Transcranial Direct Current Stimulation Improves Semantic Speech–Gesture Matching in Patients With Schizophrenia Spectrum Disorder

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Background: Patients with schizophrenia spectrum disorders (SSD) have severe deficits in speech and gesture processing that contribute considerably to the burden of this disorder. Brain imaging shows left inferior frontal gyrus involvement for impaired processing of co-verbal gestures in patients with schizophrenia. Recently, transcranial direct current stimulation (tDCS) of the left frontal lobe has been shown to modulate processing of co-verbal gestures in healthy subjects. Although tDCS has been used to reduce symptoms of patients with SSD, the effects of tDCS on gesture processing deficits remain hitherto unexplored. *Objective:* Here we tested the hypothesis that inhibitory cathodal tDCS of the left frontal lobe decreases pathological dysfunction and improves semantic processing of co-verbal gestures in patients with SSD. *Methods:* We measured ratings and reaction times in a speech–gesture semantic relatedness assessment task during application of frontal, frontoparietal, parietal, and sham tDCS to 20 patients with SSD and 29 healthy controls. *Results:* We found a specific effect of tDCS on speech–gesture relatedness ratings of patients. Frontal compared to parietal and sham stimulation significantly improved the differentiation between related and unrelated gestures. Placement of the second electrode (right frontal vs parietal) did not affect the effect of left frontal stimulation, which reduced the preexisting difference between patients and healthy controls. *Conclusion:* Here we show that left frontal tDCS can improve semantic co-verbal gesture processing in patients with SSD. tDCS could be a viable tool to normalize processing in the left frontal lobe and facilitate direct social communicative functioning in patients with SSD.

Key words: co-verbal gestures/gesture processing/left inferior frontal gyrus (IFG)/left frontal lobe/tDCS

Introduction

Gestures are an integral part of human communication.[1,2] In real life, gestures usually occur in the context of spoken language. These co-verbal gestures accompany speech and thereby improve understanding,[3,4] learning,[5,6] memory performance,[5,7,8] and reduce processing during communication.[7]

Gesture deficits are very characteristic of schizophrenia,[9–12] present at all stages of the disorder,[13–15] play an important role for social dysfunction,[16] and are a predictive marker of poor outcome.[17]

Regarding gesture production, patients' ability to imitate gestures is markedly impaired.[15,18–21] Concerning gesture perception and interpretation, patients show severe gesture recognition deficits.[9,21,22] They do not only have difficulties at correctly identifying meaningful gestures, but also tend to perceive incidental movements as meaningful gestures, to perceive neutral gestures as conveying an insulting meaning[10] and to perceive gestures as self-referential.[23]

Generally, overactivation of the superior temporal sulcus (STS) and the temporoparietal junction seems to be at the core of social communication deficits characteristic of the schizophrenic syndrome.[24] Functional magnetic resonance imaging (fMRI) research investigating the brain regions involved in perception of co-verbal gestures has shown more activation in bilateral frontal structures for patients with schizophrenia compared to control subjects.[25] Moreover, connectivity between the left STS and the left inferior frontal gyrus (IFG) seems to be impaired, especially for metaphoric gestures.[26] Another recent study linked poor performance during gesture planning and execution in patients with schizophrenia spectrum disorders (SSD) to reduced right dorsolateral prefrontal cortex and increased inferior parietal lobe activity.[27] In sum, the

neural correlates of gesture processing in schizophrenia point to a specific involvement of the frontal cortex and dysfunctional connectivity between frontotemporal brain regions.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that makes use of electrical currency to stimulate and inhibit brain regions. Anodal stimulation is generally thought to increase cortical excitability, whereas cathodal stimulation usually leads to a decrease in excitability.[28,29] tDCS has repeatedly been tested as a possible clinical treatment tool for schizophrenia.[30–35]

So far, the effects of tDCS on deficient semantic speech–gesture matching in patients with SSD have not been investigated. In a recent study, we explored the effects of left frontal tDCS on semantic speech–gesture matching in healthy subjects.[36] We found that anodal compared to cathodal stimulation of the left frontal lobe decreased reaction times and relatedness assessments for metaphoric gestures, demonstrating that tDCS may influence speech–gesture matching in healthy subjects.[36] Another recent study showed that transcranial magnetic stimulation over the left frontal cortex disrupts speech–gesture integration.[37] However, until now no study has looked at the effects of tDCS on speech–gesture processing in patients with SSD.

In this study, we investigated the effects of tDCS on speech–gesture relatedness assessment of patients with SSD. We hypothesized that left frontal tDCS would modulate impaired speech–gesture relatedness assessment of patients with SSD. fMRI evidence suggests both a general overactivation of the left IFG in schizophrenia[38] and a specific imbalance of left IFG activation for processing co-verbal gestures (decrease in ventral activation/increase in dorsal activation).[25] We therefore assumed that reducing excitability of the left frontal area using cathodal tDCS would normalize patients' assessments of speech–gesture relatedness, ie, result in higher relatedness ratings for related stimuli and more critical assessment of unrelated stimuli.

Because a single tDCS condition may be difficult to interpret, as stimulation effects may be due to stimulation at the anodal site, inhibition at the cathodal site, or both electrodes (see Reinhart et al),[39] we opted for a comprehensive design that would allow us to disentangle the effects of anode and cathode. To test our hypothesis of facilitated gesture processing by left frontal tDCS in patients with SSD, we performed exclusively frontal (LFC-RFA; left frontal cathodal and right frontal anodal) and frontoparietal (LFC-RPA; left frontal cathodal and right parietal anodal) stimulation. In addition, we included exclusively parietal (LPC-RPA; left parietal cathodal) and sham stimulation as control conditions, which we assumed not to lead to facilitation in speech–gesture matching.

Methods

Participants

All subjects were right-handed, native-level German speakers 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 local ethics committee approved the study.

Patients

Twenty patients with SSD were recruited at the Department of Psychiatry and Psychotherapy, Philipps-University, Marburg, Germany (18 male, 2 female; mean age = 38.70 years, SD = 11.70, range = 41; mean level of education as measured by the Comparative Analysis of Social Mobility in Industrial Nations (CASMIN) classification = 5.55, SD = 1.96, range = 7). Thirteen patients were diagnosed with paranoid schizophrenia (*International Classification of Diseases, Tenth Revision* [*ICD-10*] GM F20.0), 4 patients were diagnosed with schizoaffective disorder (*ICD-10* GM F25.0), 1 patient was diagnosed with residual schizophrenia (*ICD-10* GM F20.5), 1 patient was diagnosed with prodromal schizophrenia (*ICD-10* GM F21.0) and 1 patient was diagnosed with acute and transient psychotic disorder (*ICD-10* GM F23.0). All patients were under stable medication when undergoing the study and symptom severity was relatively low (mean Scale for the Assessment of Positive Symptoms = 11.17, SD = 12.91, range = 50; mean Scale for the Assessment of Negative Symptoms = 17.50, SD = 17.67, range = 57; clinical ratings were missing for 2 patients).

Healthy Controls

Twenty-nine healthy subjects served as a control group (18 male, 11 female; 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 patients based on age and education. As a result, groups did not differ significantly in age (*P* = .24) and education (*P* = .74). All healthy controls fulfilled the following inclusion criteria: history free of mental or neurologic illness and alcohol or drug abuse. Data of a subsample of 17 healthy controls have already been published elsewhere.[36]

Transcranial Direct Current Stimulation

We used a direct current stimulator from neuroConn GmbH. 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 electroencephalography (EEG) system,[36] for further details. A current of 1.5 mA was applied to the head using saline-soaked sponges (0.9% NaCl, to minimize side effects,[40,41] 5 cm × 7 cm) placed on rubber electrodes, resulting in a current density of 0.043 mA/cm². Stimulation duration was 10 min plus 10 s fade in/fade out. All parameters complied with tDCS safety guidelines.[42–44] 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 (half wave) mode for a duration of 30 s.[45]

Experiment Design

We applied anodal, cathodal, and sham stimulation to the left and right frontal (F3/F4) and parietal (CP3/CP4) areas (see figure 1).[36] Each patient took part in 4 independent tDCS sessions and underwent 4 different stimulation conditions, 1 on each day (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode): (1) frontal condition LFC-RFA, (2) frontoparietal condition LFC-RPA, (3) parietal condition LPC-RPA, and (4) sham condition. To control for effects of order and repetition, order of stimulation conditions was pseudorandomized and counterbalanced across subjects. Healthy controls underwent 3 additional inverse stimulation conditions.[36]

Speech–Gesture Relatedness Assessment Task

During stimulation, subjects were continuously presented with video clips of an actor saying a concrete (eg, "The house is located on a mountain.") or abstract sentence (eg, "The conversation is at a high level.") accompanied by a hand gesture that was either semantically unrelated or related to the sentence content (see figure 1). For each co-verbal gesture, subjects rated relatedness of sentence content and gesture. They were instructed to rate on a scale from 1 (sentence content and gesture matches very badly) to 7 (sentence content and gesture matches very well) and pressed the respective button on the keyboard. Reaction times were measured from video onset.

We used 2 different sets of stimuli (80/set) to counterbalance related and unrelated counterparts of speech–gesture pairs across subjects. Each set included 20 metaphoric related (abstract sentence + related gesture), 20 metaphoric unrelated (abstract sentence + unrelated gesture), 20 iconic related (concrete sentence + related gesture), and 20 iconic unrelated (concrete sentence + unrelated gesture) clips. We presented the video clips in pseudorandomized order. The stimulus set presented to the participant was identical in each experiment session, to maximize comparability across stimulation sessions. Thus, each subject saw only a related or unrelated version of any given sentence–gesture pair. However, across the full body of subjects, both versions were presented.
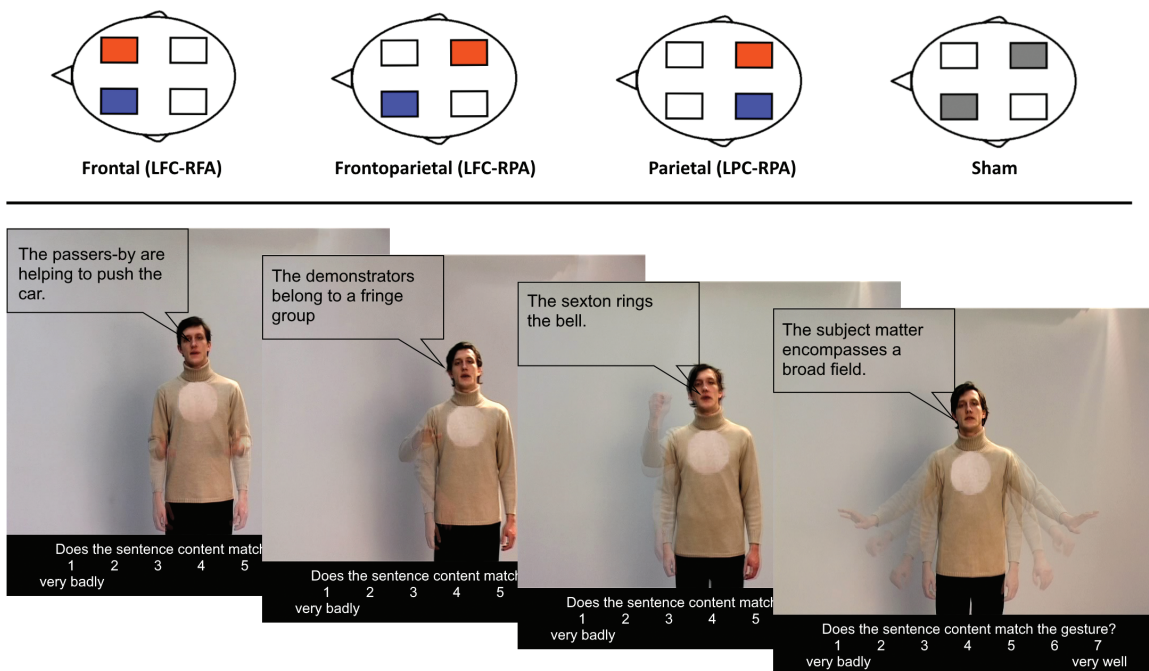
Fig. 1. Study design and speech–gesture relatedness assessment task. (A, top) Study design. Each subject underwent four stimulation sessions (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode) on 4 days. The colors indicate electrode polarization (orange = right anodal stimulation; blue = left cathodal stimulation). (B, bottom): Speech–gesture relatedness assessment task, performed during stimulation. Example clips for each of the 4 gesture types presented, from right to left: metaphoric related, iconic related, metaphoric unrelated, and iconic unrelated. Figure adopted from Schülke and Straube.[36]

Stimulus Material

The stimuli have been extensively validated and successfully made use of in other studies.[7,8,25,26,46–49] The videos looked as natural as possible and differed only in type of co-verbal gesture and relatedness. Iconic and metaphoric gestures were chosen in concordance with McNeill's definitions, illustrating form, size or movement of something concrete the speaker is referring to (iconic gestures), or being speech–related on an abstract semantic level (metaphoric gestures).[50] Sentences were of similar length (5–8 words) and grammatical form (subject–predicate–object). Unrelated gestures were not too obviously unrelated to speech and matched related gestures in terms of complexity (gesture direction and extent), smoothness, and vividness. Extensive rating proved that unrelated gestures did not contain any clear-cut semantic information and differed significantly in semantic strength from iconic[47] and metaphoric gestures.[7] Each clip had a length of 5 s. For additional information on the stimuli and their creation, see Kircher et al[46] and Green et al.[47]

Assessment of Side Effects

After each session, subjects filled out a questionnaire that consisted of 28 items (eg, headache, itching sensation, difficulty concentrating) to assess any perceived side effects.

Data Analysis

We performed generalized estimating equations (GEE) for relatedness ratings and reaction times as implemented in SPSS Statistics 19 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.[36] We used an AR (1) working correlation structure and robust (sandwich) covariance estimators for the regression coefficients. The identity link function was selected for both reaction times and ratings.

We included the following predictors in our model: Main effects: *group* (healthy controls, patients with SSD), *stimulation* (frontal, parietal, frontoparietal), *gesture type* (metaphoric, iconic), and *relatedness* (related, unrelated).

Factorial interactions: We used a comprehensive model including all factorial interactions of the aforementioned factors.

However, on the basis of our hypotheses of significant differences between healthy controls/patients and frontal/parietal stimulation, we were particularly interested in whether there would be *group*- and *stimulation*-dependent effects on *gesture type* and *relatedness* (ie, significant effects for the interactions *group × stimulation × gesture type*, *group × stimulation × relatedness,* and *group × stimulation × gesture type × relatedness*).

After running our main analysis including all 4 stimulation conditions, we performed different post hoc tests to explore the importance of electrode position: (1) frontal against parietal stimulation, to test our main hypothesis; (2) frontal against frontoparietal and frontoparietal against parietal stimulation, to elucidate which electrode might be relevant for the effects of frontoparietal stimulation; and (3) each stimulation against sham.

Finally, we analyzed the patient group separately, to check whether effects are in fact due to improvements in patients.

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, post hoc tests are not corrected for multiple comparisons.

Results

Side Effects

In sum, tDCS was well tolerated. No significant discomfort was observed during or after the experiment. There was no difference in reported side effects (rated on a scale from 1 to 5) between patients and healthy controls (overall mean for patients = 1.42, *SE* = 0.07; overall mean for healthy controls = 1.53, *SE* = 0.07; *P* = .256) and no difference between the different real stimulation conditions. However, reported side effects differed slightly but significantly between sham and real stimulation (overall mean for real stimulation conditions = 1.51, *SE* = 0.06; overall mean for sham stimulation = 1.43, *SE* = 0.05; *P* = .038). Perceived stimulation intensity was also higher for real compared to sham stimulation (mean for real stimulation = 2.27, *SE* = 1.5; mean for sham stimulation = 1.76, *SE* = 1.4).

Ratings

The overall analysis showed that patients rated related gestures as relatively more unrelated than healthy controls, whereas they rated unrelated gestures as relatively more related (table 1 and figure 2; interaction *group × relatedness*, *P* = .032), indicating reduced discrimination between conditions and an impairment of evaluating the relation between speech and gesture semantics.

Most importantly, the interaction *group × stimulation × relatedness* was significant (*P* = .028), indicating that stimulation influenced group differences (table 1 and figure 3). Post hoc tests resulted in a clear pattern: Frontal and frontoparietal stimulation alike differed significantly from parietal and sham stimulation (frontal vs sham, *P* = .031; frontal vs parietal, *P* = .021; frontoparietal vs sham, *P* = .034; frontoparietal vs parietal, *P* = .034). The interaction was not significant for comparing frontal against frontoparietal stimulation. Likewise, the contrast of parietal against sham stimulation was not significant.

Frontal and frontoparietal stimulation significantly improved discrimination between related and unrelated gestures in patients (see figure 3B). Thus, frontal and

Table 1. Results of Main Analysis

Source	df	Test of Model Effects Rating		Test of Model Effects Reaction Time	
		Wald Chi-Square	Sig.	Wald Chi-Square	Sig.
(Intercept)	1	1670.141	<0.001	6245.191	<0.001
Group	1	.348	.555	15.830	<0.001
Stimulation	3	3.603	.308	2.447	.485
Gesture type	1	4.926	.026	155.487	<0.001
Relatedness	1	412.948	<0.001	14.870	<0.001
Group × Stimulation	3	6.413	.093	3.862	.277
Group × Gesture type	1	.375	.540	5.196	.023
Group × Relatedness	1	4.577	.032	.922	.337
Stimulation × Gesture type	3	6.791	.079	3.127	.372
Stimulation × Relatedness	3	4.238	.237	5.204	.157
Gesture type × Relatedness	1	32.558	<0.001	9.997	.002
Group × Stimulation × Gesture type	3	1.294	.731	.333	.954
Group × Stimulation × Relatedness	3	9.099	.028	.783	.854
Group × Gesture type × Relatedness	1	4.974	.026	3.164	.075
Stimulation × Gesture type × Relatedness	3	3.146	.370	10.101	.018
Group × Stimulation * Gesture type × Relatedness	3	4.085	.252	4.795	.187

Note. Sig., significance.
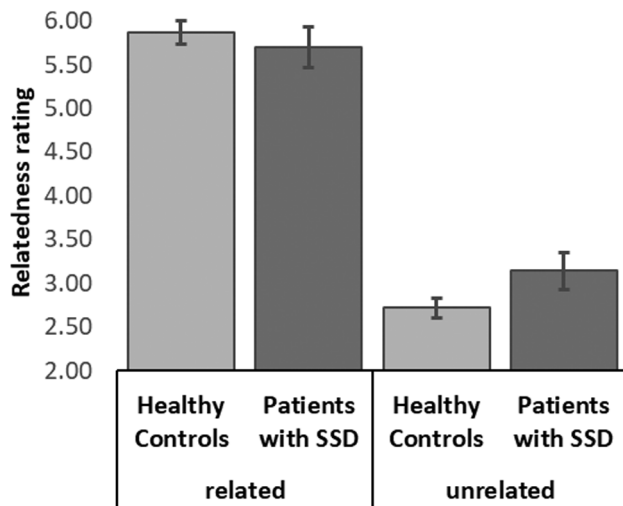
Fig. 2. Group dependence of relatedness ratings. Mean relatedness ratings (relatedness rated on a scale from 1 = very low to 7 = very high relatedness). SSD = schizophrenia spectrum disorder. Error bars indicate the standard error of the mean (SEM).

frontoparietal stimulation reduced group differences by improving patients' performance in evaluating the relationship between speech and gesture.

Moreover, we found that patients rated unrelated iconic and unrelated metaphoric gestures similarly, whereas healthy subjects rated unrelated metaphoric stimuli more critically (interaction *group × gesture type × relatedness*, *P* = .026).

Even though there was an interaction of *gesture type × relatedness*, indicating that metaphoric-related gestures were rated as being relatively less related to speech content (interaction *gesture type × relatedness*, *P* < .001), the interactions of *gesture type* with *group* and/or *stimulation* did not reach significance.

Reaction Times

Although we found no effects of stimulation on group differences regarding reaction times (table 1 and figure 4), we found that:

First, patients responded generally more slowly than healthy controls (mean reaction time = 4599 ms for patients, mean reaction time = 4158 ms for healthy controls, *P* < .001).

Second, patients and healthy subjects were both faster at responding to iconic gestures in comparison to metaphoric gestures. The advantage in reaction times for iconic gestures, however, was relatively smaller for patients (*group × gesture type*, *P* = .023; difference metaphoric – iconic for healthy controls = 279 ms, difference metaphoric – iconic for patients = 193 ms).

Third, the advantage (faster reaction times) for iconic compared to metaphoric gestures was significantly bigger for related compared to unrelated gestures (*gesture type × relatedness*, *P* = .002; difference metaphoric unrelated – iconic unrelated = 196 ms vs difference metaphoric related – iconic related = 277 ms).

Finally, stimulation influenced the interaction between *gesture type* and *relatedness* (figure 4, *stimulation × gesture type × relatedness*, *P* = .018). Post hoc tests were significant only for contrasting frontoparietal against frontal (*P* = .008), parietal (*P* = .004), and sham stimulation (*P* = .009), indicating that frontoparietal stimulation increased the difference in reaction times
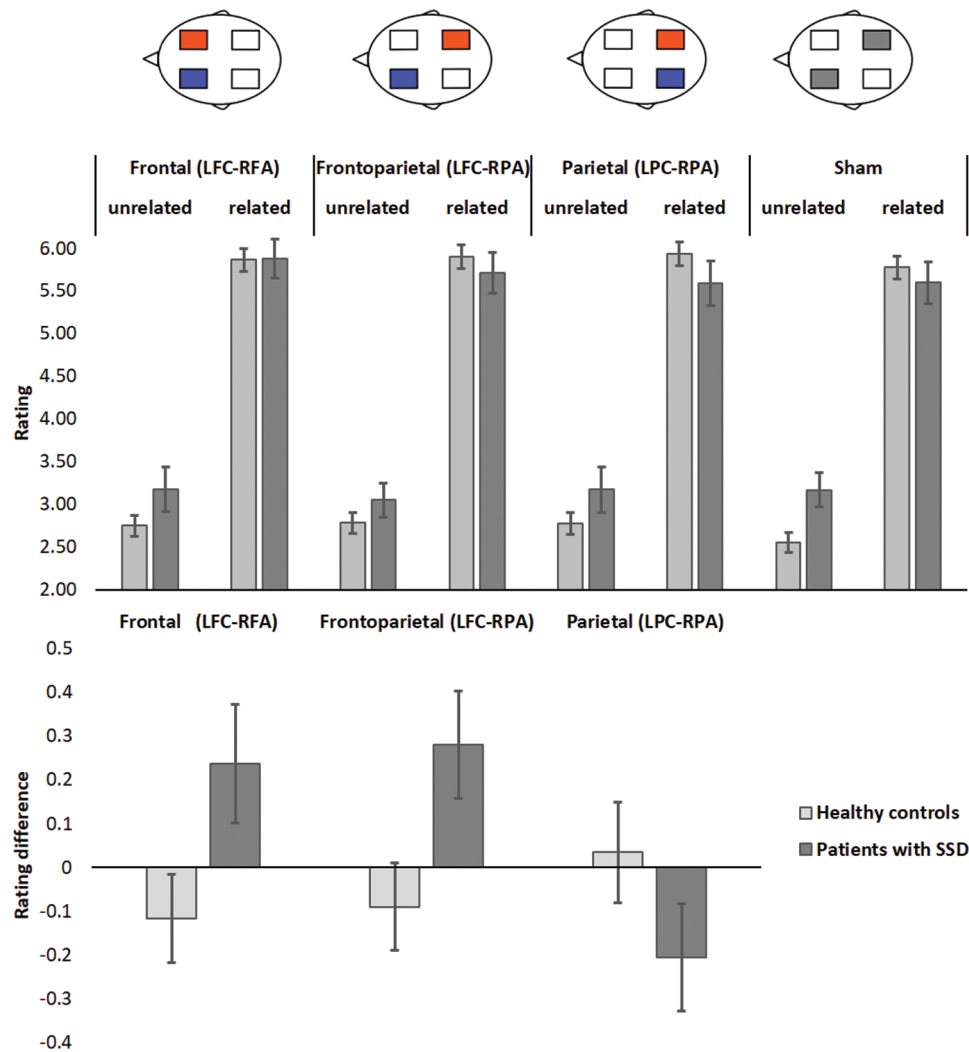
Fig. 3. Stimulation, group, and relatedness dependence of ratings. (A, top) Mean ratings (relatedness rated on a scale from 1 = very low to 7 = very high relatedness). (B, bottom) tDCS improvement in differentiation between related and unrelated gestures: Difference between real stimulation conditions and sham condition, regarding the difference in ratings between related and unrelated gestures of each condition. L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode; eg, LFC-RFA = left frontal cathodal and right frontal anodal stimulation; LFC-RPA = left frontal cathodal and right parietal anodal stimulation; LPC-RPA = left parietal cathodal stimulation. Electrode positions illustrated by head drawings above (blue = cathode; orange = anode). Error bars indicate the standard error of the mean (SEM).

between related and unrelated metaphoric gestures and facilitated processing of related metaphoric gestures. When analyzing healthy controls and patients separately, this interaction is significant only for patients ($P = .047$), indicating that the effect is driven mainly by the patient group.

Results of our patient-only analysis were consistent with results of the main model (ratings: *stimulation × relatedness*: $P = .032$, *gesture type × relatedness*: $P = .016$; reaction times: *gesture type × relatedness*: $P = .001$, *stimulation × gesture type × relatedness*: $P = .047$), indicating that stimulation influenced the evaluation of speech–gesture relatedness in patients.

Discussion

In this study, we tested the hypothesis that cathodal tDCS of the left frontal cortex can influence dysfunctional co-verbal gesture processing. We found that frontal and frontoparietal stimulation did in fact significantly improve the differentiation of related and unrelated speech–gesture conditions in patients, reducing the difference in rating behavior between patients and healthy controls.

Results

We could show that patients have substantial gesture deficits, by demonstrating for the first time that their ability
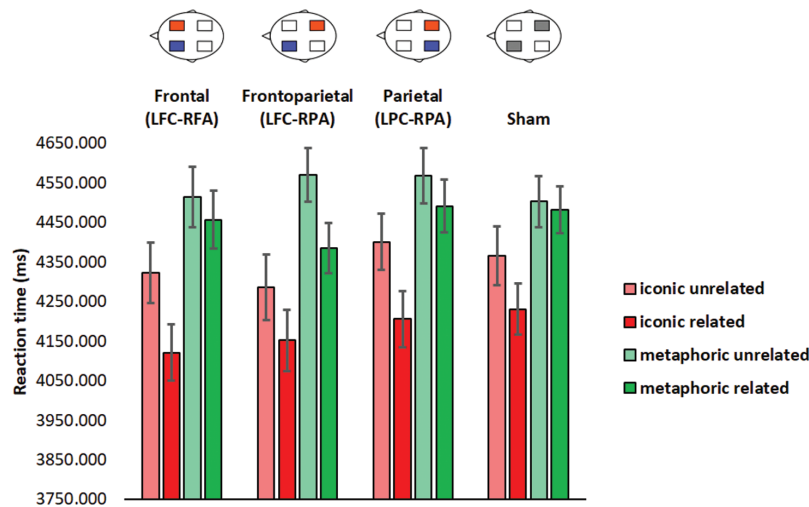
Fig. 4. Stimulation, gesture type, and relatedness dependence of mean reaction times across the entire group of patients and healthy controls. Light red: iconic unrelated. Dark red: iconic related. Light green: metaphoric unrelated. Dark green: metaphoric related. Electrode positions illustrated by head drawings above (blue = cathode; orange = anode). Error bars indicate the standard error of the mean (SEM).

to discriminate between related and unrelated co-verbal gestures is reduced. Patients tended to rate related co-verbal gestures as less related and unrelated co-verbal gestures as more related than healthy controls. Using tDCS, we were able to normalize this speech–gesture matching deficit. We found a specific stimulation effect on ratings for related, compared to unrelated, co-verbal gestures, confirming the importance of the left frontal region for assessing semantic relatedness.[51] In normal communication, gestures are usually related to speech, so it is promising for possible clinical applications that the observed effect is mainly driven by related gestures.

The left frontal inferior gyrus has been identified as an area of major overactivation in schizophrenia[38] and seems to be particularly relevant for gesture deficits.[25] Furthermore, in schizophrenia the functional connection between left IFG and left STS is weakened, especially for metaphoric gestures.[26] It is likely that cathodal tDCS has modulated pathological processing in left frontal areas and/or influenced the connectivity between the left IFG and the left STS. This would be in line with a recent review that concluded that both local excitability changes (induced by radial currents) and synaptic changes (induced by tangential currents) in the frontoparietal network are relevant for tDCS effects in patients with schizophrenia.[52]

In healthy subjects, left frontal anodal stimulation specifically decreased reaction times and ratings for metaphoric co-verbal gestures.[36] In this study, we did not include a condition with anodal stimulation of the left frontal cortex, which could be the reason that we did not find a gesture type dependent effect on ratings. A recent study with high temporal resolution due to a combined EEG-fMRI approach suggests an important involvement of the left IFG even for the processing of intrinsic

meaningful gestures[53]; this could also explain why left frontal stimulation had no differential effect on ratings between metaphoric and iconic gestures. Of course, differences in gesture processing between healthy controls and patients with SSD might play a role as well.

Moreover, the decrease in reaction times for related metaphoric gestures during frontoparietal stimulation in patients and across groups indicated at least some gesture-type-specific improvement.

Limitations

Despite the encouraging finding of improved semantic processing after left frontal tDCS, we need to interpret our results cautiously. We did not directly compare left frontal cathodal against left frontal anodal stimulation. To confirm that the improvement in relatedness assessment was indeed due to left frontal cathodal stimulation (and not to contralateral anodal stimulation), further studies should replicate our results using a left frontal cathode/anode and a relatively inactive reference electrode (placed in an area such as the cheek). In addition, the application of other brain stimulation methods such as transcranial magnetic stimulation or transcranial alternating current stimulation could also be useful to corroborate and expand our present findings.

More generally, due to the limitations of tDCS as a research tool, our study is limited with regard to elucidating the precise brain regions and mechanisms influenced by stimulation.

Outlook

Here, we showed that tDCS can improve gesture processing during stimulation (online). It should be probed if

and for how long tDCS effects on gesture processing last after stimulation (offline). Moreover, as gesture perception and gesture performance are closely related, it seems likely that tDCS may also improve gesture performance.

In the future, tDCS may be a useful tool for improving semantic processing and thereby possibly improve social functioning of patients with SSD. However, many tDCS studies in patients with schizophrenia conducted so far have applied anodal stimulation to the left dorsolateral prefrontal cortex (eg, to improve auditory hallucinations[30,54] or working memory[32–35]). Before using any tDCS protocol in clinical practice, its effects on a wide range of brain functions need to be assessed thoroughly. Eventually, optimization of stimulation duration, strength, and repetition would be necessary to establish an effective tDCS protocol for improving clinically relevant parameters of social cognition in schizophrenia.

Conclusion

Here we show for the first time that tDCS can improve semantic speech–gesture matching in patients with SSD. However, before clinical application can be considered, further research is needed to understand the mechanisms behind this effect, to examine possible side effects of stimulation, and to explore whether tDCS can be used to improve social communication and gestural processing in patients over the long term.

Funding

Acknowledgments

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