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Modulating semantic speech-gesture matching in healthy subjects and patients with schizophrenia spectrum disorder via transcranial direct current stimulation

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1 List of figures

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2 List of publications

This thesis summarizes work carried out at the Department of Psychiatry and Psychotherapy, Philipps-University Marburg. In line with the formal requirements of a cumulative dissertation, a shortened description of research findings is presented based on the following peer-reviewed journal articles:

1) Publication 1: **Schülke, R.**, & Straube, B. (2017b). Modulating the assessment of semantic speech–gesture relatedness via transcranial direct current stimulation of the left frontal cortex. *Brain stimulation*, *10*(2), 223–230. https://doi.org/10.1016/j.brs.2016.10.012

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   Presented at the 6th International Conference on Transcranial Brain Stimulation 2016 as a poster contribution: **Schülke, R.**, & Straube, B. (2017a). P164 Modulation of semantic speech-gesture matching performance by tDCS. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, *128*(3), e97. https://doi.org/10.1016/j.clinph.2016.10.285

2) Publication 2: **Schülke, R.**, & Straube, B. (2019). Transcranial Direct Current Stimulation Improves Semantic Speech-Gesture Matching in Patients With Schizophrenia Spectrum Disorder. *Schizophrenia Bulletin*, *45*(3), 522–530. https://doi.org/10.1093/schbul/sby144

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3 Index of abbreviations

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
fMRI	functional magnetic resonance imaging
GEE	generalized estimating equations
GM	German modification
ic	iconic (gestures)
ICD-10	International Statistical Classification of Diseases and Related Health Problems, tenth revision
IFG	inferior frontal gyrus
LFA	left frontal anodal (stimulation)
LFC	left frontal cathodal (stimulation)
LPA	left parietal anodal (stimulation)
LPC	left parietal cathodal (stimulation)
mp	metaphoric (gestures)
rel	related (gestures)
RFA	right frontal anodal (stimulation)
RFC	right frontal cathodal (stimulation)
RPA	right parietal anodal (stimulation)
RPC	right parietal cathodal (stimulation)
SAPS	Scale for the Assessment of Positive Symptoms
SANS	Scale for the Assessment of Negative Symptoms
SSD	schizophrenia spectrum disorders
STS	superior temporal sulcus
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
tMS	transcranial magnetic stimulation
unrel	unrelated (gestures)

4 Abstract

4.1 Background

Severe deficits in speech and gesture processing are an important characteristic of patients with schizophrenia spectrum disorders. Given that co-verbal gestures are a vital part of human communication, it is not surprising that deficits in co-verbal gesture perception and performance contribute significantly to the suffering of these patients. Brain imaging studies have shown that the left frontal cortex plays a major role for processing co-verbal gestures, both in healthy subjects and in patients with schizophrenia spectrum disorders. The left inferior frontal gyrus seems to be particularly important for the perception of metaphoric gestures, that is, gestures accompanying abstract sentence content (e.g., lifting the hand to illustrate the high quality of a discussion), compared to iconic gestures, i.e., gestures accompanying concrete sentence content (e.g., circular hand movement to illustrate a round table). Moreover, the left frontal brain area appears to be activated excessively in patients with schizophrenia spectrum disorders. So far, no study had probed whether transcranial direct current stimulation could influence co-verbal gesture processing in patients with schizophrenia.

4.2 Objective

In the first part of our study (publication 1), we investigated the functional relevance of the left frontal lobe for processing metaphoric co-verbal gestures in healthy subjects using transcranial direct current stimulation. We hypothesized a polarization dependent effect of left frontal transcranial direct current stimulation on reaction times and ratings in a speech-gesture semantic relatedness assessment task. In the second part of the study (publication 2), we investigated the effect of transcranial direct current stimulation on co-verbal processing of patients with schizophrenia spectrum disorders. We hypothesized that inhibitory cathodal transcranial direct current stimulation of the left frontal lobe would improve patients' performance in the speech-gesture semantic relatedness assessment task.

4.3 Methods

We applied anodal, cathodal and sham stimulation to the frontal, parietal and frontoparietal areas of twenty-nine healthy subjects and twenty patients with schizophrenia spectrum disorders. During stimulation, subjects watched video clips of an actor saying concrete or abstract sentences that were accompanied by semantically related or unrelated, iconic or metaphoric gestures. After each video clip, subjects immediately rated to what extent gestures were related to the sentence content (prompt: "Does the sentence content match

the gesture?", the answer was to be given on a scale from one "very badly" to seven "very well").

4.4 Results

For the first sample of seventeen healthy subjects (publication 1), we found electrode localization- and polarization-dependent changes in reaction times and ratings for metaphoric co-verbal gestures. Anodal stimulation of the left frontal lobe decreased reaction times and relatedness assessments for this type of gestures. When comparing healthy subjects and patients (publication 2), we found a specific effect of transcranial direct current stimulation on speech-gesture relatedness ratings of patients with schizophrenia spectrum disorders. Left frontal cathodal stimulation significantly improved the differentiation between related and unrelated gestures, thus reducing the pre-existing difference in speech-gesture assessment between patients and healthy controls.

4.5 Conclusion

First, we demonstrated that left frontal transcranial direct current stimulation influences processing of co-verbal metaphoric gestures in healthy subjects (publication 1). Subsequently, we showed that transcranial direct current stimulation may also improve semantic speech-gesture matching in patients with schizophrenia spectrum disorders (publication 2). In the future, transcranial direct current stimulation could be a viable tool to normalize processing in the left frontal lobe and improve social communication deficits in patients with schizophrenia spectrum disorders.

5 Zusammenfassung / German abstract

5.1 Hintergrund

Schwere Defizite bei der Verarbeitung von Sprache und Gestik sind ein wichtiges Merkmal von Patienten mit Schizophrenie-Spektrum-Störungen. Da sprachbegleitende Gesten einen essentiellen Teil menschlicher Kommunikation darstellen, ist es nicht überraschend, dass Einschränkungen bei der Wahrnehmung und Durchführung von sprachbegleitender Gestik erheblich zum Leiden dieser Patienten beitragen. Mittels bildgebender Verfahren konnte gezeigt werden, dass links frontale Cortexareale sowohl bei Gesunden als auch bei Patienten mit Schizophrenie-Spektrum-Störungen eine große Rolle bei der Verarbeitung sprachbegleitender Gestik spielen. Der linke inferiore frontale Gyrus scheint insbesondere für die Wahrnehmung metaphorischer Gesten, d.h. von Gesten die einen Satz mit abstraktem Inhalt begleiten (z.B. das Heben der Hand, um die hohe Qualität einer Diskussion darzustellen), wichtiger zu sein als für die Wahrnehmung ikonischer Gesten, d.h. von Gesten die einen Satz mit konkretem Inhalt begleiten (z.B. eine kreisförmige Bewegung der Hand, um einen runden Tisch zu veranschaulichen). Bei Patienten mit Schizophrenie liegt zudem eine übermäßige Aktivierung links frontaler Hirnareale vor. Bisher wurde noch nicht untersucht, ob transkranielle Gleichstromstimulation die gestörte Verarbeitung sprachbegleitender Gestik von Patienten mit Schizophrenie beeinflussen kann.

5.2 Zielsetzung

Im ersten Teil unserer Studie (Publikation 1) untersuchten wir mittels transkranieller Gleichstromstimulation die funktionelle Bedeutung des linken Frontallappens für die Verarbeitung metaphorischer sprachbegleitender Gestik bei gesunden Probanden. Wir stellten die Hypothese auf, dass sich links frontale transkranielle Gleichstromstimulation polarisationsabhängig auf die Bewertung der semantischen Passung von Sprache und Gestik bei einer Sprach-Gestik-Passungsbewertungsaufgabe auswirkt und sich dieser Effekt durch eine Veränderung der Reaktionszeiten und der Bewertungen der Passung feststellen lässt.

Im zweiten Teil der Studie (Publikation 2) untersuchten wir die Auswirkungen von transkranieller Gleichstromstimulation auf die Verarbeitung sprachbegleitender Gestik bei Patienten mit Schizophrenie-Spektrum-Störungen. Unsere Hypothese war, dass inhibitorische transkranielle Gleichstromstimulation des linken Frontallappens die Leistung der Patienten bei der Sprach-Gestik-Passungsbewertungsaufgabe verbessert.

5.3 Methoden

Wir führten bei neunundzwanzig gesunden Probanden sowie zwanzig Patienten mit Schizophrenie-Spektrum-Störungen anodale, kathodale und Schein-Stimulation der frontalen, parietalen und frontoparietalen Hirnareale durch. Während der Stimulation wurden den Probanden Videosequenzen eines Schauspielers gezeigt. Dieser sprach einen konkreten oder abstrakten Satz aus und begleitete diesen Satz mit einer semantisch passenden oder unpassenden, ikonischen oder metaphorischen Geste. Nach jeder Videosequenz bewerteten die Probanden sofort, in welchem Ausmaß der Satzinhalt zur Gestik passte (Frage: „Passen Satzinhalt und Gestik zusammen?“, Antwort auf einer Skala von eins „sehr schlecht“ bis sieben „sehr gut“).

5.4 Ergebnisse

Für die erste aus siebzehn gesunden Probanden bestehende Stichprobe (Publikation 1) fanden wir Veränderungen der Reaktionszeiten und Bewertungen in Abhängigkeit von Stimulationsort und Polarisation für metaphorische sprachbegleitende Gesten. Anodale Stimulation des linken Frontallappens reduzierte die Reaktionszeiten und Bewertungen der Sprach-Gestik-Passung für diesen Gestiktyp. Beim Vergleich zwischen den gesunden Probanden und den Patienten mit Schizophrenie-Spektrum-Störungen (Publikation 2) stellten wir einen spezifischen Effekt der transkraniellen Gleichstromstimulation auf die Bewertung der Sprach-Gestik-Passung bei Patienten fest. Links frontale kathodale Stimulation verbesserte die Unterscheidung zwischen passenden und unpassenden Gesten bei Patienten signifikant und reduzierte somit den Unterschied in der Bewertung der Sprach-Gestik-Passung zwischen Patienten und gesunden Probanden.

5.5 Fazit

Zunächst zeigten wir, dass links frontale transkranielle Gleichstromstimulation die Verarbeitung sprachbegleitender metaphorischer Gesten bei Gesunden beeinflusst (Publikation 1). Anschließend demonstrierten wir, dass transkranielle Gleichstromstimulation auch bei Patienten mit Schizophrenie-Spektrum-Störungen die semantische Sprach-Gestik Verarbeitung verbessern kann. Die transkranielle Gleichstromstimulation könnte möglicherweise in der Zukunft genutzt werden, um gestörte Verarbeitungsprozesse im linken Frontallappen von Patienten mit Schizophrenie zu modulieren und dadurch die Defizite dieser Patienten in der sozialen Kommunikation zu mildern.

6 Introduction

6.1 Importance of gestures for human communication

Hand gestures are a fundamental, cross-cultural feature of human communication. Some theories suggest that gestures may indeed have been the phylogenetic origin of speech (Corballis, 2003; Meister et al., 2003). Interestingly, even children blind from birth produce gestures similar to gestures of healthy children in form and content (Iverson & Goldin-Meadow, 1997).

Often, gestures occur together with speech and are thus referred to as co-verbal gestures. Co-verbal gestures are referred to as iconic if the accompanying speech content is of a concrete nature (e.g., circular hand movement to illustrate a round table; Arnheim & McNeill, 1994; McNeill, 1995). If the speech content is abstract, gestures are referred to as metaphoric (e.g., lifting the hand to indicate the high quality of a discussion). Co-verbal gestures play important roles for both speaker (intrapersonal function) and listener (interpersonal function). On the one hand, co-verbal gestures significantly facilitate comprehension (Beattie & Shovelton, 1999; Hostetter, 2011; Obermeier, Dolk, & Gunter; 2012; Goldin-Meadow & Alibali, 2013) and learning (Valenzeno, Alibali, & Klatzky, 2003; Cutica & Bucciarelli, 2008) for the listener, adding additional information not included in the speech content (Goldin-Meadow, 1999). On the other hand, gesturing also improves learning processes of the speaker and may change his way of thinking (Goldin-Meadow, 1999; Goldin-Meadow & Alibali, 2013).

6.2 Neural correlates of co-verbal gesture processing

In general, speech processing and gesture processing networks in the human brain are largely overlapping (Willems, Ozyürek, & Hagoort, 2007; Xu, Gannon, Emmorey, Smith, & Braun; 2009, Straube, Green, Weis, Kircher, & Stamatakis, 2012; Andric et al., 2013). With regard to co-verbal gestures, fMRI studies have highlighted the importance of the right and particularly the left inferior frontal gyrus (IFG) for both metaphoric (Mashal, Faust, Hendler, & Jung-Beeman, 2009; Kircher et al., 2009) and iconic (Willems, Ozyürek, & Hagoort, 2009; Ozyürek, 2014) co-verbal gestures. When contrasting metaphoric against iconic co-verbal gestures, however, the left IFG seems to be especially relevant for processing metaphoric co-speech gestures (Straube, Green, Bromberger, & Kircher, 2011). Besides, the neural correlates of co-verbal gesture processing also depend on the semantic relation between speech and gesture. Willems et al. demonstrated that unrelated (semantically anomalous in

the given context) gestures or words both lead to increased activation in the left IFG (Willems et al., 2007; publication 1, introduction).

6.3 Schizophrenia spectrum disorders (SSD)

According to the DSM-5 (fifth edition of the Diagnostic and Statistical Manual of Mental Disorders), schizophrenia spectrum disorders and other psychotic disorders are characterized by five key features: delusions (fixed beliefs not amenable to change in the light of conflicting evidence), hallucinations (perception-like experiences that occur without external stimulus), disorganized thinking (patients switch from one topic to another, answers to questions are obliquely related or completely unrelated), abnormal motor behavior (ranging from childlike “silliness” to unpredictable agitation or catatonic behavior) and negative symptoms (diminished emotional expression, avolition, alogia, anhedonia, asociality; American Psychiatric Association, 2013; Liddle, 1987; Andreasen, 1995). Like most psychiatric diseases, schizophrenia is a clinical diagnosis. In Germany, the German modification of the International Classification of Diseases, tenth revision (ICD-10 GM), is generally used to diagnose schizophrenia in clinical practice (Dilling, 2016). Patients who do not meet the full criteria of schizophrenia or display additional symptoms not usually found in patients with schizophrenia are not diagnosed with schizophrenia but with other schizophrenia spectrum diagnoses. For example, a patient who does no longer display positive symptoms but suffers from pronounced negative symptoms may be diagnosed with residual schizophrenia, while a patient with typical positive symptoms such as delusions and acoustic hallucinations who also suffers from manic or depressive symptoms may be diagnosed with schizoaffective disorder. Given differing diagnostic criteria and their individual interpretation, the estimated prevalence of schizophrenia spectrum disorders varies across studies. Recent meta analyses resulted in an estimated prevalence of 0.72% (McGrath, Saha, Chant, & Welham, 2008) and 0.75% (Moreno-Küstner, Martín, & Pastor, 2018) for schizophrenia and related disorders. Despite its relatively low prevalence, schizophrenia was one of the top 25 leading causes of disability worldwide in 2013 (Vos et al., 2015) and represents a considerable economic burden (Chong et al., 2016). While antipsychotic medication has brought considerable relief to a large number of patients, medication comes with serious side effects and not all patients benefit from medication to the same extent. In particular, the treatment of negative symptoms and social dysfunction remains challenging (Barnes, 2011). Thus, there is ample need for further research to ultimately reduce suffering of patients with SSD and improve their quality of life.

6.4 Impaired gesture processing in patients with SSD

Gesture deficits are very characteristic of schizophrenia (Berndl, Cranach, & Grüsser, 1986; Bucci, Startup, Wynn, Baker, & Lewin, 2008; Walther & Mittal, 2016), have been found to be present at all stages of the disorder (Mittal et al., 2006; Walther, Vanbellingen, Muri, Strik, & Bohlhalter, 2013) and play an important role for social dysfunctioning (Lavelle, Healey, & McCabe, 2013). In fact, a recent study has shown that gesture performance and nonverbal social perception may be a valuable marker of functional outcome in patients with schizophrenia (Walther et al., 2016).

With regards to gesture perception and interpretation, patients show severe gesture recognition deficits (publication 2, introduction). They do not only have difficulties at correctly identifying meaningful gestures, but also tend to perceive gestures as self-referential (White, Borgan, Ralley, & Shergill, 2016). Incidental movements are perceived as meaningful gestures and neutral gestures as conveying an insulting meaning (Bucci et al., 2008). Importantly, gesture deficits in patients with SSD represent a serious aspect of impairment in their own right and cannot be explained by supramodal cognitive deficits like verbal working memory impairment (Berndl et al., 1986; Walther et al., 2015).

6.5 Neural correlates of impaired gesture processing in patients with SSD

Generally, excess activation 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 (Wible, 2012). FMRI evidence suggests a general increase in activation of the left IFG in schizophrenia (Jardri R, Pouchet A, Pins D, Thomas P, 2011). For perception of co-verbal gestures, a reduced connectivity between the left STS and the left IFG for processing metaphoric gestures (Straube, Green, Sass, & Kircher, 2014) and a specific imbalance of left IFG activation for processing co-verbal gestures (decrease in ventral activation along with an increase in dorsal activation; Straube, Green, Sass, Kirner-Veselinovic, & Kircher, 2013) have also been demonstrated. In sum, aberrant processing in the frontal cortex and dysfunctional fronto-temporal connectivity seem to play a major role in impaired gesture processing of patients with SSD.

6.6 Transcranial direct current stimulation (tDCS) as a brain stimulation method

Transcranial direct current stimulation is a non-invasive brain stimulation method that applies direct current to the scalp (supplementary material, figure 1) in order to change excitability of the underlying brain areas (Nitsche & Paulus, 2000; Stagg, Antal, & Nitsche, 2018). In general, anodal stimulation causes increased excitability, whereas cathodal

stimulation causes decreased excitability. The changes in excitability of a single tDCS session endure after stimulation (Nitsche & Paulus, 2001) and may last for up to five hours (Reinhart & Woodman, 2014). While immediate tDCS effects are due to sub-threshold modulation of the resting membrane potential of nerve cells under the electrode, the long-lasting effects seem to rely on NMDA receptor-dependent long-term potentiation, as it has been shown that NMDA receptor blockers abolish the long-lasting effects of tDCS (Nitsche, Fricke et al., 2003). If performed in accordance with safety guidelines (Nitsche, Liebetanz et al., 2003), tDCS has been proven to be a safe brain stimulation method with no serious side effects in humans. An itching sensation underneath the electrodes at the beginning and the end of stimulation is frequent (Nitsche, Liebetanz et al., 2003), mild fatigue and headaches may occur as well (Poreisz, Boros, Antal, & Paulus, 2007). To date, tDCS effects on many different aspects of perception, cognition and behavior have been investigated (Shin, Foerster, & Nitsche, 2015). In recent years, the research community has begun to examine the potential of tDCS as a treatment option for psychiatric patients (Mondino et al., 2014), such as patients with schizophrenia (Agarwal et al., 2013).

6.7 TDCS to influence gesture processing

A noninvasive brain stimulation method like tDCS may serve as a tool to explore the functional relevance of a specific brain region and thereby corroborate fMRI evidence. The first study that probed a possible modulation of gestural-verbal semantic integration by tDCS used short video clips showing a masked actor performing either a symbolic or a pantomimic gesture, followed by a written word that either accurately described the gesture or was unrelated to it (Cohen-Maximov, Avirame, Floeel, & Lavidor, 2015). Subjects judged whether the word was related to the clip or not. Anodal stimulation over the right IFG coupled with cathodal stimulation over the left IFG generated faster responses to symbolic gestures than inverse stimulation or sham. However, a 2013 study investigating tDCS effects on performance in a gesture matching task found improved performance after anodal stimulation of an entirely different brain region, namely, the left parietal cortex (Weiss et al., 2013). Similarly, Bolognini et al. found that apraxia could be improved by anodal tDCS stimulation of the left posterior parietal cortex, highlighting the importance of this region for gesture planning (Bolognini et al., 2015). All of these studies looked at isolated gestures that were not accompanied by speech. Prior to our investigation, the influence of tDCS on co-verbal gesture processing had not been investigated.

6.8 TDCS in patients with SSD

TDCS has repeatedly been tested as a possible clinical treatment tool for schizophrenia (Agarwal et al., 2013; Gupta, Kelley, Pelletier-Baldelli, & Mittal, 2018). For example, Brunelin et al. found that tDCS might be a very effective tool for reducing auditory hallucinations, reporting a reduction in hallucinations for up to three months (Brunelin et al., 2012). The effects of tDCS on gesture processing deficits of patients with SSD, however, had previously remained unexplored.

6.9 Study goals

In the first part of our study (publication 1), we aimed to discern electrode localization- and polarization-dependent effects of tDCS in healthy subjects on the assessment of speech-gesture relatedness for metaphoric and iconic co-verbal gestures that were either related or unrelated to speech content. Based on earlier fMRI data, we hypothesized a specific polarization-dependent effect of left frontal tDCS on ratings and reaction times for metaphoric gestures. In particular, we predicted faster and more critical assessment during left frontal anodal stimulation.

In the second part of our study (publication 2), 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. We predicted that reducing excitability of the left frontal area using cathodal tDCS would normalize patients' assessments of speech-gesture relatedness, that is, lead to higher relatedness ratings for related stimuli and more critical assessment of relatedness for unrelated stimuli.

The study was approved by the local ethics committee (Az.: 86/15).

7 Summaries of publications

7.1 Publication 1

Modulating the assessment of semantic speech–gesture relatedness via transcranial direct current stimulation of the left frontal cortex. Schülke, R., & Straube, B. (2017b). *Brain stimulation*, *10*(2), 223–230. https://doi.org/10.1016/j.brs.2016.10.012

Many neuroimaging studies have shown that the left frontal area and the left IFG in particular are activated for processing metaphoric (Mashal et al., 2009; Kircher et al., 2009; Straube et al., 2011) and iconic (Willems et al., 2009; Ozyürek, 2014) co-verbal gestures. Direct comparison of iconic and metaphoric gestures suggests that the left IFG may be even more important for metaphoric co-verbal gestures (Straube et al., 2011; Nagels, Chatterjee, Kircher, & Straube, 2013). The functional relevance of these findings, however, remains unclear. A 2015 study investigating the effect of tDCS on processing of gestures found reduced reaction times in a semantic relatedness assessment task for cathodal stimulation of the left IFG (Cohen-Maximov et al., 2015). On the other hand, anodal tDCS of the left parietal cortex has also been found to facilitate gesture processing (Weiss et al., 2013). So far, no study had looked at the effects of tDCS on co-verbal gesture processing.

In the first part of our study (publication 1), we tested the hypothesis that different neural mechanisms contribute to the semantic assessment of the relationship between speech and gesture, depending on whether utterances refer to abstract or concrete information. We hypothesized that semantic assessment can be influenced using left frontal tDCS. To investigate the functional relevance of the left frontal lobe for processing metaphoric co-verbal gestures, we applied anodal, cathodal and sham tDCS to frontal (F3/F4), parietal (CP3/CP4) and frontoparietal (F3/CP4) brain areas of our seventeen healthy subjects who underwent seven different stimulation conditions (publication 1, figure 1; supplementary material, subsection 11.1.1/figure 1; supplementary material, subsection 11.1.2/figure 2). We measured ratings and reaction times in a speech-gesture relatedness assessment task. During tDCS (1.5 mA for a duration of 10 minutes), our subjects were watching extensively validated video clips of an actor performing iconic and metaphoric co-verbal gestures (Kircher et al., 2009; Green et al., 2009). The hand movements displayed were either related or unrelated to the verbal content of the sentences spoken by the actor. Directly after each video clip, subjects rated to what extent gestures matched the verbal content.

To analyze our data, we used generalized estimating equations (GEE) as implemented in IBM SPSS Statistics 19. GEE can be employed even more flexibly than generalized linear models (GLM). In contrast to the likelihood-based generalized linear models, GEE are a semiparametric regression method. As a result, GEE may also be used in the case of correlated observations (Hardin & Hilbe, 2003). Furthermore, GEE are very robust: Even if the correlation matrix is not chosen correctly, GEE correctly estimate parameters and standard errors (Hardin & Hilbe, 2003).

We found electrode localization- and polarization-dependent changes in reaction times and ratings for metaphoric co-verbal gestures compared to iconic gestures (significant interaction *localization * polarization * gesture type*; publication 1, table 1; publication 1, figure 2). Post-hoc tests revealed a specific effect for frontoparietal stimulation sites: Compared to cathodal stimulation, anodal stimulation of the left frontal lobe decreased reaction times and relatedness assessments for metaphoric conditions only (publication 1, table 2; publication 1, figure 3). Neither serious side effects nor significant discomfort were observed during or after stimulation.

Our data underlines the importance of the left frontal lobe for metaphoric co-verbal gestures, corroborating evidence from fMRI studies hinting at the relevance of the left IFG for processing metaphoric gestures (Kircher et al., 2009; Straube, Green, Weis, Chatterjee, & Kircher, 2009; Straube et al., 2011; Nagels et al., 2013). After left frontal anodal stimulation, subjects were not only faster at evaluating metaphoric gestures, but also became more critical regarding the semantic relation of speech and gesture. It seems likely that tDCS influences the construction and assessment of a semantic relationship between speech and gesture information. The effect, however, was only seen for the frontoparietal condition, posing the question why the exclusively frontal condition did not elicit a similar effect, despite left frontal anodal stimulation. This may be explained by the fact that not only the left, but also the right frontal area is involved in gesture processing (Dick, Goldin-Meadow, Hasson, Skipper, & Small, 2009; Straube et al., 2009; Green et al., 2009), especially for processing unrelated speech-gesture information (Cohen-Maximov et al., 2015). The right parietal area, on the other hand, does not seem to play a specific role for co-verbal gesture processing. Consequently, in the case of exclusively frontal stimulation, effects of left frontal stimulation are attenuated by simultaneous reverse stimulation of the contralateral left frontal region, while the effect of frontoparietal stimulation is probably mainly due to the left frontal electrode (see discussion, subsection 8.1 for further elaboration).

Here we showed for the first time that tDCS influences co-verbal gesture processing and thereby demonstrated the functional relevance of the left frontal lobe for processing metaphoric co-verbal gestures in healthy subjects. Thus, left frontal tDCS may be used as a tool to modulate the perception of co-verbal gestures. It remained to be explored whether tDCS could positively influence aberrant co-verbal gesture processing in patients.

7.2 Publication 2

Transcranial direct current stimulation improves semantic speech-gesture matching in patients with schizophrenia spectrum disorder. Schülke, R., & Straube, B. (2019). *Schizophrenia Bulletin*, *45*(3), 522–530. https://doi.org/10.1093/schbul/sby144

Gesture deficits are very characteristic of patients with SSD (Berndl et al., 1986; Bucci et al., 2008) and are to blame for an important proportion of social impairment in patients (Lavelle et al., 2013). These deficits are not due to supramodal cognitive dysfunction but represent a specific symptom of SSD (Berndl et al., 1986; Walther et al., 2015). A major aspect of impairment is patient's inability to perceive and recognize gestures (publication 2, introduction).

TDCS has already been tested as a clinical treatment tool for schizophrenia. First studies indicate that tDCS may effectively reduce auditory hallucinations (Brunelin et al., 2012; Gupta et al., 2018). The effects of tDCS on gesture processing, however, had not been investigated previously. After having demonstrated that tDCS influences gesture processing in healthy subjects (publication 1), our goal was to explore its effects on impaired gesture processing in patients with SSD. We predicted that reducing excitability of the left frontal area using cathodal tDCS would normalize patients' assessments of speech-gesture relatedness by reducing pathological activation of the left frontal lobe. We hypothesized that left frontal tDCS would result in higher relatedness ratings for related stimuli and more critical assessment of relatedness for unrelated stimuli.

In the second part of our study (publication 2), we tested the hypothesis that cathodal tDCS of the left frontal cortex can influence dysfunctional co-verbal gesture processing in patients with SSD. In order to examine tDCS effects on speech-gesture relatedness assessment of patients with SSD, we used the same experimental design and stimuli as in the group of healthy subjects. Patients, however, took part in four different stimulation conditions only (LFC-RFA, LFC-RPA, LPC-RPA, sham; publication 2, figure 1; supplementary material, figure 1; supplementary material, figure 2).

When comparing patients against healthy subjects using GEE, we found that patients' ability to differentiate between related and unrelated co-verbal gestures was impaired (significant interaction *group * relatedness;* publication 2, table 1; publication 2, figure 2). Patients rated related co-verbal gestures as less related and unrelated co-verbal gestures as more related than healthy controls, indicating an impairment of evaluating the semantic relation between

speech and gestures. Importantly, frontal and frontoparietal stimulation did significantly improve the differentiation between related and unrelated gestures in patients, reducing the difference in rating behaviour between patients and healthy controls (significant interaction *group * stimulation * relatedness*; publication 2, table 1; publication 2, figure 3). We thus demonstrated that tDCS can improve speech-gesture processing in patients with SSD.

We found no effect of tDCS on group differences for reaction times. There was, however, a reduction in reaction times for related metaphoric gestures during frontoparietal stimulation (interaction *stimulation * gesture type * relatedness* and respective post-hoc tests; publication 2, table 1; publication 2, figure 4), which seemed to be driven by the patient group. No significant discomfort was reported during or after stimulation.

Neuroimaging studies have demonstrated that excessive left IFG activation is one of the characteristic neural correlates of schizophrenia (Jardri R, Pouchet A, Pins D, Thomas P, 2011) and seems to be particularly relevant for gesture deficits (Straube et al., 2013). Furthermore, in schizophrenia the functional connection between left IFG and left STS is weakened, especially for metaphoric gestures (Straube et al., 2014). It seems likely that left frontal cathodal tDCS has inhibited pathological processing in left frontal areas, consequently normalizing rating behaviour. Moreover, stimulation may also have influenced the functional connectivity between the left IFG and the left STS, two regions that are disconnected during processing of co-verbal gestures in patients with schizophrenia (Straube et al., 2014). These tentative conclusions about the mechanism behind the effects observed in our study would be in line with a recent review concluding that both local excitability changes (induced by radial currents) and synaptic changes (induced by tangential currents) in the frontoparietal network are responsible for tDCS effects in patients with schizophrenia (Brunoni et al., 2014). Moreover, the relatedness dependence of the demonstrated tDCS effect on ratings for left frontal stimulation confirms the importance of the left frontal region for assessing semantic relatedness that has formerly been shown using fMRI (Willems et al., 2007).

Here we showed for the first time that left frontal tDCS can improve semantic co-verbal gesture processing in patients with SSD. Firstly, we demonstrated a deficit in discriminating between related and unrelated gestures. Secondly, we showed that left frontal cathodal tDCS specifically alleviated this deficit by improving the discrimination between related and unrelated gestures. In the future, brain stimulation techniques such as tDCS might be a treatment tool to improve social dysfunction in patients with SSD. However, further studies

are needed. TDCS needs to be optimized and its effects on a broad range of brain functions, short-term as well as long-term, have to be assessed thoroughly before considering clinical application.

7.3 Statement of contribution

I participated in planning the study and was largely responsible for its implementation. The video clips used have been created by my supervisor and have been used in various previous studies. The technical aspects of the study, such as determining the precise workflow of stimulation sessions, ensuring effectivity and safety of stimulation, creating the study protocol and testing the stimulation protocol have been my responsibility. I conducted the first stimulation sessions and instructed and supervised our assistants to conduct later stimulation sessions. Moreover, I was responsible for statistical data analysis, interpretation of our findings as well as writing and submitting the first drafts of the two manuscripts resulting in the publications outlined above. I created all figures and tables. Furthermore, I was also responsible for editing the manuscripts during the review processes.

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8 Discussion

Co-verbal gestures are an essential feature of human communication. The ability to understand the semantic relationship between verbal and non-verbal information is important for social interaction and communication. Having been neglected as an area of research for much of the twentieth century, the importance of non-verbal communication has been recognized in recent years and co-verbal gestures have received increased attention. Furthermore, the development of neuroimaging techniques has largely contributed to a better understanding of non-verbal communication in general and co-verbal gestures in particular. Several fMRI studies have investigated the neural correlates of co-verbal gesture processing in the human brain and demonstrated the importance of the left IFG for co-verbal gesture processing (Mashal et al., 2009; Kircher et al., 2009; Willems et al., 2009; Straube et al., 2011; Ozyürek, 2014). The actual functional relevance of these fMRI findings, however, had formerly remained unclear and hitherto little practical use had been made of the new discoveries. After successful identification of the brain areas involved in co-verbal gesture processing, moving beyond fMRI was a natural next step.

TDCS is a brain stimulation technique that is increasingly being used to modulate brain activity in many different areas of research. As the understanding of the physiological basics of tDCS has deepened significantly, the research community is now turning towards applying tDCS as a neuropsychological research (Shin et al., 2015; Reinhart, Cosman, Fukuda, & Woodman, 2017) and treatment tool (Brunoni et al., 2012; Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013; Mondino et al., 2014). Several studies have looked at the therapeutic potential of tDCS in schizophrenia (Agarwal et al., 2013; Brunoni et al., 2014). For example, Brunelin et al. found a beneficial effect of tDCS on auditory hallucinations that lasted up to three months (Brunelin et al., 2012). The effect of tDCS on speech gesture deficits of patients with SSD, however, had not been investigated so far.

8.1 Effects of tDCS on speech-gesture relatedness assessment of healthy subjects

In line with evidence from fMRI studies (Kircher et al., 2009; Straube et al., 2011, Straube et al., 2009), we found a significant effect of left frontal tDCS on metaphoric gestures – but not on iconic co-verbal gestures – in a speech–gesture relatedness assessment task (publication 1). Faster reaction times and more critical ratings after left frontal anodal stimulation underline the role of the left frontal cortex for assessing relatedness of metaphoric gestures.

We did not observe significant differences for the post-hoc comparison of the two frontal conditions. The comparison of the two frontoparietal conditions, on the other hand, showed a clear effect. If we assume that the left frontal area is the area relevant for stimulation effects on gesture processing, why do we observe an effect only for comparing the frontoparietal conditions? To answer this question, we need to take into consideration that the left and right frontal area are both involved in gesture processing (Dick et al., 2009; Straube et al., 2009; Green et al., 2009; Cohen-Maximov et al., 2015). The right parietal area, by contrast, is not supposed to be specifically involved. Consequently, frontoparietal stimulation only affected one task-relevant area – namely, the left frontal area – whereas frontal stimulation affected two task-related areas, the left and the right frontal area. Therefore, the effects of frontal stimulation on the left frontal area (and possibly the left IFG) have probably been attenuated by simultaneous reverse stimulation of the contralateral region, which has formerly been implicated in co-verbal gesture processing (especially for unrelated speech-gesture information; Dick et al., 2009). This explanation is supported by data from Cohen-Maximov et al. who found faster reaction times for right anodal stimulation in their written word-gesture semantic relatedness assessment task (Cohen-Maximov et al., 2015). In line with their finding, right frontal anodal stimulation (LFC-RFA) also seemed to decrease reaction times in our study, independent of gesture type, although not significantly. While the right frontal area may be relatively more important for basic perceptual processes, such as motor simulation, the left frontal area may be relatively more important for supramodal semantic processing and the evaluation of abstract information. Consequently, stimulation of the left frontal cortex directly influenced subjective ratings of relatedness and reaction times, but only for metaphoric gestures. Furthermore, it has to be noted that the left frontal components of frontal and frontoparietal stimulation are not equivalent but differ considerably in their respective distributions of current density (supplementary material, subsection 11.1.2/figure 2). This might also be part of the explanation for the observed difference in stimulation effects between the two conditions.

8.2 Effects of tDCS on speech-gesture relatedness assessment of patients with SSD

In the second part of our study, we investigated the effects of three different active tDCS conditions and sham stimulation on speech-gesture relatedness assessment in a sample of twenty patients with SSD compared to a group of twenty-nine healthy controls (publication 2). We confirmed that patients suffer from substantial deficits in gesture processing, by demonstrating for the first time that their ability 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 thus demonstrated, for the first time, that tDCS can be used to modulate speech-gesture processing in patients with SSD. 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 (e.g., Willems et al., 2007). Related gestures were rated more related after stimulation. Since gestures used in everyday conversation are usually speech-related, it is encouraging for possible clinical applications that we found an effect for ratings of related gestures.

The left frontal inferior gyrus has been identified as an area of excessive activation in schizophrenia (Jardri R, Pouchet A, Pins D, Thomas P, 2011) and seems to be particularly relevant for gesture deficits in patients (Straube et al., 2013). Furthermore, in schizophrenia the functional connection between the left IFG and the left STS is weakened, especially for metaphoric gestures (Straube et al., 2014). 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 the conclusion of a recent review 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 (Brunoni et al., 2014).

In healthy subjects, left frontal anodal stimulation specifically decreased reaction times and ratings for metaphoric co-verbal gestures. Interestingly, we did not find a gesture type specific effect when analyzing the whole group of patients and healthy subjects. A possible explanation is that while in healthy subjects the left IFG is especially relevant for processing metaphoric gestures, as supported by fMRI research (Kircher et al., 2009) and by our own tDCS study (publication 1), patients with schizophrenia fail to activate the left IFG for metaphoric gestures (Straube et al., 2013). If the left IFG is not (or less) involved in processing metaphoric gestures in patients with schizophrenia, this might explain why tDCS of the left frontal region did not specifically influence the processing of metaphoric co-verbal gestures in these patients. However, the decrease in reaction times for related metaphoric gestures during frontoparietal stimulation across groups (and still significant for the patient group when analyzing both groups separately) indicated some gesture type specific improvement in patients as well.

Very recently, another study using the same set of stimuli that we employed in our investigation confirmed that patients with schizophrenia performed worse than healthy subjects at assessing the semantic relatedness of speech and gesture and revealed that gesture deficits were linked with formal thought disorder symptomatology (Nagels, Kircher, Grosvald, Steines, & Straube, 2019). While there was no difference between the subgroup of patients with mild formal thought disorder symptoms and the subgroup of patients with severe formal thought disorder symptoms for iconic gestures, patients with severe formal thought disorder symptomatology performed significantly worse at evaluating relatedness for metaphoric gestures. This raises the question whether tDCS might specifically influence the processing of metaphoric gestures in patients with severe formal thought disorder symptomatology.

8.3 Limitations

TDCS as a research tool has its limits. The spatial resolution and the anatomic specificity of tDCS is relatively low. Although the left IFG has been mentioned repeatedly, it needs to be pointed out very clearly that our stimulation targeted the left frontal lobe as a whole. We dare to make assumptions about tDCS effects on the left IFG only because of the large amount of fMRI studies that have stressed its role for co-verbal gesture processing, some of which made use of the very same stimuli that we employed here.

Unfortunately, while we were able to have our healthy subjects undergo seven different stimulation sessions, practical considerations only allowed for four stimulation sessions in the patient group. In the pre-examination of healthy subjects, left frontal anodal stimulation led to more critical ratings and faster reaction times. Patients did not undergo the three left anodal stimulation conditions (LFA-LFC, LFA-RPC, LPA-RPC). Due to former fMRI research showing excess activation in the left frontal lobe of patients with SSD for processing co-verbal gestures, we hypothesized that left frontal cathodal stimulation would improve co-verbal gesture processing in patients and therefore did not include a left frontal anodal stimulation condition in this group. To confirm that the improvement in relatedness assessments of patients was indeed due to left frontal cathodal stimulation, further studies should use a left frontal cathode/anode and an inactive reference electrode (placed in an area such as the cheek).

8.4 Outlook

In our study, we showed that tDCS can improve gesture processing during stimulation (online) in healthy subjects and patients. 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, further studies should investigate whether tDCS may also improve active gesture performance of patients with SSD, as it has been shown that tDCS can improve gesturing in apraxia (Marangolo et al., 2011; Bolognini et al., 2015). Conducting a combined tDCS-fMRI investigation might shed light on the actual changes in neural activations caused by tDCS during gesture processing in healthy subjects and patients. Besides, the application of other brain stimulation methods such as tMS or tACS could also be useful to corroborate and extend our present findings.

In the future, tDCS may be a useful tool for improving semantic speech-gesture processing and to alleviate social dysfunction 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 to improve auditory hallucinations (Brunelin et al., 2012; Agarwal et al., 2013) or working memory (Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014; Orlov et al., 2017). Before using tDCS in clinical practice, the effects of a specific stimulation protocol on a wide range of brain functions need to be assessed thoroughly. In addition, patient variables that may possibly influence the effect of stimulation need to be examined as well. For example, it has been shown recently that nicotine smoking may diminish the effect of tDCS in patients with schizophrenia (Brunelin, Hasan, Haesebaert, Nitsche, & Poulet, 2015). 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.

8.5 Conclusion

Our results strengthen and extend former fMRI and tDCS research that highlights the role of the left frontal cortex for gesture processing. Despite the methodologically low spatial resolution of tDCS, our data support the assumption that there are remarkable differences in neural processing between metaphoric and iconic co-verbal gestures. Moreover, we demonstrated for the first time that tDCS can improve semantic speech-gesture matching in patients with SSD. However, further research is needed to understand the mechanisms behind this effect, to examine possible effects of stimulation on other brain functions and to explore whether optimized tDCS protocols can bring about sustained, clinically significant improvement of social communication and gestural processing in patients with SSD.

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10 Reprints of original publications

10.1 Publication 1

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Modulating the assessment of semantic speech–gesture relatedness via transcranial direct current stimulation of the left frontal cortex

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ABSTRACT

Background: Co-verbal gestures are crucial for communication. Neuroimaging studies suggest that the left frontal lobe may be especially important for processing metaphoric co-verbal gestures. However, so far, the specific functional relevance of the left frontal lobe in metaphoric (abstract sentence content) co-verbal gesture processing compared to iconic (concrete sentence content) co-verbal gesture processing has not been demonstrated.

Objective: We investigated the functional relevance of the left frontal lobe for processing metaphoric co-verbal gestures using transcranial direct current stimulation (tDCS). We hypothesised a polarisation dependent effect of left frontal tDCS on reaction times and ratings in a speech–gesture semantic relatedness assessment task.

Methods: We applied anodal, cathodal and sham stimulation to the frontal (F3/F4), parietal (CP3/CP4) and frontoparietal (F3/CP4) areas. During stimulation, seventeen subjects were presented with videos of an actor saying concrete or abstract sentences accompanied by related or unrelated iconic or metaphoric gestures and rated to what extent gestures were related to the sentence content.

Results: We found electrode localisation- and polarisation-dependent changes in reaction times and ratings for metaphoric co-verbal gestures compared to iconic gestures. Post-hoc tests revealed a specific polarisation effect for frontoparietal stimulation sites: compared to cathodal stimulation, anodal stimulation of the left frontal lobe decreased reaction times and relatedness assessments for metaphoric conditions only.

Conclusion: Using tDCS, we demonstrated the functional relevance of the left frontal lobe for processing metaphoric co-verbal gestures. Thus, tDCS may possibly constitute an approach to facilitate metaphoric co-verbal gesture-processing in patients with specific deficits.

1. Introduction

Gestures are a fundamental feature of human communication and play important roles for both the recipient and the speaker (e.g. Refs. [1,2]). Co-verbal gestures are a special type of gesture used during verbal communication, and several studies have underlined their importance for communication. For example, it has been shown that co-verbal gestures may facilitate learning [3,4], improve memory performance [3,5,6] and reduce processing demand in face-to-face communication (e.g. Ref. [7]).

Co-verbal gestures can be divided further into iconic and metaphoric gestures, depending on the abstractness of the corresponding speech. Gestures accompanying abstract sentences (e.g. 'the conversation is at a high level' + elevation of hand) are referred to as metaphoric gestures, while gestures that accompany concrete sentences (e.g. 'the house is located on a mountain' + elevation of hand) are called iconic gestures.

1.1. Neural correlates of co-verbal gesture processing

Previous studies investigating the neural correlates of gesture processing have consistently found that speech-processing and gesture-processing networks are largely overlapping [8–12]. Several fMRI studies have highlighted the importance of the (right and particularly left) inferior frontal gyrus (IFG) for both metaphoric [7,13,14] and iconic ([15,16], for a review) co-verbal gestures.

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When comparing metaphoric and iconic co-verbal gestures, however, the left IFG has been found to be especially relevant for processing metaphoric co-speech gestures [14].

While activation of the left IFG is a reliable finding for metaphoric co-speech gesture processing or integration, less is known about the role of the parietal lobe in speech and gesture processing. Some investigations have found activation of the inferior parietal cortex for co-verbal gestures (e.g. Refs. [17,18], for a review). In particular, fMRI data has linked the left inferior parietal lobe to gesture imitation [19], which is in line with lesion research showing defects of this area in patients with apraxia, a condition in which gesture imitation is impaired [20].

1.2. Neural correlates of processing the semantic fit of speech and gestures

In general, the left IFG seems to be involved in semantic processing [21] and is specifically involved in selection [22], retrieval (e.g. Refs. [23–25]) and semantic unification [8,26]. It has been shown that the semantic relation between speech and gestures is relevant for neural processing. Willems et al. demonstrated in an fMRI study that unrelated gestures or words (semantically anomalous in the given context) both led to increased activation in the left IFG [8]. These findings are in line with another study that found bilateral IFG activation for ambiguous words compared to unambiguous words [27]. However, in addition to left IFG activation, the processing of unrelated gestures has also been linked to activation of the right IFG [5,28], and the temporal and parietal cortices may even play a role [29].

1.3. tDCS in gesture processing

Evidence from neuroimaging is merely correlational: on its own, it does not allow the direct linking of brain structures to specific functions. A non-invasive brain stimulation method such as tDCS may serve as an excellent tool for exploring the functional relevance of the findings outlined above.

The first study that probed a possible modulation of gestural–verbal semantic integration via tDCS used short video clips showing a masked actor performing either a symbolic or a pantomimic gesture; this was followed by a written word that either accurately described the gesture/pantomime or was unrelated to it [30]. Subjects were asked to judge whether or not the gesture/pantomime was related to the clip. Anodal stimulation over the right IFG coupled with cathodal stimulation over the left IFG generated faster responses to symbolic gestures than inverse or sham stimulation.

However, a 2013 study investigating tDCS effects on performance in a gesture-matching task found improved performance after the stimulation of an entirely different brain region, namely, the left parietal cortex [31]. Pairs of pictures showing a female actress performing meaningless hand gestures and displaying either identical or slightly different gestures were presented and subjects were asked to judge whether or not the gestures matched. Faster reaction times were found for anodal tDCS over the supramarginal gyrus and angular gyrus of the inferior parietal lobe. Similarly, Bolognini et al. found that apraxia could be improved using tDCS of the left posterior parietal cortex, highlighting the importance of this region for gesture planning [32].

1.4. Current study

In sum, there is some evidence from brain imaging suggesting IFG and, possibly, parietal involvement in the assessment of speech and gesture relatedness. Initial tDCS evidence for gesture processing seems to support the importance of these brain regions. However, the influence of tDCS on the processing of co-verbal gestures has not yet been investigated and the relative contribution of frontal and parietal areas to speech–gesture relatedness assessment remains unknown.

In this study, we aimed to discern the electrode localisation- and polarisation-dependent effects of tDCS on the assessment of speech–gesture relatedness for metaphoric and iconic co-verbal gestures that were either related or unrelated to speech content. Based on earlier fMRI data, we hypothesised a specific polarisation-dependent effect of left frontal tDCS on ratings and reaction times for metaphoric gestures. In particular, we predicted faster and more critical assessment during left frontal anodal stimulation, reflected in reduced reaction times and ratings.

To disentangle the effects of electrode localisation and polarisation completely, we included two frontal, two parietal and two frontoparietal conditions as well as a sham condition in our design. In this way, we hoped to gain maximum insight into the relative contribution of each stimulated area to co-verbal gesture processing.

2. Methods and material

2.1. Participants

Seventeen healthy, right-handed native German speakers were recruited via posters placed in public buildings in Marburg, Germany (eleven male, six female, mean age = 36.41, SD = 12.96, range = 23–59). All participants fulfilled the following inclusion criteria: right-handedness, history free of mental or neurologic illness and alcohol or drug abuse, normal or corrected-to-normal vision, no hearing deficits, no electric implants. All subjects gave written informed consent prior to participation and received €150 as an expense allowance for participating in all seven sessions. The study was approved by the local ethics committee.

2.2. Transcranial direct current stimulation

In this study, we used a DC-Stimulator from neuroConn GmbH (Ilmenau). Frontal electrodes were positioned at F3/F4, while parietal electrodes were positioned at C3-P3/C4-P4 (between C3 and P3/between C4 and P4), according to the 10–20 EEG system. A current of 1.5 mA was applied to the head using saline-soaked sponges (0.9% NaCl, to minimise side effects, see Refs. [33,34], 5 cm × 7 cm) placed on rubber electrodes, resulting in a current density of 0.043 mA/cm^2. The duration of the stimulation was 10 min plus 10 s fade in/fade out. These parameters are in compliance with tDCS safety guidelines [35–37]. Sessions were performed at least 20 h apart to ensure that the tDCS effects had completely faded away by the beginning of each new session. Sham stimulation was performed using the sinus (HW) mode for a duration of 30 s, ensuring that subjects would feel the itching sometimes associated with the beginning of stimulation and would therefore be unable to distinguish between sham and real stimulation [38].

2.3. Experiment design

We applied anodal, cathodal and sham stimulation to the left and right frontal (F3/F4) and parietal (CP3/CP4) areas (see Fig. 1). Each subject took part in seven independent tDCS sessions and underwent seven different stimulation conditions, one on each day (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode): 1) two frontal conditions with inverse polarisation – LFC-RFA and LFA-RFC; 2) two frontoparietal conditions with inverse

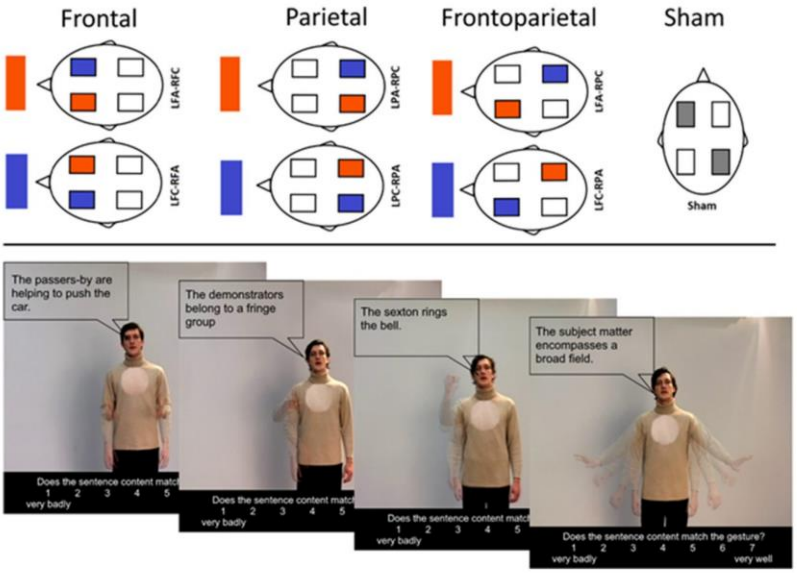

Fig. 1. Study design and speech–gesture relatedness assessment task. Top: Study design. Each subject underwent seven stimulation sessions (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode) on seven different days. The coloured bars highlight polarisation (orange = left anodal stimulation; blue = left cathodal stimulation). Bottom: Speech–gesture relatedness assessment task, performed during stimulation. Example clips for each of the four different gesture types presented, from right to left: metaphoric related, iconic related, metaphoric unrelated, iconic unrelated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

polarisation – LFC-RPA and LFA-RPC; 3) two parietal conditions with inverse polarisation – LPC-RPA and LPA-RPC; and 4) sham condition. In order to control for effects of order and repetition, the order of the stimulation conditions was pseudo-randomised and counterbalanced across subjects. However, for practical reasons, sham stimulation was always applied in one of the first four sessions.

2.4. Speech–gesture relatedness assessment task

From the beginning to the end of stimulation subjects were continuously presented with video clips of an actor saying a concrete or abstract sentence and accompanied by a hand gesture that was either semantically unrelated or related to the sentence content (see Fig. 1).

For each co-verbal gesture, subjects rated the relatedness ('Does the sentence content match the gesture?') of the sentence content and gesture on a scale from one (very badly) to seven (very well) and pressed the respective button on the keyboard. Reaction times were measured from the onset of the video.

Two different sets of stimuli (80/set) were used to counterbalance the related and unrelated counterparts of speech–gesture pairs across subjects (the first was presented to nine subjects, the second, to eight 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. The video clips were presented in pseudo-randomised order. An identical stimulus set was presented to the participant in each experiment session to maximise comparability across stimulation sessions. Thus, each subject saw only a related or unrelated version of any given sentence–gesture pair. However, both versions were presented across the full body of subjects.

2.5. Stimulus material

The stimuli used have been extensively validated and successfully made use of in other studies [5–7,11,14,29,39,40]. The videos were designed to look as natural as possible while at the same time ensuring that they only differed in the type of co-verbal gesture and whether the gesture matched the sentence content. Iconic sentences contained only one element that could be illustrated by a gesture. Gestures were chosen in concordance with McNeill's iconic gestures definition to illustrate the form, size or movement of something concrete that the speaker is referring to [41]. The sentences were of similar length (five to eight words) and grammatical form (subject–predicate–object). Unrelated gestures were chosen so as not to be too obviously unrelated to speech and to match related gestures in terms of complexity (gesture direction and extent), smoothness and vividness. Extensive rating proved that the unrelated gestures did not contain any clear-cut semantic information and that they differed significantly in semantic strength from the iconic gestures [29] and metaphoric gestures [5].

To ensure maximum naturalness, the synchrony of the speech and gesture was determined by the actor. Moreover, to ensure equal dynamics of the iconic and unrelated gestures, the latter were only roughly choreographed and not previously scripted, were developed in collaboration with the actor, and were practised to look and

feel spontaneous. Each clip had a length of 5 s. For additional information on the stimuli and their creation, see Refs. [7] and [29].

2.6. Assessment of side effects

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

2.7. Data analysis

Generalised estimating equations (GEE) were performed for relatedness ratings and reaction times, as implemented in SPSS Statistics 19 for Windows by IBM. GEE was chosen because it works well even in cases of unmeasured dependence between outcomes and was thus useful for our complex, repeated-measures design. 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: *localisation* (frontal, parietal, frontoparietal), *polarisation* (anode positioned over the left hemisphere, anode positioned over the right hemisphere), *gesture type* (metaphoric, iconic) and *relatedness* (related, unrelated).

Factorial interactions: *gesture type * relatedness*, *localisation * polarisation * gesture type*, *localisation * polarisation * relatedness*, *localisation * polarisation * gesture type * relatedness*.

Based on our hypothesis, we were interested in whether there would be localisation- and polarisation-dependent effects on gesture type and/or relatedness (i.e. significant effects for the interactions *localisation * polarisation * gesture type* and *localisation * polarisation * relatedness*).

To further explore the importance of electrode polarisation, we performed post-hoc tests comparing each condition against its respective inverse condition. Here, obviously, the factor *localisation* became redundant, while all other factors and interactions remained the same.

To explore stimulation effects and sham stimulation, a second GEE analysis was performed. Instead of the factors *localisation* and *polarisation* used in the first analysis, here, we used the single factor *stimulation* (LFC-RFA, LFA-RFC, LPC-RPA, LPA-RPC, LFC-RPA, LFA-RPC, sham), therefore allowing us to include the sham condition in our analysis.

3. Results

3.1. Side effects

Overall, tDCS was well tolerated: no serious side effects or significant discomfort were observed during or after the experiment. Comparing real and sham stimulation, we found that side effects were reported to a significantly larger extent after real stimulation but still remained at a very low level ($p = 0.001$, overall mean for real stimulation = 1.54, SE = 0.10; overall mean for sham stimulation = 1.36, SE = 0.10; on a scale from one to five) and did not differ between the real stimulation conditions. Accordingly, subjects perceived the stimulation intensity as being significantly higher for real simulation than for sham stimulation ($p < 0.001$, mean for real stimulation = 2.53, SE = 0.21; mean for sham stimulation = 1.57, SE = 0.26).

3.2. Reaction time

The main effect of *relatedness* did not reach significance, indicating that subjects were able to respond equally fast to both related and unrelated stimuli. The main effect of *gesture type*, on the other hand, was significant ($p < 0.001$). Subjects responded significantly slower for metaphoric stimuli.

Importantly, there was a significant interaction: *localisation * polarisation * gesture type*, ($p = 0.020$, see Table 1 and Fig. 2). The interaction *localisation * polarisation * relatedness* did not reach significance.

To further explore the importance of electrode localisation and polarisation, we compared the respective frontal, parietal and frontoparietal conditions (LFC-RFA vs LFA-RFC, LPC-RPA vs LPA-RPC and LFC-RPA vs LFA-RPC). Only the comparison between the two frontoparietal conditions (LFC-RPA vs LFA-RPC) resulted in a significant effect, as indicated by a significant decrease in reaction times for the interaction *polarisation * gesture type* ($p = 0.046$, see Table 2 and Fig. 3).

3.3. Rating

The main effect of *relatedness* was significant ($p < 0.001$), indicating that the stimuli could reliably be differentiated into related and unrelated stimuli. We did not find a significant main effect for gesture type, confirming that the type of co-verbal gesture had no effect on whether subjects judged stimuli as being more or less related.

Importantly, there was a significant interaction *localisation * polarisation * gesture type* ($p = 0.002$). Furthermore, the main effect of *polarisation* resulted in a trend ($p = 0.058$). The interaction *localisation * polarisation * relatedness* did not reach significance.

To explore the importance of electrode localisation and polarisation further, we compared the respective frontal, parietal and frontoparietal conditions (LFC-RFA vs LFA-RFC, LPC-RPA vs LPA-RPC and LFC-RPA vs LFA-RPC). Only the comparison between the two frontoparietal conditions (LFC-RPA vs LFA-RPC) resulted in a significant effect, as indicated by a significant interaction *polarisation * gesture type* ($p = 0.017$, see Table 2 and Fig. 3). This interaction is based on reduced relatedness ratings for the metaphoric condition, specifically, after left frontal anodal stimulation, indicating the more critical assessment of speech–gesture relatedness.

3.4. Comparison with sham condition

To explore the tDCS effects and sham stimulation, we ran a second GEE analysis including all seven conditions (Table 3). Concerning reaction times, we again found a significant effect for the interaction of stimulation and gesture type (reaction time: $p = 0.033$; rating: $p = 0.004$), confirming the results of our main analysis. Furthermore, here, the interaction *stimulation * relatedness* ($p = 0.006$) became significant for reaction times. For relatedness ratings, this interaction resulted in a trend ($p = 0.062$).

4. Discussion

The ability to understand the semantic relationship between verbal and non-verbal information – such as speech and gestures – is relevant for social interaction and communication in an interpersonal context. In this study, we tested the hypothesis that different neural mechanisms contribute to the assessment of the semantic relationship between speech and gesture, depending on whether utterances refer to abstract or concrete information. Compared to iconic co-verbal gestures, we found electrode localisation- and polarisation-dependent changes in reaction times and

Table 1
Results of main analysis.

Source	df	Tests of model effects reaction time		Tests of model effects rating	
		Wald chi-square	Sig.	Wald chi-square	Sig.
(Intercept)	1	3376.057	<0.001	784.392	<0.001
Localisation	2	0.938	0.626	2.572	0.276
Polarisation	1	0.005	0.945	3.583	0.058
Gesture type	1	148.009	<0.001	2.166	0.141
Relatedness	1	2.958	0.085	299.289	<0.001
Gesture type * relatedness	1	0.177	0.674	18.695	<0.001
Localisation * polarisation* gesture type	5	13.338	0.020	18.841	0.002
Localisation * polarisation* relatedness	5	3.280	0.657	2.259	0.812
Localisation * polarisation* gesture type * relatedness	5	5.974	0.309	3.344	0.647

ratings for metaphoric gestures. We also demonstrated for the first time the specific relevance of the left frontal cortex for processing metaphoric gestures. Naturally, the anatomic specificity of this kind of tDCS study will always be limited and results have to be interpreted with caution. Nevertheless, our data clearly support the assumption that there are remarkable differences between the neural processing of metaphoric and iconic co-verbal gestures.

4.1. Co-verbal gesture processing

In line with previous evidence from fMRI studies (e.g. Refs. [5,7,14]), we found a marked effect of left frontal tDCS for metaphoric gestures – but not for iconic co-verbal gestures – in a speech–gesture relatedness assessment task. Both reaction times and ratings of relatedness decreased during left frontal anodal stimulation when the presented gestures were metaphoric in nature. This effect strongly implies that the left IFG is functionally more relevant for processing metaphoric co-verbal gestures than it is for processing iconic co-verbal gestures.

Faster reaction times and reduced relatedness ratings during anodal stimulation suggest that the left frontal cortex plays a specific role in the relatedness assessment of metaphoric gestures. The direction of the effect indicates that participants were not only faster at evaluating metaphoric gestures but also more critical in terms of the semantic relation. Even though we cannot differentiate between the different processes in which the left frontal lobe may

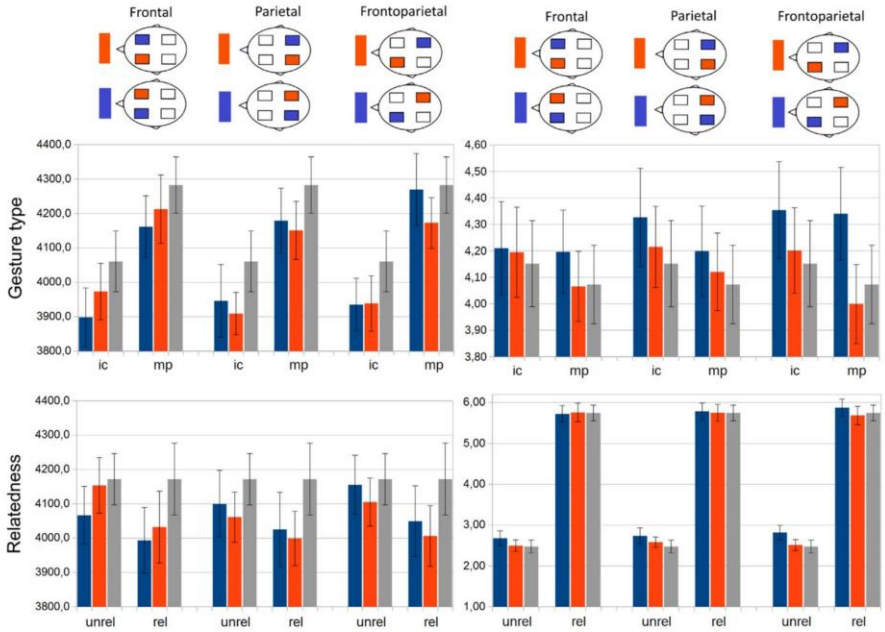

Fig. 2. Results of main analysis. Top: Gesture-type dependence of stimulation effects. Top left: mean Reaction time (ms). Top right: mean rating. Bottom: relatedness dependence of stimulation effects. Bottom left: mean reaction time (ms). Bottom right: mean rating. Bar colours indicate polarisation (orange = left anodal stimulation; blue = left cathodal stimulation; grey = sham stimulation). Video types: ic = iconic; mp = metaphoric; unrel = unrelated; rel = related. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Results of post-hoc test for frontoparietal stimulation.

Source	df	Tests of model effects reaction time		Tests of model effects rating	
		Wald chi-square	Sig.	Wald chi-square	Sig.
(Intercept)	1	3638.084	<0.001	747.927	<0.001
Polarisation	1	0.275	0.600	7.241	0.007
Gesture type	1	62.061	<0.001	1.699	0.192
Relatedness	1	3.131	0.077	287.928	<0.001
Gesture type * relatedness	1	0.046	0.829	15.246	<0.001
Polarisation * gesture type	1	3.965	0.046	5.741	0.017
Polarisation * relatedness	1	0.004	0.951	0.600	0.439
Polarisation * gesture type * relatedness	1	2.108	0.147	0.510	0.475

be involved, it is likely that the construction and assessment of a semantic relationship between speech and gesture information is influenced by tDCS.

At first glance, it might seem surprising that we did not observe significant differences for the post-hoc comparison of the two frontal conditions, whereas the contrast between the frontoparietal conditions demonstrated a clear effect. However, one must take into consideration that not only the left but also the right frontal area is involved in gesture processing [5,28–30]. The right parietal area, by contrast, is not supposed to be specifically involved in these processes. Consequently, frontoparietal stimulation only affected one task-relevant area – namely, the left frontal area – whereas the frontal stimulation conditions affected two task-related areas, the left and right frontal areas. Therefore, the effects of frontal stimulation on the left frontal area (IFG) are attenuated by simultaneous reverse stimulation of the contralateral region, which is also involved in the task (especially for processing unrelated speech–gesture information [28]). This explanation is also supported by data from Cohen-Maximov et al., who found faster reaction times for right anodal stimulation [30]. In line with their finding, in our study, right frontal anodal stimulation (LFC-RFA) also seemed to decrease reaction times compared to sham and left frontal anodal stimulation (LFA-RFC) independent of gesture type, although not significantly.

In addition, current flow underneath the left frontal electrode is naturally also affected by the position of the second electrode. The well-known effects of the second electrode on current density (e.g. Ref. [42]) could have contributed to the differences in effects between purely frontal and frontoparietal stimulation in two ways. Firstly, a greater distance between the electrodes for frontoparietal stimulation probably reduced the amount of current shunted through the scalp. Secondly, the current density under the left frontal anode was probably slightly displaced to the right frontal area in the case of exclusive frontal stimulation, whereas it was probably slightly displaced towards the right parietal area in the case of frontoparietal stimulation.

It is possible to interpret our and previous studies as convergent evidence of tDCS effects on different systems involved in gesture processing. Firstly, the right IFG may be relatively more important for basic perceptual processes (such as motor simulation). This explains why anodal stimulation of this region reduces reaction times independent of relatedness and gesture type ([30], or see Fig. 2). Secondly, the left IFG may be relatively more important for supramodal semantic processing and the evaluation of abstract information. Consequently, stimulation of this region directly changes subjective ratings of relatedness and reaction times, but only for metaphoric gestures.

4.2. Processing the semantic fit of speech and gesture

Despite some fMRI evidence hinting at the differential involvement of the left (e.g. Ref. [8]) and right [28] IFG for processing unrelated gestures, our main analysis did not result in significant relatedness-dependent effects of tDCS for our task.

Our second analysis, which included the sham condition, did, on the other hand, reveal some relatedness dependence. However, the second analysis should be considered with caution since the sham condition was always one of the first four stimulation sessions and is therefore not entirely comparable with the other conditions.

While substantial differences could possibly exist between the processing of related and unrelated co-verbal gestures, our study does not provide unambiguous evidence for relatedness-dependent effects of tDCS.

4.3. Conclusion

Our results strengthen and extend former fMRI and tDCS research highlighting frontal cortex involvement in gesture processing. Despite the methodologically low spatial resolution of tDCS, our data – set against a backdrop of extensive fMRI research (some of which employed the very same experimental stimuli) – suggest that there are remarkable differences in neural processing

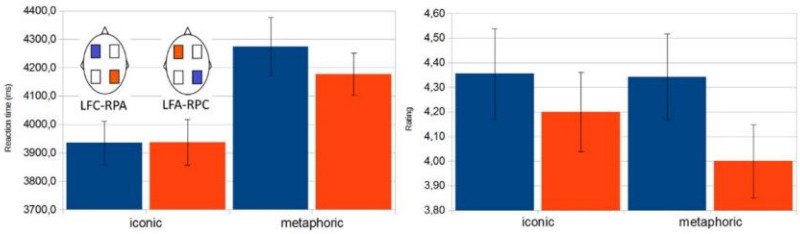

Fig. 3. Specific effects of frontoparietal stimulation for metaphoric co-verbal gestures.

Table 3
Results of sham-inclusive model.

Source	df	Tests of model effects reaction time		Tests of model effects rating	
		Wald chi-square	Sig.	Wald chi-square	Sig.
(Intercept)	1	3395.807	<0.001	798.869	<0.001
Stimulation	6	9.224	0.161	11.929	0.064
Relatedness	1	1.998	0.157	312.868	<0.001
Gesture type	1	218.392	<0.001	2.262	0.133
Stimulation * relatedness	6	18.099	0.006	12.007	0.062
Stimulation * gesture type	6	13.699	0.033	19.007	0.004
Relatedness * gesture type	1	0.604	0.437	17.320	<0.001
Stimulation * relatedness* gesture type	6	6.902	0.330	5.963	0.427

for metaphoric and iconic co-verbal gestures. The left frontal cortex seems to be especially important for processing metaphoric co-verbal gestures.

4.4. Outlook

Further studies should probe the therapeutic potential of tDCS for relieving gesture processing deficits. Interestingly, in the case of schizophrenia these deficits seem to be particularly relevant for metaphoric gestures [39], the type of gestures for which we found the behavioural advantage (decreases in reaction times and relatedness ratings) after anodal stimulation of the left frontal cortex in the present investigation. Moreover, the conservative stimulation dose applied in the present study may have been underdosed. Higher current densities and longer stimulation duration may possibly elicit stronger effects and should be explored in the future.

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Conflicts of interest

None.

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10.2 Publication 2

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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 non-invasive 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/cm^2. 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.

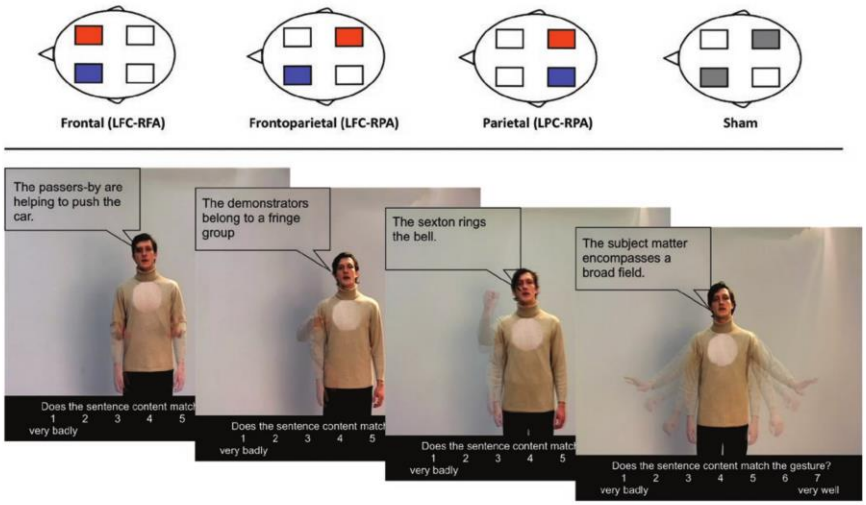

Fig. 1. Study design and speech–gesture relatedness assessment task. (A, top) Study design. Each subject underwent four stimulation sessions (L = left; R = right; F = frontal; P = parietal; C = cathode; A = anode) on 4 days. The colors indicate electrode polarization (orange = right anodal stimulation; 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.

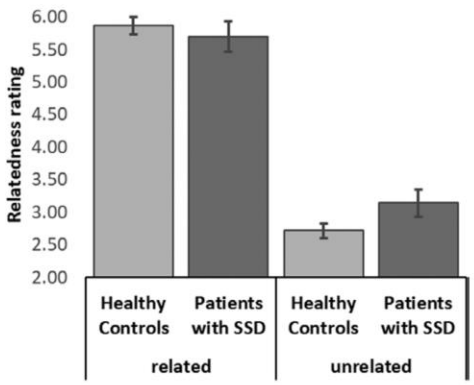

Fig. 2. Group dependence of relatedness ratings. Mean relatedness ratings (relatedness rated on a scale from 1 = very low to 7 = very high relatedness). SSD = schizophrenia spectrum disorder. Error bars indicate the standard error of the mean (SEM).

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

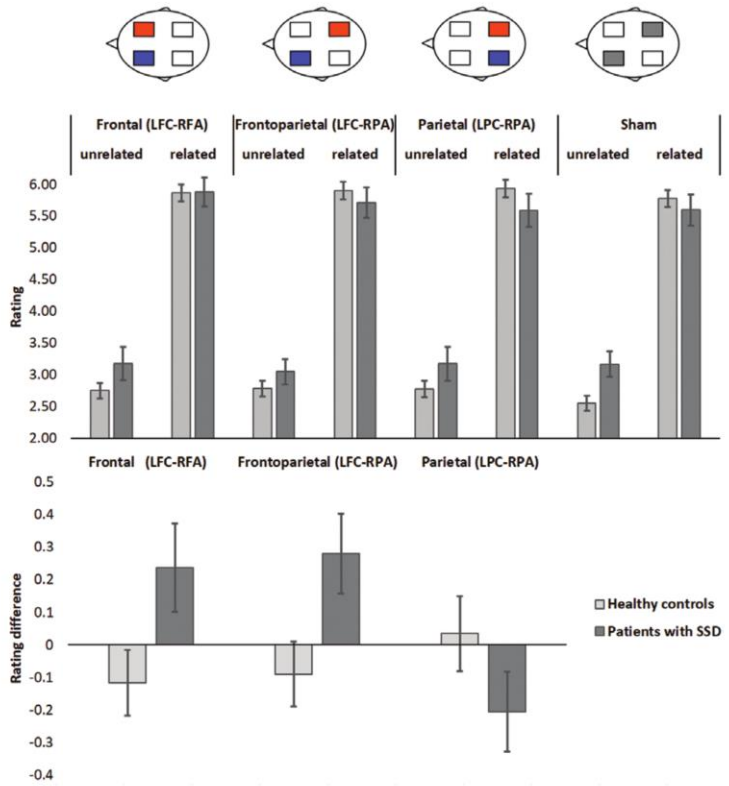

Fig. 3. Stimulation, group, and relatedness dependence of ratings. (A, top) Mean ratings (relatedness rated on a scale from 1 = very low to 7 = very high relatedness). (B, bottom) tDCS improvement in differentiation between related and unrelated gestures: Difference between real stimulation conditions 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

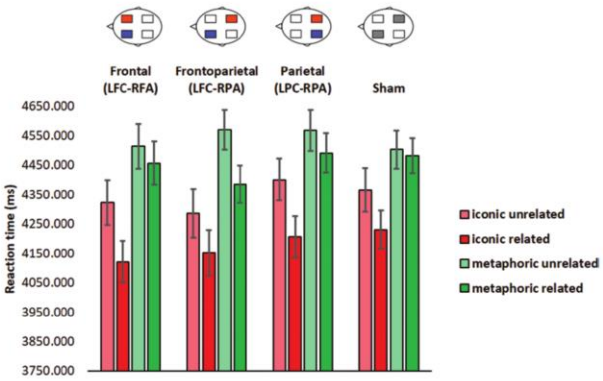

Fig. 4. Stimulation, gesture type, and relatedness dependence of mean reaction times across the entire group of patients and healthy controls. Light red: iconic unrelated. Dark red: iconic related. Light green: metaphoric unrelated. Dark green: metaphoric related. Electrode positions illustrated by head 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.

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11 Appendix

11.1 Supplementary material

11.1.1 TDCS

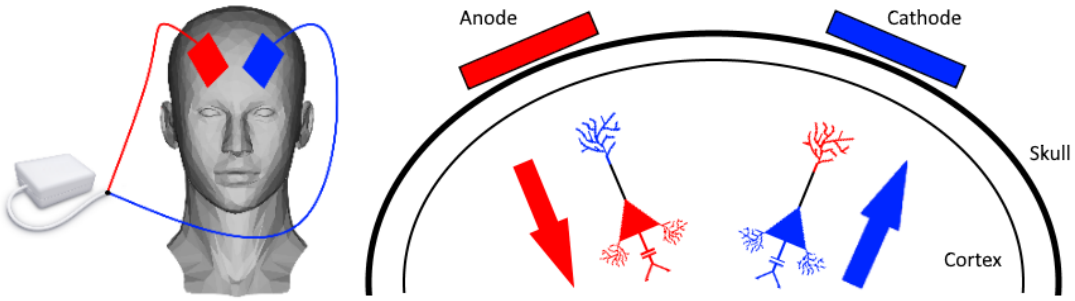

Figure 1. Transcranial direct current stimulation (tDCS). To the left: performing tDCS. Battery-powered tDCS device delivers direct current to the frontal scalp. To the right: tDCS mechanism. If neurons are orientated parallel to the direction of current, the soma of neurons under the anode is depolarized, leading to increased excitability. The soma of neurons under the cathode is hyperpolarized, leading to decreased excitability (Rahman et al., 2013).

In our study, frontal electrodes were positioned at F3/F4 and parietal electrodes were positioned at CP3/CP4. A current of 1.5 mA was applied to the head using saline-soaked sponges (0.9% NaCl, to minimize side effects; Dundas, Thickbroom, & Mastaglia, 2007; Palm et al., 2014) placed on rubber electrodes (5 cm * 7 cm), resulting in a current density of 0.043 mA/cm^2. The duration of stimulation was 10 minutes, in addition to 10 seconds fade in/fade out. Sham stimulation was performed using the sinus (half wave) mode for a duration of 30 seconds (Gandiga, Hummel, & Cohen, 2006).

11.1.2 Predicted current densities

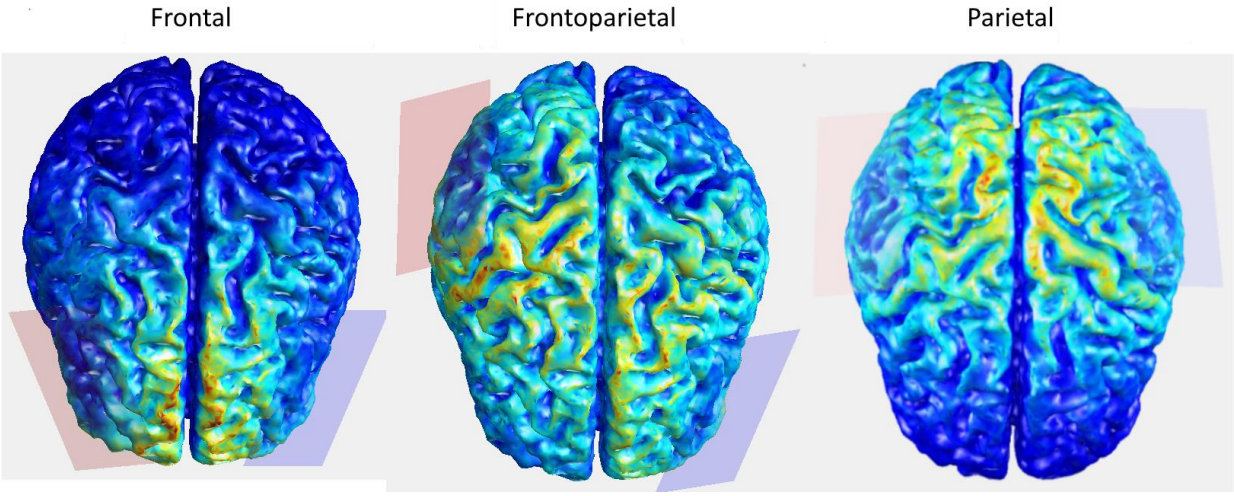

Figure 2. Predicted current densities. Calculated by COMETS (Jung, Kim, & Im, 2013). Warm colors indicate high current density. Note: Since current densities are independent of polarization, only stimulation conditions with the cathode over the left hemisphere (blue boxes) and the anode over the right hemisphere (red boxes) are displayed here.

Figure 2 shows the predicted current densities resulting from the different stimulation conditions. The current density distributions have been created using the COMETS Matlab toolbox for simulating local electric fields generated by transcranial direct current stimulation (Jung et al., 2013). Since polarization does not change current densities, only stimulation conditions with the cathode over the left hemisphere are displayed here. One can see that while there is considerable overlap between frontal and frontoparietal stimulation conditions, purely frontal stimulation does not only result in high current density of the right frontal area, but also displaces the pattern of the left hemispheric current distribution frontally. The left hemispheric component of frontoparietal stimulation, on the other hand, is located relatively more posterior and lateral. At the same time, the electrical current is less concentrated and spread over a wider frontal area.

11.2 List of academic teachers

Marburg

Bartsch
Bauer, Stefan
Bauer, Uta-Maria
Baum
Becker, Annette
Becker, Katja
Becker, Stephan
Bien
Bösner
Cetin
Cramer
Czubayko
Daut
Decher
Del Rey
Dodel
Donner-Banzhoff
Fröbius
Geraedts
Gress
Görg
Günther
Hildebrandt
Hoyer
Jansen
Kann
Kinscherf
Kircher
Kruse
Kühnert
Librizzi
Lill
Lohoff
Luster
Mahnken
Maier
Moll
Müller
Neubauer
Nimsky
Oberwinkler
Oliver
Pagenstecher
Patrascan
Peterlein
Plant
Reese
Renz
Rost
Ruchholtz
Sahmland
Schieffer
Schu
Schulze
Schüttler
Schütz
Seifart
Sekundo
Sevinc
Steiniger
Straube
Tackenberg
Teymoortash
Thieme
Timmermann
Wagner
Weihe
Wilhelm
Westermann
Worzfeld
Wrocklage
Wulf
Zavorotnyy

Paris

Annequin
Barete
Bellier
Caumes
Collin
Corvol

Fontaine
Johanet
Leverger
Lubetzki
Navarro
Papeix
Pateron
Petit
Ulinski
Varin
Vidailhet

Gießen

Dettmeyer
Knipper
Schneider

Fulda

Dörge
Haubitz
Hellinger
Hessmann
Kälble
Kellersmann
Markart
Neumann-Haefelin
Schächinger

Schanghai

Li Gang

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I am deeply grateful to my loving parents who nurtured my curiosity when I was a child and who have always unwaveringly supported my endeavours to explore the world.