al.*, 2017; Straube *et al.*, 2017*b*; Arikan *et al.*, 2019; Pazen *et al.*, 2020; Uhlmann *et al.*, 2020). In addition to these voluntary conditions, passive and/or unpredictable control conditions, such as externally generated/passive movements, have been studied (Blakemore *et al.*, 1998, 1999, 2000*b*; Arikan *et al.*, 2019; van Kemenade *et al.*, 2019*b*; Pazen *et al.*, 2020; Uhlmann *et al.*, 2020). Delay-detection tasks, in which a lengthened interval between one's own action and the resulting perceptual consequences has to be detected, have been used in several studies focusing on temporal outcome prediction (Hashimoto and Sakai, 2003; Leube *et al.*, 2003, 2010; Farrer *et al.*, 2008; van Kemenade *et al.*, 2016, 2019*a*; Straube *et al.*, 2017*b*; Pazen *et al.*, 2020; Uhlmann *et al.*, 2020). These tasks focus the participant's attention on the perceptual consequences of an action and provide a direct behavioural measure of the function of interest, namely the comparison of predicted and perceived time points of sensory information.

Patients with schizophrenia are less sensitive to delays between their own actions and the sensory consequences thereof (Leube *et al.*, 2010). This impairment might be related to disturbances in the experience of being the initiator of one's own actions and to delusions, both of which are often present in patients with schizophrenia spectrum disorder (SSD). In particular, delusions of influence/control (passivity phenomena) and auditory hallucinations in schizophrenia might result from deficits in an inferential mechanism that allows distinguishing whether or not a sensory event has been self-produced (Feinberg, 1978; Blakemore *et al.*, 2000*a*; Synofzik *et al.*, 2010). This self-other distinction is probably made by comparing the actual sensory information of one's own action with the predicted consequences (comparator mechanism). Patients have been assumed to generate imprecise predictions about the sensory consequences of self-generated actions. This idea is supported not only by the reduced delay-detection performance (Leube *et al.*, 2010) but also by a reduced detection of spatial manipulation of action consequences (e.g. rotated visual feedback in a pointing task; Synofzik *et al.*, 2010). However, no effective intervention is presently available to improve action-outcome predictions or, more generally, action-outcome monitoring in patients with SSD.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique increasingly used for modulation of central nervous system excitability in humans (see Woods *et al.*, 2016, for a review). Furthermore, the use of tDCS has been shown to improve performance in various tasks and can reduce symptoms in patients with schizophrenia (for reviews, see Gupta *et al.*, 2018; Kennedy *et al.*, 2018; Lee *et al.*, 2018; Kostova *et al.*, 2020). One general assumption is that anodal tDCS increases cortico-spinal excitability and cathodal tDCS decreases it (Nitsche and Paulus, 2000). Recent studies on healthy subjects suggest that the processing of action-outcomes can be influenced by tDCS (Khalighinejad and Haggard, 2015; Straube *et al.*, 2017*a*). For example, anodal stimulation of the left angular gyrus has been shown to reduce the perceived temporal binding between action and sensory outcome (intentional binding), independent of the location of the cathodal electrode (frontal/parietal; Khalighinejad and Haggard, 2015). In contrast, another study showed that anodal stimulation of the left dorsolateral prefrontal cortex (cathode on the right supraorbital area) increased the temporal binding of actions towards tones, but only in a subset of experiments in which participants endogenously chose between different actions (Khalighinejad *et al.*, 2016). A third study investigating intentional binding stimulated the pre-supplementary motor area and found a polarization-independent reduction of intentional binding (Cavazzana *et al.*, 2015; see also Javadi, 2015). These studies on intentional binding were complemented by our investigation of delay-detection performance with active and passive finger movements (button presses), in which we applied tDCS to frontal, parietal and frontoparietal areas in healthy participants (Straube *et al.*, 2017*a*). We found the highest detection performance after frontal stimulation. Furthermore, we found that the advantage for active versus passive conditions was larger for left hemispheric anodal than for cathodal stimulation. However, this evidence was limited to the investigation of healthy participants. To date, the tDCS effects on action-outcome monitoring in patients with SSD remain unknown.

Neuroimaging results link symptoms of passivity with increased parietal activation that fails to show stimulus-driven modulation (Pynn and DeSouza, 2013). This has been interpreted as a failed processing of efference copy signals. These differences in parietal activation compared with healthy controls (HCs) support the hypothesis that increased noise in the parietal–cerebellar network results in a failure to monitor one's own actions and to attribute

the cause to self-movement (Blakemore *et al.*, 2003; Schnell *et al.*, 2008; Pynn and DeSouza, 2013). Distinct cerebellar, parietal and prefrontal contributions to the processing and evaluation of feedback delays have recently been revealed using functional MRI in healthy participants (van Kemenade *et al.*, 2019*b*). While the cerebellum was specifically activated for feedback delays in active compared to passive movements, the activations in the parietal and temporal areas correlated with the delay-detection thresholds in both the active and passive conditions (van Kemenade *et al.*, 2019*b*). These findings complement previous neuroimaging studies suggesting that activity in the parietal lobe, and specifically activity in the angular gyrus, correlates positively with the increasing delay between the action and visual feedback (Farrer *et al.*, 2003; Leube *et al.*, 2003; David *et al.*, 2007; Farrer *et al.*, 2008; van Kemenade *et al.*, 2017). However, the medial and left frontal brain regions seem to be connected to processing in the angular gyrus during a delay-detection task (van Kemenade *et al.*, 2017). Furthermore, activity in the frontal cortex has been observed for awareness of temporal delays (Farrer *et al.*, 2003; Farrer *et al.*, 2008) or for comparisons of subjectively delayed (delay detected) versus undelayed (delay undetected) trials (Straube *et al.*, 2017*b*), suggesting an involvement of the prefrontal cortex in action-outcome monitoring as well. Nevertheless, the possibility that parietal or frontal tDCS can improve delay-detection performance in patients with SSD has not yet been explored.

The aim of this study was to investigate the effects of tDCS on action-outcome monitoring in patients with SSD using a delay-detection task in which the patients had to detect delays between self-initiated (active) and externally generated (passive) actions and their outcomes. We hypothesized that patients with SDD would show an overall reduced delay-detection performance when compared to a HC group. Based on previous studies, the delay-detection impairment in patients was predicted to be especially pronounced in active (compared to passive) trials. Concerning the tDCS effect, we expected to see a general improvement across active and passive conditions in the delay-detection task after frontal tDCS in both groups (Straube *et al.*, 2017*a*). However, as functional MRI studies revealed a parietal cortex activation in relation to intersensory processing in a delay-detection task (van Kemenade *et al.*, 2017, 2019*b*), as well as strong frontoparietal connectivity, the stimulation of the parietal cortex could also lead to better delay-detection performance across conditions and groups.

Considering previous claims that increased noise in the parietal–cerebellar network results in a failure to monitor one's own actions and to attribute the cause of self-generated movement (Spence *et al.*, 1997; Blakemore *et al.*, 2003; Schnell *et al.*, 2008; Pynn and DeSouza, 2013), we also considered that parietal and frontoparietal stimulation might increase the difference between active and passive conditions specifically in patients with SSD. Finally, we explored the effect of symptoms which had been related to efference-copy dysfunctions (e.g. passivity experiences or hallucinations; Blakemore *et al.*, 2000*a*; Leube *et al.*, 2010; Pynn and DeSouza, 2013) on tDCS-related changes by testing whether patients with greater impairment and a paranoid-hallucinatory syndrome (SSD phs+) would receive greater or lesser benefit from tDCS when compared to patients without relevant symptoms (SSD phs−).

Materials and methods

Sample description

All subjects were native-level German speakers, predominantly right-handed (except one patient and one control subject), with normal or corrected-to-normal vision, no hearing deficits and no electric implants. All subjects gave written informed consent prior to participation and received an expense allowance. The study was approved by the local ethics committee of the medical faculty of the Philipps-University Marburg, Germany (https://www.uni-marburg.de/de/fb20/fachbereich/gremien/ethik, 18 September 2020, date last accessed; registration number: 191/12).

Patients

Twenty patients with SSD were recruited at the Department of Psychiatry and Psychotherapy, Philipps-University, Marburg, Germany (Schülke and Straube, 2019). Due to technical reasons, the data from one patient were missing, leading to a final sample of 19 patients (17 males, 2 females; mean age = 37.53, SD 13.76, mean level of education as measured by the CASMIN-Classification = 5.42, SD = 1.92; see Table 1). Twelve patients were diagnosed with paranoid schizophrenia [International Classification of Diseases, Tenth Revision (ICD-10) German Modification, GM F20.0], four patients were diagnosed with schizoaffective disorder (ICD-10 GM F25.0), one patient was diagnosed with residual schizophrenia (ICD-10 GM F20.5), one patient was diagnosed with prodromal schizophrenia (ICD-10 GM F21.0) and one patient was diagnosed with acute and transient psychotic disorder (ICD-10 GM F23.0). All patients were under stable medication when undergoing the study (see Table 1).

Exploratory analyses were performed with patient subgroups with relevant symptoms, which had been related to efference-copy dysfunctions, and were defined based on the presence of hallucinations or delusions (defined based on Scale for the Assessment of Positive Symptoms subscales 1 and 2). Patients scoring three points or more on one of these subscales were considered as the SSD group with relevant symptoms (SSD phs+), and those with less than three points were coded as the SSD group without relevant symptoms (SSD phs−). Importantly, both groups did not differ in age, education, negative

Table 1 Sample characteristics

A. Sample characteristics	HC		SSD		HC versus SSD	
	Mean	SD	Mean	SD	*F*/χ2	Sig.
N	26		19			
Female/male	11/15		2/17		**5.397**	**0.020***
Age	37.269	13.757	37.526	10.746	0.005	0.946
Education	5.923	2.134	5.421	1.924	0.659	0.421
SAPS total			10.294	12.746		
SANS total			18.529	17.653		
B. Symptom subgroups	**SSD phs+**		**SSD phs−**		**SSD phs+ versus phs−**	
	Mean	SD	Mean	SD	*F*/χ2	Sig.
N	9		8			
Female/male	1/8		1/7		0.080	0.929
Age	37.333	9.618	38.750	12.815	0.067	0.799
Education	5.333	2.291	6.000	1.195	0.543	0.473
SAPS total	17.000	14.062	2.750	4.743	**7.416**	**0.016***
SAPS 1 (hallucinations)	3.667	7.616	0.000	0.000	1.841	0.195
SAPS 2 (delusions)	10.889	7.044	0.875	1.246	**15.623**	**0.001****
SAPS 2a (delusions of control)	1.111	1.269	0.000	0.000	**6.085**	**0.026***
SAPS 3 (bizarre behaviour)	0.444	1.014	0.375	0.744	0.025	0.876
SAPS 4 (formal thought disorder)	2.000	3.000	1.571	4.158	0.058	0.814
SAPS 5 (inappropriate affect)	0.111	0.333	0.714	1.254	1.944	0.185
SANS total	17.111	16.534	20.125	19.860	0.117	0.737

Positive and negative symptoms were assessed with the Scale for the Assessment of Positive Symptoms [SAPS; Andreasen (1984)], and the Scale for the Assessment of Negative Symptoms [SANS; Andreasen (1981)]. chi^2: chi-square. Significant effects ($P < 0.05$) are highlighted in bold letters. * $P < 0.05$, ** $P < 0.01$.

symptoms or other subscales of the Scale for the Assessment of Positive Symptoms, but they significantly differed in the 'delusion' sum and particularly the 'delusion of control' (Scale for the Assessment of Positive Symptoms item 15) symptom score (see Table 1). A more stringent selection based on items defining passivity phenomena (Scale for the Assessment of Positive Symptoms items, 15, 16, 17 and 18) would lead to comparable results but less balanced sample sizes (SSD phs+, $n = 7$ versus SSD phs− $N = 10$).

Healthy controls

Twenty-nine healthy subjects served as a control group (18 males, 11 females; mean age = 36.52 years, SD = 13.23, range = 40; average level of education as measured by the CASMIN-Classification = 5.97, SD = 2.11, range = 6) and were matched to the patients based on age and education (see Table 1). All HCs fulfilled the following inclusion criteria: no past or current neurologic illness and alcohol or drug abuse; free of metal implants. Data of a sub-sample of 16 HCs have already been published elsewhere (Straube *et al.*, 2017*a*).

Transcranial direct current stimulation

We used a DC-Stimulator from neuroConn GmbH (Ilmenau). Frontal electrodes were positioned at F3/F4 and parietal electrodes were positioned at C3-P3/C4-P4 (between C3 and P3/between C4 and P4), according to the 10–20 EEG system (for further details, see Schülke and Straube, 2017, 2019; Straube *et al.*, 2017*a*). A current of 1.5 mA was applied to the head using saline-soaked sponges (0.9% NaCl, to minimize side-effects, 5 cm * 7 cm) placed on rubber electrodes, resulting in a current density of 0.043 mA/cm^2. The stimulation duration was 10 min, plus 10 s fade in/fade out. All parameters complied with tDCS safety guidelines (Borckardt *et al.*, 2011; Brunelin *et al.*, 2012; Bikson *et al.*, 2016; Schwippel *et al.*, 2017). Sessions were performed at least 20 h apart to ensure that tDCS effects had completely faded away by the beginning of each new session. Sham stimulation was performed using the sinus mode for a duration of 30 s (Gandiga *et al.*, 2006). The delay-detection task (see below) was performed ~20 min after stimulation (range: 14–31 min).

Experimental design

We applied right anodal, left cathodal and sham stimulation to the frontal (F3/F4) and parietal (CP3/CP4) areas (see Fig. 1A; Schülke and Straube, 2019). Each patient took part in four independent tDCS sessions and underwent four different stimulation conditions, one on each day (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode): (i) frontal condition leftfrontal cathode–right frontal anode (LFC–RFA), (ii) parietal condition left parietal cathode–right parietal anode (LPC–

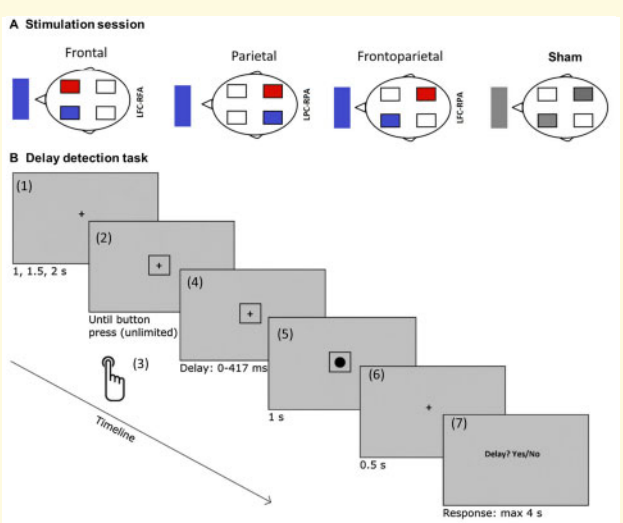


Figure 1 Study design and example trial. (**A**) Study design showing the stimulation conditions (see Schülke and Straube, 2017). Each subject underwent four stimulation sessions (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode) on four different days. The coloured bars highlight the polarization (red = right anodal stimulation; blue = left cathodal stimulation). (**B**) Example of a single trial (cf. Straube *et al.*, 2017*a*). Each trial started with an intertrial interval with a fixation cross (1), followed by a cue which appeared in the form of the outline of a square (2). This square indicated that, from that point on, participants could either press the button or the button could be pulled down (in passive blocks) by the computer (3). Both active and passive button presses elicited, after a variable delay (4), the presentation of a dot on the screen (5). After offset of the stimuli, a 500 ms interval with a fixation cross followed (6). Subsequently, the question 'Delay? Yes/No' was presented on the screen (7). Participants were given a maximum of 4 s to answer.

RPA), (iii) frontoparietal condition left frontal cathode–right parietal anode (LFC–RPA) and (iv) sham condition. To control for any effects of order and repetition, the order of stimulation conditions was pseudo-randomized and counterbalanced across subjects. The HCs underwent three additional inverse stimulation conditions (see Schülke and Straube, 2017; Straube *et al.*, 2017*a*). However, to achieve comparability to the patients who underwent four stimulation sessions only, a sham stimulation was always applied in one of the first four sessions. During stimulation, the participants viewed videos of an actor and judged the relationship of speech and co-speech gestures produced by the actor (Schülke and Straube, 2017, 2019). All experimenter were blind regarding the hypotheses. Participants were blind regarding the stimulation condition.

Delay-detection task and procedure

The delay-detection task has been described and successfully applied in previous studies (van Kemenade *et al.*, 2016; Schmalenbach *et al.*, 2017; Straube *et al.*, 2017*a*). The task was performed ~20 min after stimulation to assess tDCS effects at a time point when potential side-effects have diminished and rather durable (long-term) effects of tDCS are present (Straube *et al.*, 2017*a*). During the interval after stimulation, a causality judgment task was performed (cf. Straube *et al.*, 2011), which is not part of this study.

During the delay-detection task, the participants sat behind a computer screen (60 Hz) at a viewing distance of ~54 cm. They placed their right index fingers on the button, which was located inside a black box so that they could not see their right hands during the experiment. The action's outcome was a visual stimulus in form of a black dot (1.5° visual angle, 1 s duration), presented centrally on a grey background. Stimuli were presented using Octave and the Psychtoolbox (Brainard, 1997), either at the time of the button press or with a variable delay (0, 83, 167, 250, 333 or 417 ms, corresponding to 0, 5, 10, 15, 20 or 25 frames). Each session was further divided into an active and a passive block, presented in counterbalanced order. A custom-made device with an electromagnet was used as a button pad. In active conditions, the button was pressed actively by the participants. During passive conditions, the button was pulled down (5 mm) by the electromagnet, which was controlled by the computer. The participants' right index finger was loosely tied to the button with a soft bandage so that the finger would be pulled down with the button in passive conditions. In active conditions, the bandage stayed tied. In both active and passive conditions, the end of the movement was well noticeable. In active blocks, the participants were instructed to wait with their button press for at least 700 ms after the appearance of the cue and as long as they wanted. This was done to elicit a well-prepared, self-initiated button press, rather than an automatic action as a reflex to the cue (Rohde and Ernst, 2012; van Kemenade *et al.*, 2016). If the button was pressed too early, the text 'Too early' was presented and the trial was repeated. Participants wore earplugs, and white noise was played via headphones throughout the whole experiment to mask the sound of the electromagnet pulling the button down.

The task was always to detect delays between active/passive button presses and the presented stimuli. The participants answered 'Yes, there was a delay' (positive delay response) by pressing a button with their left middle fingers, or 'No, there was no delay' (negative delay response) by pressing a button with their left index fingers. The trial procedure is described in Fig. 1B. Participants were familiarized with the stimuli and procedure prior to the first experimental session.

The main experiment consisted of 120 trials per session, with 60 trials per condition (10 per delay) presented in a random order. Each session was divided into an active and a passive block. Each run thus comprised 60 trials and had a duration of 5 min.

Statistical analysis

We performed generalized equation estimation (GEE) for delay responses, as implemented in SPSS Statistics 25 for Windows by IBM. We chose GEE because they work well, even in cases of unmeasured dependence between outcomes, and were thus useful for our complex, repeated-measures design (see Straube *et al.*, 2011; Schülke and Straube, 2017, 2019). We used an AR (1) working correlation structure and robust (sandwich) covariance estimators for the regression coefficients. The binary logistic link function was used to model delay responses.

We included the following predictors in our model: *group* (HC, patients with SSD), *stimulation* (frontal, parietal, frontoparietal, sham), *condition* (active, passive) and *delay* (0, 83, 186, 250, 334, 417 ms). We used a comprehensive model that included all the factorial interactions of the above listed factors.

However, based on our hypotheses of significant differences between HC/patients and frontal/parietal stimulation, we were particularly interested to determine whether *group*- and *stimulation*-dependent effects would exist for *condition* and *delay* (i.e. significant effects for the interactions *group* × *stimulation* × *condition*, *group* × *stimulation* × *delay* and *group* × *stimulation* × *condition* × *delay*).

After running our main analysis, including all four stimulation conditions, we performed different *post hoc* tests for trials with no delay (0 ms) and long delays (417 ms) to explore the direction of tDCS effects compared to the sham control condition. We further tested if tDCS effects were specific for active conditions by performing direct comparisons to the passive control condition.

The identical procedure was performed for symptom subgroups (SSD phs+/− versus SSD phs+).

As all *post hoc* tests reveal different aspects of the main analyses, and as we only interpret *post hoc* tests of significant factorial interactions of the main analyses, the *post hoc* tests were not corrected for multiple comparisons.

Control analyses of the main analyses, including male subjects only, were performed to check if group differences were based on gender differences due to different proportions of female subjects in the patient ($n = 2$) or healthy subject ($n = 11$) groups.

Data availability

Data tables (including single subject raw data for all trials) and analysis scripts to replicate the reported analyses or for future explorations can be found at Zenodo (doi: 10.5281/zenodo.3968511).

Results

Comparison between patients with SSD and HCs

The overall analysis showed that SSD patients reported fewer delays than HCs did [main effect: *group*; Wald Chi-Square (df = 1) = 9.175, sig. = 0.002], especially for trials with long delays [interaction: *group* × *delay*; Wald Chi-Square (df = 5) = 11.731, sig. = 0.039, see Fig. 2 and Table 2]. Interestingly, tDCS specifically increased the overall positive delay responses in the HCs compared to the patients after parietal stimulation [interaction: *group* × *stimulation*; Wald Chi-Square (df = 3)=7.945, sig.=0.047] as indicated by the *post hoc* tests (HC, LPC–RPA versus sham: mean diff. = 0.05, std. error = 0.023, df = 1; sig. = 0.036; 95% CI: 0.00–0.09). Furthermore, the interaction *group* × *stimulation* × *delay* was significant [Wald Chi-Square (df = 15) = 84.570, sig. < 0.001; see Fig. 3A and Table 2], indicating that patients profited from frontoparietal tDCS regarding the detection of long delays (SSD group, 417 ms delay, sham versus LFC–RPA; see Supplementary Table 1A) and from frontal tDCS regarding false alarm rates in undelayed trials (SSD group, 0 ms delay, sham versus LFC–RFA, see Supplementary Table 1A). In contrast, HCs showed an increase in false delay responses in undelayed trials after frontal stimulation (HC group, 0 ms delay, sham versus LFC–RFA; see Supplementary Table 1A and Fig. 3A).

Finally, we tested the specificity of tDCS effects on active compared to passive conditions (interaction: *group* × *stimulation* × *condition* × *delay*) and found a significant effect [Wald Chi-Square (df = 15) = 42.443, sig. < 0.001; see Fig. 3B and Table 2]. Patients in active conditions profited from frontal tDCS [compared to passive conditions (SSD group, LFC–RFA, active versus passive: mean diff. = −0.09, std. error = 0.035, df = 1; sig. = 0.007; 95% CI: −0.16 to −0.03) and compared to sham stimulation (SSD group, active, LFC–RFA versus sham,

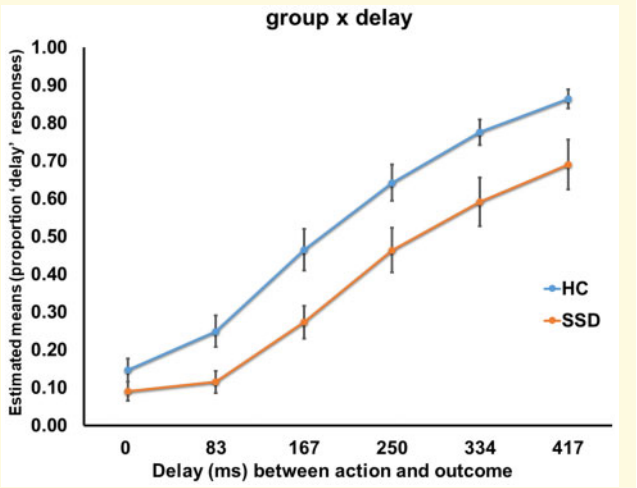


Figure 2 Proportion of positive 'delay' responses dependent on *group* (HC versus SSD), and *delay*. Interaction of *group* × *delay*, indicating reduced positive delay responses in patients with SSD, especially for action feedback with delays. Error bars indicate the standard error of the mean.

Table 2 Group comparisons (GEE models for delay responses)

HS versus SDD				SDD phs+/phs−			
	Wald Chi-Square	df	Sig.		Wald Chi-Square	df	Sig.
(Intercept)	4.850	1	0.028	(Intercept)	10.487	1	0.001
group	**9.175**	**1**	**0.002**	Group	2.555	1	0.110
stimulation	5.497	3	0.139	Stimulation	**11.314**	**3**	**0.010**
condition	1.637	1	0.201	Condition	0.934	1	0.334
delay	**166.629**	**5**	**<0.001**	Delay	**79.658**	**5**	**<0.001**
group * stimulation	**7.945**	**3**	**0.047**	group * stimulation	3.022	3	0.388
group * condition	1.642	1	0.200	group * condition	1.654	1	0.198
group * delay	**11.731**	**5**	**0.039**	group * delay	5.412	5	0.368
stimulation * condition	2.268	3	0.519	stimulation * condition	0.463	3	0.927
stimulation * delay	**38.580**	**15**	**0.001**	stimulation * delay	**18533.957**	**15**	**<0.001**
condition * delay	**26.164**	**5**	**<0.001**	condition * delay	**75.872**	**5**	**<0.001**
group * stimulation * condition	0.592	3	0.898	group * stimulation * condition	3.713	3	0.294
group * stimulation * delay	**84.570**	**15**	**<0.001**	group * stimulation * delay	**9764.594**	**15**	**<0.001**
group * condition * delay	3.456	5	0.630	group * condition * delay	**21.702**	**5**	**0.001**
stimulation * condition * delay	**77.926**	**15**	**<0.001**	stimulation * condition * delay	**484.854**	**15**	**<0.001**
group * stimulation * condition * delay	**42.443**	**15**	**<0.001**	group * stimulation * condition * delay	**1887.811**	**15**	**<0.001**

Dependent variable: response

Model: (Intercept), group, stimulation, condition, delay, group * stimulation, group * condition, group * delay, stimulation * condition, stimulation * delay, condition * delay, group * stimulation * condition, group * stimulation * delay, group * condition * delay, stimulation * condition * delay, group * stimulation * condition * delay

Control analyses with male subjects only revealed comparable results (see Supplementary Table 2). Significant effects ($P < 0.05$) are highlighted in bold letters.

Dependent variable: response

Model: (Intercept), group_phs, stimulation, condition, delay, group_phs * stimulation, group_phs * condition, group_phs * delay, stimulation * condition, stimulation * delay, condition * delay, group_phs * stimulation * condition, group_phs * stimulation * delay, group_phs * condition * delay, stimulation * condition * delay, group_phs * stimulation * condition * delay

Significant effects ($P < 0.05$) are highlighted in bold letters.

see Table 3)] regarding the detection of long delays. In contrast, in passive conditions, they profited from frontal tDCS in that they reported fewer false delays in undelayed trials (SSD group, passive, LFC–RFA versus sham; see Table 3). The active versus passive difference was also significant for long delays after parietal stimulation (SSD group, LPC–RPA, active versus passive, mean diff. = 0.14, std. error = 0.049, df = 1, sig. = 0.003, 95% CI 0.05–0.24). However, no change in contrast to the sham condition could be detected for active trials after parietal stimulation in patients with SSD (see Table 3), making it difficult to trace back the active–passive difference to parietal tDCS. The HC group, however, showed an increase in false delay responses in undelayed trials after frontal (HC group, active, LFC–RFA versus sham; see Table 3) and parietal stimulation (HC group, active, LFC–RFA versus sham; see Table 3). Control analyses with male subjects only revealed comparable results (see Supplementary Table 2).

Results of symptom-specific subgroups (SSD phs+ versus SSD phs−)

In addition to the comparison between HC and patients with SSD, we explored subgroups of patients with (phs+) and without (phs−) symptoms of a paranoid-hallucinatory syndrome (Fig. 4). We found significant group differences in the effect of stimulation on the detection of delays [interaction: *group* × *stimulation* × *delay*; Wald Chi-Square (df = 15) = 9764.594, sig. < 0.001, see Table 2 and Fig. 4A], indicating that the SSD phs− group profited from frontal tDCS concerning false alarm rates in undelayed trials after frontal tDCS (see *post hoc* test: SSD phs− group, 0 ms delay, LFC–RFA versus sham; Supplementary Table 1B), while the SSD phs+ group showed a trend after frontoparietal tDCS for improved detection performance concerning long delays (SSD phs+ group, 417 ms delay, LFC–RPA versus sham; Supplementary Table 1B). Furthermore, we found condition-specific (active versus passive) group differences in the effect of stimulation on the detection of delays [interaction: *group* × *stimulation* × *condition* × *delay*; Wald Chi-Square (df = 15) = 1887.811, sig. < 0.001, see Table 2 and Fig. 4B and C], indicating the most prominent improvement in the SSD phs− group (see Table 4 and Fig. 4B). In the SSD phs− group, the improvement was specific for active compared to passive conditions after frontal (SSD phs−, LFC–RFA, 417 ms delay, active versus passive: mean diff. = 0.10, std. error = 0.033, df = 1; sig. = 0.003; 95% CI: 0.03–0.16), parietal (SSD phs−, LPC–RPA, 417 ms delay, active versus passive: mean diff. = 0.18, std. error =

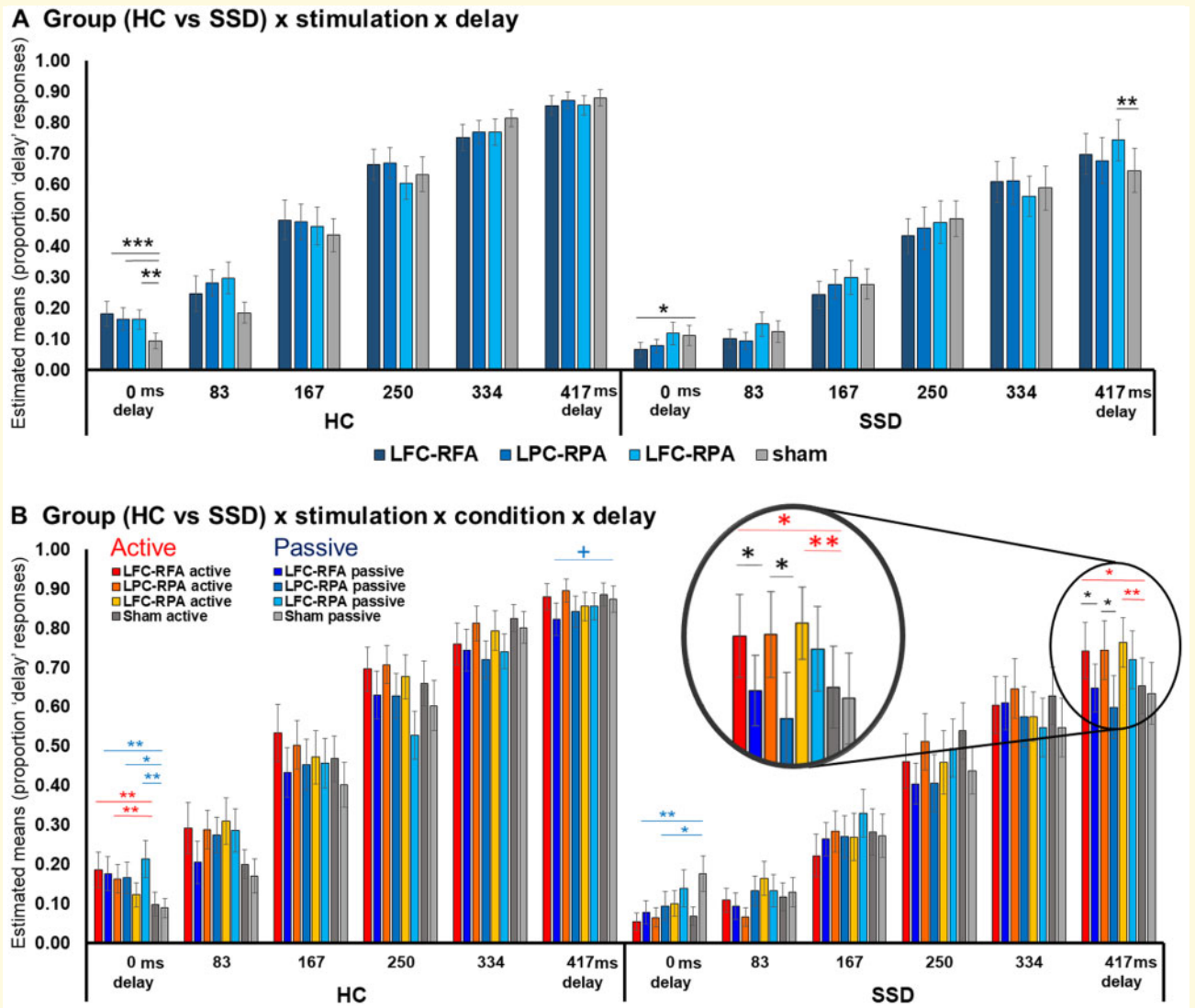


Figure 3 Group differences (HC versus SSD) in positive 'delay' responses. (**A**) Proportion of positive 'delay' responses dependent on *group* (HC versus SSD), *stimulation* and *delay*. While patients with SSD benefited from frontoparietal tDCS regarding the detection of long delays and from frontal tDCS regarding false alarm rates in undelayed trials, the HCs showed an increase in false delay responses in undelayed trials after frontal stimulation. (**B**) Proportion of positive delay responses dependent on *group* (HC versus SSD), *stimulation*, *condition* [active (red/orange/dark grey) versus passive (dark to light blue/light grey)] and *delay*. Patients specifically benefited from frontal tDCS: they reported more delays in active trials with long delays (compared to passive trials and sham stimulation), and showed a reduction in false delay responses in undelayed, passive trials. In contrast, frontal and parietal tDCS worsened performance in HCs: they showed an increase in false delay responses in undelayed (active and passive) trials (compared to sham). Stimulation conditions: frontal, LFC–RFA; parietal, LPC–RPA; frontoparietal, LFC–RPA; sham. Wald Chi-Square statistics of the GEE procedure has been used for statistical comparisons (see Materials and Method section, Tables 2 and 3 for *post hoc* comparisons). $^{+}P < 0.10$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

0.077, df = 1; sig. = 0.02; 95% CI: 0.03–0.33) and frontoparietal tDCS (SSD phs−, LFC–RPA, 417 ms delay, active versus passive: mean diff. = 0.09, std. error = 0.040, df = 1; sig. = 0.024; 95% CI: 0.01–0.17). However, compared to the sham condition, the interaction effect resulted in a trend for the frontoparietal condition and in a significant effect only for the parietal tDCS (see Table 4 and Fig. 4B). The SSD phs+ group, in contrast, profited at least in the passive conditions regarding delay detection after frontoparietal tDCS and regarding errors in the undelayed passive conditions after frontal and parietal stimulation (see Table 4 and Fig. 4C). Interestingly, in the SSD phs+ group, the active and passive conditions differed significantly after frontal stimulation as well (SSD phs+, LFC–RFA, 417 ms delay, active versus

Table 3 ***Post hoc*** **tests sham versus tDCS for delayed (417 ms) and undelayed trials in HC and SSD**

								95% Wald conf. interval for diff.	
HC sham active undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
HC	frontal	active	undelayed	**−0.09****	0.033	1	**0.008**	−0.15	−0.02
HC	parietal	active	undelayed	**−0.06****	0.024	1	**0.008**	−0.11	−0.02
HC	frontoparietal	active	undelayed	−0.02	0.027	1	0.364	−0.08	0.03
HC sham active 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
HC	frontal	active	417 ms delayed	0.00	0.029	1	0.871	−0.05	0.06
HC	parietal	active	417 ms delayed	−0.01	0.030	1	0.733	−0.07	0.05
HC	frontoparietal	active	417 ms delayed	0.03	0.043	1	0.483	−0.05	0.11
HC sham passive undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
HC	frontal	passive	undelayed	**−0.09****	0.032	1	**0.006**	−0.15	−0.03
HC	parietal	passive	undelayed	**−0.08***	0.031	1	**0.015**	−0.14	−0.01
HC	frontoparietal	passive	undelayed	**−0.12****	0.044	1	**0.005**	−0.21	−0.04
HC sham passive 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
HC	frontal	passive	417 ms delayed	0.05^{+}	0.026	1	0.053	0.00	0.1
HC	parietal	passive	417 ms delayed	0.03	0.036	1	0.390	−0.04	0.1
HC	frontoparietal	passive	417 ms delayed	0.02	0.026	1	0.486	−0.03	0.07
SSD sham active undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD	frontal	active	undelayed	0.01	0.016	1	0.431	−0.02	0.04
SSD	parietal	active	undelayed	0.00	0.032	1	0.926	−0.06	0.07
SSD	frontoparietal	active	undelayed	−0.03	0.022	1	0.129	−0.07	0.01
SSD sham active 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD	frontal	active	417 ms delayed	**−0.09***	0.042	1	**0.036**	−0.17	−0.01
SSD	parietal	active	417 ms delayed	−0.09	0.063	1	0.148	−0.21	0.03
SSD	frontoparietal	active	417 ms delayed	**−0.11****	0.040	1	**0.006**	−0.19	−0.03
SSD sham passive undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD	frontal	passive	undelayed	**0.10****	0.034	1	**0.004**	0.03	0.17
SSD	parietal	passive	undelayed	**0.08***	0.032	1	**0.010**	0.02	0.14
SSD	frontoparietal	passive	undelayed	0.04	0.034	1	0.276	−0.03	0.1
SSD sham passive 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD	frontal	passive	417 ms delayed	−0.01	0.044	1	0.761	−0.1	0.07
SSD	parietal	passive	417 ms delayed	0.03	0.039	1	0.375	−0.04	0.11
SSD	frontoparietal	passive	417 ms delayed	−0.09^{+}	0.050	1	0.085	−0.18	0.01

Stimulation conditions: frontal, LFC–RFA; parietal, LPC–RPA; frontoparietal, LFC–RPA; sham. Wald Chi-Square statistics of the GEE procedure implemented in SPSS have been used for statistical comparisons see Materials and Methods section and Table 2. Significant effects ($P < 0.05$) are highlighted in bold letters.
$^{+}P < 0.10$, $^{*}P < 0.05$, $^{**}P < 0.01$.

passive: mean diff. = 0.14, std. error = 0.040, df = 1; sig. < 0.001; 95% CI: 0.06–0.21), even though comparisons to the sham conditions revealed no relevant effects (see Table 4), except for the aforementioned effect on undelayed passive trials.

Discussion

The ability to detect delays in the expected temporal relationship between one's own actions and their sensory consequences is relevant for adaptive behaviour, for the self-other distinction of incoming sensory information and for successful interaction with our environment. In this tDCS study, we show that an action-outcome delay-detection impairment in patients with SSD can be reduced by tDCS. In general, patients with SSD, when compared to HC, demonstrated lower delay-detection rates, particularly for trials with long delays. Frontoparietal tDCS improved this deficit in both active and passive conditions; however, frontal tDCS was related to a specific effect for self-initiated compared to externally generated actions. Furthermore, frontal tDCS reduced the number of false delay responses for undelayed trials in patients. These new results provide promising evidence for the potential use of tDCS for the amelioration of action-outcome monitoring dysfunction by improving efference copy-based predictive mechanisms in patients with SSD.

As expected, we found a generally reduced delay-detection performance in patients with SSD, when compared to HC, across active and passive trials. This finding is in line with previous experiments that applied a delay-detection task without a passive control condition (Leube *et al.*, 2010) or that used a duration estimation task (Graham-Schmidt *et al.*, 2016) in patients with schizophrenia. This dysfunction across active and passive trials can be explained by impaired time perception or by impaired intersensory matching since both are relevant functions for performing our task. Dysfunctional processing of time in schizophrenia has been repeatedly reported and related to specific symptoms (Franck *et al.*, 2005; Waters and Jablensky, 2009). Furthermore, a difficulty in relating a visual stimulus to the proprioceptive, tactile information induced by (active or passive) finger

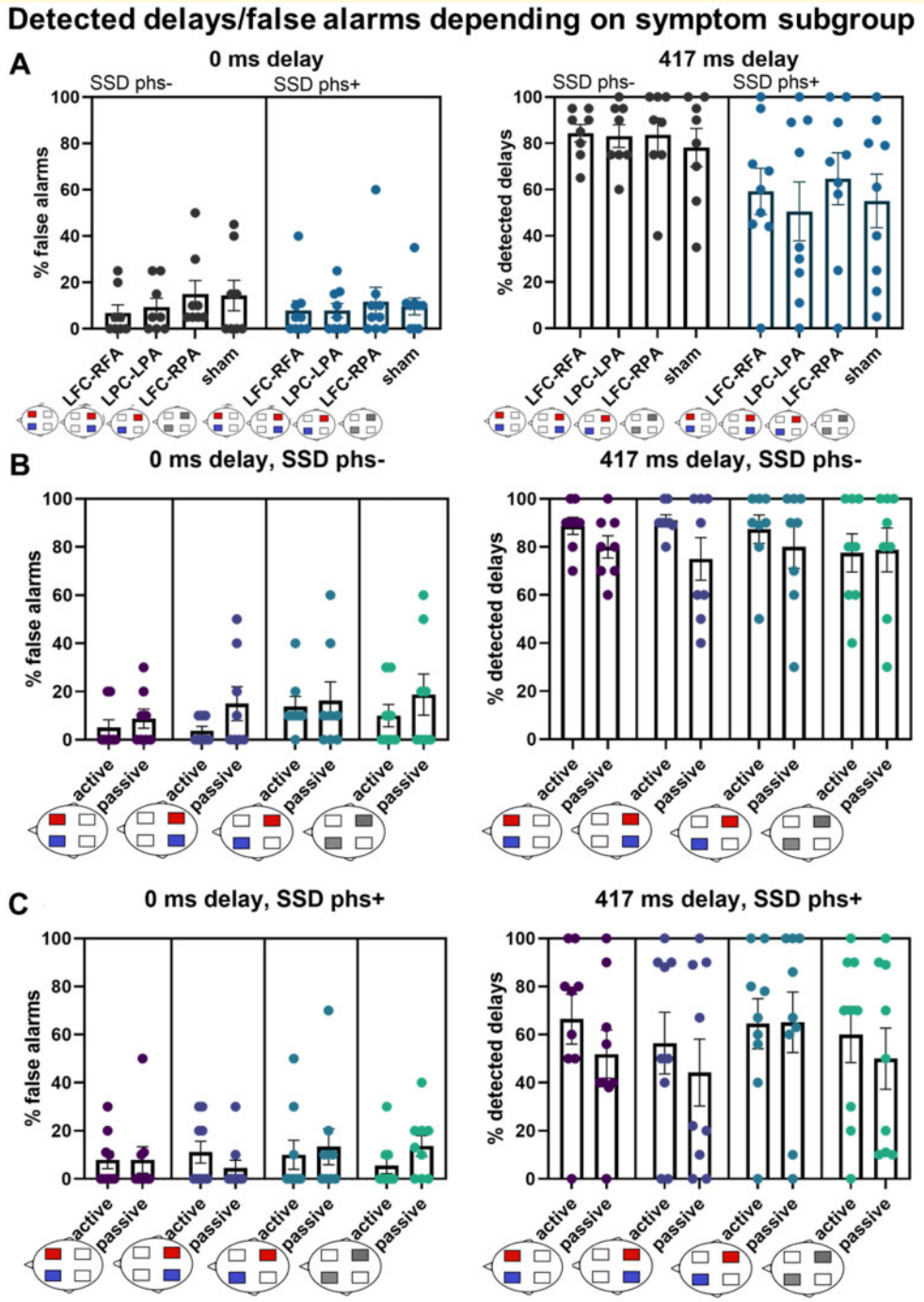


Figure 4 Detected delays/false alarms depending on symptom subgroup. (**A**) Proportion of detected delays (right)/false alarms (left) depending on *symptom subgroup* (SSD phs+: black versus SSD phs−: blue), *stimulation* [frontal (LFC–RFA); parietal (LPC–RPA); frontoparietal (LFC–RPA); sham] and delay (undelayed: left; 417 ms delay: right). While the SSD phs− group benefited from frontal tDCS regarding false alarm rates in undelayed trials, the SSD phs+ group showed no significant effects of tDCS compared to sham, but a trend for better delay detection after frontoparietal tDCS. For *post hoc* comparisons of tDCS and sham sessions for passive and active conditions, see Supplementary Table 1. (**B** and **C**) Proportion of detected delays (right)/false alarms (left) depending on *symptom subgroup* (SSD phs+ versus SSD phs−), *stimulation* [frontal (LFC–RFA), purple; parietal (LPC–RPA), blue; frontoparietal (LFC–RPA): light blue; sham: green], *condition* (active versus passive) and *delay* (left undelayed; right 417 ms delay). (**B**) Patients without relevant symptoms (SSD phs−) specifically profited in active conditions from frontal and parietal tDCS (compared to passive condition and sham stimulation) regarding the detection of long delays. A reduction of false delay responses in undelayed active trials was related to frontal tDCS, only. (**C**) Patients of the SSD phs+ group showed improvement (tDCS versus sham) in passive conditions: regarding the detection of long delays after frontoparietal stimulation and regarding false delay responses in undelayed trials after frontal and parietal stimulation. Wald Chi-Square statistics of the GEE procedure have been used for statistical comparisons (see Materials and Method section and Table 2). For *post hoc* comparisons of tDCS and sham sessions for passive and active conditions see Supplementary Table 1. For a figure similar to Fig. 3, including all delays, see Supplementary Fig. 1.

Table 4. *Post hoc* tests sham versus tDCS for delayed (417 ms) and undelayed trials in SSD phs+ and SSD phs−

								95% Wald conf. interval for diff.	
SSD phs− sham active undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs−	frontal	active	undelayed	**0.05****	0.019	1	**0.005**	0.02	0.09
SSD phs−	parietal	active	undelayed	0.06	0.042	1	0.135	−0.02	0.14
SSD phs−	frontoparietal	active	undelayed	−0.04	0.033	1	0.238	−0.10	0.03
SSD phs− sham active 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs−	frontal	active	417 ms delayed	−0.10+	0.055	1	0.061	−0.21	0.00
SSD phs−	parietal	active	417 ms delayed	**−0.13***	0.065	1	**0.040**	−0.26	−0.01
SSD phs−	frontoparietal	active	417 ms delayed	−0.10+	0.061	1	0.096	−0.22	0.02
SSD phs− sham passive undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs−	frontal	passive	undelayed	0.12+	0.063	1	0.062	−0.01	0.24
SSD phs−	parietal	passive	undelayed	0.05	0.057	1	0.393	−0.06	0.16
SSD phs−	frontoparietal	passive	undelayed	0.04	0.037	1	0.336	−0.04	0.11
SSD phs− sham passive 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs−	frontal	passive	417 ms delayed	0.01	0.067	1	0.913	−0.12	0.14
SSD phs−	parietal	passive	417 ms delayed	0.06	0.083	1	0.505	−0.11	0.22
SSD phs−	frontoparietal	passive	417 ms delayed	0.00	0.070	1	0.994	−0.14	0.14
SSD phs+ sham active undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs+	frontal	active	undelayed	−0.02	0.021	1	0.257	−0.07	0.02
SSD phs+	parietal	active	undelayed	−0.05	0.049	1	0.287	−0.15	0.04
SSD phs+	frontoparietal	active	undelayed	−0.04	0.032	1	0.194	−0.11	0.02
SSD phs+ sham active 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs+	frontal	active	417 ms delayed	−0.06	0.069	1	0.350	−0.2	0.07
SSD phs+	parietal	active	417 ms delayed	0.03	0.087	1	0.720	−0.14	0.20
SSD phs+	frontoparietal	active	417 ms delayed	−0.05	0.045	1	0.272	−0.14	0.04
SSD phs+ sham passive undelayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs+	frontal	passive	undelayed	**0.08***	0.037	1	**0.032**	0.01	0.15
SSD phs+	parietal	passive	undelayed	**0.11*****	0.028	1	**<0.001**	0.06	0.17
SSD phs+	frontoparietal	passive	undelayed	0.02	0.058	1	0.750	−0.1	0.13
SSD phs+ sham passive 417 ms delayed versus				Mean diff.	Std. error	df	Sig.	Low	High
SSD phs+	frontal	passive	417 ms delayed	−0.03	0.068	1	0.609	−0.17	0.10
SSD phs+	parietal	passive	417 ms delayed	0.04	0.030	1	0.202	−0.02	0.10
SSD phs+	frontoparietal	passive	417 ms delayed	**−0.18***	0.070	1	**0.010**	−0.32	−0.04

Stimulation conditions: frontal, LFC–RFA; parietal, LPC–RPA; frontoparietal, LFC–RPA; sham. Wald Chi-Square statistics of the GEE procedure implemented in SPSS have been used for statistical comparisons see Materials and Methods section and Table 2. Significant effects ($P < 0.05$) are highlighted in bold letters. $^{+}P < 0.10$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

movements might have reduced the delay-detection performance in the patients. We cannot disentangle the exact contribution of these processes; nevertheless, we provide some first evidence that tDCS can improve the delay-detection performance in patients with SSD, at least for the longest delays of 417 ms after frontoparietal stimulation. This improvement could be based on improved intersensory matching after anodal parietal stimulation (van Kemenade *et al.*, 2019*b*), on improved attention (Nelson *et al.*, 2014) or on modulation of time sensitivity (Hecht *et al.*, 2013) after frontal cathodal stimulation. However, neither frontal nor parietal stimulation alone induced a comparable improvement across active and passive trials, indicating a specific effect of the current flow between the left frontal and right parietal electrodes.

Interestingly, we found an opposite pattern of results in HCs and patients with SSD regarding false delay responses after frontal stimulation: While patients showed a reduction in false delay responses for undelayed trials, HCs demonstrated an increased false alarm rate after frontal, parietal and frontoparietal tDCS. In fact, tDCS led to an increased error rate (false delay responses) in HCs for both active and passive conditions, independent of stimulation site (see Fig. 3). Thus, cathodal stimulation of the left hemisphere and anodal stimulation of the right hemisphere leads to disadvantages in the delay-detection task for HC (see also, Straube *et al.*, 2017*a*), but results in better performance in patients. It might be the case that results are affected by group differences in interhemispheric rivalry, which have been reported in repetitive transcranial magnetic stimulation studies for neglect (Nyffeler *et al.*, 2019), in gesture performance in healthy subjects (Vanbellingen *et al.*, 2020) and in schizophrenia (Walther *et al.*, 2020). Thus, stimulation of a brain area may inhibit the homologue of the other hemisphere (and vice versa). Future studies should therefore investigate this possibility and whether group differences in interhemispheric rivalry can explain these opposing effects of stimulation. Nevertheless, for patients, the combination of increased detection performance and reduction in false alarms after frontal tDCS is promising, as it suggests that tDCS not only induced a shift in response bias, but it normalized responses at both ends of the response spectrum.

The exact mechanisms leading to the different effects in HCs compared to patients with SSD remain to be investigated in further tDCS and imaging studies. However, we have demonstrated the potential of tDCS for inducing an effective balance in prefrontal cortex functioning in patients, as this balance has been found dysfunctional in several studies. For example, hyperactivation of the left frontal cortex has been revealed in a causality judgment task in which patients with schizophrenia had to evaluate the causal relationship of bouncing balls, with temporal delays included between the movements (Wende *et al.*, 2015). In that study, patients were less sensitive to delays and demonstrated increased frontal cortex activation. Thus, the cathodal tDCS of the left frontal cortex in this study might have improved delay detection by normalizing/reducing the overactivation of the left frontal cortex. The HCs may possibly have demonstrated a lower level of activation in the left frontal cortex in tasks where temporal delays are relevant, so cathodal tDCS might have reduced the activation to a dysfunctional level and led to increased error rates in the delay-detection task.

Notably, we found effects across the whole SSD sample and across active and passive conditions, indicating the possibility of a more global deficit of internal models in patients with schizophrenia. In fact, internal forward models do not only inform us about the consequences of self-generated actions, since the nervous system also represents and updates internal models about external events (Roth *et al.*, 2013; Dogge *et al.*, 2019). Therefore, forward models might be more generally impaired in patients with schizophrenia (Frith *et al.*, 2000; Fletcher and Frith, 2009).

We also found specific tDCS effects on active versus passive conditions. The active and passive conditions are identical in task, delay and stimulus, and they are at least similar in tactile and proprioceptive information due to passive finger movement; therefore, the comparison of both conditions can reveal efference copy-based processes specific to voluntary actions (van Kemenade *et al.*, 2016). These efference copy-based forward models, in particular, have been considered impaired (Leube *et al.*, 2010) or imprecise (Synofzik *et al.*, 2010) in schizophrenia. The effect was less pronounced in our study, where we applied a highly comparable passive control condition (no sig. group by condition interaction); nevertheless, we provide some first evidence that frontal stimulation can distinctively improve the detection of delays in active compared to passive and sham conditions in patients with SSD. After sham stimulation, the patients detected long delays of 417 ms in ~65% of the active trials. After frontal stimulation, this proportion of detected delays increased to 74% in active trials, whereas the performance in the passive condition remained quite stable at 63% (sham) and 65% (after frontal stimulation). Thus, frontal tDCS improved the efference copy-based forward model mechanisms in patients with SSD, potentially by affecting premotor cortices and the supplementary motor area. This interpretation is in line with a tDCS study that demonstrated polarization-independent reduction of intentional binding after pre-supplementary motor area stimulation in HCs (Cavazzana *et al.*, 2015).

A reduced intentional-binding effect reflects a more accurate (less biased) objective performance. Consequently, these data are comparable to our finding of a behavioural advantage after frontal stimulation. Since the supplementary motor area is located between left and right dorsolateral prefrontal cortex, one possibility is that tDCS-induced current flow between hemispheres increased functioning of the supplementary motor area and, consequently, the sensitivity to delays (cf., Straube *et al.*, 2017*a*). However, the lateral frontal cortex has also been implicated in the temporal processing of actions and their outcomes (Khalighinejad and Haggard, 2015; Khalighinejad *et al.*, 2016). Here, we demonstrate, for the first time, a specific effect of frontal tDCS for active compared to passive conditions in patients with SSD. This indicates improved action-outcome monitoring, which probably originated from better efference copy-based predictions.

In addition to the general tDCS effects on patients with SSD, we explored symptom-specific effects related to a paranoid-hallucinatory syndrome. Impairments in efference copy-based mechanisms have usually been related to passivity phenomena/delusions of control and auditory hallucinations (Feinberg, 1978; Frith *et al.*, 2000, 2005; Leube *et al.*, 2010; Synofzik *et al.*, 2010; Pynn and DeSouza, 2013). Thus, these symptoms could influence the efficacy of tDCS in inducing improvements in our delay-detection task with active and passive finger movements. In fact, we found more prominent improvements in patients without relevant symptoms (SSD phs−) than in patients displaying these symptoms (SSD phs+; see Fig. 4B and C). For example, the detection rate of the SSD phs− group improved after frontal stimulation from 78% to 89% for the detection of the longest delays in active conditions. The SSD phs+ group, in contrast, showed only a moderate improvement, from 60% to 66% in active conditions. Furthermore, false delay responses in active conditions were significantly reduced after frontal compared to sham stimulation in the SSD phs− group (from 9% to 4%). However, when looking at the false alarm rates of the passive trials, tDCS was especially effective in patients with relevant symptoms (SSD phs+), leading to a significant reduction after frontal (7%) and parietal stimulation (4%) compared to sham stimulation (15%).

Taken together, these results indicate that all SSD patients can profit from tDCS; however, the mechanisms, amount and quality of improvement (increase in detection rates or reduction of false alarm rates) may vary considerably. Current data indicate that improving the efference copy-related processes can be especially effective in patients with few or no relevant symptoms, while intersensory matching, which is relevant in passive conditions,

could be more susceptible to improvement in patients with paranoid-hallucinatory symptoms. Nevertheless, future research is necessary to understand the underlying mechanisms and to find suitable stimulation procedures to improve efference copy-based mechanisms in patients with passivity phenomena.

Limitations

Our study was not intended or powered to detect small behavioural effects between the psychopathological subgroups (phs+/−). However, despite the limited sample size of the exploratory symptom subgroups in our study, the groups were well matched regarding other positive and negative symptoms (see Table 1). Nevertheless, these results remain exploratory, due to the limited subgroup sample sizes and lack of symptom-group assignments based on more sensitive measures of impaired self-experiences, such as the Examination of Anomalous Self-Experience scale (Parnas *et al.*, 2005). In general, all our patients were on stable medication, which could have induced or ameliorated differences between patients and HCs. However, drug effects are not likely to have caused the differences in the patient subgroups. A further limitation is the restriction to only one sham and three tDCS conditions. In particular, knowledge about the stimulation of the cerebellum (van Kemenade *et al.*, 2019*b*) or anodal stimulation of the left frontal cortex (Bose *et al.*, 2014, 2019) would be of interest and should be investigated in future studies. While our findings provide evidence for an improvement after frontal stimulation (compared to sham, compared to the passive condition and regarding reduced error rates), our results also suggest advantages after parietal and frontoparietal stimulation (e.g. for active and passive conditions). Thus, clear recommendations regarding stimulation sites are difficult to propose based on our study. Combined tDCS and functional MRI studies that consider brain activation and connectivity (Straube *et al.*, 2014; Wende *et al.*, 2015; Voss *et al.*, 2017; Wroblewski *et al.*, 2020) might provide a better understanding of the different mechanisms leading to changes in delay-detection performance in patients with SSD. Similarly, the duration of tDCS effects needs further exploration. Here, we demonstrated effects at ~25 min after stimulation; however, the effects during stimulation and at hours after stimulation also need examination in future studies. Eventually, repeated stimulation sessions might be necessary to elicit long-lasting and clinically relevant effects. Finally, our results might be quite specific for the applied task. For example, in a recent series of functional MRI studies, we demonstrated that behavioural performance for self-generated and externally generated hand movements differ between discreet and continuous action feedback during movement (Arikan *et al.*, 2019; van Kemenade *et al.*, 2019*b*; Pazen *et al.*, 2020; Uhlmann *et al.*, 2020).

Conclusion

tDCS has been used to improve functioning in patients with SSD in multiple tasks (Chang *et al.*, 2018; Gupta *et al.*, 2018; Kennedy *et al.*, 2018; Lee *et al.*, 2018; Mellin *et al.*, 2018; Mondino *et al.*, 2018; Morgan and Singh, 2018; Sreeraj *et al.*, 2018; Schülke and Straube, 2019); however, its effects on action-outcome monitoring have hitherto remained unexplored. Here, we provide some first insights into the effect of tDCS on the temporal prediction or monitoring of voluntary action outcomes in patients with SSD. The detection of delays between action and sensory consequence was generally impaired in patients with SSD, and especially in patients with relevant symptoms. Interaction analyses revealed group- and symptom-specific tDCS effects, indicating that frontal tDCS improved the detection of long delays in active conditions and reduced the proportion of false alarms in undelayed trials of passive conditions in patients. Patients without paranoid-hallucinatory symptoms (SSD phs−) profited especially from frontal tDCS in active conditions, while improvement in the SSD phs+ group was predominantly reflected in reduced false alarm rates in passive conditions. These data provide some first evidence for the potential utility of tDCS to improve action-outcome monitoring in patients with SSD, and they suggest that the presence of passivity symptoms could be a useful marker for predicting tDCS effects.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

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