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Interhemispheric facilitation of gesturing: A combined theta burst stimulation and diffusion tensor imaging study

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ABSTRACT

Background: Imaging studies point to a posture (finger vs. hand) and domain-specific neural basis of gestures. Furthermore, modulation of gestures by theta burst stimulation (TBS) may depend on interhemispheric disinhibition.
Objective/Hypothesis: In this randomized sham-controlled study, we hypothesized that dual site continuous TBS over left inferior frontal gyrus (IFG-L) and right inferior parietal gyrus (IPL-R) predominantly affects pantomime of finger postures. Furthermore, we predicted that dual cTBS improves imitation of hand gestures if the effect correlates with measures of callosal connectivity.
Methods: Forty-six healthy subjects participated in this study and were targeted with one train of TBS in different experimental sessions: baseline, sham, single site IFG-L, dual IFG-L/IPL-R, single site IPL-R. Gestures were evaluated by blinded raters using the Test for Upper Limb Apraxia (TULIA) and Postural Imitation Test (PIT). Callosal connectivity was analyzed by diffusion tensor imaging (DTI).
Results: Dual cTBS significantly improved $TULIA_{total}$ (F [3, 28] = 4.118, p = .009), but did not affect $TULIA_{pantomime}$. The beneficial effect was driven by the cTBS over IPL-R, which improved $TULIA_{imitation}$ (p = .038). Furthermore, $TULIA_{imitation}$ significantly correlated with the microstructure (fractional anisotropy) of the splenium (r = 0.420, p = .026), corrected for age and whole brain volume.
Conclusions: The study suggests that inhibition of IPL-R largely accounted for improved gesturing, possibly through transcallosal facilitation of IPL-L. Therefore, the findings may be relevant for the treatment of apraxic stroke patients. Gesture pantomime and postural gestures escaped the modulation by dual cTBS, suggesting a more widespread and/or variable neural representation.

Introduction

Praxis function denotes the ability to accurately perform skilled movements including gesturing. In everyday life, gestures may be used to support (emphasizing disagreement by a “crazy” sign) or to substitute language (signaling to leave by waving goodbye in a noisy environment) [1]. In clinical examination gesture performance is assessed by asking to imitate or pantomime meaningless (finger and hand postures) and meaningful gestures (tool related and communicative gestures) [2,3].

There is left hemispheric predominant activation in gesture performance for both hands [4–7], whereby functional imaging and lesion mapping studies point to domain-specific cortical

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representation. For instance, the left inferior parietal lobe (IPL-L) seems to be mainly responsible for imitation of hand postures [8–11] based on its role for visual-motor integration. By contrast, both left inferior frontal gyrus (IFG-L) as well as right inferior parietal lobe (IPL-R) [12] seem to be particularly involved in the pantomime (on verbal command) of finger postures, when demands on movement selection and visuospatial processing are high [4,13]. This coincides with the observation that some right brain damaged patients may be selectively impaired for these gesture types [14,15]. Furthermore, repetitive transcranial magnetic stimulation (rTMS) [16,17] and transcranial direct current stimulation (tDCS) [18–20] emerged as non-invasive techniques to investigate praxis functions. Continuous theta burst stimulation (cTBS), an inhibitory rTMS protocol, showed a transient disruption (so-called virtual lesion) of gestural behavior, if applied over the left IFG [21] and over the left IPL [17], respectively. Both studies provided evidence that gestural behavior beyond mere perceptual processing was amenable to modulation by rTMS. However, except for left IPL and imitation [17], they could not show any differential cTBS effects on postural subtypes of gestures (finger vs. hand gestures) or gesture domains (imitation vs. pantomime). One reason might be a redundant representation of different cortical areas by both left and right hemisphere (for example pantomime of finger postures by IFG-L and IPL-R). Furthermore, some gesture subtypes, such as imitation of hand postures may be more solely left hemisphere lateralized.

Gesture control may not only depend on distinct areas in right and left hemisphere, but also on their interhemispheric interaction. Inhibitory cTBS has been shown to downregulate the hyperexcitability of the contra-lesional hemisphere thereby restoring the interhemispheric balance and improving aphasia [22] or neglect [23–26]. Intact connectivity of corpus callosum (CC) is critical for the interhemispheric influence of cTBS as shown recently for neglect [27].

This randomized sham-controlled, proof of concept study aimed to explore whether dual site cTBS (over IFG-L and IPL-R) may modulate domain specific (pantomime vs. imitation, finger vs. hand postures) gestural behavior. Based on previous neuroimaging results we hypothesized that in healthy controls dual cTBS in IFG-L and IPL-R will predominantly impair pantomime of finger postures compared to baseline and sham stimulation. Furthermore, we suggested that cTBS of IPL-R in the dual site condition may improve imitation of hand postures, if the effect is correlated with the microstructural integrity of the splenium as measured by Fractional Anisotropy (FA) values, pointing to a facilitation of IPL-L as a potential mechanism.

Material and methods

Participants

Overall, 46 healthy subjects were recruited from the community and participated in this study (23 females, aged 18–77 years, 33.4 ± 14.4). All participants provided written informed consent prior to the experiment. The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee. Participants with a history of neurological disorders, severe psychiatric conditions and any contraindication for magnetic resonance imaging (MRI) or TMS (e.g. metal implants or epilepsy, respectively) were excluded. Based on our previous cTBS studies in healthy subjects using TULIA as an outcome measure [17,21] the power analysis yielded a sample size of 30 subjects providing 80% power, with a 2-sided alpha-level of 0.05, using an expected medium effect size of $\eta^2 = 0.06$. We conducted the main experiment in 31 subjects, while we performed a control experiment in 15 subjects.

Experimental protocol

Participants underwent structural MRI acquisition, before they entered the experimental protocol. Each participant received four sessions (repeated measures design): baseline without stimulation, sham over vertex, cTBS over left IFG (IFG-L) and dual cTBS (IFG-L/IPL-R) were conducted in weekly intervals. The order of these sessions was pseudorandomized. The behavioral measures immediately followed the stimulation application ("offline"). A schematic representation of the experimental protocol is depicted in Fig. 1.

The order of sessions is provided in supplementary file 1.

Continuous theta-burst stimulation

cTBS was applied by means of a MagPro R30 stimulator (MagPro, Medtronic Functional Diagnostics, Skovlunde, Denmark) connected to a round coil with 60 mm outer radius (Magnetic coil Tranducer, MC-125, Medtronic). A cTBS protocol [27] was used, consisting of a continuous train of 801 pulses delivered in 267 bursts. The burst contains 3 pulses at 30 Hz, with an interburst interval of 100 ms, leading to a total duration of 44 s for one single cTBS train. Target site location was determined according to the international 10–20 EEG system. For left IFG stimulation the cTBS was applied over F7 [28] and for right IPL stimulation cTBS was applied halfway between P4–P8 [29]. For each session correct positioning was confirmed by a second examiner. The coil was placed tangentially over the target area with the current flowing in a clockwise direction (within the coil) as viewed from above. cTBS was delivered at 80% of the participants' individual resting motor threshold (rMT). Individual rMT was defined as the lowest stimulation intensity applied over the right primary motor cortex eliciting a visible contraction of the contralateral hand muscle in at least 5 out of 10 consecutive stimuli. Sham stimulation was applied by the same cTBS protocol, however a sham coil (Magnetic Coil Transducer MC-P-B70, Medtronic) was used. For the dual site application (IFG-L/IPL-R) the IPL right stimulation immediately followed the left IFG train.

Behavioral testing

The main outcome is a validated, comprehensive test for gesture production called TULIA [2]. It consists of 48 items covering the domains imitation and pantomime in three semantic categories (meaningless, communicative and tool related). Furthermore,

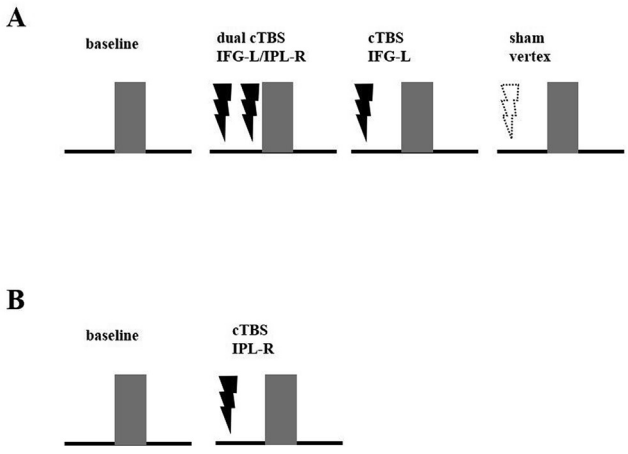

Fig. 1. Schematic representation of the main (A) and control (B) experiments for each participant (counterbalanced order): Gray rectangles represent offline behavioral testing. Bolt symbols represent stimulation: real cTBS (solid symbols) and sham stimulation (dotted symbol).

composite scores of finger and hand postures can be extracted. The performance of each item regarding temporal, spatial and content related errors is rated on a scale ranging from zero to five points (see supplementary file 2 for details of the scoring method). Thus, the TULIA score ranges from zero to 240, with higher scores reflecting better performance. The imitation or pantomime subtests have a maximum score of 120. The TULIA proved to be a suitable instrument to quantify effects of cTBS on gestural performance in healthy subjects [17,21]. There was no ceiling effect with a wide range of normal scores (194–240). The video-based scoring method allowed a sensitive detection of gestural changes. TULIA scores were rated by two blinded raters (SK, AS) with high inter-rater reliability (ICC = 0.88).

Imitation was additionally tested with a postural imitation test (PIT) for ten hand and ten finger postures [11,30]. According to the TULIA scoring system, we rated each posture on a score from zero to five, resulting in a maximum score of 100 with higher scores reflecting better performance.

In addition, participants completed the 'orientation test' a short version of the Judgement of Line orientation test (JLO), Bells test and a short version of the Boston naming test to control for confounding effects on visual spatial skills, visual attention and word retrieval, respectively. The JLO is a purely visual 30-item test, in which participants are asked to visually examine 11 lines that appear in a standard fan-shaped array at the bottom of the examination sheet. Next, participants are asked to match angles of two lines, presented on the top of the page [31]. The short version of the JLO consist of 15-items chosen from the test [32]. To score one point, the angles of both two lines must be matched correctly, thus the short version results in a maximum of 15 scores.

The Bells test is a visual exploration test performed on a horizontally disposed A4 sized page. The participant is asked to cancel all bells (35 targets) without getting distracted by the 280 distractors. The bells are pseudo-randomized over the sheet and can be organized in seven columns containing 5 bells. The scores are generated by building the ratio between missed bells on the right and the left visual field [33].

In the Boston naming test the participant is asked to name each of the 15 lines drawings. Each correctly named drawing is scored with a point, thus the short version results in a maximum of 15 scores [34].

Magnet resonance imaging acquisition

High-resolution T1-structural and DTI were obtained using a 3 T Philips Ingenia whole-body scanner (Philips Medical Systems, Best, The Netherlands) equipped with a commercial eight-element head coil array that is capable of sensitivity encoding (SENSE). We used a diffusion-weighted spin echo, echo-planar imaging sequence to obtain diffusion-weighted scans with a measured spatial resolution of $1.96 \times 2.00 \times 4.00\ mm^3$ (acquisition resolution, 112×110 pixels, 30 slices) and a reconstructed spatial resolution of $1.72 \times 1.72 \times 4.00\ mm^3$ (reconstruction matrix 128×128 pixels, 30 slices). Further imaging parameters were: FOV = $220 \times 220 \times 120\ mm^3$; TE = 74 ms; TR = 34.64 ms; $\alpha = 90$; SENSE factor P = 2; b-value b = 1,000 s/mm^2; and number of averages = 2. Diffusion was measured in 64 non-collinear directions preceded by a non-diffusion-weighted volume (reference volume). Total acquisition time was approximately 17 min.

MRI preprocessing

DTI images were preprocessed using DTIPrep [35], a program for automatic image quality control and preparation. Preprocessing included image information check, data cropping, slice-wise, interlace-wise, and gradient-wise intensity artifact correction, eddy current and head motion correction, as well as computing of DTI. We performed whole brain tractography. For the extraction of the average value of the FA indices in the participant's native space, the reconstruction method "DTI" proposed by Basser et al. (1994) [36]was performed using DSI Studio [37](http://dsi-studio.labsolver.org/). According to the Johns Hopkins University (JHU) white-matter-atlas [38] a ROI was placed in the splenium of the CC. Average FA-values were extracted for each participant from this ROI. In addition, each tensor was visually inspected to ensure good quality prior to FA map creation.

Total brain volume was calculated according to the computational anatomy toolbox (CAT12) for Statistical Parametric Mapping software (SPM12) [39,40]. Tissue segmentation of gray matter, white matter and cerebrospinal fluid was done according to the preprocessing step in CAT12 and the absolute volume (cm^3) of gray and white matter was summed up.

Experimental design and statistical analysis

For all statistical analyses, the level of significance was set at $p = .05$ (two-tailed). All values are expressed as mean ± standard deviation (SD). Statistical analyses were performed using IBM for Windows (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Several repeated-measure analyses of variance (RM-ANOVA) were performed to explore the effects of cTBS on TULIA total scores and subscores (pantomime/imitation), hereafter called $TULIA_{total\ scores}$, $TULIA_{pantomime}$, and $TULIA_{imitation}$. Also, several RM-ANOVA were performed to explore the effects of cTBS on PIT total scores and subscores (imitation hand/finger postures), hereafter called $PIT_{total\ scores}$, $PIT_{hand\ imitation}$, and $PIT_{finger\ imitation}$. Consequently, the statistical design consisted of the within-subject factors 'stimulation session' (baseline, sham, IFG-L, IFG-L/IPL-R) and 'task' (TULIA or PIT). Mauchly's test indicated that the assumption of sphericity was not violated. Post-hoc paired t-tests were done for multiple comparisons.

To explore whether other control measurements (JLO, Bells, Boston naming) were stable over the four stimulation conditions several RM-ANOVA were performed.

To further understand possible cTBS effects on praxis we performed a non-hierarchical (k-means) cluster analysis for a two clusters solution to identify subjects who showed improved ("responder") or no improved ("non-responder") praxis function. To evaluate whether microstructural variability may correlate with cTBS effects on praxis performance, partial correlations between extracted FA-values in the splenium of the CC and relative changes of praxis performance after stimulation compared to baseline or sham were performed. We used the genu of CC (GCC) as a control tract for interhemispheric microstructure and the left superior longitudinal fasciculus (SLF) for intra-hemispheric microstructure. All correlations were controlled for age and total brain volume, to reduce the effect of individual brain size as a possible confounder on diffusion tensor measures [41].

Results

Dual site cTBS stimulation improved gesturing

The RM-ANOVA showed significant interactions between 'stimulation session' (baseline, sham, IFG-L, IFG-L/IPL-R) and 'task' ($TULIA_{total\ scores}$), F [3, 28] = 4.118, $p = .009$). Post-hoc analysis revealed that dual cTBS (IFG_{left} - IPL_{right}) significantly increased $TULIA_{total\ scores}$ by a mean of 4 points (228.3 ± 9.4, range 201–240) compared to baseline (224.3 ± 8.5, range 199–240, $p = .004$), and

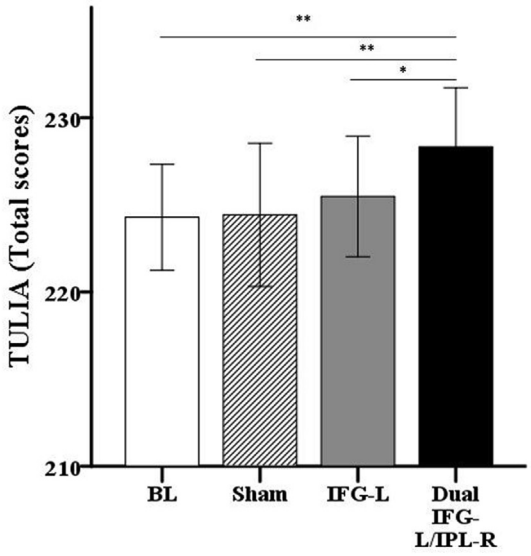

Fig. 2. Gesturing as measured by $TULIA_{total\ scores}$ * = p < 0.05, ** = p < 0.01.

sham (224.4 ± 11.4, range 191–240, $p = 0.008$). Dual cTBS also significantly increased, by a mean of 3 points, $TULIA_{total\ scores}$ compared to IFG-L (225.5 ± 9.6, range 196–240, $p = 0.036$). No differences were found between IFG-L and baseline as well as sham and baseline stimulation (see also Fig. 2).

To further validate the effect of dual cTBS we conducted a control experiment for the right IPL cTBS alone. General linear model analysis revealed a significant increase (F-value [1, 14] = 6.171, $p = .026$, $\eta^2 = 0.306$) of $TULIA_{total\ scores}$ after right IPL cTBS (229.5 ± 9.21, range 204–239) compared to baseline 222.8 ± 15.9, range 184–236) (not shown). Participants of the main (n = 31) and the control experiment (n = 15) did not differ significantly regarding age (t = 1.1, p = .27) and $TULIA_{total\ scores}$ at baseline (t = 4.2, p = .68).

The interaction effect in the main experiment was mostly driven by the items of the $TULIA_{imitation}$ (F [3, 28] = 2.918, $p = .038$), as for $TULIA_{pantomime}$ no interaction effect (F [3, 28] = 1.292, $p = .282$) could be detected. Furthermore, significant interaction effect of stimulation was found for imitation of hand and finger postures measured by $PIT_{total\ scores}$ (F [3, 28] = 3.024, $p = .034$). Post-hoc comparison revealed that dual cTBS significantly increased $PIT_{total\ scores}$ compared to baseline ($p = .022$) and sham ($p = .010$) (for PIT values see Table 1). Imitation of finger gestures (F [3, 28] = 1.98, $p = .12$) or hand gestures alone (F [3, 28] = 1.48, $p = .22$) revealed no significant interaction effect.

The RM-ANOVA of cTBS effects on control variables as spatial orientation (JLO), visual attention (Bells test) and speech production (Boston Naming) revealed no significant interaction effect (JLO: F [3, 28] = 1.65, p = .184; Bells Test: F [3, 28] = .067, p = 0.933; Boston Naming: F [3, 28] = 3.170, p = .059).

Dual site cTBS responders and non-responders

A cluster analysis revealed that after dual cTBS two subgroups exist regarding the modulation of $TULIA_{total\ scores}$. The first subgroup (n = 20) showed improvement in praxis function after dual cTBS ("responders") (TULIA raw score differences 3 to 18). The second subgroup consisted of 11 participants, who showed no change or even worsening of praxis function after dual cTBS ("non-responders") (TULIA raw score differences −17 to 2) (for the individual raw score differences see supplementary file 3). The

Table 1
Postural Imitation scores at baseline and after different stimulation conditions.

	Mean	SD	Range
$PIT_{total\ scores\ BL}$	90.71	7.06	71–100
PIT_{hand}	46.32	2.91	39–50
PIT_{finger}	44.39	5.35	30–50
$PIT_{total\ scores\ Sham}$	90.00	7.95	71–100
Hand	46.00	3.56	33–50
Finger	44.00	5.45	30–50
$PIT_{total\ scores\ IFG\text{-}L}$	91.68	5.90	80–100
Hand	46.55	2.97	38–50
Finger	45.13	4.01	37–50
$PIT_{total\ scores\ IFG\text{-}L/IPL\text{-}R}$	92.68	6.00	75–100
Hand	47.13	2.60	40–50
Finger	45.55	4.46	33–50

Note: PIT = Postural Imitation Test; SD = standard deviation; IFG-L = inferior frontal gyrus left; IPL-R: inferior parietal lobe right.

subgroups of the cluster analysis did not differ significantly regarding age ($t = .82$, $p = .421$). We also explored the differential effect of dual cTBS on gesture imitation in responders and non-responders, separately, since modulation of $TULIA_{imitation}$ accounted mainly for the results in the whole group. We detected a significant interaction effect in responders (F [3, 28] = 5.906, $p = .001$) but not in non-responders (F [3, 28] = 1.763, $p = .175$). Post-hoc analysis showed that for responders dual cTBS significantly increased imitation (117.90 ± 3.8, range 107–120) compared to baseline (114.15 ± 4.3, range 105–120; $p = .01$), sham (115.05 ± 4.9, range 101–120; $p = .0004$), and left IFG cTBS (115.50 ± 4.2, range 104–120; $p = .02$) (see also Fig. 3).

Fractional anisotropy correlates with the gestural effect of dual cTBS

Relative change of $TULIA_{total\ scores}$ after dual cTBS ((Dual cTBS− baseline)/baseline) showed a significant partial correlation with FA mean values within the splenium ($r = 0.420$, $p = .026$), corrected for age and whole brain volume. The significant correlation ($r = .466$, $p = .044$) in the responders-group was mainly responsible for this finding as the correlation in the non-responder group was not significant ($r = .262$, $p = .436$) (see also Fig. 4A).

A significant partial correlation was found between the relative change of $TULIA_{imitation}$ after dual cTBS ((Dual cTBS− baseline)/baseline) and FA mean values within the splenium ($r = 0.398$, $p = .030$). As for TULIA total scores, the relationship was explained by the correlation ($r = .524$, $p = .021$) in the responder-group, being not significant in the non-responder group ($r = .223$, $p = .510$) (see also Fig. 4B).

For the control tracts (GCC and SLF), irrespective of the responder status, no significant partial correlations were found between the relative change of $TULIA_{total\ scores}$ after dual cTBS ((Dual cTBS− baseline)/baseline) and FA mean values ($r = 0.147$, $p = .439$, for GCC and $r = 0.235$, $p = .211$, for SLF), both corrected for age and whole brain volume.

Discussion

This randomized, sham-controlled, proof of concept study aimed to investigate the effect of dual cTBS on domain-specific gesturing (pantomime vs. imitation, finger vs. hand postures) in healthy subjects. By using a dual site stimulation approach, we expected that cTBS over both IFG-L and IPL-R would impair pantomime of finger postures, which were not influenced by single site stimulation (e.g. IFG-L) [21]. Furthermore, based on the interhemispheric rivalry model [42] we hypothesized that cTBS of IPL-R in the dual site condition may improve imitation of hand postures,

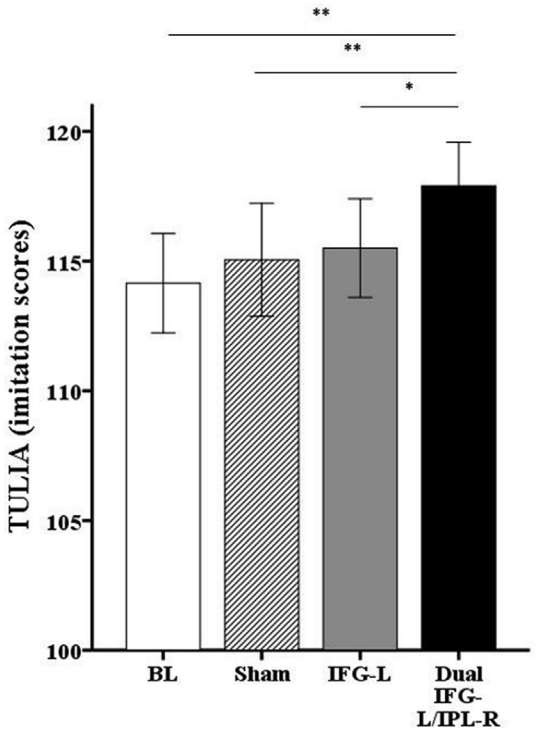

Fig. 3. Imitation as measured by $TULIA_{imitation}$, * = p < 0.05, ** = p < 0.01.

through interhemispheric facilitation of left IPL. This mechanism would be likely, if the cTBS response correlated with the microstructural integrity of the splenium [42,43]. We assumed that higher FA values reflect a better integrity in the microstructure of the splenium rendering it more efficient for interhemispheric interactions. This expectation is based on the fact that the fiber directions in the corpus callosum are highly restricted.

We demonstrated that dual cTBS significantly improved gesture performance, particularly in the imitation domain. However, we could neither find a domain specific cTBS effect for pantomime, nor for kinematic aspects of gesturing (finger vs. hand postures), which may be explained by a higher inter-individual variability in the neural representations (either at single or multiple network sites) of these gesture subtypes. To evaluate whether cTBS of the right IPL accounted for the effect of dual site stimulation we conducted a control experiment with cTBS of right IPL alone, which confirmed the results of the main dual cTBS experiment by showing improved gestural behavior. The similar effects of the dual site and single site control experiments point to a good external validity, since different populations were targeted. The effects of dual cTBS were specific as we did not find any differences between sham and baseline performances. Furthermore, a significant difference between both active stimulation conditions (IFG-L alone vs. dual cTBS) was found further underlining the robustness of our results. In addition, we did not find any confounding effects neither for spatial orientation, visual attention nor speech production. A contribution of the local (inhibitory) effect of cTBS over IPL-R cannot be ruled out, which however would have been expected

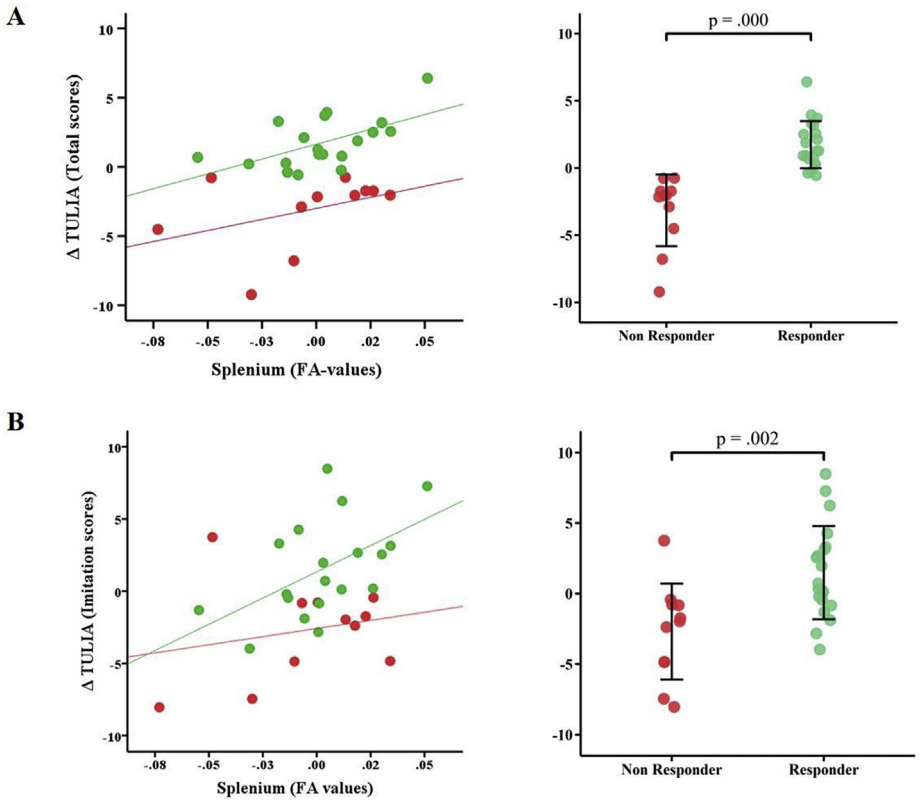

Fig. 4. A & B. Partial correlation with Fractional anisotropy (FA) values of the splenium of the corpus callosum and improvement in praxis function (ΔTULIA Total scores) after dual cTBS. Responders to cTBS (green) $r = .466$, $p = .044$, Non-responders (red) $r = .262$, $p = .436$ (A, left panel). Error bars with individual data points (A, right panel). Overall correlation $r = .420$, $p = .026$; partial correlation corrected for age and whole brain volume; $^{*}p < .05$. Partial correlation with Fractional anisotropy (FA) values of the splenium of the corpus callosum and improvement in imitation (ΔTULIA Imitation scores) after dual cTBS. Responders to cTBS (green) $r = .524$, $p = .021$, Non-responders (red) $r = .223$, $p = .510$ (B, left panel), Error bars with individual data points (B, right panel). Overall correlation $r = .398$, $p = .030$; partial correlation corrected for age and whole brain volume; $^{*}p < .05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

to deteriorate rather than to improve gestural performance, based on the role of IPL-R in visuospatial processing. Finally, cluster analysis of the data allowed to classify the subjects into two groups of responders (about 65%) and non-responders, the former showing gestural benefit from the dual site stimulation, particularly in the imitation domain.

Interestingly, the extent of gestural improvement under dual site cTBS was significantly associated with stronger fiber integrity (as measured by FA values) within the splenium. The relationship was anatomically specific as corresponding correlations with the microstructure of the GCC or the left SLF were non-significant. The findings therefore lend support to the interhemispheric rivalry model [25], according to which inhibition of right IPL may have facilitated the left IPL through splenial connections. Along this line, our results suggest that cognitive processes related to left IPL, including gesture imitation are amenable to modulation through cTBS over right IPL. Our findings are in line with a previous report [42], which showed a significant correlation between callosal microstructure and cTBS effects on visual exploration behavior, pinpointing to a modulatory role (either inhibitory or facilitatory) of the corpus callosum for interhemispheric dynamics. The cTBS effects on the non-stimulated hemisphere showed a similar strength of association with the FA values of the CC as demonstrated herein.

The fact that gestural effects after cTBS were largely explained by improved imitation scores seem to be in line with earlier findings of non-invasive brain stimulation studies [18,44]. The authors of these studies chose anodal tDCS to target left IPL directly, based on the assumption that anodal tDCS is excitatory in nature and may improve cognitive processes [45]. Weiss and colleagues found that matching of seen gestures was facilitated after one application of anodal tDCS [18], as measured by accelerated reaction time (RTs.). However, in contrast to the findings of the present study, they could not demonstrate an effect on actual gesture imitation. The authors explained the lack of effect on gestural behavior by their error rate analysis for imitation, which may have been biased due to ceiling effects [18]. The absent ceiling effect is therefore an important clinimetric feature of the TULIA [2,46], rendering the instrument very sensitive to detect gestural changes, as for imitation subscores herein [17]. Similar to Weiss and colleagues [18], Bolognini and colleagues [44] applied anodal tDCS over left posterior parietal lobe in 6 apraxic stroke patients. They demonstrated significant beneficial effects on actual gestural imitation. The effects were smaller in patients with parietal lesions, indicating that the integrity left IPL is important for functional recruitment. Conclusions from this study are however limited by the low number of participants and their divergent disease stage (3 out 6 were chronic rather than acute/subacute stroke patients). In line with our study, just recently, facilitatory effects of cathodal tDCS on gesture processing were found in schizophrenia, further underlining the validity of using non-invasive brain stimulation methods to improve gesture performance [47].

We did not find a significant cTBS effect over IFG-L alone on pantomime performance, confirming the findings from our previous study [21]. This lack of modulation by single site cTBS may have been explained by a redundant organization of praxis control. For instance, a second site such as IPL-R may have maintained the correct pantomime of finger postures. In addition, although dual site stimulation elicited, as expected, improvement mainly in the imitation domain, based on the literature the left IPL may additionally support pantomime of finger and particularly hand postures. Furthermore, very recently, it has been shown that gestural pantomime depends on the interplay of multiple cortical regions with strong functional connectivity between left ventral anterior temporal lobe, left frontal operculum and left supramarginal gyrus [48]. On the other hand, if gesturing was combined with speech, such as in co-verbal metaphoric gesturing, anodal stimulation of IFG-L solely could affect these gestures types, possibly explained by the fact both speech and these gesture types share common IFG-L neural substrate [49].

Cluster analysis separated the subjects into dual cTBS responders and non-responders. Previous studies in healthy subjects investigating interhemispheric interactions using rTMS reported similar differences in behavioral response to the stimulation [42,43]. This heterogeneity of rTMS efficacy may be explained by differences in baseline brain activity, age or stimulation parameters (for a review see Ref. [50]). Another important factor seems to be the microstructural integrity of trans-callosal pathways. Accordingly, in the present study only in responders a significant positive relationship could be detected between gestural improvement to dual cTBS and white matter microstructure of the splenium. Therefore, the structural connectivity between the left and right IPL seems to be highly important for the responsiveness to cTBS. As mentioned above, similar results were reported in a study by Chechlacz and colleagues, where the microstructural integrity in healthy subjects accounted for the individual responsiveness of TMS regarding attentional shifts [42]. Another study by Chiou and colleagues reported comparable findings with regard to the association of fractional anisotropy in CC and ipsilateral motor representation during unilateral hand movements in healthy subjects [43].

A potential limitation of our study is that we did not use a neuro-navigation system, which would have allowed a more focused stimulation of specific cortical areas [51]. This might explain why we couldn't find a significant differential cTBS effect on kinematic features of gestures (hand and finger postures) in the TULIA and PIT scores. However, for clinical application, the use of neuro-navigation system may not be feasible, because it is time consuming and expensive. Furthermore, the rTMS focality of neuro-navigation systems may be generally limited by individual differences in gyral anatomy and covering CSF layer spreading electrical fields induced by TMS [52]. Finally, in the perspective of clinical application in apraxic stroke patients improving gesture performance across all domains (imitation, pantomime) may be wishful and not requiring a more focused stimulation. However, to achieve longer lasting effects the treatment protocol will likely need multiple cTBS stimulation sessions, as already done in other cTBS studies for neglect [23,24] and aphasia [22].

Conclusion

The present findings in healthy subjects are of potential clinical relevance since we could demonstrate beneficial effects on gesture performance when applying an inhibitory cTBS protocol. The study provides a rationale to apply single site cTBS over right IPL to boost left IPL cognitive-motor functions probably through transcallosal disinhibition. Our proof of concept study may therefore pave the way for the development of treatment protocols for apraxic stroke patients by combining cTBS in the non-affected hemisphere to promote neurorehabilitation programs [53–56].

Authors contribution statement

Tim Vanbellingen: Conception, Organization, Execution, Design, Review and Critique, Writing of the first draft. Manuela Pastore-Wapp: Conception, Organization, Execution, Design, Review and Critique. Stefanie Kübel: Conception, Organization, Execution, Design, Review and Critique. Thomas Nyffeler: Conception, Organization, Review and Critique. Anne-Catherine Schüpfer, Claus Kiefer, Leopold Zizlsperger, Kai Lutz, Andreas R. Luft: Conception,

Review and Critique. Sebastian Walther: Conception, Organization, Review and Critique. Stephan Bohlhalter: Conception, Organization, Execution, Review and Critique.

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Appendix A. Supplementary data

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