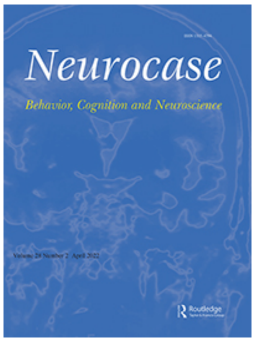

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Efficacy of transcranial Direct Current Stimulation (tDCS) combined with intensive speech therapy for language production in monozygotic twins with corpus callosum dysgenesis (CCD): A sham-controlled single subject study

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ABSTRACT
The purpose of this single subject study was to investigate whether transcranial direct current stimulation (tDCS) applied to both hemispheres combined with speech therapy can improve language learning in a pair of 5-year-old twins with corpus callosum dysgenesis (CCD). The treatment protocol included anodal tDCS with simultaneous speech therapy in one of the participants (T.D.), and sham-tDCS with the same montage, and stimulation regime concomitant with speech therapy for the other twin (A.D.). Our findings show that T.D. improved in language production when treated with speech therapy in combination with tDCS. A.D. showed evidence for a relatively minor behavioral benefit from speech therapy.

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KEYWORDS
Transcranial Direct Current Stimulation (tDCS); rehabilitation; language learning; corpus callosum dysgenesis (CCD); noninvasive brain stimulation

1. Introduction

The corpus callosum (CC) has a basic role in the organization of language in the brain. The integrative function of the central and posterior sections of the CC in the language network was revealed in a recent functional magnetic resonance imaging (fMRI) study in healthy children, allowing increased interhemispheric functional connectivity and enhanced language abilities (Bartha-Doering et al., 2021). Previous studies demonstrate that lack of normal callosal development can lead to deficits in functional connectivity that are related to impairments in specific cognitive domains (Hinkley et al., 2012). The neuropsychological profile of those with CCD are heterogeneous, ranging from subtle cognitive deficits to high-level language-related cognitive functions (Hinkley et al., 2012; Siffredi et al., 2013, 2013; Paul et al., 2016; Romaniello et al., 2017). Deficits are accruing in comprehension of syntax and pragmatics, including idioms, proverbs, prosody, and weak comprehension of humor and nonliteral language forms (Brown et al., 2005; Paul et al., 2003), and in phonological processing (Banich & Brown, 2000; Temple & Ilsleya, 1993). There is also evidence for insufficient conversation skills and restricted verbal expression of emotions in these patients (Anderson et al., 2017; Pazienza, 2012). Verbal memory functions, including encoding, retention, and retrieval are reduced in many individuals with CCD (Erickson et al., 2014). In addition, CCD children reveal significantly worse verbal fluency and naming as compared to healthy controls. Recent evidence indicates that CCD is associated not only with less interhemispheric, but also with reduced right intra-hemispheric language network connectivity related to reduced verbal abilities, which suggests a supporting role of the corpus callosum in functional language network connectivity and language abilities (Bartha-Doering et al., 2021). Reduced connectivity was found within temporal areas, between frontal and temporal regions, and between the Heschl 's gyrus and the vermis. Although language is predominantly processed in the left hemisphere in most healthy children (Szaflarski et al., 2012), stronger functional connectivity with the right hemisphere enables better verbal abilities (Bartha-Doering et al., 2021). As a result, the CC appears to play an excitatory role in the integration of both hemispheric information, and language abilities benefit from additional right hemisphere language processing that supports and interacts with left hemisphere processing. These language regions to the right appear to play a minor function in healthy right-handed children; however, the situation may be different in children with CCD (Hinkley et al., 2012; Siffredi et al., 2013). Therefore, in patients with CCD Interhemispheric exchange and hemispheric specialization are reduced, and both hemispheres are able to process specific cognitive demands to similar degrees, though with less efficiency (Bartha-Doering et al., 2021; Ocklenburg et al., 2015). Through the regulation of neuroplasticity, noninvasive brain stimulation (NIBS) is frequently utilized to promote cognitive or psychiatric rehabilitation. Because of its neuromodulatory qualities, NIBS has been seen as a promising technique for studying and influencing plasticity in the developing brain. Thus, the application of NIBS in pediatric populations with

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neurological disorders has recently been proposed (Vicario & Nitsche, 2013a; Palm et al., 2016; Hameed et al., 2017; Rivera-Urbina et al., 2017). To overcome neurogenic language deficits, speech therapy is recommended and has demonstrated beneficial effects (Davis et al., 2019; Papathanasiou et al., 2016), although in many cases, especially in patients with large brain lesions, patients do not fully recover (Rutten, 2017). According to a recent meta-analysis, cognitive training alone has limited clinical efficacy and transfer effects beyond the specific neuropsychological processes (Cortese et al., 2015). Given the limited effectiveness of available rehabilitative therapies in improving language disorders, other therapies, such as noninvasive brain stimulation, including transcranial Direct Current Stimulation (tDCS), and repetitive Transcranial Magnetic Stimulation (rTMS), have been recently explored as adjunctive interventions for the enhancement of the effect of speech therapy (Al-Janabi et al., 2014; Papathanasiou et al., 2016). Overviewing the use of NIBS in neurodevelopmental disorders reveals the feasibility and promising efficacy of NIBS to support neural plasticity and to reinforce the benefits of cognitive training (Finisguerra et al., 2019). tDCS, which was applied in the present study, is a noninvasive, well-tolerated cortical stimulation technique inducing prolonged cerebral excitability changes and promoting cerebral plasticity. It has been proposed to be useful in cognitive rehabilitation by improving memory performance, attention, mathematical abilities, and verbal learning (Fiori et al., 2017; Monti et al., 2013; Yavari et al., 2018). tDCS delivers a weak constant current to the scalp, ranging from 1 to 2 mA, using two electrodes including an anode and a cathode (Nitsche et al., 2008). It can modulate the spontaneous neuronal activity by inducing either positive (anodal) or negative (cathode) intracranial current flow in specific brain regions (Kang et al., 2018). Anodal stimulation increases cortical excitability, whereas cathode stimulation inhibits the same (Nitsche & Paulus, 2001; Terney et al., 2008). These currents change the transmembrane neuronal potential, influencing the level of excitability and hence the firing rate of neurons in response to new inputs (Wagner et al., 2007). Anodal stimulation can also cause a large rise in regional cerebral blood flow (rCBF), which could indicate neuronal activation (Merzagora et al., 2010). Local changes in ionic concentrations (hydrogen, calcium) and levels of cyclic adenosine monophosphate (cAMP), changes in protein synthesis, and regulation of N-methyl-D-aspartate (NMDA) receptor effectiveness are all linked to the effects of transcranial direct current stimulation (tDCS; Merzagora et al., 2010). Anodal stimulation reduces local concentrations of the inhibitory neurotransmitter GABA, whereas cathodal stimulation reduces local concentrations of the excitatory neurotransmitter GABA (Clark et al., 2011). Hereby we explored the hypothesis that tDCS might improve language learning in the CCD twins by improving the functional connectivity between segregated cortical areas involved in the task under study.

In the present study, we aim to investigate the combined effect of tDCS and intensive speech therapy on the language production of monozygotic twins with CCD was investigated. The main purpose of the present study was to investigate whether the application of anodal tDCS to the left temporoparietal region, which is relevant for verbal imitation (Leonard et al., 2019) and the right dorsolateral prefrontal cortex, which is involved in phonological and semantic word retrieval (Murdoch & Barwood, 2013) combined with language training, which covers both aspects, will enhance the rehabilitation process.

2. Materials and methods

2.1. Participants and settings

At the time of study conduction, the participants called T.D. and A.D. were 5-year-old, female, Persian, monozygotic twins with developmental delay in walking milestones, language and cognitive abilities, and with no history of seizures or epilepsy. The parents' chief complaint was slow language learning progress. Prior to the study, the parents received information about the probable efficacy and unknown side effects of the intervention. They were informed that the result of the study will be published. They signed written informed consent for the participation of their children in this study. The children underwent an MRI showing CCD and other structural brain anomalies (see, Table 1). They had started occupational therapy from the age of 2 years on (every other day during weekdays, including physical and mental therapy), and speech therapy from the age of 4 years on (1 day a week). 6 months after the start of the respective therapy, they could walk independently, speech therapy did, however, not result in relevant verbal communication skills, and their abilities were limited to gesturing, phonation, babbling, and limited use of proto-words. The patients did not take psychopharmacological agents. As they had profound difficulties in pointing to, and naming objects, the Test of Language Development – Persian: III (TOLD-P: 3) or other standardized tests were not applicable. Therefore, expressive vocabulary inventories (both spontaneously used and imitated words, for a detailed description see below) were recorded by their mother and speech and language therapist (SLT). Side effects of the intervention, including headache, relevant skin irritations or lesions, seizures or reluctance of the children/parents to undergo the interventions or remain in the study were considered as exclusion criteria. Interventions were administered in the play room of Paknejad Multidisciplinary Clinic.

2.2 Materials

2.2.1 tDCS.

Table 1. Participants' ages, disabilities, and MRI results.

Code name	Age (months)	Diagnosis	MRI result
T.D.	64	Developmental delay	• Shortening and dysgenesis of the corpus callosum • Colpocephaly (dilatation of the occipital horn of the lateral ventricle) • Mild thickening of cortical gyri
A.D.	64	Developmental delay	• Mild dilatation of the body and the posterior horn of both lateral and third ventricles • Mild dysgenesia of the corpus callosum

We selected the right frontal cortex and left temporo-parietal junction as target areas due to their involvement in object-naming and phonological as well as semantic word retrieval, based on previous studies. Functional imaging studies of speech production tasks highlight the involvement of a large bilateral network includes inferior frontal gyrus and temporo-parietal region of the left hemisphere (Costanzo et al., 2019; Grande et al., 2012; Kang et al., 2018; Lau et al., 2015; Mousavi et al., 2020; Murdoch & Barwood, 2013). Previous studies show that the corpus callosum dysgenesis impacts functional interactions in areas within the frontal and parietal cortices, which are implicated in cognitive domains and the degree of diminished connectivity in specific cortical regions was directly correlated with verbal processing speed and executive performance in individuals with CCD (Mancuso et al., 2019). Deficits in corpus callosum integrity impose a hard limit on the capacity of the fronto-parietal network to dynamically adapt its activity to high cognitive demands (Hearne et al., 2019).

To this aim, we fixed the anode over the F4 (right DLPFC) position (according to the international 10 20 system) and the cathode over the contralateral shoulder. We chose to stimulate the DLPFC, which is a cortical area known to be involved in executive function and is thought to be partially responsible for the language dysfunctions (Schneider & Hopp, 2011). To facilitate semantic processing, another anode was placed over the left temporo-parietal junction (CP3) (posterior perisylvian area), and the respective cathode over the contralateral shoulder (Kang et al., 2018; Liljeström et al., 2008; Silveri & Di Betta, 1997). Each tDCS session consisted of consecutive application of tDCS over both areas for a total of 30 minutes (15 minutes of real/sham tDCS over F4 and 15 minutes of real/sham tDCS over CP3). See, Table 2 for the detailed Intervention design. The stimulation was delivered by a battery-driven constant current stimulator (Activadose, Taiwan) through a pair of saline-soaked sponge electrodes (4 × 4 cm). Based on previous studies that demonstrate that tDCS with 1 mA intensity for 15 min is well tolerated, and thus may be used as a treatment method in the pediatric population (Ciechanski, 2017; Moliadze et al., 2015; Stagg et al., 2018), a constant current of 1 mA was applied for 15 minutes over the respective target areas (current density 0.0625 mA/cm^2), with a ramping period of 10 seconds both at the beginning and at the end of the stimulation. The electrodes were fixed on the head by elastic bands. For sham tDCS, the electrodes were placed according to the montage described above for real tDCS, and the stimulator was turned off after 30 sec (Woods et al., 2016).

Table 2. Intervention procedures for each participant.

Code name	Intervention description
T.D.	Real tDCS (anodal tDCS over F4 with the reference electrode over the left shoulder and anodal tDCS over CP3 with the reference electrode over the right shoulder applied sequentially) for 5 days a week (continuously for 4 weeks), combined with simultaneous speech therapy twice a week
A.D.	sham tDCS (anodal tDCS over F4 with the reference electrode over the left shoulder and anodal tDCS over CP3 with the reference electrode over the right shoulder applied sequentially) for 5 days a week (continuously for 4 weeks) combined with simultaneous speech therapy twice a week

2.2.2. Language therapy plan

The core vocabulary comprises a set of words consistently used within and across environments and between communication partners. In the present study, the participants' core vocabulary was identified by collecting language samples during interactions in multiple settings and with multiple communication partners during (a) unstructured free play with their mother at home, and (b) speech-language therapy sessions with the SLT. The children were allowed to play with any toys they liked during free play at home and in an enriched play room of the clinic, the researcher observed the participant's behavior for 30 minutes in order to determine in which items the participant showed interest by engagement with the item. The protocol included a selection of a small number of words (totally 50 words) relevant across different enjoyable contexts including free play (such as cooking, cleaning the room, painting, feeding their doll) at home and in the speech therapy session, and the patients were encouraged to repeat and use them in the respective context during baseline monitoring, combined intervention, and follow-up. This core vocabulary approach is a modified version of the approach previously described by Crosbie et al. (2005). In the initial therapy session, the mother and SLT selected 10 to 20 target words related to the play setting prepared for the children (as described above) from a larger set of 50 target words that were functionally "powerful" for the children. These words were chosen because the children frequently needed them for their favorite play and/or communication. The SLT worked with the children to elicit the respective expressive vocabulary. The aim of the therapy was to produce new words consistently, that is, the same way each time. Imitation was encouraged during both, the therapy sessions with the SLT and during home practice. Following the consultation with the SLT and watching the therapy session, the mother practiced selected words at home by requesting the child to imitate each word while playing. The mother and SLT reinforced productions of those words in everyday play setting and communicative interactions. The mother was encouraged by the SLT to speak out respective words regularly during interaction with her children. Simultaneously, she recorded and kept a diary of homework practice to track the daily production of newly imitated or spontaneously used words (Crosbie et al., 2005; Flanagan & Ttofari Eecen, 2018).

2.2.3. Vocabulary measurement

All expressed verbal utterances of the participants were recorded across different enjoyable contexts including free play (such as cooking, cleaning the room, painting, feeding their doll) at home and in the speech therapy sessions. The patients were encouraged to repeat and use the vocabulary in that context. Recorded utterances were transcribed in order to count all (old and new) imitated and spontaneously used words including both two categories: real words (RW), which have at least 50% of the phonemes of a standard word, and proto-words (PW), which have less than 50% phonemes of the standard word (adult form), but were constantly used for a specific concept. The total number of recently learned new words (i.e., RW and PW) were counted based on the weekly inventory recorded and provided by the mother and SLT. Ratings were conducted by two independent blind experienced raters. The inter-rater agreement was r = 0.99 (p < 0.001)

2.3. Procedures

2.3.1. Compliance with ethical standards

All procedures performed in the study were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.3.2. Baseline

As children were receiving SLT for 20 weeks (twice a week), their newly learned (imitated and spontaneously used) words including RW and PW were extracted from their SLT profile and mother's diary (during every day play activities) and all available recorded utterances of the children. This data was considered as baseline (before tDCS) (see, Figure 1).

2.3.3. Intervention

Table 2 outlines the intervention procedures for each child that were administered. The participants received 5 days of tDCS (real-stimulation for T.D. and Sham-stimulation for A.D.) per week for 4 weeks and they underwent 25 minutes of individualized speech therapy twice a week. In their speech therapy sessions, a core vocabulary training strategy was applied simultaneously with tDCS. The mother and speech therapist were both blind with respect to the stimulation condition (sham or real tDCS). The electrodes for sham tDCS were placed in the same manner as for real tDCS, and the stimulator was switched off after 30 seconds. This procedure ensures that participants feel the initial itching sensation at the beginning of tDCS in order to blind the patients to the respective stimulation condition (Gandiga et al., 2006). To guarantee a double-blind procedure, an independent experimenter set up the tDCS device, leaving the mother and therapist blinded to the stimulation condition. Newly imitated and spontaneously used words (RW and PW) were recorded by a sound recorder (SONY ICD-MX20) by both the mother and speech therapist separately. Then, two blind independent raters listened to the records and noted any real word or proto-word they recognized. The same speech

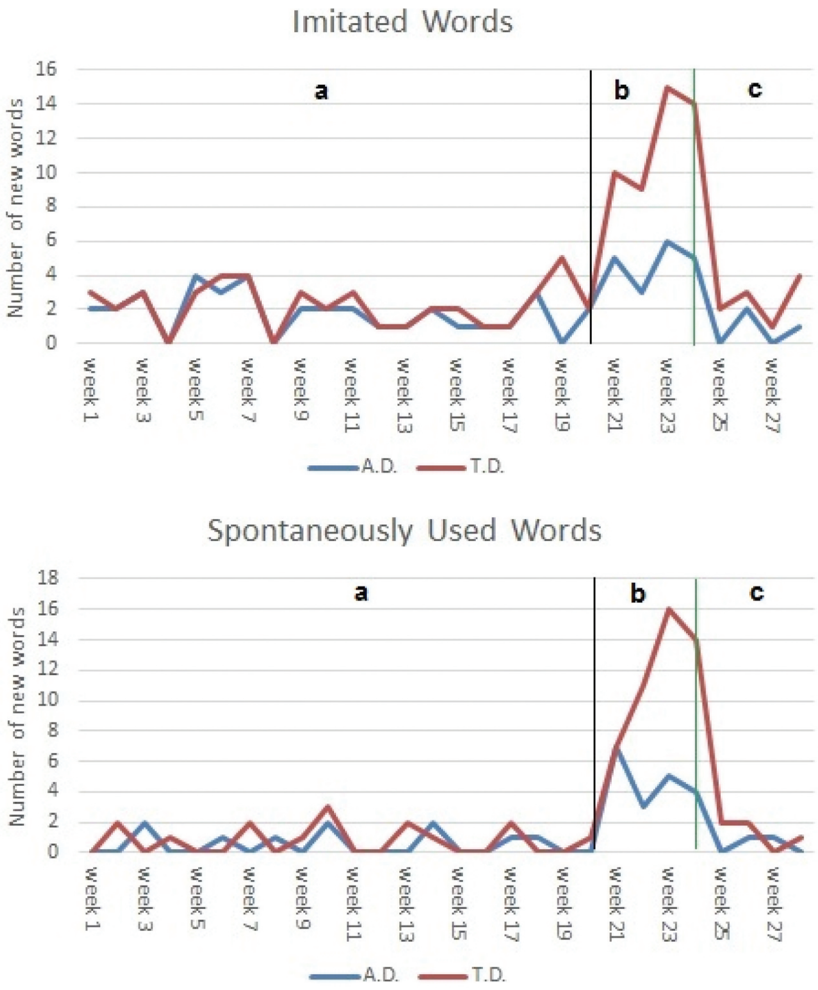

Figure 1. Imitated and spontaneous word (RW and PW) learning rate for the 3 periods: a) twice a week speech therapy for 20 weeks; b) 5 days a week brain stimulation combined with twice a week speech therapy; c) Follow-up (two sessions speech therapy per week).

evaluation procedures were followed for baseline recordings before any intervention. The total number of words learned during every week is displayed in Figure 1.

2.3.4. Follow-up

The children continued to receive their regular language therapy sessions twice a week. Vocabulary monitoring was conducted as described above (in the intervention section), and continued for 4 weeks after the combined therapy period (SLT +tDCS; Figure 1).

2.4. Design and data analysis

This sham-controlled case study had a multiple baseline between subject design. The development of expressive vocabulary under SLT was obtained weekly for 20 weeks for monitoring of baseline performance, during 4 weeks of intervention with added real or sham tDCS, and 4 weeks after intervention as follow up. By succeedingly administering different interventions, a multiple baseline design allows to make inferences about the effect of a specific intervention (Cooper et al., 2007). The standard mean difference (SMD) equation was used to calculate effect size for imitated and spontaneous RW and PW. The difference between the mean baseline (Mean$_B$) and mean intervention (Mean$_I$) was calculated and then divided by the standard deviation of baseline (Hedges et al., 2012; Olive & Smith, 2005). The same analysis was done to calculate the effect size of therapy during follow-up in comparison to baseline (Table 4).

3. Results

The comparison of the newly learned words of both twins during baseline is shown in Table 3. To assess the intervention-dependent improvement of participants, we compared baseline performance (first 20 weeks) with performance during the 4 treatment weeks with the SMD. The combined intervention improved expressive lexicons (RW and PW) of both children, as compared to baseline performance (effect size> 0.5). In both children, the effect size for both, imitated and spontaneous words, was large, but the intervention effect was more prominent in T.D., who received real stimulation (Table 3). During the 4-week post-stimulation follow-up (week 24–28), a relevant further improvement was only observed in T.D.'s spontaneous word learning rate (effect size> 0.5), while A.D.'s vocabulary development rate was reduced to baseline level, as expected (Table 4).

Table 3. The standard mean difference of baseline performance compared with intervention.

	Mean$_B$	Mean$_I$	δ n-1	SMD
T.D.'s imitated words	2.25	12	1.332	7.319
T.D.'s spontaneous words	0.75	12	0.966	11.645
A.D.'s imitated words	1.80	4.75	1.196	2.466
A.D.'s spontaneous words	0.5	4.25	0.761	4.927

Table 4. The standard mean difference of baseline performance compared with follow-up.

	Mean$_B$	Mean$_F$	δn-1	SMD
T.D.'s imitated words	2.25	2.5	1.332	0.188
T.D.'s spontaneous words	0.75	1.25	0.966	0.52
A.D.'s imitated words	1.8	0.75	1.196	0.87
A.D.'s spontaneous words	0.5	0.5	0.761	0.00

Mean$_B$ = the mean baseline
Mean$_I$ = the mean intervention
Mean$_F$ = the mean follow-up
δn-1 = the standard deviation of baseline
SMD = the standard mean difference

4. Discussion

In the present single subject sham-controlled study, the impact of adjunctive tDCS combined with speech therapy on verbal learning was explored in monozygotic twins with CCD. Both children showed only minor effects of speech therapy alone, as shown by respective baseline performance data. They benefited however from the combined intervention, and the effect size of the twin exposed to real tDCS was larger than that achieved in the twin exposed to sham stimulation. While thus there might be a gradual placebo effect involved in treatment success, this does not explain the better effects obtained in the real treatment condition. After the end of the combined treatment, language therapy was continued for 4 weeks. Here, language learning progress rate dropped in both twins, the child exposed to real tDCS beforehand however showed still improved spontaneous word learning.

As previous studies showed a contribution not only of the left, but also the right hemisphere to language-related functions (Beeman & Chiarello, 2013), and bilateral patterns of activity during speech processing and response preparation have been observed in CCD (Hinkley et al., 2016), the aim of the present study was to investigate whether stimulating the right-hemispheric homologue of Broca's area (rIFG) and left posterior parietal cortex promotes language learning in CCD. Previous studies showed that posterior inferior frontal gyrus of the right hemisphere, an area that has been shown to contribute to vocalizing through the mapping of sounds to articulatory actions, are involved in the beneficial effects of noninvasive brain stimulation (anodal tDCS or rTMS) and speech therapy methods on speech performance (Al-Janabi et al., 2014; Vines et al., 2011). T.D., who received anodal tDCS, produced more words (imitated and spontaneous) during the combined intervention, as compared to the sham-stimulated twin. This effect was even visible after the end of the combined treatment in the follow-up period for spontaneously used words. Stimulation over both hemispheres might be relevant for this effect. The right inferior frontal gyrus (rIFG) is involved in phonological word retrieval (Biesbroek et al., 2016; Birn et al., 2010; Mousavi et al., 2020) and bilateral language processing in CCD (Hinkley et al., 2016). Furthermore, in another study anodal tDCS over the right frontal cortex improved selectively the alerting component of attention (Coffman et al., 2012), which might be relevant for language learning. The other area stimulated was the left temporo-parietal region, which corresponds to the arcuate fasciculus, which is involved in word imitation (Rogalsky et al., 2015; Sierpowska et al., 2017; Costanzo et al., 2019; Leonard et al., 2019). Behaviorally, T. D. showed statistically reliable evidence for benefits from the combined treatment with respect to imitated and spontaneous word production. Since patients with CCD show a reduction of neural activity and connectivity within the fronto-parietal network (Hearne et al., 2019), stimulation of these regions may improve functionality of the auditory motor map and result in better phonological processing, improved semantic memory, and more precise repetition (Hickok, 2012).

Although previous tDCS studies showed long-lasting effects on language learning (Pasqualotto et al., 2015; Perceval et al., 2017, Costanzo et al., 2019), in the present study vocabulary acquisition rate dropped when the combined intervention period was finalized. This might be caused by the complexity of abnormal connections of the brain of patients with CCD (Lazarev et al., 2016) which critically affects cortical functioning and plasticity (Uddin et al., 2008; Zaidel, 1995). As previous studies showed, early derangement of callosal development prevents axonal crossing and causes decreased interhemispheric connectivity (Paul et al., 2007; Tovar-Moll et al., 2014; Wahl et al., 2009). Thus, it may be that for language learning in these patients, continuous support via plasticity-enhancing interventions is required, and that intensified tDCS interventions are needed to compensate for the physiological consequences of respective abnormal interhemispheric connections for longer time periods, including permanent changes.

One limitation of this single subject study is that stimulation with tDCS is not sufficiently local to infer which network was altered exactly by the intervention, although functional specificity of this stimulation has been proposed, which refers to relatively specific effects on task-related activated neuronal circuits (Polanía et al., 2011). Without additional functional imaging data, we can, however, not attribute stimulation effects specifically to the target regions (Fiori et al., 2019).

Further methodological limitations of this study include that the brain architecture gradually differed between the twins (Blokland et al., 2012) which might have affected the impact of interventions. Moreover, the verbal ability and performance of twins may have been different before intervention as well. However, as the significance of this difference cannot be examined statistically and the changes of each subject have been compared with herself, the results of the intervention are worth reporting.

Standardization of speech therapy, and interaction with the children was somewhat limited. Blinding might have been compromised due to the relevant performance differences of the children during intervention, and blinding integrity was not formally tested. This case study was conducted only in two participants, and studies in larger samples are required for confirmation of the results.

In conclusion, the results of this study suggest that combined treatment with tDCS and speech therapy improves language production in CCD. The presumed advantage of combined speech therapy with simultaneous brain stimulation should be further explored, and might be suited to shorten therapy duration. This safe and tolerable treatment protocol might have furthermore potential for participants with various neurogenic language disorders. Further studies with rigorous designs are suggested.

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