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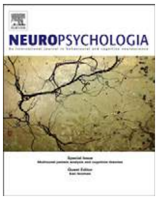

Facilitation of speech repetition accuracy by theta burst stimulation of the left posterior inferior frontal gyrus

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ABSTRACT

The posterior part of the inferior frontal gyrus (pIFG) in the left hemisphere is thought to form part of the putative human mirror neuron system and is assigned a key role in mapping sensory perception onto motor action. Accordingly, the pIFG is involved in motor imitation of the observed actions of others but it is not known to what extent speech repetition of auditory-presented sentences is also a function of the pIFG. Here we applied fMRI-guided facilitating intermittent theta burst transcranial magnetic stimulation (iTBS), or depressant continuous TBS (cTBS), or intermediate TBS (imTBS) over the left pIFG of healthy subjects and compared speech repetition accuracy of foreign Japanese sentences before and after TBS. We found that repetition accuracy improved after iTBS and, to a lesser extent, after imTBS, but remained unchanged after cTBS. In a control experiment, iTBS was applied over the left middle occipital gyrus (MOG), a region not involved in sensorimotor processing of auditory-presented speech. Repetition accuracy remained unchanged after iTBS of MOG. We argue that the stimulation type and stimulation site specific facilitating effect of iTBS over left pIFG on speech repetition accuracy indicates a causal role of the human left-hemispheric pIFG in the translation of phonological perception to motor articulatory output for repetition of speech. This effect may prove useful in rehabilitation strategies that combine repetitive speech training with iTBS of the left pIFG in speech disorders, such as aphasia after cerebral stroke.

1. Introduction

Acquisition of language skills in humans involves social interactions in earliest infancy, and speech repetition plays a fundamental role by mapping auditory and sensory input onto matching motor output (Hickok & Poeppel, 2004, 2007; Wernicke, 1874). At the level of neuronal networks in the brain, speech repetition occurs within the auditory dorsal stream, which is constituted by a temporo-parieto-frontal network including the posterior inferior frontal gyrus (pIFG) (Hickok, Houde, & Rong, 2011; Hickok & Poeppel, 2004, 2007). It has been hypothesized that, in the frontal areas, so called mirror neurons contribute to this network (Corballis, 2010; Rizzolatti & Arbib, 1998). Mirror neurons have first been characterized in macaque area F5 by discharging when the monkey performs actions and perceives the actions of others (Ferrari, Gallese, Rizzolatti, & Fogassi, 2003; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). Although still a matter of debate, area F5 of the macaque brain is thought to be partially homologous to pIFG in the human brain (Petrides & Pandya, 1994; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012). This proposition is supported by several neurophysiological and neuroimaging studies, which provided evidence for the existence of a putative mirror neuron system in the human pIFG (Fadiga, Craighero, & D'Ausilio, 2009; Fadiga, Craighero, & Olivier, 2005; Rizzolatti & Craighero, 2004).

Transcranial magnetic stimulation (TMS) represents a useful tool for investigating the mechanisms of sensorimotor integration in the human brain. One technique of investigation is single or paired pulse TMS of the primary motor cortex (M1) during observing or listening to speech while motor evoked potentials (MEP) are recorded as an index of excitability of the stimulated motor representation (Hallett, 2007). Increases in MEP amplitudes in hand muscles have been demonstrated during observation of hand and arm movements performed by another individual (Baldissera, Cavallari, Craighero, & Fadiga, 2001; Clark, Tremblay, & Ste-Marie, 2004; Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Strafella & Paus, 2000). In addition, MEP amplitudes of facial or articulatory muscles involved in speech production were facilitated during observation of speech related lip movements (Murakami, Restle, & Ziemann, 2011; Sundara, Namasivayam, & Chen, 2001; Watkins, Strafella, & Paus,

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2003), and even when just listening to speech (Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Murakami et al., 2011; Watkins et al., 2003). In an experiment that combined TMS of the face representation of the left M1 with positron emission tomography, increases in MEP amplitude in the facial orbicularis oris muscle correlated directly with metabolic activity in the left pIFG during listening to speech (Watkins & Paus, 2004). These findings supported the notion that the left pIFG facilitates excitability of the face and articulatory representations of the left M1 during speech perception, and therefore, operates at the interface of speech perception and articulation.

Another technique of investigation is to use TMS in the so called 'virtual lesion' mode (Ziemann, 2010). By applying repetitive TMS (rTMS) over a certain brain area, the activity of the stimulated network is disrupted or facilitated, which should result, respectively, in decline or improvement of behavioral performance if this network is relevant for the performed task. Two previous virtual lesion studies provided evidence for the importance of the pIFG in sensorimotor integration processing: rTMS of pIFG resulted in reduced accuracy of hitting the correct target in a finger movement imitation task (Heiser, Iacoboni, Maeda, Marcus, & Mazziotta, 2003) and delayed reaction time in an automatic finger movement imitation task (Catmur, Walsh, & Heyes, 2009).

Here we present two experiments to clarify the role of the left pIFG in sensorimotor integration of speech processing. In the main experiment we applied theta burst stimulation (TBS) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005), a particular form of rTMS, to the left pIFG, and evaluated the effects of three TBS protocols (cTBS: continuous TBS, iTBS: intermittent TBS, imTBS: intermediate TBS) on accuracy of speech repetition of a foreign language (Japanese). The task ensured specific testing of sensorimotor integration of language along the dorsal auditory stream because the foreign language provided phonological material but excluded lexical or semantic clues which would be processed in the ventral auditory stream (Hickok & Poeppel, 2004). The three TBS protocols were selected because, when applied to M1, cTBS decreased M1 excitability, iTBS increased it, and imTBS produced no change (Huang et al., 2005). However, translation of those effects in M1 to TBS effects in other brain areas, and translation to modulation of behavior is not necessarily straightforward (Bijsterbosch, Lee, Dyson-Sutton, Barker, & Woodruff, 2011; Stinear et al., 2009). Therefore, any significant modulating effect of any of the TBS protocols applied to the left pIFG on speech repetition accuracy would indicate a functional role of this area or its connected network in speech repetition. In a control experiment, iTBS was applied over the left middle occipital gyrus (MOG). We hypothesized that significant modulating effects of speech repetition accuracy would occur with TBS of pIFG but not MOG, since MOG is involved in visual processing but is not part of the auditory speech processing network.

To the best of our knowledge this is the first study that examines the importance of the left pIFG for speech repetition accuracy by using rTMS. We provide here direct evidence for a modulating role of the left pIFG in speech repetition.

2. Material and Methods

2.1. Participants

Eighteen healthy right-handed volunteers (mean age ± S.D., 26.0 ± 4.7 years) participated in this study. All subjects were German native speakers and completely naïve to Japanese language. Their educational level was homogenous as all of them were university students. Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) with a mean laterality score of 95.1 ± 8.6%. The study was approved by the Ethics Committee of medical faculty of the Goethe University Frankfurt, and conducted in accordance with the latest version of the Declaration of Helsinki. All participants gave their written informed consent prior to participation.

2.2. Speech repetition task

Subjects sat on a comfortable chair while listening to short Japanese poem sentences (IROHAKARUTA) presented via dual loudspeakers. The Japanese sentences were recorded from a native Japanese male speaker, using a video camera. Each sentence consisted of 8 up to 13 syllables and was presented 4 times at random intertrial intervals of 10–13 s before moving to the next sentence. Forty eight different sentences were prepared and divided into 6 different blocks of 8 sentences. For each experimental session one block (i.e., consisting of 4 repeats × 8 sentences = 32 trials) was randomly selected. Subjects were instructed to repeat every sentence immediately after presentation (Fig. 1A, B). Repetition accuracy was recorded by a digital video camera at every second and fourth repetition of a given sentence (i.e., 16 trials were evaluated per block of trials). For offline assessment of repetition accuracy, the audio file was separated from the video and presented to a native female Japanese rater, who was naïve to the purposes of the experiments and blinded towards Time (pre vs. post TBS) in the main and control experiment, and towards TBS Type in the main experiment (cTBS, iTBS, imTBS) in the main experiment. Speech repetition accuracy was quantified by the percentage of correctly pronounced syllables per block of trials.

2.3. Determination of active motor threshold

Active motor threshold (AMT) was determined because the intensity of TBS was related to the individual AMT in accord with established standards (Huang et al., 2005). Electromyogram (EMG) was recorded from the first dorsal interosseous (FDI) muscle of the right hand by pairs of Ag–AgCl surface electrodes in a muscle-tendon montage. The raw EMG was band pass filtered (20–2.000 Hz), digitized with an analog-to-digital converter (micro1401, CED, Cambridge, UK) at

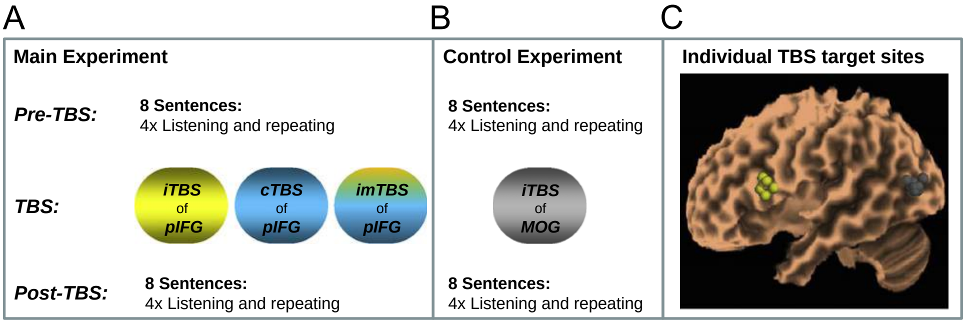

Fig. 1. Experimental design. Participants listened to short Japanese poem sentences and immediately repeated the heard sentence. One block of trials consisted of 8 sentences × 4 repeats. **A:** In the main experiment, one block of trials of speech repetition was performed before and immediately after iTBS, cTBS or imTBS to the left pIFG. Each subject was tested for all TBS types in pseudorandomized order, with sessions separated by 7 days. **B:** In the control experiment, one block of trials of speech repetition was performed before and immediately after iTBS of MOG. **C:** Sagittal view of a peeled (factor 9.3) MNI standard brain (Localite TMS Navigator software version SW-2.1 2011), indicating the individual stimulation sites (coil centers) over left-hemispheric pIFG (yellow, $n = 11$) and MOG (gray, $n = 10$). Not all stimulation sites are visible due to overlap. Stimulation sites were defined by the maximum individual fMRI activations during auditory speech perception in close vicinity to the areas of activation in the group average, and targeted by using fMRI-guided TMS neuronavigation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

a sampling rate of 5 kHz and stored on a personal computer. TMS was applied using a MagPro X100 magnetic stimulator connected to a 65 mm figure of eight coil (MagVenture, Farum, Denmark). The magnetic stimulus had a biphasic waveform with a pulse width of 100 μs. The stimulating coil was held tangentially to the skull with the coil handle pointing backwards and laterally 45° away from the anterior-posterior axis. The center of the coil junction was placed over the M1 hand area of the left hemisphere. The 'motor hot spot' was determined as the site where TMS consistently elicited the largest MEPs from the right FDI muscle. AMT was determined at this hot spot. AMT was defined as the minimum stimulus intensity that elicited small MEP amplitudes $\geq 200\,\mu V$ in at least 5 out of 10 consecutive trials during approximately 10% of maximum voluntary contraction of the right FDI muscle (Groppa et al., 2012). Stimulus intensities are indicated as percentage of the maximum stimulator output.

2.4. *Theta burst stimulation*

The MagPro X100 magnetic stimulator was also used for TBS application. The TBS pattern consisted of bursts of three pulses at 50 Hz (20 ms between each pulse), which were repeatedly delivered at 200 ms intervals (Huang et al., 2005). For iTBS, a two-second train of TBS was repeated every 10 s for a total of 600 pulses. For cTBS, the train was presented without interruption over 40 s for a total of 600 pulses. For imTBS, a 5 s train of TBS was repeated every 15 s for a total of 600 pulses. The stimulus intensity was set at 80% AMT.

2.5. *fMRI-guided TMS neuronavigation*

Prior to the experiment sessions, high-resolution structural T1-weighted images and functional magnetic resonance images (fMRI) data were obtained from each subject. The imaging data were acquired in the Brain Imaging Center Frankfurt on a 3.0-T Siemens Magnetom Allegra System equipped with a standard birdcage head coil. The fMRI was performed in a block design using BOLD-sensitive gradient echo-planner T2*-weighted gradient-echo imaging (EPI) sequence (repetition time: $TR=2000$ ms, echo time: $TE=30$ ms, field of view: $FOV=192$ mm, flip angle$=90^{\circ}$, 64×64 matrix, 30 slices, slice thickness$=2.5$ mm, voxel size$=3.0\times 3.0\times 2.5$ mm). After fMRI acquisition, a high-resolution structural T1-weighted image of the whole brain ($TR=2250$ ms, $TE=2.6$ ms, $FOV=256$ mm, flip angle 8°, 256×256 matrix, 176 slices, slice thickness$=1$ mm, voxel size$=1.0\times 1.0\times 1.0$ mm) was acquired from all subjects.

The fMRI data were obtained while the subjects were engaged either in listening to German speech (80 dB sound pressure level) and viewing visual noise, or viewing speech-related lip movements and listening to auditory white noise (70 dB sound pressure level), or listening/viewing audiovisual noise (70 dB sound pressure level). The speech movie was recorded from a native German speaking woman using a digital video camera. The audio file was separated from the video. The audio file was presented via headphones connected to a computer and the subjects were instructed to pay attention to the auditory material and, whenever applicable, to try to understand the speech. The participants wore goggles and watched the visual material on the monitor. Each task condition was presented in blocks of 30 s duration, repeated 8 times each, and presented in random sequence alternating with 30 s resting periods.

EPI data was analyzed using SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK), implemented on MATLAB2008 (Mathworks, Shelborn, MA). For data preprocessing, image volumes of each subject were realigned and spatially normalized to the stereotaxic atlas space devised by the Montreal Neurological Institute (MNI). Then the obtained images were smoothed with an 8 mm at full-width half-maximum Gaussian filter. The preprocessed images of each subject were analyzed using the standard general linear model approach. A simple *t*-contrast map of listening to the speech condition vs. noise condition was calculated for definition of the left pIFG, and a contrast of viewing speech-related lip movement vs. listening to speech was used for identification of the left MOG (control iTBS site in the control experiment to test the topographical specificity of the effects observed with iTBS of the left pIFG in the main experiment).

The target sites for TBS were identified on each subject's scalp by using an fMRI-guided TMS neuronavigation system (Localite, St. Augustin, Germany). At first, a high-resolution structural T1-weighted image of each subject's individual head was imported and a 3D image was reconstructed. The individual 3D image was standardized to the Talairach coordinate system by defining AC-PC line and falx cerebri. Five skull landmarks (nasion, bilateral corners of the eyes, and bilateral preauricular points) and about 150 points on the surface of scalp of each subject were fitted to those of the 3D image. Errors between the subject's scalp and the image were allowed within 1.5 mm. The MNI coordinates of the individual stimulated points were automatically conveyed into Talairach coordinates and displayed on the individual structural brain (Fig. 1C). The coil was visually navigated to the individual target point in real time throughout TBS application.

The preliminary target coordinates of the left pIFG were derived from a prior group fMRI study from our laboratory. The group data from the *t*-contrast map of listening to speech vs. control noise (left pIFG) were analyzed using a one-sample *t*-test. Clusters were considered significant only if they consisted of at least 40 contiguous voxels, which passed the threshold of $P<0.01$, family-wise error (FWE) corrected. We found several activated regions related to speech perception (i.e., listening to speech and viewing speech-related lip movements), including the left pIFG (BA44) (MNI coordinates, $x=-52$, $y=8$, $z=20$; unpublished data). The actual TBS target coordinates of the left pIFG were determined for each subject as the cluster of activated voxels closest to the pIFG target from the group data in order to take into account inter-individual differences in pIFG location and activation (Andoh & Paus, 2011; Murakami, Restle, & Ziemann, in press). The *t*-contrast map of the group data of viewing speech-related lip movements vs. listening to speech (left MOG) was also subjected to a one-sample *t*-test. Activation was considered significant if consisting of >40 contiguous voxels and $P<0.01$ FWE-corrected. This resulted in MNI coordinates of $x=-44$, $y=-74$, $z=6$; (unpublished data). The MNI coordinates of the individual TBS sites over the left pIFG and MOG are provided in Fig. 1C and Table 1.

Table 1
MNI coordinates of individual stimulation sites.

pIFG			**MOG**		
x	***y***	***z***	***x***	***y***	***z***
−44	10	18	−44	−74	6
−48	8	18	−44	−74	6
−48	8	20	−44	−76	8
−50	8	20	−46	−72	10
−50	10	12	−48	−78	4
−50	10	22	−48	−82	10
−50	12	16	−50	−76	4
−52	8	20	−50	−76	6
−52	8	20	−50	−78	6
−56	4	22	−50	−78	6
−54	4	16			
Means (±SEM)					
−50.4±0.7	**8.2±0.5**	**18.5±0.6**	**−47.4±0.6**	**−76.4±0.6**	**6.6±0.5**

2.6. *Statistical analysis*

The data was analyzed using SPSS for Windows, version 19.0 (IBM statistics). In the main experiment the mean percentage of correctly pronounced syllables (i.e., repetition accuracy) was analyzed using a four-way repeated measures analysis of variance (rmANOVA) with TBS Type (iTBS vs. cTBS vs. imTBS), Time (before TBS vs. after TBS), Repetition (second repetition vs. fourth repetition) and Length (sentences with 8–10 syllables vs. sentences with 11–13 syllables) as within subject factors. Length was included to identify possible effects of TBS on a verbal working memory component during speech repetition (Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004).

The repetition accuracy data of the control experiment (iTBS of MOG) were compared with those of the main experiment (iTBS of pIFG) by using a mixed ANOVA with Time (before iTBS vs. after iTBS) as within-subject factor and iTBS Site (pIFG vs. MOG) as between-subject factor. Length and Repetition were not considered because there were no significant interactions of these factors in the main experiment (see Results).

In case of a significant interaction of the main effects, post hoc paired *t*-tests Bonferroni-corrected for multiple comparisons were performed. In all tests, a value of $p<0.05$ was considered to be statistically significant.

3. Results

No subject reported any adverse effect during or after the experiments.

3.1. *Main experiment (iTBS, cTBS and imTBS of the left pIFG)*

Eleven subjects participated in the main experiment. The three TBS sessions (iTBS, cTBS, imTBS) were separated by 7 day (in the case of two subjects, 9 day) and the order of TBS type was pseudorandomized.

The four-way rmANOVA of repetition accuracy demonstrated significant main effects of Time ($F_{(1,10)}=27.83$, $p=0.0004$), Length ($F_{(1,10)}=72.60$, $p<0.0001$) and Repetition ($F_{(1,10)}=95.41$, $p<0.0001$) but not TBS Type ($F_{(2,20)}=0.66$, $p=0.53$), indicating that the amount of correctly imitated syllables improved with repetition and shorter sentences. In addition, there was a significant interaction TBS Type*Time

($F_{(2,20)}=10.09$, $p=0.0009$), while the interactions of interest, namely TBS Type*Length*Time, TBS Type*Repetition*Time, and TBS Type*Length * Repetition*Time were all non-significant (all $p>0.15$). Post hoc paired *t*-tests revealed that iTBS ($p=0.0002$) and imTBS ($p=0.0045$) but not cTBS ($p=0.59$) were associated with improvement in repetition accuracy (Fig. 2A). In addition, the changes in repetition accuracy were different from each other between all TBS Types (all $p<0.05$), with iTBS inducing a stronger improvement than imTBS (Fig. 2B).

3.2. Control experiment (iTBS of the left MOG)

Ten subjects participated in the control experiment (three had also participated in the main experiment). The control experiment was performed ~5 months after the main experiment and was specifically designed to clarify (1) whether the TBS Type*Time interaction in the main experiment was caused by a facilitating effect of iTBS on repetition accuracy, or a disrupting effect of cTBS, or both, and (2) to demonstrate topographic specificity of the findings in the main experiment.

The two-way mixed ANOVA of repetition accuracy demonstrated a significant main effect of Time ($F_{(1,19)}=21.09$, $p=0.0002$) and of the interaction between iTBS Site and Time ($F_{(1,19)}=10.03$, $p=0.0051$). The interaction was explained by a lack of change of iTBS over MOG on repetition accuracy ($p=0.37$) compared to significant improvement after iTBS over pIFG in the main experiment (see above, $p=0.0002$; Fig. 3A, B).

4. Discussion

The present study was designed to examine the role of the left pIFG during sensorimotor integration of speech processing by investigating the modulating effects of TBS on speech repetition accuracy of auditory-presented foreign language (Japanese) sentences. Speech repetition accuracy significantly improved after iTBS of the left pIFG and, to a lesser extent, after imTBS, whereas no change occurred after cTBS of pIFG. In contrast, no significant change of speech repetition accuracy was observed after iTBS of MOG. These findings allow two principal conclusions: (1) the modulating effects of TBS are topographically specific because they occurred with iTBS of pIFG but not iTBS of MOG (a control area not involved in perception or repetition of auditory-presented speech); (2) the main experiment lacked a true control condition because all three sessions involved real TBS; therefore, the results of the main experiment could be interpreted as indicating a facilitating effect of iTBS and imTBS or a disruptive effect of cTBS on repetition accuracy; this ambiguity was solved by the control experiment where repetition accuracy did not change after iTBS of MOG, indicating that iTBS and imTBS of pIFG truly facilitated speech repetition accuracy, while cTBS of pIFG was not effective.

What aspect of language processing, e.g., working memory, imitative ability, phonological processing, or the translation from phonological perception to motor articulation was facilitated by iTBS of the left pIFG cannot be distinguished by the presented experimental data. Yet, we showed recently in an independent set of yet unpublished experiments that cTBS of the left pIFG increased the error rates of repetition of auditory-presented syllables ('Ba', 'Da', 'Ga', 'Ka', 'Pa', 'Ta') and of pseudo-words, while repetition of native (German) sentences remained unaffected when compared to cTBS of a control area, the left MOG. These results indicate specific disruption of phonological processing (syllables and pseudo-words) by cTBS of left pIFG. Taken together, these data provide evidence for the notion that the left pIFG as part of the dorsal auditory stream is involved in phonological processing aspects of speech production (Hickok & Poeppel, 2004, 2007). Perception and repetition of native sentences

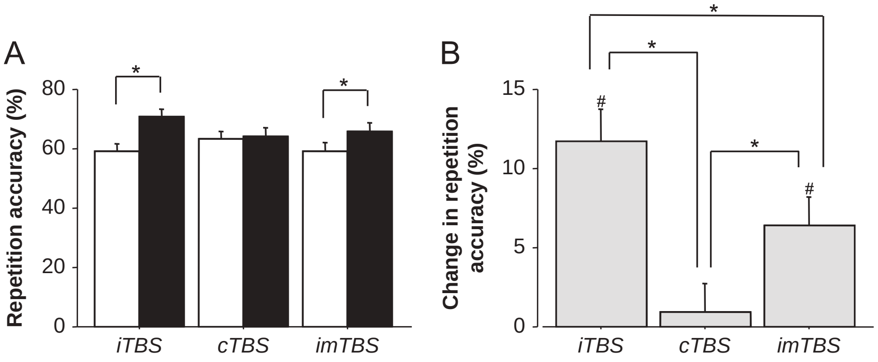

Fig. 2. Speech repetition accuracy in the main experiment. (**A**) Repetition accuracy pre (white bars) versus post TBS (black bars) improved significantly after iTBS and imTBS, whereas no significant change occurred after cTBS (paired *t*-tests, $^{*}p<0.005$). (**B**) Change in repetition accuracy (post-pre TBS). ITBS and imTBS resulted in significant improvement (one-sample *t*-tests, $^{\#}p<0.005$) and all changes in all TBS conditions were significantly different from each other (paired *t*-tests, $^{*}p<0.05$). Error bars are S.E.M.

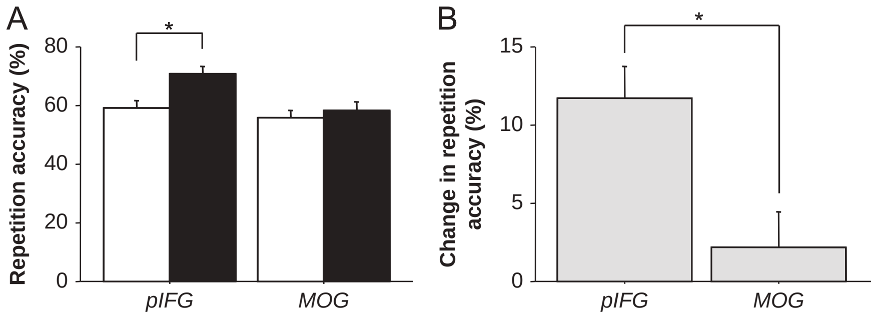

Fig. 3. Speech repetition accuracy (control experiment). (**A**) Repetition accuracy (white bars, pre iTBS; black bars, post iTBS) did not change after iTBS of MOG (see for comparison data from the main experiment: significant improvement of repetition accuracy after iTBS of pIFG). (**B**) Change in repetition accuracy (post-pre TBS). ITBS of MOG (control experiment) resulted in significantly less change compared to iTBS of pIFG (main experiments, unpaired *t*-test, $^{*}p=0.005$). Error bars are S.E.M.

were not altered, largely excluding the possibility that modulation of working memory played a significant role in the TBS effects of the left pIFG. Furthermore, this lack of an effect of pIFG stimulation on native sentences is compatible with the notion that processing of lexical and semantic material occurs in the ventral auditory stream (Hickok & Poeppel, 2004, 2007; Rauschecker, 1998; Scott, 2005). These data are convergent with those of the present study as they suggest that it is the phonological processing and/or the translation of phonological input to motor articulatory output for speech repetition of a foreign language that is enhanced by iTBS of the left pIFG. More specifically, our data support the notion that the left pIFG plays a causal role in perceptual-motor translation not only for arm/hand motor imitation (Catmur et al., 2009; Heiser et al., 2003) but also speech repetition.

This is compatible with previous findings that auditory mirror neurons exist in area F5 of the monkey (Kohler et al., 2002) and that the activation of the left pIFG during listening to speech correlates with an increase in the excitability of articulatory motor representations in M1 (Watkins & Paus, 2004), suggesting a direct link between pIFG activity and perceptual-motor translation.

In contrast to the previous studies (Catmur et al., 2009; Heiser et al., 2003) we demonstrated facilitating rather than disruptive effects of TBS on repetition accuracy. Most likely this is explained by the fact that we used iTBS in the offline mode, which induces long term potentiation-like increase of excitability when applied to M1 (Huang et al., 2005; Suppa et al., 2008), and was associated with facilitation of behavioral performance, e.g., improved tactile discrimination after iTBS of the somatosensory cortex (Ragert, Franzkowiak, Schwenkreis, Tegenthoff, & Dinse, 2008) or enhanced motor learning after iTBS of M1 (Teo, Swayne, Cheeran, Greenwood, & Rothwell, 2011). It can be speculated that facilitatory iTBS in the present study enhanced the excitability of the motor phonological system in pIFG as part of the auditory dorsal stream, including putative mirror neurons located within pIFG, and thereby, through the known effective connectivity from pIFG to M1 (Eickhoff, Heim, Zilles, & Amunts, 2009; Murakami, Restle, & Ziemann, in press) facilitated M1 activity for the intended articulatory output during speech repetition.

Of note, imTBS of pIFG also facilitated speech repetition accuracy although it did not change M1 excitability (Huang et al., 2005), and cTBS of pIFG did not change speech repetition accuracy although it decreased M1 excitability (Huang et al., 2005; Suppa et al., 2008). These apparent discrepancies strongly suggest that the effects of the different TBS protocols on M1 excitability do not directly translate to behavioral effects of TBS applied to areas other than M1. This is supported by previous studies. For example, iTBS of the left dorsal premotor cortex improved sequential reaction time of the right hand, while cTBS had no effect when compared to sham stimulation (Stinear et al., 2009). Given the fact that, in the present experiments, we were unable to demonstrate a disruptive TBS effect on speech repetition accuracy, it cannot be entirely ruled out that the left pIFG plays only a supporting rather than an essential role in perceptual-motor translation for speech repetition. In the face of other recent experimental data from our group the most likely conclusion is, however, that the human left pIFG is essential for phonological processing of language to support perceptual-motor translation for speech repetition.

In more general terms, our data are in agreement with several models of speech production that assigned the left pIFG a pivotal role in this process. For example, a recent generative model of speech production proposed that parts of Broca's area and the posterior part of the superior temporal sulcus are involved in predicting the auditory consequences of articulations, and in generating and maintaining a forward model of expected speech, which can be used as a template for auditory prediction and mismatch correction, a capacity of particular importance for learning a new language (Price, Crinion, & Macsweeney, 2011). The 'directions into velocities of articulators' model assumes parallel processing of forward predictions and motor commands, and feedback of prediction errors detected in the somatosensory and auditory cortices directly to the motor output system rather than to the higher level cortical representations of motor plans and somatosensory and auditory associations (Guenther, Ghosh, & Tourville, 2006). Finally, a recent 'state feedback control' model of speech production, which was largely built on the previous models proposed a sensorimotor integration along the speech-related auditory dorsal stream in which sensorimotor interaction primarily supports speech production by emphasizing the role of motor effects on perception (Hickok et al., 2011). Our data do not allow differentiation between these models but affirm the important role that the left pIFG plays in perceptual-motor translation of speech.

To the best of our knowledge, the present findings demonstrate for the first time facilitating effects of non-invasive brain stimulation in a speech repetition task. In addition, our results provide direct evidence for an essential role of the left pIFG for perceptual-motor translation during speech perception. Speech repetition not only represents a useful training method in acquiring new languages but also forms an integral part in therapeutic training (Lee, Fowler, Rodney, Cherney, & Small, 2010). Our data provide a rationale for combining speech repetition with facilitatory non-invasive brain stimulation over the left-hemispheric pIFG to enhance rehabilitative treatment effects in aphasia after cerebral stroke (Baker, Rorden, & Fridriksson, 2010; Fridriksson, Richardson, Baker, & Rorden, 2011; Schlaug, Marchina, & Wan, 2011; Szaflarski et al., 2011).

In conclusion, our results reinforce latest findings about a causal role of the left-hemispheric human pIFG in imitation. We have demonstrated that TBS of pIFG can modulate speech repetition accuracy in a stimulation type and stimulation site specific manner. Findings are supportive for a key role of pIFG in the putative human mirror neuron system, and thus, in the sensorimotor integration of speech processing. Combining speech repetition with facilitatory TBS of pIFG may bear significant potential for speech therapy during rehabilitation training and treatment.

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