Perturbation of the left inferior frontal gyrus triggers adaptive plasticity in the right homologous area during speech production

Gesa Hartwigsen[a,b,c,1], Dorothee Saur[b], Cathy J. Price[d], Stephan Ulmer[e,f], Annette Baumgaertner[a,g], and Hartwig R. Siebner[a,h]

[a]Department of Neurology, Christian-Albrechts-University Kiel, 24105 Kiel, Germany; [b]Language and Aphasia Laboratory, Department of Neurology, University of Leipzig, 04103 Leipzig, Germany; [c]Department of Psychology, Christian-Albrechts-University Kiel, 24118 Kiel, Germany; [d]Wellcome Trust Centre for Neuroimaging, University College London, London WC1N 3BG, United Kingdom; [e]Department of Neuroradiology, Medical Radiological Institute, 8001 Zurich, Switzerland; [f]Institute of Neuroradiology, University Hospital Schleswig-Holstein, 24105 Kiel, Germany; [g]Department of Speech and Language Pathology, Hochschule Fresenius Hamburg, 20148 Hamburg, Germany; and [h]Danish Research Center for Magnetic Resonance, Copenhagen University Hospital Hvidovre, 2650 Hvidovre, Denmark

Edited by Michael S. Gazzaniga, University of California, Santa Barbara, CA, and approved August 28, 2013 (received for review May 29, 2013)

The role of the right hemisphere in aphasia recovery after left hemisphere damage remains unclear. Increased activation of the right hemisphere has been observed after left hemisphere damage. This may simply reflect a release from transcallosal inhibition that does not contribute to language functions. Alternatively, the right hemisphere may actively contribute to language functions by supporting disrupted processing in the left hemisphere via interhemispheric connections. To test this hypothesis, we applied off-line continuous theta burst stimulation (cTBS) over the left inferior frontal gyrus (IFG) in healthy volunteers, then used functional MRI to investigate acute changes in effective connectivity between the left and right hemispheres during repetition of auditory and visual words and pseudowords. In separate sessions, we applied cTBS over the left anterior IFG (aIFG) or posterior IFG (pIFG) to test the anatomic specificity of the effects of cTBS on speech processing. Compared with cTBS over the aIFG, cTBS over the pIFG suppressed activity in the left pIFG and increased activity in the right pIFG during pseudoword vs. word repetition in both modalities. This effect was associated with a stronger facilitatory drive from the right pIFG to the left pIFG during pseudoword repetition. Critically, response became faster as the influence of the right pIFG on left pIFG increased, indicating that homologous areas in the right hemisphere actively contribute to language function after a focal left hemisphere lesion. Our findings lend further support to the notion that increased activation of homologous right hemisphere areas supports aphasia recovery after left hemisphere damage.

transcranial magnetic stimulation | dynamic causal modeling | virtual lesion | Broca's area

Numerous functional imaging studies have reported increased language-related activation of the right inferior frontal gyrus (IFG) in aphasic patients with left hemisphere damage (1–3). However, it is still a matter of debate whether the temporary recruitment of homologous right hemisphere areas after left hemisphere stroke is essential for language performance (i.e., adaptive plasticity) (2–4) or represents "maladaptive" overactivation resulting from interhemispheric disinhibition after left hemisphere infarction (5–7).

In the present study, we investigated the adaptive short-term plasticity that supports speech production after disruption to left frontal language areas. We induced neural activity related to phonetic encoding by comparing reading and auditory repetition of pseudowords and familiar words. We expected to see common effects in both visual and auditory modalities at the level of phonetic encoding, but not at the sensory input level (8). We applied transient virtual lesions in healthy volunteers to test whether an up-regulation of right hemisphere homologous language regions after a focal perturbation of left hemisphere language areas reflects reduced transcallosal inhibition from the left hemisphere to the right hemisphere or an active right hemisphere contribution that helps restore task function. We combined focal off-line continuous theta burst stimulation (cTBS) before a task with dynamic causal modeling (DCM) of MRI data. Virtual lesions were applied to the left posterior IFG (pIFG), an area previously associated with phonetic encoding during speech production (9), or to the anterior IFG (aIFG) as the control area. We then investigated cTBS-induced changes in behavior and effective connectivity between the left and right hemispheres.

We hypothesized that cTBS of the left pIFG, but not the aIFG, would suppress activity related to phonetic encoding in the targeted area, which in turn should result in up-regulation of the homologous right hemisphere region during the repetition of pseudowords as opposed to real words, independent of the modality used for stimulus presentation (i.e., auditory or visual stimulus presentation). The adaptive up-regulation of the homologous right pIFG should enable the system to restore task function (10, 11). If the up-regulation of the right hemisphere reflects mainly reduced transcallosal inhibition from the left hemisphere to the right hemisphere, then we would expect to see a cTBS-induced decrease in the inhibitory drive from the left pIFG to the right pIFG. In contrast, if the task-specific up-regulation of the right pIFG is beneficial, then right IFG activation or connectivity should correlate with faster or more accurate behavioral responses.

Applying cTBS in healthy subjects allowed us to induce a focal disruption of left IFG activity and to investigate immediate

Significance

The role of the right hemisphere in aphasia recovery is unclear. We demonstrate that a virtual lesion of left inferior frontal gyrus (IFG) decreased activity in the targeted area and increased activity in the contralateral homologous area during pseudoword repetition. This was associated with a stronger facilitatory drive from the right IFG to the left IFG. Importantly, responses became faster with increased influence of the right IFG on the left IFG. Our results shed new light on the dynamic regulation of interhemispheric interactions in the human brain. Particularly, these findings are of potential importance for understanding language recovery after left-hemispheric stroke, indicating that homologous right hemisphere areas actively contribute to language function after a left hemisphere lesion.

Author contributions: G.H., A.B., and H.R.S. designed research; G.H., D.S., and S.U. performed research; G.H., D.S., C.J.P., S.U., and H.R.S. analyzed data; and G.H., D.S., C.J.P., S.U., A.B., and H.R.S. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

[1]To whom correspondence should be addressed. E-mail: hartwigsen@psychologie.uni-kiel.de.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1310190110/-/DCSupplemental.

effects on task-related activation that are not confounded by long-term recovery. The cTBS intervention induces a lasting suppression of neuronal excitability in the targeted area. This conditioning approach is somewhat analogous to acute stroke, because cTBS might give rise to an acute adaptive reorganization within the nonaffected functional loops of the network to compensate for the cTBS-induced suppression of neuronal activity (12). Our comparison of cTBS over two distinct subregions within the IFG (i.e., pIFG vs. aIFG) enabled us to test the anatomic specificity of the lesion effect. We also included an ineffective "sham" cTBS session to investigate baseline activity in the left pIFG and right pIFG. Details of the experimental procedures are shown in Fig. 1.

Results

cTBS of the Left pIFG Decreases Activity in the Targeted Area and Increases Task-Related Activity in the Right pIFG During Pseudoword vs. Word Repetition. We first investigated the effects of cTBS over the pIFG vs. the aIFG on overt pseudoword repetition of visually and auditorily presented stimuli after eliminating the influence of semantic content by directly contrasting pseudoword repetition to word repetition. The modality-independent conjunction of auditorily and visually presented pseudowords vs. words after sham cTBS revealed strong activation in the left pIFG [$x, y, z = -51, 6, 12$; T = 4.07; Z = 3.96; $P = 0.004$, familywise error (FWE)-corrected in the left pIFG region of interest (ROI); Fig. 2*A*]. Table S1 provides details on further activation peaks outside our predefined ROIs in the left and right pIFG. After cTBS over the aIFG, the modality-independent conjunction of pseudoword vs. word repetition again showed strong activation in the left pIFG ($x, y, z = -51, 8, 12$; T = 4.01; Z = 3.94; $P = 0.01$, FWE-corrected in the left pIFG ROI; Fig. 2*B*). In contrast, there was no significant activation in the targeted left pIFG after cTBS of the left pIFG during pseudoword vs. word repetition, even after the threshold was lowered to $P < 0.01$ uncorrected (Fig. 2*C*).

Finally, we directly contrasted the effects of cTBS over the aIFG vs. the pIFG on modality-independent pseudoword vs. word repetition. Relative to cTBS of the aIFG, cTBS of the pIFG significantly decreased pseudoword activity in the targeted area ($x, y, z = -54, 12, 8$; T = 4.11; Z = 4.00; $P = 0.008$, FWE-corrected in the left pIFG ROI; Fig. 2*D*). The parameter estimates for the different cTBS conditions are summarized in Fig. 2*E*. Note that the comparison of cTBS over the aIFG vs. the pIFG on word repetition did not reveal any significant changes in task-related activation.

In addition, we investigated the effects of effective and sham cTBS over the pIFG vs. the aIFG on task-related activity in the right pIFG. We found no significant activation in the right pIFG during pseudoword vs. word repetition after either sham cTBS over the pIFG or effective cTBS over the aIFG (Fig. 3 *A* and *B*). In contrast, after cTBS over the left pIFG, we found increased activation in the contralateral right homologous area during pseudoword vs. word repetition ($x, y, z = 57, 9, 9$; T = 4.95; Z = 4.78; $P = 0.001$, FWE-corrected in the right pIFG ROI; Fig. 3*C*). Finally, a direct comparison of areas showing stronger activation increases after cTBS over the pIFG vs. the aIFG during pseudoword vs. word repetition again indicated a strong up-regulation of the right pIFG ($x, y, z = 54, 12, 8$; T = 4.54; Z = 4.49; $P = 0.001$, FWE-corrected in the right pIFG ROI; Fig. 3*D*). The parameter estimates for the different cTBS conditions are summarized in Fig. 3*E*. In addition, there was increased task-related activation in the bilateral middle temporal gyrus (MTG), right superior temporal gyrus (STG), and right middle frontal gyrus (MFG) (Table S1).

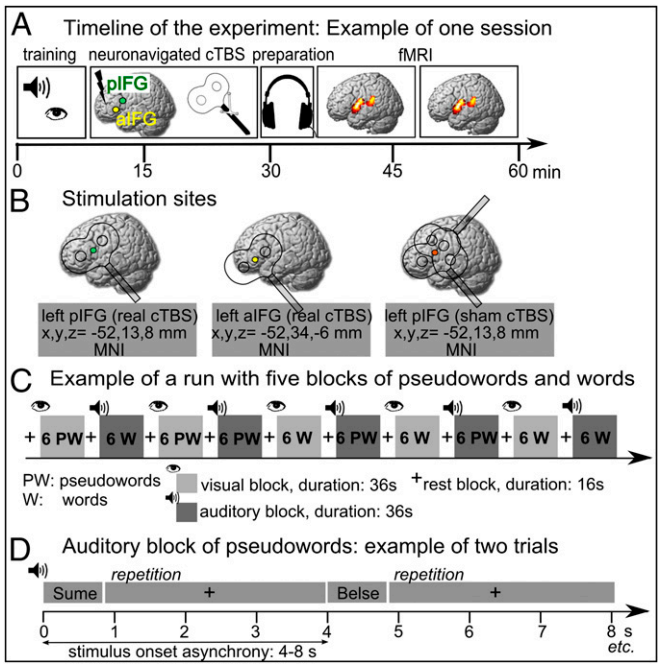

Fig. 1. Experimental design. (*A*) Timeline. The experiment consisted of three sessions. Each session started with a short training section. Afterward, real or sham cTBS was applied to either the aIFG or the pIFG. Before the two fMRI runs, subjects were equipped with earphones and a microphone. (*B*) Stimulation sites for the left aIFG and the pIFG were from a previous study demonstrating a functional anatomic subdivision of the IFG (27). (*C*) Example of a run. Each session consisted of two runs each with five blocks of pseudowords and words. Each run started and ended with a rest block. Block duration was set at 36 s, and blocks were separated by a 16-s rest, for a total duration of ~9 min per run. At the end of each rest period, a visual nonverbal cue indicated the next block. Cues consisted of a symbol of either an eye (indicating that the next block would contain visually presented stimuli) or a loudspeaker (indicating that the next block would contain auditorily presented stimuli) in a red or blue box. Blue boxes indicated that the next block would contain pseudowords; red boxes indicated real word presentation. Stimulus type (pseudowords or words) and modality (auditory or visual stimulus presentation) were kept constant during each block to ensure a constant cognitive set. Cue onset was jittered such that the cue appeared 9.5–12.5 s after the rest block onset and remained on the screen for 2.5 s. After stimulus presentation, subjects overtly repeated the respective stimulus. (*D*) Example of an auditory block of pseudowords. Each block contained six pseudowords or words separated by a randomly assigned stimulus onset asynchrony of 4–8 s. The order of runs, stimulus blocks, and presentation modalities was pseudorandomized across subjects to avoid repeating the same stimulus condition.

cTBS of the Left pIFG Increases the Facilitatory Drive from the Right pIFG to the Left pIFG During Pseudoword Repetition. We used DCM to test whether the up-regulation of the right pIFG during pseudoword repetition after suppression of the left pIFG by cTBS reflected a release of the right hemisphere from the inhibitory influence of the left hemisphere. If this were the case, then we would expect to see a decrease in the inhibitory task-related influence of the left pIFG on the right pIFG after cTBS of the left pIFG (Fig. 4*A*). Our results do not support this hypothesis, however. Among the nine models tested, variational Bayesian model selection identified model 2 with driving input to the left pIFG and modulation of the facilitatory connection from the right pIFG to the left pIFG by cTBS of the left pIFG as the winning model across subjects (Fig. 4*B*). This model had an exceedance probability of 73% (Fig. 4*C*), compared with exceedance properties of ≤11% for all of the other models.

Fig. 4*B* shows the winning model with the mean parameter estimates that were significantly different from zero. The only parameter values that survived Bonferroni correction for multiple comparisons were the driving input to the left pIFG (mean estimate, +0.12; $P = 0.001$), the intrinsic connection from the left pIFG to the right pIFG (mean estimate, +0.49; $P = 0.0001$) and the modulation of the connection from the right pIFG to the left pIFG by cTBS of the left pIFG (mean estimate, +0.65; $P = 0.001$) (Table 1). Note that cTBS over the aIFG did not significantly influence the connection from the right pIFG to the left pIFG

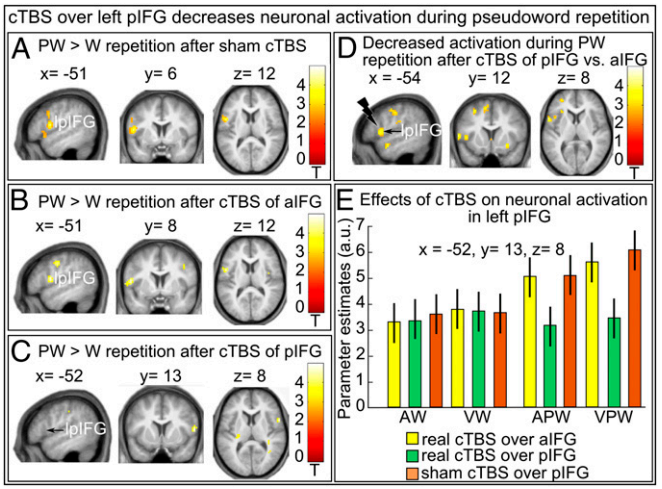

Fig. 2. Effects of cTBS on task-related activity in the left pIFG. Modality-independent conjunctions for pseudoword (PW) > word (W) repetition across auditorily and visually presented stimuli are shown. (*A–C*) Significant activation peaks after sham cTBS (*A*) or cTBS (*B*) over the left aIFG or cTBS over the left pIFG (*C*). (*D*) cTBS-induced activation changes during pseudoword repetition after cTBS over the left pIFG vs. the aIFG. (*E*) Parameter estimates (with 95% CIs) of the peak voxels at the stimulation site in the left pIFG . All comparisons were thresholded at $P < 0.001$ uncorrected and corrected for multiple comparisons using small volume corrections ($P < 0.05$, FWE-corrected) within our predefined regions of interest in the left pIFG. Spatial references are given in MNI space. AW, auditory words; VW, visual words; APW, auditory pseudowords; VPW, visual pseudowords.

($P = 0.77$). The modulatory influence of cTBS over the left pIFG on the connection between the right and left pIFG was facilitatory, corresponding to an increase in connectivity of >1,500% relative to the intrinsic (weak positive) connection strength. A direct comparison of the parameter estimates for cTBS of the pIFG vs. the aIFG confirmed a stronger facilitatory effect for cTBS of the pIFG than of the aIFG ($T = 4.12$, $P < 0.001$, paired t test).

In another analysis, we explored the modulation of the connections between the left and right pIFG by pseudoword vs. word repetition separately for cTBS over the aIFG vs. the pIFG. After cTBS over the aIFG, Bayesian model selection identified the first model with driving input to the left pIFG and modulation of the connection from the left to right pIFG by pseudoword vs. word repetition as the winning model (Fig. S1*A* and Table S2). This model had a relatively low exceedance probability of 45%. Note that the increase in the facilitatory drive from the left pIFG to the right pIFG was not significant for either pseudoword or word repetition (Table S2).

In contrast, after cTBS over the left pIFG, the most probable model identified by Bayesian model selection was the second model with driving input to the left pIFG and modulation of the connection from the right pIFG to the left pIFG by pseudoword vs. word repetition (Fig. S1*B* and Table S3). This model had an exceedance probability of 65%. Of note, the increase in the facilitatory drive from the right pIFG to the left pIFG was highly significant for pseudoword repetition, but not for word repetition (Table S3). Taken together, these results provide further evidence for a significant task-specific facilitatory modulation of the connection from the right pIFG to the left pIFG after cTBS over the left pIFG during pseudoword repetition. This is contrary to the hypothesis that cTBS over the left pIFG would decrease inhibition from the left pIFG to the right pIFG.

Effect of cTBS and Up-Regulated Right Hemispheric Activation on Task Performance. Subjects' mean speech onset times, response durations, and error rates for all conditions are reported in Table S4. For each dependent measure, a three-way repeated-measures ANOVA was conducted using the within-subject factors task (pseudoword vs. word repetition), modality (auditory vs. visual stimulus presentation), and cTBS (aIFG vs. pIFG vs. sham cTBS). A trend for a main effect of task ($P = 0.07$) indicated increased speech onset times for pseudowords relative to words independent of the cTBS condition or modality; however, there were no significant interactions between the different conditions and speech onset times (all $P > 0.13$).

There were no effects of condition on either response durations (all $P > 0.21$) or error rates (all $P > 0.25$); however, the individual mean speech onset times for pseudoword repetition were significantly negatively correlated with the individual facilitatory drive from the right pIFG to the left pIFG after cTBS of the left pIFG ($r = -0.63$, $P = 0.007$, two-tailed test; Fig. 4*D*). This relationship was significantly greater after cTBS of the pIFG relative to sham cTBS ($r_{cTBS\ -\ sham} = -0.75$, $P = 0.001$). There was no significant correlation between speech onset times for words after cTBS of the pIFG ($r = -0.32$, $P = 0.13$) or after sham cTBS (pseudowords: $r = 0.14$, $P = 0.59$; words: $r = 0.20$, $P = 0.44$) or cTBS of the left aIFG (pseudowords: $r = -0.31$, $P = 0.13$; words: $r = -0.27$, $P = 0.30$).

Discussion

In this study, we used cTBS in healthy volunteers to investigate mechanisms of interhemispheric interactions during speech production between homologous areas in the frontal cortex. In particular, we addressed the question of whether a focal virtual lesion in the left IFG simply releases the homologous right IFG from transcallosal inhibition, with no benefit on performance, or results in an adaptive up-regulation of the right hemisphere with beneficial effects on performance.

We found that relative to cTBS over the aIFG, a focal perturbation of the left pIFG decreased activity in the targeted area and increased activity in the contralateral homologous area during a simple pseudoword repetition task. Effective connectivity analyses showed that cTBS increased the facilitatory drive from the right

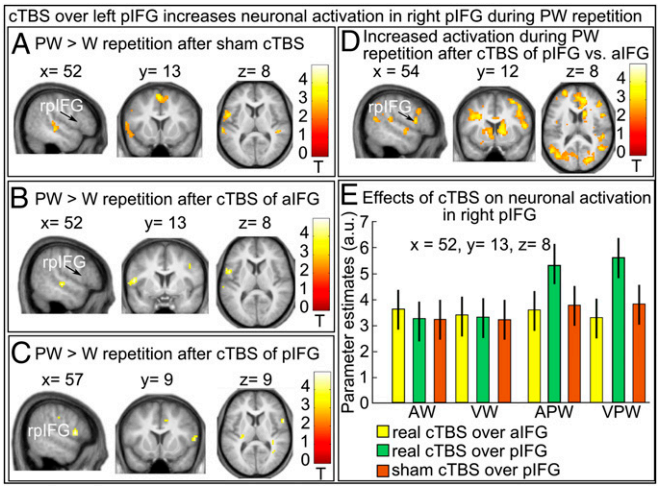

Fig. 3. Effects of cTBS on task-related activity in the right pIFG. Modality-independent conjunctions for pseudoword (PW) > word (W) repetition across auditorily and visually presented stimuli are shown. (*A–C*) Significant activation peaks after sham cTBS (*A*) or cTBS (*B*) over the left aIFG or cTBS over the left pIFG (*C*). (*D*) cTBS-induced activation changes during pseudoword repetition after cTBS over the left pIFG vs. the aIFG. (*E*) Parameter estimates (with 95% CIs) of the peak voxels in the right pIFG. All comparisons were thresholded at $P < 0.001$ uncorrected and corrected for multiple comparisons using small volume corrections ($P < 0.05$, FWE-corrected) within our predefined regions of interest in the right pIFG. Note the absence of significant activation in the right pIFG after sham cTBS or cTBS over the aIFG even with reduction of the threshold to $P < 0.01$ uncorrected. Spatial references are given in MNI space. AW, auditory words; VW, visual words; APW, auditory pseudowords; VPW, visual pseudowords.

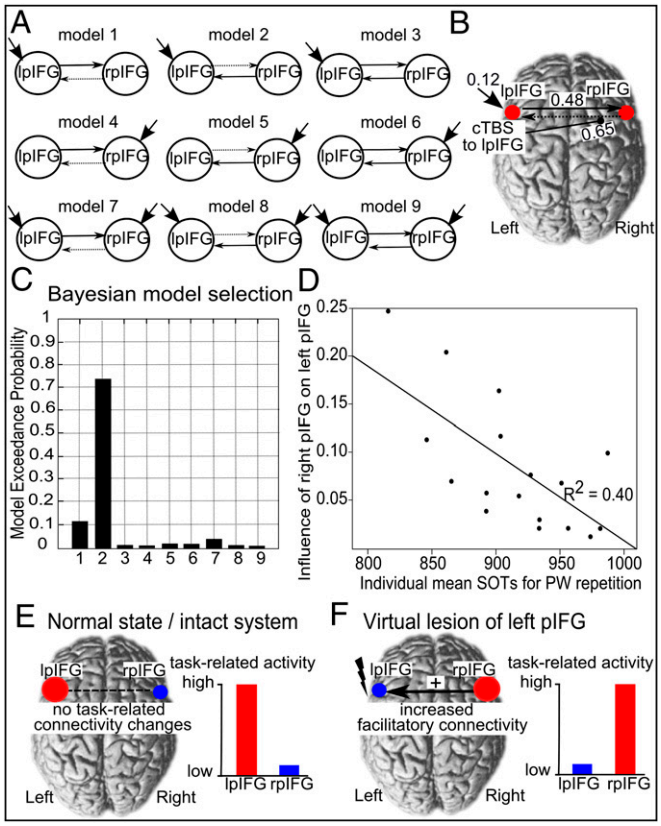

Fig. 4. DCM analyses. (*A*) The nine different DCM models tested. The models differ with respect to the driving input regions (fat solid arrows) and the external modulations by cTBS over the pIFG vs. the aIFG (solid arrows between regions). All models had the same intrinsic connections from the left pIFG to the right pIFG and from the right pIFG to the left pIFG (dotted arrows). (*B*) The winning model, with driving input to the left pIFG and modulation of the connection from the right pIFG to the left pIFG by cTBS of the left pIFG. Mean parameter estimates are given for the significant intrinsic connection from the left pIFG to the right pIFG (solid arrow), the driving input, and the cTBS modulation. (*C*) Model exceedance probabilities for all models compared with variational Bayesian model selection. (*D*) Significant correlation between the individual modulation of the connection from the right pIFG to the left pIFG after cTBS over the left pIFG and the individual mean speech onset times (SOTs) for pseudoword repetition. (*E* and *F*) Illustration of cTBS-induced changes in task-related activity and effective connectivity. (*E*) The left pIFG shows increased task-related activity during pseudoword vs. word repetition after sham cTBS or cTBS of the aIFG. cTBS does not influence the task-related connectivity between the left pIFG and the right pIFG (dotted arrow). (*F*) cTBS of the left pIFG decreases task-related activity in the targeted area and increases task-related activity in the contralateral homologous area. cTBS of the lpIFG is followed by increased facilitatory influence of the right pIFG on the left pIFG (solid arrow) during pseudoword repetition, which may help restore task function.

(nonlesioned) pIFG to the left (lesioned) pIFG without changing the influence of the left pIFG on the right pIFG. This is contrary to the prediction that the up-regulation of the right hemisphere after a focal perturbation of the left hemisphere reflects a reduction of the inhibitory transcallosal drive from the left hemisphere to the right hemisphere. Rather, our findings support the alternative hypothesis that an up-regulation in right pIFG activation or increased connectivity would contribute to language function. The evidence supporting this hypothesis is our observation of faster response times for pseudoword repetition with stronger connectivity from the right pIFG to the left pIFG after cTBS of the left pIFG. Thus, our behavioral and connectivity data suggest flexible, rapid adaptation of an interhemispheric balance during language production after a focal perturbation, indicating

Table 1. Mean parameter estimates for the winning model

Connection/parameter	Mean	SD	*t*	*P*
Intrinsic connections				
Left pIFG→right pIFG	0.4892	0.3755	5.37	0.0001*
Right pIFG→left pIFG	0.0399	0.2179	0.41	0.69
Driving input				
Left pIFG	0.1155	0.1243	3.82	0.001*
Modulation (by cTBS)				
Right pIFG→left pIFG after cTBS to pIFG	0.6522	0.5567	4.32	0.001*
Right pIFG→left pIFG after cTBS to aIFG	0.0489	0.6639	0.30	0.77

*Significant at $P < 0.05$, two-tailed, Bonferroni-corrected.

that cTBS can be used to change the functional weight between homologous areas.

Of note, the cTBS-induced short-term reorganization observed in this study was both functionally and anatomically specific. Focal cTBS selectively influenced task-related activity and effective connectivity during pseudoword repetition, but not during word repetition, when cTBS was applied over the left pIFG, but not over the aIFG. Our main findings are illustrated in a model in Fig. 4 *E* and *F*. This model predicts that without any disruptive cTBS effect, the left pIFG, but not the right pIFG, will show increased task-related activation during pseudoword repetition (indicated by the large red vs. small blue circles), but there is no significant task-related connectivity between the regions (Fig. 4*E*). In contrast, our model predicts a virtual lesion in the left pIFG (Fig. 4*F*) will result in decreased activity in the targeted left pIFG (indicated by the small blue circle) along with an adaptive up-regulation of the contralateral right pIFG (indicated by the large red circle), as well as an increase in the facilitatory drive from the right pIFG to the left pIFG.

That a cTBS-induced decrease in left IFG activity should result in an increase in adaptive activation in the contralateral homologous area may seem paradoxical. However, we would argue that the cTBS-induced lesion renders the left pIFG more sensitive to the influence of the right pIFG, as demonstrated by our effective connectivity analysis indicating that cTBS increased the facilitatory drive from the right pIFG to the left pIFG.

Some previous imaging studies suggested that the reported increase in right IFG activity after disruption of the left IFG might be a consequence of reduced transcallosal inhibition caused by the cTBS interference (13, 14); however, those studies did not allow for any causal interpretation on the direction of the effects. In this context, we wish to emphasize that our DCM analyses provide information on the direction of the interregional connections rather than implying nondirectional correlations (15). Had cTBS over the left pIFG decreased the inhibitory transcallosal drive from the left hemisphere to the right hemisphere, we would have expected to see reduced inhibitory modulation of the left pIFG on the right pIFG after cTBS over the left pIFG, but this was not the case in the present study. Rather, our winning model indicates a strong facilitatory influence of the right pIFG on the left pIFG in the presence of a dysfunctional left pIFG. Of note, the intrinsic (task-independent) connection from the right pIFG to the left pIFG of our winning model was not significant, and cTBS of the neighboring aIFG did not significantly modulate the influence of the right pIFG on the left pIFG. Moreover, we found no increased task-related activity in the right pIFG after sham cTBS. Taken together, these findings suggest that the right pIFG does not contribute to pseudoword repetition unless the left pIFG is perturbed with cTBS. We would argue that the cTBS-induced perturbation effect rendered the left pIFG more sensitive to the facilitatory influence from the right homologous area.

Note that the alternative model that assumed a modulatory influence of the left pIFG on the right pIFG (Fig. 4, model 1)

had a very low exceedance probability of 11%. Further analyses of the model parameters revealed no significant modulatory influence of cTBS over either the pIFG or the aIFG on the (positive) connection from the left pIFG to the right pIFG ($P = 0.21$ and $P = 0.44$, respectively). Taken together, these findings render the transcallosal hypothesis highly unlikely.

To date, few imaging studies have investigated short-term plasticity in the healthy language network. One study reported increased task-related activity during word recognition in the respective homologous, nontargeted area after repetitive transcranial magnetic stimulation (rTMS) of either the left or the right Wernicke's area (16). These activity increases were interpreted in terms of adaptive short-term compensation. Our results extend those of previous studies by demonstrating that the adaptive up-regulation of the nontargeted right hemisphere is associated with an increase in the facilitatory drive from the right hemisphere to the left hemisphere. This finding is consistent with other nonlanguage studies reporting increased activity in homologous right hemisphere areas after rTMS-induced disruption of left hemisphere areas (10, 11).

Based on this increase in activity, it has been claimed that the "neuronal challenge" induced by rTMS triggers compensatory short-term reorganization that calls on the homologous area in the nontargeted hemisphere. Engaging the contralateral homologous area helps preserve behavior by taking over the specific function of the left hemisphere (10). In concordance with previous studies, our results suggest that the right pIFG is able to allocate functional resources to restore task function. In this context, we wish to stress that rather than leading to a total loss of task function, rTMS induces mild dysfunction of the targeted area. Our results demonstrate that these effects are sufficient to influence task-related activity, connectivity, and behavior, as evidenced by the significant correlation between individual connectivity strength and speech onset time. Nevertheless, the individual extent of the rTMS-evoked lesion effect remains unclear. It would be of great interest to investigate whether a systematic variation of the rTMS intensity influences the extent of the virtual lesion effect.

We have determined the individual intensity threshold for inducing a virtual lesion effect in a previous study with application of rTMS during a language task (17). However, in the present study, we refrained from increasing the rTMS intensity because of the safety limits and possible side effects of the plasticity-inducing cTBS protocol. The high interindividual variability of rTMS-induced behavioral and functional effects is a widely debated issue. It has been argued that the individual responsiveness to plasticity-inducing rTMS protocols is determined by the individual anatomy or recruitment of certain interneuron networks (18), and thus the same rTMS protocol may result in improvement or deterioration of task function in different subjects. Consequently, the interindividual variability might be taken as a measure of the responsiveness to rTMS-induced effects. We would argue that although the average speech onset times among the different cTBS conditions were not significantly different in our study, subjects selectively benefited from a task-specific increase in the connection strength from the right pIFG to the left pIFG after cTBS of the pIFG during pseudoword repetition. Of note, this relationship was significantly greater for cTBS of the pIFG relative to sham cTBS. In other words, subjects with a stronger increase in the functional influence from the right pIFG to the left pIFG after cTBS of the left pIFG showed more flexible short-term adaptation (i.e., shorter speech onset times after cTBS of the pIFG relative to sham cTBS) compared with those subjects with a relatively weaker increase in the functional influence from the right pIFG to the left pIFG.

Based on our results, we argue that after a cTBS-induced lesion of the left pIFG, the right pIFG supports the remaining functions of the left pIFG and increases its functional influence on the left pIFG. This suggests that after a focal perturbation of the left pIFG, both regions contribute to restoration of task function. With respect to the implications for stroke-induced lesions, we hypothesize that these mechanisms most likely apply to incomplete lesions of the left IFG in the acute phase after stroke. Consequently, we would argue that the right pIFG has the potential to support language functions of the left hemisphere. This is supported by the notion that for some language functions, the right hemisphere performs coarser computations for the same general processes (19). Specifically, it has been demonstrated that in the healthy brain, the right pIFG is engaged in the perceptual processing of word stimuli (20) and the processing of paralinguistic features, such as emotional prosody (21). These functions might be relevant for supporting left hemisphere functions after a lesion. This suggests that, at least in the initial stages of adaptive compensation, the brain is able to flexibly recruit homologous brain regions. Accordingly, it has been argued that, after a left hemisphere lesion, the right hemisphere language areas can become more finely tuned to perform tasks normally better performed by the left hemisphere (19).

Interestingly, when directly contrasting the effects of cTBS on the left pIFG vs. the aIFG on pseudoword repetition, we found increased activation in a network of regions encompassing the right pIFG, bilateral MTG, right STG, and right MFG. This suggests that cTBS may give rise to an acute adaptive reorganization within the nontargeted functional loops of the networks to compensate for the rTMS-induced suppression of neuronal activity in those components of the network that have been perturbed with rTMS (12). The observed up-regulation of left and right temporal regions is consistent with previous studies reporting increased activity in the bilateral MTG and right STG, as well as in inferior frontal regions, during language processing after application of rTMS over Wernicke's area (16).

An adaptive up-regulation of the right pIFG after a focal lesion of the left pIFG appears to be in discordance with the results of previous studies showing improved language recovery in aphasic patients after suppression of neuronal processing in the nonlesioned right IFG with noninvasive stimulation techniques (6). The behavioral improvement seen after suppression of neuronal processing in the nonlesioned right IFG has been interpreted as a suppression of maladaptive "overactivation" in the right hemisphere, which in turn may allow for better modulation in the remaining left hemisphere networks (5, 6). However, it should be noted that the results of noninvasive brain stimulation studies on poststroke aphasia are somewhat contradictory, with some studies suggesting that right hemisphere regions may beneficially contribute to recovery in some patients (3). Thus, the adaptive task-specific up-regulation of the right pIFG observed in the present study would be more compatible with the latter studies. Indeed, it has been suggested that the recruitment of contralateral homologous areas after left hemisphere stroke is associated with language improvement (3) or maintenance of task function (16). Moreover, it has been argued that additional factors, such as premorbid laterality of language representation, time course of recovery, and lesion site and size, are important determinants of the successful integration of right hemisphere activity during poststroke reorganization of language networks (16, 22).

One possible explanation for the partly inconsistent findings across different studies is that language recovery is a dynamic process involving both hemispheres at different times to different degrees (2). We would like to argue that the acute short-term plasticity effects induced by our cTBS protocol is most comparable with the immediate reorganization effects in the acute or subacute phase after stroke. Indeed, it has been suggested that early up-regulation of the right hemisphere after left hemisphere stroke may be beneficial for language recovery after stroke (2). This suggests that to promote language recovery after stroke, it might be worthwhile to apply facilitatory protocols over right hemisphere homologous regions in the subacute phase after stroke, whereas enhancement of preserved left hemisphere functions may be more beneficial in the chronic phase after stroke (23).

In summary, our results shed important new light on the dynamic regulation of interhemispheric interactions in the healthy human brain that are highly relevant to cognitive and motor

control (e.g., spatial attention, language, manual motor control). These findings are of particular potential importance for understanding language recovery after left hemisphere stroke, challenging the simplistic notion that up-regulation of the right hemisphere after a focal perturbation of the left hemisphere is simply a passive consequence of reduced interhemispheric inhibition from the left hemisphere to the right hemisphere. Rather, our results suggest that homologous right hemisphere language areas have the intrinsic potential to take a more active role in language recovery after stroke, through an increased functional influence on the dysfunctional left hemisphere language network. The beneficial effect of the right hemispheric homologous area might depend on the degree of damage to the left hemisphere. For instance, the contribution of the right hemisphere might be greater after only partial damage to left hemisphere regions (as after cTBS) compared with after complete destruction by stroke.

Materials and Methods

Experimental Design. The same 17 right-handed native German speakers (10 females; mean age, 23.8 ± 2.2 y) from our previous study (24) with no history of neurologic disorders or head injury participated in this study. Written informed consent was obtained from all subjects before the experiment. All subjects were right-handed (laterality index >95%) (25). The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty of the University of Kiel.

The study used a two (task: repetition of pseudowords vs. words) by two (modality: auditory vs. visual stimuli) by three (cTBS: effective vs. sham cTBS of pIFG, effective cTBS of aIFG) factorial event-related within-subject design (Fig. 1). Each subject participated in all three cTBS conditions. Details of the stimuli are provided in our previous report that included the sham session of this experiment (24). Before functional MRI (fMRI), we applied neuronavigated effective or sham cTBS (26) over the left pIFG vs. the aIFG in three different sessions at least 5 d apart. After scanning, subjects quickly indicated on a questionnaire which of the pseudowords used in the experiment had been familiar to them or had reminded them of an existing word. This allowed us to model the pseudowords associated with existing words as a separate regressor, thus ensuring that the pseudowords included did not have any associated meanings. Details of stimulus presentation, response collection, and image acquisition have been reported previously (24).

cTBS. We used neuronavigated cTBS (TMS Navigator; Localite) based on coregistered individual T1-weighted MRI images to navigate the rTMS coil and maintain its exact location and orientation throughout all sessions. cTBS was performed using the mean Montreal Neurological Institute (MNI) coordinates for the left pIFG (i.e., pars opercularis: $x, y, z = -52, 13, 8$ mm) and the aIFG (i.e., pars orbitalis: $x, y, z = -52, 34, -6$ mm) from a previous study reporting a functional subdivision of Broca's area (27) (Fig. 1*A*). Using these stereotactic coordinates, the individual stimulation sites were determined by calculating the inverse of the normalization transformation and transforming the coordinates from standard to "individual" space for each subject. More detailed information is provided in *SI Materials and Methods*.

Data Analyses. Task-related changes in the blood oxygenation level-dependent signal were analyzed using SPM 8 (Wellcome Trust Centre for Neuroimaging; www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 7.7 (Mathworks) (28). Conjunction analyses were conducted to delineate areas activated across both visually and auditorily presented stimuli for pseudoword repetition in contrast to real word repetition (*SI Materials and Methods*).

Effective connectivity between the left pIFG and the right pIFG was tested with DCM 10 (29) in SPM8 (*SI Materials and Methods*). The aim of our DCM analysis was to identify how cTBS influences the connections between the left pIFG and the right pIFG and whether this modulation is facilitatory or inhibitory. The model space included nine different models with full intrinsic connectivity (Fig. 4*A*). The driving input was set to either the left pIFG or the right pIFG alone and to both regions, and the modulatory effects of two cTBS locations (cTBS of the aIFG vs. the pIFG) on the connections between these regions were specified for each subject. The individual cTBS coordinates for the left pIFG and the right homologous area served as seed regions in each subject.

ACKNOWLEDGMENTS. This study was funded by the Bundesministerium für Bildung und Forschung (Grant 01GW0663). G.H. is supported by the Deutsche Forschungsgemeinschaft (Grant 589421). H.R.S. was supported by a Grant of Excellence sponsored by the Lundbeck Foundation for Mapping, Modulation, and Modeling the Control of Actions (R59 A5399) and by the University of Copenhagen's Excellence Program for Interdisciplinary Research [project PROGRAM (Information PROminence and GRAMmar in Mind and Brain)].

1. Raboyeau G, et al. (2008) Right hemisphere activation in recovery from aphasia: Lesion effect or function recruitment? *Neurology* 70(4):290–298.
2. Saur D, et al. (2006) Dynamics of language reorganization after stroke. *Brain* 129(Pt 6):1371–1384.
3. Winhuisen L, et al. (2005) Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: A combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* 36(8):1759–1763.
4. Thiel A, et al. (2005) Essential language function of the right hemisphere in brain tumor patients. *Ann Neurol* 57(1):128–131.
5. Naeser MA, et al. (2005) Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study. *Brain Lang* 93(1):95–105.
6. Naeser MA, et al. (2005) Improved naming after TMS treatments in a chronic, global aphasia patient: case report. *Neurocase* 11(3):182–193.
7. Martin PI, et al. (2009) Overt naming fMRI pre- and post-TMS: Two nonfluent aphasia patients, with and without improved naming post-TMS. *Brain Lang* 111(1):20–35.
8. Alario FX, Chainay H, Lehericy S, Cohen L (2006) The role of the supplementary motor area (SMA) in word production. *Brain Res* 1076(1):129–143.
9. Ghosh SS, Tourville JA, Guenther FH (2008) A neuroimaging study of premotor lateralization and cerebellar involvement in the production of phonemes and syllables. *J Speech Lang Hear Res* 51(5):1183–1202.
10. Sack AT, Camprodon JA, Pascual-Leone A, Goebel R (2005) The dynamics of interhemispheric compensatory processes in mental imagery. *Science* 308(5722):702–704.
11. O'Shea J, Johansen-Berg H, Trief D, Göbel S, Rushworth MF (2007) Functionally specific reorganization in human premotor cortex. *Neuron* 54(3):479–490.
12. Hartwigsen G, Siebner HR (2012) Probing the involvement of the right hemisphere in language processing with online transcranial magnetic stimulation in healthy volunteers. *Aphasiology* 26(9):1131–1152.
13. Thiel A, et al. (2006) Direct demonstration of transcallosal disinhibition in language networks. *J Cereb Blood Flow Metab* 26(9):1122–1127.
14. Heiss WD, Thiel A, Kessler J, Herholz K (2003) Disturbance and recovery of language function: Correlates in PET activation studies. *Neuroimage* 20(Suppl 1):S42–S49.
15. Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. *Neuroimage* 19(4):1273–1302.
16. Andoh J, Paus T (2011) Combining functional neuroimaging with off-line brain stimulation: Modulation of task-related activity in language areas. *J Cogn Neurosci* 23(2):349–361.
17. Hartwigsen G, et al. (2010) Phonological decisions require both the left and right supramarginal gyri. *Proc Natl Acad Sci USA* 107(38):16494–16499.
18. Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC (2013) The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex* 23(7):1593–1605.
19. Jung-Beeman M (2005) Bilateral brain processes for comprehending natural language. *Trends Cogn Sci* 9(11):512–518.
20. Baumgaertner A, Hartwigsen G, Roman Siebner H (2013) Right-hemispheric processing of non-linguistic word features: Implications for mapping language recovery after stroke. *Hum Brain Mapp* 34(6):1293–1305.
21. Roser ME, Fiser J, Aslin RN, Gazzaniga MS (2011) Right hemisphere dominance in visual statistical learning. *J Cogn Neurosci* 23(5):1088–1099.
22. Chrysikou EG, Hamilton RH (2011) Noninvasive brain stimulation in the treatment of aphasia: Exploring interhemispheric relationships and their implications for neurorehabilitation. *Restor Neurol Neurosci* 29(6):375–394.
23. Hartwigsen G, Siebner HR (2013) Novel methods to study aphasia recovery after stroke. *Clinical Recovery from CNS Damage*, Frontiers of Neurology and Neuroscience, eds Naritomi H, Krieger DW (Karger, Basel), Vol 32.
24. Hartwigsen G, et al. (2013) Increased facilitatory connectivity from the pre-SMA to the left dorsal premotor cortex during pseudoword repetition. *J Cogn Neurosci* 25(4):580–594.
25. Oldfield RC (1971) The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9(1):97–113.
26. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human motor cortex. *Neuron* 45(2):201–206.
27. Gough PM, Nobre AC, Devlin JT (2005) Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *J Neurosci* 25(35):8010–8016.
28. Friston KJ, et al. (1995) Spatial registration and normalization of images. *Hum Brain Mapp* 3:165–189.
29. Stephan KE, et al. (2010) Ten simple rules for dynamic causal modeling. *Neuroimage* 49(4):3099–3109.